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Hypertonicity: Clinical entities, manifestations and treatment

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Abstract

Hypertonicity causes severe clinical manifestations and is associated with mortality and severe short-term and long-term neurological sequelae. The main clinical syndromes of hypertonicity are hypernatremia and hyperglycemia. Hypernatremia results from relative excess of body sodium over body water. Loss of water in excess of intake, gain of sodium salts in excess of losses or a combination of the two are the main mechanisms of hypernatremia. Hypernatremia can be hypervolemic, euvolemic or hypovolemic. The management of hypernatremia addresses both a quantitative replacement of water and, if present, sodium deficit, and correction of the underlying pathophysiologic process that led to hypernatremia. Hypertonicity in hyperglycemia has two components, solute gain secondary to glucose accumulation in the extracellular compartment and water loss through hyperglycemic osmotic diuresis in excess of the losses of sodium and potassium. Differentiating between these two components of hypertonicity has major therapeutic implications because the first component will be reversed simply by normalization of serum glucose concentration while the second component will require hypotonic fluid replacement. An estimate of the magnitude of the relative water deficit secondary to osmotic diuresis is obtained by the corrected sodium concentration, which represents a calculated value of the serum sodium concentration that would result from reduction of the serum glucose concentration to a normal level.

Key words: Hypertonicity; Hypernatremia; Osmotic diuresis; Hyperglycemia; Water diuresis

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Core tip: States of hypertonicity cause transfer of fluid from inside the body cells into the fluid compartment surrounding the cells. The shrinking of the brain cells in hypertonicity causes severe manifestations and even death. The management of hypertonicity requires administration of intravenous solutions. The volume and the composition of the administered solutions are calculated by various equations. Close monitoring of the condition of the patient and frequent measurements of appropriate blood chemistries during treatment are critical steps for a favorable outcome. The two major states of hypertonicity are hypernatremia, an elevation of the concentration of sodium in the blood, and hyperglycemia, an elevation of the concentration of glucose in the blood. The management of severe hypertonicity in hypernatremia and hyperglycemia encounters different obstacles and requires different equations for the quantitative replacement of body fluid deficits.

Rondon-Berrios H, Argyropoulos C, Ing TS, Raj DS, Malhotra D, Agaba EI, Rohrscheib M, Khitan ZJ, Murata GH, Shapiro JI, Tzamaloukas AH. Hypertonicity: Clinical entities, manifestations and treatment. *World J Nephrol* 2017; 6(1): 1-13 Available from: URL: <http://www.wjgnet.com/2220-6124/full/v6/i1/1.htm> DOI: <http://dx.doi.org/10.5527/wjn.v6.i1.1>

INTRODUCTION

A previous report discussed pathophysiological aspects, quantitative predictions and experimental testing of hypertonicity^[1]. Knowledge of these fields is critical in understanding the clinical consequences of hypertonicity and in guiding their correction. Hypertonicity causes severe clinical manifestations and death. In addition to the degree of hypertonicity, the rapidity of its development is an important factor in the severity of its clinical manifestations, whether one deals with hypertonicity developing *de novo* or as a complication of treatment of a hypotonic state. In the second case, severe neurological manifestations may develop after rapid rises in tonicity even when it does not reach hypertonicity levels^[2]. The neurological manifestations of hypertonicity are secondary to cell shrinking due to osmotic transfer of water out of cells^[1]. Spontaneous restoration of cell volume after development of hypertonicity is achieved following cellular solute gain by intracellular transfer of extracellular electrolytes and both intracellular entry and cellular formation of new organic osmolytes^[1].

Intracellular acquisition of organic osmolytes following a hypertonic stimulus is slower than electrolyte acquisition because it depends on slow tonicity-induced transcription and expression of genes regulating osmolyte transport and generation processes^[1]. Consequently cellular acquisition of organic osmolytes characterizes the chronicity of a hypertonic state. Hypertonicity of less than 48 h duration is categorized as acute while hypertonicity of longer than 48 h duration is categorized as chronic. The slow nature of organic osmolyte acquisition has clinical consequences both during rapid development of hypertonicity when rates of increase in tonicity exceed the capacity of the brain to acquire organic osmolytes and during its treatment when the slow loss of brain osmolytes may cause swelling of the brain cells^[3-6]. This report presents the pathology, clinical manifestations, major categories, and principles of correction of hypertonicity.

PATHOLOGY AND CLINICAL MANIFESTATIONS OF HYPERTONICITY

The pathology of the brain has been studied in both patients who died during hypertonic episodes^[7] and experiments in animals subjected acutely to severe hypertonicity^[8]. The histologic changes are the consequence of decrease in the brain cell volume. In acute hypertonicity the brain

looks shrunken with many petechial hemorrhages and larger hemorrhages in the subarachnoid space. The hemorrhages are a consequence of brain shrinking. They result from tearing of bridging veins which cross the subdural space. There are also subdural fluid collections and hematomas, vascular congestion and venous occlusion and thrombosis^[7,8].

The clinical manifestations of acute hypertonicity result from both shrinking of the brain cells and vascular changes. Very young and very old patients are most commonly affected by this disorder. The manifestations of acute hypertonicity vary between these two age groups. Children with acute hypertonicity typically present with symptoms that progress in severity from irritability, restlessness and muscular twitching to hyperreflexia and seizures^[9,10]. Elderly with hypertonicity may present with lethargy, delirium and coma, but rarely if ever develop seizures^[10,11]. Patients with hypertonicity may develop fever, nausea and vomiting^[10]. Intense thirst is a frequent complaint of patients with hypertonicity who are not comatose^[9,10]. Clinical signs of hypovolemia (orthostatic hypotension and pulse increase, decreased skin turgor, flat neck veins, dry mucous membranes) may be present when the hypertonic state was created by net loss of hypotonic fluids^[9,10]. Death may follow coma and seizures^[7]. Mortality is high in children with acute hypertonicity^[10]. One study reported severe neurological deficits in the majority of infants who survived severe episodes of hypertonicity^[12]. However, these infants were also suffering from other illnesses that can cause permanent neurological damage (e.g., meningitis). The degree of hypertonicity correlates with the depression of sensorium in hospitalized elderly patients with hypernatremia^[13].

Chronic hypertonic states may manifest with only subtle neurological changes even when hypertonicity is severe. However, mortality in adults with chronic hypertonicity is also high^[11]. The osmotic demyelination syndrome following rapid rise in serum tonicity during correction of hyponatremia or during acute hypernatremia has a high mortality and may cause severe neurological deficits^[14].

CLINICAL SYNDROMES OF HYPERTONICITY

Hypertonicity denotes relative excess of solute with extracellular distribution over body water regardless of whether body water is normal, reduced or excessive. Relative excess of solutes distributed in body water cause rises in the osmolality of body fluids, but has no effects on tonicity. Sodium salts, including sodium chloride and sodium bicarbonate, are the major extracellular solutes. Although the largest, by far, amount of sodium easily accessible to osmotic events is in the extracellular compartment, its apparent volume of distribution is total body water. This means that extracellular sodium concentration represents the fraction of total extracellular

sodium and total intracellular potassium over total body water when there are no excesses of other extracellular solutes^[15]. Hypernatremia from relative excess of sodium salts represents a major category of hypertonicity^[16-18]. Unlike hyponatremia, which may be associated with hypotonicity, isotonicity or hypertonicity, hypernatremia routinely indicates hypertonicity. A rare exception is encountered when the serum sodium concentration ($[Na]_s$) is overestimated if it is measured by indirect ion-selective potentiometry in subjects with decreased serum solid content^[19]. The degree of overestimation of $[Na]_s$ in this instance is modest. For example, indirect potentiometry would report a $[Na]_s$ value of 148.5 mmol/L in a patient with true $[Na]_s$ equal to 145 mmol/L and serum solids equal to an extremely low 2% of his/her serum volume^[19].

In addition to sodium salts, other solutes with extracellular distribution can cause hypertonicity. As in the case of relative sodium excess, gain in other extracellular solutes leads to osmotic exit of water from the intracellular compartment. The osmotic water transfer dilutes the extracellular solutes. Sodium salts normally represent the great majority of these solutes. As a consequence of the osmotic fluid shift into the intracellular compartment, hypertonicity is typically associated with hyponatremia in case of excess of extracellular solutes other than sodium salts. Solutes responsible for hypertonic hyponatremia may be exogenous, e.g., mannitol, or endogenous, e.g., glucose^[20,21]. This report will analyze the topics of hypernatremia and hyperglycemia, which represent the most common syndromes of hypertonicity. However, it should be remembered that hypertonicity secondary to exogenous solutes is the source of diagnostic miscues and potential mismanagement of patients presenting with hyponatremia if the previous infusion history is not known to the treating medical practitioners^[22].

HYPERNATREMIA

Hypernatremia, defined as a $[Na]_s$ exceeding 145 mmol/L, has an estimated prevalence of 2% among patients admitted to hospitals and is less common than hyponatremia, which is seen in about 10% of this population^[23].

Pathophysiology of hypernatremia - clinical states leading to hypernatremia

The determinants of $[Na]_s$, when there are no excesses of other extracellular solutes, are total exchangeable body sodium, total exchangeable body potassium and total body water^[24]. Like hyponatremia^[14,25,26], hypernatremia results from isolated or combined changes of these determinants. While hyponatremia secondary to potassium deficits has been documented, hypernatremia secondary to potassium excess has not been reported, to our knowledge. This may be due to the limitations of available methods measuring total body potassium, to the lethal consequences of even small potassium gains,

Table 1 Body sodium and water changes leading to hypernatremia

Nae	Body H ₂ O	Clinical example
↔	↓	Diabetes insipidus
↑	↔	Salt tablet ingestion
↑↑	↑	Hypertonic infusions containing sodium salts
↓	↓↓	Loop diuretics, excessive sweating, osmotic diarrhea, osmotic diuresis
↑	↓	Not seen in practice

Nae: Exchangeable body sodium; ↓ = decrease; ↓↓ = greater decrease; ↑ = increase; ↑↑ = greater increase, ↔ = no change.

Table 2 Clinical states causing hypernatremia from inadequate water intake

Lack of water sources
Subject lost in desert
Inability of patient to drink water or ask for it
Tracheal intubation and sedation
Dementia
Delirium
Paranoia
Severe depression
Adipsia or hypodipsia caused by central nervous system disorder compromising the neural pathways of thirst
Granulomas, <i>e.g.</i> , sarcoidosis
Tumors, <i>e.g.</i> , craniopharyngioma, seminoma, lymphoma, astrocytoma
Degenerative processes, <i>e.g.</i> , Parkinson's disease
Congenital syndromes, <i>e.g.</i> , ectodactyly-ectodermal dysplasia-cleftlip-palate syndrome
Diabetes insipidus (a fraction of the patients)

or to a combination of the two mechanisms. Anyway, hypernatremia should be analyzed as a disorder of the relationship between body sodium and body water. Table 1 shows potential combinations of changes in body sodium and water resulting in hypernatremia and clinical examples for each pathophysiologic combination.

Body water abnormalities are the cause of hypernatremia in a large number of cases. In these subjects hypernatremia develops following a discrepancy between water intake and water output resulting in net water deficit. This discrepancy is usually the result of inadequate water intake in the setting of normal or increased water losses. Table 2 shows clinical conditions characterized by inadequate water intake and leading to hypernatremia.

Under normal conditions, water losses through respiration, the gastrointestinal fluids, the urine and the skin constitute the obligatory water loss. Obligatory water loss is normally in relative excess to the losses in sodium and potassium. Patients unable to replete their obligatory losses of water are prone to hypernatremia. However, even increased water loss does not cause hypernatremia in conscious individuals, except in exceptional cases. Hypertonicity is the major stimulus of thirst^[27]. Nephrectomized animals subjected to hypertonic stimuli consumed enough water to maintain their serum tonicity

Table 3 Clinical states causing excessive water loss

Extrarenal water loss
Gastrointestinal losses
Vomiting
Nasogastric drainage
Ileostomy
Pancreatobiliary fistula
Diarrhea (non-secretory)
Laxatives, <i>e.g.</i> , lactulose
Skin
Excessive sweating
Respiratory airways
Hyperpnea
Tracheal intubation
Mechanical ventilation
Excessive renal water losses
Osmotic (solute) diuresis
Osmotic diuretics, <i>e.g.</i> , mannitol
Glucosuria, <i>e.g.</i> , hyperglycemia, sodium-glucose transporter 2 (SGLT2) inhibitors
Urea diuresis, <i>e.g.</i> , diuresis post-acute tubular necrosis, post-obstructive diuresis, use of catabolic medications (corticosteroids, tetracyclines, <i>etc.</i>), high protein intake, urea treatment for hyponatremia
Salt diuresis, <i>e.g.</i> , intravenous infusion of saline, high salt intake
Water diuresis
Central diabetes insipidus
Idiopathic (most common)
Genetic: Familial (mutation causing misfolding of vasopressin), congenital hypopituitarism, Wolfram syndrome (diabetes insipidus, diabetes mellitus, optic atrophy, deafness)
Acquired: Neurosurgery, head trauma, brain tumors, infiltrative disorders (sarcoidosis, Langerhans cell histiocytosis, <i>etc.</i>)
Nephrogenic diabetes insipidus
Genetic: Inactivating mutations of V2 receptor gene (most common) or aquaporin 2 gene
Acquired:
Renal disease (chronic renal failure, post-acute tubular necrosis, obstructive nephropathy, sickle cell disease, autosomal dominant polycystic kidney disease)
Electrolyte disorders: Hypokalemia, hypercalcemia
Drugs: Lithium, amphotericin, demeclocycline, ifosfamide,
V2 receptor antagonists
Gestation: Increased placental production of vasopressinase
Upward resetting of the osmostat (reset osmostat): Primary hyperaldosteronism (thought to be secondary to volume expansion and resulting in modest hypernatremia, up to 147 mmol/L)

within the baseline normal levels^[28]. Increased water loss leads to increased water intake in conscious individuals having free access to water. Consequently, large water loss does not result in significant hypernatremia unless it is enormous or it is combined with inability to drink water for various reasons (Table 2).

Table 3 shows clinical states causing excessive water loss. Large water losses causing hypernatremia can be of extrarenal or renal origin. Extrarenal sites of water loss are the skin, the respiratory system and the gastrointestinal tract. Fluid losses from the gastrointestinal tract can be of enormous magnitude, are routinely hypotonic and lead to hypernatremia particularly in infants or children^[29,30]. Table 4 shows the electrolyte composition of gastrointestinal fluids^[31].

The ability of the kidneys to concentrate the urine

Table 4 Electrolyte composition of various gastrointestinal fluids

Fluid source	Sodium (mmol/L)	Potassium (mmol/L)
Vomiting, nasogastric drainage	20-100	10-15
Secretory diarrhea	40-140	15-40
Non-secretory diarrhea	50-100	15-20
Adapted ileostomy	40-90	5
New ileostomy	115-140	5-15
Sweat	38-45	5

Data obtained from ref. [21].

constitutes the main defense against excessive water loss^[10]. Two general mechanisms are responsible for renal water loss secondary to reduced urinary concentrating capacity: (1) decreased vasopressin production (diabetes insipidus) or impaired renal response to vasopressin (nephrogenic diabetes insipidus)^[19,32]; and (2) increased urinary solute excretion (solute or osmotic diuresis). Osmotic diuresis leads to increased losses of both water and monovalent cations. The tendency to develop hypernatremia in this setting is due to the lower cation concentration (sodium plus potassium) in the urine than in plasma which leads to water loss in excess of the cation loss^[33,34].

In a minority of cases, hypernatremia results from pure sodium excess, although this is usually associated with a lack of access to water. Isolated increase in body sodium may occur as a result of intake of salt tablets or infusion of hypertonic solutions of sodium salts. Salt poisoning from near-drowning in sea water^[35], during environmental disasters or after suicidal attempts with soy sauce ingestion^[36] have also been reported.

Diagnostic approach to hypernatremia

Like hyponatremia, hypernatremia is classified as hypervolemic, hypovolemic, or euvolemic^[10,37]. The history and physical examination assist in the diagnosis of the type of hypernatremia and of its pathogenesis. Hypervolemic hypernatremia is encountered after ingestion of salt, often in the form of salt tablets. Both accidental and suicidal salt ingestion leading to severe hypernatremia have been reported. In hospitalized patients, hypervolemic hypernatremia develops after infusion of saline or sodium bicarbonate solutions without adequate water content^[38-40]. Hypervolemic hypernatremia, with weight gain and edema formation is the most common category of hypernatremia developing after saline infusions in patients exhibiting difficulty in excreting solute loads^[40]. Hypervolemic hypernatremia without edema may develop in patients with primary hyperaldosteronism, Cushing syndrome, or after ingestion of salt tablets or infusion of hypertonic sodium bicarbonate and has been noticed in the past immediately following dialysis with a dialysate containing high concentrations of dextrose^[10].

Hypovolemic or euvolemic hypernatremia occur in clinical settings that may be similar. The contribution of physical examination in the differential diagnosis between

these two categories of hypernatremia is questionable when there are no clear-cut clinical signs of hypovolemia. History is of greater assistance in differentiating between hypovolemic and euvolemic hyponatremia in this case. Careful questioning addressing the presence or absence of thirst and the volume of urine allows further categorization of both hypovolemic and euvolemic hypernatremia. Figure 1 shows a diagnostic scheme for these two categories of hypernatremia.

Presence or absence of thirst and polyuria, and daily urinary solute load are the three characteristics of hypovolemic or euvolemic hypernatremias allowing a correct diagnosis of their pathophysiology (Figure 1). The combination of urine with high osmolality, and absence of polyuria and of high urinary solute output indicates either extrarenal water loss, when it is associated with thirst, or adipsia or hypodipsia, when thirst is absent. Polyuria associated with high urine osmolality and consequently with high urine solute load is a sign of osmotic diuresis. Polyuria associated with dilute urine and normal urine solute load is a sign of diabetes insipidus. In this last case, the response to desmopressin infusion leads to distinction between central and nephrogenic diabetes insipidus.

Treatment of hypernatremia

Acute hypernatremia, which is not encountered often, should be considered a medical emergency in the presence of severe neurological manifestations, *e.g.*, seizures, or when $[Na]_s$ exceeds 160 mmol/L. Its treatment consists of intravenous infusion of large volumes of 5% dextrose in water (D5/W). The goal is to normalize $[Na]_s$ within 24 h. Hypotonic saline should be infused instead of D5/W when hypernatremia and volume deficit are present together.

Hypernatremia is chronic in the majority of instances. Chronic hypernatremia typically causes minimal symptoms or may be asymptomatic. The treatment of chronic hypernatremia has two aims. The first aim is to correct the existing deficit of water, and the deficit of sodium when present, by administration of water or hypotonic saline. Cerebral edema secondary to excessive entry of water into brain cells, primarily astrocytes, may complicate a rapid decline in $[Na]_s$ in severe chronic hypernatremia. Rapid correction of chronic hypernatremia in infants and children has resulted in seizures^[7]. The target rate of decrease in $[Na]_s$ is 10 mmol/L in 24 h. The volume of hypotonic saline (V_3) that is needed to produce a desired decrease in $[Na]_s$ is calculated as follows: The determinants of the final serum sodium concentration ($[Na]_{s2}$) include V_3 , the presenting serum sodium concentration ($[Na]_{s1}$), the sodium concentration in the infused hypotonic saline ($[Na]_{s3}$) and the initial body water (V_1). The value of the desired serum sodium concentration is calculated as^[1]:

$$[Na]_{s2} = ([Na]_{s1} \times V_1 + [Na]_{s3} \times V_3) / (V_1 + V_3) \quad (1).$$

By rearranging equation 1, the following value of V_3 for a desired $[Na]_{s2}$ is: $V_3 = V_1 \times ([Na]_{s1} - [Na]_{s2}) / ([Na]_{s2} - [Na]_{s3})$ (2).

For example, equation 2 calculates that the volume

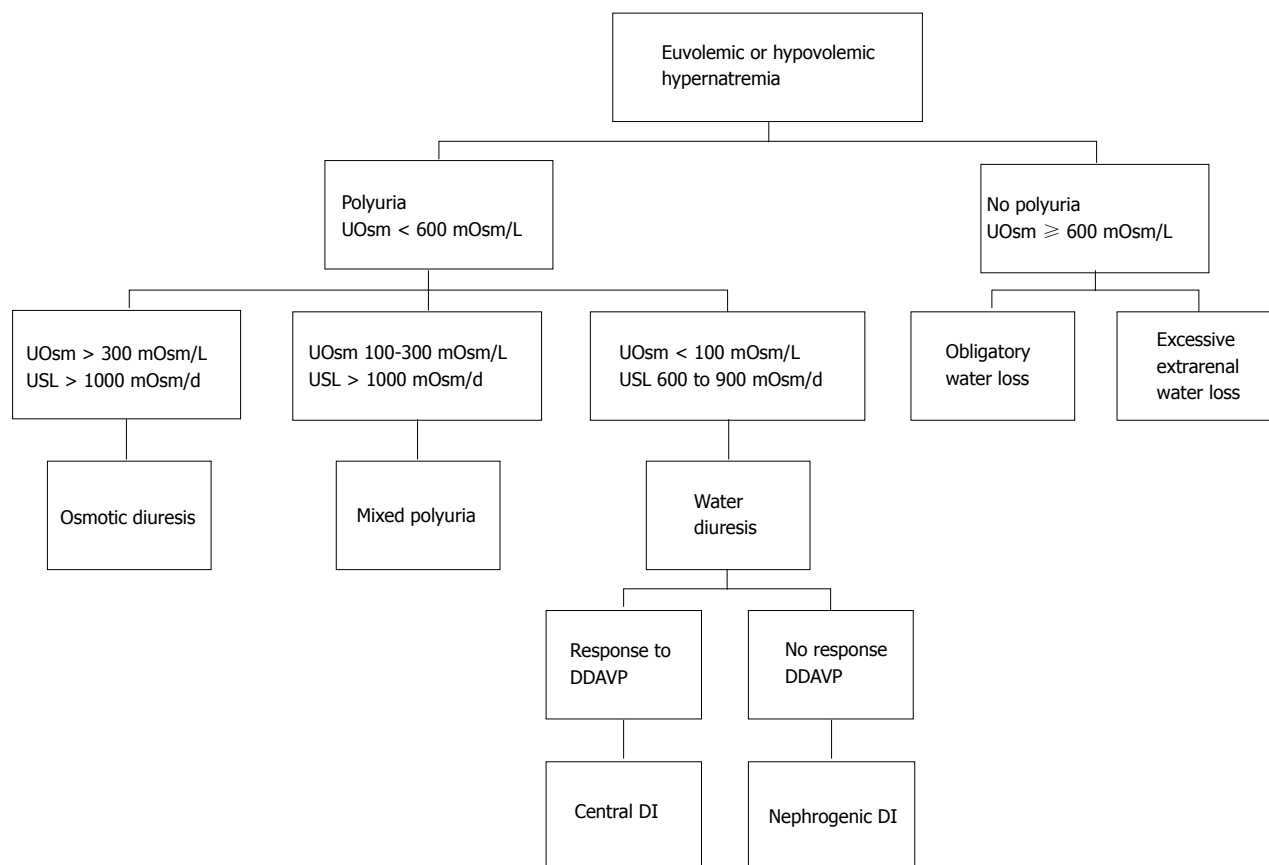


Figure 1 Diagnosis of hypovolemic and euvoletic hypernatremia. UOsm: Urine osmolality; USL: Urine solute load; GI: Gastrointestinal; DDAVP: Desmopressin; DI: Diabetes insipidus; Osm: Osmolality.

V_3 of half-normal saline ($[Na]_{s3} = 77$ mmol/L) needed to reduce $[Na]_s$ from a $[Na]_{s1}$ value of 150 mmol/L to a $[Na]_{s2}$ value of 140 mmol/L in a person with initial body water (V_1) equal to 40 L is 6.67 L. Emphasis should be placed on entering as $[Na]_{s3}$ in equation 2 the sum of sodium plus potassium concentrations in the infusate^[18,25]. Figure 2 shows the effect on $[Na]_s$ of infusion of various volumes of solutions containing various combinations of sodium and potassium concentrations.

When the replacement fluid consists only of water, e.g., when 5% dextrose in water is infused, equation 2 takes the form: $V_3 = V_1 \times ([Na]_{s1} - [Na]_{s2}) / [Na]_{s2}$ (3).

According to equation 3, the volume of dextrose in water required to reduce $[Na]_s$ from 150 to 140 mmol/L in a person with V_1 equal to 40 L is 2.86 L.

The calculation of the volume of hypotonic saline or water required for a desired decrease in $[Na]_s$ by the method presented is subject to two types of error. The first potential error stems from the estimate of initial body water introduced in equations 2 and 3. Body water is calculated by formulas derived by comparing measurements of body water by dilution of an index substance (e.g., heavy water, tritiated water, and antipyrine) to anthropometric measurements. For adult patients, the anthropometric Watson formulas calculate body water as a function of gender, height, weight and, in men only, age^[41]. For children, body water is calculated

by the Mellits-Cheek formulas by the use of gender, weight and height^[42]. Both the Watson and Mellits-Cheek formulas were derived from studies in subjects with euvolectia. Consequently, these formulas should be expected to provide a reasonable approximation of body water in subjects with euvolectia, but will systematically overestimate body water in subjects with hypovolemtia and underestimate body water in subjects with hypervolemtia^[43]. If the weight at euvolectia has been recorded recently, an approximation of the body water at hypovolemtia or hypervolemtia can be obtained by calculating body water at the euvolectic weight and then subtracting from or adding to the euvolectic value of body water the difference between the euvolectic weight and the weight at presentation with volume abnormality^[44]. This adjustment of body water is not feasible in most instances, particularly in chronic hypernatremia. In any case, the estimate of body water at presentation with hypernatremia is prone to significant errors.

The second source of error is ongoing losses of fluid and monovalent cations during treatment. These losses, from the urinary tract, the gastrointestinal tract, the airways or the skin can be large but are not predictable and are not included in the equations calculating the volumes infused. Figure 3 shows the effects of varying urine volume with varying urinary monovalent cation

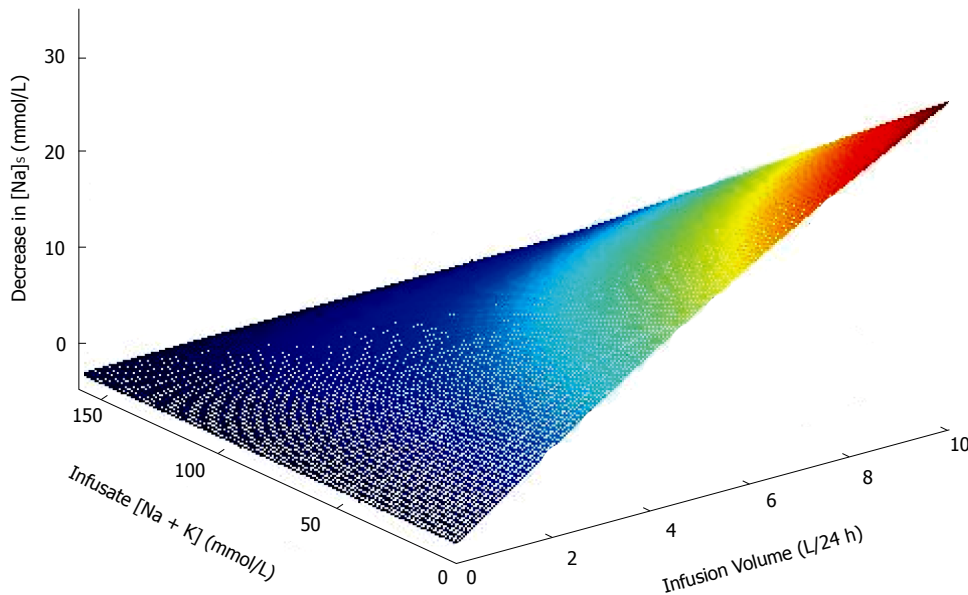


Figure 2 Effect on $[Na]_s$ of varying volumes of infusate containing varying total monovalent cation concentration (sum of sodium plus potassium concentrations) in a patient with initial body water of 40 L and $[Na]_{s1}$ of 150 mmol/L.

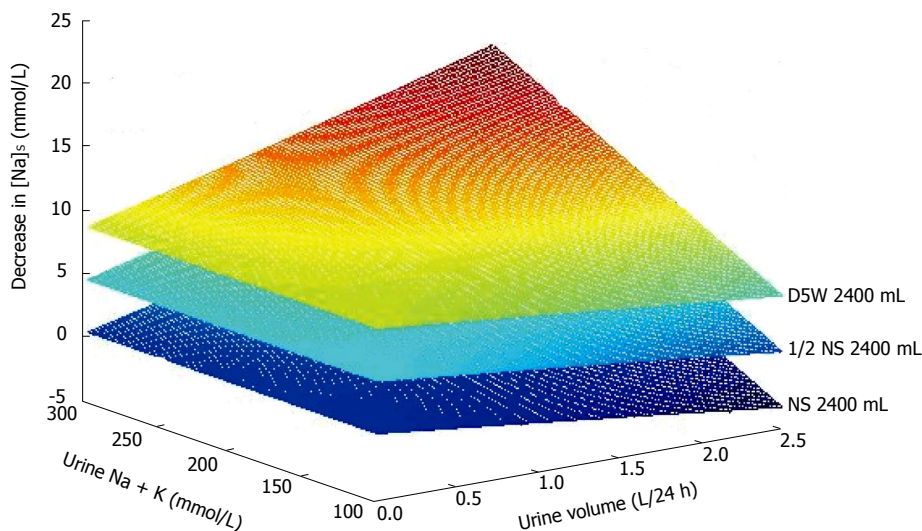


Figure 3 Effect on $[Na]_s$ of varying 24-h urinary volume containing varying total monovalent cation concentration (sum of sodium plus potassium concentrations) in a patient with initial body water of 40 L and $[Na]_{s1}$ of 150 mmol/L infused with the same volume (2.4 L) of 5% dextrose in water, or “half-normal” saline ($[Na]_{s3} = 77$ mmol/L) or “normal” saline ($[Na]_{s3} = 154$ mmol/L).

(sodium plus potassium) concentrations on the change in $[Na]_s$ in a patient infused with the same volume of solutions containing various sodium concentrations.

Because of the potential magnitude of the errors introduced by body water estimates and urinary losses, close monitoring of the patient during treatment of hypernatremia is the critical measure of success. In addition to the clinical status and both $[Na]_s$ and serum glucose concentration ($[Glu]_s$), the volume and electrolyte composition of external losses should be monitored. Serum measurements should be done frequently, *e.g.*, every 4–6 h. Fluid and electrolyte losses should be replaced concomitantly with the calculated replacement fluid for correction of hypernatremia. Differences between changes

in $[Na]_s$ observed and predicted by formulas 2 or 3 should lead to a search for the cause of these differences (*i.e.*, erroneous values for body water used in the formulas or not accounted for losses in water and monovalent cations). Emergency hemodialysis^[45,46] or peritoneal dialysis^[47] should be considered in extreme cases of symptomatic hypernatremia or in severe hypernatremia in patients with end-stage renal disease with volume overload who may tolerate poorly even 5% dextrose in water infusions.

The second treatment aim is to manage the underlying cause of hypernatremia. For example, administration of corticosteroids may correct adipsia caused by neurosarcoidosis; intranasal or subcutaneous desmopressin (dDAVP) corrects the urinary concentrating defect

of central diabetes insipidus; in nephrogenic diabetes insipidus, a diet low in sodium and protein reduces the urinary solute load and volume and thiazide diuretics induce hypovolemia which causes increased proximal tubular reabsorption of sodium and water, decreased delivery of water to the vasopressin-sensitive sites in the collecting tubules and reduction in the urine output.

HYPERGLYCEMIA

Hypertonicity is one of the cardinal manifestations of hyperglycemic crises^[48]. Assessment and management of hypertonicity in severe hyperglycemia are critical^[49].

Degree of hypertonicity in hyperglycemia

Serum tonicity ($[\text{Ton}]$), in mOsm/L or mmol/L, is calculated in hyperglycemia as $[\text{Glu}]_s + 2 \times [\text{Na}]_s$ with $[\text{Glu}]_s$ expressed in mmol/L^[20]. The error from considering the osmotic coefficient of sodium salts in the serum as equal to 2 in this calculation is insignificant in most instances. When $[\text{Na}]_s$ is determined by indirect potentiometry, a significant underestimation of tonicity calculated by this formula occurs in hyperglycemic states associated with decreased water fraction of the serum, *e.g.*, in patients with hyperlipidemia or elevated serum protein concentration. The normal range of serum tonicity is 280-290 mOsm/L.

Evaluation of the degree of hypertonicity in hypernatremia is simple. The rise in tonicity ($\Delta[\text{Ton}]$) in this case is equal to $2 \times \Delta[\text{Na}]_s$ where $\Delta[\text{Na}]_s$ is the rise in $[\text{Na}]_s$ above a normal level. In contrast to hypernatremia, evaluation of the degree of hypertonicity in hyperglycemia is complex. In this case, the mechanism of hypertonicity consists of two major influences, the primary (direct) effect of rise in extracellular solute content secondary to glucose gain and the secondary effects of hyperglycemia on solute and water balances. These effects are analyzed below.

Direct effect of hyperglycemia on body fluid tonicity

The solute gain during development of hyperglycemia results in rises of different magnitude in serum glucose concentration ($\Delta[\text{Glu}]_s$) and tonicity ($\Delta[\text{Ton}]$). The difference between $\Delta[\text{Glu}]_s$ and $\Delta[\text{Ton}]$, when they are both expressed in mOsm/L, results from the fact that $\Delta[\text{Glu}]_s$ represents the fraction solute (glucose) gain over extracellular volume (V_e) while $\Delta[\text{Ton}]$ represents the fraction solute gain over body water (V)^[1,16]. The relationship between $\Delta[\text{Ton}]$ and $\Delta[\text{Glu}]_s$ can be visualized as follows: At first approximation the amount of glucose gained, expressed in mmol or mOsm, and the amount of total solute gained are equal, or: $\Delta[\text{Ton}] \times V = \Delta[\text{Glu}]_s \times V_e$ (4).

Division of both sides of equation 4 by $\Delta[\text{Glu}]_s \times V$ reveals: $\Delta[\text{Ton}]/\Delta[\text{Glu}]_s = V_e/V$ (5).

Equation 5 is the key to understanding the internal factors that affect the rise in tonicity in hyperglycemia. Extracellular volume status influences the degree of

hypertonicity in hyperglycemic episodes^[50,51]. Figure 4 shows examples of $\Delta[\text{Ton}]$ at the same $\Delta[\text{Glu}]_s$ (100 mmol/L or 1800 mg/dL) in euvoolemia, hypovolemia, hypervolemia and extreme hypervolemia. In euvoolemia, extracellular volume is approximately one-third of body water and, therefore, the fraction $\Delta[\text{Ton}]/\Delta[\text{Glu}]_s$ should be around 0.33. $\Delta[\text{Ton}]/\Delta[\text{Glu}]_s$ values lower than 0.33 should be encountered in hypovolemia and values higher than 0.33 should be encountered in hypervolemia^[50-52].

The degree of hyperglycemia is another factor potentially influencing the relationship between $\Delta[\text{Ton}]$ and $\Delta[\text{Glu}]_s$. Robin and collaborators calculated a progressive rise of the value $\Delta[\text{Ton}]/\Delta[\text{Glu}]_s$ as $[\text{Glu}]_s$ increases progressively^[53]. The effect of hyperglycemia on $\Delta[\text{Ton}]$ is mediated by the commensurate increase in extracellular volume, which increases progressively, while intracellular volume decreases by the same volume as $[\text{Glu}]_s$ increases, if external losses of water and solute are negligible^[52]. Figure 5 shows calculations of the extracellular fraction of body water in various degrees of hyperglycemia. The degree of hyperglycemia that can be expected to have clinically relevant effects on the rise in tonicity is extreme^[52].

$\Delta[\text{Ton}]$ values lower than the corresponding $\Delta[\text{Glu}]_s$ values are obtained in hyperglycemia because of the osmotic translocation of intracellular fluid into the extracellular compartment secondary to extracellular solute (glucose) gain. The net osmotic fluid shift stops when intracellular osmolality, which is increasing with the loss of intracellular fluid, becomes equal to the extracellular osmolality, which is decreasing with the extracellular gain of fluid. The attenuation of the rise in extracellular osmolality secondary to the internal osmotic fluid shift is expressed as a decrease in $[\text{Na}]_s$. In this case, $\Delta[\text{Ton}]$ is the algebraic sum of the rise in serum glucose concentration ($\Delta[\text{Glu}]_s$) and the decrease in serum sodium salt concentration ($2 \times [\text{Na}]_s$). Therefore: $\Delta[\text{Ton}] = \Delta[\text{Glu}]_s - 2 \times [\text{Na}]_s$ (6).

where $[\text{Na}]_s$ is the baseline euglycemic $[\text{Na}]_s$ minus the hyperglycemic $[\text{Na}]_s$. Thus the effect of the various internal factors affecting the rise in tonicity for any given rise in $[\text{Glu}]_s$ is mediated through the decrease in $[\text{Na}]_s$. The decrease in $[\text{Na}]_s$ caused by hyperglycemia, therefore, becomes an important part of the calculations of the tonicity of the replacement solutions.

The decrease in $[\text{Na}]_s$ as a result of osmotic fluid addition to the extracellular compartment during development of hyperglycemia should be equal to the increase in $[\text{Na}]_s$ after correction of hyperglycemia when there are no other influences on $[\text{Na}]_s$. Estimating the drop in $[\text{Na}]_s$ for a given rise in $[\text{Glu}]_s$ and therefore predicting the rise in $[\text{Na}]_s$ after correction of the hyperglycemia has important therapeutic implications. The effects of internal osmotic fluid transfers on $[\text{Na}]_s$ will be reversed with correction of hyperglycemia without the need for additional interventions. These effects should be differentiated from the effects of other processes affecting $[\text{Na}]_s$ routinely in severe hyperglycemic episodes because

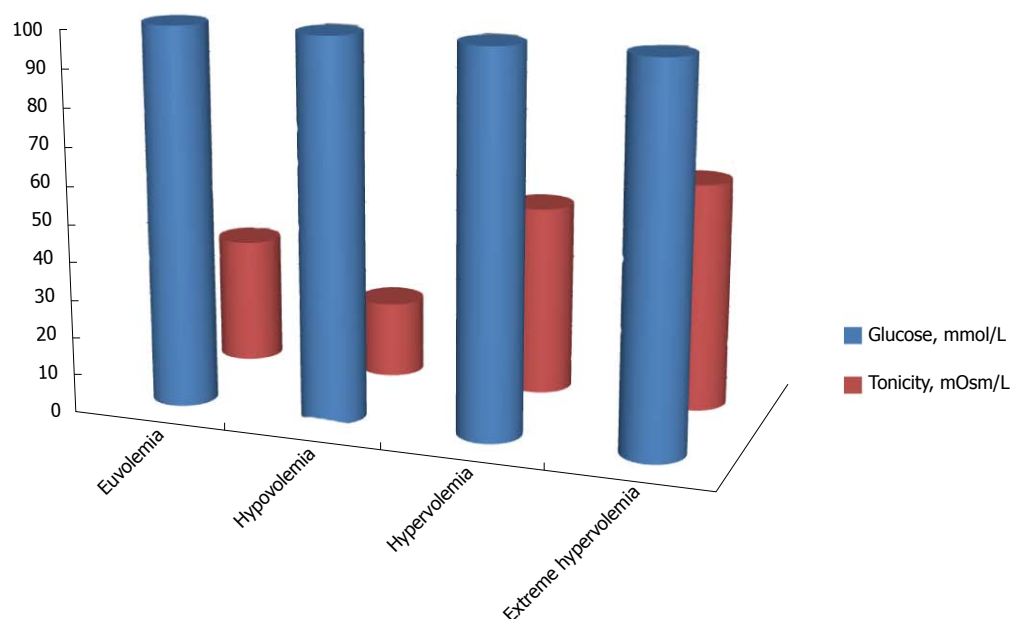


Figure 4 Increase in tonicity for the same degree of hyperglycemia (100 mmol/L) at various states of extracellular volume.

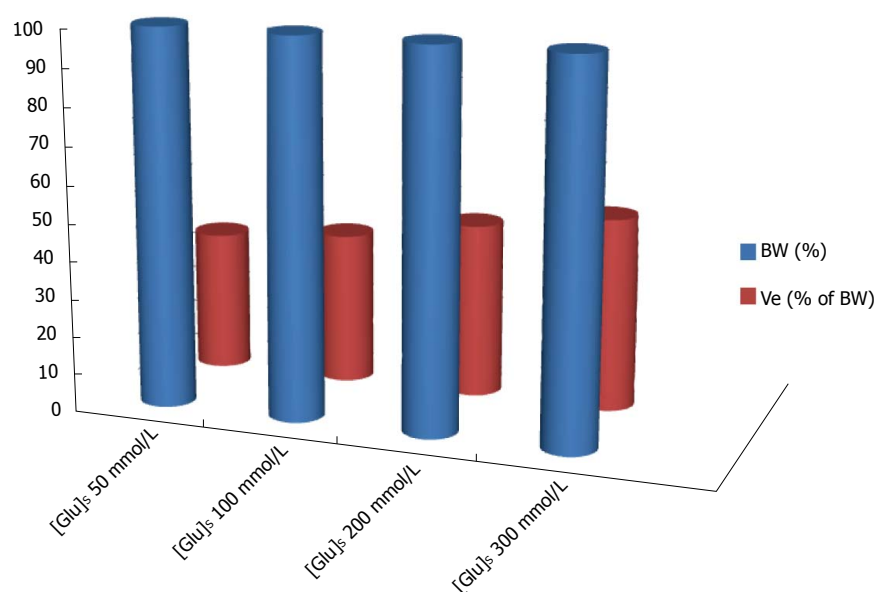


Figure 5 Increase in tonicity expressed as a percent of the increase in serum glucose concentration in progressive hyperglycemia.

these other influences on $[Na]_s$ require additional therapeutic measures^[20,54]. The Katz formula, which calculates only the effects of the internal osmotic fluid shift resulting from hyperglycemia, predicts a decrease in $[Na]_s$ by 1.6 mmol/L for each 100 mg/dL (5.6 mmol/L) increase in $[Glu]_s$ ^[55]. Using formula 6, the fraction $\Delta[Ton]/\Delta[Glu]_s$ predicted by the Katz formula is equal to 0.43^[49]. This fraction, which represents a modest degree of hypervolemia (Figure 2), reflects the extracellular expansion that results from the internal osmotic fluid shift during development of hyperglycemia^[56].

Clinical evaluation of the Katz formula is complicated by the indirect effects of hyperglycemia on serum tonicity^[54]. Hyperglycemia in oligoanuric patients allows

the study of this formula with minimal interference from these indirect effects. Studies of $\Delta[Ton]/\Delta[Glu]_s$ in hyperglycemic patients on chronic dialysis observed mean $\Delta[Ton]/\Delta[Glu]_s$ values very close to 0.43^[56,57]. Figure 6 shows the mean changes in tonicity predicted by the Katz formula and observed in severe hyperglycemic episodes in patients on chronic dialysis treated with insulin infusion and no other interventions^[56]. Predicted and observed $\Delta[Ton]/\Delta[Glu]_s$ values were close.

High $\Delta[Ton]/\Delta[Glu]_s$ values were observed during treatment of hyperglycemia only in a small number of dialysis patients with profound hypervolemia^[56]. The relationship $\Delta[Ton]/\Delta[Glu]_s$ during treatment of severe hyperglycemic episodes in patients on dialysis with

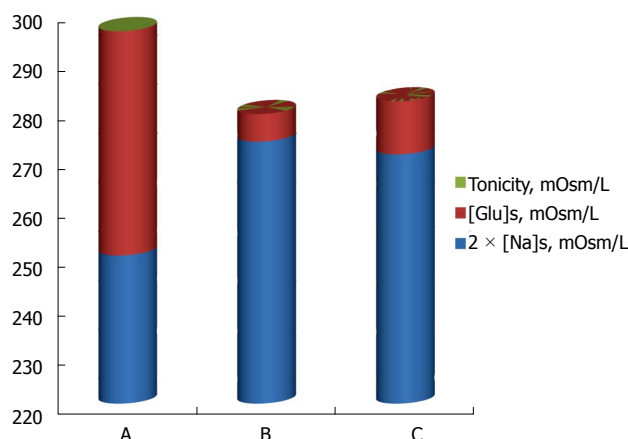


Figure 6 Mean values of $[\text{Na}]_s$, $[\text{Glu}]_s$ and serum tonicity in hyperglycemia in patients on chronic dialysis. The figure shows the mean values of $[\text{Na}]_s$, $[\text{Glu}]_s$ and tonicity in 148 episodes of severe hyperglycemia treated only with insulin infusion^[40]. A: Values recorded at presentation with hyperglycemia; B: Values predicted by the corrected $[\text{Na}]_s$ ^[47]; C: Values of observed $[\text{Na}]_s$ and $[\text{Glu}]_s$ and calculated tonicity at the end of treatment when $[\text{Glu}]_s$ had declined to desired levels. Tonicity was calculated as $[\text{Glu}]_s + 2 \times [\text{Na}]_s$ in A, B and C. The average level of tonicity after treatment predicted by the use of predicted $[\text{Na}]_s$ (B) was very close to the corresponding measured level (C).

insulin infusion and no other measures was used to evaluate the state of extracellular volume in one study^[58]. In this study, the observed $\Delta[\text{Ton}]/\Delta[\text{Glu}]_s$ values allowed proper characterization of the volume status in a small number of patients with pronounced edema and a larger number of subjects whose body weight was close to their dry weight^[58]. We did not find any reports documenting the effect of the degree of hyperglycemia on $\Delta[\text{Ton}]/\Delta[\text{Glu}]_s$. We suggest that the Katz formula can be expected to predict with reasonable accuracy the value of $\Delta[\text{Ton}]/\Delta[\text{Glu}]_s$ that results from the direct effect of correction of hyperglycemia in patients with absence of severe hypervolemia. Application of the Katz formula in the prediction of the change in tonicity secondary to correction of hyperglycemia in patients with severe volume disturbances will require special caution^[49,56].

Indirect effects of hyperglycemia on body fluid tonicity

In addition to its hypertonic effect from accumulation of glucose in extracellular fluids, hyperglycemia has two other indirect influences on tonicity. The first indirect effect of hyperglycemia is the result of osmotic diuresis secondary to glucosuria. Osmotic diuresis in severe or protracted hyperglycemia can be massive and leads to water losses in excess of monovalent cation losses^[20,21]. Loss of water in excess of the losses of potassium and sodium leads to elevation in $[\text{Na}]_s$ ^[21] which in several studies analyzing severe hyperglycemic episodes was within the normal range or even in the hypernatremic range in the face of profound hyperglycemia^[21,56].

The second indirect effect of hyperglycemia is fluid intake secondary to thirst. Hyperglycemia causes a lesser degree of thirst than hypernatremia causing similar levels of hypertonicity^[16]. Water gain secondary to thirst and fluid intake during development of hyperglycemia

is not enough to compensate for the water loss through osmotic diuresis in severe cases of hyperglycemia. Hyperglycemic patients with oligoanuria develop minimal or no osmotic diuresis. In the absence of any other change in solute and water balance in these patients, water intake driven by hyperglycemic thirst should lead to hyponatremia after correction of hyperglycemia even though $[\text{Na}]_s$ rises as $[\text{Glu}]_s$ decreases^[49]. Hyponatremia after correction of severe hyperglycemia with insulin infusion and no other interventions was documented in approximately one third of the cases in patients on chronic dialysis^[59].

Management of hypertonicity in hyperglycemia

In addition to correction of hyperglycemia and ketoacidosis, when present, the treatment of hyperglycemic crises addresses the critical areas of hypovolemia, potassium deficit and hypertonicity plus less frequently other deficits, e.g., deficits of phosphate or magnesium^[49,60]. Current guidelines address all these disturbances of hyperglycemic crises^[48]. This report will focus on the management of hyperglycemic hypertonicity.

Hyperglycemic hypertonicity has two components, gain in solute secondary to the rise in $[\text{Glu}]_s$ and excessive loss of water over sodium and potassium secondary to hyperglycemic osmotic diuresis. The second component represents a relatively small part of hypertonicity in reported series of diabetic ketoacidosis and the major component of hypertonicity in reported series of hyperosmolar hyperglycemic syndrome^[56]. The management of hyperglycemic hypertonicity requires setting of specific targets for each one of these two components. Correction of hyperglycemia without any other change in body water or solute leads to loss of extracellular solute and decrease in tonicity^[61,62].

Calculation of the degree of hypertonicity secondary to osmotic diuresis is obscured for the duration of hyperglycemia by the effect of elevated $[\text{Glu}]_s$ on $[\text{Na}]_s$ levels. The calculation of the corrected $[\text{Na}]_s$ by Al-Kudsi and collaborators^[63] provides a valuable tool allowing quantitative evaluation of the component of hyperglycemic hypertonicity that results from osmotic diuresis^[64,65]. The corrected $[\text{Na}]_s$ uses Katz's formula to compute the value of $[\text{Na}]_s$ that would result from correction of the hyperglycemia if there are no changes in the balances of water, sodium and potassium, as follows^[63]:

$$\text{Corrected } [\text{Na}]_s = [\text{Na}]_{s1} + 1.6 \times ([\text{Glu}]_{s1} - 100)100 \quad (7).$$

where $[\text{Na}]_{s1}$ and $[\text{Glu}]_{s1}$ are respectively the sodium and glucose concentrations at hyperglycemia. $[\text{Glu}]_{s1}$ is expressed in mg/dL in formula 7. Both $[\text{Glu}]_s$ and corrected $[\text{Na}]_s$ are treatment targets of hyperglycemic hypertonicity.

As in hypernatremia, rapid correction of hypertonicity has the risk of causing cerebral edema in hyperglycemia^[66]. The decrease in tonicity during correction of hyperglycemia should not exceed 3 mOsm/L per hour^[67]. The hourly rate of decrease in $[\text{Glu}]_s$ proposed in guidelines is 50-75 mg/dL or 2.8-4.2 mmol/L^[67]. At this rate of decline in $[\text{Glu}]_s$,

the rate of decline in tonicity will be 1.2-1.8 mOsm/L if $[\text{Na}]_s$ rises concomitantly at the rate predicted by the Katz formula^[49]. If this rate of decline in $[\text{Glu}]_s$ is achieved, the proposed maximal hourly rate of decline in the corrected $[\text{Na}]_s$ is 0.6-0.9 mmol/L^[49]. The corrected $[\text{Na}]_s$ should be computed after each measurement of serum chemistries and its value should be used as $[\text{Na}]_{s1}$ in the calculation of the infused volume of hypotonic fluids by equation 2. In this way, the corrected $[\text{Na}]_s$ is used in the same manner as the serum sodium concentration during treatment of hypernatremia. The treatment should aim to a continuous decrease in corrected $[\text{Na}]_s$ as long as its values remain elevated.

The management of hypertonicity in severe hyperglycemia encounters even greater difficulties than its management in severe hypernatremia. In hyperglycemic crises water, sodium and potassium deficits are routinely large and can be massive. Their severity may draw attention away from hypertonicity^[49]. In addition, the calculation of corrected $[\text{Na}]_s$ with the use of the Katz formula adds another degree of uncertainty. As noted, the value $\Delta[\text{Ton}]/\Delta[\text{Glu}]_s$ receives a significant influence from the relationship between extracellular volume and body water, which is subjected to great variation in hyperglycemia. Finally, osmotic diuresis persists as long as $[\text{Glu}]_s$ remains elevated and may even increase when volume deficits are replaced and renal function is restored causing large losses of water and electrolytes during treatment of hyperglycemia^[49]. For these reasons, the need to monitor the clinical status of the patient, serum chemistries and urinary losses is, if anything, even more important during treatment of severe hyperglycemia than during treatment of hypernatremia.

CONCLUSION

Hypertonicity secondary to hypernatremia or hyperglycemia is the source of life-threatening clinical manifestations and its treatment provides great challenges to clinicians. Equations calculating the fluid and electrolyte deficits are of help in the prescription of hypertonicity treatment and in following its results. Comparison of observed and predicted by these equations changes should be used to detect and correct potential errors in the calculations from the predictive equations (e.g., body water estimates) and problems caused by large fluid losses during treatment. Close monitoring during treatment of clinical status, appropriate serum chemistries and external losses of fluid and monovalent cations is a critical step. Adjustment of treatment guided by the findings in each monitoring step is essential for successful outcomes.

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Functional coupling of V-ATPase and CLC-5

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Abstract

Dent's disease is an X-linked renal tubulopathy characterized by low molecular weight proteinuria, hypercalciuria and progressive renal failure. Disease aetiology is associated with mutations in the *CLCN5* gene coding for the electrogenic $2\text{Cl}^-/\text{H}^+$ antiporter chloride channel 5 (CLC-5), which is expressed in the apical endosomes of renal proximal tubules with the vacuolar type H^+ -ATPase (V-ATPase). Initially identified as a member of the CLC family of Cl^- channels, CLC-5 was presumed to provide Cl^- shunt into the endosomal lumen to dissipate H^+ accumulation by V-ATPase, thereby facilitating efficient endosomal acidification. However, recent findings showing that CLC-5 is in fact not a Cl^- channel but a $2\text{Cl}^-/\text{H}^+$ antiporter challenged this classical shunt model, leading to a renewed and intense debate on its physiological roles. Cl^- accumulation *via* CLC-5 is predicted to play a critical role in endocytosis, as illustrated in mice carrying an artificial Cl^- channel mutation E211A that developed defective endocytosis but normal endosomal acidification. Conversely, a recent functional analysis of a newly identified disease-causing Cl^- channel mutation E211Q in a patient with typical Dent's disease confirmed the functional coupling between V-ATPase and CLC-5 in endosomal acidification, lending support to the classical shunt model. In this editorial, we will address the current recognition of the physiological role of CLC-5 with a specific focus on the functional coupling of V-ATPase and CLC-5.

Key words: V-ATPase; CLC-5; Endocytosis; Endosomal acidification; Dent's disease; Gating glutamate; E211Q

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Core tip: Chloride channel 5 (CLC-5) mutations cause Dent's disease, which is characterized by renal proximal

tubulopathy due to defective endocytosis. Recent revelations that CLC-5 is a $2\text{Cl}^-/\text{H}^+$ antiporter and not a Cl^- channel challenged the classical model proposing CLC-5 as a Cl^- shunt to facilitate V-ATPase-mediated endosomal acidification. Therefore, physiological roles of CLC-5 and its interaction with V-ATPase in endosomal acidification and/or endocytosis are intensely debated. Recent functional analysis of a novel pure Cl^- channel mutant from a Dent's disease patient indicated a possible functional coupling between V-ATPase and CLC-5 not only in endosomal acidification but also at the plasma membrane.

Satoh N, Suzuki M, Nakamura M, Suzuki A, Horita S, Seki G, Moriya K. Functional coupling of V-ATPase and CLC-5. *World J Nephrol* 2017; 6(1): 14-20 Available from: URL: <http://www.wjgnet.com/2220-6124/full/v6/i1/14.htm> DOI: <http://dx.doi.org/10.5527/wjn.v6.i1.14>

INTRODUCTION

Renal proximal tubular cells have a high capacity for the uptake of various proteins in primary urine *via* receptor-mediated endocytosis. Acidified condition in intracellular organelles such as endosomes and lysosomes is essential for the normal endocytic pathway consisting of ligand-receptor dissociation, recycling of the uncoupled receptors to the cell surface and transport of the released ligands to lysosomes for degradation^[1,2].

Intravesicular acidification is achieved mainly by the active H^+ -pumping of vacuolar ATPase (V-ATPase)^[1,3]. Conversely, chloride channel 5 (CLC-5), long believed to be a pure chloride channel as the name implies, colocalizes with V-ATPase and is suggested to be involved in V-ATPase-mediated endosomal acidification by shunting Cl^- to neutralize the positive charge due to H^+ accumulation^[4]. Indeed, mutations in CLC-5 cause Dent's disease, which is characterized by renal proximal tubulopathy due to defective endocytosis^[5,6], suggesting that V-ATPase and CLC-5 are functionally coupled in endosomes. However, recent reports demonstrating that CLC-5 is not a Cl^- channel but in fact functions as a $2\text{Cl}^-/\text{H}^+$ antiporter demands re-evaluation of its physiological roles and the pathogenesis of Dent's disease^[7-9]. Although the debate is ongoing on whether Cl^- accumulation^[10] or CLC-5-induced V-ATPase activation is more important for normal endocytosis, we recently demonstrated that impaired endosomal acidification derived from inadequate V-ATPase activation by mutated CLC-5 may be the underlying pathology in Dent's disease^[11]. Moreover, we identified such functional relationship between V-ATPase and CLC-5 even at the plasma membrane of mouse proximal tubules.

CLC-5 AND DENT'S DISEASE

CLC-5, a member of the CLC family, was originally identified by cloning of a voltage-gated chloride channel, CLC-0, from *Torpedo marmorata* electric organ^[12]. Several human mutations in corresponding genes of the

CLC family are known to cause genetic disorders such as myotonia congenita (CLC-1), Barter syndrome (CLC-Kb), osteopetrosis (CLC-7) and Dent's disease (CLC-5)^[13,14].

Dent's disease is an X-linked proximal renal tubulopathy arising from mutations in the *CLCN5* gene encoding for the electrogenic $2\text{Cl}^-/\text{H}^+$ antiporter CLC-5^[7-9] and is characterized by low molecular weight (LMW) proteinuria, hypercalciuria, nephrocalcinosis, nephrolithiasis and slowly progressive renal failure^[15,16]. In addition, affected patients present with various clinical signs of proximal tubular dysfunction including glycosuria, aminoaciduria, hyperphosphaturia and uricosuria, which is consistent with partial Fanconi syndrome^[5]. These manifestations usually remain subtle or asymptomatic during childhood; however, Dent's disease leads to chronic renal insufficiency over a few decades. Furthermore, in the absence of effective therapy, early diagnosis for Dent's disease only allows for conservative therapy to prevent kidney stones and progression of chronic renal insufficiency^[16].

TISSUE AND SUBCELLULAR DISTRIBUTION OF CLC-5

CLC-5 is abundantly expressed in renal and intestinal epithelial cells, though it is also expressed in brain, lung and, to a lesser extent, liver^[17]. In the kidney, CLC-5 expression is highest in proximal tubules and intercalated cells of the collecting ducts^[18]. Especially in proximal tubules, a major site for urinary LMW protein reabsorption *via* receptor-mediated endocytosis^[17,19], CLC-5 is predominantly located in early endosomes, colocalizing with V-ATPase^[4,20]. Additionally, CLC-5 is also found to an extent in the apical membrane of proximal tubules, as suggested by its robust plasma membrane expression in HEK293 cells as well as in *Xenopus laevis* oocytes following heterologous overexpression^[4,18].

FUNCTIONS OF INTRACELLULAR V-ATPASE

V-ATPase is a large multi-subunit complex that is ubiquitously expressed in intracellular organelles of eukaryotic cells such as endosomes, lysosomes, secretory granules and trans-Golgi network^[21,22]. V-ATPase pumps H^+ across membranes using energy generated by ATP hydrolysis and provides an acidic intraorganellar environment that is critical for normal endocytic pathway^[22-24]. Thus, V-ATPase lowers luminal pH of early endosomes and promotes the dissociation of internalized ligand-receptor complexes, which is essential for both recycling of the uncoupled receptors to cell surface and transport of the released ligands first to late endosomes and then to lysosomes for protein degradation^[24-27].

FUNCTIONS OF PLASMA MEMBRANE V-ATPASE

In addition to intracellular organelles, V-ATPase is also

highly expressed in plasma membrane of specialized cells in kidney and other tissues. Though V-ATPase is found over the entire length of the nephron, it is abundantly expressed in renal proximal tubular cells^[2,28,29] and intercalated cells of the collecting duct^[21,29,30], playing a pivotal role in acid-base homeostasis.

Proximal tubular cells secrete H^+ from cytosol to tubular lumen *via* Na^+/H^+ exchangers (NHEs), mainly NHE3^[31] on apical membrane, and reabsorb approximately 80% of the filtered HCO_3^- ^[32-34]. V-ATPase is assumed to be partially involved in this reabsorption process along the proximal tubules^[26,35,36]. In the collecting duct, alpha-intercalated cells secrete H^+ into the urine *via* apical membrane V-ATPase, while beta-intercalated cells export H^+ into the vessel lumen *via* basolateral membrane V-ATPase, regulating final urine acidification. Genetic defects in specific V-ATPase subunits are known to cause renal tubular acidosis (RTA)^[37-39]. Specifically, mutations in *ATP6V0A4* and *ATP6V0B1* coding for $\alpha 4$ and $B1$ subunits, respectively, lead to distal RTA in humans^[38,40].

NONCANONICAL FUNCTIONS OF INTRACELLULAR V-ATPASE

While the conventional functions of intracellular V-ATPase are well established, recent studies suggested that V-ATPase might have noncanonical functions as well^[41]. For example, V-ATPase achieves the desired acidic endosomal pH in order to regulate the budding of endosomal carrier vesicles, where V-ATPase itself functions as not only a proton pump but also a pH sensor^[1,42,43]. Luminal pH information is hypothesized to be detected by V-ATPase and transmitted to the cytosolic side *via* conformational changes in its transmembrane $\alpha 2$ isoform. This in turn results in the recruitment of ADP-ribosylation factor (ARF)-6 (ARF-6) and ARF-nucleotide binding-site opener (ARNO), both of which are involved in endocytosis by regulating the formation of endosomal carrier vesicles. Conversely, lysosomal V-ATPase is also suggested to constitute an important component of the lysosomal-associated amino acid sensing machinery^[44]. Although the precise mechanism underlying this function of V-ATPase is unknown, accumulation of amino acids in lysosomes activates Rag guanosine triphosphatases (GTPases)^[45] that promote the translocation of the master growth regulator mechanistic target of rapamycin complex 1 (mTORC1) to the lysosomal membrane^[46,47]. In this process, the interaction between V-ATPase and the regulator that anchors Rag GTPases to the lysosomes is necessary for amino acid-induced signal transduction^[48]. Therefore, lysosomal V-ATPase performs pivotal roles as both a proton pump and an amino acid sensor transmitting signals to activate mTORC1, which is essential for lysosomal function^[49].

FUNCTIONAL COUPLING OF V-ATPASE AND CLC-5

As indicated above, active H^+ pumping by V-ATPase

contributes to the preservation of an acidic luminal pH within intracellular organelles including endosomes and lysosomes, which is required for normal endocytic process. In contrast, two different strains of CLC-5 knockout mice developed LMW proteinuria, typical symptoms of Dent's disease due to defective endocytosis^[50,51]. Furthermore, Günther *et al.*^[6] showed that endosomes isolated from CLC-5 knockout mice were acidified at a significantly lower rate and to a lesser extent than those from wild-type mice. Subsequent analyses verified the lower luminal concentrations of Cl^- and H^+ in early endosomes isolated from proximal tubules of CLC-5 knockout mice^[52]. These observations, in conjunction with the colocalization of CLC-5 with V-ATPase in early endosomes, strongly suggest that V-ATPase and CLC-5 are functionally coupled during endosomal acidification and/or endocytosis.

Indeed, since its identification as a member of the CLC family, CLC-5 was considered to be a Cl^- channel^[53] that provided Cl^- to counter and dissipate positive charge (H^+) accumulation generated by V-ATPase, thereby facilitating efficient endosomal acidification. This Cl^- shunt model facilitated by functional V-ATPase coupling with CLC-5 was considered essential for normal endocytosis^[25]. However, recent studies demonstrating that CLC-5 is not a Cl^- channel but a $2Cl^-/H^+$ antiporter forced comprehensive reevaluation of these physiological roles of CLC-5^[7-9], given that the $2Cl^-/H^+$ antiporter would result in ineffective acidification due to parallel H^+ efflux at the expense of wasted energy (ATP) by V-ATPase. Thus, physiological roles of CLC-5 as a $2Cl^-/H^+$ antiporter and its interaction with V-ATPase in endosomal acidification and/or endocytosis remain unknown and have become an important issue in the field.

PHYSIOLOGICAL ROLES OF CLC-5 IN ENDOCYTOSIS: Cl^- ACCUMULATION OR V-ATPASE ACTIVATION?

Analysis of a mutation in the so-called gating glutamate at position 211 (E211), a conserved residue that serves as a central gate for H^+ -coupled Cl^- transport^[54,55], may provide a key in understanding the complex nature of CLC-5 functions. Novarino and colleagues generated mice carrying the E211A mutation which deprived H^+ transport of CLC-5, altering it to a simple Cl^- conductance^[10], and these mice developed defective endocytosis similar to that observed in CLC-5 knockout mice. Surprisingly, however, endosomal acidification was preserved in E211A mice in contrast to CLC-5 knockout mice (Figure 1). Therefore, they proposed that endosomal Cl^- accumulation rather than endosomal acidification might be critical for renal endocytosis. However, mutations in the gating glutamate, such as that is present in E211A mutant mice, have not yet been identified in patients with Dent's disease.

We recently analyzed a previously unrecognized mutation of E211 to glutamine (E211Q) that was found in a typical Dent's disease patient^[56] and confirmed that

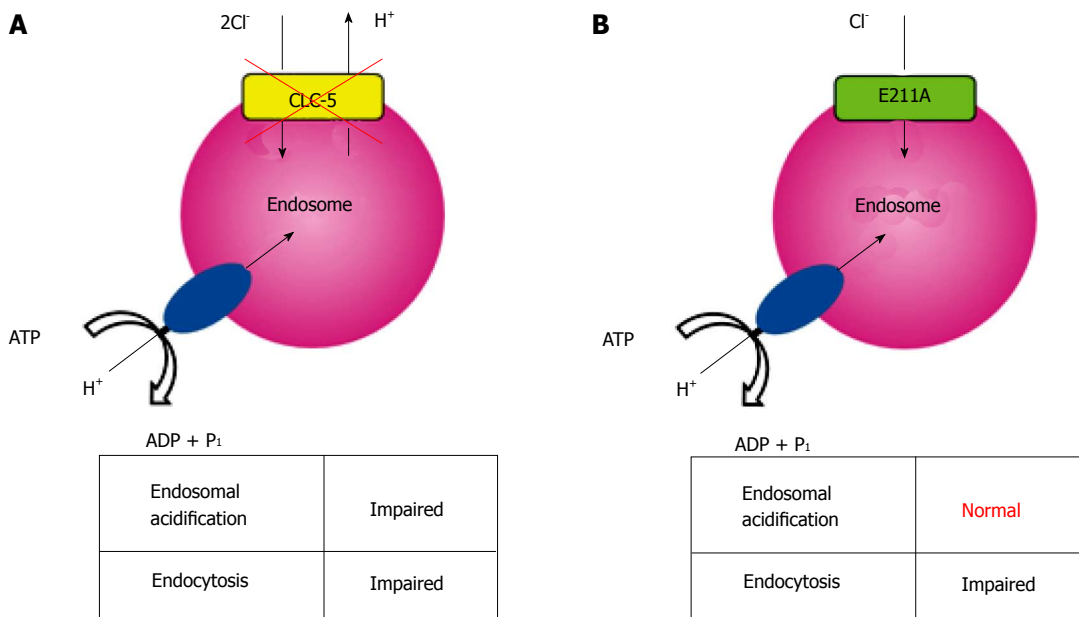


Figure 1 Effects of CLC-5 inactivation on endosomal acidification and endocytosis. A: In CLC-5 knockout mice, both endosomal acidification and endocytosis are impaired, resulting in a Dent's disease-like phenotype; B: E211A, an artificial mutation of the gating glutamate of CLC-5, converts its function from a 2Cl⁻/H⁺ antiporter into a pure Cl⁻ conductance. E211A knock-in mice exhibit defective endocytosis and manifestations similar to those observed in Dent's disease manifestations but retain normal endosomal acidification.

functional coupling between V-ATPase and CLC-5 occurred in endosomal acidification^[11]. Electrophysiological studies in *Xenopus laevis* oocytes demonstrated that the disease-causing mutant E211Q had similar characteristics to the artificial mutant E211A. Thus, E211Q mutation also abolished H⁺ transport of CLC-5 and altered it to a simple Cl⁻ conductance, which was supported by the molecular modelling of CLC-5 mutants^[11]. Upon heterologous overexpression in HEK293 cells, both Cl⁻ channel mutants, E211Q and E211A, enhanced bafilomycin-sensitive endosomal acidification. However, acidification was greater in endosomes expressing wild-type CLC-5. Because CLC-5-induced endosomal acidification reflected V-ATPase activity, these results indicated that the 2Cl⁻/H⁺ exchange mode of CLC-5 was required for maximal endosomal acidification^[11]. Indeed, simulation studies on lysosomal acidification *via* CLC-7, another CLC member with Cl⁻/H⁺ exchange function, lent support to the model in which the Cl⁻/H⁺ exchange mode was more advantageous than the Cl⁻ channel mode in intravesicular acidification^[57,58]. Our results revealed that the conversion of CLC-5 from a 2Cl⁻/H⁺ antiporter into a Cl⁻ conductance is the definite cause of Dent's disease. More importantly, we showed that impaired endosomal acidification *via* inadequate V-ATPase activation should be considered as a pivotal component of the aetiology in Dent's disease. These potential roles of CLC-5 in endosome are summarized in Figure 2.

Based on the accumulating data, the cause of discrepancy in endosomal acidification by Cl⁻ channel mutants between mice proximal tubules and HEK293 cells remains unclear. Significant basal acidification was still found in endocytic vesicles isolated from CLC-5 knockout mouse kidneys^[6]. In contrast, in the absence of endogenous CLC-5^[59], the basal V-ATPase activity

in HEK293 cells was quite subtle. Therefore, a small difference in endosomal acidification generated by the E211A mutant that was detectable in HEK293 cells might have been overlooked in proximal tubules obtained from E211A mice. Of course, genetically altered mice could have potentially developed compensatory mechanisms. However, a convincing model for the interaction between CLC-5 and V-ATPase in endosomes continues to be a focus of intense debate.

FUNCTIONAL COUPLING OF V-ATPASE AND CLC-5 AT THE PLASMA MEMBRANE

Physiological significance of CLC-5 at the plasma membrane is not clear^[14]. Therefore, we also investigated the impact of CLC-5 on plasma membrane V-ATPase function by measuring hypotonicity-induced V-ATPase activity as previously reported^[60,61]. Heterologous overexpression of both E211Q and E211A mutants in HEK293 cells led to the moderate activation of membrane V-ATPase. However, wild-type CLC-5 induced even higher V-ATPase activation, which was in harmony with the degree of endosomal acidification. This V-ATPase activation by hypotonicity was observed even in isolated mouse proximal tubules. Furthermore, siRNA-mediated gene silencing for CLC-5 strongly reduced V-ATPase activity, suggesting the presence of tight functional coupling between V-ATPase and CLC-5 even in apical membrane of intact proximal tubules. Although the detailed mechanisms by which CLC-5 activates the membrane V-ATPase are unknown, noncanonical roles of V-ATPase may allow several possible explanations. In addition to the abovementioned multiple

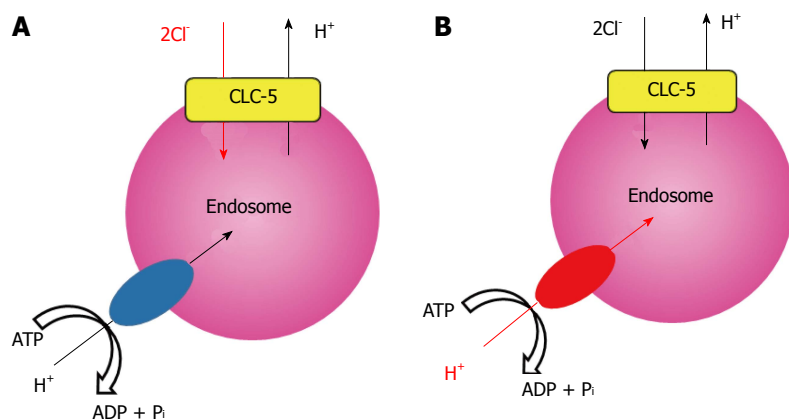


Figure 2 Potential roles of CLC-5 in endosomes. A: In this model, Cl⁻ accumulation by CLC-5 is critical for normal endocytosis; B: In contrast, 2Cl⁻/H⁺ exchange mode of CLC-5 activates V-ATPase which is required for maximal endosomal acidification.

V-ATPase functions, it is known that CLC-5 mediates the assembly with other proteins, and several binding proteins have already been proposed^[14]. Therefore, it is possible that the 2Cl⁻/H⁺ exchange mode of CLC-5 induces V-ATPase activation by recruiting unknown cellular factors and/or by directly modifying the function of V-ATPase^[11].

CONCLUSION

Loss-of-function mutations in CLC-5 were definitely shown to cause Dent's disease phenotypes in humans as well as in mouse models, suggesting the indispensability of CLC-5 for normal endocytic pathway. However, it remains unclear whether Cl⁻ accumulation or V-ATPase-mediated acidification by CLC-5 is more important for normal endocytosis. Our recent study focusing on disease-causing mechanisms of the E211Q mutant of CLC-5 revealed that impaired endosomal acidification caused by inadequate CLC-5-induced V-ATPase activation may play a key role in the aetiology of Dent's disease. However, future studies are necessary to clarify the potentially critical role of endosomal Cl⁻ accumulation, as suggested by the findings in mice carrying the E211A mutation.

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Basic Study

Acetylsalicylic acid interferes with embryonic kidney growth and development by a prostaglandin-independent mechanism

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Institutional review board statement: The present investigation was performed in accordance with the Home Office Guidance on the operation of the Animals (Scientific Procedures) Act (Great Britain Home Office, 2000). However, the study only used tissues from animals which fell outside of the ASPA remit (*i.e.*, organs were isolated from fetuses before 2/3 gestation was completed) and thus no specific “procedures” were carried out requiring explicit ethical approval.

Conflict-of-interest statement: The authors declare that they have no competing interests.

Data sharing statement: Statistical code, and some datasets available from the corresponding author at simon.welham@nottingham.ac.uk.

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Abstract

AIM

To evaluate the effects of the non-selective, non-steroidal anti-inflammatory drug (NSAID) acetylsalicylic acid (ASA), on *ex vivo* embryonic kidney growth and development.

METHODS

Pairs of fetal mouse kidneys at embryonic day 12.5 were cultured *ex vivo* in increasing concentrations of ASA (0.04-0.4 mg/mL) for up to 7 d. One organ from each pair was grown in control media and was used as the internal control for the experimental contralateral organ. In some experiments, organs were treated with ASA for 48 h and then transferred either to control media alone or control media containing 10 μ mol/L prostaglandin E₂ (PGE₂) for a further 5 d. Fetal kidneys were additionally obtained from prostaglandin synthase 2 homozygous null or heterozygous (PTGS2^{-/-} and PTGS2^{+/-}) embryos and grown in culture. Kidney cross-sectional area was used to determine treatment effects on kidney growth. Whole-mount labelling to fluorescently detect laminin enabled crude determination of epithelial branching using confocal

microscopy.

RESULTS

Increasing ASA concentration (0.1, 0.2 and 0.4 mg/mL) significantly inhibited metanephric growth ($P < 0.05$). After 7 d of culture, exposure to 0.2 mg/mL and 0.4 mg/mL reduced organ size to 53% and 23% of control organ size respectively ($P < 0.01$). Addition of 10 μ mol/L PGE₂ to culture media after exposure to 0.2 mg/mL ASA for 48 h resulted in a return of growth area to control levels. Application of control media alone after cessation of ASA exposure showed no benefit on kidney growth. Despite the apparent recovery of growth area with 10 μ mol/L PGE₂, no obvious renal tubular structures were formed. The number of epithelial tips generated after 48 h exposure to ASA was reduced by 40% (0.2 mg/mL; $P < 0.05$) and 47% (0.4 mg/mL; $P < 0.01$). Finally, growth of PTGS2^{-/-} and PTGS2^{+/-} kidneys in organ culture showed no differences, indicating that PTGS2 derived PGE₂ may at best have a minor role.

CONCLUSION

ASA reduces early renal growth and development but the role of prostaglandins in this may be minor.

Key words: Acetylsalicylic acid; Nephrogenesis; Kidney culture; Non-steroidal anti-inflammatory drug; Prostaglandins; Prostaglandin synthase 2

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Core tip: Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used as painkillers and are available without prescription. They act by inhibiting cyclooxygenase activity thereby preventing prostaglandin synthesis *via* the prostaglandin synthase enzymes prostaglandin synthase 1 (PTGS1) and PTGS2. Although NSAIDs cross the placenta, they are among the most common drugs prescribed during the first trimester of pregnancy and estimated prevalence of usage is more than 25% of pregnant women. NSAID use during pregnancy has been associated with abnormal renal development and renal failure in the offspring at birth. These may impact the individual throughout their adult life.

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INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin and ibuprofen are commonly used analgesics for the treatment of low-grade pain and inflammation. NSAIDs are available without prescription and are

frequently taken during pregnancy^[1]. Up to 25% of women self-prescribe NSAIDs to treat common ailments during pregnancy^[2-4]. Although there is clear evidence to suggest that aspirin and other NSAIDs can cross the placenta, recent research on aspirin use in pregnancy has largely been based on the examination of structural birth defects as an outcome^[5-7]. The key findings from these studies were that NSAID use during pregnancy does not appear to be a major risk factor for inducing birth defects. However, potentially more subtle effects of maternal NSAID consumption on fetal tissue and organ development have received little attention.

NSAIDs act by inhibition of cyclooxygenase enzymes which catalyse the conversion of arachidonic acid to prostaglandins. Two isoforms exist, prostaglandin synthase 1 (PTGS1) and prostaglandin synthase 2 (PTGS2). Although they share a very similar structure they differ in their pattern of regulation and physiological function^[8]. PTGS1 is expressed constitutively in most tissues and is thought to have a cellular "housekeeping" and cytoprotective role^[9]. In contrast, PTGS2 is induced as a result of an inflammatory response in most tissues^[10], but is constitutively expressed in the fetal and adult kidney^[11], highlighting the role for PTGS2 derived prostaglandins in adult kidney function and suggesting a role in kidney development.

Fetal rat kidneys can synthesise prostaglandins prostaglandin E₂ (PGE₂), PGD₂, PGI₂, and PGF_{2 α} , as well as thromboxanes and leukotrienes^[12,13]. This corresponds to intense PTGS2 immunoreactivity and mRNA expression in a subset of thick ascending limb epithelial cells near the macula densa in developing nephrons suggesting a role for PTGS2 derivatives in the maturation and/or early function of nephrons^[14]. Disruption of prostaglandin synthesis during early renal development through PTGS2 inhibition suggests that prostaglandins may be required for normal renal development^[15-17]. PTGS2 knockout mice exhibit a severe reduction in the number of nephrons^[16] and postnatally are observed to possess many immature glomeruli and tubules as well as a thinner outer cortex^[18].

PTGS2 inhibitors, such as Aspirin, impair glomerulogenesis during gestation^[19]. Clinical studies have revealed various abnormalities such as renal maldevelopment and renal non function syndrome in newborns of mothers treated with NSAIDs during pregnancy^[20,21]. Histological analysis of the kidneys revealed crowded glomeruli and few differentiated proximal tubules in the inner cortex^[20]. Long term effects of NSAID administration during pregnancy reveal structural and functional abnormalities in the rodent kidney. Ultra-structural changes in fetal glomeruli in rats treated with indomethacin were demonstrated by Sessa *et al*^[22], in the form of enlarged Golgi. A further study provides evidence that chronic administration of indomethacin to pregnant rhesus monkeys also causes neonatal renal hypoplasia decreasing kidney mass by 15%^[23].

Evidence from PTGS2^{-/-} mice, however, suggests that the role of prostaglandins in renal development is most

likely to be during postnatal maturation in these animals. PTGS2^{-/-} mice have apparently normal kidneys at birth, but subsequently exhibit developmental impairment in the postnatal period immediately prior to the final termination of development. This suggests either that the role for prostaglandins derived from PTGS2 in renal development is only during this short postnatal stage of maturation, or that sufficient prostaglandins are obtained exogenously from the mother prior to birth.

In this study, we examined the requirement for prostaglandin production on early kidney development using global blockade with acetyl-salicylic acid (ASA). We show a significant and terminal detrimental effect on growth of *ex-vivo* fetal mouse kidneys after exposure to ASA and further that this effect is likely to be independent of the inhibition of prostaglandin generation from the PTGS2 gene due to successful culture of PTGS2^{-/-} organs.

MATERIALS AND METHODS

Reagents

All reagents were purchased from Sigma-Aldrich chemical company (Poole, Dorset, United Kingdom) unless otherwise stated.

Generation of timed pregnancies

The present investigation was performed in accordance with the Home Office Guidance on the operation of the Animals (Scientific Procedures) Act (Great Britain Home Office, 2000). Outbred ICR (Institute for Cancer Research) mice were maintained on a 12-h light-dark cycle with free access to standard laboratory chow and water. Male and female mice were housed together and embryonic day 0.5 (E0.5) was designated upon detection of a vaginal plug, indicating mating, on the floor of the cage. Litters were removed 12 d after plugging. Whole metanephroi were micro-dissected from the E12.5 embryos under sterile conditions, at which point, they were termed Day 0 for *ex vivo* studies (Barak and Boyle 2011). Ethical approval for this study was provided by the University of Nottingham's local Animal Welfare and Ethical Review Board.

Culture of isolated whole embryonic kidneys

Fetal kidneys were cultured individually on Millicell inserts (12 mm diameter, 0.4 µm pore; Millipore Corporation, Billerica, MA, United States) in 24-well culture plates with DMEM F-12 media supplemented with penicillin (100 U/mL), streptomycin (100 µg/mL), insulin (10 mg/L), sodium selenite (5 g/L), and transferrin (5.5 mg/L) at 37 °C in a humidified atmosphere of air-5% CO₂ for up to 7 d. Media was changed every 24-48 h. For experimental NSAID treatment, DMEM media was supplemented with 0.04 mg/mL (0.2 mmol/L), 0.1 mg/mL (0.56 mmol/L), 0.2 mg/mL (1.1 mmol/L) or 0.4 mg/mL (2.2 mmol/L) acetyl salicylic acid (ASA; aspirin) in line with other *in vitro* studies^[24-27].

Recovery experiments included 48 h pre-treatment with 0.2 mg/mL ASA before replacing with control

media or media supplemented with 10 µmol/L PGE₂ from day 3-7. All metanephroi that were treated with ASA and or PGE₂ were compared to their untreated contra-lateral controls for analysis.

Imaging and measurements

During 7 d of culture, metanephros growth was monitored and recorded every 24 h using a Leica DMIL microscope [Leica Microsystems Ltd, Milton Keynes, Bucks, United Kingdom] fitted with a Leica DFC420C digital camera. Cross-sectional areas of whole metanephroi were determined using Image Pro Plus v5.1 (Media Cybernetics, Corporation, Silver Spring, MD, United States). A free-hand drawing tool was used to precisely draw around each metanephros and calculate the total cross-sectional surface area. Cross sectional surface area measurements were converted to µm² (using micrometer validation) and metanephroi treated with ASA and or PGE₂ were compared with their untreated contralateral controls.

Whole-mount immunofluorescence

Kidneys were fixed in 4% PFA in PBS for 20 min, washed in PBS, permeabilised in 0.2% triton X 100 in PBS overnight at 4 °C. All 4 °C incubation steps were carried out with rolling. Antibodies were diluted in PBS. Organs were washed in PBS incubated with the primary antibody against laminin (L9393, Sigma; incubated at 1:100 dilution) overnight at 4 °C. Kidneys were washed in PBS and incubated with secondary antibody (Anti-Rabbit IgG, FITC F0205, Dako UK Ltd; incubated at 1:20 dilution) overnight at 4 °C. Finally, organs were washed three times in PBS and mounted on slides (pre-prepared with a ring of hardened DPX to preserve the 3D structure of the kidney) in Vectashield Hardset (Vector Laboratories). Organs were imaged using a confocal microscope [Leica Microsystems (UK) Ltd, Milton Keynes, Bucks, United Kingdom].

Statistical analysis

Statistical analysis was performed using SPSS version 16. Growth data were analysed with day of culture (0 = baseline, day 1 and day 2) as a repeated measure with genotype as a fixed effect in the model. Nested effects in the model, *e.g.*, siblings (males and females) from the same litter and paired organs from the same individual (left kidney = control, right kidney = treated) were accounted for in the model as random effects (litterID/pupID). Analysis of data at single time points was by one-way ANOVA, blocking for individual ID. Results are presented as means ± SEM with ^a*P* ≤ 0.05 considered statistically significant. Letters are used throughout to represent statistical differences as follows; ^b*P* < 0.01 and ^c*P* < 0.005.

RESULTS

Effect of ASA on growth of E12.5 mouse kidneys

E12.5 mouse kidneys were cultured for seven days in the presence or absence of ASA. Control organs grew

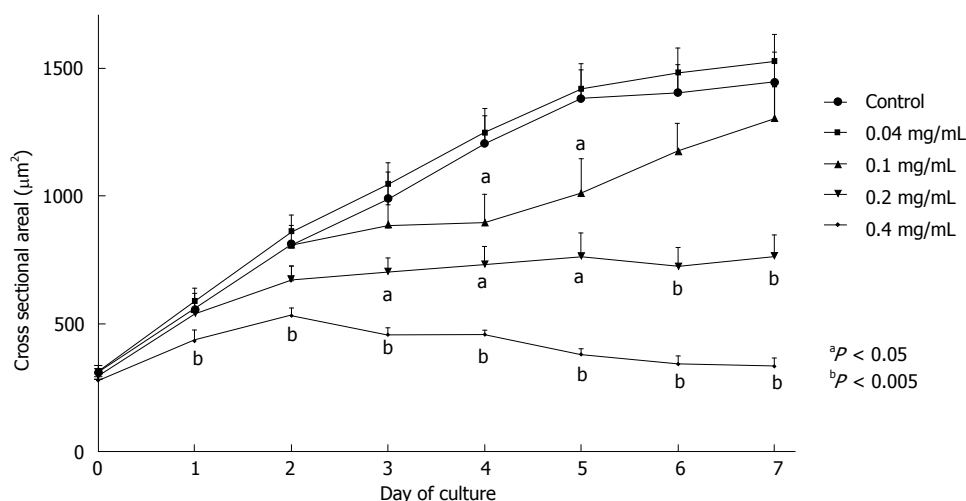


Figure 1 Growth curves for cross section area for acetylsalicylic acid treatments. Cross-section metanephroi area was used to produce growth curves of individual ASA treatments and their contralateral controls ($n = 8-12$). Controls are represents together as there were no differences between controls of each treatment group. ^a $P < 0.05$, ^b $P < 0.005$ denotes statistical differences with control organs. ASA: Acetylsalicylic acid.

robustly over the course of 7 d, increasing in size by more than 3.5 fold (386%; Figure 1). Incubation in ASA at 0.04 mg/mL did not affect organ growth, however incubation in concentrations of ASA above 0.04 mg/mL resulted in increasingly severe growth impairment (Figure 1). Growth of kidneys exposed to 0.2 mg/mL ASA was significantly reduced by day 3 of treatment and organs remained growth impaired for the duration of culture ($P < 0.05$; Figure 1). Doubling the concentration of ASA to 0.4 mg/mL led to more severe growth restriction by as early as 24 h of culture ($P < 0.05$; Figure 1). Continued exposure to ASA (> 0.04 mg/mL) beyond three days of culture consistently resulted in organ disintegration by day 7.

We assessed the influence of ASA on branching morphogenesis by counting the generation of epithelial tips in organs labelled to detect laminin (Figure 2). We found that the number of observable epithelial tips was reduced by 40% and 43% after exposure to ASA for 2 d at concentrations of 0.2 mg/mL and 0.4 mg/mL respectively ($P < 0.005$).

Effect of prostaglandins on the adverse actions of ASA

To determine whether the adverse effects of ASA on early renal development could be reversed, embryonic kidneys were cultured in the presence of either 0.2 mg/mL or 0.4 mg/mL ASA for 48 h and subsequently returned to control media or media containing PGE₂ (10 μmol/L), or PGE₂ combined with 0.2 mg/mL or 0.4 mg/mL ASA during days 2-7 of culture. As expected, exposure to ASA for 48 h (culture days 0-2) blunted embryonic kidney growth compared with their untreated contralateral kidneys ($P < 0.05$; Figure 3A and B). Replacement of ASA containing media with control culture media (for days 0-2) resulted in a small increase in size. However, kidneys still remained significantly smaller than contralateral controls for each day of culture (days 2-7; Figure 3A and B). Embryonic kidneys exposed to ASA for

48 h and subsequently treated with 10 μmol/L PGE₂ in control media (for culture days 2-7) grew more quickly than those in control media alone (Figure 3C and D) such that by culture day 7 their cross-sectional areas matched contra-lateral control kidneys. Nevertheless, despite recovery of growth of kidneys by PGE₂ the kidneys remained structurally immature, lacking developing tubules observed in controls. In addition, the blunted growth of ASA treated kidneys grown in culture media containing both PGE₂ and ASA from days 2-7, were significantly smaller than their contra-lateral controls and failed to increase in size throughout the culture period ($P < 0.05$). These experiments suggested that blockade of prostaglandins by ASA may have permanent detrimental consequences for fetal kidney growth.

Therefore, to determine if the growth impairment seen in the presence of ASA might indicate a requirement for PTGS2 derived prostanoids, we cultured kidneys from PTGS2 null (PTGS2^{-/-}) or PTGS2 heterozygous (PTGS2^{+/-}) mice. Growth of organs from PTGS2^{-/-} and PTGS2^{+/-} mice ($n = 3$ for each group including contralaterals as internal controls) were unaffected by genotype, increasing by 74% ± 11% vs 62% ± 13% respectively after 48 h ($P = 0.13$). Size of organs was comparable at all time points with those from wild type ICR mice.

DISCUSSION

In this study we have demonstrated that exposure of the developing kidney to aspirin impairs overall growth. Such impairment of growth suggested at best a minor role for prostaglandins, as organs examined *ex-vivo* from mice genetically manipulated to prevent prostaglandin production (PTGS2^{-/-}) were able to grow similarly to kidneys from control mice.

PTGS1^{-/-} mice exhibit no renal phenotype^[28] and PTGS2^{-/-} mice only appear to show evidence of renal malformation during postnatal life^[19]. This has been

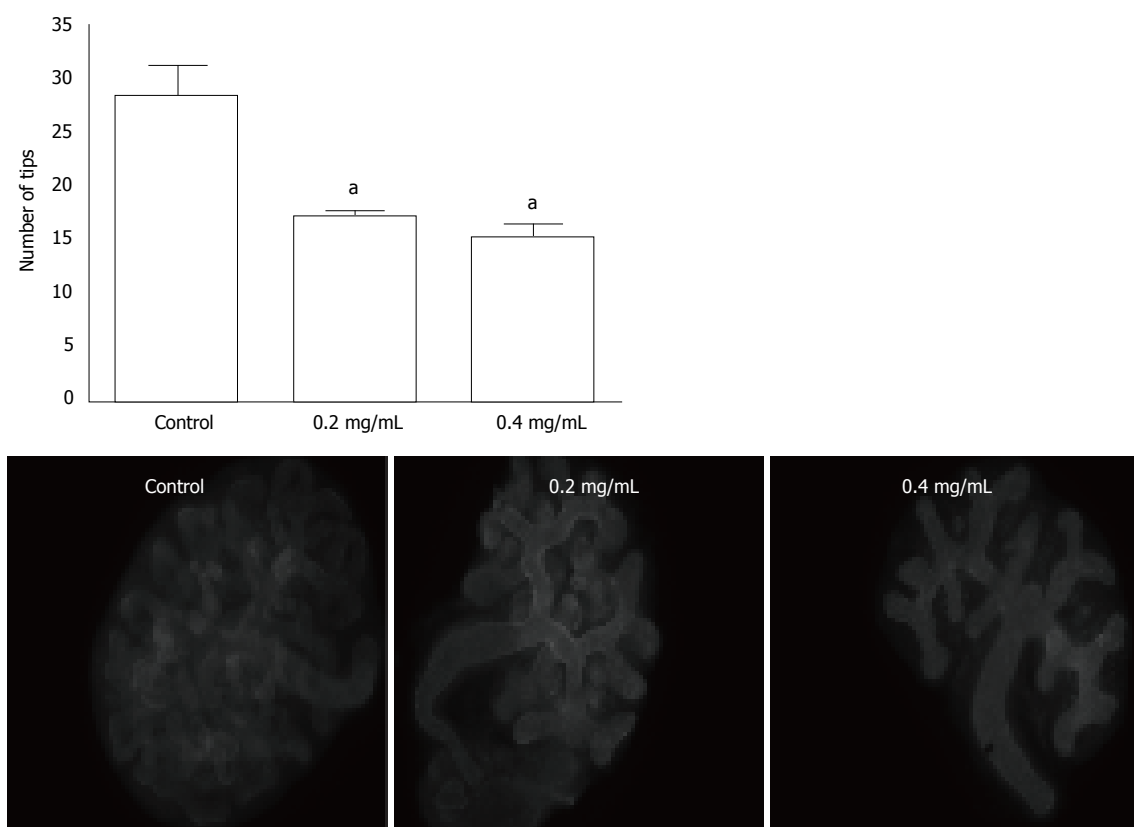


Figure 2 Assessment of epithelial branching. Fetal kidneys were grown for 48 h in the presence of 0.2 mg/mL or 0.4 mg/mL ASA ($n = 3$ and 4 respectively; Controls $n = 5$). Organs were fixed and processed for laminin labelling. Upper panel shows mean number of tips counted per group. ^a $P < 0.05$, denotes statistical differences with control organs. Lower panel shows an example image of a control, 0.2 mg/mL or 0.4 mg/mL ASA exposed organ. ASA: Acetylsalicylic acid.

suggested to indicate that there may be little or no requirement for prostaglandins in the early (fetal) stages of kidney development, however this does not preclude the possibility that maternally derived prostanoids replace those otherwise acquired from endogenous production.

The role PTGS derived products play in controlling embryonic and organ growth has been previously explored. Incubation of cultured whole rat embryos with the PTGS1/2 inhibitor ASA or Indomethacin for 48 h exhibited dysmorphogenesis. Furthermore, the teratogenic effects of each inhibitor were diminished following PGE₂ supplementation^[29]. Mice and rats treated with PTGS2 selective inhibitors throughout pregnancy produce offspring with kidneys which exhibit impaired development similar to that observed in PTGS2 knockout mice, including reduced glomerular diameter and the presence of numerous immature glomeruli^[19]. However, this was only apparent when administration was continued during the postnatal period until weaning at P21. When organs were examined at P0, there was no difference between any of the groups. In addition, the authors found no effect of administration of the PTGS1 selective inhibitor SC58560 at any stage in development.

A reduction in the nephrogenic zone following PTGS2 inhibition was observed in the study by Kornhoff^[19] and by PTGS1 and 2 inhibition in preterm baboons treated with ibuprofen to pharmacologically close the ductus arteriosus^[30]. A reduction in nephrogenic zone growth is

suggestive of either an early cessation of nephrogenesis and or premature renal maturation. These adverse effects of PTGS1/2 inhibition may result in a nephron deficit, and have detrimental consequences on renal health in later life^[31].

We did not determine the identity of the cells which were most affected in our experiments, so are unable to make a specific statement about the population of nephrogenic precursors. However, we would speculate that reduction in the population of nephron progenitors would significantly hamper further development^[32]. An important factor with regard to the phenotype most normally observed after PTGS inhibition is that the final glomeruli to be formed are immature and very closely apposed to the underside of the renal capsule. This is not necessarily something that would be observed as a result of a reduced population of nephron precursors. It rather argues in favour of an impairment of maturation of the vasculature. This might not be all that surprising considering the final location of the PTGS2 in the adult kidney and its requirement for vasodilation^[33].

Long term use of NSAIDS can restrict blood flow to such an extent in the kidney that these organs exhibit phenotypic changes reminiscent of ischemic damage^[33,34]. It seems possible that the ability to vasodilate the developing afferent arterioles is potentially a requirement for the final stages of glomerular maturation. Assessment of this role may require grafting of developing organs

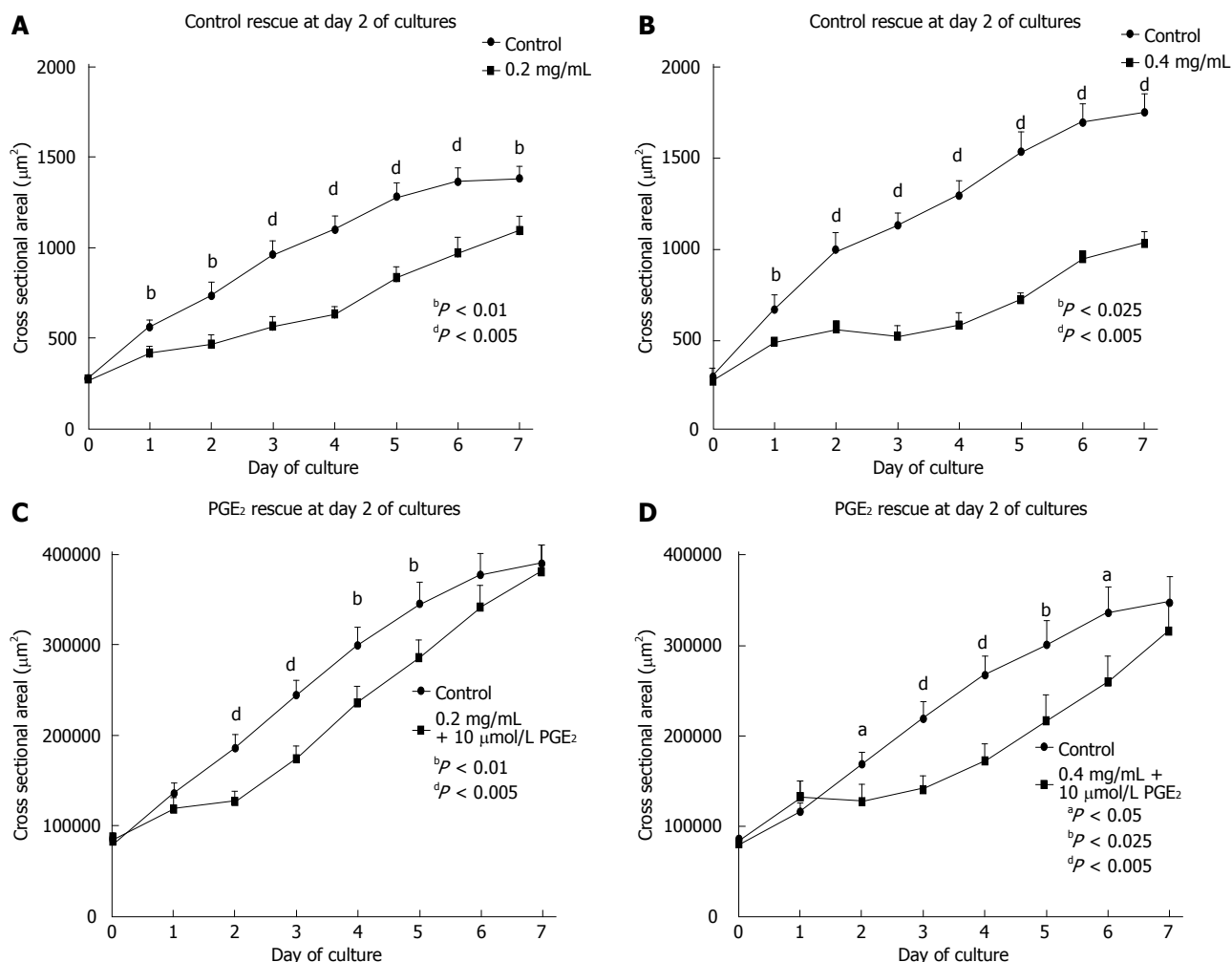


Figure 3 Growth curves for cross section area of embryonic kidneys initially treated with acetylsalicylic acid followed by “rescue” treatment. Cross-section metanephroi area were used to produce growth curves of individual embryonic kidneys treated with 0.2 mg/mL (A and C) or 0.4 mg/mL (B and D) ASA from days 0-2, then rescued with either control media alone (A and B) or control media plus 10 µmol/L PGE₂ (C and D) during culture days 3-7. All embryonic kidneys in culture were compared against their contralateral controls that were exposed to control culture medium from days 0-7 ($n = 8-12$). ASA: Acetylsalicylic acid.

onto an external vasculature or the use of a carefully targeted mouse mutant possessing loci enabling deletion of PTGS2 within the afferent arteriole which may be regulated by exogenous means (*i.e.*, temporal application of tamoxifen). This would potentially enable deletion of PTGS2 from some groups of arterioles and not others, labelling of those arterioles and examination of the influence of the loss of PTGS2 on the development of their associated glomeruli.

Whilst we show there to be no influence of genotype on the ability to grow in organ culture, we did not include wild-type litter mates in the culture system. Instead we used heterozygotes as controls. Recently published work^[35] has demonstrated that there is in fact an influence of the reduction of gene dosage on renal structural and functional outcome. However, the differences compared with wild-type, whilst significant were relatively small and differed greatly with those seen in homozygotes. Therefore, although we cannot definitively state that our experiments show there to be no influence of a loss of PTGS2 on fetal renal growth in ex-vivo culture, we are reasonably confident that this is

indeed the case.

Limitations of the study

As has been mentioned above, we were unable to perform detailed analysis of the cell types most influenced by exposure to ASA. Such information would be particularly helpful in establishing the specific mechanism by which ASA impairs early organogenesis, particularly since this appears to be prostaglandin independent and therefore occurs *via* a process distinct from organ disruption seen by PTGS2 deletion. Additionally, the data presented here are exclusively derived from organ explant culture experiments and therefore may not be wholly reflective of the process of renal developmental impairment seen *in vivo* after overconsumption of ASA or similar NSAIDs. Future studies will be required to address these issues in order to clarify the precise pathways of damage and the specific relevance to humans.

In conclusion, the work we describe in this study adds to the wider data which suggests that, for early kidney development, there is no specific requirement for prostaglandins. Kidneys from animals lacking

PTGS2 grew entirely normally in *ex vivo* culture without the requirement for exogenous prostaglandins. This strongly suggests that fetal renal development does not require inducible prostaglandin production. We cannot entirely rule out a requirement for other prostaglandins in these studies since the PTGS2^{-/-} organs will still have retained PTGS1 expression, however, since no demonstration of its requirement for renal development has been identified^[28] we would suggest that our data argue against a role for prostaglandins in mediating nephrogenesis in the fetus. Our data further suggests that the impairment of growth induced by exposure of organs to ASA in *ex vivo* culture is likely due to factors independent of their ability to produce prostaglandins.

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COMMENTS

Background

Exposure to non-steroidal anti-inflammatory drugs (NSAIDs) is not uncommon for unborn fetuses and also for premature infants. There are clear nephrotoxic effects of NSAIDs during specific stages of kidney development. Considerable work has shown the requirement for inducible prostaglandin synthase 2 (PTGS2) on the final maturation of the kidney but the literature suggests that this may not be required for the earlier stages of kidney development despite the apparent expression of this gene and expression of relevant PG receptors.

Research frontiers

It is unclear whether the late malformation due to pharmacological PG blockade is exclusively due to the lack of prostaglandins, or whether alternative pathways of damage might be active. The apparent requirement for PGs during final maturation may suggest that PG mediated vasodilation within the final stages of tubular development is needed to permit glomerular maturation.

Innovations and breakthroughs

In this work, the authors show that the structural deficit induced by exposure of early developing kidneys to NSAIDs is likely independent of PG production. The authors also show that there is no specific requirement of PGs derived from the inducible PTGS2 for early kidney development and clarify with organ culture that maternally derived PGs probably don't replace any required PGs generated from within the organ.

Applications

Work needs to be conducted to determine the precise requirement for PG production in the final maturation of the renal vasculature and whether this indicates a specific need for blood flow to be maintained to facilitate maturation. In addition, the work here clarifies the need to establish the non-PG effects of NSAIDs on renal maturation. By understanding these two aspects of NSAID treatment/loss of PG production or signalling, may help to modify treatments particularly for premature infants faced with a requirement to receive NSAIDs.

Peer-review

The study is relevant for research field and the experiments are clear and result in consistent findings.

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Basic Study

Immunohistochemical expression of intrarenal renin angiotensin system components in response to tempol in rats fed a high salt diet

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Abstract

AIM

To determine the effect of tempol in normal rats fed high salt on arterial pressure and the balance between antagonist components of the renal renin-angiotensin system.

METHODS

Sprague-Dawley rats were fed with 8% NaCl high-salt (HS) or 0.4% NaCl (normal-salt, NS) diet for 3 wk, with or without tempol (T) (1 mmol/L, administered in drinking water). Mean arterial pressure (MAP), glomerular

filtration rate (GFR), and urinary sodium excretion (UVNa) were measured. We evaluated angiotensin II (Ang II), angiotensin 1-7 (Ang 1-7), angiotensin converting enzyme 2 (ACE2), mas receptor (MasR), angiotensin type 1 receptor (AT1R) and angiotensin type 2 receptor (AT2R) in renal tissues by immunohistochemistry.

RESULTS

The intake of high sodium produced a slight but significant increase in MAP and differentially regulated components of the renal renin-angiotensin system (RAS). This included an increase in Ang II and AT1R, and decrease in ACE-2 staining intensity using immunohistochemistry. Antioxidant supplementation with tempol increased natriuresis and GFR, prevented changes in blood pressure and reversed the imbalance of renal RAS components. This includes a decrease in Ang II and AT1R, as increase in AT2, ACE2, Ang (1-7) and MasR staining intensity using immunohistochemistry. In addition, the natriuretic effects of tempol were observed in NS-T group, which showed an increased staining intensity of AT2, ACE2, Ang (1-7) and MasR.

CONCLUSION

These findings suggest that a high salt diet leads to changes in the homeostasis and balance between opposing components of the renal RAS in hypertension to favour an increase in Ang II. Chronic antioxidant supplementation can modulate the balance between the natriuretic and antinatriuretic components of the renal RAS.

Key words: Kidney; Angiotensin II; Tempol; Angiotensin 1-7; High sodium diet

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Core tip: This study explored the effect of tempol on arterial pressure and the balance between antagonist components of the renal renin-angiotensin system in rats fed high salt for 3 wk. A high salt diet altered the balance between opposing components of renal renin-angiotensin system (RAS), favouring the angiotensin II arm. Tempol supplementation improves the balance between the natriuretic and antinatriuretic components of the renal RAS.

Cao G, Della Penna SL, Kouyoumdzian NM, Choi MR, Gorzalczany S, Fernández BE, Toblli JE, Rosón MI. Immunohistochemical expression of intrarenal renin angiotensin system components in response to tempol in rats fed a high salt diet. *World J Nephrol* 2017; 6(1): 29-40 Available from: URL: <http://www.wjgnet.com/2220-6124/full/v6/i1/29.htm> DOI: <http://dx.doi.org/10.5527/wjn.v6.i1.29>

INTRODUCTION

Several studies have shown that the current dietary

intake of salt in Western societies is an important factor for the genesis of hypertension and may even cause blood pressure-independent target organ damage, including the kidney^[1,2]. It is well known that a high salt intake increases the oxidative stress in the kidney of normal and salt-sensitive rats^[3-5]. In this regard, we have reported that the administration of tempol (4-hydroxy-2,2,6,6-tetramethylpiperidine-*N*-oxyl), a permeate superoxide dismutase mimetic^[6] commonly used to scavenge superoxide anion, prevented oxidative stress and produced a natriuretic and diuretic effect in Sprague Dawley rats fed a high salt diet^[7].

The renin-angiotensin system (RAS) essentially controls the sodium homeostasis and blood pressure^[8]. Furthermore, a local RAS that is expressed in the kidneys and operate independently of the systemic RAS, may also contribute to long-term blood pressure control and cause renal injury when it is associated with a high salt diet^[7,9-11]. Angiotensin II (Ang II), the main effector of RAS, acts through two receptor subtypes named angiotensin II type-1 receptor (AT1R) and type-2 receptor (AT2R). It is well known that the triad angiotensin I converting enzyme (ACE)/Ang II /AT1R is closely involved in signaling pathways that mediate vasoconstriction, antinatriuresis, release of cytokines and accumulation of inflammatory cells in the kidney, all factors which together tend to increase blood pressure^[12,13]. On the other hand, activation of AT2R is associated with vasodilatation, apoptosis, anti-proliferation and natriuresis, which contribute to lower blood pressure^[14]. Therefore, AT2R is considered a physiological antagonist of AT1R. The discovery of the Ang II breakdown enzyme, angiotensin I converting enzyme 2 (ACE2) in addition to ACE, enhanced the complexity and understanding of generation and degradation of Ang II in hypertension^[15,16]. ACE2 leads to generation of Ang-(1-7) that stimulates Mas receptor (MasR), antagonizing AT1R-mediated effects, and favouring vasodilatation, natriuresis, anti-fibrogenic and anti-proliferative actions^[17,18]. Hyper-activation of the RAS, mainly *via* enhanced AT1R function, contributes to excessive sodium reabsorption in the kidney, like in salt-sensitive hypertension^[19]. There is evidence that AT1R activation decreases ACE2 activity and Ang-(1-7) production^[16]. These findings suggest the presence of an imbalance between opposing components of the renal RAS, namely the hypertensive axis, ACE-Ang II-AT1R vs the anti-hypertensive axis, AT2 and ACE2-Ang (1-7)-MasR in the development of hypertension.

Although it is well known that the intake of sodium is a regulatory factor to control the activity of renal axis ACE-Ang II-AT1R components, the regulation of renal axis AT2 and ACE2-Ang (1-7)-MasR in response to high sodium intake is not fully understood to date. Hereby, it remains unclear whether the increased oxidative stress observed in salt-sensitive hypertension is associated to an imbalance of renal RAS components or not.

We hypothesized that a high sodium intake, through oxidative stress development, may induce an imbalance between the hypertensive and anti-hypertensive com-

ponents of the renal RAS, contributing to the pathogenesis of hypertension. Considering this assertion, we explored the effect of tempol (used as an inhibitor of oxidative stress) in normal rats fed a high salt intake on the balance between the antagonist components of the renal RAS.

MATERIALS AND METHODS

Animal model

Male Sprague Dawley rats, 5-6 wk-old (180-200 g body weight), were used in the experiments. The animals were housed in steel cages in a controlled room temperature at $23\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$, exposed to a daily 12-h light-dark cycle (light on 07:00 a.m. to 07:00 p.m.), fed for three weeks with the diets described below, and given tap water ad libitum. Experiments were conducted in accordance with the institutional University of Buenos Aires guidelines for the care and use of research animals. The experiments were performed in animals randomly divided in four groups ($n = 6$ each group): (1) NS (control): Animals fed with a normosodic diet (0.4% NaCl); (2) HS: Fed with a hypersodic diet (8% NaCl); (3) NS-T: Fed with a normosodic diet (0.4% NaCl), plus 1 mmol/L tempol (Sigma-Aldrich Inc, St. Louis, Missouri, United States), administered in the drinking water; (4) HS-T: Fed with a hypersodic diet (8% NaCl), plus 1 mmol/L tempol administered in the drinking water. After a 3-wk diet, the rats were intraperitoneally anaesthetized with urethane (1.2 g/kg). A PE-90 tubing (3 cm long) was inserted into the trachea to maintain an open airway. The left femoral vein was catheterized with a Silastic cannula (0.12 mm i.d.) for continuous infusion. The right carotid artery was also catheterized with a T4 tube for blood sampling and for continuous mean arterial pressure recording (MAP) by means of a Statham GOULD P23ID transducer coupled to a Grass Polygraph 79D during all the procedures. The bladder was cannulated for urine collection using a PE-75 cannula. A femoral vein infusion with isotonic saline solution, 0.15 mol/L NaCl (ISS) was performed at a 0.04 mL/min rate (Syringe Infusion Pump, SageTM, Orion) for 60 min to allow reaching a steady diuresis and permitting urine collection in all groups. Then, ISS infusion continued for another 60 min at the same rate as an experimental period. Blood samples were collected at 30 min and urine samples were collected along the 60 min of ISS infusion for sodium, potassium and creatinine measurement.

Urine and blood measurements

Urinary and plasmatic sodium and creatinine were measured by standard methods using an autoanalyzer. Creatinine clearance was assessed in order to evaluate glomerular filtration rate (GFR). GFR and sodium fractional excretion (FE_{Na}) were calculated according to a standard formula. Urinary sodium excretion is expressed as $\mu\text{mol/min}$ per kilogram, GFR as mL/min and FE_{Na} as percentage.

Kidney processing for histological examination

At the end of the infusion period, the left kidney was perfused with ISS through the abdominal aorta until the blood was washed out and the parenchyma showed a pale appearance. The kidney was rapidly excised, decapsuled, longitudinally cut and harvested for immunohistochemical studies. Tissues were fixed in phosphate-buffered 10% formaldehyde (pH 7.2) and included in paraffin. For immunohistochemistry, renal sections were deparaffined and rehydrated, and endogenous peroxidase activity was blocked by treatment with 0.5 % H_2O_2 in methanol for 20 min. Local Ang II, ACE 2, AT1R, AT2, Ang (1-7) and MasR were detected using the following specific antibodies: human anti-Ang II (Peninsula, CA; United States, dilution of 1:500), rabbit anti-Ang (1-7) (Santa Cruz Biotechnology, Inc, United States; dilution: 1:200), rabbit anti-ACE2 (Santa Cruz Biotechnology, Inc, United States; dilution: 1:200), rabbit anti-AT1 (Santa Cruz Biotechnology, Inc, United States; dilution: 1:200), rabbit anti-AT2 (Santa Cruz Biotechnology, Inc; dilution: 1:200) and rabbit anti-MasR (Abcam, Cambridge, MA, United States, dilution: 1:100). Immunostaining was carried out by means of a commercial modified avidin-biotin-peroxidase complex technique (Vectastain ABC kit, Universal Elite, Vector Laboratories, CA, United States) and counterstained with hematoxylin. Histological sections were observed in a Nikon E400 light microscope (Nikon Instrument Group, Melville, New York, United States). The antibodies used in this study worked well in nephron segments, especially in tubules^[20-25]. Immunoreactivities for Ang II, ACE 2, AT1R, AT2R, Ang (1-7) and MasR in renal tissue are expressed as integrated optical density (IOD) $\pm$ SEM using a model for automated computer image analysis to quantify immunohistochemical stains in hematoxylin counterstained histological sections^[26].

Statistical analysis

Results from urine, blood measurements and MAP are expressed as mean $\pm$ SEM. Gaussian distribution was evaluated by the Kolmogorov and Smirnov method and comparisons between groups were carried out using ANOVA followed by the Newman-Keuls test. P values < 0.05 were considered significant.

RESULTS

MAP, GFR and excretory function

In Table 1, it can be observed that HS diet increased MAP, UV_{Na} and $\text{FE}_{\text{Na}}(\%)$, but did not alter GFR, respect to NS fed animals. Interestingly, even though the administration of Tempol to NS group did not modify MAP levels and $\text{FE}_{\text{Na}}(\%)$, it increased GFR and UV_{Na} respect to NS group. Moreover, tempol administration to HS group, restored MAP to control NS levels, increased GFR to similar levels of NS-T group and increased further UV_{Na} and FE_{Na} values.

Table 1 High-salt diet increased mean arterial pressure, urinary sodium excretion and sodium fractional excretion (%), but did not alter glomerular filtration rate, respect to normal salt fed animals

	NS	NS-T	HS	HS-T
MAP (mmHg)	92 ± 3	94 ± 3	108 ± 3 ^a	95 ± 2 ^c
GFR (mL/min)	1.50 ± 0.1	3.2 ± 0.5 ^c	1.52 ± 0.2	3.1 ± 0.6 ^c
UV _{Na} (μmol/min per kilogram)	0.25 ± 0.1	2.03 ± 0.90 ^c	3.56 ± 0.70 ^a	13.2 ± 1.2 ^{a,c}
FE _{Na} (%)	0.06 ± 0.02	0.10 ± 0.06	0.50 ± 0.08 ^a	1.20 ± 0.15 ^{a,c}

All values are mean ± SEM (*n* = 5-6 per group), ^a*P* < 0.05 *vs* respective NS group, ^c*P* < 0.05 *vs* respective group without tempol. NS: Normal salt diet group; HS: High salt diet group; NS-T: Normal salt diet plus tempol group; HS-T: High salt diet plus tempol group; MAP: Mean arterial pressure; GFR: Glomerular filtration rate; UV_{Na}: Urinary sodium excretion; FE_{Na}: Fractional sodium excretion.

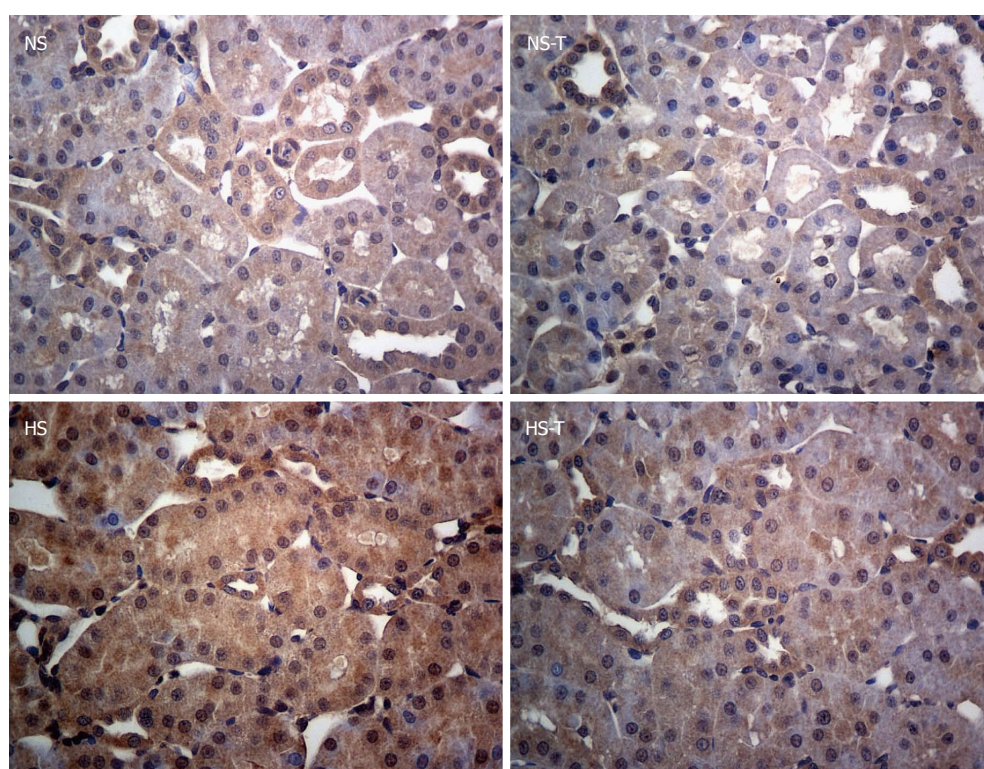


Figure 1 The graphs show the quantitative evaluation of Angiotensin II immunostaining in renal tissue. Data are expressed as mean ± SEM; ^a*P* < 0.05 *vs* the respective NS group, ^c*P* < 0.05 *vs* the respective group without tempol. The photomicrographs represent Ang II immunostaining in NS, HS, NS-T and HS-T groups. Original magnification: 400 ×. IOD: Integrated optic density; NS: Normal salt diet group; HS: High salt diet group; NS-T: Normal salt diet plus tempol group; HS-T: High salt diet plus tempol group.

Intrarenal Ang II expression

Figure 1 shows Ang II immunoexpression in renal

tissues. Immunohistochemical analysis of renal sections revealed positive staining for Ang II in all tubular

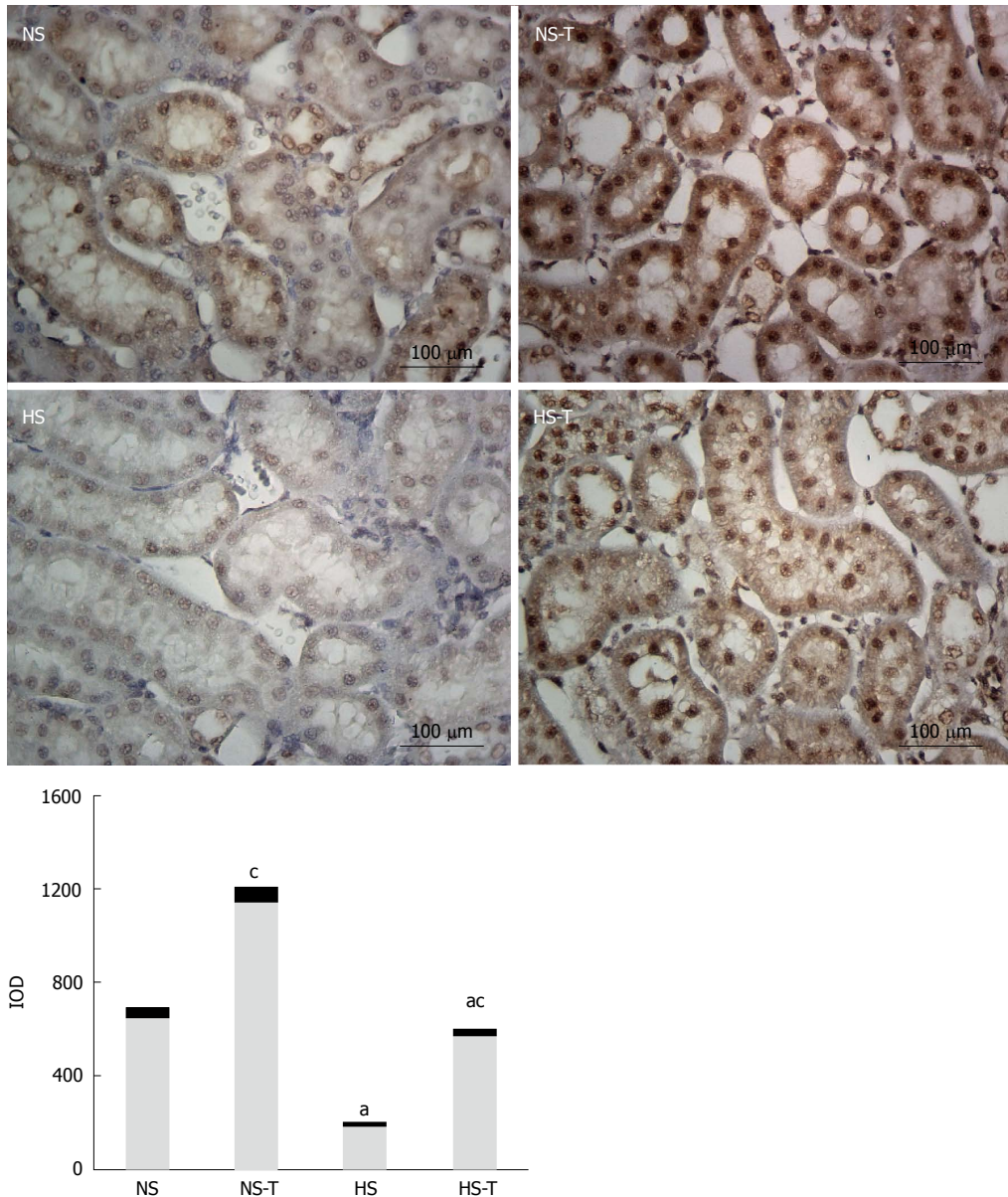


Figure 2 The graphs show the quantitative evaluation of angiotensin converting enzyme 2 immunostaining in renal tissue. Data are expressed as mean $\pm$ SEM; $^aP < 0.05$ vs the respective NS group, $^cP < 0.05$ vs the respective group without tempol. The photomicrographs represent ACE2 immunostaining in NS, HS, NS-T and HS-T groups. Original magnification: 400 $\times$. IOD: Integrated optic density; NS: Normal salt diet group; HS: High salt diet group; NS-T: Normal salt diet plus tempol group; HS-T: High salt diet plus tempol group; ACE2: Angiotensin converting enzyme 2.

sections of the nephron examined. HS diet increased Ang II expression with respect to NS group. Tempol administration, which did not reduce Ang II staining significantly in NS-T, decreased Ang II staining in HS-T animals, but remaining higher in NS-T group.

Intrarenal ACE2 expression

Figure 2 shows ACE2 immunoexpression in renal tissues. The study focused on tubular expression, where ACE2 staining was more evident, whereas in glomeruli it was very low. ACE2 appeared to be expressed in the endothelium of larger vessels which was closer to the renal hilum. In renal tubules where the differences between groups are more significant, ACE2 staining was expressed, in order of density, in proximal con-

volute tubules, distal convolute tubules located in the juxtamedullary area, and in collecting tubules.

HS diet decreased ACE2 immunoexpression compared to NS fed animals. Tempol administration nearly duplicated ACE2 staining in both groups, NS-T and HS-T respect to NS and HS groups, respectively, showing in HS-T group similar levels than those in NS control group.

Intrarenal Ang (1-7) expression

Figure 3 shows Ang 1-7 immunoexpression in renal tissues. Positive staining for Ang 1-7 was observed in all tubular sections examined. HS diet did not modify Ang (1-7) expression with respect to NS group. Tempol increased Ang 1-7 staining in NS-T animals and further increased in HS-T group.

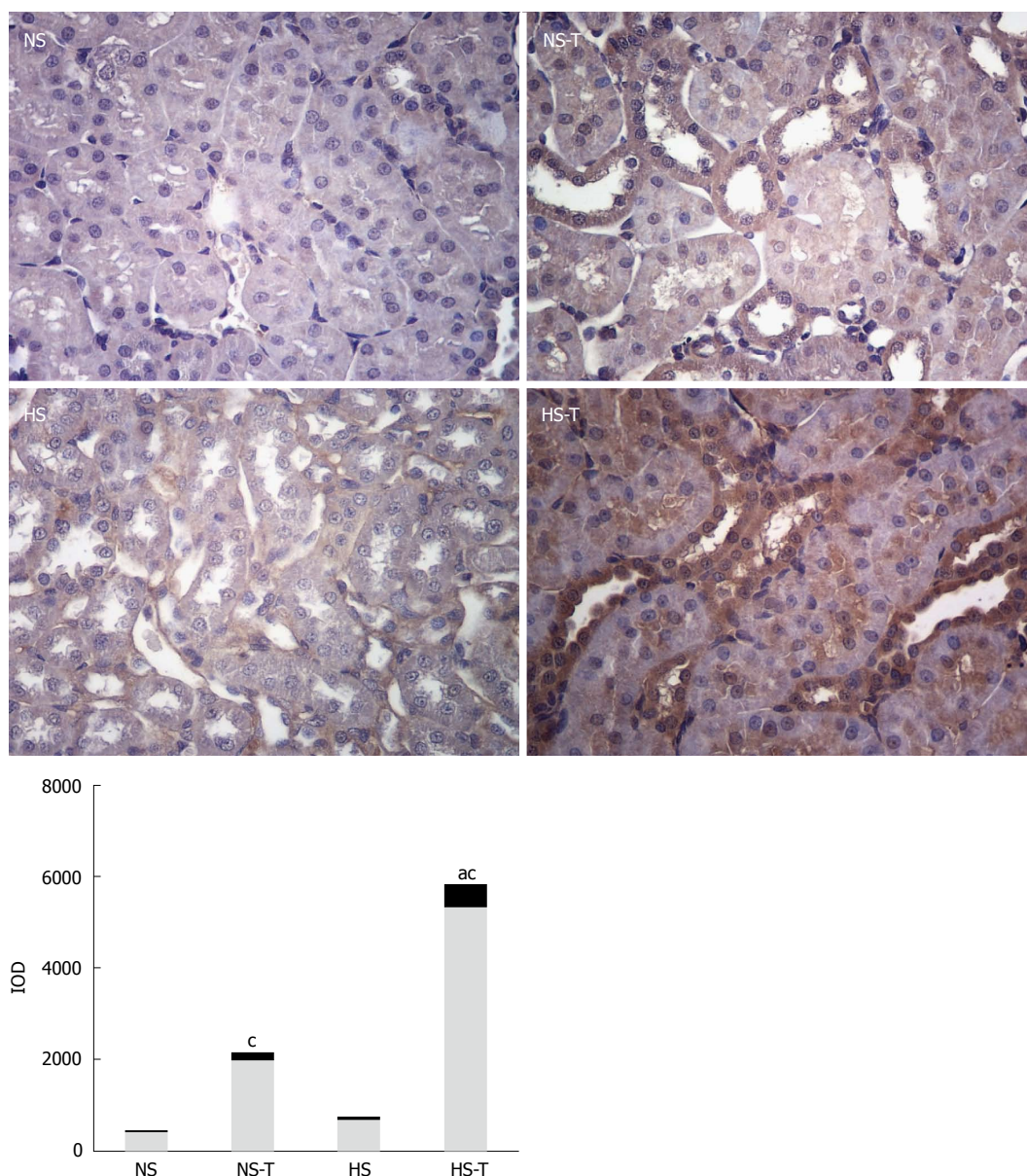


Figure 3 The graphs show the quantitative evaluation of Angiotensin 1-7 immunostaining in renal tissue. Data are expressed as mean $\pm$ SEM; $^aP < 0.05$ vs the respective NS group, $^bP < 0.05$ vs the respective group without tempol. The photomicrographs represent Ang 1-7 immunostaining in NS, HS, NS-T and HS-T groups. Original magnification: 400 $\times$. IOD: Integrated optic density; NS: Normal salt diet group; HS: High salt diet group; NS-T: Normal salt diet plus tempol group; HS-T: High salt diet plus tempol group.

Intrarenal MasR expression

Figure 4 shows MasR immunoexpression in renal tissues. HS diet decreased MasR staining respect to NS control group, while tempol nearly doubled in MasR staining in NS-T and H-T groups compared to NS and HS groups, respectively. MasR expression remained lower in HS-T group respect to NS-T group.

Intrarenal AT1R expression

Figure 5 shows AT1R immunoexpression in renal tissues. HS diet increased AT1R expression compared to NS group. Tempol administration prevented changes in AT1R staining in HS-T group with respect to HS group. No differences were observed in AT1R staining between NS-T and NS groups.

Intrarenal AT2R expression

Figure 6 shows AT2R immunoexpression in renal tissues. High salt diet did not change AT2R expression compared to NS group. Tempol administration increased AT2R staining in NS-T and H-T groups respect to NS and HS groups, respectively. No differences were observed in AT2R staining between NS-T and HS-T groups.

DISCUSSION

Our current study shows that a high sodium intake, besides increasing blood pressure, may also deregulate the components of the renal RAS. In HS diet-fed animals, we observed increased Ang II and AT1R, and decreased ACE-2 immunoexpression, suggesting an altered

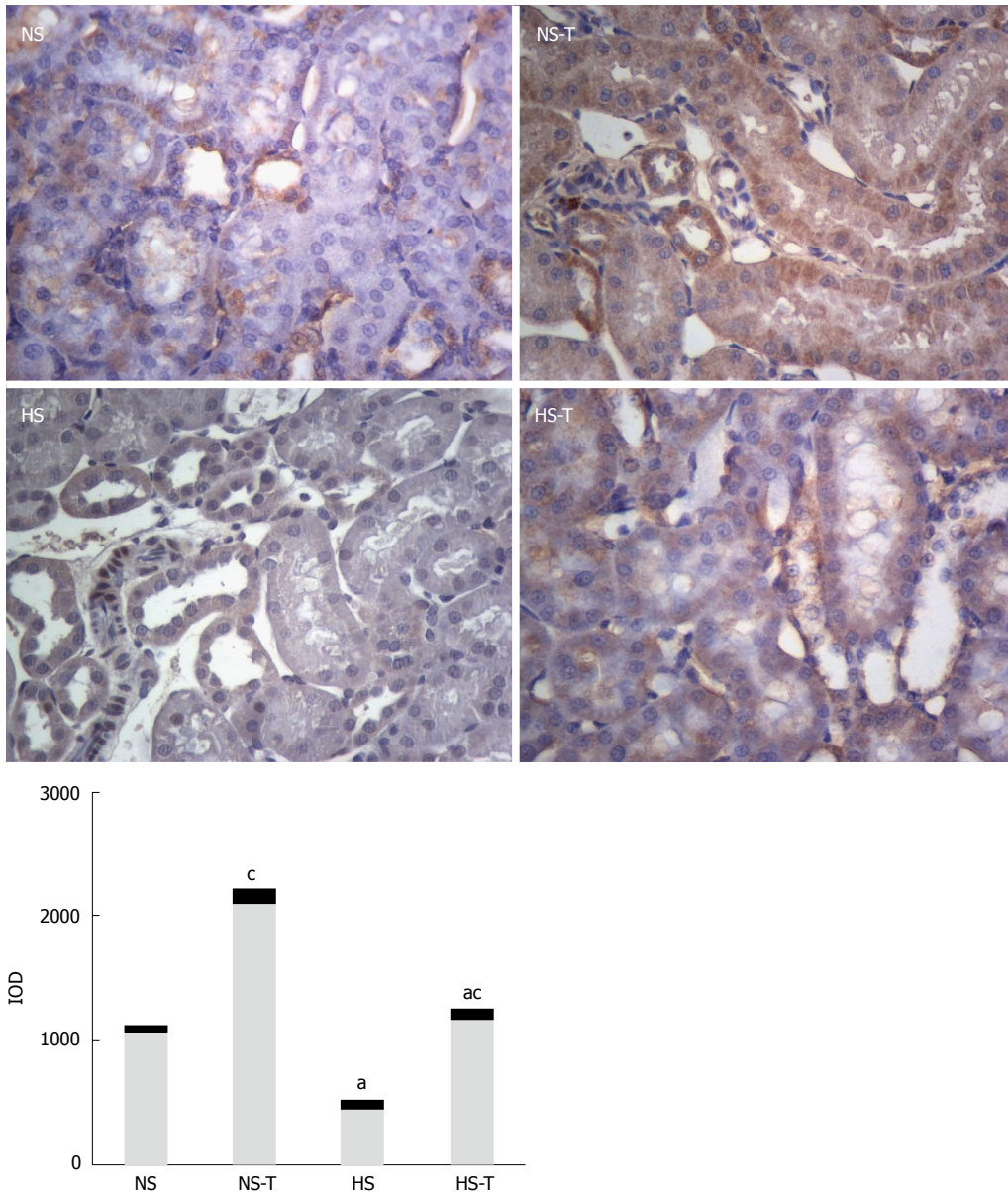


Figure 4 The graphs show the quantitative evaluation of Mas receptor immunostaining in renal tissue. Data are expressed as mean $\pm$ SEM; $^aP < 0.05$ vs the respective NS group, $^cP < 0.05$ vs the respective group without tempol. The photomicrographs represent MasR immunostaining in NS, HS, NS-T and HS-T groups. Original magnification: 400 $\times$. IOD: Integrated optic density; NS: Normal salt diet group; HS: High salt diet group; NS-T: Normal salt diet plus tempol group; HS-T: High salt diet plus tempol group; MasR: Mas receptor.

production and/or degradation of Ang II. Antioxidant supplementation with tempol in rats which were fed a high salt diet, not only prevented the increase in blood pressure, but also reversed the imbalance of renal RAS components. Indeed, tempol decreased Ang II and AT1R overexpression and increased AT2, ACE2, Ang 1-7 and MasR expression. This result was associated with enhanced diuresis and natriuresis, which may justify the decrease in blood pressure observed in these animals. In addition, the natriuretic effect of tempol was also observed in NS-T group, which simultaneously showed increased AT2, ACE2, Ang (1-7) and MasR immunoexpression.

Many reports indicate that oxidative stress is an important contributing factor in hypertension^[27-31].

Hypertensive patients and animal models of hypertension have shown increased reactive oxygen species production and decreased antioxidant capacity^[32,33]. Tempol, has been shown to reduce oxidative stress and attenuate hypertension in obese Zucker rats, Dahl salt-sensitive and spontaneously hypertensive rats (SHR)^[34-38]. In addition, we have previously reported that tempol can prevent the increase in renal oxidative stress and arterial pressure in Sprague Dawley rats fed a high salt diet^[7].

It is well known that the proximal tubule synthesizes and secretes Ang II to the lumen in the kidney^[39,40]. Our current study, using a model of oxidative stress in rats fed a high salt diet, showing that Ang II expression increased and ACE2 expression decreased in renal tissues. Considering that ACE2 is the enzyme that

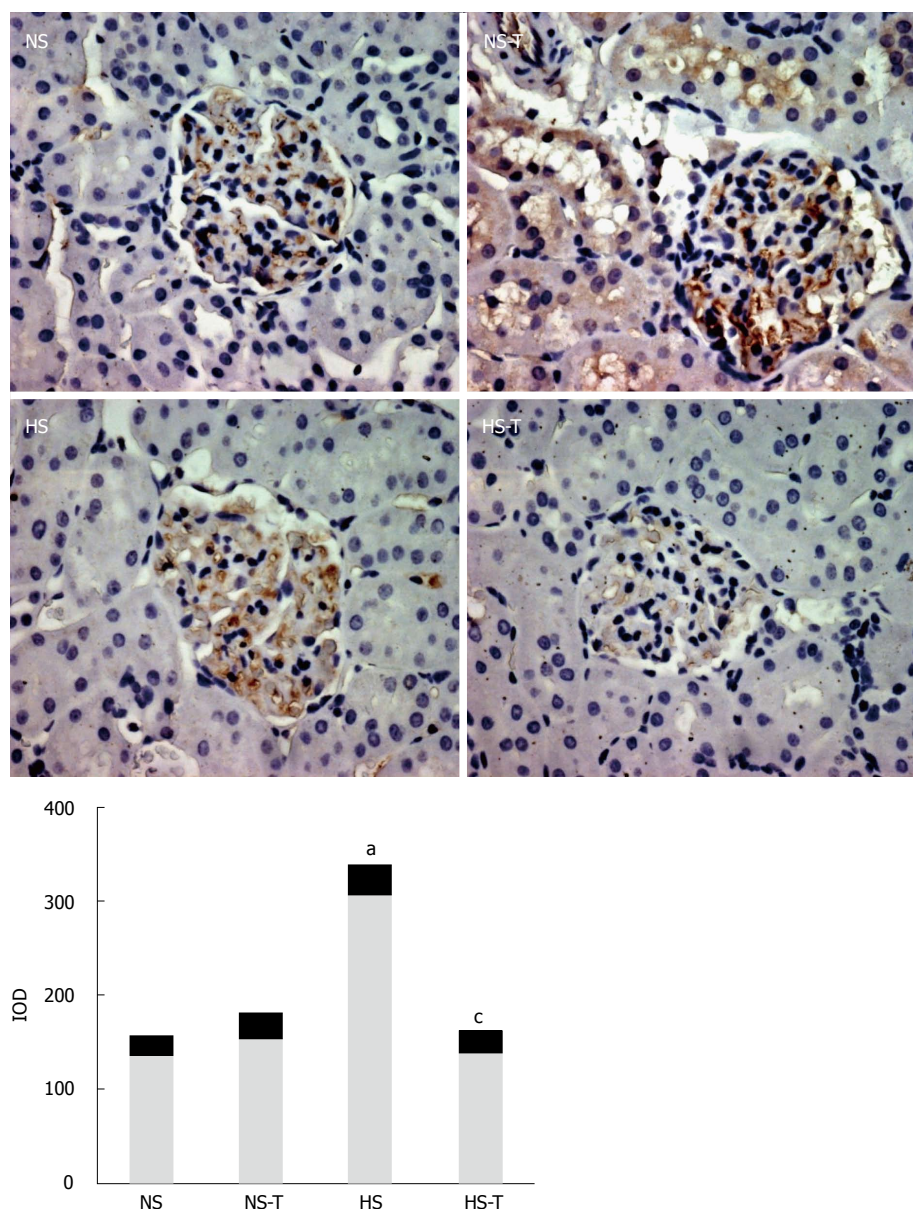


Figure 5 The graphs show the quantitative evaluation of angiotensin type 1 receptor immunostaining in renal tissue. Data are expressed as mean $\pm$ SEM; ^a $P < 0.05$ vs the respective NS group, ^c $P < 0.05$ vs the respective group without tempol. The photomicrographs represent AT1R immunostaining in NS, HS, NS-T and HS-T groups. Original magnification: 400 $\times$. IOD: Integrated optic density; NS: Normal salt diet group; HS: High salt diet group; NS-T: Normal salt diet plus tempol group; HS-T: High salt diet plus tempol group; AT1R: Angiotensin type 1 receptor.

metabolizes Ang II to Ang 1-7, one might assume that the higher expression of Ang II is due to reduced expression of ACE2. With this in mind, Deshotels *et al.*^[41] have described that Ang II is able to up-regulate ACE and down-regulate ACE2 expressions in human kidney tubular cells, associated with activation of extracellular regulated (ERK)1/2 and p38 mitogen-activated protein (MAP) kinases, a component that was blocked by the angiotensin II AT1R antagonist losartan, but not by the AT2 receptor blocker PD123319.

Down-regulation of ACE2 by Ang II represents a novel positive feed-forward system as noted in the brain^[42,43]. Our findings suggest that down-regulation of ACE2 in high salt fed animals may favour decreased Ang II degradation.

Moreover, the increase of ACE2 expression in tempol treated rats in HS-T group, could explain the decline of Ang II and the enhancement of Ang (1-7) expression observed in this group.

Interestingly, however, the increasing effects of tempol on ACE2 and Ang (1-7) expression were also observed in the rats fed with NS. Thus, we can suggest that these effects of tempol are independent of dietary sodium load. Moreover, these results suggest, that intrarenal mechanisms that regulate the differential expression of Ang II and ACE2 exacerbated by a high-sodium diet, would not be a dependent mechanism of oxidative stress. In this sense it has been shown that in physiological conditions, acute renal sympathetic nerve activity modulates sodium reabsorption by increasing

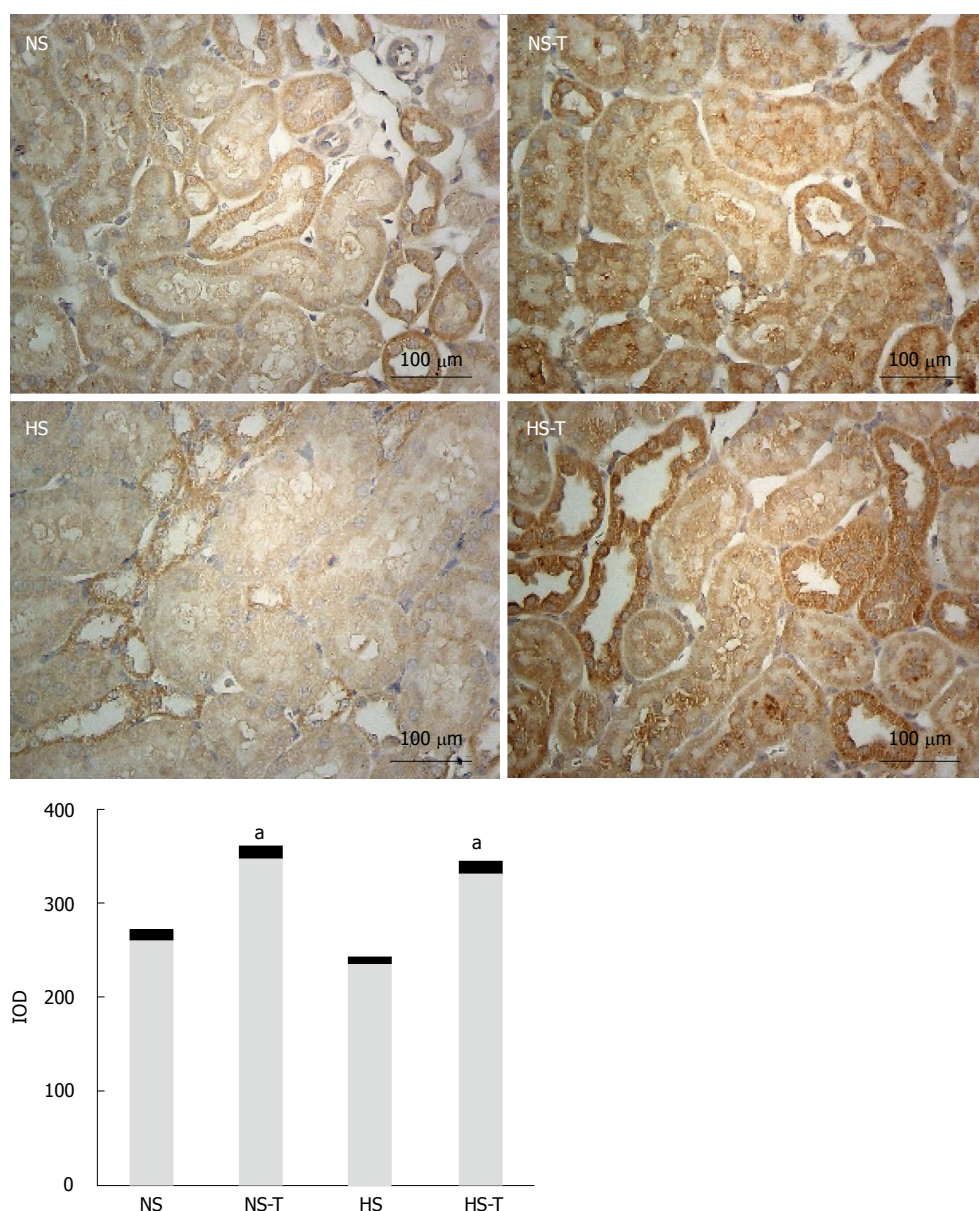


Figure 6 The graphs show the quantitative evaluation of angiotensin type 2 receptor immunostaining in renal tissue. Data are expressed as mean $\pm$ SEM; ^a P < 0.05 vs the respective group without tempol. The photomicrographs represent AT2R immunostaining in NS, HS, NS-T and HS-T groups. Original magnification: 400 $\times$. IOD: Integrated optic density; NS: Normal salt diet group; HS: High salt diet group; NS-T: Normal salt diet plus tempol group; HS-T: High salt diet plus tempol group; AT2R: Angiotensin type 2 receptor.

intrarenal Ang II generation and activation of the luminal membrane AT1R^[44]. It has been recently shown that activation of renal nervous system results in higher levels of intrarenal angiotensinogen and Ang II independent of changes in renal function and systemic RAS^[45].

In this study results show that HS diet decreased MasR expression while tempol treatment increased Ang 1-7 and AT2R expression, and restored MasR levels. As tempol also increased MasR expression in rats fed with NS diet, this action of tempol seems to be independent from sodium overload in the diet. These changes may aid the natriuretic effect and normalization of blood pressure in HS-T animals.

Altogether, the results suggest that the signalling pathways of the renal RAS could be physiologically

regulated by the redox state.

It is known that Ang (1-7) reduces vasoconstriction, water retention, salt intake, cell proliferation and reactive oxygen stress, displaying also a renoprotective effect^[46]. Thus, our results suggest that in the renal RAS, the ACE2-Ang (1-7)-Mas axis counteracts the ACE-Ang II-AT1 axis.

It has been reported that Ang II may directly stimulate nuclear AT1 receptors to induce transcriptional responses, which may be associated with stimulation of tubular epithelial sodium transport and inflammatory response^[47,48]. When these effects are inhibited by tempol, they may increase distal sodium overload, which in turn may increase the tubule-glomerular feedback, thus decreasing the GFR. However, tempol also reduces

sodium signalling in the macula dense^[49], as well as afferent arteriole responses^[50], contributing to moderate the tubule-glomerular feedback response and to increase GFR, as we observed in the current study.

Finally, our results are in line with reports of studies performed in obesity-related hypertension, where it was suggested that a high sodium intake that provokes hypertension is also able to regulate differentially and shift the balance between opposing components of the renal RAS^[51]. Additionally, antioxidant treatment with tempol reversed the imbalance of renal RAS components and led to diuresis and natriuresis, lowering obesity-related hypertension. Furthermore, a high salt diet in SHR produced glomerular hypertrophy and decreased ACE2 and nephrin expressions^[52].

In conclusion, our results show that a high sodium diet may alter the physiological balance between opposing components of the renal RAS, favouring increased Ang II and down-regulation of ACE2. Chronic antioxidant supplementation that attenuates oxidative stress can improve the imbalance between the natriuretic and antinatriuretic components of the renal RAS and decrease hypertensive blood pressure levels.

COMMENTS

Background

The renin-angiotensin system (RAS) is a key regulator of renal function and hydrosaline balance controlling arterial pressure. The aim of this study was to determine the effect of tempol on antagonist components of RAS in renal tissue in rats a high salt intake.

Research frontiers

To date, no study has been undertaken to assess the effectiveness of tempol in rats with imbalance between opposing components of the renal RAS on hypertension and moderate renal impairment. Further studies are required to elucidate whether oxidative stress directly contributes to altered blood pressure by high salt consume.

Innovations and breakthroughs

This study found that chronic antioxidant supplementation that attenuates oxidative stress can improve the imbalance between the natriuretic and antinatriuretic components of the renal RAS and decrease hypertensive blood pressure levels, suggesting that tempol may regulate renal function through renal RAS regulation.

Applications

Although this study provides promising data regarding oxidative stress as a possible target for renal inflammation and hypertension, it should be noted that there are no selective superoxide inhibitors approved for human use. Drugs that possess antioxidant properties, such as apocynin, may be potential therapies, but require further investigation in experimental models of high salt diet.

Terminology

The altered function of the RAS could be a contributing factor to the renal alterations induced by salt excess. To further explore this issue, the authors evaluated the consequences of chronic tempol administration on the *in vivo* levels of Ang II, Ang-(1-7), angiotensin I converting enzyme 2, and Mas receptor in kidney of rats fed a high salt diet. In tissues such as kidney, heart, and vasculature, Ang II, through the AT1 receptor, promotes vasoconstriction, reactive oxygen species production, and extracellular matrix remodeling, and can activate multiple intracellular signaling pathways leading to inflammatory response and tissue injury. In many cases, the AT2 receptor has been shown to

counterbalance the actions exerted through the AT1 receptor. Advances in the field led to the recognition of other active components of the RAS metabolism, such as Ang- (1-7), ACE2, a homolog of classic ACE that forms Ang-(1-7) directly from Ang II and indirectly from Ang I, and the Ang-(1-7)-specific G-protein-coupled receptor Mas. The ACE2/Ang-(1-7)/Mas receptor axis opposes the vascular and proliferative effects of Ang II and exerts complex renal actions in chronic renal diseases and hypertension.

Peer-review

The paper is interesting and well written.

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Retrospective Cohort Study

Hyponatremic hypertensive syndrome - a retrospective cohort study

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Informed consent statement: Informed consent was taken from the parents of the patients enrolled for this study.

Conflict-of-interest statement: The authors declare no conflicts of interest regarding this manuscript.

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Abstract

AIM

To ascertain the frequency of hyponatremic hypertensive syndrome (HHS) in a cohort of children with hypertensive emergency in a tertiary pediatric hospital.

METHODS

A retrospective review was undertaken among children with hypertensive emergency admitted in our tertiary children hospital between June 2014 and December 2015 with an aim to identify any children with HHS. Three children with HHS were identified during this period.

RESULTS

The 3 patients with HHS presented with hypertensive emergency. They were initially managed with Labetalol infusion and thereafter switched to oral anti-hypertensives (combination of Nifedipine sustained release, Hydralazine and Beta Blocker). All 3 were diagnosed to have unilateral renal artery stenosis. One child was lost to follow up, whereas the other 2 underwent renal angioplasty which was followed with normalization of blood pressure.

CONCLUSION

Despite activation of renin angiotensin axis secondary to renal artery stenosis, these groups of children have significant hyponatremia. Renal re-vascularisation produces excellent results in most of them.

Key words: Hypertension; Hyponatremia; Renovascular; Encephalopathy; Paediatric

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Core tip: Renovascular hypertension can occur secondary to renal artery stenosis which can sometime present as hyponatremic hypertensive syndrome (HHS). Though deemed a rare disease we identified within a span of 18 mo, 3 children with HHS presentation characterized by hypertension, hyponatremia, hypokalemia and metabolic alkalosis. Despite activation of renin angiotensin axis secondary to renal artery stenosis, they had significant hyponatremia. Renal re-vascularisation produced excellent results in 2 children who underwent surgery whereas another child was lost to follow up.

Mukherjee D, Sinha R, Akhtar MS, Saha AS. Hyponatremic hypertensive syndrome - a retrospective cohort study. *World J Nephrol* 2017; 6(1): 41-44 Available from: URL: <http://www.wjgnet.com/2220-6124/full/v6/i1/41.htm> DOI: <http://dx.doi.org/10.5527/wjn.v6.i1.41>

INTRODUCTION

Reno vascular hypertension secondary to renal artery stenosis is often a treatable cause of pediatric and accounts for 5%-25% cases of secondary hypertension^[1]. Unilateral renal artery stenosis presenting as hypertensive hyponatremic syndrome (HHS) has been infrequently reported in pediatrics, with only three case series till date^[2-4]. Our study was performed in order to determine its incidence among children admitted with hypertensive emergency in a tertiary care pediatric hospital.

MATERIALS AND METHODS

We undertook a retrospective case notes review of all children admitted with hypertensive emergency within a period of 18 mo from June 2014 to December 2015. Ten such children were identified all of whom had undergone biochemical and radiological investigation as needed for determination of disease etiology. Out of this cohort 3 were diagnosed to have HHS.

RESULTS

Case 1

The 5 years old boy presented with convulsions and vomiting for 6 d and obtunded sensorium for 3 d. Examination revealed elevated blood pressure (BP) (236/132 mmHg, 95th P = 108/71), brisk deep tendon reflexes with extensor planters and eye examination consistent with hypertensive retinopathy. He was having feeble peripheral pulses and was hypovolemic. He also had hyponatremic, hypokalemic, metabolic alkalosis with normal creatinine and elevated renin and aldosterone (Table 1). Ultra-sonography (USG) showed a small left kidney (5.7 cm) with loss of cortico-medullary distinction and enlarged hyperechogenic right kidney (7.1 cm). Computed tomography angiography (Figure 1A) confirmed occlusion of

left renal artery distal to the origin, along with duplication of the artery. Magnetic resonance imaging (MRI) brain showed posterior reversible encephalopathy syndrome (PRES).

Case 2

Eight years old boy presented with complain of headache for a week with increasing thirst and polyuria. He was having altered sensorium and convulsions prior to admission. He appeared hypovolemic with feeble peripheral pulses, possibly contributed by the polyuria. His BP was 184/110 mmHg (95th P = 114/75). There was left sided hemiparesis along with 6th and 7th nerve palsy. Ophthalmological examination was consistent for hypertensive retinopathy. Investigations revealed hyponatremic, hypokalemic, metabolic alkalosis along with normal creatinine (Table 1). USG with Doppler revealed bilateral hyper-echogenic kidneys with right relatively bigger (7.5 cm) than the left (6.2 cm) and suspected decreased blood flow in the left kidney. Renin and aldosterone was elevated. Digital subtraction angiography (DSA) of kidneys confirmed 90% stenosis of the left renal artery. MRI brain was consistent for PRES (Figure 1B).

Case 3

The 12 years old boy was admitted with headache for 1 mo, increased thirst, polyuria for 15 d and obtunded sensorium for 4 d. There was a documented decrease in weight of 800 g over the last 2 wk, possibly because of the polyuria. BP was 244/166 mmHg (95th P = 121/79). Ophthalmological examination was consistent with hypertensive retinopathy. Investigation showed hyponatremic, hypokalemic, metabolic alkalosis and normal creatinine (Table 1). USG doppler revealed "parvus-tardus" like flow in left renal artery, with enlarged hyper-echogenic right kidney. MRI brain was consistent with PRES. Digital subtraction angiography confirmed left renal artery stenosis (Figure 1C).

All three cases had high urinary sodium indicating natriuresis as the cause of the hyponatremia (Table 1).

The patients were diagnosed to have HHS presenting as hypertensive emergency. They were initially managed with Labetalol infusion and thereafter switched to oral anti-hypertensives (combination of Nifedipine sustained release, Hydralazine and Beta Blocker). Case 1 and 2 were given 3% NaCl and all required potassium supplements. Electrolyte abnormalities gradually corrected with normalization of BP.

Case 1 was advised PTA but was lost to follow up after 3 mo till when he was hypertensive (132/86 mmHg) despite being on Enalapril, Nifedipine and Atenolol. His electrolytes had normalized but he continued to have significant proteinuria; case 2 underwent percutaneous transluminal balloon angioplasty (PTA), which restored normal blood flow. His sodium normalized in 2 wk and urinalysis by 8 wk. At last follow up (20 mo) he remains off anti hypertensive with normal BP and renal profile;

Table 1 Relevant clinical parameter

	Case 1	Case 2		Case3	
	Pre renal vascularisation	Pre renal vascularisation	Post renal vascularisation	Pre renal vascularisation	Post renal vascularisation
Serum sodium (mmol/L)	112	127	139	126	137
Serum potassium (mmol/L)	3.2	3.1	3.9	3.2	4.2
Serum calcium (mg/dL)	7.9	7.5	8.8	8.4	8.7
Serum albumin (mg/dL)	2.3	2.7	3.6	2.9	3.9
Urine protein	3+	2+	Negative	2+	Negative
Urine RBCs	Absent	Absent	Absent	Absent	Absent
Urine protein/creatinine ratio	6.847	3.912	< 0.2	4.362	< 0.2
Urine sodium (mmol/24 h)	115	123	33	109	28
Blood pH	7.448	7.532	7.422	7.605	7.392
Blood bicarbonate	33.4	31.8	27.2	32.2	25.4
Serum renin (ng/mL per hour) (normal: 1.31-3.95)	21.06	32.8	3.05	25.04	3.24
Serum aldosterone (ng/dL) (normal: 1-16)	117.2	143.6	14.2	135.8	15.8
Urine osmolality mOsm/kg of water	Not done	Not done		770	
MRI brain	PRES	PRES		PRES	

Revascularization procedure could not be done. MRI: Magnetic resonance imaging; PRES: Posterior reversible encephalopathy syndrome.

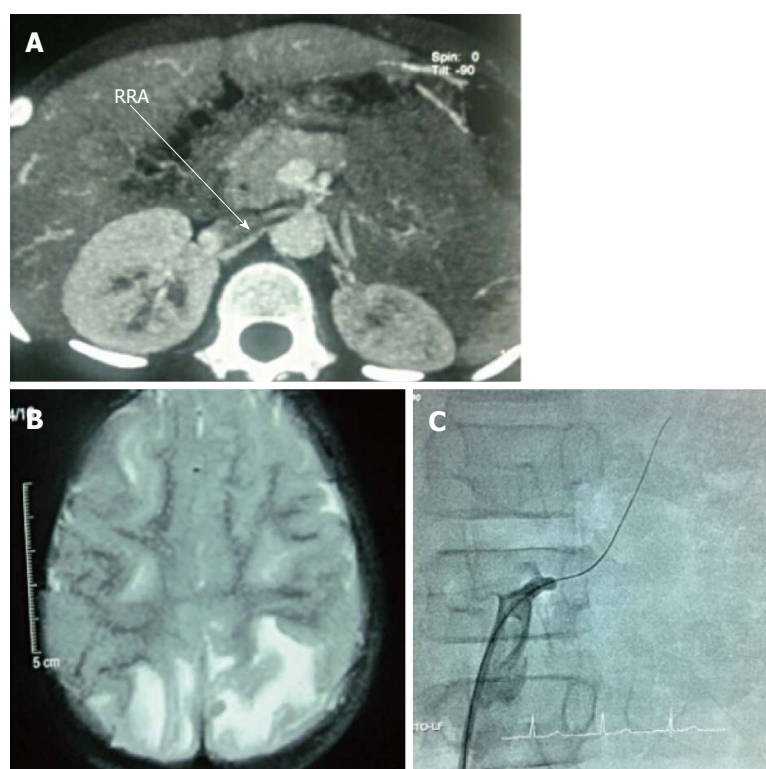


Figure 1 The angiography of three cases. A: CT angiography shows narrowing of left renal artery with duplication of artery. Small left kidney with compensatory hypertrophy of right kidney; B: MRI brain shows posterior reversible encephalopathy syndrome; C: Digital subtraction angiography shows stenosed left renal artery. MRI: Magnetic resonance imaging; CT: Computed tomography.

Case 3 underwent a failed balloon angioplasty of left renal artery followed by successful renal artery stenting. At 9 mo follow up, his electrolytes and urinalysis had normalized and he had normal BP (110/70 mmHg) on 1.25 mg of Enalapril. The USG changes in the contralateral kidney also normalized by last follow up for Case 2 and 3.

DISCUSSION

Hilden reported a series of cases in 5 adults associated

with hypertensive encephalopathy, hyponatremia and hyponatremia. This was coined as HHS by Seracini *et al*^[1]. It is characterized by severe hypertension along with hyponatremia secondary to natriuresis, making this association unique, as hypertension is usually associated with activation of renin aldosterone axis (RAS), which is characterized with salt retention. Although deemed rare we identified 3 children with HHS in our cohort of 10 children with hypertensive emergency within a span of 18 mo.

Atkinson *et al*^[5] postulated that unilateral decreased

renal blood flow results in increased renin secretion which increases the level of angiotensin II (AII) and thereby the level of aldosterone. Increased AII causes arterial hypertension resulting in pressure diuresis and natriuresis from the non-contracted normally functioning contra-lateral kidney, thereby causing polyuria and polydipsia. AII and aldosterone causes potassium loss and ultimately hypokalemia, which further stimulates renin secretion. Hyponatremia has also been known to increase aldosterone secretion^[5]. Polyuria causes increasing thirst and volume depletion and thereby causes secretion of anti diuretic hormone, which also contributes to hyponatremia. Thus, activation of RAS in presence of the hypertrophied contra-lateral kidney sets up a vicious cycle leading to natriuresis and hyponatremia along with the usual hypokalemia and metabolic alkalosis^[5]. Glycosuria and hypercalciuria suggesting tubule interstitial involvement have also been reported^[2,6]. Glomerular hyper-filtration secondary to arterial hypertension results in proteinuria as well as the reversible cortical hyperechogenicity of the normal kidney^[1-5,7]. As seen in our series, correcting the stenosis and controlling the BP usually corrects the proteinuria, electrolyte abnormalities and the hyper-echogenicity of the normal kidney^[1-4].

Altered sensorium seen in our children was likely secondary to hypertensive encephalopathy and all our cases had MRI brain consistent with PRES^[8]. In addition, concomitant hyponatremia might also have been contributing factor.

Management includes initial BP control followed by correction of the underlying etiology which in our cases was the left renal artery stenosis. In presence of unilateral renal artery stenosis, angiotensin converting enzyme inhibitors are the preferred medications but this should be avoided if bilateral stenosis is suspected. Revascularization with PTA is the preferred final intervention^[1-3,5,9].

In conclusion, we hope our findings will increase the awareness of this syndrome as this unique combination of hypertension, hyponatremia and natriuresis is strongly suggestive of compromised unilateral renal blood flow. As we identified three such cases over a span of only 18 mo, we do echo statement by other academicians that this may not be as rare as it is thought to be^[3].

COMMENTS

Background

Renovascular hypertension can occur secondary to renal artery stenosis (RAS), which can sometime present as hyponatremic hypertensive syndrome (HHS). Despite activation of RAS secondary to renal artery stenosis, they had

significant hyponatremia.

Research frontiers

This study was performed in order to determine its incidence among children admitted with hypertensive emergency in a tertiary care pediatric hospital.

Innovations and breakthroughs

Renal re-vascularisation produced excellent results.

Applications

The findings will increase the awareness of this syndrome as this unique combination of hypertension, hyponatremia and natriuresis is strongly suggestive of compromised unilateral renal blood flow.

Terminology

HHS: High blood pressure with low plasma sodium.

Peer-review

This is a well-written paper.

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Retrospective Study

Laparoscopic vs open donor nephrectomy: Lessons learnt from single academic center experience

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Conflict-of-interest statement: The authors report no conflict of interest.

Data sharing statement: Technical appendix, statistical code and data set available from the corresponding author at tsoulfasg@gmail.com. Consent was not obtained but the obtained data are anonymized and risk of identification is low.

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Abstract

AIM

To compare laparoscopic and open living donor nephrectomy, based on the results from a single center during a decade.

METHODS

This is a retrospective review of all living donor nephrectomies performed at the Massachusetts General Hospital, Harvard Medical School, Boston, between 1/1998 - 12/2009. Overall there were 490 living donors, with 279 undergoing laparoscopic living donor nephrectomy (LLDN) and 211 undergoing open donor nephrectomy (OLDN). Demographic data, operating room time, the effect of the learning curve, the number of conversions from laparoscopic to open surgery, donor preoperative glomerular filtration rate and creatinine (Cr), donor and recipient postoperative Cr, delayed graft function and donor complications were analyzed. Statistical analysis was performed.

RESULTS

Overall there was no statistically significant difference between the LLDN and the OLDN groups regarding operating time, donor preoperative renal function, donor and recipient postoperative kidney function, delayed graft function or the incidence of major complications. When the last 100 laparoscopic cases were analyzed, there was a statistically significant difference regarding operating time in favor of the LLDN, pointing out the importance of the learning curve. Furthermore, another significant difference between the two groups was the decreased length of stay for the LLDN (2.87 d for LLDN vs 3.6 d for OLDN).

CONCLUSION

Recognizing the importance of the learning curve, this paper provides evidence that LLDN has a safety profile comparable to OLDN and decreased length of stay for the donor.

Key words: Laparoscopic donor nephrectomy; Open donor nephrectomy; Living donor renal transplantation; Complications; Surgical technique; Renal graft function

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Core tip: The experience of the Massachusetts General Hospital was reviewed to compare laparoscopic vs open donor nephrectomy in a 10-year period. A review of the results of operating room time and conversions to open made the importance of the learning curve apparent. Although there was no difference in the recipient kidney function, the length of hospital stay was significantly shorter for the laparoscopic procedure. Overall, the laparoscopic donor nephrectomy appears to be the preferred surgical approach, considering the importance of the learning curve.

Tsoulfas G, Agorastou P, Ko DSC, Hertl M, Elias N, Cosimi AB, Kawai T. Laparoscopic vs open donor nephrectomy: Lessons learnt from single academic center experience. *World J Nephrol* 2017; 6(1): 45-52 Available from: URL: <http://www.wjgnet.com/2220-6124/full/v6/i1/45.htm> DOI: <http://dx.doi.org/10.5527/wjn.v6.i1.45>

INTRODUCTION

Laparoscopic living donor nephrectomy (LLDN) is not a novel procedure, since the first one was performed in 1995 by Ratner *et al*^[1] and it was subsequently made easier to learn with the description of the hand-assisted approach by Wolf *et al*^[2] and Slakey *et al*^[3]. This, together with the appeal of a less invasive procedure, led to the majority of living donor nephrectomies (LDN) being performed laparoscopically by 2005 according to the United Network of Organ Sharing, and with several large series arguing in favor of the safety and efficacy of

the procedure, as well as its positive effect on increasing the donor pool^[4-7]. Despite this positive momentum, it is interesting that there are still many questions that remain unanswered, or at least not fully answered.

A review of current trends and practice patterns by Wright *et al*^[8] in 2008, surveyed 58 fellowship training programs for renal transplantation in the United States accredited by the American Society of Transplant Surgeons. With 32 centers responding (55%), and representing approximately 40% of laparoscopic living donor nephrectomies in the United States, it became obvious that there is variability among different centers. Specifically, there were differences in donor selection [about one third of centers excluding donors with a body mass index (BMI) > 40 kg/m² or only 40% of centers considering a kidney with a simple cyst suitable for donation], choice of laparoscopic technique (40% of centers using only pure laparoscopy, 20% only hand-assisted laparoscopy and the rest a combination), and technical surgical aspects (whether to control the renal artery of the donor with a vascular stapler or a plastic or metal clip, or the type of incision)^[8].

More importantly, and even though a concern about underreporting remains, there have been reviews of the literature which have reported at least eight perioperative deaths with LLDN^[9]. The seriousness of this can only be fully understood if we consider that living donation represents a unique type of surgical procedure, where a healthy person undergoes an operation with significant risk, without any biological benefit for themselves; that is, the donor will not feel any better or be any healthier after the surgery. For this reason, we have to understand that the safety of the living donor is paramount. That is the main reason why, despite the existing studies, it is very important to welcome further studies evaluating the results of living donation, as well as to encourage centers to assess their own results and share the lessons learnt. This becomes even more critical today, given the fact that because of the progress of LLDN, there is increasing pressure to use more high-risk donors, such as those with a higher BMI or donors with complex renal anatomy.

MATERIALS AND METHODS

Patient characteristics

From January 1998 to December 2009, there were 490 LDN performed at the Massachusetts General Hospital, including 279 LLDNs and 211 open living donor nephrectomies (OLDNs) (Table 1). The decision between the open or the laparoscopic procedure, after the latter was introduced at our center in 1998, was a combination of patient's and surgeon's preference. Although originally the left kidney was the preferred one for the LLDNs, because of the longer vein, with increasing experience, kidney side, number of renal arteries or previous surgeries were not obstacles to LLDN. The main criterion regarding the procurement was choosing the "less healthy" kidney, so that the "better" one would remain with the living donor.

Table 1 Laparoscopic vs open living donor nephrectomy - January 1998 to December 2008

Laparoscopic nephrectomy	279
Left	260
Right	19
Open nephrectomy	211
Left	156
Right	55

All donors and recipients underwent extensive preoperative evaluation and testing by a multidisciplinary team before the decision was made to proceed with the donation. Patients underwent three-dimensional computed tomography and computed tomographic angiography, in order to evaluate renal size and anatomy, as well as the presence of any abnormalities. Donor and recipient medical records were reviewed, after approval from the Institutional Review Board. Information that was collected and analyzed included epidemiological data, and the LLDN and OLDN groups were compared regarding pre-, intra- and post-operative parameters, including pre- and post-operative donor and recipient renal function, operative time, the effect of the learning curve, delayed graft function, length of stay and complications. Delayed graft function was defined as the need for hemodialysis within a week after the transplantation. Additionally, the reasons for conversion from laparoscopic to open LDN were recorded. There were no statistically significant differences between the LLDN and the OLDN groups regarding age or gender.

Statistical analysis

Data are expressed as mean $\pm$ standard deviation. Statistical analysis used Student *t* test to assess group differences for continuous variable and statistical significance was defined as $P < 0.05$.

Surgical technique

There were five different attending surgeons performing the donor nephrectomy, with the surgical team also including a transplant fellow. In the first 20 LLDN, there were two attending surgeons present and participating. The surgical technique for the OLDN was a standard retroperitoneal flank approach, without a rib resection. For the LLDN, the initial preferred technique was that of a hand-assisted transperitoneal laparoscopic procedure, given the increased security that it provides to the surgeon. Patients were in a flexed, lateral decubitus position and initial access consisted of the placement of a handport either around the area of the umbilicus or through a low transverse incision, which could later be used to retrieve the kidney. Frequently, a 7-9 cm Pfannenstiel incision was chosen, given the improved cosmetic result. The intraabdominal pressure was set to 10-12 mmHg, to avoid any effect on renal perfusion. Urine output was maintained at a brisk rate using aggressive intravenous hydration, supplemented with

diuretics, and 5000 U of unfractionated heparin (when there was no contraindication) was given just prior to the renal artery occlusion. Originally, the artery was secured using locking polymer clips, but because of instances where the clips were not secure on the artery leading to bleeding, the decision was made that both the renal artery and vein would subsequently be secured with linear staplers. In the case of the right kidney being retrieved, the right renal vein was exposed at its insertion into the inferior vena cava and caval countertraction was applied just prior to firing the endovascular stapler, so that adequate length could be obtained. The postoperative protocol included analgesia with intravenous ketorolac on-demand (limited number of doses for only one day), removal of the Foley catheter on postoperative day 1 and advancing to a regular diet on day 2.

RESULTS

The LLDN and OLDN groups are presented in Table 1, including the information whether a left or a right kidney was retrieved. The preoperative glomerular filtration rate was similar (LLDN = 128.4 ± 32 mL/min vs OLDN = 123.6 ± 26 mL/min) between the donors for the two groups (Table 2). The reasons for which the right kidney was chosen included number of arteries or veins, presence of cysts, size, presence of stones and a tortuous ureter, with the guiding principle being to always have the better kidney remain with the donor. Specifically, in the LLDN out of the 19 right nephrectomies, the right kidney was chosen in 15 donors because of a single artery, in 2 patients because of the presence of numerous cysts mainly on the right side and 1 patient because of a significant size difference with the left kidney being much larger than the right and in 1 patient because of the presence of stones in the right kidney that were removed *ex vivo*. In the case of the open LDN, there were 55 right kidneys used. Out of these, in 43 patients the right kidney was chosen because of a single artery, in 6 patients because of size differences between the two kidneys, in 4 patients because of the presence of cysts on the right kidney and in 2 patients because of a tortuous ureter. The small sample size did not allow for statistical differences between the two groups. The operating room time is shown in Figure 1 with the additional information of whether it was a left or right kidney, as well as the number of renal arteries. Analysis of the operating room time reveals no statistically significant difference between the LLDN and OLDN (LLDN = 227 ± 58 min vs OLDN = 244 ± 62 min). Interestingly enough, when the most recent 100 LLDN cases with single artery kidneys are compared to the last 100 OLDN cases with single artery, there is actually a statistically significant difference in favor of the laparoscopic procedure (100 recent LLDN = 205 ± 42 min vs OLDN = 234 ± 61 min, $P < 0.001$). The value of the learning curve is further showcased in Figure 2, where we can clearly see that there is a

Lap	Left	260			OR time	Recent 100
			1RA	211	240 ± 64 (min)	205 ± 42
			2RA	48	251 ± 58	
			4RA	1	228	
	Right	19				
			1RA	15	225 ± 59	
			2RA	3	222 ± 45	
			4RA	1	218	
	Open	156				
			1RA	99	234 ± 61	
			2RA	53	268 ± 69	
			4RA	4	253 ± 59	
	Right	55				
			1RA	43	243 ± 54	
			2RA	12	206 ± 38	

 $P < 0.001$

Figure 1 Laparoscopic vs open living donor nephrectomy - operating room time.

Table 2 Comparison of laparoscopic vs open living donor nephrectomy

	Laparoscopic LDN	Open LDN
Donor preoperative GFR (mL/min $\pm$ SD)	128.4 ± 32	123.6 ± 26
Donor preop Cr (mean $\pm$ SD)	0.96 ± 0.4	0.88 ± 0.4
Operative time (min $\pm$ SD)	227 ± 58	244 ± 62
Donor postop Cr 1 mo (mean $\pm$ SD)	1.43 ± 0.9	1.39 ± 0.8
Delayed graft function (%)	7.2% (20/279)	6.6% (14/211)
Recipient postop Cr 1 mo (mean $\pm$ SD)	1.43 ± 1.4	1.39 ± 1.1
Major complications (%)	7.5% (21/279)	8.5% (18/211)

LDN: Living donor nephrectomy; GFR: Glomerular filtration rate.

trend towards decreased operating room time as the years progressed and the experience accumulated. Another example of this is the number of conversions, which were a total of 18/279 (6.45%). The reasons for the conversions are shown in Table 3. There were no reoperations or readmissions required in these donors. The important point regarding the learning curve is that, as we can see in Figure 3, there was a decrease of conversions over the years, with no conversions occurring during the last two years.

Regarding the efficacy of living donation, a key measure is recipient renal function. There were no statistically significant differences between the LLDN and the OLDN groups in recipient renal function at 1 wk (LLDN = 1.6 ± 1.2 mg/dL vs OLDN = 1.65 ± 1.3 mg/dL), or at 1 mo (LLDN = 1.43 ± 1.4 mg/dL vs OLDN = 1.39 ± 1.1 mg/dL), irrespective of whether the left or right donor kidney was transplanted (Figure 4, Table 2). Additionally, there was no statistically significant difference in the incidence of delayed graft function between the two groups (LLDN = 7.2% or 20/279 vs OLDN = 6.6% or 14/211). As far as the donor renal function is concerned, both the preoperative creatinine values (LLDN = 0.96 ± 0.4 mg/dL vs OLDN = 0.88 ± 0.4 mg/dL) and the postoperative ones at 1 mo (LLDN = 1.43 ± 0.9 mg/dL vs OLDN = 1.39 ± 0.8 mg/dL) were similar between the

Table 3 Reasons for conversion from laparoscopic to open living donor nephrectomy

Reasons for conversion	Number of patients ($n = 18$)
Bleeding	8
Adhesions	5
Anatomy	5

two groups (Table 2).

The one area where there was a statistically significant difference between the two groups was the length of stay (LLDN = 2.8 ± 0.91 vs OLDN = 3.6 ± 0.85) with donors in the laparoscopic group leaving the hospital earlier than their counterparts who had undergone an open procedure (Figure 5). Part of the reason was a postoperative fast-track protocol for the laparoscopic donors that included analgesia with intravenous ketorolac on-demand, removal of the Foley catheter on postoperative day 1 and advancing to a regular diet on postoperative day 2.

Finally, regarding the postoperative complications, although there was no statistically significant difference in the number of major complications between the two groups (LLDN = 7.5% or 21/279 patients vs OLDN = 8.5% or 18/211 patients), there was a difference in the types of complications with ileus, respiratory problems and incisional hernias being more frequent in the open living donor group. Regarding the timing of the complications, they were all in the immediate postoperative period (within 30 d), with the only exception being two episodes of ileus which occurred in the OLDN group. Specifically, these patients presented with ileus more than 6 mo after the surgery and were treated conservatively with bowel rest with success in both cases.

DISCUSSION

This report is a comparison of LLDN and OLDN. In order to do that, we present the experience of a single academic center over a 10-year period, starting with the advent of LLDN and how it evolved over time to the point that it came to replace OLDN as the main type of living renal donor procurement surgery. A review of our results reveals that although there was no statistical difference in the operating time between the two groups as a whole, when looking at the last 100 cases of LLDN with a left kidney and comparing them to the same number of OLDN with a left kidney, there was a significant improvement in the operating time in favor of the laparoscopic procedure. This serves to underline the importance of the learning curve, which is also shown in our results by the decreasing operating time over the years, as well as the decreased number of conversions in the laparoscopic group.

Additionally, when looking at donor and recipient renal function, as well as the incidence of delayed graft function, there is no difference between the two groups, leading to the conclusion that LLDN is at least

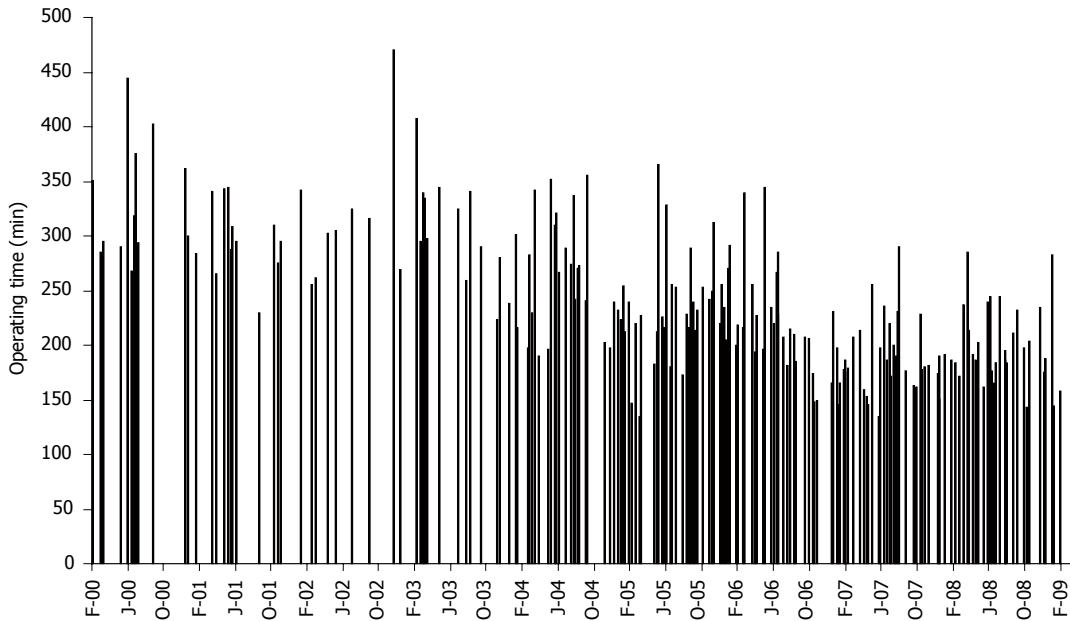


Figure 2 Laparoscopic living donor nephrectomy - the effect of the learning curve.

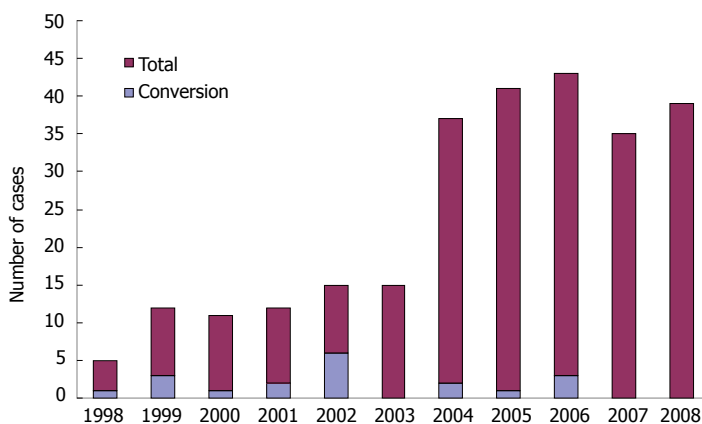


Figure 3 Laparoscopic donor nephrectomy - conversion to open cases by year.

as efficacious as OLDN when it comes down to renal function. The one area where there was a difference, was that of the length of stay, where donors spent almost a day less in the hospital following the laparoscopic procedure. Finally, in terms of their safety profile, there was no difference in the incidence of major complications, which shows that the LLDN is at least as safe as the OLDN. Interestingly enough, there was a difference in the types of complications, with pulmonary complications, ileus and incisional hernias being more frequent in the OLDN group, something which is not unexpected considering the larger incision.

These results compare well to other studies in the literature, as a meta-analysis by Nanidis *et al.*^[10] showed that LLDN is a safe alternative to the open technique, and that although open nephrectomy was associated with shorter operating times (when only randomized controlled studies were analyzed), there was no difference in recipient postoperative renal function or the incidence of delayed graft function. The authors similarly found that donors undergoing laparoscopic nephrectomy

were able to benefit from a shorter hospital stay. In contrast to our study, the authors report that when only randomized controlled trials were analyzed, it appeared that the rate of total postoperative complications favored the open procedure^[10]. However, they do point out that this result was not reproducible in the sensitivity analysis, probably because the numbers of the randomized controlled trials were so low that a definitive conclusion could not be safely drawn. There are other large series of LLDN, where the laparoscopic technique is at least as safe as the open one, with overall complication rates around 6%-6.5%, similar to ours^[11,12]. Obviously, one of the big questions is whether there is an issue of publication bias with underreporting of complications, as a survey of American transplant centers by Matas *et al.*^[13] showed a 0.03% mortality rate, as well as higher reoperation and readmission rates after laparoscopy. Although this must be taken very seriously into account, it could also be explained by factors such as these cases being early on in the learning curve of a center, as well as by the fact that transplant centers are more sensitive (and

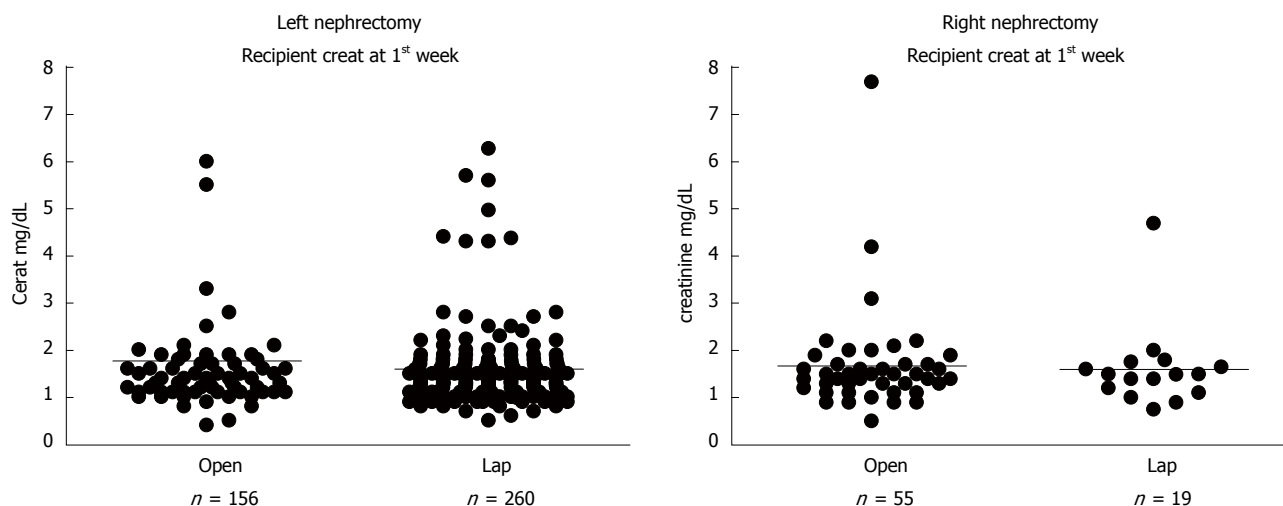


Figure 4 Laparoscopic vs open living donor nephrectomy - recipient kidney function at 1st week.

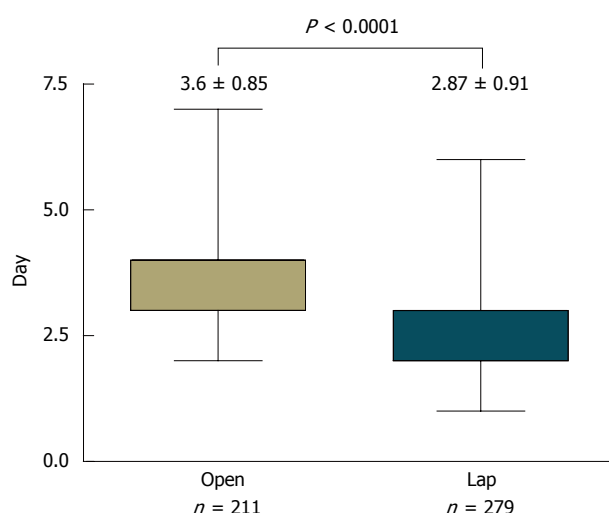


Figure 5 Laparoscopic living donor nephrectomy - length of stay (days).

rightly so) with any potential complication having to do with a living donor, making a readmission much likelier.

When trying to compare the LLDN with the OLDN, we have to remember that there are inherent difficulties in any long-term comparison given that the laparoscopic procedure is evolving over time, both in terms of the patient selection, as well as in terms of the technical aspects. Regarding the latter, an example is the manner chosen to control the renal artery. In the first several cases we were using the self-locking plastic clips to ligate the artery prior to transecting it, with the main reason being that a better length on the artery can be obtained. Unfortunately, due to episodes of bleeding secondary to the clips falling off, we had to change to a different technique with the use of a vascular stapler to ligate the renal artery and vein, and inspect the stapler line before transecting the vessel. Our experience in this aspect appears to be similar to other centers, including a survey of all 893 surgeon-members of the American Society of Transplant Surgeons with a 24% response

rate, which reported 66 and 39 episodes of arterial and venous hemorrhage, with two episodes of donor deaths due to bleeding and with the locking and standard clips applied to the renal artery being associated with a higher risk, and thus leading to warnings against their use^[14,15]. Another issue is that of the use of the left or right donor kidney. Specifically, initially there was a preference for the left-sided kidney, given the concerns for vascular control and vessel length^[16]. However, the combination of increased experience and the need to increase the living donor population to try to cover the existing need, and despite the technical difficulties, has led to significant efforts to perform right LLDN in the group of patients where left renal donation might not be ideal because of the anatomy or functional issues^[17,18].

The question of using the left or the right kidney is part of a bigger issue having to do with choosing the right living donor. The basic elements of that are identifying a person who will be able to donate a kidney that is functioning well, while at the same time preserving the well-being of the donor throughout the whole process^[19,20]. This has become even more critical as, given the success of living donation, there is increased pressure to include more high risk donors, such as those with obesity, older or younger donors, hypertensive donors, and those with preexisting conditions, such as kidney stones, that might affect the renal function post-donation^[21-24]. Additionally, in the United States and in certain other countries there is also the existence of nondirected or altruistic donors or paired exchanges of living donors in the case of sensitized recipients or blood group issues^[25,26]. All of the above stress the need for a living donor registry, where the goal would be to determine the collective experience regarding complications and long-term outcomes^[9]. The advantages of this registry would be the ability to provide accurate outcome information to both donors and recipients, assist programs in assessing their results, identify problems in a timely fashion where

intervention is possible, and increase public confidence in the process of donation^[7]. There have been some efforts along these lines, such as the European Living Donation and Public Health (EULID) project, which included mandatory registration and follow-up data, as well as regular audits of the 11 nations that initially organized this effort^[27].

One of the key points in our study is the importance of the learning curve, as we can see by the improvement in the operating time, as well as the decrease in the number of conversions. However, we have to understand that this also remains a continuously evolving matter, given the fact that the procedure itself is evolving with a significant number of variations on the surgical technique, such as the robotic nephrectomy, the natural orifice transluminal endoscopic surgery and single incision laparoscopic surgery using a single port^[28-35]. These elements of progress should be embraced, while at the same time collecting all the necessary data to evaluate them fully in the long-term, with the primary consideration always being the welfare of the living donor. Another point having to do with the learning curve is the transfer of surgical knowledge and training. Specifically, in order to train the next generation of surgeons performing laparoscopic living donor nephrectomies, the attending performing the surgery needs to train the fellow, and potentially the general surgical resident. However, given the fact that there is no room for errors in the case of living donation, the best way to start is in the case of laparoscopic nephrectomies performed for other etiologies, such as malignancy or infection. This way the trainee can “graduate” to the more complex procedure. It is essential to remember that this is not a “standard” laparoscopic nephrectomy, given the fact that the care and accuracy during the donor kidney extraction will play a critical role in the subsequent function of this kidney. For these reasons, the surgeon needs to be cognizant of the relevant physiology, in addition to possessing surgical excellence.

In conclusion, there are limitations to this study. These include its retrospective nature, the fact that it is from a single center, as well as the time period of a decade that it spans. The latter point has to do with the changes in techniques and instrumentation which have occurred and which unfortunately represent a limitation of any study in such a rapidly evolving field of medicine and surgery. However, despite these limitations, the study has shown that LLDN can be as efficacious and at least as safe as OLDN, while at the same time offering the advantage of decreased length of stay and improved cosmesis, both of which can have a positive impact on potential living donors. We have seen the paramount importance of the learning curve, as well as the fact that this is an active process where lessons are continuously learnt, making it necessary to make adjustments to ensure the safety of the donor and the recipient. This evolving process makes it necessary for different centers to share their experience, ideally in the form of a donor registry, so that all can benefit from

these lessons.

COMMENTS

Background

Progress in surgical technique and instrumentation has led to a significant increase of laparoscopic compared to open living donor nephrectomies (OLDN), based on patient and physician preferences.

Research frontiers

Despite the evolution of laparoscopic or minimally invasive donor nephrectomy, there are still questions remaining regarding its efficacy and safety profile. Some of the reasons for this are the continuous evolution in surgical techniques and instruments (thus making comparisons more difficult), as well as issues of underreporting when it comes down to donor complications. This study aims to provide added evidence in this debate and to help clarify the role of laparoscopic living donor nephrectomy (LLDN).

Innovations and breakthroughs

In this study describing the experience of the Massachusetts General Hospital Transplant Division in the decade between 1998 and 2009 with OLDN and LLDN, the authors have seen that there is no difference regarding the efficacy and safety profile of the two procedures. The one statistically significant difference is the decreased length of stay seen with the laparoscopic LDN compared to the open. However, the most useful lesson is the importance of the learning curve, as that leads to the necessary technical excellence required.

Applications

This study adds to the existing evidence showing that laparoscopic or minimally invasive LDN has the potential to become the predominant surgical technique for renal living donation. This will undoubtedly also increase the popularity of the procedure for people considering donation, given the less “intrusive” nature of minimally invasive surgery.

Terminology

Living donor nephrectomy: It is the surgical procedure whereby one of the kidneys of a living donor is removed (either in an open manner or with a minimally invasive procedure) and transplanted in a recipient.

Peer-review

The study is an interesting one. Clear writing and lucid illustrations get the message across well.

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Severe hyperkalemia following blood transfusions: Is there a link?

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Abstract

Patients with gastrointestinal bleeding often require large volume blood transfusion. Among the various side effects of blood transfusion, the increase of potassium levels is a serious one which is often overlooked. We report a case of severe hyperkalemia in a patient with gastric bleeding after large volume transfusion of packed red blood cells. The patient had hyperkalemia at baseline associated with his receiving medication as well as acute renal failure following hypovolemia. The baseline hyperkalemia was further aggravated after massive transfusions of packed red blood cells in a short period of time. The associated pathogenetic mechanisms resulting in the increase of potassium levels are presented. A number of risk factors which increase the risk of hyperkalemia after blood transfusion are discussed. Moreover, appropriate management strategies for the prevention of blood transfusion associated hyperkalemia are also presented. Physicians should always keep in mind the possibility of hyperkalemia in cases of blood transfusion.

Key words: Hyperkalemia; Blood transfusions; Packed red blood cells; Renal function; Gastrointestinal bleeding

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Core tip: Blood transfusion is associated with a wide range of potential complications. Among them, the increase of serum potassium levels is sometimes overlooked. Hyperkalemia is a potential deadly complication, especially when the patient has already increased potassium levels at baseline. A number of pathogenetic mechanisms associated with the development of hyperkalemia in patients receiving transfusions are discussed in the present case report. Moreover, the necessary precautions for minimizing the risk of transfusion-induced hyperkalemia are also presented.

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INTRODUCTION

Transfusion of red blood cells is associated with a wide range of potential complications^[1]. These include mainly febrile non-hemolytic transfusion reactions, allergic reactions, transfusion-associated circulatory overload, infections, acute lung injury and hemolytic reactions^[2]. An increase in serum potassium levels associated with blood transfusion is often overlooked^[3]. Herein, we describe the case of a patient with massive hematemesis who manifested an aggravation of baseline hyperkalemia after large volume transfusion and discuss the underlying pathophysiology.

CASE REPORT

A 90-year-old patient was admitted to our hospital due to several episodes of hematemesis which were soon followed by hematochezia. He was currently receiving treatment with benazepril (20 mg/d) and hydrochlorothiazide (25 mg/d) for hypertension as well as tamsulosin (0.4 mg/d) for benign prostate hypertrophy. All these medications were discontinued following the patient's hospital admission. He had undergone partial gastrectomy (Billroth II) 10 years ago due to a perforated peptic ulcer.

Upon admission he was hemodynamically unstable and normal saline was administered pending transfusion with packed red blood cells (PRBCs). Admission laboratory testing revealed anemia, acute renal failure and hyperkalemia (6.14 mEq/L) without indications of hemolysis (Table 1). The electrocardiogram showed sinus rhythm tachycardia without changes related to hyperkalemia. The patient was oliguric during the first 15 h of hospitalization. Arterial blood gases were consistent with metabolic acidosis (Table 1). Monitoring of hematologic, renal, electrolyte and acid base parameters was performed multiple times per day.

Within 12 h the patient required transfusion with 4 PRBC units which were already stored for 30 to 35 d. At the time of admission, the patient had lost and was continuing to lose large volume of blood and was therefore at a critical status. The need to rapidly and efficiently manage the hemorrhagic-hypovolemic shock mandated massive volume blood transfusion using the readily available at the time unwashed PRBC units. Management of hyperkalemia consisted of intravenous administration, in parallel with the transfusions, of a solution made by combining 1 Lt 5% dextrose in water (D/W 5%) together with 15 IU fast acting insulin. The above solution of glucose and insulin was selected in order to both achieve a rapid decrease of potassium levels as well as minimize the risk of hypoglycemia in a

patient already at a critical status. When the patient was hemodynamically stable, he underwent an emergency endoscopy which revealed a large ulcer at the site of the anastomosis without active bleeding at the time.

Following blood transfusions, the patient quickly restored normal diuresis and blood pressure. However, potassium further increased to a maximum of 6.97 mmol/L on day 2. This suggests that the aggravation of hyperkalemia was associated with the rapid massive transfusion rather than the initial oliguria and renal impairment. The administration of the D/W 5% with insulin solution was continued and serum potassium levels gradually decreased to normal (Table 1). As a result, no additional measures to reduce potassium levels were required. On day 3 a relapse of gastric bleeding occurred and the patient required another blood transfusion with a total of 7 PRBC units (which were also already stored for 30 to 35 d) as well as with fresh frozen plasma. However, this time the transfusion of the 7 PRBCs was done over a much greater period (4 d) instead of the initial rapid transfusion of the first 4 PRBCs, which were administered in only 12 h. No further increase in serum potassium was observed. Thereafter, the patient had an uneventful recovery and was discharged after 15 d with normal serum electrolyte concentrations.

DISCUSSION

There is evidence that transfusion of PRBCs can lead to increased potassium levels, especially in cases of large volume transfusion^[4]. This was an interesting case of a patient with massive gastric hemorrhage and hyperkalemia at baseline which was aggravated following PRBCs transfusion.

Persistent hyperkalemia is observed only when urinary potassium excretory capacity is reduced due to renal failure, effective circulating volume depletion or more commonly hypoaldosteronism^[5]. However, increased potassium intake and movement of potassium from cells into extracellular fluid may also play a prominent role in the pathogenesis of hyperkalemia^[5]. Causes of increased potassium intake include a rapid intravenous infusion, the administration of potassium penicillin mainly as an intravenous bolus, the ingestion of a KCl containing salt substitute or potassium supplements and the use of stored blood for transfusions^[6].

Hyperkalemia evident upon admission could be due to the coexistent prerenal azotemia associated with oliguria and subsequently decreased potassium excretion^[5]. In fact, volume depletion leads to decreased glomerular filtration rate and increased proximal sodium and water reabsorption. As a result, there is a marked decrease of fluid and sodium delivery to the distal nephron, leading to a decreased potassium secretion^[7]. This impairment in renal potassium excretion is counterbalanced by the hypovolemic-induced secondary aldosteronism. However, in our case the simultaneous administration of benazepril impairs the synthesis

Table 1 Patient's parameters during hospitalization

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 10	Day 16	Normal ranges
Ht (%)	26.4	22.9	19.7	23.3	26	26.9	31.4	33.7	
Hb (gr/dL)	8.5	7.7	6.7	8.3	9	9.2	10.8	10.8	
PRBCs	4	2	2	2	1	0	0	0	
Cre (mg/dL)	1.53	1.73	2.12	1.81	1.43	1.41	1.34	1.22	0.6-1.2
Ure (mg/dL)	97	136	190	158	102	74	45	38	11-54
K ⁺ (mEq/L)	6.14	6.97	5.65	4.69	4.21	4.08	4.12	4.84	3.5-5.3
Na ⁺ (mEq/L)	140	140	141	138	141	142	140	143	136-146
Glc (mg/dL)	178	129	90	94	121	119	87	107	70-125
pH	7.32	7.35	7.36	7.42	7.45		7.5		
HCO ₃ (mEq/L)	13.7	15.8	16.8	21.1	23.3		22.1		
pCO ₂ (mmHg)	27.6	29.2	30.3	33.2	34		28.8		

To convert hemoglobin from gr/dL to gr/L multiply by 10; to convert serum creatinine from mg/dL to $\mu\text{mol/L}$ multiply with 88.4; to convert serum urea from mg/dL to mmol/L multiply by 0.357; to convert serum glucose from mg/dL to mmol/L divide with 18. Ht: Hematocrit; Hb: Hemoglobin; Cre: Creatinine; Ure: Urea; PRBCs: Packed red blood cells received at the specific day.

of angiotensin II and therefore aldosterone, thus contributing to the profound hyperkalemia observed at patient's admission. It has been suggested that impaired potassium entry into cells observed in patients with hypovolemia can also lead to increased potassium levels^[7].

Hyperkalemia may contribute to the pathogenesis of the patient's coexistent metabolic acidosis at baseline by suppressing ammoniagenesis in the proximal tubules and decreasing medullary thick ascending limb NH_4^+ transport, which in turn decreases medullary accumulation of ammonium^[8]. As a result, hyperkalemia can decrease ammonium excretion, which is the major component of net acid excretion by the kidneys. Even though acidosis can directly increase potassium levels by both redistribution of potassium out of cells (in cases of mineral acidosis) and by decreased potassium secretion in distal tubules^[5], in the present case the mild degree of acidosis is not a major factor for the pathogenesis of hyperkalemia.

The patient had restored normal diuresis and normal blood pressure 15 h after admission. Despite the improvement of blood pressure, diuresis, the continuous administration of D/W 5% plus insulin solution as well as the discontinuation of benazepril, a further increase of potassium levels was observed. Acute renal failure is associated with hyperkalemia when it is accompanied with low urine flow, oliguria and therefore low sodium delivery to the distal tubule, leading to decreased renal potassium excretion. However, in our case the patient had restored normal diuresis. As a result, it is less likely that the observed hyperkalemia is a consequence of acute renal failure. As a result, this aggravation of hyperkalemia can be attributed to the initial rapid transfusion of PRBCs rather than a hypovolemic state. The patient also received transfusion of additional 7 PRBCs between days 2 and 5 of hospitalization. However, these transfusions were not accompanied by further elevation of potassium levels. This can be attributed to the much greater period over which these transfusions took place.

The use of stored blood for transfusions is followed

by an increase of serum potassium levels^[9]. Indeed, a prospective study showed that potassium levels increase more pronounced in patients who receive blood stored for more than 12 d^[10]. In fact, potassium is gradually released from red blood cells of the stored blood, resulting in an extracellular potassium concentration that by 21 d can reach up to 30 mEq/L in whole blood and up to 90 mEq/L in PRBCs^[9]. Furthermore, the lysis and destruction of red blood cells, especially in the transfusion of older PRBCs, can further increase potassium levels^[3]. In addition, the significantly decreased blood volume of our patient at baseline in combination with the high volume transfusion would make him more susceptible to potassium levels elevation from the PRBCs transfusion^[3]. Indeed, the patient's circulating blood volume had been markedly reduced after the gastric hemorrhage and thus its capacity to dilute exogenously loaded potassium was limited.

The risk of potassium overload can be minimized by selecting only blood collected less than 5 d prior to transfusion and by washing any unit of blood immediately before infusion to remove extracellular potassium^[11]. Furthermore, the use of potassium absorption filters during transfusion may also decrease potassium loading^[12,13]. Moreover, factors that also play a role in the increase of potassium levels are the rate and volume of transfusion as well as the patient's circulating pre-transfusion blood volume.

All things considered, hyperkalemia should be not overlooked in patients receiving large volume blood transfusions. A high level of suspicion and prompt management is warranted by the physician.

COMMENTS

Case characteristics

A patient with large volume blood loss due to gastrointestinal bleeding presented requiring emergency mass blood transfusion.

Clinical diagnosis

An aggravation of baseline hyperkalemia was observed after massive blood

transfusion in short time.

Differential diagnosis

Hyperkalemia associated with: Massive blood transfusion or acute renal failure.

Laboratory diagnosis

Baseline hyperkalemia associated with the patient's medications as well as hypovolemia was further aggravated after massive blood transfusions.

Imaging diagnosis

The patient underwent endoscopy which revealed a large ulcer at the site of a previous gastric anastomosis.

Pathological diagnosis

Hyperkalemia following massive blood transfusion in short time.

Treatment

Intravenous administration of a solution consisting of dextrose in water (D/W 5%) together with fast acting insulin, discontinuation of the angiotensin converting enzyme inhibitor that patient was receiving and restoration of blood volume in order to improve renal function.

Related reports

Hyperkalemia following blood transfusion is a complication which is sometime overlooked and can lead to fatal complications especially in patients of critical condition as is often the case in the emergency department.

Term explanation

PRBC: Packed red blood cells.

Experiences and lessons

Hyperkalemia is a sometimes overlooked but serious complication of blood transfusion, especially in patients with comorbidities and comedications that predispose to higher baseline potassium levels.

Peer-review

This is a good case, well managed, well written, and discussed.

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FGF23 and inflammation

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Abstract

Systemic inflammation is a recognized feature in chronic kidney disease (CKD). The role of systemic inflammation in the pathogenesis of vascular calcification was recently settled. FGF23 was recently accused as a direct stimulus of systemic inflammation. This finding explains the strong association of FGF23 to vascular calcification and increased mortality among CKD.

Key words: Chronic kidney disease; Inflammation; Vascular calcification; FGF23; Phosphate binders

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Core tip: In this letter, the authors confirm the direct offending role of FGF23 in the pathogenesis of vascular calcification and increased mortality among chronic kidney disease patients.

Sharaf El Din UAA, Salem MM, Abdulazim DO. FGF23 and inflammation. *World J Nephrol* 2017; 6(1): 57-58 Available from: URL: <http://www.wjgnet.com/2220-6124/full/v6/i1/57.htm>
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TO THE EDITOR

In the September 6 issue of *World J Nephrol*, the review article titled "Vascular calcification: When should we interfere in chronic kidney disease patients and how?" showed that the exact pathogenesis of inflammation in chronic kidney disease (CKD) is not fully understood and that many of the inflammatory markers and mediators can promote vascular calcification (VC) in CKD patients. These factors include interleukin 1 (IL-1), IL-6, C-reactive protein and tumor necrosis factor alpha (TNF α)^[1-4]. *In vivo* molecular imaging techniques have disclosed that VC is preceded by inflammation within the arterial wall^[5,6]. Similar finding was confirmed by a longitudinal study using positron emission tomography (PET)/computed tomographic (CT) scan^[7].

The positive correlation between FGF23 and VC was reported by many groups^[8,9]. Similar results were reported in healthy older men, irrespective of traditional risk factors^[10] and in children with CKD^[11]. Inflammation markers can mitigate the correlation between FGF-23 and vascular calcification^[12].

In November issue of kidney international (KI), Singh *et al*^[13] demonstrated that FGF23 stimulates the

hepatic secretion of the inflammatory markers IL-6 and C-reactive protein. This finding demonstrates the contribution of FGF23 to the chronic inflammatory status of CKD. It also highlights the role of FGF23 in the vessel inflammation that precedes arterial calcification. In addition, this finding stimulates the energetic control of FGF23 starting in the very early days of stage 2 in CKD patients as we recommended in our review^[14]. Lastly, this study supported the value of phosphate binders that can suppress FGF23 and the possible link between such agents and their anti-inflammatory effects and their impact on overall mortality^[15-18].

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Application of established pathophysiologic processes brings greater clarity to diagnosis and treatment of hyponatremia

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Abstract

Hyponatremia, serum sodium < 135 mEq/L, is the most common electrolyte abnormality and is in a

state of flux. Hyponatremic patients are symptomatic and should be treated but our inability to consistently determine the causes of hyponatremia has hampered the delivery of appropriate therapy. This is especially applicable to differentiating syndrome of inappropriate antidiuresis (SIAD) from cerebral salt wasting (CSW) or more appropriately, renal salt wasting (RSW), because of divergent therapeutic goals, to water-restrict in SIAD and administer salt and water in RSW. Differentiating SIAD from RSW is extremely difficult because of identical clinical parameters that define both syndromes and the mindset that CSW occurs rarely. It is thus insufficient to make the diagnosis of SIAD simply because it meets the defined characteristics. We review the pathophysiology of SIAD and RSW, the evolution of an algorithm that is based on determinations of fractional excretion of urate and distinctive responses to saline infusions to differentiate SIAD from RSW. This algorithm also simplifies the diagnosis of hyponatremic patients due to Addison's disease, reset osmostat and prerenal states. It is a common perception that we cannot accurately assess the volume status of a patient by clinical criteria. Our algorithm eliminates the need to determine the volume status with the realization that too many factors affect plasma renin, aldosterone, atrial/brain natriuretic peptide or urine sodium concentration to be useful. Reports and increasing recognition of RSW occurring in patients without evidence of cerebral disease should thus elicit the need to consider RSW in a broader group of patients and to question any diagnosis of SIAD. Based on the accumulation of supporting data, we make the clinically important proposal to change CSW to RSW, to eliminate reset osmostat as type C SIAD and stress the need for a new definition of SIAD.

Key words: Hyponatremia; Cerebral-renal salt wasting; Fractional excretion of urate

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Core tip: When dealing with normo-volemic, non-edematous hyponatremic patients the initial treatment should be *i.v.* normal saline, combined with measuring the fractional excretion of urate. As serum sodium is corrected, the patients with syndrome of inappropriate antidiuresis (SIAD) will normalize the fractional excretion of urate, while patients with cerebral-renal salt wasting will have a persistently elevated fractional excretion of urate. It appears that patients with SIAD will have a slow or no increase in serum sodium with saline, while patients with renal salt wasting will have a more rapid increase in serum sodium.

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INTRODUCTION

Hyponatremia, defined as a serum sodium < 135 mEq/L, is the most common electrolyte abnormality that is undergoing changes in methodology with the potential of bringing greater clarity to diagnosis and improved therapeutic outcomes. The present approach initiates the work up of a hyponatremic patient by assessing the status of their extracellular volume despite a unanimous agreement that we cannot accurately estimate the volume status of patients by usual clinical criteria^[1-3]. Nevertheless, we continue to attempt to determine whether the patient is euvoletic, hypovolemic or hypervolemic while considering other nuances such as urine sodium concentration (UNa), urine osmolality (Uosm), serum osmolality and hormones such as renin, aldosterone and atrial/brain natriuretic peptide. We decided to abandon the very tenuous volume approach to hyponatremia and constructed a new algorithm that will hopefully bring greater clarity to the diagnosis and treatment of hyponatremia in addition to encouraging others to explore other parameters that might resolve many of the controversies that exist today.

In this review, we will discuss the evolution of a new approach that will hopefully create changes that are based on credible and reproducible data. We will stress the complexity and importance of differentiating syndrome of inappropriate antidiuresis (SIAD) from cerebral salt wasting (CSW) or more appropriately renal salt wasting (RSW). The importance of this differentiation can be appreciated by our realization that virtually all patients with hyponatremia are symptomatic and should, therefore, be treated^[4-9]. Hyponatremia has created a perfect storm for complications by increasing osteoporosis, especially in an elderly population that is

Table 1 Listing the clinical features that are found in syndrome of inappropriate anti-diuretic hormone and cerebral salt wasting/renal salt wasting

Findings common to both SIADH and RSW

Association with intracranial disease
Hyponatremia
Concentrated urine
Urine sodium [Na] usually > 20 mEq/L
Non-edematous
Hypouricemia, with increased fractional excretion urate [FEurate]
Only difference between SIADH and RSW
Volume state: Normal/high in SIADH, low in RSW

Note: How the overlapping features are the most commonly encountered clinically in both syndromes and how the presence of edema can be found in CSW/RSW. SIADH: Syndrome of inappropriate anti-diuretic hormone; RSW: Renal salt wasting; FE: Fractional excretion; CSW: Cerebral salt wasting.

already undergoing bone demineralization, and inducing a fourfold increase in falls and fractures^[6,7,10]. Textbooks and review articles in medicine consider CSW to be a rare clinical entity as compared to neurosurgeons and critical care physicians who consider CSW/RSW to be common. There is thus an urgency to differentiate CSW/RSW from SIAD because of differences in therapeutic goals, to water-restrict in SIAD and administer salt and water in CSW/RSW. Differentiating CSW/RSW from SIAD has been further complicated by having identical key parameters that identify both syndromes (Table 1). Both syndromes present with hyponatremia, hypouricemia, increased fractional excretion of urate (FEurate), concentrated urine, urine sodium usually > 20 mEq/L with normal renal, adrenal and thyroid function (Table 1). The diagnosis of SIAD cannot, therefore, be made merely because it fulfills the criteria used to define SIAD^[11]. A major difference between both syndromes is the volume status (euvoletic/hypervolemic in SIAD and hypovolemic in CSW/RSW), the assessment of which is universally agreed to be inaccurate and not very useful; yet we continue to initiate the evaluation of hyponatremic patients by first addressing their volume status. This diagnostic and therapeutic dilemma has been further complicated by our reports of unequivocal cases of RSW occurring without clinical evidence of cerebral disease, which led to our proposal to change CSW to RSW^[12-14]. This important change in nomenclature has important clinical implications because RSW would not be considered in the absence of cerebral disease. The true prevalence of RSW is, therefore, not known and cannot be considered a rare entity until a study of a broader population of patients has been conducted.

EVOLUTION OF A NEW ALGORITHM

The report of hypouricemia, serum urate < 4 mg/dL, with increased FEurate of > 10%, coexisting with hyponatremia in SIAD by Beck in 1979 concluded that the coexistence of hypouricemia and hyponatremia differentiated SIAD from most other causes of hypona-

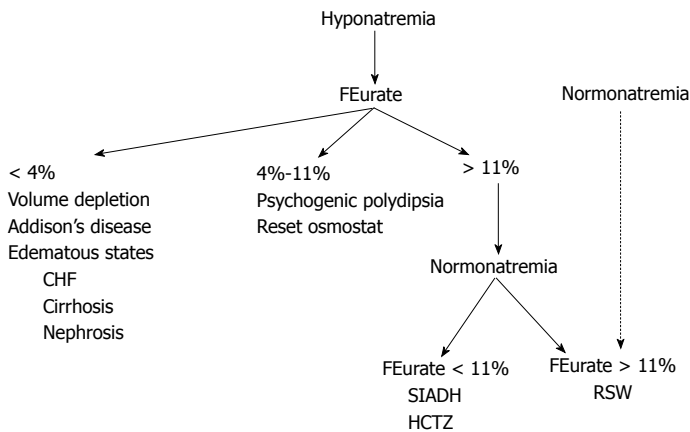


Figure 1 Proposed algorithm based on determinations of FEurate to evaluate hyponatremic patients without the need to assess the volume status of the patient or determinations of UNa, plasma renin or aldosterone levels. The dotted line connecting normonatremia and RSW with FEurate > 11% needs further verification. Modified from Ref. [28]. SIADH: Syndrome of inappropriate anti-diuretic hormone; RSW: Renal salt wasting; HCTZ: Hydrochlorothiazide; CHF: Congestive heart failure.

tremia^[15]. Interestingly, the increased FEurate in SIAD returned to normal when the hyponatremia was corrected by water restriction^[15]. Others not only demonstrated this unique relationship between hypouricemia and hyponatremia in SIAD but also noted normalization of a previously increased FEurate with correction of hyponatremia by water restriction^[15-20]. We encountered a patient with bronchogenic carcinoma and hypouricemia and increased FEurate, concentrated urine, UNa of 42 mEq/L and normal renal, adrenal and thyroid function, who presented with postural hypotension and reflex tachycardia that was consistent with volume depletion. He responded well to saline infusions with a rapid rise in serum sodium but in view of the coexistence of hyponatremia, hypouricemia and increased FEurate a diagnosis of SIAD was made. Despite the absence of cerebral disease and negative CT scan of brain a diagnosis of salt wasting was made because of postural hypotension with reflex tachycardia and a rapid increase in serum sodium. We corrected the hyponatremia by water restriction to determine whether FEurate would normalize or remain increased as postulated. Correcting the hyponatremia by water restriction and salt supplementation resulted in symptoms of hypovolemia, including return of postural hypotension with reflex tachycardia, postural dizziness, slurred speech, somnolence and staggered gait. The serum sodium finally increased to 138 mEq/L while FEurate remained increased at 14.7%. The clinical course of the patient was highly consistent with volume depletion due to RSW as the persistently increased FEurate after correction of hyponatremia was pathophysiologically different from SIAD. We instead postulated it might be a common feature of RSW^[21]. We proceeded to report FEurate to be persistently increased after correction of hyponatremia by water restriction in a patient with metastatic pancreatic carcinoma with ascites, edema and serum albumin of 1.1 mg/dL, bronchogenic carcinoma metastatic to brain, disseminated cryptococcosus with meningitis and uncomplicated Hodgkin's disease^[21]. Absence of cerebral disease in 3 of the 5 patients suggested at this time that RSW can occur without clinical evidence of cerebral disease but we waited until we had stronger evidence for RSW to make such a proposal. We

reported hypouricemia, hyponatremia, increased FEurate (many with normonatremia and some after correction of hyponatremia) and cerebral atrophy in patients with various intracranial diseases and in AIDS, 10 of whom had postural hypotension and CVP of 0 cmH₂O that were consistent with RSW^[22-24]. As a result of these studies, we felt we had enough data to propose differentiating SIAD from RSW by correcting the hyponatremia and observing whether there was normalization of a previously increased FEurate as in SIAD or was persistently increased as in RSW (Figures 1 and 2)^[14,25-28]. This unique relationship between FEurate and serum sodium appears to have identified two pathophysiologically different groups of patients.

Reset osmostat

While attempting to sort out the relationship between FEurate and serum sodium, we encountered hyponatremic patients who met the criteria for SIAD and RSW but had normal FEurates^[29]. Of 14 consecutive hyponatremic patients with normal FEurate, 6 had spontaneously excreted dilute urines which was diagnostic of a reset osmostat (RO). The remaining 8 patients had a normal water-loading test to prove the diagnosis of RO, 6 of whom had undetectable plasma antidiuretic hormone (ADH) levels at a time when the urine was dilute to prove further the diagnosis of RO (Figure 3)^[29]. As noted in Figure 3, type C SIAD represents patients with RO, which was found to make up about 30% of the patients studied^[29,30]. Our experience is that many hyponatremic patients admitted to the hospital have intercurrent illnesses that reset their osmostat and normalizes after resolution of their intercurrent illness. This was exemplified by a patient with a renal transplant who presented with mild hyponatremia of 133 mEq/L on a routine outpatient visit. He later developed a fever for 10 d and was admitted to the hospital with a pneumocystis pneumoniae infection after falling and being confused with a serum sodium of 119 mEq/L. A diagnosis of RO was made by noting spontaneously excreted dilute urine of only 92 mosm/kg and normal FEurate of 7% and 8%. His serum sodium returned to normal one month after successful treatment of his pneumonia. This case illustrates how a slowly evolving pneumonia had

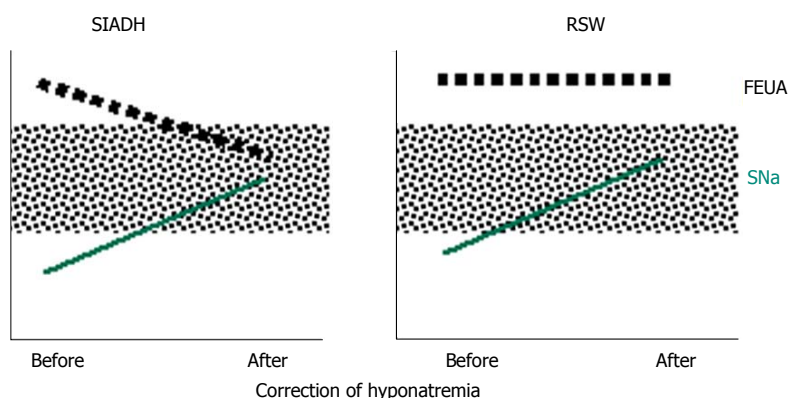


Figure 2 Figure depicting the relationship between serum sodium and FEurate in syndrome of inappropriate anti-diuretic hormone and renal salt wasting. Dotted areas denote normal values. Note FEurate to be increased when patients with SIADH and RSW are hyponatremic but normalize in SIADH and remain increased in RSW. Modified from Ref. [28]. SIADH: Syndrome of inappropriate anti-diuretic hormone; RSW: Renal salt wasting; FEUA: Feurate; SNa: Serum sodium.

Table 2 Summary of extracellular volume expansion with isotonic, hypotonic and hypertonic saline on fractional excretion of sodium [FENa] and urate [FEurate] at control and experimental periods after saline administration. Note the meager changes in FEurate despite very high FENa

	FENa (%)		FEurate (%)		Ref.
	Control	Exp	Control	Exp	
Isotonic	1.04	4.43	7.98	9.76	[36]
	1.6	8.2	5.0	5.8	
Hypertonic	2.9	18.6	5.4	12.1	[35]
	1.4	14.5	12.5	18.7	
Hypotonic	1.1	6.1	4.0	7.3	[35]

Printed with permission Ref. [26]. Exp: Experimental.

gradually lowered his osmostat and serum sodium^[31]. RO, however, can also exist chronically for over 10 years and the persistently normal FEurate is not consistent with the proposal that chronic hyponatremia is responsible for the high FEurate in SIAD^[29,32]. While a normal FEurate has effectively identified patients with RO, patients with psychogenic polydipsia also have a normal FEurate, but differentiating RO from psychogenic polydipsia can be readily made by the large volumes of water ingested and polyuria with dilute urines in psychogenic polydipsia (Figure 1)^[33]. Not only did this study simplify the diagnosis of RO but it provided additional data to support our proposal that FEurate was superior to hypouricemia when evaluating patients with hyponatremia. We have noted normal or increased FEurate with hypouricemia and increased FEurate with normonatremia^[22,24,29]. It also provided important pathophysiologic data to propose eliminating RO as a subtype of SIAD by virtue of a normal FEurate and predictable inhibition of ADH secretion by water loading^[30].

ADDITIONAL CONTRIBUTIONS OF DETERMINING FEURATE

Determinations of FEurate have also been extremely useful in identifying the cause of hyponatremia in other clinical conditions. In a recent publication, we report a hyponatremic patient with a bronchogenic carcinoma who met the criteria for SIAD and RSW (Table 1). His unresponsiveness to liberal amounts of saline was most

consistent with SIAD so to prove the diagnosis of SIAD we administered 1.5% hypertonic saline to increase serum sodium to 138 mEq/L while observing a gradual decrease in FEurate from 26.2% at baseline, to 11% and 8% (Figure 4)^[31]. This maneuver not only provided a potentially convenient way to differentiate SIAD from RSW by correcting the hyponatremia to see if FEurate normalizes as in SIAD or remains persistently increased as in RSW (Figures 1 and 2). It also confirmed our long-held contention that contrary to popular opinion, saline has only a meager effect on FEurate (Table 2)^[26,34-36].

RSW with edema

Determining FEurate was pivotal in a patient with advanced Hodgkin's disease who presented with a serum sodium of 127 mEq/L, Uosm of 308 mosm/kg, a 20 pound weight gain over one month with increasing edema of both lower extremities, postural hypotension with reflex tachycardia, ascites, pleural effusion, urine sodium of only 10 mEq/L, decreased cardiac output and normal renal, thyroid and adrenal function^[31]. The nephrology attending made a diagnosis of RSW based on the combination of a high FEurate of 17.2% and postural hypotension and reflex tachycardia that was consistent with a volume depleted state. The lower extremity edema was postulated to be due to obstruction of the inferior vena, a finding that was later confirmed by CT scan of the abdomen. Isotonic saline was administered and within 10 h after initiation of saline therapy, the Uosm decreased to 140 mosm/kg when a plasma ADH was undetectable. The dilution of urine and undetectable plasma ADH level illustrated how saline eliminated the more potent volume stimulus for ADH secretion and allowed the coexisting hypo-osmolality to inhibit ADH secretion (Figure 5)^[37]. Because of the increase in free water excretion his serum sodium increased by 6 mEq/L within 12 h so D5W was administered to prevent serum sodium from increasing beyond 6 mEq/L per day to prevent osmotic demyelination^[38]. On the second day, the medical team, using the unreliable volume approach, made an alternate diagnosis of congestive heart failure that was based on the edema, ascites, pleural effusion, UNa of 10 mEq/L, concentrated urine and decreased cardiac output (actually due to volume depletion) and administered

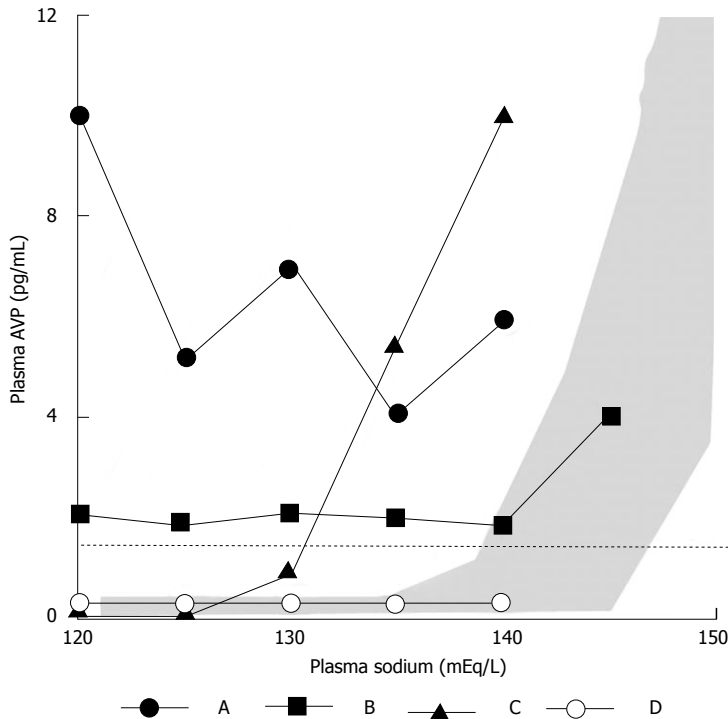


Figure 3 Types of the syndrome of inappropriate anti-diuretic hormone. Printed with permission, Ref. [66]. AVP: Arginine vasopressin.

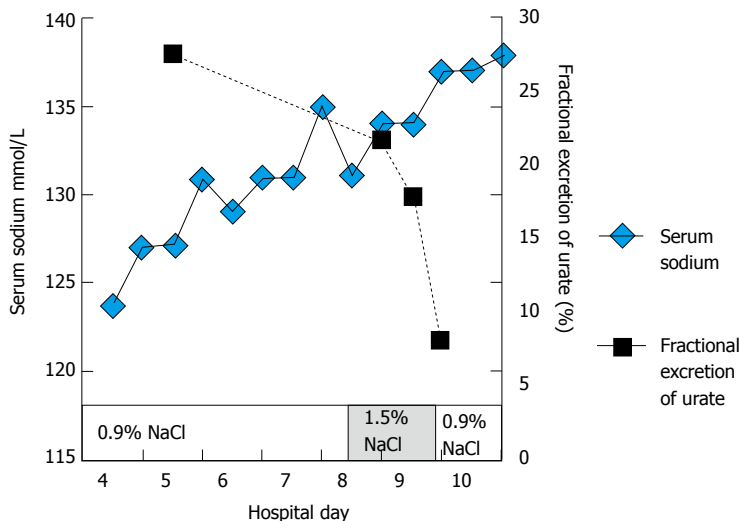


Figure 4 Illustrating how FEurate progressively decreases from an increased rate of 26.2% to a normal of 8% as serum sodium increases to a normal of 138 mEq/L in syndrome of inappropriate anti-diuretic hormone. Normalization of serum sodium did not occur after receiving large volumes of isotonic saline and was possible by using 1.5% hypertonic saline after receiving volumes of isotonic saline. The increase in serum sodium from 131 to 135 mEq/L occurred when he was on very large salt supplementation. This figure also confirms saline does not increase FEurate. Printed with permission, Ref. [31].

furosemide. Because the proximal tubule is the main site of natriuretic activity in RSW, see below, the large sodium load that would ordinarily be transported by the distal nephron was inhibited by furosemide resulting in a markedly increased urine output and hemodynamic instability that required large volumes of saline to attain hemodynamic stability. The initial finding of a high FEurate was pivotal in arriving at the diagnosis of RSW because a patient in heart failure and normal kidneys would decrease FEurate to < 4% (Figure 1)^[31]. The UNa of only 10 mEq/L was consistent with a prerenal state in which proximal tubule solute reabsorption increases to give rise to low UNa, decreased FEurate of < 4% and the hallmark increase in BUN to creatinine ratio^[39]. The low UNa was actually indicative of a decreased appetite and low salt intake, which can occur in RSW and SIAD.

Addison's disease

Addison's disease is a well-known cause of RSW, but in contrast to other causes of RSW, mineralocorticoid deficiency induces a defect in sodium transport in the distal nephron to create a volume depleted state with an intact proximal tubule where urate is exclusively transported^[40]. The volume depletion in Addison's disease due to a defect in sodium transport in the distal tubule leads to the classic prerenal state in which an intact proximal tubule increases solute transport to give rise to the oft-used increase in the BUN to creatinine ratio to characterize a prerenal state^[39]. So the low FEurate of 1.4% was a simple means of identifying Addison's disease as the cause of hyponatremia^[31]. The hyperkalemia, high UNa of 140 mEq/L, high ACTH and low cortisol levels accompanied the low FEurate and the

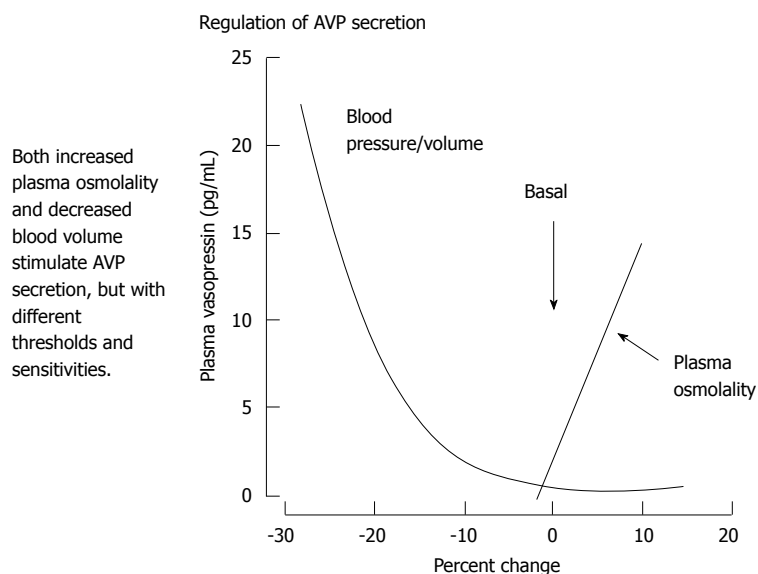


Figure 5 Effect of changes in extracellular volume, pressure and osmolality on plasma vasopressin levels. Note the marked increase in vasopressin levels with volume depletion which is more potent than the osmolar stimulus so a volume depleted will maintain high vasopressin levels despite the coexisting hypo osmolality of plasma. Printed with permission, Stricker *et al*^[37]. AVP: Arginine vasopressin.

dilution of urine after initiation of saline led to a rapid increase in serum sodium that required D5W infusions to retard the rate of increase in serum sodium to avoid osmotic demyelination. These features collectively strengthened the diagnosis of volume depletion due to RSW of distal tubular origin^[31]. A low FE_{urate} of 1.4% in a hyponatremic patient should thus include Addison's disease (Figure 1)^[31].

We have accumulated sufficient data to rely on the value of determining FE_{urate} in hyponatremic conditions. While the algorithm can effectively diagnose conditions such as RO, psychogenic polydipsia, Addison's disease and prerenal causes of hyponatremia, there is still the formidable task of differentiating SIAD from CSW/RSW. The diagnosis of SIAD cannot be made simply by satisfying the definition of SIAD, which is virtually identical to CSW/RSW (Table 1). We will review the salient pathophysiological features of both syndromes, highlight some important pathophysiological differences, critically review the literature and present a suggested approach to differentiate SIAD from RSW.

PATHOPHYSIOLOGY OF SIAD

The syndrome of inappropriate secretion of antidiuretic hormone, first described in 1957 by Schwartz *et al*^[41] and known simply as SIAD, rightfully deserves to be regarded as a syndrome that was derived by pure reason, recognizing patients who had identical clinical characteristics as healthy subjects receiving daily injections of ADH without being able to determine ADH levels in plasma^[42]. It is now well-known that ADH can be ectopically produced without being responsive to volume and osmolar stimuli, hence the term inappropriate secretion of ADH, that is, ADH levels being increased in the presence of euolemia and hypo-osmolality of plasma. They initially go into negative sodium balance and then quickly reach a steady state where sodium input equals sodium output^[43]. Because

of persistently increased ADH levels, renal water reabsorption decreases serum sodium levels. They eventually escape the effects of ADH by increasing urine volume in part by markedly decreasing renal aquaporin-2 protein^[44]. Patients with SIAD typically present with hyponatremia and hypochloremia, hypouricemia with increased FE_{urate}, concentrated urine, UNa usually exceeding 20 mEq/L, absence of edema and normal renal, thyroid and adrenal function (Table 1). They are considered to be euolemic according to textbook descriptions of the syndrome but are actually hypervolemic as determined by sulfate space and the gold standard radio isotope dilution methods, using ⁵¹chromium-labeled red blood cells and/or radio iodinated serum albumin^[13,42,45,46]. Plasma renin and aldosterone levels are normally suppressed and because of the volume expansion, ANP levels are increased. Euolemia is a necessary prerequisite to the diagnosis of SIAD because hypovolemia is a normal and potent stimulus for ADH secretion and takes precedence over the inhibitory effect of plasma hypo-osmolality (Figure 5). Unfortunately, extracellular volume cannot be accurately assessed by usual clinical criteria^[1-3]. SIAD is frequently associated with a myriad of comorbid conditions that often involve the pulmonary and central nervous systems. Because ADH increases renal water retention, treatment is to water restrict these patients to < 1000 mL/d with some salt supplementation or inhibit the V2 receptor for ADH, the vaptans^[47].

Need for reclassification and redefinition of SIAD

SIAD is currently classified by 4 different types of responses to serum hypo-osmolality (Figure 3), type A with ADH levels being increased throughout a wide spectrum of serum osmolalities, Type B where ADH levels remain slightly increased as serum osmolality decreases, type C a reset osmostat with ADH being inhibited at a lower serum osmolality than normal and type D where ADH levels are suppressed throughout the

spectrum of serum osmolalities due to a gain in function of the V2 receptor that is referred to as nephrogenic syndrome of inappropriate antidiuresis^[30]. Because the patients selected for this study were considered to be euvoletic by unreliable clinical methods, it is probable that type B SIAD may be renal salt wasters because the patients in this study were given hypertonic saline to increase serum osmolality to normal and then given a water load to determine ADH levels as serum osmolality decreased. The assumption is that these patients had RSW but remained volume depleted to maintain increased levels of ADH despite the hypertonic saline^[30]. The classification of type C SIAD has also come under scrutiny because patients with RO have pathophysiologic differences from SIAD by a normal FE_{urate} as compared to being increased in SIAD and noting how lowering serum osmolality appropriately and predictably inhibits ADH secretion^[29]. RO should thus be considered a separate clinical syndrome and eliminated as type C SIAD. Elimination of RO as a subtype of SIAD should thus lead to a redefinition of SIAD by eliminating the U_{osm} of < 100 mosm/kg, since excretion of dilute urines, U_{osm} < P_{osm}, is extremely unusual in SIAD, *vide infra*^[11,30].

CEREBRAL/RENAL SALT WASTING

CSW, as first described by Peters *et al.*^[48] in 1950, had fallen into disrepute for many years in part because, as previously reviewed, they did not prove RSW in their report. SIAD became the preferred and dominant syndrome. RSW is now accepted as a legitimate syndrome that exists and is being recognized with greater frequency. It appears that a natriuretic factor, as discussed below, initiates RSW by increasing renal salt and water excretion to a point where the patient becomes volume depleted, the extent being determined by the combination of the severity of the inhibition on sodium transport and salt and water intake. The defect in sodium transport appears to reside in the proximal tubule because urate, which is transported exclusively in the proximal tubule by reabsorbing and secreting transporters, is also reduced^[40]. An increase in BUN to creatinine ratio as previously proposed in RSW has not been confirmed by recent reports addressing this problem^[12,13]. In RSW, similarities in the BUN to creatinine ratio in SIAD and RSW can be explained by the reduced sodium and water reabsorption in the proximal tubule that cannot establish a urea concentration gradient that is necessary for passive urea reabsorption to occur^[49]. The patient initially goes into a state of negative sodium balance, but like SIAD eventually reaches a new steady state where input of salt matches output by activation of humoral, hemodynamic and neuronal factors, but reaches a steady state at a lower extracellular volume. UNa can thus be low if sodium intake is low as can be noted in both SIAD and RSW and is, thus, not a consistently reliable marker of both syndromes. It is extremely unlikely that atrial or brain

natriuretic peptides are responsible for RSW as proposed since their main meager action is in the distal tubule and have been found to be elevated in disparate conditions such as SIAD, subarachnoid hemorrhage (SAH) and salt retaining states such as congestive heart failure and low normal in an unequivocal case of RSW^[12].

In contrast to SIAD, ADH levels in RSW are appropriately increased because the more potent volume stimulus perpetuates the hyponatremia despite the increasing plasma hypo osmolality (Figure 5). As we demonstrated in 4 previous unequivocal cases of RSW, saline eliminates the volume stimulus for ADH secretion to reduce ADH to undetectable levels and allowing the coexistent hypo-osmolality to inhibit ADH secretion, which induces free water excretion by diluting the urine and promptly increasing serum sodium (Figure 6)^[12,13,31]. In contrast, saline did not dilute the urine or significantly increase serum sodium in two documented cases of SIAD in whom the diagnosis of SIAD was made by an increased FE_{urate} and hypervolemia as determined by gold standard radioisotope dilution methods by ⁵¹chromium-labeled red blood cells and radio iodinated serum albumin (Figure 7)^[13]. This same maneuver has been used by others to propose a volume-depleted hyponatremic state if isotonic saline increases serum sodium increases by more than 5 mEq/L and at the same time commenting on our inability to assess accurately the volume status of patients by clinical criteria^[1].

Our case of a hyponatremic patient with a hip fracture and no clinical evidence of cerebral disease illustrates the essential features of RSW and proves unequivocally the existence of RSW^[12]. When seen in consultation, she was hyponatremic and hyperchloremic with normal renal, adrenal and thyroid function, concentrated urine, U_{osm} 321 mosm/kg and a UNa of only 6 mEq/L. Her hyponatremia was initially thought to be due to a volume-depleted state with normal renal function that would give rise to a prerenal state where proximal tubule solute reabsorption would increase to give rise to a low FE_{urate} of usually < 4%^[39]. A low serum urate of 3.4 mg/dL led to a determination of FE_{urate} which was elevated at 29.6% and was thus included in our IRB-approved protocol. Her baseline plasma renin, aldosterone and ADH levels were increased, ANP was low normal at 35 pg/mL and blood volume as determined by ⁵¹chromium-labeled red blood cells and radio-iodinated serum albumin was reduced by 7.1%^[12]. She received isotonic saline and as can be seen in Figure 6, U_{osm} progressively decreased to dilute levels 13 h after initiation of isotonic saline infusion when plasma ADH was undetectable as would be expected in a hypovolemic, hyponatremic patient with RSW. The excretion of free water promptly increased serum sodium to normal within 48 h when FE_{urate} remained persistently increased (Figure 6)^[12]. The patient reported feeling much better and was hungry upon arising 18 h after initiation of isotonic saline infusion, which reflected an improvement of

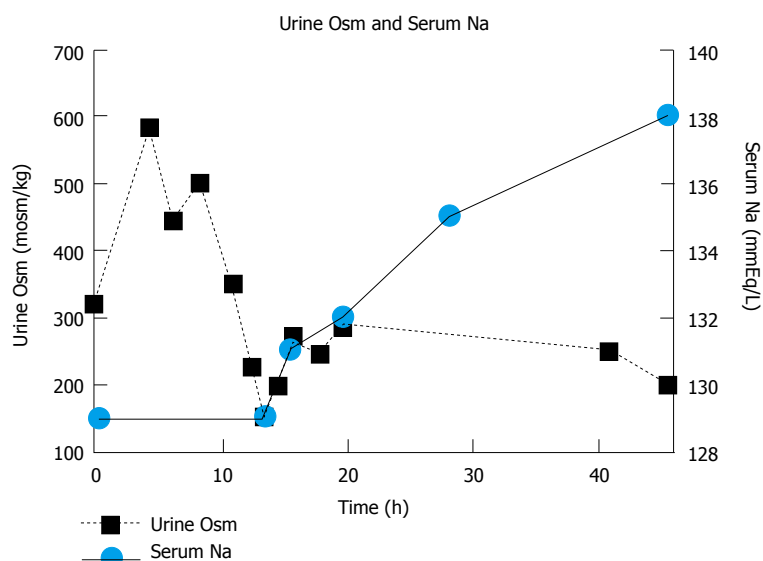


Figure 6 Changes in urine osmolality and serum sodium concentration during isotonic infusion in a hyponatremic patient with a hip fracture without clinical evidence of cerebral disease. The low Uosm at baseline reflected a low sodium intake when UNa was only 6 mEq/L and a weakened medullary solute concentration, which increased rapidly with a marked increase in Uosm after 4 h of saline infusion. Plasma antidiuretic hormone (ADH) was increased with increased plasma renin and aldosterone levels at baseline and ADH level was undetectable when the urine was dilute 13 h with increase in serum sodium to 138 mEq/L within 48 h after initiation of isotonic saline infusion. Printed with permission, Ref. [12].

her volume depleted state by an erroneous diagnosis of SIAD and fluid restricted for 10 d prior to our intervention. This patient satisfies all of the important features of RSW by the persistence of an elevated FEurate after correction of hyponatremia (Figures 1 and 2), and illustrated the appropriate increase in plasma ADH, elimination of the volume stimulus by saline to permit the coexistent hypo-osmolality to inhibit ADH secretion, excretion of dilute urines and prompt correction of hyponatremia. It also illustrates how RSW can occur without clinical evidence of cerebral disease, how the low ANP is a very unlikely cause of RSW, how fluid restriction of a patient with RSW for an erroneous diagnosis of SIAD can increase morbidity and how a low salt intake can result in low UNa even in RSW (and in SIAD as well). A similar case of RSW associated with an uncomplicated pneumonia and no evidence of cerebral disease responded to isotonic saline infusions by diluting the urine and correcting the hyponatremia within 48 h after initiation of isotonic saline infusions^[13]. This case provided us with enough credible data to activate our earlier instincts by proposing to change CSW to RSW^[14].

COMMENTS ON NATRIURESIS IN RSW AND RELATIONSHIP BETWEEN NATREMIA AND URATE TRANSPORT

Natriuresis in RSW. The syndrome of RSW has been clearly established from a clinical perspective but the mechanism by which this occurs has not been resolved. The consistency with which we were encountering urate transport abnormalities in RSW suggested that a circulating natriuretic factor, if present, would have its major effect on proximal tubule sodium transport. But because of the ability of the distal tubule to increase sodium transport, we reasoned that sodium excretion induced by a factor affecting proximal sodium transport might be minimized or nullified. To this end we elected to study lithium transport in rats exposed to plasma

from neurosurgical patients who have been reported to have RSW and high FEurates^[24,45,46,50]. Without entering into the controversy whether or not lithium is exclusively transported in the proximal tubule, lithium is known to be transported on a 1:1 basis with sodium almost exclusively in the proximal tubule under ambient conditions^[51]. We injected the plasma from 21 neurosurgical patients, 14 of whom had FEurates exceeding 10%, and 14 age and gender-matched controls into rats and demonstrated a significant increase in FENa from 0.29% to 0.59% and FELithium from 24% to 36.6%, in controls and neurosurgical patients, respectively^[52].

We extended our interest in patients with increased FEurate with normonatremia by investigating patients with Alzheimer's disease (AD) who have been reported to be hypouricemic^[53]. We studied 18 patients with advanced AD, mini-mental examination scores of < 10, and compared them to 6 patients with multi-infarct or vascular dementia (MID) and 11 normal age and gender-matched controls. All patients were normonatremic except for one hyponatremic patient with AD, FEurate being significantly higher and serum urate lower in AD as compared to the other groups. Infusion of the sera from all groups of patients resulted in FENa of 0.33%, 0.38% and 0.63% and FELithium 27.2%, 31.2% and 41.7% in control, MID and AD, respectively. FENa and FELithium were significantly increased in AD as compared to control and MID. In both the neurosurgical and AD rat studies, the distal sodium load of 36.6% and 41.7% as determined by the FELithium, had a significant sodium uptake by the distal nephron to account for the FENa of only 0.59% and 0.63% in the final urine. The RSW patient with B cell lymphoma obstructing the inferior vena cava had a similarly high distal sodium load that was inhibited by furosemide to generate an exaggerated diuresis that resulted in profound hemodynamic instability^[31]. Interestingly, there were no differences in blood pressure or inulin clearances throughout both studies.

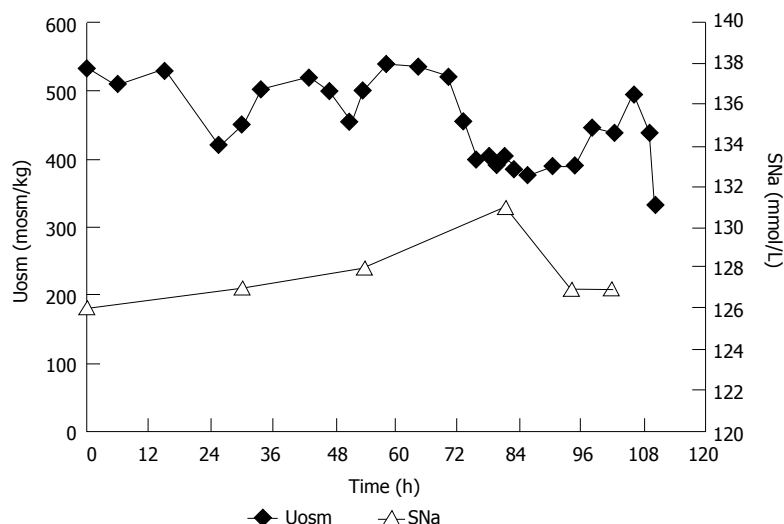


Figure 7 Effect of isotonic infusion in patient with syndrome of inappropriate anti-diuretic hormone in whom blood volume determination by ^{51} chromium-labeled red blood cells and radio iodinated serum albumin was increased. Note persistently increased urine osmolality or failure of urine to become dilute or correction of hyponatremia which are common features of SIAD response to isotonic saline infusion. Printed with permission, Ref. [13]. SIADH: Syndrome of inappropriate anti-diuretic hormone; SNa: Serum sodium; Uosm: Urine osmolality.

In a third group of studies, proteins were purified from ammonium sulfate precipitates of urine proteins and placed in transwells to determine transport of radioactive sodium, ^{22}Na , across cultured porcine proximal tubule cells, LLC-PK1 cells, grown to confluency on a semipermeable membrane. Urine proteins from normonatremic neurosurgical patients with increased FEurate inhibited ^{22}Na transport across cultured LC-PK1 cells as compared to those with normal FEurate^[54].

These studies demonstrate the presence of a natriuretic factor in the plasma and urine of normonatremic neurosurgical patients with increased FEurate and in sera of normonatremic AD patients with increased FEurate. The natriuretic factor has its major effect on proximal tubule sodium transport to support our proposal that a high FEurate in the presence of normonatremia might be a marker of RSW without going through a phase of hyponatremia (Figure 1). Future studies must address this interesting possibility. Atrial or brain natriuretic peptides are extremely unlikely as the natriuretic factor in RSW because their main site of action is in the inner medullary collecting duct^[55].

Relationship between natremia and FEurate

The intriguing relationship between serum sodium and FEurate has been uniquely coupled in many hyponatremic and non hyponatremic conditions such as RSW. Because the natriuretic factor present in the plasma of patients with RSW affect sodium transport mainly in the proximal tubule, it would be interesting to speculate that the natriuretic factor might also affect reabsorbing and/or secretory transporters or anion exchangers for urate in the proximal tubule^[40]. This circulating factor can have effects on the sodium and urate transporters regardless of whether the patient is hyponatremic or normonatremic.

The relationship between sodium and urate in SIAD continues to elude any rational explanations. It can be readily understood why FEurate remains persistently increased in the presence of normonatremia in RSW, but in SIAD, normalization of FEurate after correction

of hyponatremia has not been fully explained. Some have implicated the V1 receptor activity of pitressin to explain the increase in FEurate in SIAD but others were able to induce SIAD with increased FEurate in healthy volunteers by DDAVP which lacks any V1 activity. In addition, the V1 activity of pitressin is an unlikely cause of the increase in FEurate in SIAD because pitressin levels are still increased when FEurate normalizes after correction of hyponatremia^[56]. The same group has made commendable efforts to explain the increase in FEurate in SIAD by implicating chronic hyponatremia, but the normal FEurate reported in psychogenic polydipsia and reset osmostat where hyponatremia has been documented for up to 10 years do not support such an hypothesis^[32]. At the present time, the relationship between serum sodium and FEurate remains unexplained in SIAD.

Prevalence of RSW

The prevalence of RSW in hyponatremic patients is presently unknown because of multiple factors: (1) the term CSW confined RSW to patients with cerebral disease; (2) textbooks and review articles in internal medicine consistently consider CSW to be a rare entity or is not included as a clinical entity of hyponatremia; (3) utilizing the ineffective volume approach to hyponatremia; and (4) lack of application of the pathophysiologic characteristics in the evaluations of SIAD and RSW. As noted in Table 1, overlapping of key clinical parameters that characterize SIAD and RSW makes it extremely difficult to differentiate one syndrome from the other. One key difference is to determine the volume status of the patient by credible means at a time when they are hyponatremic. There are 3 studies in hyponatremic and normonatremic neurosurgical patients that determined intravascular volume by gold standard radio isotope dilution methods, using ^{51} chrome-labeled red blood cells and/or radio iodinated serum albumin. As can be seen in Table 3, 83% and 94% of patient with UNa exceeding 40 mEq/L and a variety of neurosurgical diseases had decreased blood volumes that were

Table 3 Summary of volume studies by gold standard radio-isotope dilution methods in hyponatremic and normonatremic neurosurgical patients^[45,46,50]

Ref.	n of patients	Low blood volume RSW	Increased blood volume SIADH	Urine Na mEq/L
Nelson <i>et al</i> ^[45] HN	12	10 (83%)	2	41-203
Wijicks <i>et al</i> ^[46] HN	9	8 (89%)	1	--
NN	12	8 (67%)	4	
Sivakumar <i>et al</i> ^[50] HN	18	17 (94%)		43-210

RSW much more common than SIAD. Printed with permission, Ref. [26]. SIADH: Syndrome of inappropriate anti-diuretic hormone; RSW: Renal salt wasting; HN: Hyponatremic; NN: Normonatremic.

consistent with CSW/RSW. By comparison only 3 of the 39 patients studied had increased blood volumes that were consistent with SIAD^[45,46,50]. Interestingly, 67% of normonatremic patients with SAH had decreased blood volumes that were consistent with RSW while only 33% had increased volume consistent with SIAD. RSW occurring in normonatremic patients is consistent with the popular view of CSW/RSW but we would like further clarification of whether normonatremia in the presence of a high FEurate is indicative of RSW (Figure 1). Fluid restricting patients with SAH was harmful by increasing morbidity and mortality so it is customary to administer saline to patients with SAH because of the prevalence of RSW in patients with SAH^[57].

These volume studies in neurosurgical patients overcame the most important deficiency when trying to differentiate SIAD from RSW, but are rarely considered when discussing CSW. Instead, a retrospective study of patients with SAH where CSW was found in only 6.5% of patients with hyponatremia, the majority being SIAD, is cited to prove the rarity of CSW/RSW^[58,59]. In two retrospective studies they determined without defining their method of analysis that 4.8% and 2.7% of patients had combined CSW and SIAD, a highly incongruous combination that might occur, but would be extremely difficult to prove, especially in a retrospective study^[59,60]. We critically reviewed many flawed articles on CSW/RSW in a previous publication and feel it is important to comment on a more recent prospective study of hyponatremia in patients with SAH by the same group which concluded that the hyponatremia was again due to SIAD^[28,61]. The diagnosis of SIAD was made because they fulfilled the definition of SIAD without commenting on the same definition being applicable to RSW. The accompanying editorial to this manuscript agreed with the findings in this large study and alluded to the rarity of CSW^[62]. A critical review of this manuscript reveals that the authors followed the recommendation to administer saline rather than fluid-restrict hyponatremic patients with SAH^[57]. Virtually every patient received isotonic saline from the time of admission to the hospital, none were fluid restricted and none received hypertonic saline or a vaptan class of drugs at any time.

It is intriguing to note that 36 of 49 patients developed hyponatremia within 3 d after SAH. This unaddressed outcome raises questions as to whether the patients received free water or desalinated when UNA exceeded 150 mEq/L while receiving isotonic saline^[63]. Every patient corrected their hyponatremia during the hospitalization with the median time of correction being 3 d. Because of the correction of hyponatremia, they concluded that the "syndrome" was short lived. It is well known that patients with SIAD do not respond to saline infusions to correct their hyponatremia; otherwise there would be no need for fluid restriction or treatment with the vaptan class of drugs. Instead, a more likely diagnosis is RSW, which is consistent with the volume studies performed in patients with SAH (Table 3)^[46]. Isotonic saline eliminated the volume stimulus for ADH secretion and permitted the coexisting hypo-osmolality to inhibit ADH secretion, excrete dilute urines and predictably correct the hyponatremia, which does not happen in SIAD^[12,13,31]. ADH levels would have been undetectable at the time of excretion of dilute urines as we demonstrated in cases of RSW within 24-48 h after initiation of isotonic saline therapy^[12,31]. We contend that these patients would have had high FEurates exceeding 11% and would have remained increased when serum sodium returned to normal (Figures 1 and 2). Correction of hyponatremia would not mean there was resolution of the underlying RSW. The reader is encouraged to read a more thorough critical review of controversial papers in the literature^[28].

Differentiating SIAD from RSW

As noted in Table 1 and Figures 1 and 2, SIAD and RSW share common clinical parameters including an increased FEurate > 11%. An increased FEurate most often involves RSW and SIAD with hydrochlorothiazide (HCTZ) and possibly selective serotonin reuptake inhibitors (SSRIs) drugs coming into the picture. Discontinuation of HCTZ and SSRIs should result in correction of the hyponatremia but persistence of the hyponatremia and increased FEurate would indicate that SIAD must be differentiated from RSW in order to arrive at the proper therapeutic strategy of water-restricting or administering V2 receptor blockers for SIAD or administer saline for RSW. We have now accumulated enough data to utilize two strategies to differentiate SIAD from RSW. The first is to correct the hyponatremia by either water-restriction or use of hypertonic saline to determine whether FEurate normalizes as in SIAD or remains increased as in RSW (Figures 1, 2 and 4). It is important to note that contrary to common perceptions, saline has a very meager effect on FEurate as noted in Figure 4, Table 2. This is illustrated by Figure 4 when large volumes of saline, including hypertonic saline, gradually decreased FEurate from 26.2% to 8% as serum sodium increased to normal to confirm the diagnosis of SIAD^[31].

The other alternative is to administer saline soon after FEurate has been shown to be increased, > 11%. As discussed above, the urine will usually become dilute

within the first 24-48 h after initiation of saline infusion in RSW with a rapid increase in serum sodium which should not increase by more than 4-6 mEq/L per 24 h to prevent osmotic demyelination^[38]. The rapid increase can be slowed by infusing D5W or administering DDAVP intranasally realizing that the recommended correction to prevent osmotic demyelination is based on 24 h and not less^[38]. In a thorough review of the literature, we have found dilution of urine in SIAD only under two conditions, infusing isotonic saline at a rate of 16 mL/min for 2 h in the first case of SIAD reported in 1957 and extreme salt restriction in experimentally induced SIAD in normal human subjects^[42,43]. It would appear therefore that the differentiation of SIAD from RSW can be accomplished by noting normalization of a previously increased FEurate as in SIAD or persistence of increased FEurate in RSW after correction of hyponatremia and response to saline infusions (Figures 1, 2, 6 and 7).

By utilizing both strategies and the algorithm in Table 2 and Figure 3 in a completed study of 52 patients with hyponatremia outside of the neurosurgical intensive care unit, we found about an equal number of patients with SIAD, RO and RSW with the majority of patients with RSW to be free of clinical evidence of cerebral disease. The surprising large number of patients with RSW and absence of cerebral disease in more than 80% of these patients supports our previous proposal to change CSW to RSW^[14]. This change has enormous clinical relevance because RSW would not be considered in the absence cerebral disease^[64].

FEphosphate

We have previously stated that an increased FEphosphate > 20% at baseline is consistent with RSW^[21]. We have encountered only one patient with an increased FEphosphate with RSW, but while it might be potentially useful in differentiating SIAD from RSW, there are pitfalls that can alter its value. We have demonstrated in a previous renal micropuncture study that phosphate transport is very sensitive to saline infusions, because parathyroid hormone (PTH) increases rapidly as calcium and possibly magnesium decrease in serum to stimulate PTH release^[65]. Since saline is frequently administered to patients with hyponatremia, determinations of FEphosphate must be performed at baseline or analyzed according to whether or not the patient was receiving saline at the time the test was performed.

CONCLUSION

Hyponatremia, the most common electrolyte, is undergoing fundamental changes that would benefit from a new mindset of abandoning the volume approach. We present an algorithm based on supportive data where the determination of FEurate has been helpful in arriving at a more accurate diagnosis of the causes of hyponatremia. The realization that hyponatremic patients are symptomatic has led to the recommendation to treat virtually all hyponatremics, thus

creating an urgency to differentiate SIAD from RSW because of divergent therapeutic goals. The clinical utility of applying two distinctive pathophysiologic characteristics to distinguish SIAD from RSW, such as: (1) demonstrating normalization of a previously increased FEurate in SIAD and persistent increase in FEurate as in RSW after correction of hyponatremia by water restriction or hypertonic saline or; (2) to note whether infusion of isotonic saline induces excretion of dilute urines with a prompt increase in serum sodium as in RSW or continued excretion of concentrated urines without correction of hyponatremia as in SIAD. Utilization of this pathophysiologic approach has uncovered many with RSW without cerebral disease. So contrary to popular perceptions of the rarity of CSW/RSW, it is probable that the increase in morbidity and mortality associated with hyponatremia may in part be iatrogenic because patients with RSW are being fluid-restricted for an erroneous diagnosis of SIAD. Finally, we feel it is time to abandon the volume approach to patients with hyponatremia and to appreciate the unreliability of determining plasma renin and aldosterone levels because of so many circumstances such as the use of ACE inhibitor, angiotensin II receptor blockers or saline that affect their blood levels, and to be aware of the following comments to which we have supporting data: (1) have less reliance on UNa in RSW and SIAD as sodium excretion is dependent on sodium intake; (2) the misconceptions of having an increased BUN to creatinine ratio in RSW when there is no difference; (3) appreciate the remarkable overlapping of common clinical characteristics between SIAD and RSW (Table 1); and (4) because of the expanding prevalence of RSW occurring in all hyponatremic patients, we must be vigilant in insisting on clearly distinguishing SIAD from RSW in the future and to question previous reports on SIAD, realizing that RSW could be included in significant numbers. We feel we have accumulated enough data to support these final comments and to encourage others to expand our efforts to derive the true prevalence of RSW in a broad population of hyponatremic and normonatremic patients.

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Monoclonal gammopathy of renal significance: Diagnostic workup

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commonly the consequence of renal deposition of monoclonal immunoglobulin or its components. The differential diagnosis is difficult and renal biopsy is essential. To distinguish many of these pathologies is necessary to use techniques that are not always available, even in tertiary central hospitals. This review will discuss the clinical presentation, pathologic features, treatment, prognosis and common diagnostic difficulties of these entities.

Key words: Algorithm; Immunoglobulin; Monoclonal gammopathy of renal significance; M protein; Monoclonal gammopathy of undetermined significance

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Core tip: Monoclonal gammopathy of renal significance is a wide group of kidney diseases. We discuss the most common diagnostic difficulties and suggest an algorithm for clinical approach. Screening for monoclonal immunoglobulin and an appropriate hematologic workup are fundamental and, sometimes a difficult challenge. Kidney biopsy is required to determine the exact nature of the lesion and to evaluate the severity of renal disease. Therefore, clinical and pathologic features are also discussed.

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Abstract

The clinical spectrum of diseases associated with monoclonal gammopathies is wide and they are most

INTRODUCTION

The term monoclonal gammopathy of renal significance (MGRS) is a recent concept, introduced in 2012, to

Table 1 Monoclonal gammopathy of renal significance associated renal lesions

Organized immunoglobulin deposits	
Fibrillar deposits	Immunoglobulin related amyloidosis Fibrillar glomerulonephritis
Microtubular deposits	Immunotactoid glomerulopathy Type I cryoglobulinemic glomerulonephritis
Non-organized immunoglobulin deposits	
Monoclonal	Light chain deposition disease
Immunoglobulin	Light and heavy chain deposition disease
Deposition disease	Heavy deposition disease
Proliferative glomerulonephritis with monoclonal IgG deposits	
C3 glomerulopathy with monoclonal gammopathy	

distinguish the nephropathic nature of these diseases from the truly benign monoclonal gammopathy of undetermined significance^[1-3].

Renal damage is caused by the deposition of secreted monoclonal immunoglobulin (MIg) or its fragments, produced by a B-cell or plasma cell clone. They are heterogeneous in nature and are not always related to the presence of a detectable M component in serum and/or urine.

The immunoglobulin (Ig) deposits associated to MGRS can be classified into two categories (Table 1). The first is characterized by organized deposits: Immunoglobulin related amyloidosis, fibrillar glomerulonephritis, immunotactoid and type I cryoglobulinemic glomerulonephritis. The second disease category is characterized by non-organized electro-dense granular deposits in clinical pathological entities as MIg deposition disease, proliferative glomerulonephritis with monoclonal IgG deposits and C3 glomerulopathy with monoclonal gammopathy. We decided to address only diseases with glomerular involvement.

Several mechanisms that induce injury have been described, such as deposition and precipitation of MIg in the different components of the kidney (glomeruli, vessels, interstitium)^[4], dysregulation of the complement pathway by the MIg^[5], and the MIg itself acting like autoantibodies against complement factor or phospholipase A2 receptor^[6]. Other mechanisms are still unknown.

Diagnostic workup

Screening for MIg and an appropriate hematologic workup are essential. It should include serum (SPEP), urine electrophoresis, immunofixation studies and free light-chain assays (FLC) if conventional electrophoresis studies are negative. FLC is more sensitive for the detection of light chains than urine immunofixation. Results may be affected by the presence of renal failure, but a Kappa(κ)/lambda(λ) light-chain ratio > 3.0 is unlikely to be due to renal insufficiency alone.

MIg may be undetectable by these methods reflecting the "small" size of the underlying clone.

It is mandatory to characterize the clone by bone

marrow aspirate and biopsy, to establish the therapeutic strategy.

The M protein in light chain deposition disease can be identified by FLC, however only 25%-76% of the cases can be identified by SPEP or immunofixation studies^[2,4]. In light chain amyloidosis, SPEP and immunofixation can identify the M protein in 66%-80% of the cases and FLC in 76%-88%^[2].

A review of systems especially renal, cardiac, skin and nervous system should be performed when evaluating patients with monoclonal gammopathy.

Kidney biopsy is therefore required to determine the exact nature of the lesion and severity of renal disease, and in most situations, detailed immunofluorescence (IF) and electron microscopic (EM) studies are needed to allow the identification of deposits composition and pattern of organization (Figure 1).

Hence, with such difficulties diagnosing and classifying these diseases, it is easy to understand that misdiagnosis and delayed treatment can occur, with an adverse impact on renal and patient prognosis. In this review we discuss the diagnostic approach, clinical and pathologic features of MGRS lesions related to Ig deposits and the diagnostic difficulties posed in the clinical practice.

ORGANIZED FIBRILLAR IG DEPOSITS

Immunoglobulin related amyloidosis

Free Ig subunits secreted by a single clone of B cells, mostly light chains (λ or κ isotype), are the cause of the most common and severe amyloidosis affecting the kidney. The fibrils in Ig light chain (AL) amyloidosis are derived from the variable region of λ light chains in approximately seventy-five percent of cases, and κ in the remaining^[7,8]. The involvement of an Ig heavy chain in amyloidosis (heavy chain only - AH; and heavy chains and light chains - AHL amyloidosis) remains extremely rare.

By light microscopy, amyloid deposits are amorphous and acellular pale eosinophilic material. The glomeruli may show massive amyloid deposits, typically without increase in cellularity. Amyloid deposits may also involve arterioles, arteries, interstitium and tubules. Definitive diagnosis is made by Congo red stain detecting apple-green birefringence under polarized light^[8,9]. By EM, amyloid appears as nonbranching fibrils with a diameter of 8 to 10 nm^[9].

On IF microscopy, the staining for a single AL with negativity for Ig heavy chain, is diagnostic of AL. Deposition of the variable region explains why IF microscopy with anti- λ and anti- κ light chain antibodies is often weakly positive^[10]. It is important to be aware that the absence of reactivity for either heavy or light chain does not rule out AL/AH/AHL disease^[9].

Problematic amyloid cases, such as those with equivocal IF (which is more frequent with heavy chains than with light chains) can be accurately typed by laser

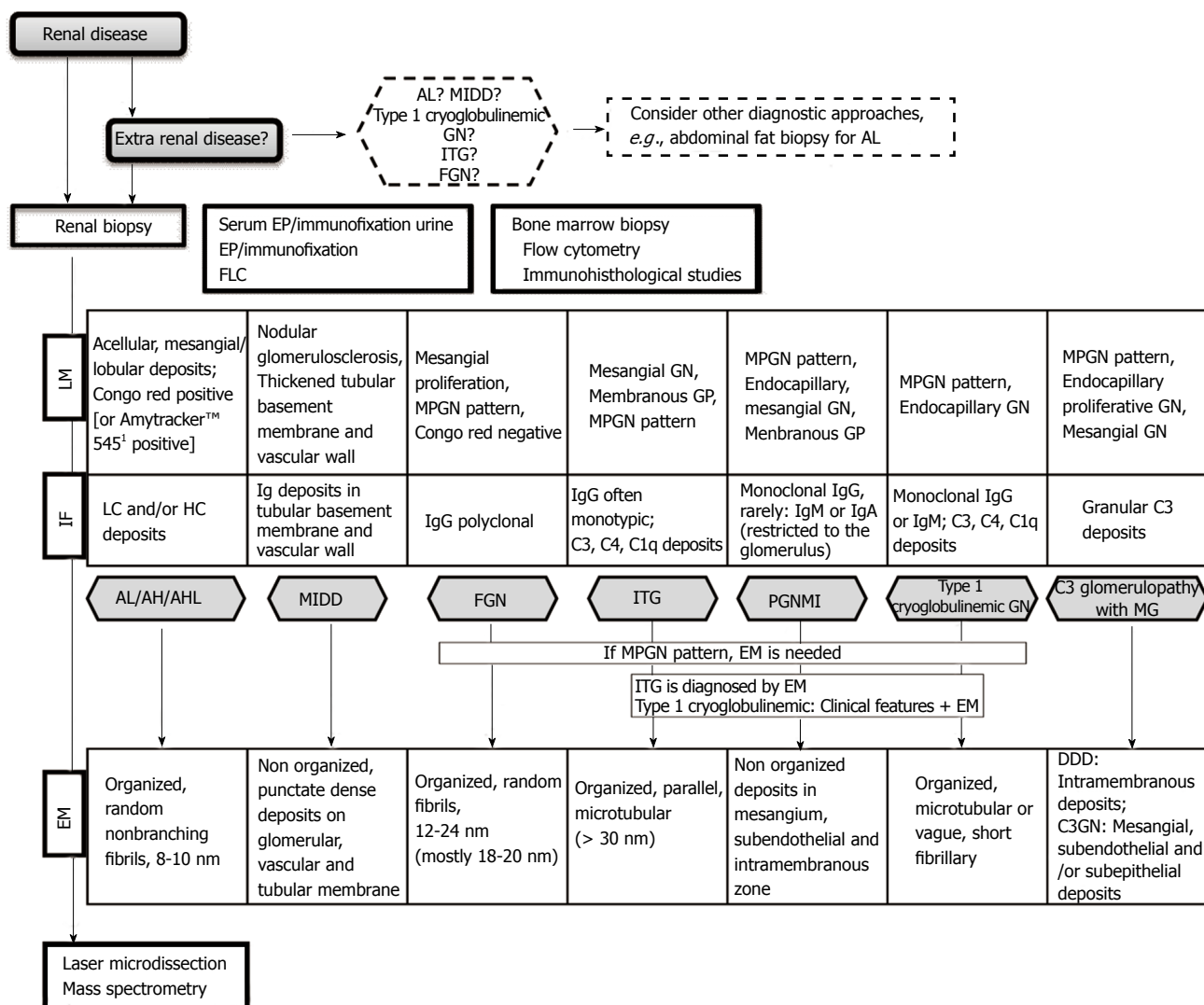


Figure 1 Diagnostic work up. ¹New sensitive method for early detection of amyloidosis in humans^[36]. AH: Immunoglobulin heavy chain; AHL: Immunoglobulin heavy and light chain; AL: Immunoglobulin light chain; C3GN: C3 glomerulonephritis; DDD: Dense deposits disease; EM: Electronic microscopy; EP: Electrophoresis; FGN: Fibrillary glomerulonephritis; FLC: Free light chain assay; GN: Glomerulonephritis; GP: Glomerulopathy; IF: Immunofluorescence; Ig: Immunoglobulin; ITG: Immunotactoid glomerulonephritis; LC: Light chain; LM: Light microscopy; MG: Monoclonal gammopathy; MIDD: Monoclonal immunoglobulin deposition disease; MPGN: Membranoproliferative glomerulonephritis; PGNMID: Proliferative glomerulonephritis with monoclonal immunoglobulin deposits.

microdissection and mass spectrometry. This methods can identify the type of renal amyloidosis in more than 97% of cases, and can distinguish it from non-amyloid fibrillar glomerulonephritis^[8,11,12].

The majority of patients will have a detectable serum and/or urinary M protein. All patients require immunofixation of serum and urine and FLC ratio.

AL/AH/AHL are associated with a higher degree of proteinuria and a higher frequency of nephrotic syndrome compared with the other types of amyloidosis^[12]. On presentation renal impairment may be present.

The goal of current treatment approaches for AL amyloidosis is to eradicate the clonal plasma cells that produce the amyloidogenic light chain. The prognosis of AL amyloidosis has improved substantially during the past decade with the increasing use of aggressive anti-plasma cell treatment^[9].

Fibrillary glomerulonephritis

Fibrillary glomerulonephritis (FGN) is a rare primary glomerular disease. The fibrillar deposits have larger thickness than amyloid and are Congo red negative^[13,14]. However, size alone, is an insufficient criterion for the diagnosis^[13]. Light microscopy typically shows mesangial proliferation and a membranoproliferative glomerulonephritis (MPGN) pattern. The fibrils are deposited in the mesangium, glomerular basement membranes, or both. Tubular or interstitial deposits are rare. On IF, polyclonal glomerular Ig deposits (typically IgG, and light chains) are more common than monotypic glomerular deposits^[15]. Occasionally staining for IgG may occur in a membranous pattern and IgG4 is the dominant subclass. The mesangial staining suggests the specific diagnosis, confirmed by negative Congo red stain and by EM. The EM findings show the presence of randomly aligned fibrils that resemble amyloid fibrils but

are larger.

In a case series report, one third of the cases occurred in patients with history of malignancy (most commonly carcinoma) or autoimmune diseases (most commonly Crohn's disease, systemic lupus, Graves' disease, and idiopathic thrombocytopenic purpura)^[16]. These cases should not be considered MGRS. In the same case series^[16], 11% stained for IgG and light chains, which can lead to believe that the FGN is also a type of MGRS. M-spike was detected by SPEP/immunofixation in only 16% of 61 patients with fibrillary glomerulonephritis from a case series of a single medical center^[16].

Clinically, FGN most often presents in middle aged to older patients. Patients typically present with proteinuria, 50% within nephrotic range, with or without renal insufficiency, hematuria or hypertension^[15-17]. The outcome is frequently poor, progression to end-stage renal disease occurs in approximately half of the patients within years^[15-17].

The differential diagnosis between other MPGN can be difficult without EM, which can delay the treatment targeted to the B cell or plasma cell clone. However an optimal treatment are yet to be demonstrated and prospective and controlled studies are needed to determine the appropriated therapeutic regimen. There is an ongoing phase 2 clinical trial to evaluate Rituximab as a treatment option^[18]. Recurrence (20%) in transplant allograft has been reported^[15].

ORGANIZED MICROTUBULAR IG DEPOSITS

Immunotactoid glomerulopathy

Immunotactoid (microtubular) glomerulopathy (ITG) is a glomerular disease characterized by the presence of Congo red negative organized glomerular deposits generally limited to the glomerulus, stain by IF for IgG (in most cases monoclonal) and complement. Renal biopsy shows lobular MPGN or membranous pattern^[13,15,19]. The microtubular structure often measure > 30 nm in diameter by EM and are often organized in parallel arrays^[17]. ITG occurs in an older population and is typically presented as a nephrotic syndrome. Hypocomplementemia is common^[15,17].

Underlying hematologic malignancy is frequent, and the most common is chronic lymphocytic leukemia (in contrast to AL amyloidosis and monoclonal immunoglobulin deposition disease in which the most common is myeloma)^[13,19]. Lymphoplasmacytic lymphoma and MGRS are also common^[13,19].

FGN and ITG can be overlooked when EM is not performed. Even with EM, the diagnosis can be difficult in a variety of circumstances: When fibrils are subepithelial; when they have an atypical ultrastructural appearance; when deposits of cryoglobulins are microtubular and indistinguishable from these; and when fibrils or microtubules are of a smaller admeasured size^[17].

Type I cryoglobulinemic glomerulonephritis

Cryoglobulinemia is defined as the presence of circulating immunoglobulins that precipitate with cold temperature and dissolve with rewarming. Type I cryoglobulinemia consist of a single monoclonal immunoglobulin (usually of IgG or IgM class), while types II and III are mixed cryoglobulinemias, with a monoclonal component in type II and only polyclonal immunoglobulins in type III^[20,21]. By light microscopy typical features are membranoproliferative or endocapillary proliferative glomerulonephritis with intraluminal periodic acid-Schiff positive (hyaline-like) deposits. IF microscopy demonstrates the presence of IgM and IgG as well as complement components. On EM, deposits are predominantly subendothelial and intracapillary. They may have a vague short fibrillar substructure, and sometimes a tubular configuration.

Type I cryoglobulin is associate with plasma cell dyscrasias or B-cell lymphoproliferative disorders (multiple myeloma, Waldenstrom macroglobulinemia, chronic lymphocytic leukemia, B-cell non-Hodgkin lymphoma, MGRS, and hairy cell leukemia)^[20]. Occurrence of cutaneous involvement (palpable purpura) is frequent and neurologic manifestations can vary from pure sensory axonopathy to mononeuritis multiplex^[20]. Hypocomplementemia is not as frequent as in type II cryoglobulinemia^[21].

The treatment of this entity is primarily directed to the underlying hematologic malignancy^[20].

NON-ORGANIZED IG DEPOSITS

Monoclonal immunoglobulin deposition disease

In clinical and pathologic terms, light-chain, light and heavy chain, and heavy chain deposition disease (LCDD, LHCD, HCDD, respectively) are similar and may therefore be referred as monoclonal immunoglobulin deposition disease (MIDD)^[4,22]. The majority of kidney diseases in MIDD are secondary to deposition of light chains (κ in most cases) instead of heavy chains or intact Ig^[23]. These forms differ from amyloidosis in that the deposits lack affinity for Congo red and do not have a fibrillar organization.

Usually they show nodular sclerosing lesions and thickening of tubular basement membranes on light microscopy; a membranoproliferative pattern has also been described. Diffuse linear staining of monoclonal light/heavy chains along the glomerular and tubular basement membranes is shown on IF and punctate dense deposits along the glomerular and tubular basement membranes on EM^[4,24].

The deposits in HCDD are composed of the Ig heavy chain, which typically lacks the first constant domain (CH1). IgD deposition disease was recently described based on laser microdissection and mass spectrometry in which the IF studies were negative for Ig deposits^[25].

MIDD is typically diagnosed in the sixth decade, in the presence of renal insufficiency and proteinuria, often

accompanied by nephrotic syndrome or hypertension. It can occur in the absence of a detectable malignant process, even after prolonged follow-up^[4]. In some case series clinical evidence of dysproteinemia was frequent, with myeloma and MGRS being described^[4,24]. Treatment of the underlying dysproteinemia should be considered, and studies have shown that chemotherapy and stem cell transplantation are an effective therapy for renal dysfunction in MIDD^[24,26,27]. Recurrence in transplant allograft has been reported^[24].

Proliferative glomerulonephritis with monoclonal IgG deposits

Monoclonal gammopathy is an important cause of membranoproliferative glomerulonephritis pattern, which is an immune complex-mediated glomerulonephritis characterized by subendothelial and mesangial immune complexes deposition. Nars and colleagues, described this entity of proliferative glomerulonephritis associated with monoclonal IgG deposition^[28]. A similar entity with deposition of monoclonal IgM or IgA has been described^[29,30].

IF demonstrates deposits restricted to the glomerulus that stained for a single light-chain isotype and a single heavy-chain subtype, most commonly IgG3^[31]. EM reveals mesangial, subendothelial and intramembranous granular non-organized deposits.

In cases of endocapillary proliferative or membranoproliferative glomerulonephritis in which the deposits stain for IgG and a single light chain, differential diagnoses should be made with type 1 cryoglobulinemic glomerulonephritis, and ITG^[28]. The diagnosis of ITG is established by EM and type 1 cryoglobulinemic glomerulonephritis should be excluded by clinical features. A specific clone was identified in 5% to 25% in some case series^[28,31].

Proliferative glomerulonephritis with monoclonal IgG deposits is typically presented with proteinuria, variable degrees of hematuria, renal insufficiency and hypertension. Hypocomplementemia (mostly of the C3 component) is frequent.

Treatment recommendations are based on clinical experience with small numbers of patients. Immunosuppressive therapy have been used with variable outcomes^[32].

C3 glomerulopathy with monoclonal gammopathy

C3 glomerulopathy is characterized by the accumulation of complement component C3 in glomeruli caused by abnormal control of complement activation, degradation or deposition.

On light microscopy it could show a variety of appearances: Mesangial proliferation, membranoproliferative pattern, endocapillary proliferation or crescent formation. C3 glomerulonephritis (C3GN) and dense deposit disease (DDD) are its subtypes and can be distinguished by EM. DDD is characterized by replacement of the basement membrane by highly electron dense deposits. C3GN is characterized by mesangial, subendothelial and/

or subepithelial granular deposits that are less electron dense^[33,34].

C3 glomerulopathy could be an unusual complication of plasma cell dyscrasia^[35]. Monoclonal protein (which in this case, does not deposit in the glomeruli) can interfere with complement regulating proteins such as factor H, and act as a C3 nephritic factor resulting in a pathological activation of the alternative pathway of complement.

The clinical presentation is usually with hematuria, proteinuria with or without renal insufficiency. Serum C3 levels can be low.

The optimal treatment remains undefined. There have been contradictory reports in published literature, about the efficacy of treatment based on glucocorticoid, mycophenolate mofetil, and rituximab^[5,33]. There are many ongoing innovative approaches using eculizumab^[33]. Studies have been reported in which the use of eculizumab in dense deposit disease and C3 glomerulonephritis resulted in proteinuria reduction and/or serum albumin normalization and/or creatinine decrease^[33].

The risk for recurrence of C3 glomerulopathy is high, but one must take into account that all these results are based on small data sets^[33].

In order to facilitate and summarize the clinical approach of the different entities mentioned above, we decided to build up a diagnostic work up algorithm, which we here propose (Figure 1).

CONCLUSION

Monoclonal immunoglobulin can cause a variety of renal diseases resulting from the direct renal deposition and precipitation or, from an indirect mechanism, for example, *via* dysregulation of the complement pathway.

In this group of renal disorders the differential diagnosis can be a clinical challenge and that's why we considered that an algorithm for the approach has to be developed and improved.

A common clinical challenge begins with the identification of the underlying clone. Standardized diagnostic evaluations need to be carried out as summarize above. Diagnosis requires a detailed hematologic evaluation and kidney biopsy. Morphologic alterations on light microscopy and immunofluorescence often need to be integrated with the changes on electron microscopy.

The lack of experience in dealing with these diseases can delay treatment. Increased cognizance and appreciation of this clinical-pathological entity and associated treatment options may improve patient outcomes.

Successful treatment is based on chemotherapy that should be adapted to the underlying clone and renal function. A multidisciplinary team consisting of nephrologists and hematologists should take responsibility for an individualized therapeutic approach as no standardized treatments based on prospective studies exist.

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Retrospective Study

Acute kidney injury following spinal instrumentation surgery in children

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Author contributions: Jöbsis JJ and Alabbas A contributed equally in data collection and drafting the manuscript; Mammen C designed and supervised the study; Reilly C and Mulpuri K revised the manuscript for important intellectual content; Milner R offered statistical support; all authors have read and approved the final version to be published.

Institutional review board statement: This study is retrospective, involving anonymous clinical data without affecting the patient's rights and welfare. The study was reviewed and approved by the BC Children's Hospital/University of British Columbia Institutional Review Board.

Informed consent statement: As per the BC Children's Hospital Institutional Review Board, informed consent was not required for this retrospective study. Subjects are not identifiable from any data presented in this manuscript.

Conflict-of-interest statement: None of the authors have any conflicts of interest related to this research topic.

Data sharing statement: Technical appendix, statistical code and dataset available from the corresponding author at jjobsis@tergooi.nl. Informed consent was not obtained, but the presented data are anonymized and risk of identification is low.

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Abstract

AIM

To determine acute kidney injury (AKI) incidence and potential risk factors of AKI in children undergoing spinal instrumentation surgery.

METHODS

AKI incidence in children undergoing spinal instrumentation surgery at British Columbia Children's Hospital between January 2006 and December 2008 was determined by the Acute Kidney Injury Network classification using serum creatinine and urine output criteria. During this specific time period, all patients following spinal surgery were monitored in the pediatric intensive care unit and had an indwelling Foley catheter permitting hourly urine output recording. Cases of AKI were identified from our database. From the remaining cohort, we selected group-matched controls that did not satisfy criteria for AKI. The controls were matched for sex, age and underlying diagnosis (idiopathic vs non-idiopathic scoliosis).

RESULTS

Thirty five of 208 patients met criteria for AKI with an incidence of 17% (95%CI: 12%-23%). Of all children who developed AKI, 17 (49%) developed mild AKI (AKI Stage 1), 17 (49%) developed moderate AKI (Stage 2) and 1 patient (3%) met criteria for severe AKI (Stage 3). An inverse relationship was observed with AKI incidence and the amount of fluids received intra-operatively. An inverse relationship was observed with AKI incidence and the amount of fluids received intra-operatively classified by fluid tertiles: 70% incidence in those that received the least amount of fluids *vs* 29% that received the most fluids (> 7.9 , $P = 0.02$). Patients who developed AKI were more frequently exposed to nephrotoxins (non steroidal anti inflammatory drugs or aminoglycosides) than control patients during their peri-operative course (60% *vs* 22%, $P < 0.001$).

CONCLUSION

We observed a high incidence of AKI following spinal instrumentation surgery in children that is potentially related to the frequent use of nephrotoxins and the amount of fluid administered peri-operatively.

Key words: Acute kidney injury; Epidemiology; Acute Kidney Injury Network; Spinal surgery; Children

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Core tip: We are the first to report a high incidence of acute kidney injury (AKI) of 17% in children undergoing orthopaedic spinal instrumentation surgery utilizing the Acute Kidney Injury Network definition. A relationship was observed between the development of AKI and the use of nephrotoxins including non-steroidal anti-inflammatory drugs and lower amounts of intravenous fluid administered peri-operatively. These results suggest that there are modifiable AKI risk factors with the potential of reducing AKI incidence in this understudied population. Further prospective studies with the use of novel AKI biomarkers are needed to validate our novel results.

Jöbsis JJ, Alabbas A, Milner R, Reilly C, Mulpuri K, Mammen C. Acute kidney injury following spinal instrumentation surgery in children. *World J Nephrol* 2017; 6(2): 79-85 Available from: URL: <http://www.wjgnet.com/2220-6124/full/v6/i2/79.htm> DOI: <http://dx.doi.org/10.5527/wjn.v6.i2.79>

INTRODUCTION

Over the past decade, there has been a major epidemiological shift in paediatric acute kidney injury (AKI) etiology. Previously, AKI was most often caused by primary renal diseases. Currently, the majority of AKI cases are related to secondary insults including sepsis and nephrotoxins. A high incidence of AKI has been

reported in various paediatric populations including 5% of all paediatrics hospitalizations, 10%-17.9% of paediatric intensive care unit (PICU) admissions, 82% of the most severely-ill children admitted to the PICU and up to 62% of infants following cardiac surgery^[1-7]. Several studies have also revealed an increased morbidity and mortality associated with pediatric AKI in critically-ill children and an increased risk of chronic kidney disease in survivors of AKI^[1-8].

Outside of cardiac surgery patients, the epidemiology of AKI has not been well studied in other paediatric surgical populations including those undergoing major orthopaedic surgeries. The aim of this retrospective study was to define the incidence of AKI in children following spinal instrumentation surgery and to identify potential modifiable risk factors that may direct potential change in future practice.

MATERIALS AND METHODS

We performed a nested case-control study of children undergoing orthopaedic spinal instrumentation surgery for scoliosis at BC Children's Hospital (Vancouver, Canada). From a local database, we identified a cohort of 208 patients who had undergone spinal instrumentation surgery at our centre between January 2006 and December 2008. During this specific time period, all patients following spinal surgery were monitored in the PICU for at least 24 h post-operatively. All patients had an indwelling Foley catheter during their stay in the PICU with hourly urine output recording. Cases of AKI were identified from our database using the following criteria as per the Acute Kidney Injury Network (AKIN) definition: A 50% rise in serum creatinine (SCr) and/or urine output (U/O) < 0.5 mL/kg per hour for at least 6 h. AKIN staging criteria (stages 1-3), are shown in Table 1. From the remaining cohort, we selected group-matched controls that did not satisfy criteria for AKI. The controls were matched for sex, age and underlying diagnosis (idiopathic *vs* non-idiopathic scoliosis) (Figure 1). Abstracted data from our database included demographics (age at surgery, gender), pre-operative data (weight and height, hemoglobin, SCr, serum sodium, baseline blood pressure), intra-operative data (duration of surgery, intravenous fluid intake, urine output, blood pressure monitoring, use of nephrotoxins including non-steroidal anti-inflammatory drugs (NSAIDs) and aminoglycosides as well as post-operative data from the PICU and hospital admissions (serial SCr measurements, serum sodium, hourly urine output until Foley catheter removed, fluid intake, nephrotoxin use, ICU/hospital length of stay, and mortality). Data were supplemented, if required, with further chart review. Study data were collected and managed using REDCap electronic data capture tools hosted at BC Children's Hospital.

All statistical analyses were performed with SPSS software (v 18.0; IBM SPSS Software for Predictive Analytics). Continuous variables following a normal

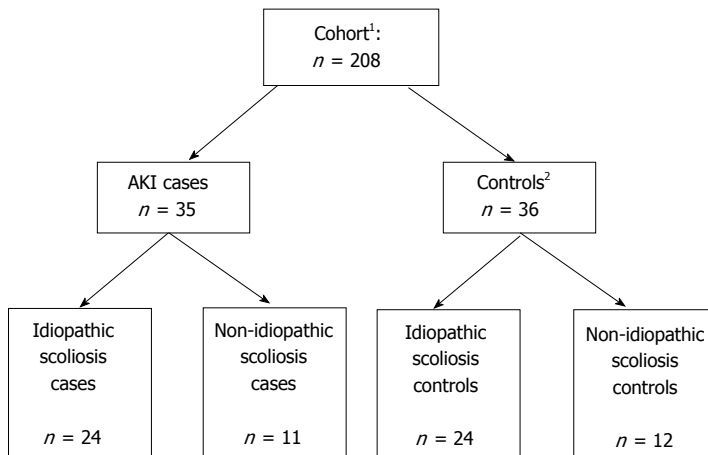


Figure 1 Patient flow chart. ¹The cohort consists of all patients undergoing spinal instrumentation surgery between January 2006 and December 2008 at British Columbia Children's Hospital (Vancouver, Canada); ²Controls were matched for sex, age, and underlying diagnosis (idiopathic vs non-idiopathic scoliosis).

Table 1 Acute Kidney Injury Network criteria

Acute Kidney Injury Network criteria	Stage 1	Stage 2	Stage 3
Serum creatinine	1.5-1.9 times baseline or ≥ 0.3 mg/dL (≥ 26.5 μmol/L) increase	2.0-2.9 times baseline or ≥ 4 mg/dL (353.6 μmol/L) increase or Need for RRT	3.0 times baseline or ≥ 4 mg/dL (353.6 μmol/L) increase or Need for RRT
Urine output	< 0.5 mL/kg per hour for ≥ 6-12 h	< 0.5 mL/kg per hour for ≥ 12 h	< 0.3 mL/kg per hour for ≥ 24 h or Anuria ≥ 12 h

Table 2 Baseline patient characteristics

Variables	AKI (n = 35)	Non-AKI (n = 36)	Total (n = 71)
Age (yr)	15.4 ± 1.75	14.4 ± 1.95	14.9 ± 1.90
Sex (male)	9 (26%)	6 (17%)	15 (21%)
Idiopathic scoliosis	24 (69%)	24 (67%)	48 (68%)
Weight (kg)	56.5 ± 16.0	45.2 ± 11.9	50.7 ± 15.1
Height (cm)	161 ± 9.8	155 ± 10.6	158 ± 10.6
BSA (kg/m ²)	1.58 ± 0.27	1.38 ± 0.23	1.48 ± 0.27
Pre-op syst BP (mmHg)	116 ± 13.4	113 ± 9.8	114 ± 11.7
Pre-op diast BP (mmHg)	71 ± 11.1	71 ± 8.9	71 ± 9.9
Baseline creatinine (μmol/L)	49.9 ± 15.2	47.4 ± 13.1	48.7 ± 14.1
Baseline Hb (g/L)	138 ± 11.7	137 ± 13.1	137 ± 12.4

AKI: Acute kidney injury; Hb: Hemoglobin; BSA: Body surface area; BP: Blood pressure.

distribution were expressed as mean and standard deviation (SD). Variables following a non-normal distribution were expressed as median and interquartile range (IQR). Categorical variables were expressed as proportions. Two-sided *t* tests were used to compare means. χ^2 test was used to compare proportions. Mann-Whitney *U* test and Kruskal-Wallis tests were used to compare medians as appropriate. In all analyses, a *P* value < 0.05 was considered statistically significant. We divided patients into tertiles based on their intra-operative fluid administration in milliliter/kilogram per hour (corrected for patient size and duration of surgery) to explore the relationship between intra-operative fluid practices and AKI (comparison of AKI incidence between fluid tertiles). We also identified peri-operative (surgical or ICU) nephrotoxin exposure in each of the fluid tertiles to determine the relationship of fluid administration and nephrotoxin exposure to the development of AKI.

RESULTS

Incidence, timing, and severity of AKI

Thirty five of the 208 patients met criteria for AKI with an incidence of 17% (95%CI: 12%-23%). A total of 36 patients were selected as controls. Table 2 lists the patient baseline pre-operative characteristics. No clinically significant differences were noted between AKI and non-AKI patients including demographics, pre-operative renal function, and haemoglobin levels. Forty-

eight (68%) of patients had surgery for "idiopathic" scoliosis. Twenty three (32%) had surgery for "non-idiopathic" scoliosis with primary diagnoses including Cerebral Palsy (11), Spondylolisthesis (4), Spina Bifida (2), Arnold-Chiari malformation (3) and miscellaneous (3). No patient had an elevated serum creatinine for age before surgery to suggest pre-operative AKI. However, patients with non-idiopathic scoliosis had a significantly lower baseline serum creatinine value of 38 μmol/L (SD 14.8) compared to 54 μmol/L (SD 10.9) in patients with idiopathic scoliosis (*P* = 0.05).

Of all children who developed AKI, 17 (49%) developed mild AKI (AKIN Stage 1), 17 (49%) developed moderate AKI (AKIN stage 2) and 1 patient (3%) met criteria for severe AKI (AKIN stage 3). All patients met criteria for AKI based on urine output while only 2 patients met criteria for both serum creatinine and urine output change. Patients who met criteria for AKIN stages 1 and 2 did so after a mean of 9.1 (SD 4.2) and 13.8 (SD 3.4) h following admission to PICU respectively. The single patient with severe AKI based on urine output developed oliguria 24 h after PICU admission. The mean maximum serum creatinine rise (% from baseline) was higher in patients with AKI (0%, SD ± 22%) compared to patients without AKI (-7%, SD ± 12%), but did not reach statistical significance (*P* = 0.09).

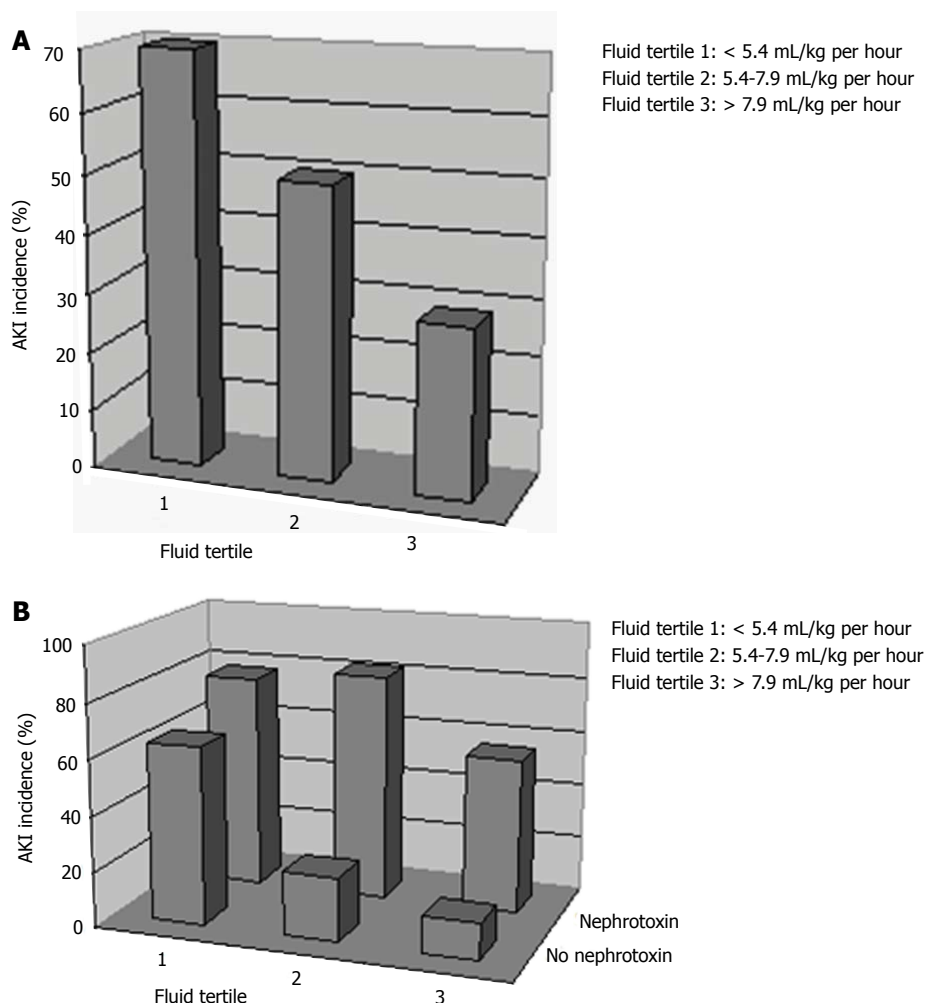


Figure 2 Acute kidney injury incidence according to intra-operative fluid management and nephrotoxin exposure. A: Acute kidney injury (AKI) incidence according to fluid tertile: Fluid tertile 1 (70%) vs fluid tertile 2 (50%) vs fluid tertile 3 (29%) ($P = 0.02$); B: AKI incidence according to fluid tertile and nephrotoxin exposure: Fluid tertile 1 with nephrotoxin exposure (75%) vs fluid tertile 3 with no nephrotoxin exposure (10%) ($P = 0.04$).

Intra-operative course

Table 3 compares several intra-operative and post-operative (PICU admission) variables between AKI and non-AKI patients. Overall, mean duration of surgery was 8.4 h (SD 2.3 h). Duration of surgery, decreases in blood pressure during surgery, percentage requiring blood transfusions, and decreases in haemoglobin levels were similar in AKI and non-AKI patients (all $P > 0.05$). There was wide practice variation in intra-operative fluid volume administration between patients. All intravenous fluid administered was isotonic. The mean recorded urine output during surgery was 2.1 (SD 1.4) mL/kg per hour and was not statistically different between AKI and non-AKI patients [1.9 mL/kg per hour (SD 1.1) vs 2.4 mL/kg per hour (SD 1.5) respectively ($P = 0.17$)]. We classified all children into tertiles according to intra-operative fluids received, corrected for patient weight and surgery duration: < 5.4 mL/kg per hour, 5.4-7.9 mL/kg per hour, and > 7.9 mL/kg per hour. An inverse relationship was observed with the incidence of AKI and the amount of fluids received intra-operatively: 70%, 50%, 29% AKI incidence in the 1st, 2nd and 3rd fluid tertiles respectively ($P = 0.02$) (Figure 2A). The

lowest recorded mean intra-operative serum sodium was 138 mmol/L (SD 2.4) while 4 patients (2%) developed hyponatremia during surgery (serum sodium < 135 mmol/L). During surgery, 14 out of 71 patients (19.7%) were exposed to a nephrotoxic medication (either aminoglycosides or NSAIDs). The majority of these patients (78.6%) received a dose of intravenous Ketorolac (NSAID) while 21.4% were exposed to intravenous Gentamycin (aminoglycoside). Overall, there was no difference in intra-operative nephrotoxin exposure between AKI and control groups (23% vs 17%) ($P = 0.5$).

Post-operative course

A detailed summary of post-operative variables in AKI and non-AKI patients is shown in Table 2. Mean urine output was reduced at 0.9 (SD 0.4) mL/kg per hour during the PICU admission. Patients who developed AKI post-operatively had significantly lower urine output (0.7 mL/kg per hour vs 1.1 mL/kg per hour) and a higher cumulative fluid balance (positive 1.3 L vs positive 0.8 L) compared to control patients during their PICU admission (both $P < 0.05$). The lowest recorded mean

Table 3 Intra-operative/post-operative course

	AKI (<i>n</i> = 35)	Non-AKI (<i>n</i> = 36)	<i>P</i> value
Intra-operative course			
Duration of surgery (h)	8.5 ± 2.4	8.2 ± 2.1	0.54
Cumulative intra-operative fluid administration (mL)	2555 ± 973	2732 ± 1264	0.51
Cumulative intra-operative fluid administration (mL/kg per hour)	6.2 ± 2.9	7.5 ± 3.3	0.08
Intra-operative urine output (mL/kg per hour)	1.9 ± 1.1	2.4 ± 1.5	0.17
Intra-operative fluid balance (L)	1.2 ± 1.0	1.3 ± 1.1	0.70
Max BP decline during surgery			
Systolic (% from baseline)	27 ± 12	33 ± 14	0.36
Diastolic (% from baseline)	30 ± 9	34 ± 13	0.93
Patients requiring blood transfusion [<i>n</i> (%)]	7 (20%)	12 (33%)	0.21
Nephrotoxin exposure [<i>n</i> (%)]	8 (23%)	6 (17%)	0.51
Post-operative course			
Duration of PICU stay (d)	1 (IQR 0, range 17)	1 (IQR 0, range 6)	0.77
Cumulative PICU fluid administration (mL)	2069 (IQR 886)	1918 (IQR 1048)	0.15
Cumulative PICU fluid administration (mL/kg per hour)	2.1 ± 0.8	2.3 ± 0.7	0.31
PICU urine output (mL/kg per hour)	0.7 ± 0.4	1.1 ± 0.4	< 0.001
PICU fluid balance (L)	1.3 ± 1.0	0.8 ± 0.8	0.02
Max Hb drop (% from baseline)	26 ± 9	26 ± 10	0.94
Nephrotoxin exposure in PICU	18 (51%)	4 (11%)	< 0.001

AKI: Acute kidney injury; PICU: Paediatric intensive care unit.

post-operative serum sodium was 137 mmol/L (SD 2.8). Overall, 10 patients (14%) developed hyponatremia either during surgery or post-operatively. In patients who developed hyponatremia, the mean value of lowest sodium recorded was 133 mmol/L (SD 1.5). Patients who developed AKI were exposed to nephrotoxins (either aminoglycosides or NSAIDs) more frequently than control patients during their PICU admission (51% vs 11%, $P < 0.001$). Ninety-one percent of the patients exposed to NSAIDs received intravenous Ketorolac while the remainder received oral Ibuprofen. All patients with aminoglycoside exposure received intravenous Gentamycin. Overall, 21/35 (60%) patients who developed AKI were exposed to a nephrotoxic medication either during surgery or ICU admission compared to 8/36 (22%) of controls ($P = 0.001$). Figure 2B shows the relationship of intra-operative fluid administration and peri-operative nephrotoxin exposure on the development of AKI. The highest incidence of AKI was seen in patients exposed to less amounts of fluids intra-operatively (1st and 2nd fluid tertiles) while also being exposed to a nephrotoxin (75% and 80% AKI incidence respectively) while the lowest AKI incidence was observed in patients exposed to the highest amounts of fluids (3rd fluid tertile) with no exposure to a nephrotoxin (10% AKI incidence) ($P = 0.04$). Thirteen patients (18%) required mechanical ventilation in PICU with a mean duration of 1.8 (SD 1.2) d. Of those 13 children, 7 (20%) were in the AKI group vs 6 (17%) in the non-AKI group. Children with AKI were ventilated longer (mean 2.2 d vs 1.4 d in the control group; however this difference was not statistically significant ($P = 0.7$).

Mortality and hospital/PICU length of stay

There were no cases of mortality seen in any of the patients following surgery. Median hospital length of

stay in all patients was 6 d (IQR 3, range 4-49 d). Median ICU length of stay in all patients was 1 d (IQR 0, range 0-18 d). ICU length of stay was similar in AKI (median 1 d, IQR 0 d, range 17 d) and non-AKI patients (median 1 d, IQR 0 d, range 6 d) ($P = 0.95$). Similarly, hospital length of stay was similar in patients with AKI (median 6 d, IQR 3 d, range 25) and without AKI (median 6 d, IQR 2 d, range 45 d, $P = 0.77$). However, the single patient with severe AKI (AKIN stage 3) had a more prolonged PICU and hospital length of stay at 4 and 12 d respectively.

DISCUSSION

We report a high estimated AKI incidence of 17% in children undergoing orthopaedic spinal instrumentation surgery utilizing a standardized AKI definition. A number of recent adult studies have reported AKI incidences from 3.9%-16% following major orthopaedic surgeries^[9-11]. There have been no prior epidemiological AKI studies in any paediatric orthopaedic populations.

In our cohort, no patient had pre-existing kidney dysfunction prior to surgery, which suggests that our high incidence of AKI may be primarily related to peri-operative risk factors. We identified 2 potential risk factors that may be related to the development of AKI in this population: (1) lower intravenous fluid exposure in the intra-operative period; and (2) high peri-operative nephrotoxin exposure with 60% of the AKI population being exposed to NSAIDs or aminoglycosides. The exact interaction between peri-operative fluid and nephrotoxin exposure towards the development of AKI cannot be determined in our retrospective analysis, but our results suggest that patients who are exposed to the highest amounts of fluids intra-operatively without nephrotoxin exposure may be more protected against

AKI. Interestingly, a recent adult orthopaedic study showed that peri-operative dehydration, administration of NSAIDs, and use of nephrotoxic antibiotics were all independently associated with the development of post-operative kidney dysfunction^[11]. According to a large epidemiological study analyzing the most common AKI etiologies in children, AKI related to nephrotoxin exposure accounts for up to 16% of in-hospital paediatric AKI^[12]. Outside of fluid intake and use of nephrotoxins, there may be other complex intra-operative factors related to AKI that we were not able to study based on the retrospective nature of our study. For example, a recent local observational study involving 30 children undergoing scoliosis surgery found that a significantly reduced cardiac output (18.5% reduction) was associated with the prolonged prone positioning required for these surgeries^[13]. Reduced cardiac output may lead to a state of poor renal perfusion during these lengthy procedures, which may put these children at a higher risk of AKI compared to other general surgical populations.

Even though the rise of creatinine trended higher in AKI patients compared to controls, it is interesting to note that the majority of AKI patients in our cohort were "oliguric" without significant rises in serum creatinine that often did not meet the creatinine criteria of the AKIN definition (at least 50% rise in creatinine). This may be partly related to a reduction of serum creatinine concentration associated with hemo-dilution effects and relative fluid overload as the majority of our patients demonstrated a cumulative positive fluid balance intra-operatively and in the ICU post-operatively. In addition, approximately 1/3 of our surgical cohort had an underlying condition including spina bifida and cerebral palsy (non-idiopathic scoliosis population). The significantly lower baseline serum creatinine values observed in our non-idiopathic scoliosis patients implies that a significantly low muscle mass state may limit an appreciable rise in serum creatinine during an episode of AKI. This is also a population where the use of recently validated AKI biomarkers representing early tubular damage [e.g., neutrophil gelatinase associated lipocalin (NGAL), interleukin-18 (IL-18), and kidney-injury molecule (KIM-1)] may be warranted in future orthopaedic AKI studies due to the potential issues of serum creatinine in this highly prevalent group of patients^[14-16]. Lastly, serum creatinine, was not monitored frequently past 24 h post-operatively in the majority of patients with the potential of higher rises in creatinine being missed in many patients.

Another potential reason for oliguria in this population is the syndrome of inappropriate anti-diuretic hormone (SIADH), which has been reported in adult and some paediatric spinal orthopedic literature^[17-19]. The diagnosis of SIADH requires the presence of hyponatremia (serum sodium < 135 mmol/L). In our cohort, only 10 patients (14%) overall were recorded with hyponatremia either during surgery or post-operatively, and only 5 of the AKI patients (14%) had documented hyponatremia. Mean serum sodium levels were the

same in AKI and non-AKI patients both intra (138) and post-operatively (137). Even though we were not able to completely exclude SIADH with serum ADH levels and urine osmolality values, it is unlikely that SIADH was the primary cause of oliguria based on several reasons. As shown in a paediatric study of SIADH in children following spinal fusion surgery, serum ADH levels peaked immediately post-op and declined by 6 h after surgery^[20]. Our stage 1 AKI patients ($n = 17$) met criteria for oliguria (< 0.5 mL/kg per hour for at least 6 h) at a mean of 9.1 h after surgery and stage 2 AKI patients ($n = 17$) met criteria (< 0.5 cc/kg per hour for at least 12 h) at a mean of 13.8 h post-operatively, well after the peak of serum ADH levels was observed in prior studies^[20]. In addition, the AKIN criteria for oliguria is strict (Stage 1: < 0.5 mL/kg per hour for at least 6 h) and is often more severe than what is observed in patients with SIADH. Therefore, SIADH as a primary reason for fulfilling AKIN urine output criteria is unlikely, but will need to be further explored in future prospective studies.

Unlike recent studies involving paediatric cardiac surgery patients, peri-operative AKI was not associated with morbidity (increased hospital/ICU length of stay) or mortality in children undergoing spinal instrumentation surgery. This needs to be studied prospectively in larger orthopaedic populations before any further conclusions are made due to the potential concerns of our study being under-powered with a relatively small sample size. Regardless, the relatively high incidence of AKI in our cohort cannot be ignored, especially in the context of several recent adult and paediatric publications revealing an increased risk of chronic kidney disease following a single episode of AKI including those of milder severity^[3-8].

In conclusion, we observed a high incidence of AKI following spinal instrumentation surgery in children that is potentially related to the frequent use of nephrotoxins and the amount of fluid administered peri-operatively.

COMMENTS

Background

Outside of cardiac surgery patients, the epidemiology of acute kidney injury (AKI) has not been well studied in other paediatric surgical populations including those undergoing major orthopaedic surgeries.

Research frontiers

Several studies have revealed an increased morbidity and mortality associated with pediatric AKI and an increased risk of chronic kidney disease in survivors of AKI.

Innovations and breakthroughs

The authors report a high incidence of AKI following spinal instrumentation surgery in children that is potentially related to the frequent use of nephrotoxins and the amount of fluid administered peri-operatively.

Applications

This study suggests that there are modifiable AKI risk factors with the potential of reducing AKI incidence in this understudied population.

Terminology

Acute kidney injury network (AKIN)-criteria: A set of criteria based on urine output or rise in serum creatinine to define AKI, according to the AKIN.

Peer-review

This is an interesting study which is well done and with new findings. It will be interesting to get more data about renal function after 3-5 years to have an idea about the impact of AKI on the long term renal prognosis.

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Contrast-induced acute kidney injury: A review of practical points

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Abstract

Contrast-induced acute kidney injury (CI-AKI) is one

of the most common causes of AKI in clinical practice. CI-AKI has been found to be strongly associated with morbidity and mortality of the patients. Furthermore, CI-AKI may not be always reversible and it may be associated with the development of chronic kidney disease. Pathophysiology of CI-AKI is not exactly understood and there is no consensus on the preventive strategies. CI-AKI is an active research area thus clinicians should be updated periodically about this topic. In this review, we aimed to discuss the indications of contrast-enhanced imaging, types of contrast media and their impact on nephrotoxicity, major pathophysiological mechanisms, risk factors and preventive strategies of CI-AKI and alternative non-contrast-enhanced imaging methods.

Key words: Angiography; Nephrotoxicity; Computed tomography; Contrast-induced acute kidney injury; Contrast media; Cholesterol embolization syndrome; Hemodialysis; Contrast nephropathy

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Core tip: The best preventive measure of contrast-induced acute kidney injury is to avoid unnecessary contrast administration which requires a good knowledge of indications and risk factors of contrast-enhanced imaging. Recently, alternative non-contrast-enhanced imaging modalities have been developed which may help us to decrease the frequency of contrast administration. In this review, these alternative modalities are discussed concisely. Type, osmolality, molecular structure and viscosity of contrast media (CM) are important determinants of nephrotoxicity. Major studies and meta-analyses comparing CM in terms of renal safety are also discussed.

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INTRODUCTION

Medical imaging has become an important diagnostic and therapeutic tool in clinical medicine in the era of great technological advances. Contrast media (CM) are increasingly used for better imaging in a broad spectrum of areas such as diagnostic computed tomography (CT) and magnetic resonance imaging (MRI), procedures of interventional radiology and percutaneous transluminal coronary angioplasty (PTCA). There are several adverse effects of CM including nausea, vomiting, thyroid dysfunction and hypersensitivity reactions such as urticaria, laryngeal edema, bronchospasm, hypotension and anaphylactoid shock^[1].

Contrast-induced acute kidney injury (CI-AKI) is one of the most important adverse effects of CM. In the past, CI-AKI was considered to be a mild state with asymptomatic and transient elevations in serum creatinine values however recent studies have demonstrated that both short term and long-term mortality rates have been found to be significantly higher in patients with CI-AKI compared to patients without CI-AKI^[2]. Furthermore, a history of CI-AKI may be associated with development of chronic kidney disease (CKD) and progression to end-stage renal disease (ESRD) in long term^[3,4].

In this review, we aimed to discuss the indications of contrast-enhanced imaging, types of CM and their impact on nephrotoxicity, major pathophysiological mechanism of CI-AKI, risk factors and preventive strategies of CI-AKI and alternative non-contrast-enhanced imaging methods.

DEFINITION OF CM

CM is a chemical substance which is used to improve the image quality of various body parts, to differentiate pathological from healthy tissues and to better delineate vascular structures. CM may be used by the way of oral route, intravascular or also through other luminal organs however absorption and nephrotoxic effects of CM used other than intravascular route may be negligible. In this review, the effects of intravascular administration of CM will be discussed.

DEFINITION OF CI-AKI

Various definitions of CI-AKI have been used in the literature. The most widely used definition is the increase in serum creatinine ≥ 0.5 mg/dL or 25% increase of serum creatinine from the baseline value at 48 h after CM administration. However timing of serum creatinine analysis after CM-enhanced imaging is controversial. Measurement as early as 12 h after the procedure (% change of creatinine from baseline) was found to significantly predict CI-AKI and furthermore it was

associated with the development of renal damage after 30 d^[5]. Serum cystatin C levels have also been evaluated as an early marker of CI-AKI. In the study by Briguori *et al.*^[6] performed on CKD patients undergoing PTCA, increase of cystatin C levels $\geq 10\%$ at 24 h after the procedure was found to reliably predict the patients with high risk of CI-AKI.

EPIDEMIOLOGY OF CI-AKI

Incidence of CI-AKI in patients undergoing elective, non-emergent contrast-enhanced CT has been found to be very low, $< 1\%$ ^[7]. In CKD patients, incidence of CI-AKI after intravenous CM administration was found to be 4%^[8]. However incidence of CI-AKI following contrast-enhanced CT performed in an emergency setting was found to be higher, $> 10\%$ which might reflect the underlying severe clinical status of the patient^[9]. Critically ill patients seem to be much more vulnerable to CI-AKI. In a study performed on critically ill patients without pre-existing renal disease, serum creatinine levels were elevated $\geq 25\%$ from the baseline in 18% of the patients after CM-enhanced CT^[10].

Incidence of CI-AKI in patients undergoing PTCA with normal baseline renal function was reported to be $< 3\%$ ^[11]. However, the incidence of CI-AKI was found to be as high as 40% in CKD patients undergoing PTCA^[12,13].

NEPHROTOXICITY OF MRI CONTRAST AGENTS

Until recently, MRI contrast agents also called gadolinium-based contrast agents (GBCA) have been considered to be safe in terms of nephrotoxicity. However GBCA has also been reported to cause AKI especially at high doses used for angiography in patients with pre-existing CKD and diabetic nephropathy^[14-16]. In an *in vitro* study, cytotoxicity of GBCA was compared to that of iodinated CM in renal tubular cells at angiographic concentrations and GBCA was not less cytotoxic compared with iomeprol^[17]. In another study, urinary interleukin-18 and N-acetyl-glucosaminidase levels were found to increase transiently after administration of GBCA in patients with normal renal function^[18]. These results suggest that GBCA also induces cytotoxicity in renal tubular cells. Another important adverse effect of GBCA is the specific clinical entity called nephrogenic systemic fibrosis (NSF) which occurs especially in patients with CKD. NSF is a potentially mortal complication associated with GBCA. Recently, a relationship between previous gadolinium administrations and high signal intensity in the several parts of the brain has been suggested independent of renal function^[19,20]. Gadolinium concentration in tissue was found to be strongly associated with cumulative gadolinium dose^[21]. Currently, clinical significance of gadolinium deposition in tissues is unclear; further studies are needed to clarify this issue.

In clinical practice, although GBCA are considered to

Table 1 Common indications for contrast media use in medical imaging

Diagnosis and treatment of vascular diseases such as coronary artery disease, pulmonary thromboembolism, arteriovenous malformations, aneurysms, arterial dissections and thrombosis
Diagnosis and staging of neoplastic diseases and mass lesions
Diagnosis of inflammatory and infectious diseases such as multiple sclerosis, meningitis, pancreatitis, diverticulitis

be relatively safer than iodinated CM, risks of AKI, NSF and brain deposition should be kept in mind^[14,16].

CLINICAL ISSUES NECESSITATING CM USE

It is important for clinicians to know the indications of contrast-enhanced imaging to avoid unnecessary contrast administration and its related complications. Common indications of CM use in clinical medicine are presented in Table 1. Accordingly, vascular, neoplastic and inflammatory diseases necessitate contrast-enhanced imaging. However CM is not usually suitable for the imaging of intracranial hemorrhages, cervical trauma, simple bone fractures, interstitial lung diseases and urinary system stones.

TYPES OF IODINATED CM AND THEIR IMPACT ON NEPHROTOXICITY

Type, osmolality, molecular structure and viscosity of CM are important determinants of nephrotoxicity associated with these agents (Table 2). Hyperosmolar CM (HOCM) was shown to more frequently cause CI-AKI compared with low-osmolal CM (LOCM)^[22]. However HOCM are no more used in clinical practice. There are controversial results in studies comparing iso-osmolal CM (IOCM) and LOCM as seen in Table 3. In most of these studies, no difference was found between IOCM and LOCM in terms of renal safety. Meta-analyses comparing IOCM and LOCM are presented in Table 4. In the meta-analysis by Reed *et al.*^[23], iodixanol (IOCM) was found to be associated with a reduced risk of CI-AKI compared to iohexol (LOCM) however risk of CI-AKI was not significantly different between iodixanol and other LOCM. In a very recent meta-analysis by Eng *et al.*^[24], a modest decrease in the risk of CI-AKI was found with iodixanol (IOCM) when compared to other LOCM however no difference was found between the groups in terms of risk of renal replacement therapy, cardiovascular outcomes or death. Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommended to use LOCM or IOCM instead of HOCM however due to lack of reliable evidence, no recommendation was made about the preference of IOCM or LOCM^[25].

IOCM has lower osmolality compared with LOCM, however since IOCM has dimeric structure, it has higher

viscosity than that of monomeric LOCM. Viscosity rather than osmolality determines the resistance to blood flow, thus IOCM may impair renal medullary blood flow to a greater extent compared to LOCM^[26]. Lack of clear superiority of IOCM over LOCM in terms of renal safety may be caused by higher viscosity of IOCM.

MAJOR PATHOPHYSIOLOGICAL MECHANISMS OF CI-AKI

Exact pathophysiological mechanism of CI-AKI is not known and includes complex cascades of events. Proposed mechanisms of CI-AKI are presented in Table 5. The most important elements of pathophysiological mechanism of CI-AKI seem to be the medullary hypoxia due to CM-induced medullary vasoconstriction^[27-29] and direct renal tubular cytotoxicity^[30-33]. CM-induced vasoconstriction is not exactly understood but it is probably caused by an imbalance between vasoconstrictive (endothelin, adenosine) and vasodilatory mediators (nitric oxide and prostacyclin)^[28,32,34]. The contribution of oxidative stress seems to be an important and complementary event that further exacerbates CI-AKI^[32,35,36].

In normal physiological state, renal medullary blood flow and oxygen tension are relatively lower than those of the renal cortex. Furthermore, thick ascending limb located in the outer part of the renal medulla has a high-rate of ion transport with increased oxygen consumption exacerbating the relative hypoxia of the renal medulla. The most susceptible part of the nephron to hypoxia is well-known to be the renal medulla. CM is shown to decrease the oxygen tension of the renal medulla and simultaneously CM - induced osmotic diuresis causes increased sodium delivery to thick ascending limb leading to increased oxygen demand^[27,37].

CM is known to cause direct mesangial and tubular cell toxicity. Proposed mechanisms of CM-induced cytotoxicity include oxidative stress, cellular energy failure, impaired cellular calcium homeostasis and increased apoptosis^[33,38-40]. In the study by Peer *et al.*^[33], iodinated CM at different concentrations was found to induce apoptosis in both mesangial and tubular cells. The relationship between hypoxia, oxidative stress and direct cytotoxicity is not well-understood in the context of CI-AKI. Previously, a mismatch between the metabolic demands and the perfusion of renal medulla, in another words "relative hypoxia" was suggested to cause increased oxidative stress leading to further cytotoxicity^[36]. However, recently, in the study by Liu *et al.*^[32], CM-induced direct cytotoxicity has been shown to cause increased oxidative stress even in the absence of hypoxia. Oxidative stress seemed to be a consequence not a cause of renal tubular injury. Furthermore, in this study CM was found to increase tubuloglomerular feedback which might contribute to disturbances of renal perfusion and filtration^[32]. It may suggested that direct cytotoxicity of CM may be the primary event that pull the trigger rather than hypoxia, hypoperfusion or oxidative stress in the pathophysiological mechanism of CI-AKI.

Table 2 Types, osmolalities and molecular structures of iodinated-contrast media

Osmolality	High osmolal (> 1400 mosm/kg)	Low osmolal (500-850 mosm/kg)	Iso-osmolal (290 mosm/kg)
Molecular structure	Ionic/monomer	Ionic/dimer	Non-ionic/monomer
Name of molecule	Diatrizoate (Hypaque)	Ioxaglate (Hexabrix)	Iohexol (Omnipaque) Iopamidol (Isovue) Ioversol (Optiray) Iopromide (Ultravist) Iopentol (Imagopaque) Iomeprol (Iomeron)

Table 3 Major studies comparing low-osmolal and iso-osmolal contrast media in terms of renal safety

Ref.	Baseline renal functions/patient population	Procedure/administration route	Compared drugs	Aim of the study/primary end points	Results
Feldkamp <i>et al</i> ^[94]	Normal GFR	PTCA (intra-arterial)	Iodixanol (IOCM) <i>vs</i> Iopromide (LOCM)	≥ 25% increase in SCr at 48 h	No difference
Hardiek <i>et al</i> ^[95]	Normal GFR, diabetic patients	PTCA (intra-arterial)	Iodixanol (IOCM) <i>vs</i> Iopamidol (LOCM)	≥ 25% increase in SCr days 1, 3 and 7	No difference
Aspelin <i>et al</i> ^[96] (NEPHRIC)	CKD, diabetic patients	PTCA (intra-arterial)	Iodixanol (IOCM) <i>vs</i> Iohexol (LOCM)	Peak increase in SCr day 0-3	Iso-osmolal safer than low-osmolal CM
Jo <i>et al</i> ^[97] (RECOVER)	CKD	PTCA (intra-arterial)	Iodixanol (IOCM) <i>vs</i> Ioxaglate (LOCM)	Increase in SCr ≥ 25% or ≥ 0.5 mg/dL within 2 d	Iso-osmolal safer than low-osmolal CM
Solomon <i>et al</i> ^[98] (CARE)	CKD	PTCA (intra-arterial)	Iodixanol (IOCM) <i>vs</i> Iopamidol (LOCM)	Increase in SCr > 0.5 mg/dL at 45-120 h	No difference
Rudnick <i>et al</i> ^[99] (VALOR)	CKD	PTCA (intra-arterial)	Iodixanol (IOCM) <i>vs</i> Ioversol (LOCM)	Increase in SCr > 0.5 mg/dL within 72 h	No difference
Barrett <i>et al</i> ^[8] (IMPACT)	CKD	CT (intravenous)	Iodixanol (IOCM) <i>vs</i> Iopamidol (LOCM)	Increase in SCr > 0.5 mg/dL or ≥ 25% at 48-72 h	No difference
Kuhn <i>et al</i> ^[100] (PREDICT)	CKD	CT (intravenous)	Iodixanol (IOCM) <i>vs</i> Iopamidol (LOCM)	Increase in SCr > 0.5 mg/dL within 48-72 h	No difference
Thomsen <i>et al</i> ^[101] (ACTIVE)	CKD	CT (intravenous)	Iodixanol (IOCM) <i>vs</i> Iomeprol (LOCM)	Increase in SCr > 0.5 mg/dL at 48-72 h	Low-osmolal safer than iso-osmolal CM
Nguyen <i>et al</i> ^[102]	CKD	CT (intravenous)	Iodixanol (IOCM) <i>vs</i> Iopromide (LOCM)	Peak rise in SCr days 1-3	Iso-osmolal safer than low-osmolal CM
Wessely <i>et al</i> ^[103]	CKD	PTCA (intra-arterial)	Iodixanol (IOCM) <i>vs</i> Iomeprol (LOCM)	Peak increase in SCr	No difference

CM: Contrast media; CKD: Chronic kidney disease; LOCM: Low-osmolal contrast media; CT: Computed tomography; PTCA: Percutaneous transluminal coronary angioplasty.

CM - induced increase in blood and renal tubular viscosity may lead to resistance to blood flow and further exacerbate the medullary hypoxia^[41]. Another important mechanism may be the mitochondrial dysfunction, especially ionic CM was found to impair the mitochondrial functions and membrane potentials in proximal tubular cells^[42].

RISK FACTORS FOR CI-AKI

Patients who are scheduled to have a contrast-enhanced diagnostic or interventional procedure should be evaluated for risk factors of CI-AKI (Table 6). Most important risk factors for CI-AKI are pre-existing CKD (GFR < 60 mL/min per 1.73 m²) and diabetes mellitus which may have additive effects on each other. In a study performed on patients undergoing contrast-enhanced CT, incidence of CI-AKI was found to be higher in diabetic CKD patients compared with non-diabetic CKD patients^[43].

Impacts of the type of imaging procedure and administration route of CM on CI-AKI

Type of the contrast-enhanced procedure seems to be an important determinant of CI-AKI. As aforementioned in this review, risk of CI-AKI with invasive PTCA seems to be higher compared to that of contrast-enhanced CT. This difference of the risk of CI-AKI between the two procedures may be caused by two reasons: (1) clinical status and comorbidities of the patients; and (2) administration route of the CM. Patients undergoing PTCA usually have significant ischemic heart disease and advanced atherosclerosis. During PTCA, significant hypotension may occur leading to ischemic nephropathy in addition to CI-AKI. Another important adverse event that may occur with invasive angiographic procedures is the cholesterol embolization syndrome (CES) which is sometimes hard to differentiate from CI-AKI. Administration route of the CM may also be important in the occurrence of CI-AKI. For contrast enhanced CT, CM is given intravenously, however

Table 4 Meta-analyses comparing iso-osmolal and low-osmolal contrast media in terms of renal safety

Metaanalyses	Baseline renal functions	Procedure/administration route	Compared drugs	Results
McCullough <i>et al</i> ^[104] (16 trials)	Both normal GFR and CKD	PTCA (intra-arterial)	Iodixanol (IOCM) <i>vs</i> various LOCM	Iodixanol safer than LOCM, <i>e.p.</i> in patients with CKD or CKD + diabetes mellitus
Reed <i>et al</i> ^[23] (16 trials)	Both normal GFR and CKD	PTCA + CT (intra-arterial + intravenous)	Iodixanol (IOCM) <i>vs</i> various LOCM	Overall, no difference. However, iodixanol safer than ioxaglate and iohexol
Heinrich <i>et al</i> ^[48] (25 trials)	Both normal GFR and CKD	PTCA + IV urography + CT (intra-arterial + intravenous)	Iodixanol (IOCM) <i>vs</i> various LOCM	Overall, no difference. However, iodixanol safer than iohexol in CKD patients when CM used <i>via</i> intra-arterial route
From <i>et al</i> ^[105] (36 trials)	Both normal GFR and CKD	PTCA + CT (intra-arterial + intravenous)	Iodixanol (IOCM) <i>vs</i> various LOCM	Overall, no difference. Iodixanol safer than iohexol
Eng <i>et al</i> ^[24] (29 trials)	Both normal GFR and CKD	PTCA + IV urography + CT (intra-arterial + intravenous)	Iodixanol (IOCM) <i>vs</i> various LOCM	Iodixanol slightly safer than LOCM but the lower risk did not exceed a minimally important clinical difference

CM: Contrast media; CKD: Chronic kidney disease; LOCM: Low-osmolal contrast media; CT: Computed tomography; PTCA: Percutaneous transluminal coronary angioplasty.

Table 5 Proposed pathophysiological mechanisms of contrast-induced acute kidney injury

Medullary vasoconstriction and hypoxia^[27-29]
 Direct cytotoxicity to renal tubular cells^[30-33]
 Release of vasoconstrictive mediators: Endothelin, adenosine, angiotensin II, vasopressin^[28]
 Reduction of vasodilatory mediators: Nitric oxide, prostacyclin^[28,32,34]
 Increased oxidative stress^[32,35,36]
 Impairment of tubulo-glomerular feedback^[32]
 Increased blood and renal tubular viscosity^[41]
 Impairment of mitochondrial function and mitochondrial membrane potential^[42]

in PTCA, CM is given intra-arterially. Risk of CI-AKI has been found to be higher with intra-arterial CM compared to intravenous CM administration especially when CM is used suprarenally^[44,45]. With suprarenal intra-arterial administration of CM, peak CM concentration within the kidney was found to be higher^[46]. In the meta-analysis by Dong *et al*^[47], risk of CI-AKI with intra-arterial iodixanol was found to be significantly lower when compared with intra-arterial LOCM. However no difference was found between IOCM and LOCM in terms of renal safety when CM was used intravenously. Similarly, in another meta-analysis by Heinrich *et al*^[48], iodixanol was found to be safer than iohexol in CKD patients undergoing a procedure with intra-arterial CM administration. Iodixanol (IOCM) may be suggested to be a better choice for patients in the interventional cardiology setting^[47].

Volume of CM

Lower doses of CM (definitions of low dose are variable: < 30-125 mL) were found to be less nephrotoxic^[49,50]. In a study by Manske *et al*^[49], low dose of CM was defined as < 5 mL/kg per serum creatinine. Recently, newer CT modalities have been developed using low tube voltage and low CM volume to reduce radiation exposure and the risk of CI-AKI without sacrificing image quality^[51-53]. However it should be kept in mind that even very low doses of CM may lead to CI-AKI in patients with high

Table 6 Patient-related and contrast media-related risk factors for contrast-induced acute kidney injury

Patient-related risk factors
 Pre-existing CKD
 Diabetes mellitus and diabetic nephropathy
 Older age
 Simultaneous use of nephrotoxic drugs
 Multiple myeloma
 States of reduced kidney perfusion
 Dehydration
 Congestive heart failure
 Hemodynamic instability
 Contrast-media related risk factors
 High volume of CM
 Use of hyperosmolal CM
 Multiple exposure to CM in short-term
 Intra-arterial administration

CKD: Chronic kidney disease; CM: Contrast media.

risk factors.

RISK SCORING FOR CI-AKI

Several risk scoring systems have been developed to predict the CI-AKI. In the study by Mehran *et al*^[54], CI-AKI was defined as an increase $\geq 25\%$ and/or ≥ 0.5 mg/dL in serum creatinine at 48 h after PCI and they proposed a CI-AKI risk stratification score based on 8 readily available variables including (1) patient-related features such as age > 75 years, diabetes mellitus, chronic congestive heart failure (CHF), acute pulmonary edema, hypotension, anemia, and CKD; (2) procedure-related features such as the use of IABP or increasing volumes of CM. Integer scores of these risk factors were determined as: Hypotension, 5; IABP, 5; CHF, 5; age > 75 years, 4; anemia, 3; diabetes mellitus, 3; each 100 mL of CM, 1; serum creatinine > 1.5 mg/dL, 4; eGFR = 40-60 mL/min per 1.73 m², 2; eGFR = 20-40 mL/min per 1.73 m², 4; eGFR < 20 mL/min per 1.73 m², 6. These scores are summed up and total risk score is obtained. For example, if total risk score is ≤ 5 , risk of CI-AKI is 7.5% and risk of

Table 7 Strategies to reduce the risk of contrast-induced acute kidney injury

Assess the risk of CI-AKI
Assess the need of contrast-enhancement, avoid unnecessary contrast administration
Avoid concomitant use of other nephrotoxic drugs
Hydrate the patient with isotonic saline and/or sodium bicarbonate before and after the procedure
N-acetyl-cysteine 1200 mg orally twice daily
Prefer iso-osmolal or hypo-osmolal CM
Use minimum amount of CM
Check renal functions within 1 wk of the procedure

CI-AKI: Contrast-induced acute kidney injury; CM: Contrast media.

dialysis is 0.04%. However risk of CI-AKI is 57% and risk of dialysis is approximately 13% with a total risk score of ≥ 16 . In conclusion, in this study, increasing total risk score was found to exponentially predict increased risk of CI-AKI. Another simple risk scoring for CI-AKI in patients undergoing PTCI is composed of age, creatinine and ejection fraction (ACEF score) which has been found to be an independent and useful predictor of CI-AKI defined as a rise in serum creatinine ≥ 0.5 mg/dL^[55,56].

TREATMENT OF CI-AKI

There is no specific treatment for CI-AKI. There is no evidence that any of the preventive strategies are helpful once the CI-AKI develops. Similar to the management of other types of AKI, stabilization of hemodynamic parameters and maintenance of normal fluid and electrolyte balance is crucial. Thus, prevention may be the only treatment modality for CI-AKI.

PREVENTION OF CI-AKI

Preventive strategies of CI-AKI are presented in Table 7. First things first, to prevent CI-AKI, avoid unnecessary contrast administration which requires good communication between the clinician and the radiologist. Clinicians should be informed about the medical imaging techniques alternative to contrast-enhanced medical imaging. If contrast use is inevitable, every patient should be evaluated for the risk factors for CI-AKI. Re-evaluation of concomitant use of other nephrotoxic drugs is of the utmost importance. Non-steroid anti-inflammatory drugs and nephrotoxic antibiotics such as aminoglycosides, colistin and antifungals such as amphotericin B should not be used if clinically possible.

Intravenous hydration

Various strategies and drugs have been tried to prevent CI-AKI in the literature (Table 8), however intravascular hydration seems to be the best preventive measure against CI-AKI^[57-59].

In a prospective randomized study, hydration with isotonic (0.9% saline) and half-isotonic (0.45% sodium chloride plus 5% glucose) solutions were compared in

Table 8 Experimental drugs and procedures to prevent contrast-induced acute kidney injury

Drugs
Hydration with isotonic saline ^[57-59]
N-acetyl-cysteine ^[69,106-110]
Sodium bicarbonate ^[58,68,108,109,111]
Theophylline ^[112-114]
Mannitol ^[115]
Furosemide ^[115-117]
Ascorbic acid (vitamin C) ^[118]
Tocopherol (vitamin E) ^[119]
Statins ^[120-124]
Mesna ^[125]
Dopamine ^[126]
Fenoldopam (dopamin agonist) ^[127]
Calcium channel blockers (verapamil, diltiazem) ^[128]
Adenosine ^[129]
Endothelin receptor antagonists ^[130]
Atrial natriuretic peptide ^[131]
Iloprost (PGI ₂ analogue) ^[132]
Misoprostol (PGE ₁ analogue) ^[133]
Trimetazidine ^[134]
Erythropoietin ^[135,136]
Nebivolol ^[137]
Sodium citrate ^[138]
Procedures
Remote ischemic preconditioning ^[72,73]
Prophylactic hemodialysis/hemofiltration/hemodiafiltration ^[71,139,140]

terms of efficiency in prevention of CI-AKI in patients undergoing coronary angioplasty. Hydration was performed before, during and after the procedure and total amount of hydration was approximately 2000 mL. In this study, isotonic hydration was found to be superior to half-isotonic hydration in the prevention of CI-AKI^[57]. In a study performed on patients undergoing non-emergency cardiac catheterization, saline hydration starting from 12 h before the procedure was compared to unrestricted oral fluid intake^[59]. Patients in the first group received normal saline for 24 h (at a rate of 1 mL/kg per hour). Intravenous saline hydration was found to decrease the both incidence and severity of CI-AKI. In contrast, in a very recent prospective, randomized, non-inferiority study performed on CKD patients (eGFR: 30-59 mL/min per 1.73 m²) undergoing an elective procedure with CM, patients were randomly assigned to receive intravenous 0.9% NaCl or no prophylaxis^[60]. No prophylaxis group was found to be non-inferior to prophylaxis group and furthermore it was found to be cost-effective. However, despite the results of this study, we still strongly recommend hydration especially in patients with high risk of CI-AKI. Hypervolemia should be avoided during hydration of the patients. Monitorization of left ventricular end diastolic pressure was found to be a useful and effective way of guiding fluid replacement in a randomized controlled trial^[61]. Further studies are needed to prove the efficacy of hydration in prevention of CI-AKI.

Sodium bicarbonate

There is controversy about the efficacy of sodium bicarbonate to prevent CI-AKI, several studies found

sodium bicarbonate as protective against CI-AKI^[62,63] while others found no beneficial effect^[64-66]. In a meta-analysis, sodium bicarbonate was found to be protective against CI-AKI but with a borderline significance^[63]. In another 2 meta-analyses, no difference was found between bicarbonate and saline in terms of prevention from CI-AKI^[67,68].

There is no standard dose of sodium bicarbonate for the prevention of CI-AKI. In a study, bicarbonate solution was prepared by adding 154 mL of 1000 mEq/L sodium bicarbonate to 846 mL of 5% dextrose in H₂O^[62]. In this study, hydration with sodium bicarbonate before contrast exposure is more effective than hydration with sodium chloride for prophylaxis of CI-AKI. In another study, bicarbonate solution was prepared with 75 mL of 8.4% sodium bicarbonate added to 1 L of isotonic saline^[65]. In this study, no difference was found between sodium bicarbonate plus saline group and hydration with only saline group in terms of prevention from CI-AKI. Since sodium bicarbonate contains high amount of sodium, risk of hypervolemia should be taken into consideration especially in patients with congestive heart failure and CKD and dose of the bicarbonate should be individualized.

N-acetylcysteine

N-acetylcysteine (NAC) did not decrease the risk of CI-AKI in patients undergoing PTCA in a large randomized trial^[69]. There are several meta-analyses about the efficacy of NAC against CI-AKI with both non-significant^[70] and significant results^[67]. Although the strength of the evidence is low, NAC is a well tolerated, inexpensive drug and it has a relatively good profile of adverse effects. Thus, in 2012, KDIGO suggested NAC for patients with high risk of CI-AKI^[25]. There is no consensus on the dose of the NAC however it is usually used at a dose of 600-1200 mg orally twice daily.

Prophylactic hemodialysis/hemofiltration

Prophylactic hemodialysis (HD) and hemofiltration (HF) were not found to be protective against CI-AKI. In the meta-analysis including 8 studies of HD and 3 studies of HF, no beneficial effects of these treatment modalities was found against CI-AKI^[71]. Furthermore, HD was found to increase the risk of CI-AKI. Thus prophylactic renal replacement treatments are not recommended.

Remote ischemic preconditioning

Remote ischemic preconditioning (RIP) is an interesting procedure that has been evaluated as a potential protective mechanism of CI-AKI. RIP depends on a hypothesis that a transient ischemia of an organ may protect against an ischemic injury of another distant organ. Mostly, RIP has been induced by arm ischemia performed by inflation of blood pressure cuffs. In preliminary studies, RIP has been found to decrease the risk of CI-AKI^[72,73]. However further randomized clinical trials are needed before a recommendation can be made.

Should we stop ACEI/ARB treatments before the contrast-enhanced imaging?

Some clinicians may prefer to stop angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) before the contrast administration because ACEI/ARB are considered to increase the risk of CI-AKI. Supporting these concerns, in a retrospective study, use of ACEI/ARBs during PTCA was found to be independently associated with increased risk of CI-AKI^[74]. However in a prospective randomized trial, discontinuation of ACEI/ARB treatments 24 h before PTCA did not influence the incidence of CI-AKI in patients with CKD^[75]. We think that, cessation of ACEI/ARB treatments for only 1 d before the procedure might not be adequate because renal hemodynamic effects of these drugs might last longer. In a very recent meta-analysis, ACEI use was not found to have a significant effect on the CI-AKI in patients undergoing PTCA^[76]. In summary, there is not enough evidence to recommend withholding or continuing ACEI/ARB treatments before contrast-enhanced imaging.

Should we stop metformin treatment before the contrast-enhanced imaging?

Metformin is not a nephrotoxic drug however it is excreted by the kidney. Metformin is known to cause severe lactic acidosis in patients with renal impairment. About 8% of cases reporting metformin induced lactic acidosis were found to be associated with CI-AKI^[77]. Cessation of metformin at least 48 h before the contrast administration is a common but controversial clinical practice^[78]. According to other researchers, the risk of metformin induced lactic acidosis is extremely low in patients with normal renal function thus discontinuation of metformin is considered unnecessary in non-uremic patients^[79]. We think that it will be appropriate to discontinue metformin especially in CKD patients who are planned to have a contrast-enhanced procedure.

ALTERNATIVE NON-CONTRAST ENHANCED IMAGING TECHNIQUES

In the era of rapidly evolving technology, new non-contrast-enhanced imaging modalities have been developed (Table 9). Most of these modalities are MRI-based techniques. Knowledge of these new techniques may be beneficial for the renal health of the patients needing contrast-enhanced imaging and interventions. Preference of these imaging modalities may be discussed between the clinician and radiologist.

CONTRAST USE IN END-STAGE RENAL DISEASE

There are two concerns about the use of iodinated CM in patients with ESRD; risk of loss of residual renal function (RRF) and CM-induced hypervolemia.

Table 9 Alternative non-contrast enhanced imaging techniques

Name of the technique	Clinical indications	Notes
TOF MR angiography	Cerebral aneurysm Stroke Atherosclerotic carotid disease Arteriovenous malformation	No contrast agent is required
ECG-gated fast spin echo MR angiography	Peripheral artery disease (less frequently) Peripheral artery disease Thoraco-abdominal aortic aneurysm	No contrast agent is required. Higher image quality compared to TOF MR angiography in peripheral arterial imaging
SSFP MR imaging	Coronary artery disease Myocardial viability and function Pericardial diseases Renal artery stenosis Congenital heart diseases	No contrast agent is required.
Arterial spin labeling with/without SSFP	Native and transplanted renal renal artery stenosis Renal perfusion Cerebral blood flow Characterization of masses	Evaluation of organ perfusion When combined with SSFP, it can be used as an angiographic imaging
Phase contrast MR imaging	Imaging of major thoraco-abdominal vascular structures Congenital heart disease Renal artery stenosis	No contrast agent is required. Quantification of blood flow and velocity
Carbon-dioxide angiography	Peripheral artery disease (mostly infra-diaphragmatic)	No contrast agent is required. Non-allergenic, non-nephrotoxic, inexpensive. Neurotoxic, risk of air trapping and distal ischemia

TOF: Time-of-flight; MR: Magnetic resonance; ECG: Electrocardiography; SSFP: Steady-state free precession.

RRF is associated with better outcome and survival in patients with ESRD^[80]. Thus it should be preserved by avoiding unnecessary use of CM and nephrotoxic drugs. HD treatment after iodinated CM exposure was not shown to preserve RRF in patients with ESRD^[81].

Another concern about the contrast administration is the hypervolemia that may be induced by the CM. Sometimes clinicians may prefer to perform HD immediately after contrast enhanced imaging. However as reported by Hamani *et al*^[82], new non-ionic LOCM does not seem to increase serum osmolality, arterial blood pressure and it does not cause hypervolemia. Thus immediate HD may not be warranted to prevent hypervolemia in stable chronic HD patients.

GBCA should be better avoided in ESRD patients because of the risk of potentially mortal complication: NSF which is a systemic fibrosing disease that occurs due to exposure to GBCA especially in patients with GFR < 30 mL/min^[83]. If it is inevitable to use GBCA in ESRD patients, immediate HD after the imaging procedure should be considered because GBCA has been shown to be effectively removed by HD^[84]. However no proof exists that HD after GBCA exposure reduces the risk of NSF.

In HD patients without urine output (no RRF), if contrast-enhanced imaging is required, CT is clearly preferred over MRI to avoid the risk of NSF.

PROGNOSIS OF CI-AKI

Short and long term mortalities of patients with CI-AKI have been shown to be higher compared with patients

without CI-AKI^[85-87]. However there are few studies about the long-term renal prognosis of patients who developed CI-AKI. In a prospective study performed on patients with symptomatic peripheral artery disease undergoing PTCA, patients with CI-AKI were found to be at increased risk of long-term loss of renal function, cardiovascular events, and death^[88]. In this study, one year after the procedure, decline in eGFR was significantly higher in patients with CI-AKI compared with patients without CI-AKI (12.4 mL/min vs 6.2 mL/min). In another observational study on CKD patients undergoing PTCA, persistent renal dysfunction was defined as the decrease of creatinine clearance $\geq$ 25% of baseline values at 3 mo^[3]. In this study, overall incidence of CI-AKI was found to be 12%, and persistent renal dysfunction was found in 18.6% of CI-AKI patients. Similarly, in another study performed on patients undergoing PTCA, continuous deterioration of kidney function (CDKF) was defined as > 25% increase in serum creatinine or serum creatinine > 0.5 mg/dL above baseline at 6 to 8 mo after PTCA^[4]. In this study CDFK was found in 16% of the study population and this group of patients was found to have significantly higher 5-year mortality rate. In a large study performed to find the incidence of CKD onset after PTCA, incidence of new-onset CKD within 6 mo of the procedure was found to be 0.9%^[89]. Furthermore, in this study trans-radial access site was found to be associated with less CKD than the femoral approach.

CES

The most important alternative diagnosis of AKI after

contrast-enhanced imaging especially PTCA is the CES which is rarer than CI-AKI however long-term renal survival is significantly worse than CI-AKI^[90]. CES manifests later than CI-AKI, usually 1-2 wk after the procedure. Dislodgement of cholesterol crystals from the atherosclerotic plaques leads to embolization of the small peripheral arterioles causing a multisystemic disease with allergic-immunological features including eosinophilia, hypocomplementemia, livedo reticularis, distal gangrenes with palpable pulses (blue-toe syndrome) and pathognomonic Hollenhorst plaques on ophthalmologic examination^[91]. Renal biopsy reveals empty clefts within the obliterated lumens of the arterioles^[90]. Differentiation of CI-AKI and CES is important because these two diseases may have different types of treatment modalities. Once developed, CI-AKI necessitates only supportive measures. However since CES is a type of allergic-immunological disease, anti-inflammatory treatments such as corticosteroids and cyclophosphamide may be considered^[92,93]. But there is no proof of efficacy of these anti-inflammatory treatments on CES.

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Role of different imaging modalities of vascular calcification in predicting outcomes in chronic kidney disease

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Abstract

Vascular calcification (VC) is common among patients

with chronic kidney disease (CKD). The severity of VC is associated with increased risk of cardiovascular events and mortality. Risk factors for VC include traditional cardiovascular risk factors as well as CKD-related risk factors such as increased calcium and phosphate load. VC is observed in arteries of all sizes from small arterioles to aorta, both in the intima and the media of arterial wall. Several imaging techniques have been utilized in the evaluation of the extent and the severity of VC. Plain radiographs are simple and readily available but with the limitation of decreased sensitivity and subjective and semi-quantitative quantification methods. Mammography, especially useful among women, offers a unique way to study breast arterial calcification, which is largely a medial-type calcification. Ultrasonography is suitable for calcification in superficial arteries. Analyses of wall thickness and lumen size are also possible. Computed tomography (CT) scan, the gold standard, is the most sensitive technique for evaluation of VC. CT scan of coronary artery calcification is not only useful for cardiovascular risk stratification but also offers an accurate and an objective analysis of the severity and progression.

Key words: Coronary calcification; Aortic calcification; Hemodialysis; Dialysis; Ultrasound; Mammogram; Plain X-ray

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Core tip: Vascular calcification (VC) is common among patients with chronic kidney disease. VC is observed in arteries of all sizes. Several imaging techniques have been utilized in the evaluation of VC. Plain radiographs are simple, readily available and can somewhat differentiate between intimal and medial calcification. Mammography detects medial calcification and is especially useful among women. Ultrasonography is suitable for superficial arteries. Analyses of wall thickness and lumen size are possible. Computed tomography, the gold

standard, is the most sensitive technique and offers the most accurate analysis of the severity and progression of VC.

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INTRODUCTION

Vascular calcification (VC) is common among patients with chronic kidney disease (CKD). The severity of VC is associated with increased risk of cardiovascular events and mortality. Several risk factors specific to CKD population including increased calcium and phosphate load and loss of calcification inhibitors influence the development and the progression of VC. In CKD, VC is observed in arteries of all sizes from small arterioles to aorta and are located in the intima and/or the media of arterial wall. Intimal calcification occurs predominantly in large arteries in association with atherosclerotic plaques resulting in lumen narrowing. Medial calcification can occur in larger arteries as well as smaller muscle-type arteries and arterioles. The lumen of the artery with medial calcification is largely patent but the wall is hardened causing poor arterial compliance and decreased blood flow. Similar to general population, the degree of VC in CKD is strongly associated with cardiovascular (CV) disease and mortality. The review of pathogenesis and clinical implications of VC can be found elsewhere^[1]. Different imaging modalities ranging from simple plain radiographs to computed tomography (CT) have been utilized in the examination and the quantification VC. The present review focuses on different imaging techniques and their abilities to predict long-term outcomes in CKD population.

PLAIN RADIOGRAPHS

Several types of plain radiograph have been used to detect and quantify the amount of VC in different areas of the body. Plain radiographs are cheap, readily available and have the advantage of being able to somewhat differentiate between intimal and medial calcification.

Lateral lumbar spine radiograph

Lateral lumbar spine X-ray has been utilized in the evaluation of atherosclerosis and calcification of abdominal aorta since 1950s (Figure 1)^[2,3]. In 1980s, the relationship between aortic calcification in the pre-lumbar region and the risk of future CV death was documented^[4]. In 1997, using lateral lumbar spine X-rays from 617 Framingham heart study participants, Kauppila *et al.*^[5] established a simple scoring method that provided a simple and low

cost assessment of the degree of atherosclerotic vascular disease. In two large cohorts of men and women without CKD, this semi-quantitative measurement showed the ability to predict future coronary artery disease (CAD), congestive heart failure, CV events and CV mortality^[6,7]. When applying Kauppila score to hemodialysis patients, the degree of calcification was highly correlated with coronary artery calcification score (CAC score) obtained from the electron beam CT and arterial stiffness analyzed by the pulse wave velocity (PWV)^[8,9]. In two large cohorts of maintenance hemodialysis patients, Kauppila score could predict all-cause and CV mortality and non-fatal CV events^[10,11]. Due to such evidence, the 2009 Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommended lateral lumbar spine X-ray for the assessment of VC burden in dialysis patients^[12]. Few studies have also reported the use of lateral abdominal X-ray in non-dialysis CKD population^[13,14]. The calcification score obtained from lateral lumbar spine radiograph was highly correlated to the score obtained by CT^[15]. As kidney function declined, the degree of calcification increased and Kauppila score ≥ 4 predicted future CV events^[16,17]. Tables 1 and 2 summarize different imaging techniques, the predictable outcomes and the available scoring systems associated with them.

Chest radiograph

Aortic arch calcification can readily be seen in a postero-anterior (PA) or antero-posterior chest X-ray and the entire aortic arch can be visualized in a lateral chest radiograph (Figure 2). The prognostic significance of aortic arch calcification has been described since 1950s^[18,19]. In the Framingham cohort, the degree of thoracic aortic calcification doubled with each decade of age and its presence was associated with a twofold increase in the risk of CV death, CAD, stroke and peripheral arterial disease (PAD)^[20]. In another cohort of over 100000 men and women in United States, the presence of aortic arch calcification on PA chest X-ray was associated with older age, smoking, hypertension and elevated cholesterol and increased the risk of CAD and stroke^[21]. In dialysis population, a simple scoring system of aortic arch calcification in PA chest X-ray was devised by Ogawa *et al.*^[22] that showed high correlation with calcification score obtained by CT. The severity of aortic arch calcification correlated with age, dialysis vintage, PWV, cardiothoracic ratio and parathyroid hormone level and displayed the ability to predict future CV events and mortality^[23-26]. In peritoneal dialysis patients, the severity and progression of aortic arch calcification were independent predictors of all-cause and CV mortality^[27]. In addition to the PA view, lateral chest X-ray offers another viewing angle of the entire aortic arch. The analysis of progression of aortic arch calcification on lateral chest X-ray in chronic dialysis patients revealed the association with hypercalcemia, hyperparathyroidism and future all-cause and CV mortality^[28]. In the recent meta-analysis that included 3256 dialysis patients, the presence of aortic arch

Table 1 Summary of different imaging modalities for vascular calcification in chronic kidney disease

Types of X-rays	Calcification area	Advantages	Limitations	Scoring methods	Outcomes prediction
Plain radiography					
Lateral lumbar spine	Abdominal aorta	Simple	Subjective quantification	Kaupilla <i>et al</i> ^[5]	CV events, mortality
Postero-anterior chest	Aortic arch	Simple, readily available in almost all patients		Ogawa <i>et al</i> ^[22]	CV events, mortality
Lateral chest	Aortic arch	Simple		Noordzij <i>et al</i> ^[28]	Mortality
Antero-posterior pelvis	Iliac and femoral arteries	Simple, allow differentiation between intimal- and medial-type calcification		Adragão <i>et al</i> ^[33]	CV events, mortality
Hand	Radial, ulnar and digital arteries	Simple, allow analysis of medial-type calcification		Adragão <i>et al</i> ^[33]	Outcome data is lacking
Foot	Tibial, dorsalis pedis, plantar and digital arteries			Not available	Outcome data is lacking
Mammography	Intramammary arteries	Readily available in most women, allow analysis of medial-type calcification	Subjective quantification	Not available	PAD events
Ultrasonography	Carotid, femoral and peripheral arteries	No radiation exposure, allow evaluation of arterial wall thickness and lumen size	Only superficial arteries can be evaluated, subjective quantification	Not available	CV events, mortality
Computed tomography					
Chest	Coronary arteries	Intravenous contrast is not required, the most objective and reproducible quantification which allows analysis of progression	Cost, radiation exposure, does not allow differentiation between intimal- and medial-type calcification	Agatston <i>et al</i> ^[63]	CV events, mortality
Abdomen	Thoracic aorta Abdominal aorta			Callister <i>et al</i> ^[100] Hong <i>et al</i> ^[101]	CV events, mortality

CV: Cardiovascular; PAD: Peripheral arterial disease.



Figure 1 Abdominal aortic calcification seen on lateral lumbar spine radiograph.

calcification was associated with a greater risk of CV and overall mortality^[29].

Pelvic radiograph

Pelvic X-ray can be used to evaluate calcification in iliac and femoral arteries. As mentioned above, in peripheral branches of aorta, the prevalence of medial calcification increases. Intimal and medial calcification can be somewhat differentiated by different characteristics seen on plain X-rays. The discrete plaque with irregular and patchy distribution represents calcification in the intima, whereas the uniform linear railroad track-type is the characteristic of calcification in the media (Figure 3)^[30,31]. The presence of medial calcification in diabetic patients is a strong predictor of future CV events, stroke, PAD

and mortality^[30]. In hemodialysis patients, the presence of medial calcification in iliac and/or femoral arteries in pelvic X-ray was not associated with aging, CV disease or diabetes but rather related to prolonged dialysis vintage, increased serum calcium, phosphate, parathyroid hormone and the dose of calcium binder suggesting the close relationship between medial calcification and uremic milieu^[31]. Both intimal and medial calcification seen on pelvic X-ray showed the ability to predict overall and CV mortality in hemodialysis patients^[31]. A simple VC score of the medial-type calcification seen on pelvic X-ray and bilateral PA view of both hands was introduced by Adragao *et al*^[32]. Increased Adragao score in hemodialysis patients was positively correlated with arterial stiffness, future CV events and mortality^[33]. The degree of pelvic arterial calcification showed 67% sensitivity and 85% specificity for the prediction of CAC score ≥ 100 and above 80% sensitivity and specificity for the prediction of CAC ≥ 400 ^[34].

Hand and foot radiographs

The presence of calcification in small arteries of hands and feet are largely due to medial calcification, therefore, the linear tram-track calcification along the length of the artery is a typical finding (Figure 4). The earlier study of calcification of small arteries in hands and feet of diabetic patients revealed the association between medial calcification and microvascular complications (diabetic neuropathy, retinopathy and nephropathy)^[35]. In patients taking warfarin, the increase in VC in ankle and foot that was limited to a medial pattern was observed^[36]. In CKD

Table 2 Summary of scoring systems for vascular calcification in chronic kidney disease

Scoring methods	Calcification area	Details
Kaupila <i>et al</i> ^[25]	Abdominal aorta between L1-L4 in a lateral lumbar spine radiograph	The length of calcification in the anterior and posterior wall of the aorta in front of each vertebra is scored between 0-3. Total score is the sum of calcification in both walls of the aorta between L1-L4
Ogawa <i>et al</i> ^[22]	Aortic knob in a PA chest radiograph	A scale with 16 circumferences is attached to the aortic knob. The number of sections with calcification are counted
Noordzij <i>et al</i> ^[28]	Aortic arch in a lateral chest radiograph	Visual inspection of calcification. The degree of calcification is categorized into no (score 0), moderate (score 1) or severe (score 2) calcification
Adragao <i>et al</i> ^[32]	Iliac and femoral arteries in a pelvic radiograph and arteries of both hands in a bilateral hand radiograph	The pelvic radiograph is divided into four sections by a horizontal line over the top of both femoral heads and a vertical line over the vertebral column. The bilateral hand radiograph is divided by a vertical line which separates each hand and a horizontal line over the top of metacarpal bones. The presence of linear calcifications in each section is counted as 1
Agatston <i>et al</i> ^[63] (CAC score by area)	Coronary arteries in a thoracic CT scan	CT images of 3 mm thickness are acquired from the carina to the diaphragm. The calcified lesion in coronary arteries is the area of at least 0.5 mm ² that has a threshold density ≥ 130 HU. The density score 1 = 130-199 HU, 2 = 200-299 HU, 3 = 300-399 HU and 4 ≥ 400 HU. The calcification area is then multiplied by the density score
Callister <i>et al</i> ^[100] Hokanson <i>et al</i> ^[102] (CAC score by volume)	Coronary arteries in a thoracic CT scan	Coronary calcium volume score is obtained from the multiplication of calcification area by the section thickness. A square root is applied to the volume score in order to decrease the variability among those with high scores
Hong <i>et al</i> ^[101] (Calcium mass score)	Coronary arteries in a thoracic CT scan	Measurement of the absolute mass of CaHA. The procedure uses a phantom containing different concentrations of CaHA placed beneath the thorax in order to calibrate the segmented coronary calcium. The absolute score is expressed as milligrams of CaHA
Moe <i>et al</i> ^[83] Chertow <i>et al</i> ^[103] Yildiz ^[104] DeLoach ^[105]	Different portions of thoracic aorta visualized in a thoracic CT scan	The scores are based on the area calcification as described by Agatston <i>et al</i> or the volume calcification as described by Callister <i>et al</i> or Hokanson <i>et al</i>
Kabaya <i>et al</i> ^[106] Taniwaki <i>et al</i> ^[107] Yamada <i>et al</i> ^[108] (Aortic calcification index)	Abdominal aorta 10-15 cm in length above the bifurcation in abdominal CT scan	Abdominal aorta is evaluated in 10-15 CT slices at 0.8-1 cm interval. The proportion of aortic circumference covered by calcification is quantified in relation to the total circumference in each slice. The score is total calcification in all slices

CT: Computed tomography; CaHA: Calcium hydroxyapatite.

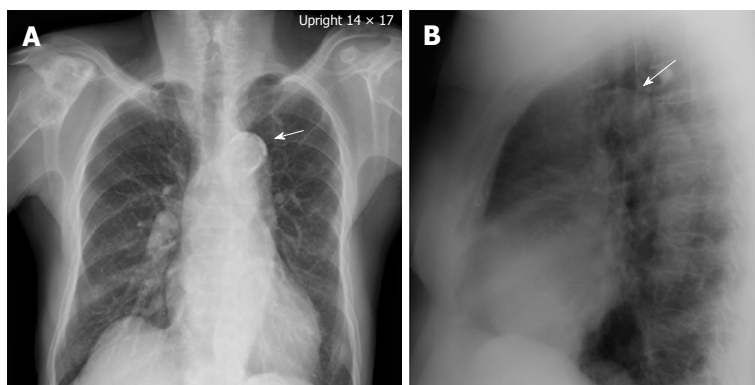


Figure 2 Aortic arch calcification (arrow) seen on postero-anterior chest radiograph (A) and lateral chest radiograph (B).

patients, the earliest and commonest sites of calcification were ankles, followed by feet, hands and wrists^[37]. Longer dialysis vintage and increased serum phosphate were positively associated with VC of hand arteries whereas PAD was associated with VC of foot arteries^[38,39].

MAMMOGRAPHY

In 1980, the presence of intramammary arterial calcifications characterized as linear tram-track medial-type calcification was reported in association with diabetes

(Figure 5)^[40]. The subsequent study that performed a biopsy of such calcification confirmed the histologic finding of medial calcification^[41]. In women over 40-50 years of age, the presence of breast arterial calcification (BAC) was associated with CV disease and portended a markedly increased risk of CV events and mortality^[42-45]. In women taking warfarin, the prevalence of BAC was 50% greater than those not taking the drug and increased with the duration of therapy reaching as high as 75% in patients with at least 5 years of exposure^[46]. In CKD patients, BAC occurred more frequently than non-CKD subjects with the



Figure 3 Plaque-like intimal calcification (black arrow) and uniform linear railroad track-like medial calcification (white arrow).

prevalence of 25% in CKD stage 3, 40% in CKD stages 4-5 and over 60% in CKD stage 5D compared to 20% in age and diabetes-matched non-CKD subjects^[47]. Increased severity of BAC was associated with aging, diabetes and dialysis duration and predicted new PAD events^[48].

ULTRASONOGRAPHY

Ultrasonography has the benefit of no radiation exposure and offers a unique mean to evaluate arterial wall thickness and lumen size. The resolution of ultrasound depends on the depth of field, therefore, ultrasound is suitable for imaging of superficial arteries such as carotid, femoral and peripheral arteries. The quantification is largely subjective and operator dependent. Ultrasound assessment of carotid arterial atherosclerotic disease has become the first choice for screening of carotid artery stenosis. Carotid intima-media thickness (IMT) is also an early atherosclerotic risk marker, therefore, most studies focus on carotid IMT rather than calcification, which is a late event. The review of carotid IMT and outcomes is beyond the scope of this review. In elderly subjects, calcified carotid plaques predicted mortality and CV outcomes independent of traditional CV risk factors^[49]. In ESRD patients, calcified plaques in carotid and femoral arteries were present in 71% compared to 21% in age-matched control^[50]. Patients with calcification were significantly older, predominantly male, and had a higher prevalence of previous CV disease. The presence of calcification was associated with increased carotid IMT and higher number of plaques^[51]. Another study in hemodialysis patients found the association between carotid calcification with age, duration of dialysis, calcium x phosphate product and prescribed dose of calcium-based phosphate binder^[52,53]. Carotid arterial calcification was also an independent risk factor for composite CV events in incident hemodialysis patients^[54]. Similarly, in peritoneal dialysis patients, the prevalence of carotid calcification was high and was associated with diabetes mellitus, increased left ventricular mass index, and lower survival rate^[55]. The calcification score of combined sites evaluated by both ultrasonography and plain X-rays of

carotid artery, abdominal aorta, iliofemoral axis, and legs predicted all-cause and CV mortality^[56].

CT

Non-contrast CT is the gold standard for detection and quantification of VC. CT is equipped with a software program which allows a more sensitive and objective quantification of calcification. Multi-slice CT has largely replaced electron beam CT due to its improved image quality, accuracy and reproducibility^[57]. Due to high sensitivity and accuracy, analyses of progression or changes after treatment are possible. CT of large arteries such as aorta and its branches and coronary arteries have been utilized to classify CV risk in both general and CKD populations. The disadvantage of CT lies in the cost and the amount of radiation exposure which is approximately 30 times higher than a plain X-ray^[58]. CT does not differentiate between intimal and medial calcification and may not be suitable for evaluation of medial-type calcification in small arteries.

Coronary arteries

The significance of CAC detected by CT (Figure 6) has been recognized since 1980s^[59]. The presence of CAC was associated with aging, hypertension, diabetes, obesity, hyperlipidemia, angiographic coronary stenosis and histopathologic atherosclerosis^[60-62]. The quantification method of CAC reported by Agatston *et al*^[63] showed excellent inter-observer agreement and has the ability to predict CV events with high sensitivity and specificity^[63-65]. The Expert Consensus Document of the American College of Cardiology/American Heart Association stated that the sensitivity and specificity of CT in detection of coronary artery stenosis or occlusion was 90.5% and 49.2% respectively^[66]. When the prognostic accuracy of CAC score was evaluated in a large cohort of asymptomatic subjects between 50-70 years of age, CAC score was able to predict CAD events independent of standard CV risk factors and was superior to the Framingham risk index in predicting the events^[67]. When compared to thoracic and abdominal aortic calcification, CAC was most strongly associated with major CAD events, followed by major CV events, and all-cause mortality independent of Framingham risk factors^[68]. In CKD, increased prevalence and severity of CAC are well documented. The prevalence up to 80%-90% has been reported in ESRD population^[69-72]. In dialysis patients, the degree of CAC was more pronounced in older patients, male gender, patients with diabetes, longer dialysis vintage, high serum calcium and phosphate and high calcium intake^[69,70]. Similar to general population, the severity of CAC in dialysis patients predicted early mortality after adjustments for other risk factors^[73,74]. In non-dialysis CKD stages 3-5, the prevalence of CAC was as high as 40%-70% compared to 13% in age-matched non-CKD subjects and the severity was 10 times that of general population^[75,76]. A strong and graded relationship

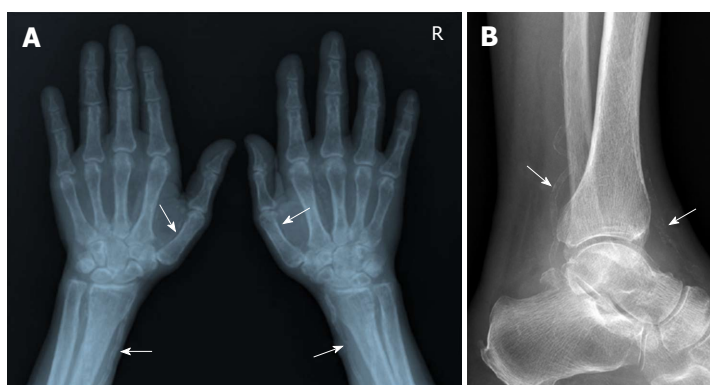


Figure 4 Medial calcification in small arteries in hands (A) and foot (B).

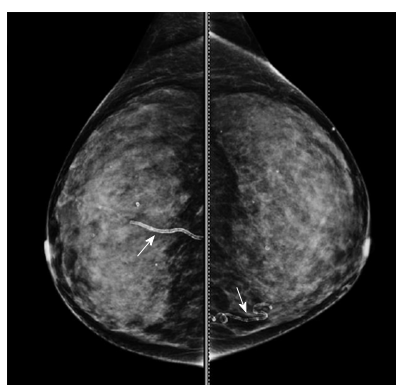


Figure 5 Breast arterial calcification with the typical linear tram-track medial-type calcification (arrows).

between lower estimated glomerular filtration rate (eGFR) and increasing CAC was documented^[76]. Aging, diabetes, male gender, body mass index, eGFR and serum phosphate were associated with the degree of CAC and the rapid progression rate was observed paralleling the severity^[77-79]. The presence of CAC in non-dialysis CKD also adversely affected patient survival and the addition of CAC score to traditional risk factors improved the prediction of CV risks in non-dialysis CKD population^[15,80].

Aorta

The evaluation of abdominal aortic calcification by CT has been reported since 1984^[81]. Similar to CAC, aortic calcification likely influences subsequent CV events. Different areas of the aorta from the arch to the bifurcation have been chosen by different investigators^[82]. In general, atherosclerosis and calcification are observed more frequently at the bifurcation where turbulent flow occurs, therefore, several investigators chose the part of abdominal aorta just above common iliac arteries. Several scoring methods have been devised that can largely be categorized into two types of techniques; the first technique is based on Agatston's method or "calcification score by area" and the other technique is "calcification score by volume"^[83]. Different terms have been used for the quantification method such as aortic calcification area index, aortic calcification index,

aortic calcification volume, etc^[82]. Aortic calcification normally appears approximately a decade after CAC. Aging, male gender, diabetes and hypertension are among important risk factors. At the age of 50, the prevalence of abdominal aortic calcification is 15%-20% and increases to 90% by the age of 70^[84]. The degree of thoracic aortic calcification (excluding aortic arch and proximal descending aorta) evaluated in the CT scan originally aimed at CAC assessment (Figure 6) was found to predict CV events, CV mortality and all-cause mortality albeit with much less robustness than CAC^[85-87]. The recent study also suggested that thoracic aortic calcification might not improve the 10-year estimation of prognosis beyond traditional risk factors^[88]. Normally, the aortic arch and the proximal descending aorta have much more concentrated calcification than the descending thoracic aorta^[89]. In a cohort of elderly subjects, aortic arch calcification predicted CV and all-cause mortality and addition of aortic arch calcification to CAC score moderately improved the predictive value for outcome^[90]. The prognostic significance of abdominal aortic calcification beyond the Framingham risk factors has also been documented^[68]. In a large cohort of over 2000 men and women, abdominal aortic calcification above the bifurcation of iliac arteries was predictive of CAD and CV events as well as CV and overall mortality^[91]. In hemodialysis patients, the prevalence of aortic calcification was high and the severity was associated with aging, male gender, diabetes, increased systolic blood pressure, increased serum calcium and phosphate and longer dialysis vintage^[92,93]. Aortic calcification was observed with increasing frequency from the thoracic aorta to upper abdominal aorta and lower abdominal aorta^[94]. In two cohorts of maintenance hemodialysis patients, abdominal aortic calcification predicted CV and overall mortality and nonfatal CV events^[93,95]. Calcification of the lower part of abdominal aorta appeared to be the most predictive of CV events and mortality^[94]. In non-dialysis CKD patients, the prevalence of calcification in abdominal aorta was 50% in CKD stage 3 and 80%-90% in CKD stages 4-5. The degree of VC was associated with aging, declining renal function, increasing serum phosphate and high PWV^[16,96,97]. With advancing CKD

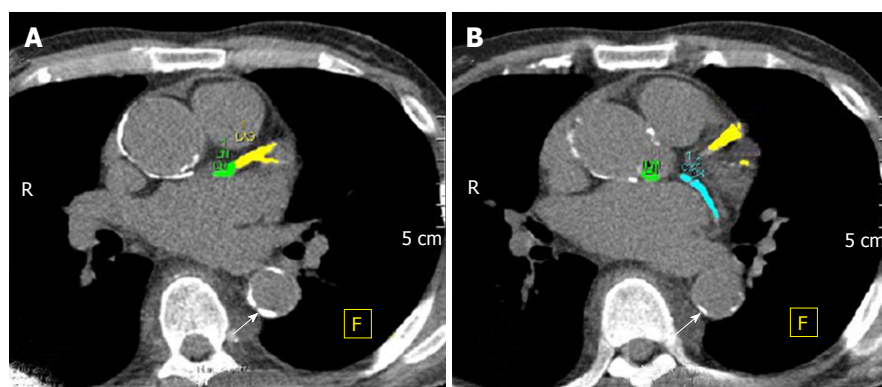


Figure 6 Coronary artery calcification (marked with colors) and descending thoracic aortic calcification (arrows) seen on non-contrast multislice computed tomography.

stages, the progression occurred more rapidly^[98]. The severity of calcification was an independent predictor for de novo CV events in CKD stages 4-5 patients^[99].

CONCLUSION

In summary, VC can be detected by several imaging techniques. Plain radiographs are simple and readily available and the presence of VC can be examined in a single X-ray film. Plain radiographs also allow differentiation between intimal and medial calcification, which comes in useful in CKD population. Mammography is especially advantageous among women because the severity of medial calcification can be assessed in images acquired during the routine screening mammogram. Ultrasonography offers a mean to evaluate arterial wall thickness and lumen size as well as calcification with the benefit of no radiation exposure. CT scan, the gold standard, is the most sensitive technique that offers an accurate and an objective analysis of the severity of VC. Plain radiographs are appropriate in situations where risk evaluation is the main focus, whereas CT scan is indispensable for accurate analysis of progression or changes after intervention.

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Targeting cannabinoid signaling for peritoneal dialysis-induced oxidative stress and fibrosis

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Abstract

Long-term exposure to bioincompatible peritoneal dialysis (PD) solutions frequently results in peritoneal fibrosis and ultrafiltration failure, which limits the life-long use of and leads to the cessation of PD therapy. Therefore, it is important to elucidate the pathogenesis of peritoneal fibrosis in order to design therapeutic strategies to prevent its occurrence. Peritoneal fibrosis is associated with a chronic inflammatory status as well as an elevated oxidative stress (OS) status. Beyond uremia *per se*, OS also results from chronic exposure to high glucose load, glucose degradation products, advanced glycation end products, and hypertonic stress. Therapy targeting the cannabinoid (CB) signaling pathway has been reported in several chronic inflammatory diseases with elevated OS. We recently reported that the intra-peritoneal administration of CB receptor ligands, including CB₁ receptor antagonists

and CB₂ receptor agonists, ameliorated dialysis-related peritoneal fibrosis. As targeting the CB signaling pathway has been reported to be beneficial in attenuating the processes of several chronic inflammatory diseases, we reviewed the interaction among the cannabinoid system, inflammation, and OS, through which clinicians ultimately aim to prolong the peritoneal survival of PD patients.

Key words: Reactive oxygen species; Peritoneal fibrosis; Peritoneal dialysis; Cannabinoid signaling; Oxidative stress

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Core tip: Long-term exposure to bioincompatible peritoneal dialysis (PD) solutions frequently results in peritoneal fibrosis and ultrafiltration failure, which limits the life-long use of PD therapy. Beyond uremia *per se*, oxidative stress (OS) also results from chronic exposure to high glucose load, glucose degradation products, advanced glycation end products, and hypertonic stress in PD patients. Therapy targeting the cannabinoid signaling pathway has been reported in several chronic inflammatory diseases with elevated OS. In this article, we review the interaction among the cannabinoid system, inflammation, and OS, through which the health-care professionals ultimately aim to prolong the peritoneal survival of PD patients.

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REVIEW ARTICLE

As chronic kidney disease progresses to end-stage renal disease, uremia ensues requiring the use of long-term dialysis therapy. Both uremia and dialysis give rise to elevated oxidative stress (OS)^[1-4], which is detrimental to the patients' health. A recent survey indicated that approximately 11% of dialysis patients undergo peritoneal dialysis (PD) therapy worldwide, estimating to be more than 272000 patients with an 8% annual growth rate globally^[5]. Beyond uremia *per se*, PD patients are at an increased risk of inflammation and OS, both systemically and locally, because of the chronic exposure to high glucose load^[6-15], advanced glycosylated end products (AGEs)^[16-18], glucose degradation products (GDPs)^[18-21], and hypertonic stress^[9,22-24]. After long-term exposure to various GDPs and AGEs, mesothelial cells of PD patients undergo a de-differentiation process, followed by peritoneal fibrosis and ultrafiltration failure^[25-29]. In a large peritoneal biopsy study, peritoneal tissue samples from 212 subjects including healthy controls, hemodialysis and PD patients were examined. They found that peritoneal fibrosis was absent in normal individuals but was present

in 28% of samples from hemodialysis patients and up to 56% of biopsies from PD patients^[30]. Although whether a uremia-induced chronic inflammation status causes OS or OS leads to a proinflammatory process in uremic patients remains uncertain^[1,4,31], therapeutic strategies for peritoneal damage targeting OS have been reported, such as antioxidants^[12,18,32,33], scavenging agents for reactive oxygen species (ROS)^[34-36], the trace element selenium^[37], and gaseous mediators^[38,39].

Cannabinoid (CB) signaling has also been reported to be effective in treating a variety of disease entities with elevated OS, including diabetic macrovascular and microvascular complications^[40-50], cardiomyopathies^[51-57], liver injury and fibrosis^[58-64], cholangiopathies^[65], colitis^[66,67], drug nephrotoxicity^[68,69], and autoimmune diseases^[70] (Table 1). Since the peritoneum of long-term PD patients is under a chronic pro-inflammatory status, it is possible that the CB receptor (CBR) signaling system may be inappropriately modulated. In this article, we reviewed the sources and influence of OS in PD patients, and the therapeutic rationale and mechanisms of targeting the CB signaling system to reduce OS.

HIGH GLUCOSE AND GDP INCREASE OS

Uremia *per se* and dialysis therapy both lead to a pro-oxidant status, which can lead to increased OS in patients receiving hemodialysis or PD therapy^[1-4]. In particular, PD patients are exposed to hypertonic glucose solution on a long-term basis, which is not only toxic to mesothelial cells^[6,71] but also promotes immune cell apoptosis^[72]. Moreover, the high-temperature sterilization process produces GDPs such as methylglyoxal (MGO), acetaldehyde, formaldehyde, and 3-deoxyglucosone in PD dialysate^[73-76]. GDPs possess strong oxidative properties and toxicity, and can induce AGEs^[77]. In addition, it has been demonstrated that MGO, a key GDP, in PD dialysates inhibits the insulin signaling pathway, resulting in increased endogenous ROS production and subsequent cell injury^[78]. Furthermore, 2-33 μmol/L of MGO has been reported to be present in commercial glucose-based PD fluids^[79,80].

After long-term exposure to various GDPs and AGEs, mesothelial cells undergo a de-differentiation process and peritoneal fibrosis ensues^[25-29]. Furthermore, these sites of chronic inflammatory have been associated with progressive peritoneal angiogenesis^[29,81-83], and finally a reduction in the efficacy of PD. However, therapeutic strategies for these pathogenic processes have not been fully developed^[81], and so some PD patients still develop peritoneal fibrosis or even encapsulating peritoneal sclerosis, a disastrous and highly fatal condition.

Low GDP PD dialysates can prevent peritoneal injury by PD-induced OS. However, the relatively high cost limits their full implementation. Moreover, even though the concentration of GDPs in the new generation of PD dialysates is low, it still exists^[84-86]. Meanwhile, as long as the PD dialysate is glucose-based, glucose load *per se* results in ROS production^[6-15]. Fortunately,

Table 1 Summary of cannabinoid signaling on modulation of diseases with increased oxidative stress

Disease	Species	Disease model	Ref.
Diabetes mellitus			
Microvascular complications			
Nephropathy	Mouse	<i>In vivo</i>	[49,50]
Retinopathy	Mouse, rat	<i>In vivo</i>	[43,44]
Neuropathy	Mouse, rat	<i>In vivo</i>	[45-47]
Macrovascular complications	Mouse, rat	<i>In vivo</i>	[40,41]
Cardiomyopathy			
Diabetic cardiomyopathy	Mouse	<i>In vivo</i>	[57]
	Human cardiomyocyte	<i>In vitro</i>	[57]
Myocardial ischemia/reperfusion	Mouse	<i>In vivo</i>	[51,53,54]
Ageing-related cardiomyopathy	Mouse	<i>In vivo</i>	[55]
Doxorubicin-induced cardiomyopathy	Mouse	<i>In vivo</i>	[52,56]
	Human cardiomyocyte	<i>In vitro</i>	[56]
	Rat cardiomyocyte	<i>In vitro</i>	[52]
	Mouse	<i>In vivo</i>	[68,69]
Cisplatin nephropathy			
Liver injury/fibrosis			
Ischemia/reperfusion hepatocyte injury	Mouse	<i>In vivo</i>	[59]
CCl ₄ -induced hepatocyte injury	Mouse	<i>In vivo</i>	[59]
Alcoholic liver fibrosis	Mouse	<i>In vivo</i>	[62]
Fibrotic activation of hepatic stellate cells	Human, rat, mouse	<i>In vitro</i>	[58,60,63,64]
Biliary diseases			
Cholangiopathies	Mouse	<i>In vivo</i>	[65]
	Mouse cholangiocyte	<i>In vitro</i>	[65]
Enteric diseases			
Inflammatory bowel disease	Mouse	<i>In vivo</i>	[66]
Colitis	Mouse	<i>In vivo</i>	[67]
Autoimmune systemic sclerosis	Mouse	<i>In vivo</i>	[70]

therapies reducing peritoneal OS are under investigation, and include antioxidants^[12,18,32,33], ROS scavengers^[34-36], selenium^[37], and gaseous mediators^[38,39] (Figure 1).

HYPERTONIC DIALYSATE-INDUCED OSMOTIC STRESS AND OXIDATIVE INJURY

In addition to low GDP PD dialysates, non-glucose-based PD dialysates such as icodextrin are free of GDPs and have been shown to be beneficial in fluid control and small solute clearance^[87]. It has also been reported that peritoneal OS is reduced when using icodextrin compared with conventional PD dialysates^[88].

However, other studies have reported conflicting results in that the osmotic stress, a type of stress resulted from hypertonic PD dialysate exposure, leads to oxidative DNA damage of peritoneal mesothelial cells through lipid peroxidation. Such peritoneal oxidative injury may then lead to mesothelial cell death either through apoptosis or necrosis^[9,22-24]. Therefore, persistent efforts are warranted to develop an optimal solution.

THE CANNABINOID SIGNALING PATHWAY AND ITS MOLECULAR MECHANISMS ON INFLAMMATION AND FIBROSIS

Our recent study suggested that using CBR ligands as an

additive in PD dialysate may be a promising solution to treat dialysis-induced peritoneal inflammation^[89]. There are two subtypes of CBRs, type 1 CB receptor (CB₁R) and type 2 CB receptor (CB₂R). The former mainly exists in the brain and regulates inhibitory neurotransmitters on neurons through the psychoactive drug cannabis or endocannabinoids such as anandamide. Nevertheless, it has recently been found that CB₁R also exists in tissues other than that of the central nervous system, and that its function varies in different organs^[73]. CB₁R antagonists and CB₂R agonists have been shown to decrease inflammation and OS^[48], and previous studies have also shown that CBR plays an important role in liver fibrogenesis^[90-94]. Moreover, hepatic fibrosis can be rescued by knockout of the CB₁R gene or by administration of the CB₁R antagonist^[93,95,96]. In contrast, CB₂R is located on immune cells and modulates cytokine release^[97,98]. Recent studies have shown that the activation of CB₂R ameliorates liver fibrogenesis through inhibiting myofibroblast cell proliferation^[92,99]. Furthermore, CBR ligands such as cannabidiol have been proven to be well-tolerated without adverse effects when administered to humans on a long-term basis^[48].

Only a few studies have been published on pharmacological modulation targeting peritoneal inflammation and fibrogenesis using CBR ligands^[100]. Our recent study indicated that the pharmacological effects of CBR ligands against dialysate-induced peritoneal fibrosis may involve a diverse signaling system including the TGF- β 1-PI3K pathway^[89], and that this offers a promising therapeutic strategy for the prevention of peritoneal fibrosis in patients receiving long-term PD. Therefore, we suggest that CBR signaling might play an important role in the patho-

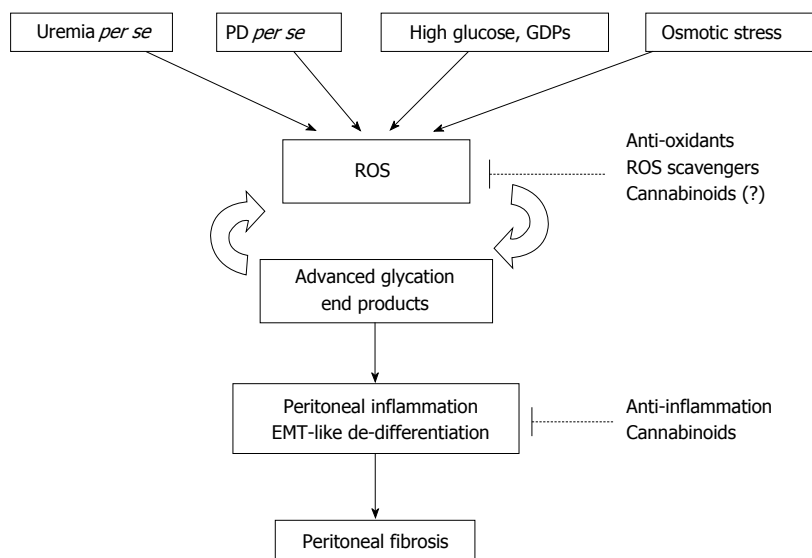


Figure 1 Peritoneal dialysis-induced oxidative stress and peritoneal fibrosis. PD: Peritoneal dialysis; GDPs: Glucose degradation products; EMT: Epithelial-mesenchymal transition; ROS: Reactive oxygen species.

genesis of dialysis-induced peritoneal inflammation and ROS production, which required further studies.

CELLULAR SOURCES OF REACTIVE OXYGEN SPECIES IN PD-INDUCED FIBROSIS

In vitro data showed that, upon GDP and AGE exposure during PD, cellular OS of human peritoneal mesothelial cells were induced through activation of protein kinase C, nicotinamide adenine dinucleotide phosphate oxidase, and mitochondrial metabolism. In turn, the generated ROS upregulate fibronectin expression by mesothelial cells^[7]. An *in vivo* study demonstrated 8-hydroxy-2'-deoxyguanosine (8-OHdG)-positive cells, indicating cells with increased OS, were observed throughout the fibrotic peritoneal tissue. Further immunofluorescent analysis revealed that 8-OHdG-positive cells also co-stained with mesothelin (mesothelial cells), CD68 (macrophages), CD31 (vascular endothelial cells), and α -smooth muscle actin (fibroblasts)^[34], suggesting that OS was also increased in cells other than mesothelial cells. However, whether these fibroblasts with increased cellular OS were derived from an epithelial-mesenchymal transition (EMT)-like process of mesothelial cells is unknown.

As aforementioned, it has been reported that CB₂R is located on immune cells and modulates cytokine release^[97,98]. The CB₂R expression of human lymphocytes was downregulated by TGF- β stimulation^[101], which was not seen in human mesothelial cells^[89]. These findings suggest that TGF- β 1 might have different physiological function in different cell types. Meanwhile, CB₂R activation might exert its anti-fibrotic effects not directly to cells undergoing fibrotic change but indirectly through modulating the immune cells. Such interaction among different types of cells underlines the pathophysiological role of CBR signaling pathway in uremic and/or dialysis

injuries, which is partly supported by a recent study showing that systemic administration of interleukin-10, an anti-inflammatory cytokines secreted by M2 macrophages, significantly reduced fibrous peritoneal thickening^[102]. Therefore, current evidence indicates that beyond mesothelial cells, macrophages and vascular endothelial cells also contribute to ROS production during PD-induced peritoneal fibrosis.

THERAPEUTIC POTENTIAL OF CANNABINOID SIGNALING ON PD-INDUCED OS AND INFLAMMATION

It has been reported that modulating the CB signaling system is beneficial in treating various diseases resulting from increased OS including diabetic macrovascular and microvascular complications^[41-43,48,57], cardiomyopathies^[51,55-57], liver injury and fibrosis^[58,60-64,103], cholangiopathies^[65], colitis^[66,67], drug nephrotoxicity^[68,69], and autoimmune diseases^[70]. At present, evidences of the therapeutic benefit of CBR ligands on peritoneal OS are lacking and deserve investigations.

Furthermore, recent studies have also shown significant anti-fibrogenic effects of CBR ligands in the liver^[91-93,95,96,99]. However, the effects of CBR ligands on peritoneal tissue have rarely been studied, with only one recent study reporting that the CB₂R agonist reduced the number of peritoneal macrophages in a murine peritonitis model induced by thioglycollate, an AGE derivative^[104]. Furthermore, we recently demonstrated that both the selective CB₁R antagonist (AM281) and the selective CB₂R agonist (AM1241) were able to ameliorate MGO-induced peritoneal fibrosis *in vivo*, indicating that pharmacological modulation of CBR may be a feasible approach to optimize the biocompatibility of peritoneal dialysis fluid. However, ACEA, a CB₁R agonist, has been shown to have an opposite effect to AM281 with regards type I collagen

expression in cultured mesothelial cells, indicating specific anti-fibrogenic activity of the CB₁R antagonist^[89].

During peritoneal fibrosis, mesothelial cells undergo a process of myofibroblastic conversion. This is a complex process which has been reported to be associated with increased levels of TGF- β 1, leptin, metalloproteinase-2, vascular endothelial growth factor, Snail, and the receptor for advanced glycosylated end products^[79,105,106]. TGF- β 1 has long been known to play crucial roles in the fibrogenic process of the peritoneum^[107,108]. A previous study demonstrated that a high glucose load stimulates the production of TGF- β 1 in peritoneal mesothelial cells^[109]. Moreover, AGEs have been shown to increase the expression of TGF- β 1, contribute to the development of sub-mesothelial fibrosis^[110], and significantly contribute to increases in peritoneal OS. Meanwhile, our recent study showed that such EMT-like processes can be attenuated by the selective CB₁R antagonist, AM281^[89]. It is quite possible that OS is involved in the CBR-related pharmacological effects against peritoneal fibrosis. However, the exact pathogenic mechanisms between the CBR signaling pathway and uremic and/or dialysis injuries remain largely unknown.

CONCLUSION

Compared with hemodialysis patients, the chronic use of PD dialysate exposes PD patients to additional OS. The influence of such OS on the patients' health can be both systemic and local, leading to cardiovascular diseases and peritoneal fibrosis, respectively. It has been shown that OS plays a critical role in the pathogenesis of chronic inflammatory diseases, and therefore targeting the CB signaling system may offer a potential therapeutic strategy to reduce dialysis-induced peritoneal fibrosis and eventually to prolong the peritoneal survival of PD patients.

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Cold dialysis and its impact on renal patients' health: An evidence-based mini review

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Abstract

Chronic renal disease is associated with advanced age, diabetes, hypertension, obesity, musculoskeletal problems and cardiovascular disease, the latter being the main cause of mortality in patients receiving haemodialysis (HD). Cooled dialysate (35 °C-36 °C) is recently employed to reduce the incidence of intradialytic hypotension in patients on chronic HD. The studies to date that have evaluated cooled dialysate are limited, however, data suggest that cooled dialysate improves hemodynamic tolerability of dialysis, minimizes hypotension and exerts a protective effect over major organs including the heart and brain. The current evidence-based review is dealing with the protective effect of cold dialysis and the benefits of it in aspects affecting patients' quality of care and life. There is evidence to suggest that cold dialysis can reduce cardiovascular mortality. However, large multicentre randomized clinical trials are urgently needed to provide further supporting evidence in order to incorporate cold dialysis in routine clinical practice.

Key words: Mortality; Cardiovascular diseases; Fatigue; Hypotension; Shivering; Renal failure

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Core tip: Cooled dialysate (35 °C-36 °C) is recently employed to reduce the incidence of intradialytic hypotension in patients on chronic haemodialysis. The studies to date that have evaluated cooled dialysate are limited, however, data suggest that cooled dialysate improves hemodynamic tolerability of dialysis and exerts a protective effect over major organs. There is evidence

to suggest that cold dialysis can reduce cardiovascular mortality and improve patients' levels of post-dialysis fatigue further improving general health and quality of life.

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INTRODUCTION

Chronic renal disease is nowadays recognised as a world-wide public health problem^[1] while cardiovascular diseases are the main cause of mortality in end-stage renal patients receiving haemodialysis (HD) therapy^[2]. HD *per se* is associated with cardiovascular and haemodynamic stress that could lead to recurrent and cumulative ischemic events to vital organs such as the brain and the myocardium. This stress is associated with perfusion abnormalities leading to myocardial hypoperfusion and myocardial stunning during HD sessions^[3].

One of the most common HD complications, affecting 20%-30% of chronic HD patients, is intradialytic hypotension (IDH) which significantly impacts patients' quality of life and overall health^[4]. Moreover, hypotensive episodes, together with the commonly experienced post-dialysis fatigue as well as myopathy and arrhythmias, contribute to an increased risk for falls and long lasting disabilities^[5]. It seems that one of the most effective, inexpensive and low risk interventions to improve haemodynamic stability during HD therapy is to lower the dialysate temperature by one or two degrees Celsius^[6,7]. This is called "cold" dialysis and it is gradually becoming a popular way of managing HD side effects to prevent IDH and post dialysis fatigue.

WHAT IS COLD DIALYSIS?

The dialysate temperature is traditionally set to 37 °C as a means of keeping stable the HD patient's body core temperature and maintain isothermia (between 36.5 °C-36.9 °C). In reality however, the "warm dialysis" does not maintain isothermia but induce a mild hyperthermic effect which on average, rise the core temperature by approximately 0.5°-0.7° Celsius^[8], which contributes further to high incidence of hypotensive episodes (as eloquently discussed in Pizzarelli^[7] 2007). In "cold" dialysis the temperature of the dialysate is set at least one degree below the standard dialysate temperature, with the majority of the cold dialysis studies using dialysate temperatures between 35 °C-36 °C^[9,10]. A better approach would be to personalise the dialysate temperature for each patient (for example by using the changes in body core temperature or 0.5 °C below resting

body core temperature). An attempt to offer personalised isothermic HD throughout the session may be an even better approach; however this is quite difficult to achieve (for example due to eating habits of patients or other internal or external variations)^[7]. In the clinical setting, most of the times, the temperature is set one degree below the standard clinical practice and guided by the patients comfort levels^[10].

The use of cold dialysis started in 1980s as an attempt to control the burden of IDH^[11,12]. Since then, the extracorporeal cooling of blood on dialysis has been employed as a countermeasure to reduce episodes of IDH, however many other benefits have been observed on patients' overall health and quality of life levels^[13].

BENEFITS OF COLD DIALYSIS

The benefits of the cold dialysis in patients' health are based on the fact that lowering the body core temperature will improve systemic vascular resistance and therefore improve haemodynamic stability^[14]. Other reasons speculated for the observed benefits are the avoidance of heat accumulation and hence counterproductive thermoregulatory vasodilation, and the catecholamine surge (especially during shivering) which in turn stimulate peripheral vasoconstriction and cardiac inotropy^[12,13]. In particular, even with modest heat storage, profound haemodynamic changes take place, including a reduction in peripheral vascular resistances, elevated heart rate, cardiac output and increased muscle sympathetic nerve activity, resulting in increased blood flow to the skin and leaving the body defenceless to hypotension^[15], a phenomenon that does not take place during cold stress. It should be noted, that at least in healthy subjects, the response to heat accumulation will occur even in the face of a "hypovolaemic stress"^[16], a further consideration in HD patients.

Intradialytic hypotension

IDH is an independent risk factor for cardiovascular mortality in HD patients^[17] and significantly affects patients post dialysis energy levels and overall quality of life^[18]. Many therapeutic interventions have been applied in order to reduce IDH, however, a single approach that would successfully prevent or solve this issue doesn't yet appear to exist. Cold dialysis is a very promising approach for the prevention of IDH with many studies reporting improvements in haemodynamic stability including reduction in heart rate, cardiac output and stroke volume leading to high arterial blood pressure maintaining thus a greater total peripheral resistance^[6,15]. A study has shown that IDH occurred 7.1 times less frequently with cold dialysis while the post-dialysis mean arterial pressure was higher with cool-temperature dialysis by 11.3 mmHg^[14]. In addition, cold dialysis resulted in significantly fewer nursing trips to patient's bed and even fewer interventions for the treatment of IDH, positively influencing the functionality of the HD unit^[19] and the

Table 1 Pros and cons implementing “cold dialysis”

Measurable and perceived benefits	Measurable and perceived side effects
Reduce intradialytic hypotension incidences Induce hemodynamic stability Reduce ischemic brain injuries and preserving brain's white matter Improve cardiac functionality and morphology indices Control arterial blood pressure during and after haemodialysis Reduce post-dialysis fatigue Increase energy levels Dialysis efficiency is not changed Improve overall perception of general health Reduce the number of nursing interventions during HD Can be delivered without additional cost and is universally applicable	Possible patient discomfort (shivering)

HD: Haemodialysis.

level of overall care.

Cardiovascular and cerebrovascular risk

HD patients are at high risk of cardiovascular mortality which has been reported as 15%-20%^[20] and 38%^[2] of all cause deaths. The causes of the high cardiovascular mortality are multifactorial including traditional (diabetes, hypertension) and non-traditional (uremic-related), however, the HD *per se* is a very strong contributor into the overall mortality affecting myocardial functionality (e.g., myocardial stunning and hibernation) and morphology^[21]. Benefits of the long term cold dialysis (1 year) have been reported in the recent literature in both brain and heart tissues. In the brain, cold dialysis seems to induce a protective effect from injurious perfusion of the cerebral vascular beds, thus minimizing HD induced brain injuries^[9]. In the heart, after a long term induction of cold dialysis (0.5 °C below body core temperature) positive changes in resting ejection fraction were observed accompanied with significant reductions in both left ventricular mass and left ventricular end-diastolic volumes while the aortic distensibility was preserved, thus minimizing the risk for future cardiovascular events^[22].

Dialysis efficiency

Due to the vasoconstriction effect induced by the cold dialysis, it was postulated that dialysis efficiency indices would be reduced as a result of the increased compartmentalization of urea and the post-dialysis increased rebound effect^[23]. Many studies including two systematic reviews concluded that cold dialysis do not change blood volume, urea rebound or effective Kt/V index leaving dialysis efficiency unchanged^[6,14] while one study showed significant improvements in urea removal and Kt/V^[24].

Patients perception

In general, HD patients tolerate long term cold dialysis very well, reporting high levels of satisfaction (76%-80%), less fatigue, faster recovery times after dialysis, feeling more energetic, with better cognitive capacity and having the overall sensation that their general health

has dramatically improved (Table 1)^[14,24,25]. Most authors reported that at the end of the trial period, a large number of patients requested to always be dialysed with a cooler dialysate^[13]. It seems that cold dialysis has also a positive impact in dialysis units' functionality since many studies have reported a reduced number of nursing interventions during HD and less in-patient admissions for treating post-dialysis hypotensive symptoms^[13]. The most commonly reported cold dialysis side effects are related to cold sensation with 20% of the patients reporting to be feeling cold^[13] while some studies have also reported incidences of shivering^[25]. No other serious disadvantages of cold dialysis have been reported in the recent literature, however, the lack of long term interventions and properly designed randomized clinical trials justifies the modest implementation of cold dialysis in the majority of the dialysis units worldwide.

CONCLUSIONS AND RECOMMENDATIONS

Lowering the dialysate temperature in HD patients' routine therapies can reduce the rate of intradialytic hypotension by increasing peripheral resistance leading to increased intradialytic mean arterial pressure without jeopardising dialysis adequacy. There is evidence to suggest that cold dialysis can reduce cardiovascular mortality and improve patients' levels of post-dialysis fatigue further improving general health and quality of life. Large, multicentre, randomized clinical trials are urgently needed to provide further supporting evidence on aspects related to mortality and major adverse cardiovascular events.

KEY POINTS

Cold dialysis is achieved by lowering the dialysate temperature to 35 °C-36 °C or 0.5 °C below resting body core temperature. Cold dialysis can be implemented with no additional cost and is universally applicable. Cold dialysis reduces incidence of intradialytic hypotension and improve patients' “energy” levels. Cold dialysis could induce some general discomfort to the patients.

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Role of imaging in the evaluation of renal dysfunction in heart failure patients

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Abstract

Heart failure and kidney disease share common pathophysiological pathways which can lead to mutual dysfunction, known as cardiorenal syndrome. In heart failure patients, renal impairment is related to hemodynamic and non-hemodynamic factors. Both decreased renal blood flow and renal venous congestion due to heart failure could lead to impaired renal function. Kidney disease and worsening renal function are independently associated with poor prognosis in heart failure patients, both in acute and chronic clinical settings. The aim of this review is to assess the role of renal imaging modalities in the evaluation and management of heart failure patients. Renal imaging techniques could complete laboratory data, as estimated glomerular filtration rate, exploring different pathophysiological factors involved in kidney disease and adding valuable information about renal structure and function. In particular, Doppler examination of arterial and venous hemodynamics is a feasible and non invasive technique, which has proven to be a reliable method for prognostic stratification in patients with cardiorenal syndrome. The renal resistance index, a measure related to renal hemodynamics, can be calculated from the Doppler evaluation of arterial flow. Moreover, the analysis of Doppler venous flow patterns can integrate information from the arterial study and evaluate renal congestion. Other imaging modalities are promising, but still confined to research purposes.

Key words: Heart failure; Doppler; Renal resistance index; Hemodynamics; Venous Doppler; Prognosis; Cardiorenal syndrome; Chronic kidney disease

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Core tip: Kidney disease is a common condition affecting

heart failure patients. Cardiorenal syndrome defines the complex interaction with mutual deterioration of these organs. This review aims to describe currently available renal imaging techniques, especially arterial and venous Doppler, and to discuss the potential usefulness of promising research methodologies.

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INTRODUCTION

Over the last few years, there has been growing interest in the interaction between heart and kidney disease, especially in the clinical setting of heart failure (HF). Cardiovascular and renal diseases share common pathophysiological pathways, as the heart function is greatly influenced by fluid balance operated by the kidney. On the other hand, renal function is strictly dependent of blood flow and pressure, both downstream and upstream of the heart^[1,2]. This interaction can lead to a mutual deterioration that has been defined as cardiorenal syndrome (CRS), *i.e.* the complex condition in which the acute or chronic impairment of one organ can lead to the deterioration of the other^[3].

The mechanisms involved in the pathogenesis of renal dysfunction in acute and chronic scenarios are primarily hemodynamic. Both decreased renal blood flow and renal venous congestion are independent determinants of worsening renal function (WRF) in patients with heart failure^[4]. Impaired cardiac index or intravascular volume depletion caused by aggressive diuretic therapy lead to renal hypoperfusion and eventually to reduction of glomerular filtration rate (GFR). Furthermore, renal venous congestion has an even greater importance in WRF^[5]. High venous pressure can increase renal interstitial pressure and glomerular capillary pressure, impairing filtration function and reducing GFR^[6]. In addition, non hemodynamic factors are involved in WRF, such as neuro-hormonal hyperactivation, endothelial dysfunction and underlying intrinsic kidney disease. Renal impairment and WRF are independently associated with mortality in HF patients, both in acute and chronic settings^[7-10].

Different imaging modalities can explore renal dysfunction, regarding anatomy, perfusion and estimated pressures. The aim of this paper is to analyze the use of current techniques in the diagnosis and management of heart failure patients. Renal imaging techniques are summarized in Table 1, with respective advantages and limitations. In particular, we will focus on renal Doppler techniques used to calculate arterial resistive index and evaluate abnormal spectral venous patterns in order to identify venous congestion.

RENAL ULTRASONOGRAPHY

Ultrasound is a safe, low-cost and easily available technique for the morphological evaluation of kidneys. It is especially helpful in differentiating acute from chronic kidney disease and ruling out urinary obstruction as a cause of renal impairment. Normal renal long axis is 10-12 cm and is associated with height^[11]. Reduced dimensions are usually seen in chronic kidney disease, although not every chronic alteration may show small kidneys. Increased kidney volume may occur in infiltrative diseases (lymphoma, amyloid nephropathy), parenchymal edema and inflammation, and renal vein thrombosis. Normal parenchyma is isoechoic or hypoechoic compared to the liver. Increased echogenicity is typically associated with chronic disease and is caused by the presence of fibrosis, inflammatory infiltrates and proteinaceous casts^[12,13].

In the acute prerenal failure due to HF (*i.e.*, cardiorenal syndrome type 1), there are no specific findings at the conventional ultrasound examination. In the absence of pre-existing abnormalities, renal dimensions and cortical thickness are generally normal. Increased echogenicity may occur in case of long-standing renal hypoperfusion. Furthermore, signs of urinary tract obstruction are absent and the bladder should be empty^[14].

In cardiorenal syndrome type 2 nonspecific ultrasonographic parameters of chronicity have been observed. Renal dimensions are reduced, with thinner cortex and reduced cortex-medulla ratio. Hyperechoic cortical parenchyma is commonly caused by interstitial fibrosis. As for kidney disease associated with acute heart failure, no signs of urinary obstruction are expected, provided no renal comorbidity are present^[15].

RENAL ARTERY ECHO DOPPLER AND ARTERIAL RENAL RESISTANCE INDEX

The role of ultrasound in HF patients is greater when the study of renal flow by pulsed Doppler technique is considered. In particular, Doppler evaluation allows the evaluation of both arterial and venous renal blood flow.

Doppler technique to assess arterial resistance index

The evaluation of arterial flow provides a measure which reflects the complex pathophysiological mechanisms underlying the progression of renal kidney disease in HF, *i.e.*, the arterial renal resistance index (RRI). The non invasive evaluation of renal arterial hemodynamics is currently allowed by use of Doppler ultrasound. Resistance index is a commonly used variable calculated by the spectral analysis of arterial Doppler waveform using Pourcelot's formula, *i.e.*, peak systolic velocity minus end-diastolic velocity, divided by peak systolic velocity^[16] (Figure 1). In the kidney circulation, RRI is calculated analyzing the intrarenal arterial waveform at the level of segmental arteries^[17]. The classical ultrasound technique used in order to evaluate renal arteries is the anterior approach with a convex probe. It is also

Table 1 Advantages and limitations of renal imaging techniques

	Clinical relevance	Advantages	Limitations
Bidimensional ultrasonography	Morphological evaluation (dimensions; echogenicity; corticomedullary ratio)	Fast; highly feasible in clinical practice; excludes obstructive uropathy and some parenchymal abnormalities	Nonspecific
Arterial RI (Doppler)	Indirect evaluation of arterial hemodynamics (resistances and vascular compliance) and parenchymal alterations	Fast; highly feasible in clinical practice; prognostic value	Influenced by renal obstructive arterial disease; lower accuracy with irregular rhythms
Venous pattern (Doppler)	Indirect evaluation of venous congestion, right atrial function and parenchymal compliance	Fast; highly feasible in clinical practice; prognostic value	Lack of standardization
Computed tomography	Evaluation of GFR through measurement of contrast wash-out	High spatial resolution	Nephrotoxicity of contrast media; radiation exposure
Nuclear imaging	GFR and RBF estimation through DTPA and MAG3 ^{99m} Tc labelled uptake intensity measurement	Low radiation dose	Radiation exposure
MRI		No radiation exposure	Time consuming; expensive
Phase-contrast MRI	Evaluation of RBF	No use of Gadolinium	Breathing movement artefacts
Dynamic MRI	Evaluation of GFR through measurement of signal attenuation	Reliable	Particularly time consuming (> 70 min)
BOLD MRI	Evaluation of renal parenchymal oxygenation exploiting superparamagnetic properties of desoxyHb	No use of Gadolinium; unique method to assess this parameter	Lack of standardization; low signal change of BOLD effect; no clinical applications
MRI detectable nanoparticles	Evaluation of single-glomerulus volume and structural changes	No use of Gadolinium; unique method to image renal parenchyma at microscopic level	Prone to movement artefacts; possible toxicity of nanoparticles; no clinical applications

BOLD: Blood oxygen level dependent; GFR: Glomerular filtration rate; MRI: Magnetic resonance imaging; RBF: Renal blood flow.

possible to perform the Doppler analysis during a routine echocardiographic examination with the same probe and the patient in a sitting position, with a posterior approach to the kidney^[18].

In healthy adults, normal renal RI values are around 0.60, with a difference between the two kidneys of less than 5%-8%^[19]. An RI of 0.70 or higher is considered abnormal and generally predictive of an unfavourable outcome^[17,20]. RI reproducibility is considered good in most cases: When performed by experienced investigators, intra-observer variability ranged from 2.07% to 5.1% and inter-observer variability ranged from 3.61% to 6.2%. Differences in RI values between 0.05 and 0.04 are not significant^[21].

Physiopathological mechanisms related to RRI

Glomerular blood pressure, and consequently renal blood flow (RBF), is one of the main driving forces of glomerular filtration. Unlike other organs, RBF is not primarily regulated on the basis of oxygen demand. Reflex (myogenic reflex and tubular-glomerular feedback) and neurohormonal mechanisms are mainly involved in the control of RBF, acting at the level of efferent and afferent arteriolar tone. The autoregulation mechanisms stabilize renal perfusion within a range of arterial pressure between 70 and 180 mmHg. RBF and GFR are adjusted in parallel and fluctuations of arterial pressure, both in physiological and in pathological conditions within the autoregulatory range, will not lead to substantial changes

in filtration. Out of autoregulatory range, GFR becomes greatly dependent on RBF^[22,23].

In normal conditions, a decrease in cardiac output (CO) will cause the autoregulatory system to reduce renal resistances, in order to keep renal flow (and GFR) within normal range. A depletion or an overrule of these regulatory systems by neurohormonal mechanisms, as in heart failure, could potentially determine a dissociation between CO and RBF, related to an increase of intrarenal resistances. So the increase of arterial resistances, *e.g.*, due to hyperactivation of sympathetic nervous system, could lead to a disproportional decrease in renal perfusion pressure and RBF in the presence of reduced CO, that will result in a deteriorated glomerular filtration and WRF^[23]. In renal circulation, the arterial resistances are affected by a number of factors other than the arteriolar tone: Arterial stiffness, atherosclerosis, parenchymal lesions and renal venous congestion.

A sustained increase in renal resistances, due to long-standing vasoconstriction, leads to a decrease in the number of the perfused vessels without anatomical changes in microvascular anatomy. The functional (or structural) loss of vessels has been termed vascular rarefaction^[24]. A persistent functional rarefaction, whatever the cause, may lead to progressive vascular changes (*i.e.*, vascular remodelling) caused by tissue ischemia, release of enzymes and growth factors which in turn result in fibrosis. Therefore the functional rarefaction could cause a structural rarefaction, with an actual reduction in

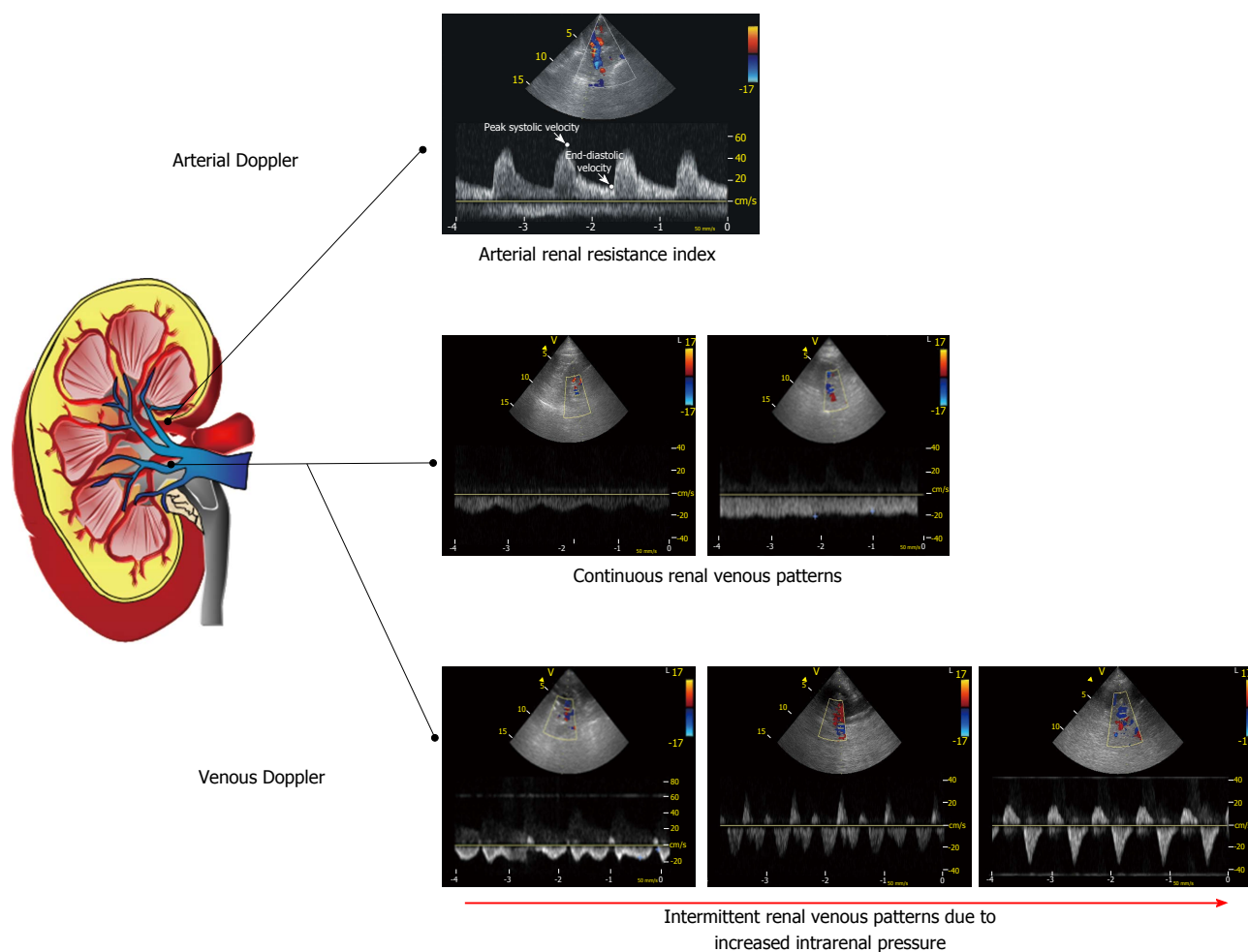


Figure 1 The arterial and venous Doppler evaluation is summarised. For renal venous Doppler the continuous and intermittent patterns are represented.

renal vasculature and a permanent increase in arterial resistances^[25]. The microvascular rarefaction is associated with reduced RBF and, eventually, impaired glomerular function.

Renal arterial resistance index and clinical correlates

RI doesn't reflect vascular resistances with a totally linear relationship, instead it has a complex interaction with resistances and vascular compliance, as evaluated in experimental *in-vitro* and *ex-vivo* models^[26-29]. Heart rate and rhythm disturbances can also independently affect RI values, as different diastolic duration in extreme bradycardia and tachycardia can alter end-diastolic velocity^[30,31].

A recent study evaluated the physiological and pathological determinants of RI in a population of chronic heart failure patients with depressed ejection fraction. As expected from the results of experimental models, RI was independently correlated with factors commonly associated with renal artery abnormalities and increased arterial stiffness, such as age, diabetes, and pulse pressure. Other significant predictors are systolic pulmonary pressure, GFR, and NYHA class. Furthermore, central venous pressure (CVP) is also a significant determinant of RI, because an increase in CVP

and intra-abdominal pressure will lead to an increase in renal interstitial pressure and consequently in vascular resistances^[18].

The prognostic role of RI was initially evaluated in patients with renal parenchymal abnormalities. Increased RI values were associated with tubulointerstitial and vascular lesions at the renal biopsy^[32]. Moreover, patients with higher values showed poorer renal prognosis, with a greater risk of worsening renal function over time^[33].

Prognostic relevance of RRI in HF

In the clinical setting of HF, renal RI was first evaluated in a population of patients with HF with preserved ejection fraction. RI was higher in patients with HF, compared to controls affected only by arterial hypertension and it was also associated with poor prognosis^[34]. The role of RI in predicting worse outcomes was also studied in the setting of HF with reduced ejection fraction^[18]. In this series of CHF outpatients, RI was independently associated with a composite endpoint reflecting HF progression: Hospitalization due to acute decompensated HF, urgent heart transplantation and death due to worsening HF. The prognostic role of RI was independent from GFR, as patients with an RI above 0.75 were at higher risk of events irrespective of GFR values^[18]. Subsequently, RI

was also associated with all-cause mortality in the same population^[35]. In the setting of CHF, RI was independently associated with one year worsening of renal function (increase in creatinine level > 0.3 mg/dL) and with an usage of high doses of loop diuretics^[36,37]. Therefore higher values of RI could predict poor diuretic response and identify patients prone to diuretic resistance, possibly because increased renal resistances lead to a reduced delivery of diuretic drugs to the site of action.

Renal RI shows an incremental role compared to GFR in the evaluation of renal function in HF patients. Taking into account different pathophysiological pathways, RI could be used together with estimated GFR in order to better define renal function in this population, considering not only glomerular filtration function, but also hemodynamic and systemic factors eventually related to WRF and prognosis.

RENAL VENOUS ECHO DOPPLER AND VENOUS PATTERNS

Doppler technique to assess venous flow

In addition to arterial flow profile, echo Doppler techniques allow the analysis of venous flow. The Doppler assessment of renal venous waveform is performed at the middle tract level of an interlobar vein, based on color Doppler signals. Venous waveform is recorded at the end of expiration of suspended respiration with a posterior approach and the patient in a lateral decubitus position or in a sitting position (Figure 1). Renal venous impedance index (VII) is a measure of vein pulsatility and is calculated from Doppler waveform, *i.e.*, maximum velocity minus minimum velocity, divided by maximum velocity.

Physiopathological mechanisms related to venous flow pattern

Besides reduced arterial flow, the role of increased central venous pressure and renal venous congestion is now widely accepted as one of the main pathophysiological mechanisms in impaired renal function both in chronic and acute decompensated heart failure^[5,38]. *Ex-vivo* animal models, as far back as the 1931, have demonstrated the association between renal venous congestion and reduced RBF. In isolated kidneys, increased venous pressure leads to greater reduction in RBF, compared to changes in renal arterial pressure^[39]. Subsequently, it has been reported that patients with HF have elevated renal venous pressure compared to subjects with no evidence of cardiovascular or renal disease^[40].

The consequences of venous congestion for renal hemodynamics and function are different. A high renal venous pressure would cause congestion of peritubular and glomerular capillaries, reducing the arterio-venous gradient over renal circulation and thereby impairing blood flow. In normal kidneys, the autoregulation will keep GFR within normal range despite the decrease in RBF. If

regulation mechanisms are depleted, the reduced pressure gradient could impair glomerular filtration and lead to renal dysfunction. Furthermore, venous hypertension will also be transmitted to the low-compliance interstitium, because of the stiffness of renal capsule, causing an increase in interstitial pressure. The high renal interstitial pressure will increase tubular pressure and, upstream, also the Bowman's capsule hydrostatic pressure, reducing the gradient between glomerular capillary pressure and capsular pressure, one of the basic forces for filtration function. Decreasing the net filtration pressure, renal congestion will directly affect GFR, independently from RBF^[17].

Venous flow pattern and clinical correlates

Renal veins have phasic flow associated with respiration and right atrial function. Left vein phasicity is attenuated because of the entrapment in the fork between the abdominal aorta and the superior mesenteric artery. Veins are high capacitance vessels, with negligible resistance to blood flow, so pulsatility is strictly dependent on surrounding tissue compliance. The main determinants of intrarenal vein flow patterns are parenchymal histology, central venous pressure and abdominal pressure^[41]. Besides the association with tissue characteristics, renal venous flow is strictly dependent on right heart function. The increase in CVP during end-diastole (corresponding to atrial contraction) can be transmitted to renal veins, especially in patients with congested inferior vena cava and hepatic veins as in HF, causing the damping or eventually the reversal of vein flow.

Renal venous flow was initially evaluated in obstructive kidney disease: Since one of the main determinants of pulsatility is parenchymal compliance, it has been thought that Doppler waveform could be useful to diagnose acute obstructive uropathy before anatomical alterations occur. In fact reduced tissue compliance, caused by uropathy, results in dampening of the renal venous signal^[42,43]. Moreover, venous Doppler study showed a greater sensitivity than RI in order to evaluate obstructive uropathy^[44]. Venous waveforms have also been evaluated in a population of patients with diabetic nephropathy: Diabetic patients show diminished venous modulation, with significantly lower VII values compared to healthy subjects. This could be due to interstitial fibrosis progressively reducing parenchymal compliance^[41].

Prognostic relevance of venous pattern in HF

Iida *et al.*^[45] evaluate intrarenal venous flow and VII in a population of outpatients and hospitalized patients affected by heart failure. They found three vein flow patterns: Continuous, biphasic discontinuous and monophasic discontinuous. Patients with monophasic flow were generally older, with worse renal function, elevated right atrial pressure (RAP) and lower hepatic S/D ratio. At the multivariate analysis intermittent patterns were associated with significant hemodynamic factors reflecting venous

congestion. In particular, monophasic pattern was associated with right ventricular fractional area change, moderate to severe tricuspid regurgitation, higher RAP and lower hepatic S/D ratio. Furthermore, discontinuous patterns were associated with worse prognosis, independently of CVP and hepatic vein flow^[45].

Recently our group evaluated renal venous waveform in a large population of HF outpatients with reduced ejection fraction. Five venous patterns were identified: Flow with normal velocity decrease of telediastolic velocity without interruption (pattern A); continuous flow with reduced modulation (pattern B); forward flow with short presystolic interruption or reversal (pattern C); polyphasic intermittent flow (pattern D); monophasic intermittent flow, with one forward and one reversal wave (pattern E). As in the previous study, patients with intermittent flow patterns (pattern D and E) had worse clinical conditions in our series: They had higher estimated RAP and pulmonary artery systolic pressure, more severe tricuspid regurgitation and worse renal function. Moreover, we confirmed the prognostic role of venous patterns in HF: Pattern C, D and E were associated with events during follow-up at the univariate and multivariate analysis. Patients with intermittent pattern (D and E) showed worse prognosis compared to other groups, while pattern C was associated with an intermediate risk for events. In pattern C we observed the interruption or reversal of flow during atrial contraction, probably related to mild increase in CVP. This pattern may identify patients in the early phase of renal congestion. Differently from the study of Iida *et al.*^[45], there were no prognostic differences between polyphasic and monophasic intermittent patterns, they are both related to worse venous congestion and identify patients at higher risk^[46].

In conclusion, venous Doppler evaluation shows an incremental prognostic role in the clinical setting of heart failure. Information about renal congestion carried by venous patterns may integrate the arterial study performed with RI in order to better characterize the renal impairment in HF.

COMPUTED TOMOGRAPHY

Albeit computed tomography (CT) is considered the gold standard in the assessment of renal stones and masses, its role in the evaluation of kidney function, referred as GFR and RBF, is limited in clinical practice. The so-called "functional CT" can provide useful information about GFR, but it is currently only performed in a few centres and its suitability, particularly in patients with impaired renal function, is hampered by the risk of contrast induced nephrotoxicity^[47].

In this regard, Hackstein *et al.*^[48] have demonstrated a good correlation between GFR, measured with iopromide plasma clearance (considered the gold standard method in this study), and GFR measured by triphasic helical CT of the abdomen (*i.e.*, unenhanced examination followed by two contrast medium enhanced exams in

the arterial and portovenous phase). Nevertheless this study highlighted several limitations regarding the routine use of this technique in clinical practice; first of all, patients with acute kidney injury having been excluded from recruitment, they could not be eligible for this technique; secondly, to justify radiation exposure, GFR measurement by functional CT was performed in patients who underwent triphasic helical CT for clinical reasons other than kidney dysfunction^[48]. In the setting of heart failure, there is very scarce literature about this topic.

NUCLEAR IMAGING

The functional evaluation of kidneys is commonly performed with the use of radioisotopes, with Technetium (99m Tc) preferred above all for its short half-life and low radiation exposure, bound to non-metabolized molecules, namely DTPA for GFR measurement and MAG3 for renal blood flow. This technique can help us to distinguish between the different forms of AKI. In case of prerenal azotemia (as in the setting of cardiorenal syndrome type 1) renal uptake of MAG3 is normal, within 1-2 min following injection, whereas in parenchymal and vascular diseases (as in Acute Tubular Necrosis) it is expected to be reduced. In the late phase, about 20 min after tracer injection, we would expect a rise in renal uptake in patients with pre-renal or renal AKI, and a decrease of it in case of obstructive uropathy^[47,49].

In addition to functional data, important structural information can be obtained by performing Positron Emission Tomography (PET). This technique, when combined with CT scanning has the great advantage of combining anatomic and functional data, thus enabling localization of abnormally functioning renal areas. However nowadays its clinical applications are scarce and usually limited to research purposes^[47].

MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI) offers the optimal combination between spatial resolution and functional evaluation, in other words between a structural and a functional study^[50,51]. Furthermore, it avoids the use of iodinated contrast media and radioisotopes, which is obviously of great advantage in patients suffering from CKD. The main issues with this promising imaging modality are the lack of standardization in its different protocols, with the subsequent inter-observer variability, and the need for interventional studies that should validate this technique showing their clinical value.

MRI provides a pretty wide range of approaches in the assessment of renal function: From the classical parameters GFR and RBF to more innovative ones, such as renal blood oxygenation^[52] and single glomerulus volume^[53].

Information about RBF is classically obtained by phase-contrast MRI of the renal artery. This method exploits the magnetic properties of the water molecules, located in the blood, when excited by the magnetic

fields^[54]. This can let us avoid the use of gadolinium and hence, it is particularly useful in those patients, with severely reduced kidney function (GFR < 30 mL/min), in whom the use of gadolinium would expose the risk of SNF (systemic nephrogenic fibrosis).

On the other hand, the determination of GFR is substantially based on the evaluation of the filtration rate of a substance (gadolinium) which is filtered by the glomerular membrane but not reabsorbed from the tubular lumen, just like inulin (used as the gold standard in the assessment of GFR).

In this regard, the most common approaches in clinical practice are two^[52]: The first, Patlak-Rutland plot technique, refers to a two compartmental model (only preglomerular and intra-tubular compartments are taken into account) and evaluates the change in signal intensity of a ROI located in the renal cortex; the extent of the signal increase in the cortex after bolus injection is correlated with glomerular filtration rate^[55]. The second consists of evaluating the GFR by considering the wash-out of the filtration marker, *i.e.*, gadolinium, from the interstitial space, represented by a ROI in the liver^[56]. This method has been adopted in both healthy and CKD affected patients showing reasonably good results^[57,58]. The main draw-back is the long time required for acquisition (about 70 min)^[52].

Alternatively, GFR can be obtained indirectly from the measurement of renal blood flow (RBF) and renal extraction fraction (REF) which is derived from the intensity gradient of the gadolinium between the renal artery and renal vein. As the REF is equal to the ratio between GFR and RBF, the GFR is determined through the product between RBF and REF^[52,59].

Recently, the world of MRI for the study of kidney function has seen a further development towards the microscopic level and molecular imaging, such as with blood oxygen level dependent (BOLD) MRI and MRI detectable nanoparticles. The BOLD MRI offers the unique chance of evaluating renal tissue oxygenation relying on the different magnetic properties of haemoglobin. Oxygenated haemoglobin is diamagnetic, while deoxygenated haemoglobin shows paramagnetic activity, thus yielding a drop in the T2* curve that corresponds to a decrease in image signal intensity^[60]. Despite still being in a primordial phase and hampered by the variability of absolute values between the studies, this technique shows indisputable advantages when compared to other gross types of renal function evaluation and could open the door to a possible use in clinical settings not necessarily related only to primitive renal disease. This could be the case, for example, with cardiorenal syndrome type 1, *i.e.*, acute deterioration of kidney function secondary to heart failure. We know from physiology, confirmed by a few studies^[52], that renal parenchyma exhibits inhomogeneous oxygenation and that the medulla region is more sensitive to a reduction in blood oxygen supply. We can then postulate that, a drop in renal perfusion, secondary to heart dysfunction, could lead to a rise in deoxygenated blood to the medulla and thus

in T2* curve decay well before an increase in serum creatinine would be detectable.

When the limits of BOLD effect are overcome we will be able to use this technique to deeply understand the mechanisms underlying CRS and, possibly, promptly recognize and prevent kidney ischemia at an early stage. Currently there are no studies or trials available about this topic.

Moreover, the technique based on utilization of MRI detectable nanoparticles is also promising.

This revolutionary method would allow the evaluation of the volume and of the structural changes involving the single glomerulus, using an MRI detectable targeted marker. The specific molecule adopted is ferritin, which, with its superparamagnetic properties, can perturbate the magnetic fields of nearby protons and reduce their T2 and T2* relaxation time. This, in turn, will result in a reduction of the MRI signal intensity or, in other words, in a dark spot. Furthermore, ferritin is artificially cationized in order to consent binding with negative charges of proteoglycans located in the basal glomerulus membrane (BGM). In this way, after the systemic injection of the detectable molecule, we are able to image every glomerulus as a dark spot in the renal cortex^[53].

The horizons opened by this method are obviously huge but, for now, confined mainly to preclinical studies.

CONCLUSION

Kidney disease in the setting of heart failure identifies patients prone to adverse events independently from cardiac function. Therefore, the assessment of renal function has a key role in the management of HF patients. Renal imaging could have a complementary role in relation to laboratory data: Imaging techniques explore different pathophysiological pathways involved in renal disease and may identify a worsening of function even before an increase in serum creatinine occurs. In particular, Doppler examination of arterial and venous waveforms provides a feasible and non invasive evaluation of renal hemodynamics, considering systemic and parenchymal factors involved in cardiorenal interaction. With regard to other imaging modalities, even though they seem promising in providing insight to kidney function and microscopic changes, most of them are, so far, still confined to research purposes.

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Case Control Study

Any link of gout disease control among hypertensive patients and onset of end-stage renal disease? Results from a population-based study

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Abstract

AIM

To determine the impact of allopurinol non-adherence as a proxy for uncontrolled disease on primary prevention of end-stage renal disease (ESRD).

METHODS

A cohort of 2752 patients with gout diagnosis was reconstructed using the Québec Régie de l'assurance maladie du Québec and MedEcho administrative databases. Eligible patients were new users of allopurinol, aged 45-85, with a diagnosis of hypertension, and treated with an antihypertensive drug between 1997 and 2007.

RESULTS

Major risk factor for ESRD onset was chronic kidney disease at stages 1 to 3 [rate ratio (RR) = 8.00; 95% confidence interval (CI): 3.16-22.3 and the severity of hypertension (≥ 3 vs < 3 antihypertensives)] was a trending risk factor as a crude estimate (RR = 1.94; 95%CI: 0.68-5.51). Of 341 patients, cases ($n = 22$) and controls ($n = 319$), high adherence level ($\geq 80\%$) to allopurinol therapy, compared with lower adherence level ($< 80\%$), was associated with a lower rate of ESRD onset (RR = 0.35; 95%CI: 0.13-0.91).

CONCLUSION

Gout control seem to be associated with a significant

decreased risk of ESRD onset in hypertensive populations, further research should be conducted confirming this potential associated risk.

Key words: Allopurinol; End-stage renal disease; Gout; Hyperuricemia; Medication adherence; Serum uric acid

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Core tip: The question of whether serum uric acid has a pathogenic role in the onset and progression of chronic kidney disease (CKD) remains unanswered. Hyperuricemia and gout is common in CKD, and treatment adherence in gout patients is suboptimal and therefore a therapeutic challenge. Our population-based study assessed the impact of gout disease control on the risk of end stage renal disease (ESRD). Our study suggest that adherence to allopurinol of $\geq 80\%$ as a proxy for gout control is associated with a significant, 65% reduction in the risk of ESRD onset.

Perreault S, Nuevo J, Baumgartner S, Morlock R. Any link of gout disease control among hypertensive patients and onset of end-stage renal disease? Results from a population-based study. *World J Nephrol* 2017; 6(3): 132-142. Available from: URL: <http://www.wjgnet.com/2220-6124/full/v6/i3/132.htm> DOI: <http://dx.doi.org/10.5527/wjn.v6.i3.132>

INTRODUCTION

Gout is a chronic disease and one of the most common inflammatory arthritis conditions among adults. Gout is caused primarily by inefficient renal excretion of uric acid, resulting in increased serum uric acid (sUA) levels (*i.e.*, hyperuricemia), and ultimately, deposition of monosodium urate crystals within joints, connective tissue, kidneys, and other organs. The accumulation of crystal deposits lead to acute, painful inflammatory arthritis (*i.e.*, flares) and tophi; if not appropriately treated, gout can cause permanent joint destruction, bone erosion, and kidney damage^[1]. The prevalence estimates of gout from the 2007 to 2008 United States National Health and Nutrition Examination Survey are 5.6% among men and 2.0% among women^[2].

The pathogenesis of gout is well established, and the role of sUA for acute and chronic conditions of gout is linked to the deposition of monosodium urate crystals. Reducing sUA levels prevents further crystal deposition and allows dissolution of existing deposits, effectively curing the disease. The American College of Rheumatology^[3] and European League Against Rheumatism^[4] have published guidelines for the use of urate-lowering therapies for gout management. Targeting sUA is important in the management of gout because high levels are linked to up to a 3-times risk of an acute gout flare^[5] and a higher annual frequency of flares^[6]. Moreover, studies report continued poor outcomes in gout patients^[7], in-

cluding recurrent flares, functional incapacity, and risk of additional joint damage, as well as the potential for renal and cardiovascular complications^[8]. The potential relationship of elevated sUA and all-cause mortality has also been suggested by several population-based^[9,10] cohort studies. Recent estimates have shown that overall aggregate annual costs for the medical care of gout patients exceeded \$20 billion in the United States alone, with provisional estimates of annual direct and indirect costs of gout patient care totaling over \$6 billion^[11].

In a recent meta-analysis on adherence to allopurinol, it was clear that allopurinol adherence was suboptimal and therefore a therapeutic challenge in gout^[12]. Among the systematic reviews provided in the meta-analysis, 1 study evaluated adherence rates among patients with 7 different medical conditions, including hypertension (72.3%), hypothyroidism (68.4%), diabetes mellitus (65.4%), seizure disorders (60.8%), hypercholesterolemia (54.6%), osteoporosis (51.2%), and gout (36.8%), suggesting that adherence was worst in gout^[13].

These results highlight the need for more research on the impact of allopurinol non-adherence on major clinical outcomes, such as kidney disease. In fact, hyperuricemia is common in chronic kidney disease (CKD), and it is thought to develop secondary to a decrease in glomerular filtration rate or hyperinsulinemia in the metabolic syndrome^[14]. It is generally accepted that hyperuricemia is prevalent among patients with several risk factors for cardiovascular disease (CVD)^[15], and elevated sUA levels have been found to predict the risk of developing CVD or CKD in the general population^[16,17]. However, the question of whether sUA has a pathogenic role in the onset and progression of CKD remains unanswered.

Several observational studies have investigated whether an elevated sUA level is an independent risk factor for the development and progression of CKD, but the results were inconclusive and conflicting^[18]. A previous study reported that 20%-60% of patients with gout and hyperuricemia developed renal impairment that was accompanied by histological damage of glomerulosclerosis, interstitial fibrosis, and arteriosclerosis^[19]. Again, elevated sUA levels have been reported to predict the development of renal insufficiency in individuals with normal renal function^[20].

Recent data underscoring the growing problem of gout and its associated comorbid conditions have called for the need for more research of its impact on major outcomes. Evidence from large data sets has reported uric acid levels to be associated with the risk of end-stage renal disease (ESRD)^[21-23]. Clinical evidence from randomized clinical trials is now emerging showing that allopurinol may slow the progression of CKD^[24]. In a study using continued allopurinol treatment as a proxy for control, long-term treatment was suggestive of slowing the rate of kidney disease progression and reducing CV risk^[25]. Thus, the present study assessed the impact of allopurinol non-adherence as a proxy for uncontrolled disease^[25] on primary prevention of ESRD among patients newly treated with allopurinol for gout treatment. The objective was to

assess the impact of gout disease control on the risk of ESRD among gout patients newly treated with allopurinol in a cohort of patients who initiated antihypertensive agents for essential hypertension.

MATERIALS AND METHODS

Data sources

This population-based study utilized the Régie de l'assurance maladie du Québec (RAMQ) and MedEcho databases, both of which are components of public health care insurance program management for Quebec, Canada. Specific types of health data comprise the RAMQ databases: (1) a demographic information file of all registrants, containing gender, age, postal code, and, if applicable, year of death; and (2) a medical services file, consisting of all inpatient/ambulatory medical services claims, that includes procedure/diagnostic code data, *i.e.*, date, type, and site (office, emergency room, hospital). Diagnostic coding was performed according to the International Classification of Disease, Ninth Revision (*ICD-9*) and, from 2006 onward, *ICD-10*.

The Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures enclose and define the procedure codes. All drugs prescribed to patients who take RAMQ-insured medications are contained in the pharmaceutical file. The pharmaceutical file includes the name and dose of the drug, its quantity, date of treatment dispensation, and the quantity of days dispensed, as indicated by the pharmacist. Lastly, the MedEcho database file contains data on acute care hospitalizations, (*e.g.*, admission date, length of stay, and primary/secondary diagnoses). Each of the database files also provided a unique identifier (individual health insurance number).

The first 2 RAMQ datasets contain information on all of those with provincial public health insurance plan coverage, comprising the total Quebec population. Prescription claims dataset (pharmaceutical file) data are from provincial public prescription drug insurance plan beneficiaries, representing approximately 43% of Quebec residents between the ages of 45 and 64, and about 94% of those aged ≥ 65 years. This dataset provides an accurate measure of identifying drugs that are prescribed to patients and is a validated research tool utilized in pharmacoepidemiologic studies. RAMQ database medical services claims have been also used as part of validity studies^[26-30].

Cohort definition

Subjects identified were aged 45 to 85 and newly treated with either angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, β -blockers, calcium channel blockers, diuretics, or a combination between January 1, 1999 and June 30, 2007; these subjects were also required to have an essential hypertension diagnosis (*ICD-9* code: 401 and *ICD-10* code: I10) for 2 years prior to the cohort entry date. The study cohort included 222582 individuals.

The exclusion criteria were as follows: (1) patients with hematologic cancer *ICD-9* code 200-208 or *ICD-10* code C77-C96 in the 5-year period prior to the cohort entry date; (2) other disorders of purine and pyrimidine metabolism *ICD-9* code 277.2 or *ICD-10* code E79.0, E79.1, E79.8, E79.9 in the 5-year period prior to the cohort entry date; (3) patients with tumor lysis syndrome *ICD-9* code 277.88 or *ICD-10* E88.3, E88.8, E88.9 in the 5-year period prior to the cohort entry date; (4) patients with familial Mediterranean fever *ICD-9* code 277.31 or *ICD-10* code E85.0 in the 5-year period prior to the cohort entry date; (5) patients with hemodialysis or peritoneal dialysis for more than 3 consecutive months in the 5-year period prior to the cohort entry date; (6) patients with autoimmune/congenital kidney diseases, as these conditions are highly associated with kidney diseases and, as a result, are also highly predictive of ESRD; (7) patients with kidney transplantation; and (8) patients with expected CKD of stage 4 and 5 using *ICD-9* or *ICD-10* with the presence of drug markers (in the 2 years prior to cohort entry date): Calcium carbonate ≥ 1200 mg/d or calcitriol (≥ 0.25 μ g/d or ≥ 1.75 μ g/wk or ≥ 7.5 μ g/30 d) or doxercalciférol (≥ 2.5 μ g/d or ≥ 17.5 μ g/wk or ≥ 75 μ g/30 d) or alfacalcidol (≥ 0.25 μ g/d or ≥ 1.75 μ g/wk or ≥ 7.5 μ g/30 d).

We defined the patients as newly treated with allopurinol if they had not taken any allopurinol in 1 year during the follow-up. The date of the cohort entry is defined by the date of the first claim of allopurinol. In order to be eligible, patients needed to also have had a diagnosis of gout, defined as meeting all of the following criteria: (1) having a diagnosis of gout defined by *ICD-9* code 712.0 (*Gout arthritis*) or *ICD-9* code 274 (*Gout*) or *ICD-10* code M10.0 (*Idiopathic gout*) or *ICD-10* M10.9 (*Non-specify gout*) during the follow-up period; and (2) users of at least 2 claims of colchicine during the follow-up period (meaning any time during the follow-up prior and post inclusion in the cohort).

The study cohort included all new users of allopurinol who were followed from the date of first allopurinol claim issuance until the onset of ESRD or study period end (*i.e.*, June 30, 2008). Individuals were censored when they lost RAMQ drug insurance coverage or died during follow-up. Subjects were followed for a period of 1 year to 9.5 years.

Nested case-control study

We conducted a nested case-control study to estimate rate ratios (RR) of ESRD associated with adherence to allopurinol for gout treatment. The definition of ESRD (case) comprised a composite endpoint that represented patients with a medical procedure lasting ≥ 3 mo^a for peritoneal dialysis, hemodialysis, or renal transplantation. The date of ESRD was defined as the index date. All cases were identified and up to 15 controls were randomly selected from the cohort based on the risk set of each case using density sampling. Sampling for each control was selected in proportion to time contribution to

the person-time at risk in the source population (*i.e.*, the whole cohort), giving an unbiased estimate of the RR. A hallmark of the risk set is that a cohort member who serves as control at one point in time may later become a case, and the same cohort member may be selected as a control for more than 1 case. Cases and controls were matched for age, sex, and entry into the cohort.

Ascertainment of ESRD

The primary outcome was ESRD described by the (case) composite endpoint case definition above. All patients were followed up to study end or primary outcome.

Exposure to allopurinol during the follow-up period

The definition of allopurinol adherence was described as the degree at which patients use allopurinol as prescribed. Adherence estimation was determined *via* "medication possession ratio" (MPR), which was calculated as the total number of days' supply of medication dispensed divided by follow-up length. Evaluation of patient adherence was conducted from initiation of follow-up to index date (date of ESRD) or to time of non-cases' selection. MPR was dichotomized, with an MPR threshold set to $< 80\%$ in order to identify those who were non-adherent, which is aligned to the medical literature. We also used categorical exposure. In many databases, serum urate is not captured and adherence to urate-lowering therapy may be a proxy for disease control^[31,32].

Variables for assessing risk factors for gout and associated co-morbidities

Social assistance status and gender at the time of cohort entry was established using RAMQ database beneficiary file data. Risk factors for gout and associated comorbidities were considered using drug markers or ICD-9/ICD-10. Associated comorbidities were ischemic heart disease, heart failure, cardiac dysrhythmias, dyslipidemia, diabetes, CKD at grades 1 to 3, acute renal failure, cerebrovascular disease, peripheral vascular disease, pulmonary disease (chronic obstructive pulmonary disease or asthma), dementia, rheumatic disease, and gastrointestinal disease. Diagnosis and medical procedures were identified in the 5 years preceding cohort entry, while pharmacological treatment was identified in the 2 years preceding cohort entry date. Indirect measurement of hypertension severity was established by the number of antihypertensive medications ($1, 2, \geq 3$) during the year prior to the index date.

Statistical analysis

Comparison of characteristics of controlled and uncontrolled patients was calculated using *t*-test for continuous variables and χ^2 test for categorical variables. Through multivariate analysis, a conditional logistic regression model was constructed to evaluate the association between allopurinol adherence and ESRD. When studying a time-dependent exposure, as adherence to allopurinol in our study, an additional level of complexity is introduced based upon the need to account for a time-dependent

exposure; this can be achieved *via* a cohort analysis using Cox regression that includes time-dependent covariates. Alternatively, the use of a nested case-control approach is appropriate, providing exposure and covariate information for controls and reflecting values corresponding to the selection time of their respective case. When studying time-dependent exposures, nested case-control analyses can yield similar results to that of Cox regression on the full cohort; the advantage being that there is superior computational efficiency with conditional logistic regression (given that only a sample of all possible controls are included in each case's risk set). Aside from computational efficiency, the use of nested case-control studies offer additional advantages, including the possibility of matching controls to cases on the basis of possible fixed or time-dependent confounding covariates for which estimation of effect is not of interest.

To further weigh the strength of the findings, sensitivity analyses were performed to validate our approach. The validity of the approach was done by analyzing 2 drug variables (*i.e.*, benzodiazepines, proton pump inhibitors) and examining varying usage patterns (adherence level $< 80\%$ and $\geq 80\%$). The goal was to determine whether adherence to non-renal-protective drugs was also associated with a reduced ESRD risk. By considering the potential influence of adherence to different classes of drugs, we were able to ensure that any impact on ESRD was due to allopurinol non-adherence, and not the potential influence from simultaneously discontinuing several other medications.

Unselected multivariable models were constructed to maximize adjustment for co-variables. Based on the number of cases, we included only CKD and severity of hypertension to obtain the adjusted estimators. RRs and 95% confidence intervals (CIs) were calculated for each independent variable in the multivariable models. Residuals from regression models were assessed for assumptions violations of multicollinearity or deviance. A precision threshold of 5% was utilized for all analyses and was executed utilizing SAS version 9.3 (SAS Institute, Cary, North Carolina, United States).

RESULTS

Patient characteristics

After inclusion/exclusion criteria were applied (Figure 1), the resulting cohort at entry comprised 2752 patients with a mean age of 67 years; more than 82% of them were male, 23% of advanced age (> 75 years), close to 50% had at least 1 CVD, 33.5% had dyslipidemia, 20.7% had diabetes, 12.7% had CKD, 21.1% were thiazides users, 34.3% were low acetylsalicylic acid users, and 42.8% were nonsteroidal anti-inflammatory drug (NSAID) users (Table 1).

Table 2 provides a listing of patient demographic and clinical characteristics at cohort entry, stratified by adherence level within the cohort. No major clinically significant difference was observed between the groups. The median time of follow-up was 3.9 years. Over the

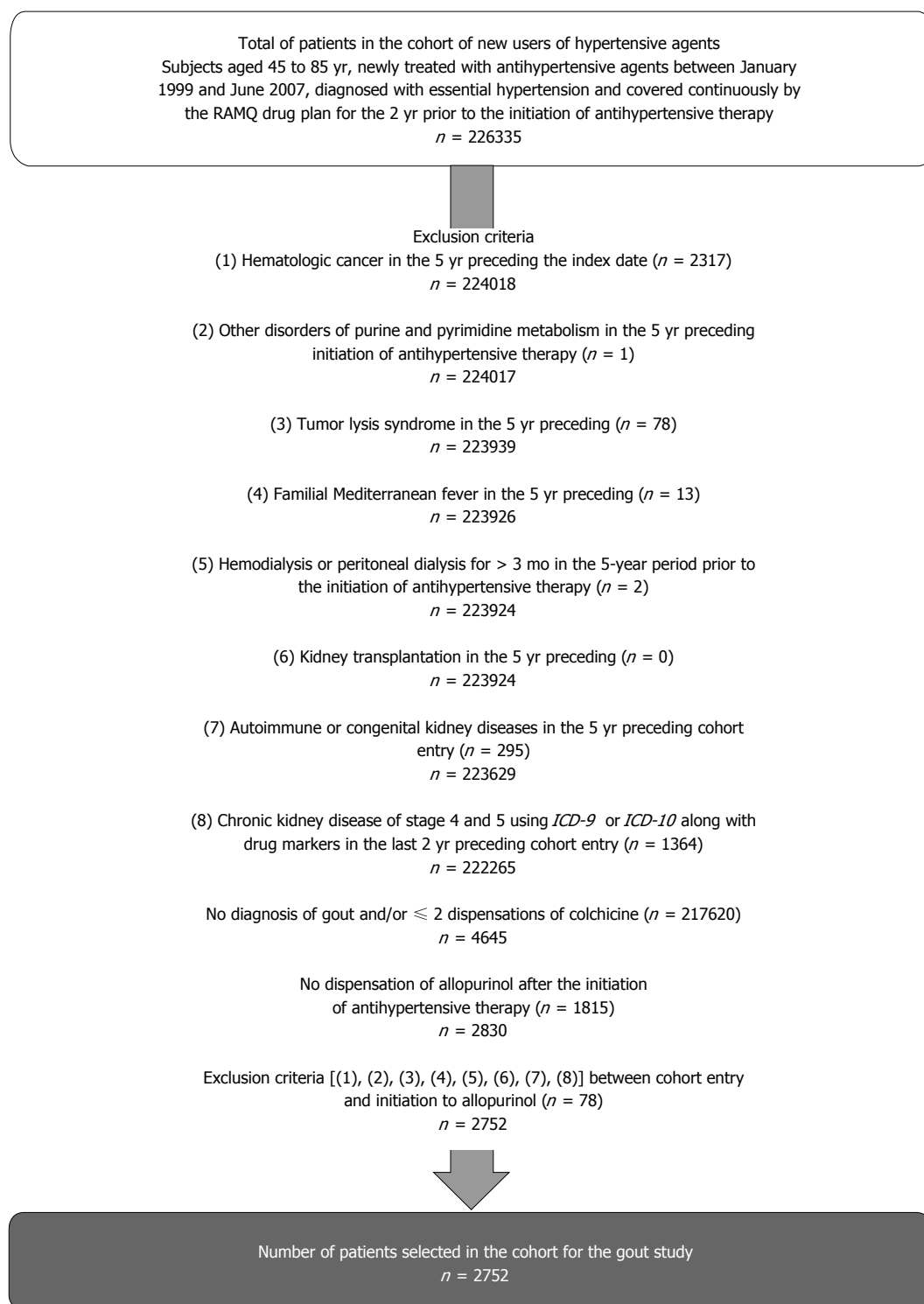


Figure 1 Flowchart of inclusion and exclusion criteria: Exclusion criteria were applied in the 5 years preceding the cohort entry date for diagnoses and medical procedures and 2 years prior to the cohort entry date for medication. RAMQ: Régie de l'assurance maladie du Québec.

time of follow-up, 22 ESRD cases (0.80%, or 0.2 per 100 person-years) were identified. Over the course of follow-up for the entire cohort, the death rate was 6.7% (183 deaths, or 1.58 per 100 person-years). The allopurinol exposure at the baseline level and during follow-up is provided in Table 3.

As shown in Table 4, among the 22 cases (matched for age, sex, and time period), CVD and associated

risk factors, as well as other comorbidities were higher among controls compared with cases. In contrast, CKD at a grade lower than 4, acute renal failure, and severity of hypertension were higher among cases than controls.

Impact of allopurinol adherence level on ESRD

The incidence rate of ESRD for high adherence subjects compared with lower adherence is shown in Figure 2.

Table 1 Demographic and clinical characteristics of new users of allopurinol treatment in a cohort of treated for hypertension from 1999 to 2007

All patients (n)	2752
Mean (SD) age, yr ¹	67 (9)
Risk factors for gout, % (n)	
Advanced age (> 75 yr) ¹	23.0 (634)
Male ¹	82.8 (2278)
Obesity ²	6.5 (179)
Drug use, % (n)	
Thiazides ³	21.1 (581)
Low dose acetylsalicylic acid ³	34.3 (945)
Niacin ³	0.4 (11)
Alcoholic diagnosis ³	1.3 (35)
Thyroid problems ³	12.9 (356)
Associated comorbidities, % (n)	
Ischemic heart disease ²	30.9 (849)
Heart failure ²	10.5 (288)
Cardiac dysrhythmias ²	12.5 (343)
Atrial fibrillation and flutter ²	8.1 (224)
Peripheral vascular disease ²	11.7 (321)
Cerebrovascular disease ²	12.0 (330)
Dyslipidemia ²	33.5 (921)
Diabetes ²	20.7 (569)
Chronic kidney disease at grade 1 to 3 ⁴	12.7 (350)
Acute renal failure ²	4.3 (117)
Pulmonary disease (COPD/asthma) ²	30.8 (847)
Dementia ²	2.7 (73)
Rheumatic disease ²	6.3 (174)
Gastrointestinal disease ²	7.9 (218)
Drug use for gout treatment, % (n)	
NSAIDs ³	42.8 (1178)
Colchicine ³	29.3 (806)
Intra-articular corticosteroids ³	5.9 (163)
Oral corticosteroids ³	2.4 (65)
Narcotics ³	12.8 (353)

¹At treatment initiation; ²ICD-9 or ICD-10 identified in the 5 years preceding cohort entry; ³Pharmacologic treatment identified in the 2 years preceding cohort entry; ⁴Chronic kidney disease at grade 1 to 3 defined as having ICD-9 or ICD-10 with the absence of medication for phosphate binding or for hyperparathyroidism control. COPD: Chronic obstructive pulmonary disease; NSAIDs: Nonsteroidal anti-inflammatory drugs.

The mean (SD) adherence level to allopurinol was 65.7% (32.6%). The adjusted RR of ESRD was significantly lower in the high adherence group compared with the lower adherence group (RR = 0.35; 95%CI: 0.13-0.91) (Table 5). We identified 22 cases with ESRD during follow-up. High adherence ($\geq 80\%$) to allopurinol therapy compared with lower adherence ($< 80\%$) was associated with a reduction of ESRD. Major risk factors for ESRD were CKD at stage 1 to 3 (RR = 8.00; 95%CI: 3.16-22.3) and a trend for severity of hypertension (RR = 1.19; 95%CI: 0.38-3.74). Adjusted variables were limited in number, given the low number of cases, and subgroup analyses were unable to be conducted.

Validation of methodological approach

An adherence rate of $> 80\%$ to proton pump inhibitors (RR = 0.90; 95%CI: 0.20-4.01) or benzodiazepines (RR = 1.24; 95%CI: 0.35-4.39) did not impact onset of ESRD. High allopurinol adherence specifically was associated with reduction of ESRD; however, with non-

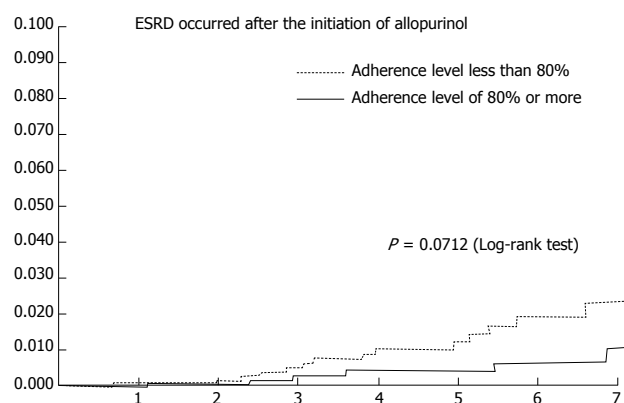


Figure 2 Nonadjusted cumulative incidence rate of end-stage renal disease among high adherence level compared with the low level of adherence of allopurinol over time in years. ESRD: End-stage renal disease.

renal protective drugs, this effect was not present.

DISCUSSION

This study shows that allopurinol treatment adherence of $\geq 80\%$ as a proxy for gout control in this newly-treated population is associated with a significant 65% decrease in the risk of ESRD onset. The association seems to take more than 3 years of exposure, suggesting that allopurinol efficacy in preventing ESRD may need many years before manifesting. This aligns with the medical literature and supports the assertion that the development of ESRD occurs over an extended time period^[33].

Our results are in accordance with recent publications, which suggest that lowering sUA levels may slow progression of renal disease. Siu *et al.*^[34] reported that the treatment of asymptomatic hyperuricemia in patients with mild renal disease (CKD stage 3) resulted in delayed disease progression. Likewise, Kanbay *et al.*^[35] reported that treatment with asymptomatic hyperuricemia improved renal function.

The present study results indicate that CKD at a lower stage and the severity of hypertension disease are associated with increased risk of ESRD onset^[36-41]. The most difficult aspect of assessing the impact of allopurinol and disease control in the development or progression of CKD is the number of confounders. Here, we were limited in the number of adjusted variables given the low number of cases, and we were unable to conduct a subgroup analysis. In addition, we were limited to control for severity of hypertension. The concept of an ideal blood pressure target for patients with kidney disease is highly debated^[42]. Two critical factors arise: Follow-up time and proteinuria; both factors appear to be important in influencing blood pressure effects in nephroprotection. Our study design does not allow for the verification of the proteinuria hypotheses; however, the importance of time can be agreed upon, as a more significant effect of good allopurinol adherence over more than 3 years was observed. We were also unable to discern what the targeted or achieved blood pressure levels were for our

Table 2 Demographic and clinical characteristics of adherent and non-adherent patients to allopurinol treatment in a cohort of newly treated antihypertensive patients from 1999 to 2007

Variables	Adherent to allopurinol	Non-adherent to allopurinol	P-value
All patients (n)	1392	1360	
Mean (SD) age (yr) ¹	67 (9)	67 (9)	0.4457
Risk factors for gout, % (n)			
Advanced age (> 75 yr) ¹	22.2 (309)	23.9 (325)	0.2900
Male ¹	84.2 (1172)	81.3 (1106)	0.0367
Obesity ²	6.4 (89)	6.6 (90)	0.8117
Drug use			
Thiazides ³	20.0 (278)	22.3 (303)	0.1380
Low dose acetylsalicylic acid ³	35.8 (499)	32.8 (446)	0.0917
Niacin ³	0.4 (5)	0.4 (6)	0.7333
Alcoholic diagnosis ²	1.2 (16)	1.4 (19)	0.5622
Thyroid problems ²	13.1 (182)	12.8 (174)	0.8264
Associated comorbidities, % (n)			
Ischemic heart disease ²	31.3 (435)	30.4 (414)	0.6460
Chronic heart failure ²	10.7 (149)	10.2 (139)	0.6787
Cardiac dysrhythmias ²	11.5 (160)	13.5 (183)	0.1193
Atrial fibrillation and flutter ²	7.5 (104)	8.8 (120)	0.1946
Peripheral vascular disease ²	12.1 (168)	11.3 (153)	0.5034
Cerebrovascular disease ²	12.3 (172)	11.6 (158)	0.5509
Dyslipidemia ²	35.0 (487)	31.9 (434)	0.0875
Diabetes ²	21.1 (294)	20.2 (275)	0.5599
Chronic kidney disease at grade 1 to 3 ⁴	12.7 (177)	12.7 (173)	0.9968
Acute renal failure ²	4.3 (60)	4.2 (57)	0.8769
Pulmonary disease (COPD/asthma) ²	31.4 (437)	30.1 (410)	0.4787
Dementia ²	2.9 (40)	2.4 (33)	0.4656
Rheumatic disease ²	5.0 (69)	7.7 (105)	0.0029
Gastrointestinal disease ²	7.5 (105)	8.3 (113)	0.4571
Drug use for gout treatment ³ , % (n)			
NSAIDs ³	37.8 (526)	47.9 (652)	< 0.0001
Colchicine ³	26.9 (374)	31.8 (432)	0.0048
Intra-articular corticosteroids ³	6.4 (89)	5.4 (74)	0.2899
Oral corticosteroids ³	1.9 (27)	2.8 (38)	0.1400
Narcotics ³	12.9 (179)	12.8 (174)	0.9593

¹At treatment initiation; ²ICD-9 or ICD-10 identified in the 5 years preceding cohort entry; ³Pharmacologic treatment identified in the 2 years preceding cohort entry; ⁴Chronic kidney disease at grade 1 to 3 defined as having ICD-9 or ICD-10 with the absence of medication for phosphate binding or for hyperparathyroidism control. COPD: Chronic obstructive pulmonary disease; NSAIDs: Nonsteroidal anti-inflammatory drugs.

Table 3 Exposure to allopurinol

	Baseline	During follow-up
Patients (n)	2752	2570
Allopurinol		
Mean dose used during the period (± SD)	210.9 (± 97.5)	243.3 (± 128.2)
Proportion of patients taking < 300 mg (%)	64.7 (1782)	53.5 (1374)
Proportion of patients taking 300 mg (%)	33.5 (921)	40.8 (1049)
Proportion of patients taking > 300 mg (%)	1.8 (49)	5.7 (147)
Febuxostat		
Proportion of patients who received at least 1 claim of febuxostat (%)	0 (0)	0 (0)
Mean dose used during the period (± SD)	NA	NA

NA: Not applicable.

cohort. If lower blood pressure does not convey a lower ESRD risk (a controversial subject), and if our chronic renal failure patients and controls had in fact ended up with lower blood pressures (< 130/80), then this may decrease the strength of the observed association.

The study design took the potential for some methodology-based limitations into consideration. In order to avoid selection bias, only incident allopurinol users were included. Nevertheless, additional limitations potentially

remain. First, to control for certain risk factors involved in CKD development, we included any variables that were relevant within the regression model. Since those with higher amounts of comorbidities have a higher likelihood for ESRD, we adjusted for limited risk factors given the number of observed cases. Regardless, one cannot exclude residual confounding due to inaccurate/incomplete measurement of covariates or unmeasured confounders. As an example, patients not adhering to

Table 4 Characteristics of patients with end-stage renal disease and their matched controls

	Cases occurring in the follow-up and their controls	
	Cases (<i>n</i> = 22)	Controls (<i>n</i> = 319)
Characteristics, % (<i>n</i>) unless otherwise noted		
Allopurinol adherence $\geq 80\%$	31.8 (7)	57.1 (182)
Age (mean, continuous) ¹	74.2 (60-78)	74.8 (60-78)
Older than 75 yr ¹	36.4 (8)	38.6 (123)
Ischemic heart disease ²	18.2 (4)	24.8 (79)
Heart failure ²	9.1 (2)	8.5 (27)
Cardiac dysrhythmias ²	0 (0)	8.2 (26)
Atrial fibrillation ²	0 (0)	4.7 (15)
Peripheral arterial disease ²	9.1 (2)	12.5 (40)
Cerebrovascular disease ²	18.2 (4)	14.7 (47)
Dyslipidemia ²	13.6 (3)	29.8 (95)
Diabetes ²	18.2 (4)	19.1 (258)
Chronic kidney disease with grade 1 to 3 ³	54.6 (12)	12.9 (41)
Acute renal failure ²	9.1 (2)	3.1 (10)
Pulmonary disease (COPD/asthma) ²	22.7 (5)	37.6 (120)
Dementia ²	4.6 (1)	1.6 (5)
Rheumatic disease ²	4.6 (1)	5.6 (18)
Gastrointestinal disease ²	4.6 (1)	11.3 (36)
Severity of hypertension (1-yr prior to ESRD)		
No use of antihypertensive agent	4.6 (1)	8.8 (28)
Monotherapy	36.4 (8)	43.0 (137)
2 antihypertensive agents	36.4 (8)	35.1 (112)
≥ 3 antihypertensive agents	22.7 (5)	13.2 (42)

¹At treatment initiation; ²ICD-9 or ICD-10 identified in the 5 years preceding cohort entry; ³Chronic kidney disease at grade 1 to 3 defined as having ICD-9 or ICD-10 with the absence of medication for phosphate binding or for hyperparathyroidism control. COPD: Chronic obstructive pulmonary disease; ESRD: End-stage renal disease.

Table 5 Rate ratio of end-stage renal disease

	Rate ratio (95%CI)	
	Cases occurring at follow-up and their controls	
	Crude	Adjusted
Allopurinol adherence level		
< 80%	Reference	Reference
$\geq 80\%$	0.35 (0.14-0.89)	0.35 (0.13-0.91)
Chronic kidney disease at grade 1 to 3 ¹	8.06 (3.28-19.77)	8.00 (3.16-20.25)
Severity of hypertension (1 yr prior to ESRD)		
< 3 antihypertensive agents	Reference	Reference
≥ 3 antihypertensive agents	1.94 (0.68-5.51)	1.19 (0.38-3.74)

¹Chronic kidney disease at grade 1 to 3 defined as having ICD-9 or ICD-10 with the absence of medication for phosphate binding or for hyperparathyroidism control. Chronic kidney disease and severity of hypertension were the variables used to obtain the adjusted estimators. CI: Confidence interval; ESRD: End-stage renal disease.

treatment could likely have additional factors contributing to worse outcomes, such as lower socioeconomic status, adverse health behaviors, and depression^[43]. Nonetheless, we were able to adjust for these factors.

Our sensitivity analyses regarding the differential class effects of drug adherence on ESRD suggest that adherence-related benefits are associated with medication that lowered sUA levels. The benefit on reduction of ESRD in our study was seen specifically with better adherence to medication that lowered sUA levels, but not with other types of medications such as proton pump inhibitors or benzodiazepines. Still, the possibility remained for "healthy user bias"^[44,45]. This term refers to a population of patients that exhibit good adherence to medication as part of an overall healthy lifestyle, and therefore, have less comorbidities and, as a result, exhibit decreased risk

of disease development overall. Of note, recent literature discussing differential drug adherence class effects on long-term survival proposed that the associated benefits related to pharmacotherapeutic adherence are mediated more so by the effects of the drugs rather than by healthy adherence behaviors^[46]. Another possibility could have been reverse causality. Each patient's glomerular filtration rate were unknown based on the information available from the administrative databases utilized in this observational study; however, renal function decline was likely to be gradual over the course of a few years, while adherence remained quite constant after the first year and until the index date in both cases and controls. Hence, it is not believed that decreasing renal function resulted in patients becoming more compliant to medication.

Additionally, the evidence surrounding the safety and

efficacy of allopurinol among patients with CKD presents an inconsistency of results^[47]. We should be aware of the potential risk of allopurinol use among those patients, and we need to titrate according to target sUA level or switch to febuxostat^[48]. In our study, we do not suspect that allopurinol non-adherence was related to CKD progression; this is because febuxostat was available to the physician, but the opportunity to switch the patient was not carried out.

Characteristics potentially influencing a doctor's medication choice, such as unmeasured comorbidities and missing sUA level/blood pressure control data, were not able to be controlled for in our analysis; this potentially could result in residual confounding effects. In addition, adjusting for clinical severity, *e.g.*, precise glomerular filtration rate, CKD etiology, proteinuria, is not allowable with the use of databases. However, these conditions *per se* are not traditionally associated with better adherence. Also, due to diagnostic coding errors, it is possible that history of renal disease may not have been identified in certain individuals. The probability of this occurring, however, would have been low, as for all individuals, relevant medical/drug information was accessible for all individuals for a several-year period prior to cohort entry. For instance, 12 of the 22 ESRD events had previous CKD (classified as grade 1 to 3); 2 had a history of acute renal failure, and the 8 remaining cases developed CKD during follow-up as the cause of ESRD. Patients with previously diagnosed gout (as opposed to those with newly diagnosed gout) also may have greater motivation to take their medication based on prior gout attack experiences^[49]. Patients with previously diagnosed gout may be at higher risk, but this could not be adjusted because of the low number of cases. NSAID use may also be a confounder since its use may cause progression among patients who have pre-existing kidney disease^[50]. After adjusting for age, gender, and comorbidities, high cumulative NSAID use was associated with a 26% risk of a rapid decline in estimated glomerular filtration rate relative to those who did not use NSAIDs (OR = 1.26, 95%CI: 1.04–1.53). For instance, in our study, we noticed a difference in NSAID users between adherent (37.8%) and non-adherent (47.9%) participants; however, we could not adjust because of the low number of cases. Nevertheless, we do not expect that this difference could have a major impact, given that there was no difference among patients with CKD at grade 1 to 3 for the low and high allopurinol adherence levels.

Finally, prescription refill patterns were used to assess exposure; therefore, whether the dispensed medication was actually taken by the patient cannot be ascertained. Nevertheless, evidence suggests a good correlation between cumulative drug exposure, pharmacy dispensing records, and gaps in medication supply^[51]. Furthermore, no information with respect to potential adverse drug effects was available within the data, which could potentially explain early medication discontinuation. Available evidence has shown that adverse drug effects generally occur in the earlier, rather than later, phases of

treatment; therefore, it is unlikely to significantly account for non-adherence of preventive therapy^[52].

To summarize, this Canadian population-based study showed an association with significant benefit between good allopurinol adherence, as a proxy for disease control, and ESRD onset, but further research should be conducted to confirm this potential associated risk.

A key factor to determining success with various treatment approaches is improved adherence to pharmacotherapy. As a result, greater awareness should be taken accordingly, as improved patient outcomes can result. Assessing medication adherence should be a routine part of clinical practice. Devising strategies to optimize long-term allopurinol adherence, as well as other measures of adequate disease control, must be encouraged in order to lower or, at a minimum, delay the occurrence of ESRD in patients with gout.

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COMMENTS

Background

Gout is characterized by elevated serum uric acid (sUA) levels and is commonly treated with urate-lowering treatment allopurinol; however, allopurinol adherence is suboptimal and therefore a therapeutic challenge in gout. Some evidence from large data sets has reported sUA to be associated with the risk of end-stage renal disease (ESRD), and hyperuricemia in general is common in chronic kidney disease (CKD).

Research frontiers

Several observational studies have been either inconclusive or conflicting as to whether elevated sUA is an independent risk factor for the development and progression of CKD. The pathogenic role of sUA in the onset and progression of CKD, and the relationship of sUA management in this context, remains largely unanswered.

Innovations and breakthroughs

This study examines a large cohort of over 220000 individuals followed for up to 9 years and utilizes long-term real-world evidence to examine the impact of gout control on the onset of ESRD.

Applications

This study found a potential association with significant benefit between good adherence to allopurinol and ESRD onset. Optimizing long-term allopurinol adherence and other measures of disease control must be encouraged in order to lower or, as a minimum, delay the occurrence of ESRD in patients with gout.

Peer-review

In their manuscript Perreault *et al* studied an important topic; the possible role of allopurinol non-adherence in the development of end-stage renal disease in gout patients. The authors used very sophisticated statistics in their case control study on a high patient population.

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Retrospective Study

Advanced wasting in peritoneal dialysis patients

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Abstract

AIM

To identify patients with end-stage renal disease treated by peritoneal dialysis (PD) who had zero body fat (BF) as determined by analysis of body composition using anthropometric formulas estimating body water (V) and to compare nutritional parameters between these patients and PD patients whose BF was above zero.

METHODS

Body weight (W) consists of fat-free mass (FFM) and

BF. Anthropometric formulas for calculating V allow the calculation of FFM as $V/0.73$, where 0.73 is the water fraction of FFM at normal hydration. Wasting from loss of BF has adverse survival outcomes in PD. Advanced wasting was defined as zero BF when $V/0.73$ is equal to or exceeds W. This study, which analyzed 439 PD patients at their first clearance study, used the Watson formulas estimating V to identify patients with $V_{\text{Watson}}/0.73 \geq W$ and compared their nutritional indices with those of PD patients with $V_{\text{Watson}}/0.73 < W$.

RESULTS

The study identified at the first clearance study two male patients with $V_{\text{Watson}}/0.73 \geq W$ among 439 patients on PD. Compared to 260 other male patients on PD, the two subjects with advanced wasting had exceptionally low body mass index and serum albumin concentration. The first of the two subjects also had very low values for serum creatinine concentration and total (in urine and spent peritoneal dialysate) creatinine excretion rate while the second subject had an elevated serum creatinine concentration and high creatinine excretion rate due, most probably, to non-compliance with the PD prescription.

CONCLUSION

Advanced wasting (zero BF) in PD patients, identified by the anthropometric formulas that estimate V, while rare, is associated with indices of poor somatic and visceral nutrition.

Key words: Weight deficit; Fat-free mass; Nutrition; Body water; Anthropometry; Peritoneal dialysis; Watson formulas; Wasting

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Core tip: This retrospective study of patients with end-stage renal disease treated by peritoneal dialysis (PD) analyzed the relationship between advanced wasting and other indicators of nutritional status, including body weight and serum albumin concentration. Advanced wasting was defined as zero body fat based on estimates of body water obtained from formulas based on gender, age, height and weight. Only two male patients, both young, were identified as having advanced wasting among the 439 patients (262 men and 177 women) on PD we studied. Both of these patients with advanced wasting had poor nutrition as evidenced by their remarkably low body weights and serum albumin levels. We conclude that advanced wasting, as defined in this study, is rare in patients on PD, but when present is strongly indicative of an exceedingly poor overall state of nutrition.

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INTRODUCTION

The overall prognosis and survival of patients with chronic diseases, including those whose end-stage renal disease is treated by dialysis, is strongly linked to their nutritional status. The nutritional status of patients on chronic peritoneal dialysis (PD) has been assessed by anthropometry^[1-3], biochemical parameters including serum albumin^[4,5] and pre-albumin^[5,6], and evaluation of body composition by bioelectrical impedance^[7-9], dual energy X-ray absorptiometry^[10,11], and measurement of total body potassium by stable isotopic methods^[10].

In addition to the aforementioned direct analytical methods, indices estimated from the excretion of nitrogenous products in urine and in spent dialysate have also been applied to evaluate nutrition in patients receiving PD. These nutritional indices include the protein nitrogen appearance (PNA), which is derived from the excretion of urea nitrogen and provides an estimate of dietary protein intake^[12], and lean body mass (LBM) which is estimated from the excretion of creatinine and provides an estimate of muscle mass^[13]. A composite nutritional index derived by combining findings from history, physical examination and clinical laboratory analyses has been applied in PD patients^[14,15].

This report addresses the identification and overall nutritional status of an advanced degree of weight deficit in PD patients. Weight deficit is encountered in approximately 7.5% of the patients on PD^[2] and may result from muscle loss (sarcopenia) or from grossly diminished body fat (BF)^[16]. Under several circumstances sarcopenia is associated with obesity rather than weight loss. In contrast, loss of BF is always associated with weight deficit. Low BF is defined as BF < 20% of body weight in women and < 12% of body weight in men^[17]. BF can be assessed by anthropometry (skin-fold thickness), dual energy absorptiometry, bioelectrical impedance, and other methods usually restricted to research studies. Measurement of body water (V) by radioisotope dilution is one of the standard research methods for assessing BF and has been applied in PD studies^[10]. In PD patients, V, which is needed for the calculation of fractional urea clearance (Kt/V urea) for assessing the adequacy of PD, is routinely estimated by anthropometric formulas. Estimates of V from anthropometric formulas can also be used to estimate BF^[18,19].

Wasting in PD patients has been associated with adverse outcomes. This study had two aims: The first aim was to provide a definition of advanced wasting in PD patients by estimating BF calculated from V obtained from anthropometric formulas; the second was to identify PD patients with advanced wasting and to evaluate the association of advanced wasting with other traditional indices of nutritional status.

MATERIALS AND METHODS

Definition of advanced wasting

Table 1 defines the abbreviations used in this report.

Table 1 Abbreviations used in this report

Abbreviation	Interpretation
V	Body water, L; V_{Watson} = body water estimated by the Watson formula
W	Body weight, kg
IW	Ideal body weight, kg
BF	Body fat, kg
FFM	Fat-free mass, kg
BMI	Body mass index, kg/m^2
PNA	Protein nitrogen appearance, g; nPNA/W = PNA normalized to W, g/kg ; nPNA/IW = PNA normalized to IW, g/kg
Cr Ex	Creatinine excretion rate, $\text{mg}/24\text{-h}$; $(\text{MCr Ex})/\text{W}$ = measured Cr Ex normalized to W, $(\text{mg}/\text{kg})/24\text{-h}$; $(\text{MCr Ex})/\text{IW}$ = Measured Cr Ex normalized to IW, $(\text{mg}/\text{kg})/24\text{-h}$
M/P Cr Ex	Measured/Predicted creatinine excretion rate
LBM	Lean body mass estimated from Cr Ex, kg; LBM/W = LBM normalized to W; LBM/IW = LBM normalized to IW

Advanced wasting has been defined as zero BF calculated using an anthropometric formula to estimate V ^[18]. This calculation is based on the assumption that body weight (W) consists of fat-free body mass (FFM) and BF. When hydration abnormalities are absent, the water content of FFM, which essentially represents all the water in the body because fat contains miniscule amounts of water, is constant at 73% ($\text{FFM} = V/0.73$)^[20]. The fraction of body weight represented by water (V/W) is low in obese subjects in whom BF is a large component of W and, conversely, high in patients with weight deficit in whom BF is a small fraction of W. Thus, the V/W ratio increases progressively as body weight decreases due to loss of BF. Accordingly, this increase in the ratio V/W becomes evident when V is calculated by means of anthropometric formulas^[21]. The value $V/0.73$ approaches W with progressive weight loss and becomes equal to W at a specific weight and larger than W below this weight^[18]. Subjects with FFM calculated as $V/0.73$ equal to or larger than W have zero BF. Therefore, it is reasonable to define advanced wasting as $V/0.73 \geq W$.

Patients and nutrition indices

Using the Watson formulas^[22] to calculate V (V_{Watson}), we computed FFM as $V_{\text{Watson}}/0.73$ and compared it to W in 439 patients (262 men and 177 women) on PD. This comparison was performed at the time of the first determination of urea and creatinine clearances for assessment of the adequacy of PD. We compared nutrition indices between PD patients with $V_{\text{Watson}}/0.73 \geq W$ and those with $V_{\text{Watson}}/0.73 < W$.

Ideal weight (IW) was calculated by the method of Hamwi^[23,24]. PNA was calculated by the method of Bergstrom^[12] and normalized to both actual weight (nPNA/W) and ideal weight (nPNA/IW)^[25]. LBM estimated from creatinine kinetics was computed according to the method of Keshaviah^[13] and normalized to both actual weight (LBM/W) and ideal weight (LBM/IW). Measured creatinine excretion in dialysate plus urine was normalized to actual weight $[(\text{MCr Ex})/\text{W}]$, ideal weight $[(\text{MCr Ex})/\text{IW}]$, and predicted creatinine excretion (M/P Cr Ex). Predicted creatinine excretion was calculated using the formula: $\text{Cr Ex, mg}/24\text{-h} = 302.150 - 4.380 \times \text{Age, years} + 171.234 \times \text{Gender (women: 0; men: 1)} -$

$39.041 \times \text{Diabetes (no: 0; yes: 1)} + 11.730 \times \text{Weight, kg}$ ^[26]. Measured and computed nutrition indices were compared between patients with $V_{\text{Watson}}/0.73 \geq W$ and their respective 95% CIs in patients with $V_{\text{Watson}}/0.73 < W$ (the control group). Statistical analysis was performed using SYSTAT version 13.1.

RESULTS

Table 2 summarizes the clinical characteristics of the only two patients (Patient 1, Patient 2) with $V_{\text{Watson}}/0.73 \geq W$ we identified among the 439 PD subjects analyzed. The frequency of advanced wasting was 0.5% in the population studied. Both subjects with advanced wasting were young (23 years or less), had renal failure due to primary glomerular diseases from childhood, were short and had a low body weight at the first clearance study. In both patients, body weight had changed by < 1 kg between initiation of PD and the first clearance study. Both Kt/V urea and creatinine clearance were inadequate in Patient 1 but adequate in Patient 2. Peritoneal transport characterized by a peritoneal equilibration test^[27] was high in Patient 1 and low-average in Patient 2.

Table 3 compares the nutrition indices for Patients 1 and 2 with those of the control group of the remaining 260 male patients. Body mass index (BMI), the ratio of body weight to ideal weight (W/IW) and the serum albumin concentration were below the lower 95% confidence limit of the control group in both Patient 1 and Patient 2. In Patient 1, the serum urea nitrogen and creatinine levels were below the corresponding lower 95% confidence limits of the control group. In Patient 2 the serum urea nitrogen level was within the 95% confidence interval of the control group, while the serum creatinine level was above the upper 95% confidence limit of the control group.

In both Patient 1 and Patient 2 the nPNA/W and nPNA/IW values were within the 95% confidence interval of the control group. Normalized creatinine excretion values ($\text{MCr Ex}/\text{W}$), ($\text{MCr Ex}/\text{IW}$) and the various indices derived from creatinine excretion ($\text{M}/\text{P Cr Ex}$, LBM/W , LBM/IW) were below the corresponding lower 95% confidence limits of the control group in Patient 1 and above the corresponding upper 95% confidence limits of

Table 2 Clinical characteristics of peritoneal dialysis patients with advanced wasting

Clinical characteristic	Patient 1	Patient 2
Sex	Male	Male
Cause of ESRD	Glomerulonephritis	Glomerulonephritis
Age, yr	21	23
Height, cm	149	155
Weight, kg	36.7	40.0
Kt/V urea ¹ , weekly	1.34	2.92
Creatinine clearance ¹ , L/1.73 m ² weekly	49	218
Peritoneal transport (4-h D/P creatinine) ²	High (0.84)	Low-average (0.54)

¹Total (renal plus peritoneal) clearance; ²Characterized by the value of the 4-h dialysate/plasma (D/P) creatinine concentration ratio in a peritoneal equilibration test (PET)^[27]. ESRD: End-stage renal disease.

the control group in Patient 2 (Table 3).

DISCUSSION

This report has two main findings: First, the incidence of advanced wasting defined as zero BF as determined using the Watson formula estimating V was very low in patients on PD at the time of their first formal clearance study. Second, the two PD patients with advanced wasting defined by the use of the Watson formulas had very low body weight and serum albumin levels. However, several indices of nutritional status derived from urea nitrogen and creatinine excretion in these patients appeared to be normal or even elevated.

Weight excess and deficit are routinely evaluated in most populations by BMI, whereas deviation from ideal weight is used less frequently. The cut-off value for weight deficit is commonly set at a BMI of 18.5 kg/m² in guidelines for the general population^[28] or at a W/IW ratio of < 0.9 in PD patients^[1,2]. The BMI values that correspond to a W/IW of 0.9 are 18.8 kg/m² in women and 21.2 kg/m² in men when ideal weight is estimated from the Hamwi formulas^[29]. There is, in general, good agreement between BMI, W/IW and BF expressed as a fraction of body weight. However, there is substantial disagreement between BMI and W/IW estimates in the classification of individuals on PD as obese, normal weight or underweight^[30]. In addition, there is substantial disagreement between BMI and lean body mass, and consequently between BMI and BF when estimated by DXA in PD patients^[29].

In addition to the discrepancies between BMI and W/IW listed above, weight status classification on the basis of BMI or W/IW is subject to error because it does not take into account sarcopenia when it is associated with obesity or changing body composition as people age. Classification of weight deficit by BF content is subject to fewer errors^[16], but may require expensive, sophisticated technology that is usually available only for research studies. Identification of patients with BF deficit is important because numerous studies support the

Table 3 Nutrition indices in two males with advanced wasting (Patient 1, Patient 2) and a control group

Nutrition index	Patient 1	Patent 2	Control group ¹
V _{Watson} /0.73	1.036	1.030	0.744 (0.521-0.932)
BMI, kg/m ²	16.5	16.6	25.5 (18.9-32.8)
W/IW	0.778	0.816	1.151 (0.935-1.367)
Serum albumin, g/dL	2.60	2.80	3.60 (3.15-4.05)
Serum urea nitrogen, mg/dL	41.0	58.0	56.8 (43.2-70.4)
Serum creatinine, mg/dL	2.02	13.55	7.38 (5.25-9.51)
nPNA/W, g/kg per 24 h	0.94	1.21	0.86 (0.70-1.02)
nPNA/IW, g/kg per 24-h	0.81	1.07	0.99 (0.75-1.13)
(MCr Ex)/W, mg/kg per 24-h	13.0	35.9	18.7 (13.9-23.5)
(MCr Ex)/IW, mg/kg per 24-h	11.4	27.9	21.5 (17.5-25.5)
M/P Cr Ex	0.51	1.680	0.97 (0.55-1.39)
LBM/W	0.64	1.420	0.66 (0.55-0.77)
LBM/IW	0.52	1.100	0.76 (0.66-0.86)

¹The control group consisted of 260 men on PD analyzed in their first clearance study. The values in the control group column indicate mean (95%CI). BMI: Body mass index; PNA: Protein nitrogen appearance; LBM: Lean body mass; IW: Ideal body weight; PD: Peritoneal dialysis.

assertion that low BF is associated with a poor outcome for PD patients.

The effect of weight deficit or obesity on the outcomes of chronic dialysis was first evaluated in hemodialysis patients in whom weight deficit was identified as a predictor of poor survival, while obesity was found to offer a survival advantage^[31,32]. The effect of obesity on the outcome of patients receiving PD is less clear. A large retrospective study of United States Medicare PD patients found that obesity does offer a survival advantage^[33]. Subsequent studies in the United States reported that the survival advantage of obesity was much weaker for PD patients compared to hemodialysis patients^[34,35] and that obesity is a risk factor for peritonitis^[36]. Kutner and Zhang^[37] reported that the relationship between obesity and survival of PD patients is modified by race and gender, with obese white women on PD having a high risk of mortality. The influence of race on the outcomes of obesity in PD was confirmed by similar studies conducted in Asia^[38] and in Australia and New Zealand^[39]. Other studies reported either adverse effects^[40,41] or no effect^[42,43] of obesity on the survival of PD patients.

The focus of the present report is advanced weight deficit, not obesity. Unlike obesity where there is disagreement about its effect on the survival of patients treated by PD, the adverse effects of weight deficit on the outcomes of PD have been uniformly concordant^[33,39-43]. Weight loss in the first year of PD is associated with an increased risk of death^[44]. Finally, a recent meta-analysis confirmed the risk of mortality from low body weight of PD patients^[45].

In the present report, we analyzed the nutritional status of PD patients identified as having advanced wasting based on the use of anthropometric formulas to estimate V. In the two PD patients identified as having advanced wasting using this method, the finding of very low BMI and serum albumin levels confirmed a poor nutritional status, whereas nutrition indices based on

creatinine excretion provided conflicting findings. The potential pitfalls of creatinine excretion as a nutritional index in PD patients should be recognized.

An elevated serum creatinine value at the onset of PD^[3], together with a high rate of creatinine excretion^[46] is predictive of relatively long survival of PD patients. Creatinine production and excretion are directly related to muscle mass. High rates of creatinine excretion are indicative of preserved muscle mass and, therefore, good somatic nutrition^[46]. However, high creatinine excretion rates are also encountered in clinical states causing muscle destruction, including certain disease states and drugs, and in unsteady states following rapid increases in creatinine clearance in patients with azotemia. Examples of clinical states causing rapid rise in creatinine clearance include elimination of the cause of urinary retention, correction of prerenal azotemia due to hypovolemia, hemodialysis sessions and resumption of the prescribed dose of PD by patients with previous poor compliance with the PD prescription. In this last case, calculating the M/P Cr in the unsteady state immediately following resumption of the prescribed PD dose has been proposed as an indicator of poor compliance with the prescribed dose of PD^[47]. Creatinine excretion rates producing LBM/W values $\geq 0.9 \times W$ are strong indicators of non-compliance^[48]. LBM/W computed from creatinine excretion data is, on average, about 10% lower than fat-free mass (FFM) calculated as $V_{\text{Watson}}/0.73$ ^[49]. The higher value of LBM/W compared to $V_{\text{Watson}}/0.73$ in Patient 2 (Table 3), who had no catabolic neuromuscular disease and was on no medications causing rhabdomyolysis, suggests that non-compliance was the reason for his very high creatinine excretion rate. Strong clinical evidence of non-compliance supports this conclusion.

The main limitations of the present report are the small number of patients categorized as having advanced wasting and especially the lack of information about survival, morbidity and overall quality of life in the two patients with advanced wasting and the control group. Further studies will be needed to evaluate the relationship between various nutrition indices in PD patients classified by anthropometric estimates of V as having advanced wasting and the outcomes of these patients. Another limitation is that anthropometric formulas may not provide accurate estimates of V at very low body weights, particularly in patients with sarcopenia and weight deficit. To test whether there are differences between various anthropometric formulas, we repeated the calculations using all formulas that estimate V ^[18] (data not shown). For all these calculations, both Patient 1 and Patient 2 exhibited a $V/0.73$ value that exceeded W. Thus, the characterization of advanced wasting in Patients 1 and 2 was consistent regardless of the anthropometric formula we used to estimate V. A third limitation of this report is that anthropometric V values systematically underestimate V in patients with edema^[50]. Edema is common in PD populations^[51-53]. Values $V/0.73$ greater than W when V is estimated by anthropometric formulas

may result in some cases from combined loss of BF and severe sarcopenia or from wasting with water excess. In this second instance the degree of wasting is even greater than the degree suggested by $V/0.73$. We suggest that a patient's hydration status should be evaluated in patients when $V/0.73 > W$.

In conclusion, anthropometric formulas calculating V can accurately identify PD patients with advanced wasting. PD patients with advanced wasting identified by this method have poor nutrition indices. Special diagnostic and therapeutic efforts addressing the nutrition of these patients are required.

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COMMENTS

Background

Weight deficit caused by loss of body fat (BF) has adverse effects on the state of health and survival of patients with end-stage renal disease. BF is estimated as the difference between body weight and fat-free body mass. At normal hydration, fat-free body mass can be calculated as the fraction body water (V) over 0.73 fat-free body mass. Thus fat-free body mass and BF can be computed from V. In this study, the authors computed BF using anthropometric V estimates obtained at the first clearance study to evaluate adequacy of peritoneal dialysis (PD) and compared nutrition indices between the small number of patients with advanced body wasting (zero BF) and a large control group of patients with BF greater than zero.

Research frontiers

Because of the recognized effect of preservation of BF and fat-free body mass in patients on chronic dialysis, evaluation of body composition in these subjects has been an important focus of research. Various research methods have been applied in the study of body composition. These research methods require both costs for equipment and expertise. These requirements apply even to bioelectrical impedance analysis, which is the simplest method for evaluating body composition.

Innovations and breakthroughs

In contrast to research methods for evaluating body composition, the method proposed in this report utilizes only information and measurements necessary for evaluating the adequacy of PD and does not require any additional instruments or expertise. The method has no added cost.

Applications

Computation of BF using anthropometric V estimates could allow simple and free of any costs monitoring of body composition in PD patients. Body composition estimates from this method could be compared to both indices of nutrition and results of research methods evaluating body composition. These comparisons will establish the place of the method presented in this report in the clinical monitoring of PD patients.

Terminology

The following symbols are essential for comprehending this method. W: Body weight; FFM: Fat-free mass; BF: Body fat; V: Body water. The following equations express the method: $W = \text{FFM} + \text{BF}$; $\text{FFM} = V/0.73$; $\text{BF} = W - V/0.73$.

Peer-review

This manuscript is clinically interesting.

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Retrospective Study

Clinicopathological spectrum of snake bite-induced acute kidney injury from India

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Abstract

AIM

To study the clinico-pathological spectrum of snake bite-induced acute kidney injury (AKI).

METHODS

A retrospective study of patients admitted at Indira Gandhi Medical College Hospital, Shimla with snake bite-induced AKI from July 2003 to June 2016. Medical records were evaluated for patient's information on demographic, clinical characteristics, complications and outcome. Outcomes of duration of hospital stay, requirement for intensive care unit support, treatment with dialysis, survival and mortality were analyzed. The survival and non survival groups were compared to see the difference in the demographic factors, clinical characteristics, laboratory results, and complications. In patients subjected to kidney biopsy, the findings of histopathological examination of the kidney biopsies were also analyzed.

RESULTS

One hundred and twenty-one patients were diagnosed with snake bite-induced AKI. Mean age was 42.2 ± 15.1 years and majority (58%) were women. Clinical details were available in 88 patients. The mean duration of arrival at hospital was 3.4 ± 3.7 d with a range of 1 to

30 d. Eighty percent had oliguria and 55% had history of having passed red or brown colored urine. Coagulation defect was seen in 89% patients. The hematological and biochemical laboratory abnormalities were: Anemia (80.7%), leukocytosis (75%), thrombocytopenia (47.7%), hyperkalemia (25%), severe metabolic acidosis (39.8%), hepatic dysfunction (40.9%), hemolysis (85.2%) and rhabdomyolysis (68.2%). Main complications were: Gastrointestinal bleed (12.5%), seizure/encephalopathy (10.2%), hypertension, pneumonia/acute respiratory distress syndrome (ARDS) and disseminated intravascular coagulation (9.1% each), hypotension and multi organ failure (MOF) (4.5% each). Eighty-two percent patients required renal replacement therapy. One hundred and ten (90.9%) patient survived and 11 (9.1%) patients died. As compared to the survival group, the white blood cell count ($P = 0.023$) and bilirubin levels ($P = 0.006$) were significant higher and albumin levels were significantly lower (0.005) in patients who died. The proportion of patients with pneumonia/ARDS ($P = 0.001$), seizure/encephalopathy ($P = 0.005$), MOF ($P = 0.05$) and need for intensive care unit support (0.001) was significantly higher and duration of hospital stay was significantly shorter ($P = 0.012$) in patients who died. Kidney biopsy was done in total of 22 patients. Predominant lesion on kidney biopsy was acute tubular necrosis (ATN) in 20 (91%) cases. In 11 cases had severe ATN and in other nine (41%) cases kidney biopsy showed features of ATN associated with mild to moderate acute interstitial nephritis (AIN). One patient only had moderate AIN and one had patchy renal cortical necrosis (RCN).

CONCLUSION

AKI due to snake bite is severe and a high proportion requires renal replacement therapy. On renal histology ATN and AIN are common, RCN is rare.

Key words: Acute kidney injury; Acute tubular necrosis; Acute interstitial nephritis; Envenomation; Hemolysis; Renal cortical necrosis; Rhabdomyolysis; Snake bite

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Core tip: Acute kidney injury (AKI) due to snake bite is an important cause of community acquired tropical AKI. Clinicopathological spectrum of snake-induced AKI has changed. Intravascular hemolysis and rhabdomyolysis is common and is the main cause of AKI due to snake bite. AKI is severe and high proportion of patients requires renal replacement therapy. Complications of pneumonia/acute respiratory distress syndrome, seizure/encephalopathy, multi organ failure, the need for intensive care support and a shorter hospital stay are factors associated with mortality. On renal histology acute tubular necrosis and acute interstitial nephritis is common, renal cortical necrosis is rare. Early administration of anti-snake-venom and alkaline diuresis may help in prevention of AKI.

of snake bite-induced acute kidney injury from India. *World J Nephrol* 2017; 6(3): 150-161 Available from: URL: <http://www.wjgnet.com/2220-6124/full/v6/i3/150.htm> DOI: <http://dx.doi.org/10.5527/wjn.v6.i3.150>

INTRODUCTION

Snake bite is a significant public health problem causing considerable morbidity and mortality worldwide, particularly in tropics. Snakebite is now recognized as a Neglected Tropical Disease by the World Health Organization (WHO)^[1]. According to WHO estimates about 5 million people are bitten each year by poisonous snakes which results in 2.5 million envenomations, at least 100000 deaths, and 300000 amputations and other permanent disabilities^[2]. Majority of snakebite induced deaths occur in Asia and Sub-Saharan Africa^[1]. The mortality due to venomous snakebite in India is estimated between 35000-50000 per annum, which is the highest in the world^[1,3]. The mortality due to venomous snakebite in India continuous to be high due to various social, economic and cultural reasons^[4].

Over 3000 species of snakes are known worldwide, of which around 600 are considered to be venomous. There are 2 important groups (families) of venomous snakes in south-east Asia - Elapidae have short permanently erect fangs. This family includes the cobras, king cobra, kraits, coral snakes, and the sea snakes. Viperidae have long fangs, which are normally folded up against the upper jaw, but when the snake strikes, are erected. There are 2 subgroups, the typical vipers (Viperinae) and the pit vipers (Crotalinae)^[5]. Medically Important snakes of India include the so called "Big 4", Russell's viper (*Daboia russelli*), Cobra (*Naja naja*), Common Krait (*Bungarus caeruleus*) and Saw scaled viper (*Echis carinatus*) that occur throughout the country. The pit viper species - Malabar, green and the hump-nosed, sea snakes and others like the king cobra (*Ophiophagus hannah*), monocle cobra (*Naja kaouthia*), Banded Krait (*Bungarus fasciatus*) and *Echis sochureki* are important causes in certain geographical areas^[5,6]. The principle effects of envenomation is on the nervous system, kidneys, heart, lungs, liver, blood coagulation system, vascular endothelium and local effects at the site of bite^[7].

Acute kidney injury (AKI) is an important complication of snake bite and a major cause of mortality. AKI is common after bites from myotoxic or hemotoxic snakes. These snakes are Russell's viper, saw-scaled viper, hump-nosed pit viper, green pit viper, and sea-snake. Renal pathologic changes include tubular necrosis, cortical necrosis, interstitial nephritis, glomerulonephritis, and vasculitis. Hemodynamic alterations caused by vasoactive mediators and cytokines and direct nephrotoxicity account significantly for the development of nephropathy. Hemorrhage, hypotension, disseminated intravascular coagulation (DIC), intravascular hemolysis, and rhabdomyolysis enhance renal ischemia leading to AKI^[8].

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The incidence of AKI caused by these snakes varies from 5% to 29% depending on the species of snake and the severity of envenomation^[9-11]. The onset of AKI is from a few hours to as late as 96 h after the bite. The duration of AKI after snake bite generally ranges from 2 to 3 wk. Tubular necrosis is an important pathological correlate of AKI. Prolonged AKI with oligoanuria after snake bite is indicative of cortical necrosis or acute tubular necrosis associated with interstitial nephritis or extracapillary glomerulonephritis^[8].

Himachal Pradesh is a mountainous state in the northern part of India. It is the least urbanized state with more than 90% of the population living in rural areas^[12]. Eco-rich vegetation due to a long rainy season, abundant flora and fauna and a scattered population using paths traversing rural and forest lands makes people in these areas particularly prone to snake bite^[13]. The reptilian fauna shows geographical variation in habitation of medically important venomous snake species. Existence of venomous snakes like *Trimeresurus albolabris* (white lipped pit viper), *Gloydius himalayanus* (himalayan pit viper) and *Naja oxiana* (black cobra) has been documented in the state of Himachal Pradesh, in addition to the common "Big 4" which are found throughout India^[14].

Indira Gandhi Medical College Hospital, Shimla is the only tertiary-care hospital in the state of Himachal Pradesh. We retrospectively analyzed the records to study the clinico-pathological spectrum of Snake bite-induced AKI seen during last 13 years at this hospital.

MATERIALS AND METHODS

The study was a retrospective analysis conducted on patients admitted at Indira Gandhi Medical College Hospital, Shimla with snake bite-induced AKI over a period of 13 years (July 2003-June 2016). The inclusion and exclusion criteria were defined as follows.

Inclusion criteria

Inclusion criteria were: (1) definitive history of snake bite; (2) clinical picture consistent with snake bite, as presence of fang marks or cellulitis or coagulopathy or neuromuscular paralysis; (3) presence of AKI as defined using KDIGO criteria based on serum creatinine (increase in serum creatinine by ≥ 0.3 mg/dL within 48 h or increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 d^[15]). It was presumed that the patient had normal renal function if the serum creatinine was 1.5 mg/dL; and (4) presence of at least one or more indication of renal replacement therapy.

Exclusion criteria

Exclusion criteria were: (1) patients with pre-existent renal disease (serum creatinine > 1.5 mg/dL prior to snake bite or ultrasonography of abdomen suggestive of bilateral small kidneys/loss of corticomedullary differentiation/obstructive nephropathy/ other renal pathology); (2)

diagnosed cases of hypertension /diabetes mellitus; and (3) exposure to nephrotoxic drugs/toxins.

All the patients were subjected to detailed history and clinical examination. A bedside twenty minute whole blood clotting test (20WBCT) was performed to look for coagulation defect. Hematological and biochemical investigations were performed in all patients. Patients were administered tetanus toxoid injection, if not received previously. Polyvalent anti-snake venom (ASV) was provided where needed (each vial of serum contains 10 mL, and each 1 mL neutralizes 0.6 mg cobra, 0.6 mg Russell's viper, 0.45 mg common krait, and 0.45 mg saw-scaled viper venoms) according to the standard protocol. Patients showing signs of neuromuscular paralysis were given injection neostigmine with prior atropine. Doses were repeated as needed based on clinical response. Supportive treatment (intravenous fluids, blood components, antibiotics and analgesics) was given. Patient subjected to dialysis as per standard hospital protocol. Ventilatory support was needed for patients with respiratory failure, either due to neuromuscular paralysis or pulmonary edema.

Medical record were evaluated for patient's information including age, gender, month of the bite, time from snake bite to arrival at hospital and site of the snake bite.

Laboratory results of hemoglobin, leukocyte count, platelet count, blood urea, serum creatinine, serum electrolytes of sodium and potassium, serum albumin, serum bilirubin, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT), alkaline phosphatase, creatine kinase (CK), lactate dehydrogenase (LDH) and arterial blood gas analysis and the prevalence of anemia (Hemoglobin < 12 g/dL), leucocytosis, thrombocytopenia, hyperkalemia, hypoalbuminemia, hepatic dysfunction, severe metabolic acidosis (pH 7.2), hemolysis and rhabdomyolysis were recorded. Peak values or worst results of these laboratory parameters during the admission were used for analysis. The complications of hypotension, hypertension, chest infection, acute respiratory distress syndrome (ARDS), myocarditis, myocardial infarction, gastro-intestinal bleed, seizure and encephalopathy, DIC and multi organ failure (MOF) seen during the hospitalization were recorded.

Outcomes of duration of hospital stay (DOHS), requirement for intensive care unit (ICU) support, treatment with dialysis, survival and mortality were analyzed. The survival and non survival groups were compared to see the difference in the demographic factors, laboratory results, clinical characteristics and complications between the two groups.

In this study, the clinical symptoms and complications of snake envenoming were classified using WHO guidelines for the clinical management of snakebites in the southeast Asian region^[5].

Coagulation defect primarily detected by 20WBCT or visible spontaneous systemic bleeding documented by the referring health institution or observed at this hospital was recorded. Evidence of neurotoxicity: Ptosis, external ophthalmoplegia, muscle paralysis, inability to lift the head, etc. Hypotension was defined as an

Table 1 Demographic and clinical characteristics of the study patients (*n* = 121)

Gender	
Male, <i>n</i> (%)	51 (42.1)
Female, <i>n</i> (%)	70 (57.9)
Age (yr)	
Mean $\pm$ SD	42.2 $\pm$ 15.1
Range	14-84
Month of the bite	
March, <i>n</i> (%)	1 (0.8)
April, <i>n</i> (%)	8 (6.6)
May, <i>n</i> (%)	10 (8.3)
June, <i>n</i> (%)	20 (16.5)
July, <i>n</i> (%)	16 (13.2)
August, <i>n</i> (%)	22 (18.2)
September, <i>n</i> (%)	29 (24)
October, <i>n</i> (%)	10 (8.3)
November, <i>n</i> (%)	5 (4.1)
Duration at arrival (d)	
Mean $\pm$ SD	3.4 $\pm$ 3.7 ^a
Median	3
Range	1-30
Duration of hospital stay (d)	
Mean $\pm$ SD	12.4 $\pm$ 7.7 ^a
Median	10
Range	1-40
Bite site	
Lower limb, <i>n</i> (%)	75 (85.2)
Upper limb, <i>n</i> (%)	13 (14.8)
Oliguria, <i>n</i> (%)	70 (79.5) ^a
Hematuria, <i>n</i> (%)	48 (54.5) ^a
Limb swelling/cellulitis, <i>n</i> (%)	12 (13.6) ^a
Neurotoxicity, <i>n</i> (%)	5 (5.7) ^a
Coagulation defect, <i>n</i> (%)	78 (88.6) ^a
ASV given, <i>n</i> (%)	85 (96.6) ^a
Blood transfusion, <i>n</i> (%)	15 (17) ^a
ICU support, <i>n</i> (%)	10 (11.4) ^a
Dialysis therapy, <i>n</i> (%)	99 (81.8)
Hemodialysis	
Mean $\pm$ SD	3.5 $\pm$ 3.7
Median	3
Range	1-20
Outcome	
Survived, <i>n</i> (%)	110 (90.9)
Died, <i>n</i> (%)	11 (9.1)

^aClinical details available in 88 patients. ASV: Anti-snake venom; ICU: Intensive care unit.

arterial systolic blood pressure below 90 mmHg and hypertension by a blood pressure of 140/90 mmHg.

Hepatic dysfunction was defined as an AST or ALT over 60 IU/L. Intravascular hemolysis by presence of anemia, jaundice, reticulocytosis, abnormal peripheral blood smear and raised serum LDH levels. Rhabdomyolysis was characterized by elevated serum CK levels of five or more times the normal levels, with a suggestive clinical picture and without heart and cerebral injury^[11,16].

To diagnose disseminated intravascular coagulation, we used the guidelines for screening tests proposed by Yu *et al.*^[17]. Patients remaining oligoanuric or whose serum creatinine did not decrease satisfactorily at the end of three weeks underwent kidney biopsy which was examined with light and immunofluorescence microscopy. Findings of histopathological examination of the kidney biopsies

were also analyzed. Permission from the Institutional Review Board and the hospital authorities was obtained for the study [No. HFW(MS)G-5(Ethic)/2015-9078].

Statistical analysis

The data collected were stored using a computer program. Continuous data are expressed as means $\pm$ SD, and the means of the two study groups were compared using an unpaired *t* test. Nominal data are expressed as frequencies or proportions, and the χ^2 test and Fisher's exact test were used to compare the differences in frequency between the two study groups. For non-normal data, a Mann-Whitney *U* test was performed. Multivariate binary logistic regression analysis was done for factors predictive mortality. A *P*-value < 0.05 was considered statistically significant. All statistics were carried out using SPSS, version 16 (SPSS, Chicago, IL, United States).

RESULTS

A total of 121 patients were diagnosed with snake bite-induced AKI during the study period. Eighty-one patients had AKI out of a total of 447 patients who were admitted for snake bite during a period of 5.5 years (January 2011 to June 2016), with 18.1% incidence of Snake bite-induced AKI.

Baseline demographic and clinical characteristics

Table 1 shows the demographic and clinical characteristics of the study patients. Mean age of the patients was 42.2 $\pm$ 15.1 years. Fifty-one (42.1%) patients were male and 70 (57.9%) were female. Majority (86.8%) of the snake bite accidents occurred in summer and monsoon months. The snake bite occurred in monsoon months (July-September) in 67 (55.4%), summer months (April-June) in 38 (31.4%), and the other 16 (13.2%) in winter months (October-March). All the snake bite accidents had occurred in rural areas. Clinical details were available in total of 88 (72.7%) patients. The mean duration of arrival at hospital after snake bite was 3.4 $\pm$ 3.7 d with a range of 1 to 30 d. Seventy (79.5%) patients had oliguria and 48 (54.5%) had a history of hematuria or having passed dark brown/black urine. Majority (85.2%) of the patients had sustained bite on lower extremities. Limb swelling/cellulitis was seen in 12 (13.6%) patients and 5 (5.7%) patients had associated neurotoxicity. Coagulation defect was seen/documentated in 78 (88.6%) patients.

Laboratory results

The mean hemoglobin was 9.6 $\pm$ 2.6 g/dL, white blood cell (WBC) count was 15 $\pm$ 7.4 ($\times 10^3/\text{mm}^3$) and platelet count was 117 $\pm$ 58 ($\times 10^3/\text{mm}^3$). The mean values of peak serum urea and creatinine were 169 $\pm$ 75 mg/dL and 7.2 $\pm$ 4.2 mg/dL respectively. The serum albumin 3.2 $\pm$ 0.4 g/dL, bilirubin 1.4 $\pm$ 1.4 mg/dL, AST 152 $\pm$ 296 IU/L, and ALT was 106 $\pm$ 163 IU/L. The mean values of creatine kinase were 2072 $\pm$ 4287 U/L and lactate dehydrogenase was 1153 $\pm$ 1015 IU/L (Table 2). The

Table 2 Laboratory results of the study patients (*n* = 88)

	Mean $\pm$ SD	Range
Hemoglobin (g/dL)	9.6 $\pm$ 2.6	3.8-16
WBC count ($\times 10^3/\text{mm}^3$)	15 $\pm$ 7.4	4.8-47.9
Platelets ($\times 10^3/\text{mm}^3$)	117 $\pm$ 58	18-230
Urea (mg/dL)	169 $\pm$ 75	54-440
Creatinine (mg/dL)	7.2 $\pm$ 4.2	1.6-19.2
Sodium (mEq/L)	134 $\pm$ 8.1	108-145
Potassium (mEq/L)	5 $\pm$ 0.8	3.2-7.2
Albumin (g/dL)	3.2 $\pm$ 0.4	2.5-4.1
Bilirubin (mg/dL)	1.4 $\pm$ 1.4	0.3-7.5
AST (U/L)	152 $\pm$ 296	16-1606
ALT (U/L)	106 $\pm$ 163	10-800
Alk. phosph. (U/L)	93 $\pm$ 66	18-432
CK (U/L)	2072 $\pm$ 4287	24-22000
LDH (U/L)	1153 $\pm$ 1015	70-4705

ALP: Alkaline phosphatase; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; CK: Creatine kinase; LDH: Lactate dehydrogenase; Alk. phosph.: Alkaline phosphatase.

Table 3 Frequency of various of hematological and biochemical disorders (*n* = 88)

Anemia Hb < 12 g/dL, <i>n</i> (%)	71 (80.7)
Leukocytosis, <i>n</i> (%)	66 (75)
Thrombocytopenia, <i>n</i> (%)	42 (47.7)
Hyperkalemia, <i>n</i> (%)	22 (25)
Severe metabolic acidosis, <i>n</i> (%)	35 (39.8)
Hepatic dysfunction, <i>n</i> (%)	36 (40.9)
Hypoalbuminemia, <i>n</i> (%)	54 (61.4)
Hemolysis, <i>n</i> (%)	75 (85.2)
Rhabdomyolysis, <i>n</i> (%)	60 (68.2)

hematological and biochemical laboratory abnormalities were: Anemia (80.7%), leukocytosis (75%), thrombocytopenia (47.7%), hyperkalemia (25%), severe metabolic acidosis (39.8%), hepatic dysfunction (40.9%), hemolysis (85.2%) and rhabdomyolysis (68.2%) (Table 3). Fifty-three (60.2%) patients had both intravascular hemolysis and rhabdomyolysis.

Complications

Main complications were: Gastrointestinal bleed (12.5%), seizure/encephalopathy (10.2%), hypertension, pneumonia/ARDS and DIC (9.1% each), hypotension and MOF (4.5% each), myocarditis and myocardial infarction (1.1% each) (Table 4).

Clinical outcomes

Polyvalent ASV was administered to 85 (96.6%) patients. Fifteen (17%) patients required blood transfusion and 10 (11.4%) patients required ICU support. The mean DOHS were 12.4 $\pm$ 7.7 with a range of 1-40 d. Ninety-nine (81.8%) patients required dialysis. The mean number of hemodialysis (HD) treatments per patient was 3.5 $\pm$ 3.7 with a range of 1-20. 110 (90.9%) patient survived and 11 (9.1%) patients died (Table 1). Eighty-six (97.7%) AKI patients had complete renal function recovery whereas 2 patients had partial renal function recovery on

Table 4 Complications in the study patients (*n* = 88)

Pneumonia/ARDS	8 (9.1)
Hypertension	8 (9.1)
Hypotension	4 (4.5)
Myocarditis	1 (1.1)
Myocardial infarction	1 (1.1)
Gastrointestinal bleed	11 (12.5)
DIC	8 (9.1)
Seizure/Encephalopathy	9 (10.2)
MOF	4 (4.5)

DIC: Disseminated intravascular coagulation; MOF: Multi organ failure; ARDS: Acute respiratory distress syndrome.

follow-up.

Comparative demographic and laboratory results between survival and non-survival group

Table 5 shows the comparison of the demographic and laboratory results between survival and non-survival groups. Patients in the non-survival group had a significantly shorter DOHS ($P = 0.012$) as compared to that in the survival group. As compared to the survival group, the WBC count ($P = 0.023$) and bilirubin levels ($P = 0.006$) were significant higher and albumin levels were significantly lower (0.005) in patients who died.

Comparative clinical characteristics and complications between survival and non-survival group

Table 6 shows the comparison of the clinical characteristics and complications between survival and non-survival groups. The proportion of patients with pneumonia/ARDS ($P = 0.001$), seizure/encephalopathy ($P = 0.005$), MOF ($P = 0.05$) and need for ICU support (0.001) was significantly higher in patients who died.

There were no significant differences in the demographic and clinical characteristics, severity of hematological and biochemical abnormalities, other complications and need for dialysis therapy between groups.

Renal histology

Renal histology was studied in 22 (25%) patients (Table 7). Predominant lesion on kidney biopsy was acute tubular necrosis in (ATN) 20 (91%) patients, 11 patients had severe ATN (Figure 1A) and other nine (40.9%) had ATN associated with mild to moderate acute interstitial nephritis (AIN) (Figure 1B). One (4.5%) patient only had moderate AIN (Figure 2A) on biopsy. Renal cortical necrosis (RCN) which was patchy involving 35%-40% of cortical segment (Figure 2B) was present in one patient with prolonged anuria lasting for more than 4 wk. There was a lapse of 24 h when this patient had treatment with ASV.

DISCUSSION

Epidemiology

Snake bite is predominantly an occupational hazard in the rural tropics. The incidence of snake-bites depends

Table 5 Comparison of demographic and laboratory results between survival and non survival group (*n* = 88)

	Survived (<i>n</i> = 79)	Died (<i>n</i> = 9)	<i>P</i> value
Age (yr)	43 ± 15.7	39 ± 12.2	0.460 ^a
Sex			
Male, <i>n</i> (%)	34 (43)	2 (22.2)	0.299 ^c
Female, <i>n</i> (%)	45 (57)	7 (77.8)	
Duration at arrival (d)	3.4 ± 3.9	2.9 ± 0.8	0.536 ^b
Duration of hospital stay (d)	12.9 ± 7.2	8.8 ± 11.4	0.012 ^b
Hemoglobin (g/dL)	9.6 ± 2.7	8.9 ± 2.4	0.435 ^a
WBC count (× 10 ³ /mm ³)	14.5 ± 7.3	19.7 ± 7.5	0.023 ^b
Platelets (× 10 ³ /mm ³)	119 ± 57	95 ± 67	0.218
Urea (mg/dL)	167 ± 78	186 ± 43	0.466
Creatinine (mg/dL)	7 ± 4.1	7 ± 2	0.997
Sodium (mEq/L)	135 ± 8	138 ± 4.6	0.182
Potassium (mEq/L)	4.8 ± 0.8	5.1 ± 1.2	0.392
Albumin (g/dL)	3.3 ± 0.4	3 ± 0.3	0.005
Bilirubin (mg/dL)	1.2 ± 1.1	3.1 ± 2.2	0.006 ^b
AST (U/L)	141 ± 283	254 ± 398	0.231 ^b
ALT (U/L)	101 ± 158	156 ± 200	0.102 ^b
ALP (U/L)	90 ± 67	122 ± 54	0.057 ^b
CK (U/L)	1811 ± 3762	4069 ± 7181	0.298 ^b
LDH (U/L)	1106 ± 1027	1684 ± 732	0.052 ^b

^aIndependent samples *t*-test, sig. (2-tailed); ^bMann-Whitney *U* test, Sig. (2-tailed), non parametric independent samples test; ^c χ^2 with Fisher's Exact test Exact sig. (2-sided). ALP: Alkaline phosphatase; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; CK: Creatine kinase; LDH: Lactate dehydrogenase.

critically on the frequency of contact between snakes and humans. Seasonal peaks of snake-bite incidence are usually associated with increases in agricultural activity or seasonal rains, perhaps coinciding with unusual movement and activity by snakes. Snakebites and snakebite fatalities peak during the monsoon season in India^[18,19] and worldwide^[3], probably reflecting agricultural activity, flooding, increased snake activity, and abundance of their natural prey. All the snake bite accidents in the current study had occurred in rural areas and majority of them happened during monsoon months.

The kidney, a highly vascularized organ with excretory function, is prone to venom toxicity as an innocent bystander. AKI, the most significant of all the renal manifestations, has been reported with varying frequency in different studies^[8]. Many studies have appeared in literature on snake bite-induced AKI over a decade after the landmark study by Chugh^[9] (Table 8). They have mainly come from Asia^[9,6-30] and South America^[11,25]. These studies both retrospective^[9,21,22,25,27-29] and prospective^[11,20,23,24,26,30] have been carried over a period of 1-25 years. All except one^[26] have been in adult patients. The incidence of AKI in adults ranged from 8%-45%^[9,11,20-25] whereas the incidence in children is reported to be 46%^[26]. An incidence of 18.1% was found in the current study. Similar to our study the mean age of the patients ranged from 24-43 years in various studies^[9,11,20-25,28-30] except for one study^[27] from China where the mean age of the patients was 66 years.

Males are more often bitten than females, except where the work force is predominantly female (e.g., tea

Table 6 Comparison of clinical characteristic, laboratory abnormalities and complications between survival and non survival group (*n* = 88)

	Survived (<i>n</i> = 79)	Died (<i>n</i> = 9)	<i>P</i> value ^a
Oliguria, <i>n</i> (%)	62 (78.5)	8 (88.9)	0.679
Hematuria, <i>n</i> (%)	44 (55.7)	4 (44.4)	0.726
Anemia, <i>n</i> (%)	64 (81)	7 (77.8)	1.000
Leukocytosis, <i>n</i> (%)	57 (72.2)	9 (100)	0.105
Thrombocytopenia, <i>n</i> (%)	37 (46.8)	5 (55.6)	0.731
Hyperkalemia, <i>n</i> (%)	19 (24.1)	3 (33.3)	0.685
Metabolic acidosis, <i>n</i> (%)	29 (36.7)	6 (66.7)	0.147
Hypoalbuminemia, <i>n</i> (%)	46 (58.2)	8 (88.9)	0.145
Hepatic dysfunction, <i>n</i> (%)	32 (40.5)	4 (44.4)	1.000
Hemolysis, <i>n</i> (%)	67 (84.8)	8 (88.9)	1.000
Rhabdomyolysis, <i>n</i> (%)	55 (69.6)	5 (55.6)	0.457
Pneumonia/ARDS, <i>n</i> (%)	3 (3.8)	5 (55.6)	0.001
Seizure/Encephalopathy, <i>n</i> (%)	5 (6.3)	4 (44.1)	0.005
Multiorgan failure, <i>n</i> (%)	2 (2.5)	2 (22.2)	0.050
ICU support, <i>n</i> (%)	5 (6.3)	5 (55.6)	0.001
Dialysis, <i>n</i> (%)	57 (72.2)	9 (100)	0.105

^a χ^2 with Fisher's Exact test. ICU: Intensive care unit; ARDS: Acute respiratory distress syndrome.

Table 7 Kidney biopsy results (*n* = 22)

Acute tubular necrosis, <i>n</i> (%)	11 (50)
Acute tubular necrosis + acute interstitial nephritis, <i>n</i> (%)	9 (40.9)
Acute interstitial nephritis, <i>n</i> (%)	1 (4.5)
Acute cortical necrosis, <i>n</i> (%)	1 (4.5)

and coffee picking)^[5]. Majority (58%) of patients in our study was found to be women in working age group whereas majority (50%-83%) of the victims in other studies was male^[11,20-26,28-30]. Female preponderance in our study was due to involvement of women in hills in cutting grass for fodder more frequently.

Most snake-bites happen when the snake is trodden on, either in the dark or in undergrowth, by someone who is bare-footed or wearing only sandals. Bite site in majority (85.2%) of patients in current study was lower limb similar (72%-99%) to that in other studies^[11,20-24,30]. Education on prevention of snake bite should be imparted among farmers and field workers. They should be advised to use long boots and not to walk on their bare feet or disturb snakes in the fields. Our study showed that we can prevent a large number of snake bites by protecting our feet.

Pathogenesis

Although bites from all the venomous snakes are known to cause AKI, a substantial proportion of these cases results from viper bites. Most Indian patients are victims of Russell's viper or *Echis carinatus* bites^[9]. Snake venom is complex poisons consisting of hundreds of different proteins: Enzymes, polypeptide toxins and non-toxic proteins. Phospholipase A2 is the most widespread and extensively studied of all venom enzymes. It damages mitochondria, red blood cells, leucocytes, platelets, peripheral nerve endings, skeletal muscle, vascular

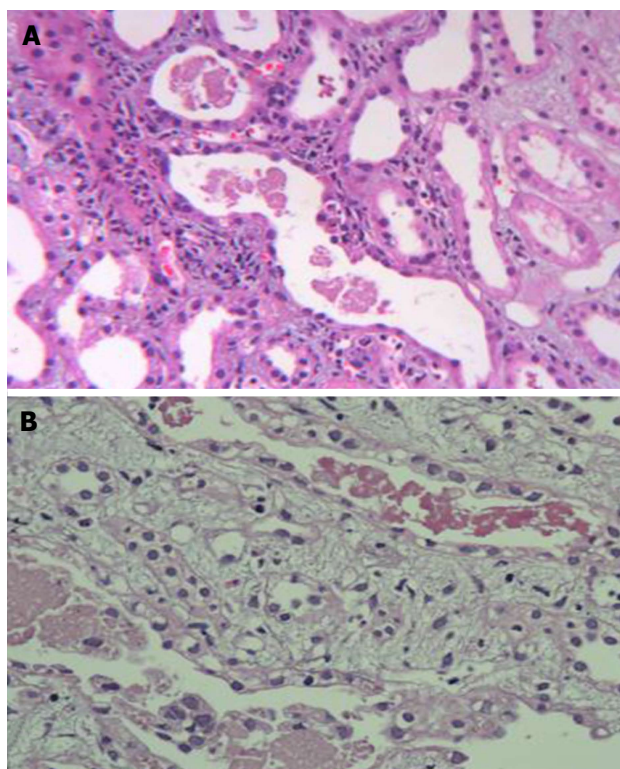


Figure 1 Kidney biopsy images. A: Severe acute tubular necrosis; B: Acute tubular necrosis associated with moderate interstitial nephritis.

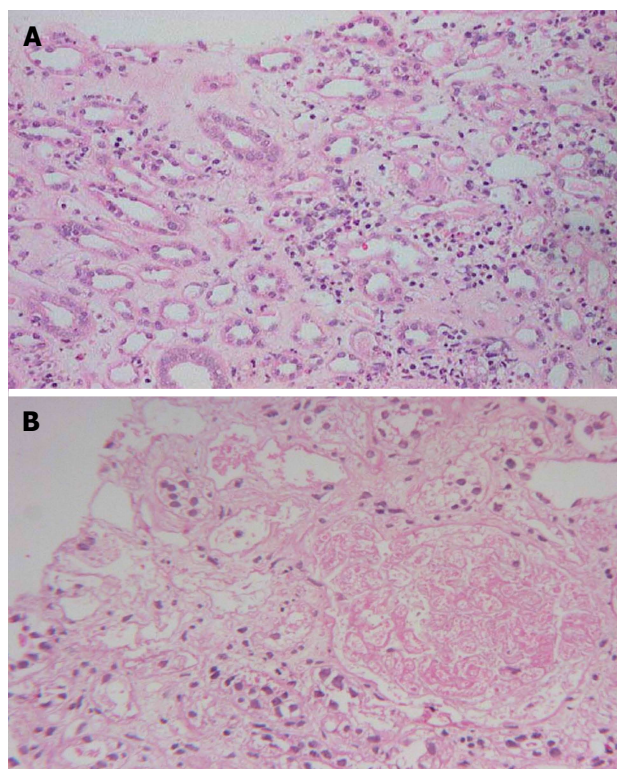


Figure 2 Kidney biopsy images. A: Moderate acute interstitial nephritis; B: Patchy cortical necrosis.

endothelium, and other membranes, produces presynaptic neurotoxic activity, opiate-like sedative effects, leads to the autopharmacological release of histamine and anti-coagulation. Viper bites cause various systemic symptoms such as: Coagulopathy; haemolysis; AKI; a generalized increase in capillary permeability; rhabdomyolysis; and neurotoxicity^[5,8]. Hemoglobinuria caused by intravascular hemolysis and myoglobinuria resulting from rhabdomyolysis contribute importantly to the development of AKI after snake bite. Hemorrhage, hypotension, disseminated intravascular coagulation, intravascular hemolysis, and rhabdomyolysis enhance renal ischemia leading to renal failure. Enzymatic activities of snake venoms account for direct nephrotoxicity. Immunologic mechanism plays a minor role^[8].

Clinical characteristics

In various studies, the symptoms of oligoanuria has been reported to be 13.8%-100%^[9,11,20,21,23,24,26,28,30] and hematuria/black colored urine 24.6%-80%^[9,11,20,22,24,26,29] as compared to that of 79.5% and 54.5% respectively in our study. Cellulitis was 39%-98.7%^[20,23-26,28-30] as compared to that of 13.6% observed in our study, hypotension of 4.5% observed in current study as compared to that of 6.3%-45.2% in other studies^[9,20,23,24,27,29,30], neurotoxicity of 5.7% as compared to that of 3.2%-100% in other studies^[11,23,25,28,29]. Bleeding/coagulopathy which is a major symptom of systemic viper poisoning was observed in 88.6% patients as compared to 27.8%-65.8% in other studies of snake bite-induced

AKI^[11,20,23-26,28-30].

Among laboratory investigations - hemoglobin of ranged from 7-13.3 g/dL in other studies^[9,21,23,25,27,28] as compared to 9.6 g/dL in this study, WBC count ranged from $11.5-19.3 \times 10^3/\text{mL}$ ^[21,25,27,28] as compared to $15 \times 10^3/\text{mL}$ in current study, serum urea 85-233 mg/dL^[9,20,21,23-25] as compared to 169 mg/dL and serum creatinine 2-9.2 mg/dL^[9,20,21,23-26] as compared to 7.2 mg/dL in this study have been reported. Intravascular hemolysis has been reported in various studies to be 13.8%-54%^[9,20,24], thrombocytopenia 9.7%-60%^[9,20,21,30], and DIC 11.1%-43%^[9,20,21,24,30] as compared to that of 85.2%, 47.7%, and 9.1 respectively in our study.

Rhabdomyolysis is well known cause of AKI^[16]. Bites by sea-snakes are a common cause of rhabdomyolysis and myoglobinuria. Several Australian snakes are both myotoxic and hemotoxic. In Asia, Russell's viper venom in certain geographic areas can cause both intravascular hemolysis and rhabdomyolysis^[5,8]. Most of the studies of snake bite-induced AKI have only looked at the hematological and coagulation profile^[9,20-30]. In our study all AKI patients were investigated for evidence of hemolysis and rhabdomyolysis. Rhabdomyolysis was observed in 68.2% of patients as compared to 100% of AKI following viper bite by Pinho *et al.*^[11]. It might have been missed in some of them due to delayed arrival at our hospital. Majority (60.2%) of our patients had both hemolysis and rhabdomyolysis. Both hemoglobinuria and myoglobinuria contribute to the development of AKI. Intravascular hemolysis and rhabdomyolysis were

Table 8 Studies of snake bite-induced acute kidney injury

Ref.	Chugh ^[9]	Pinho <i>et al.</i> ^[11]	Athappan <i>et al.</i> ^[20]	Danis <i>et al.</i> ^[21]	David <i>et al.</i> ^[22]	Dharod <i>et al.</i> ^[23]	Harshavardhan <i>et al.</i> ^[24]	Albuquerque <i>et al.</i> ^[25]	Krishnamurthy <i>et al.</i> ^[26]	Li <i>et al.</i> ^[27]	Naqvi <i>et al.</i> ^[28]	Singh <i>et al.</i> ^[29]	Mukhopadhyay <i>et al.</i> ^[30]	The present study
Year	1989	2005	2008	2008	2012	2013	2013	2014	2015	2016	2016	2016	2016	2016
Place	Chandigarh	São Paulo	Madurai	Diyarbakir	Vellore	Nagpur	Hassan	Fortaleza	Puducherry	Chengdu	Karachi	Barabanki	Kolkata	Shimla
Country	India	Brazil	India	Turkey	India	India	India	Brazil	India	China	Pakistan	India	India	India
Type of study	Retro- spective	Pro- spective	Pro- spective	Retro- spective	Retro- spective	Pro- spective	Prospective	Retro- spective	Prospective	Retro- spective	Retro- spective	Retro- spective	Prospective	Retrospective
Time period (yr)	22	3.6	2	7	10	1.7	1	10	1.6	1.8	25	1.5	1.3	13
Total patients (n)	246	100	1548	200	533	281	246	276	61	119	-	138	460	-
AKI, n (%)	70 (28)	29 (29)	159 (10.3)	16 (8)	143 (26.8)	87 (31)	36 (14.6)	42 (15.2)	28 (45.9)	16 (13.4)	115	62 (44.9)	155 (33.7)	121 (18.1) ^b
Age (yr) mean ± SD	27.1 ± 15.8	24	39.1	40.3 ± 18.8	32 ± 15.9	36.1 ± 14.6	41.2 ± 12.4	43 ± 20	8	66 ± 7	35.9 ± 15	34.1 ± 1.6	36.3 ± 1.3	42.2 ± 15.1
Male (%)	-	83	56.7	50	69.4	70.1	55.5	76.2	53.6	50	62	80.6	69	42.1
Duration at arrival (d) Mean ± SD	-	< 0.5	0.9	0.1 ± 0.1	< 1	0.9 ± 1.8	0.9	1	0.2	1.3 ± 0.9	8.8 ± 5.6	2.8 ± 1.3	3.2 ^a	3.4 ± 3.7
Bite site at lower limb (%)	-	83	98.7	88	71.7	78.2	81.2	-	-	-	-	-	88.7	85.2
Oligo-anuria, n (%)	94	13.8	100	37.5	-	100	94	-	60.7	-	94	-	66	79.5
Hematuria (%)	80	83	70	-	64.3	-	80	-	24.6	-	-	58.1	-	54.5
Limb swelling/cellulitis (%)	-	98.7	-	-	92	91.6	0	57.1	39	-	41	51.6	63.2	13.6
Hypotension (%)	16	-	17.7	-	-	19.5	33.3	-	-	6.3	-	45.2	33.5	4.5
Neurotoxicity (%)	-	100	-	-	-	12.1	-	28.6	-	-	12.1	3.2	-	5.7
Bleeding/coagulopathy (%)	-	83	27.8	-	-	83	38.8	52.4	37.7	-	65.2	50	65.8	88.6
Hemoglobin (g/dL)	7 ± 2.6	-	-	13.2 ± 3.4	-	7.2 ± 1.4	-	9.4 ± 2.5	-	13.3 ± 1.2	8.3	-	-	9.6 ± 2.6
WBC count (× 10 ³ /mL)	-	-	-	19.3 ± 3.7	-	-	-	13.6 ± 5.2	-	11.5 ± 3.8	13.2	-	-	15 ± 7.4
Urea (mg/dL)	233 ± 107	-	100	113 ± 78	-	163 ± 83	85 ± 29.2	107 ± 74	-	-	-	-	-	169 ± 75
Creatinine (mg/dL)	9.2 ± 3.4	-	4.2	2.9 ± 0.5	-	4.9 ± 2.5	3.1 ± 1.5	3 ± 2.9	-	-	-	-	4.6 ± 0.2	7.2 ± 4.2
Hemolysis (%)	54	-	28.1	-	-	-	13.8	-	-	-	-	-	-	85.2
Thrombocytopenia (%)	14	-	25.2	60	-	-	-	-	-	-	-	-	9.7	47.7
DIC (%)	43	-	27.8	25	-	-	11.1	-	-	-	-	-	27.1	9.1
RRT (%)	75.7	24.1	45.3	25	57	55.2	44.4	30.6	35.7	-	92.2	-	100	81.8
DOHS (d)	-	-	5	6.7 ± 3.6	-	-	9	8	8	11.6 ± 2.7	-	-	11	10
Mortality (%)	28.6	10.3	22.6	18	21	39.1	22.2	0	14.3	6.3	13	-	29.7	9.1

^aBite to hemodialysis initiation time; ^bEighty-one (18.1%) out of total of 447 snake bite had AKI. DIC: Disseminated intravascular coagulation; RRT: Renal replacement therapy; DOHS: Duration of hospital stay.

the main cause of AKI in our study patients.

Various procoagulant enzymes are found in viper venoms, which activate different steps of the clotting cascade resulting in a state of DIC. Bleeding tendencies can also cause severe blood loss resulting in hypotension, further adding to the renal insult or causing one when none existed. Fibrin thrombi in renal microvasculature glomerular capillaries, microangiopathic hemolytic anemia and thrombocytopenia in patients with cortical necrosis strongly suggest that DIC plays a major pathogenetic role in snake bite-induced cortical necrosis. Thus, bleeding tendencies secondary to DIC are a major factor in the development of AKI in patients of snake bite, especially those involving vipers^[9,23]. DIC was observed in 9.1% patients in our study as compared to 11.1%-43% reported in other studies^[9,20,21,24,30]. Since all patients were not investigated for evidence of DIC, we had DIC in a lower percentage of our patients.

Median duration of arrival at hospital in our study was 3 d as compared to duration of arrival from bite to the hospital or to receipt of ASV ranging from few hours to 8.8 d in other studies^[11,20-30].

Incidence of complications is directly proportional to the duration of venom in the blood prior to neutralization by ASV. The early institution of ASV is beneficial in preventing complications however severe is the systemic envenomation^[31]. Vijeth *et al*^[32] found that none of the patient of snake bites with coagulopathy who received ASV within 8 h of being bitten developed renal abnormality. Patients who were left untreated due to late arrival at the hospital, the renal abnormality correlated well with the degree of coagulation abnormality.

The risk factors associated with development of AKI in snake bite are native treatment^[26], bite to needle time more than 2 h^[20], age^[11,24,27], bite to hospital/ASV time^[11,20,23,24,27,29], black or brown urine^[29,33], bleeding manifestations^[25,26,29], hypotension/shock^[23,24], cellulitis^[20,24,29], regional lymphadenopathy^[20,24], abdominal pain/tenderness and vomiting^[29], 20 WBCT > 20 min^[33], prolonged bleeding time^[23], prolonged prothrombin time^[23], low hemoglobin^[23], high WBC count^[21], low serum albumin^[21], and a high serum bilirubin^[23], CK > 2000 U/L^[11], albuminuria^[23], intravascular hemolysis^[20,24], DIC^[21,24], complications of septicemia^[24] and ARDS^[24], and a longer DOHS^[25].

The basic therapeutic approach for AKI in patients bitten by snakes is the same as that for AKI any other cause. Early administration of ASV is a vital therapeutic measure. Alkalization of urine by sodium bicarbonate helps in the prevention of AKI in the patient who has myoglobinuria or hemoglobinuria provided that this is performed early when dark urine is observed or when the snake is known to be myotoxic or hemotoxic. In patients with intravascular hemolysis and/or rhabdomyolysis, maintenance of a high urine output by increasing fluid intake and giving a diuretic, as well as rendering the urine alkaline early in the course of the disease may prevent renal damage^[8,9,11,16]. Snake bite-induced AKI can be catabolic with rapid rise in blood urea and serum creatinine levels, hyperkalemia and severe metabolic acidosis. Early and frequent peritoneal dialyses and hemodialyses are life saving for AKI. Muscular symptoms caused by bites from sea snakes are improved by hemodialysis^[8]. High proportion (82%) of our study patients had severe renal failure and received renal replacement therapy. Frequency of patients having received renal replacement therapy in other studies ranged from 24%-100%^[9,11,20-26,30]. Each patient in our study received three sessions of hemodialysis similar that reported in the study by Harshavardhan *et al*^[30].

Clinical outcomes

Median DOHS in our study was 10 d as compared to 5-12 d reported in other studies^[9,20,21,24-27,30]. AKI is a strong predictor of mortality among the in-hospital patients with snake bite^[22,34]. Mortality of 9.1% was observed in our study. There was no mortality in the study from Brazil by Albuquerque *et al*^[25]. However a mortality ranging from 6.3%-39.1% has been reported in other studies of snake bite-induced AKI^[9,11,20-24,26,28,30].

The mean values of WBC counts and serum bilirubin were significantly higher and albumin levels were significantly lower in the fatal cases in our study. This suggests that the fatal cases might have had more severe envenomation. Because albumin is a relatively slow-reacting negative acute-phase reactant it may be associated with higher mortality in AKI^[35]. Hypoalbuminemia was as result of a generalized increase in capillary permeability and bleeding complications. In these patients later or concomitant development of pneumonia and ARDS led to a fatal outcome. Further, complication of pneumonia/ARDS, seizure/encephalopathy, MOF, need for ICU support, and shorter DOHS were associated with mortality. Studies have found bite to needle time more than 2 h^[20,24], hypotension/shock^[20,24,30], bleeding manifestations^[20], coagulopathy^[36], thrombocytopenia^[28], intravascular hemolysis^[20], DIC^[24,30], septicemia^[24], encephalopathy^[36] as risk factors/predictors for mortality in snake bite-induced AKI.

Several factors contribute to the increased mortality such as taking treatment from native healers, problems in transport, lack of availability of ASV, high cost and lack of hospital based facilities in rural areas and inadequate knowledge among medical practitioners regarding snake bite management^[3,5,37]. At the community level, inappropriate first-aid measures such as incision, suction and herbal treatment are performed and vital time is lost before the victim is transported to a treatment centre^[37,38]. Education strategies to inform the communities regarding appropriate first aid, rapid transport and management are necessary.

Renal pathology

The renal lesions of clinical significance in envenomed patients are ATN, and patchy or diffuse RCN. Glomerulonephritis, interstitial nephritis, and papillary necrosis have been reported in rare patients. Tubulointerstitial lesions, predominantly ATN, are observed in 70% to 80% of patients with AKI^[9]. Biopsies carried out early reveal morphological features of severe acute tubular injury with intratubular pigmented granular casts. Varying degree of acute tubulointerstitial nephritis and interstitial edema may be found. Late biopsies reveal regenerating tubular epithelium^[9]. High proportion (91%) of patients subjected to kidney biopsy had ATN in our study. In addition, 41% of them had associated finding of mild to moderate AIN.

AIN was considered to be a rare after snake bite but according to recent studies AIN after snake bite is not uncommon^[39,40]. AIN accounted for 5.7%-11.9% of snakebite-related AKI. All patients had severe envenomation at presentation^[39,40], very high ASV requirement^[39] and had prolonged renal failure^[39,40]. Kidney biopsy found a mixed infiltrate composed of predominantly lymphocytes, with variable proportions of other cells including eosinophils neutrophils and plasma cells. The reason for development of this pathology is not clear, but direct venom related effects possibly lead to development of the interstitial inflammation *via* various cytokines, mediators and adhe-

sions molecules^[39,40]. AIN was found to be reversible with corticosteroids therapy^[40]. However, the long-term outcome was found to be worse as compared with those who did not have AIN, as majority patient developed chronic kidney disease (CKD) on follow-up. Overall AIN was present in 45% of renal biopsies in our study. One patient in our study only had moderate AIN on biopsy and completely recovered after a course of corticosteroids therapy. There was no difference in the clinical picture between the patients of ATN and AIN. Patients remaining oligoanuric or whose serum creatinine did not decrease satisfactorily at the end of three weeks should be subjected to kidney biopsy. The kidney biopsy has a diagnostic, prognostic and therapeutic value in such patients. Patients with ATN or ATN associated with AIN are likely to recover. Those with AIN on kidney biopsy may be treated with a course of steroids to hasten the recovery and to prevent development of fibrosis. RCN carries a bad prognosis for renal recovery.

RCN is characterized by patchy or diffuse ischemic destruction of all the elements of renal cortex resulting from significantly diminished renal arterial perfusion due to vascular spasm and microvascular injury. In addition, direct endothelial injury particularly in setting of sepsis, eclampsia, haemolytic uremic syndrome and snake bite may lead to endovascular thrombosis with subsequent renal ischemia. It is a rare cause of AKI in developed countries whereas in developing countries it accounts for 3% of all causes of AKI^[41]. The renal lesion that carries the most sinister prognosis is documented in patients bitten by Russell's viper and *Echis carinatus* is RCN^[5,9]. Patients with AKI who suffered oliguria for more than four weeks suggest the possibility of bilateral renal cortical necrosis. This can be confirmed by renal biopsy or contrast enhanced computed tomography (CT) scans of the kidneys. Patients with patchy cortical necrosis show delayed and partial recovery of renal function but those with diffuse cortical necrosis require regular maintenance dialysis and eventual renal transplantation^[41]. RCN has been observed in 27 (24%) kidney biopsies out of total of 112 kidney biopsies carried out in patients of snake bite-induced AKI from India and Pakistan^[9,28,39,40,42,43]. None had RCN on biopsy in two studies^[39,40]. In our study one patient (4.5%) with patchy cortical necrosis on kidney biopsy had partial recovery of renal function and came off dialysis. Incidence of RCN in our study over 13 years was 0.8% as compared to 11.3% observed over 25 years in a recent study from Pakistan^[28]. Delay in getting the ASV as in our case or lack of ASV treatment in high proportion (75%) of cases as reported in study by Chugh *et al*^[44] might be a factor in development of this renal lesion.

Most of the patients of ATN and AIN recover by few weeks, with the help of renal replacement therapy, but who develops RCN requires renal replacement therapy on a long term basis. Further, long-term outcome of snake bite-induced severe dialysis-requiring AKI is not benign with a significant percentage of patients continuing to have features of persistent renal damage in the form of

renal dysfunction, proteinuria, or hypertension^[43]. CKD is an outcome of severe AKI following snake envenoming probably predicted by the length of RRT^[44]. Among the patient who survived in the current study, all except two had complete renal recovery in hospital or on short term follow-up but long term outcome could not studied due to lack of such follow-up.

Study limitations

Our study is large series on clinico-pathological spectrum of snake bite-induced AKI from India. There are certain imitations in this study. Firstly it was a retrospective study carried out at a tertiary care renal unit where patients were referred from far flung rural areas. Most of the patient consult the traditional healers first, or wait to become severely symptomatic and the critical initial management period was lost. There were delays in seeking treatment at health centres and getting treatment with ASV due to its non-availability at peripheral health centres. Majority of the patients first received ASV at our centre. Secondly many clinical details might have been missed due to failure on the part of peripheral hospitals to observe or document them. The special investigations like complete coagulation profile as evidence for DIC were not done in all patients, identification of snake species and ELISA test to identify the snake venom are the other lacunae. Finally, we also could not assess long term residual injury in these cases of snake envenomation, although this is being increasingly recognized^[43,45].

In conclusion, snake bite-induced AKI is an important cause of community acquired tropical AKI. The AKI due to snake bite was severe and a high proportion (82%) of patients required renal replacement therapy and the outcome was fatal in 9.1% of cases. A high WBC count, high total bilirubin, a low serum albumin, the complications of pneumonia/ARDS, seizure/encephalopathy, MOF, the need for ICU support and a shorter DOHS were factors associated with mortality. On renal histology ATN and AIN were common, RCN was rare.

AKI is an important complication of snake bite that may lead to mortality. Clinico-pathological spectrum of snake-induced AKI has changed. Intravascular hemolysis and rhabdomyolysis is common and is the main cause of AKI due to snake bite. AKI is severe and high proportion of patients require renal replacement therapy. Complications of pneumonia/ARDS, seizure/encephalopathy, multi organ failure, the need for intensive care support and a shorter hospital stay are factors associated with mortality. ATN and AIN are common findings on renal histology. RCN is a rare presentation. Early ASV administration and alkaline diuresis may help in prevention of AKI. Proper supportive management after ASV administration is of utmost importance, for a good patient outcome. Kidney biopsy is important and has a diagnostic, prognostic and therapeutic value for patients not showing satisfactory improvement by three weeks; ATN or AIN are likely to recover whereas RCN has poor renal recovery.

COMMENTS

Background

Snake bite envenomation is a major public health problem in tropical countries. Acute kidney injury (AKI) is an important complication and major cause of mortality in patients with snake bites. Although bites from all the venomous snakes are known to cause AKI, a substantial proportion of these cases results from viper bites. Exact pathogenesis of AKI following snake bite is not well established. The pathogenesis of renal lesions is multifactorial and has been attributed to the nephrotoxicity of venom, hypotension, circulatory collapse, and intravascular hemolysis with hemoglobinuria, myoglobinuria, disseminated intravascular coagulation, hemolytic uremic syndrome, sepsis, and other factors such as hypersensitivity to venomous or antivenomous protein. On pathological investigations two main renal lesions responsible for AKI are tubular necrosis and renal cortical necrosis.

Research frontiers

There is no study on clinicopathological spectrum of snake bite-induced AKI in the last more than quarter of a century. The authors did a retrospective study to analyze clinicopathological spectrum of snake bite-induced AKI over a 13-year period.

Innovations and breakthroughs

The authors' study is large series on clinicopathological spectrum of snake bite-induced AKI in the last 25 years. Most of the studies of snake bite-induced AKI have only looked at the hematological and coagulation profile. In the present study all AKI patients were investigated for evidence of hemolysis and rhabdomyolysis. The authors found that the clinicopathological spectrum of snake-induced AKI has changed. Intravascular hemolysis and rhabdomyolysis is common and is the main cause of AKI due to snake bite. AKI is severe and a high proportion of patients require renal replacement therapy. Complications of pneumonia/acute respiratory distress syndrome, seizure/encephalopathy, multi organ failure, the need for intensive care support and a shorter hospital stay are factors associated with mortality. On renal histology acute tubular necrosis and acute interstitial nephritis is common, renal cortical necrosis is rare.

Applications

This study suggests that intravascular hemolysis and rhabdomyolysis is common, and is the main cause of AKI due to snake bite. Early administration anti-snake venom and alkaline diuresis may help in prevention of AKI. Dialysis and a proper supportive treatment are of utmost importance in the cases which are complicated by renal failure. The kidney biopsy has a diagnostic, prognostic and therapeutic value for patients not showing satisfactory improvement by three weeks; acute tubular necrosis or acute interstitial nephritis are likely to recover whereas renal cortical necrosis (RCN) has poor renal recovery.

Terminology

RCN: It is characterized by patchy or diffuse ischemic destruction of all the elements of renal cortex resulting from significantly diminished renal arterial perfusion due to vascular spasm and microvascular injury. In addition, direct endothelial injury particularly in setting of sepsis, eclampsia, hemolytic uremic syndrome and snake bite may lead to endovascular thrombosis with subsequent renal ischemia. This renal lesion carries the most sinister prognosis.

Peer-review

The study is interesting and inclusive for the readers of the special field.

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Retrospective Study

Acute kidney injury from different poisonous substances

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Abstract

AIM

To report our experience of acute kidney injury (AKI) developed after exposure to poisonous substance.

METHODS

Retrospective study where data was collected from case records of patients coming to this institute during January 1990 to May 2016. This institution is a tertiary care center for renal care in the metropolitan city of Karachi, Pakistan. History of ingested substance, symptoms on presentation, basic laboratory tests on arrival, mode of treatment and outcome were recorded from all patients and are presented here. Patients developing AKI after snake envenomation or scorpion stings are not included in this study.

RESULTS

During studied period 184 cases of AKI developing after poisoning were seen at our institution. The largest group was from paraphenyline diamine poisoning comprising 135 patients, followed by methanol in 8, organophosphorus compounds in 5, paraquat in 5, copper sulphate in 5, tartaric acid in 4, phenobarbitone in 3 and benzodiazepines, datura, rat killer, fish gall bladder, arsenic, boiler water, ammonium dichromate, acetic acid and herbs with lesser frequency. In 8 patients multiple substances were ingested in combination. Renal replacement therapy was required in 96% of patients. Complete recovery was seen in 72.28% patients, 20% died during acute phase of illness.

CONCLUSION

It is important to report poisonous substances causing vital organ failure to increase awareness among general population as well as health care providers.

Key words: Paraphenylene diamine; Organophosphorus compounds; Paraquat; Methanol; Poisons; Acute kidney injury

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Core tip: During our daily life we are exposed to certain substances/compounds, which may be used as pesticides, herbicides, insecticides, coloring inks, photocopying or may found in some plants. Use of these compounds intentionally or accidentally as per oral ingestion and absorption *via* gastro intestinal tract or taken *via* par-enteral route may cause hazardous, sometimes lethal effects. Current study highlights acute kidney injury as result of some of these poisons, dealt at a tertiary renal care unit. Awareness regarding pathophysiological consequences, need of early referral to particular specialized center and at society level at par is important issue addressed here.

Naqvi R. Acute kidney injury from different poisonous substances. *World J Nephrol* 2017; 6(3): 162-167 Available from: URL: <http://www.wjgnet.com/2220-6124/full/v6/i3/162.htm> DOI: <http://dx.doi.org/10.5527/wjn.v6.i3.162>

INTRODUCTION

Paraphenylene diamine (PPD) is a derivative of aniline. Human exposure is primarily through hair dyes and fortified "henna" which is used for tattooing. Occupational exposure is through photocopying and printing inks, black rubber, lithography plates, etc^[1]. Poisoning with PPD can cause oro-pharyngeal and gastrointestinal symptoms, hepatic involvement and later neurological involvement. Acute kidney injury (AKI) was reported in two cases from India in 1982^[2]. Earlier we have published a large series of 100 cases developing AKI after PPD poisoning. Rhabdomyolysis leading to acute tubular necrosis (ATN) and pigment nephropathy remains main pathophysiology of AKI after PPD poisoning^[3]. Methanol, also known as wood alcohol, is a commonly used organic solvent that can cause metabolic acidosis, neurologic sequelae, and even death. It is a constituent of many commercially available industrial solvents and of poorly adulterated alcoholic beverages, in Pakistan called as "katchi sharab". Toxicity with ingestion of methanol, which is more often in larger groups of people, remains a common problem in many parts of the developing world, especially among members of lower socioeconomic classes. AKI may be associated with other signs of severity in methanol poisoning, but it is almost always reversible in survivors. The pathophysiology of AKI developing after methanol poisoning is multifactorial but ultimately leads to acute tubular necrosis^[4].

Organo phosphorus (OP) compounds are frequently used as pesticides, herbicides, and even chemical warfare agents, large cohort has recently been published by Lee *et al*^[5], though study is population based it highlights risks of AKI development after exposure to OP poisoning. The rapid accumulation of acetylcholine in synaptic junctions

of central nervous system and peripheral tissues results in cholinergic crises and this may lead to ischemic ATN^[5]. Paraquat (1,1'-dimethyl-4,4'-bipyridylum dichloride) is widely used as a herbicide. Toxicity is usually seen following ingestion, which could be accidental or intentional and may range from mild to fulminant (according to dose ingested) leading to death. In addition to local irritation, multi organ failure (MOF), including kidney, may occur^[6]. Tartaric acid is a white crystalline organic acid that can be extracted from plants. It is commonly mixed with sodium bicarbonate and is sold as baking powder used as a leavening agent in food preparation. The acid itself is added to foods to add sour taste^[7]. Over dosage of tartaric acid can give rise AKI, gastro intestinal symptoms and cardio-vascular collapse. Volume loss from GI in form of intractable vomiting can lead to ATN^[8].

CuSO₄, one of the most available salts of copper, is a blue and odorless salt that is used in various products such as fungicides, algacides, herbicides and insecticides^[9]. Copper sulfate can be absorbed through the gastrointestinal tract, lungs and skin causing both systemic and local toxicity. AKI has also been reported after CuSO₄ poisoning^[10]. Symptoms related to systemic toxicity include delirium, stupor, coma, convulsion, hypotension, shock, respiratory failure, pallor and jaundice. Methemoglobinemia, rhabdomyolysis and hepatotoxicity have also been reported. Pigment nephropathy and ATN are most probable patho-physiological mechanisms here^[11].

Datura is a poison from some flowering plants, contain tropane alkaloids such as scopolamine, hyoscyamine, and atropine, primarily in their seeds and flowers. Because of the presence of these substances, Datura has been used for centuries in some cultures as a poison^[12]. Datura toxins may be ingested accidentally by consumption of honey produced by several wasp species, In some parts of Europe and India, Datura has been a popular poison for suicide and murder. From 1950 to 1965, the State Chemical Laboratories in Agra, India, investigated 2778 deaths caused by ingesting Datura^[13]. Due to the potent combination of anticholinergic substances it contains, Datura intoxication typically produces effects similar to that of an anticholinergic and ischemic ATN may result. Other possibility of interstitial edema and direct nephrotoxic effect can not be ruled out.

Rat killer or rodent killers can give rise accidental or intentional harm to human. Components of available rat killers are; Brodifacoum, Diphacinone, Warfarin and Bromadiolone. All of these substances are anti coagulants and can cause severe coagulopathy after ingestion^[14]. Acute volume loss can lead to ischemic ATN and hemoglobin pigments can also cause blockade of tubular lumina.

Ichthyotoxic AKI has been reported after fish gall bladder ingestion previously. Toxin is believed to be cyprinol sulphate. This poisoning can involve gastrointestinal, hepatic, cardiac and neurological systems along with kidneys^[15]. AKI can occur as part of MOF or ischemic ATN or acute tubule-interstitial nephritis (ATIN) may be a

Table 1 Contribution from different substances (n = 184)

Poisonous substance	No. of patients	%
PPD	135	73.36
Methanol	8	4.34
CuSO ₄	5	2.71
OP	5	2.71
Paraquat	5	2.71
Tartric acid	4	2.17
Phenobarbitone	3	1.63
Benzodiazepines	2	1.08
Datura	2	1.08
Ammonium dichromate	1	0.54
Rat killer	1	0.54
Fish gallbladder	1	0.54
Acetic acid	1	0.54
Arsenic	1	0.54
Boiler water	1	0.54
Multiple substances taken in combination	9	4.89

PPD: Paraphenylene diamine; OP: Organo phosphorus.

possibility. Arsenic has been used in many medicines and was widely used to treat syphilis until the mid 20th century. It is currently used to treat acute promyelocytic leukaemia and other myeloproliferative disorders^[16]. It has also been used as a pigment, a pesticide and a poison. AKI with acute hemolysis has been reported after acute arsenic poisoning^[17,18].

Ischemia reperfusion injury and tubular necrosis can result with Benzodiazepines ingestion^[19]. Ammonium dichromate is an inorganic compound frequently used in screen and color printing. Being a strong oxidizing agent, it can cause oxygen free radical injury and renal tubular necrosis^[20]. Acetic acid is an organic acid that is used for homemade vegetable preserves and is available in grocery stores easily. Coma, shock, hemolysis and anuric renal failure has been reported with poisoning with acetic acid^[21]. The patho-physiological mechanisms here could be pigment nephropathy and ATN or ATIN.

MATERIALS AND METHODS

Case records of all patients registered in emergency room of Sindh Institute of Urology and Transplantation (SIUT), Karachi, with diagnosis of AKI which was labeled upon findings of sudden rise in serum creatinine and decline in urine output in a previously healthy person after ingestion of one of the poisonous substances listed in Table 1. Renal ultrasound was done in all patients on the day of registration and all had normal size non-obstructed kidneys. Patients with previous co morbidities like diabetes mellitus, hypertension or known kidney disease were excluded. Patients developing AKI after snake bite or scorpion stings are also not included in the present study as published earlier separately (see references below in discussion). Clinical history, presenting symptoms, laboratory investigations including complete blood count, renal and hepatic chemistry, serum lactate dehydrogenase, international normalization ratio for coagulation and urinalysis from day of admission

were recorded. Other features recorded were need for renal replacement therapy and patient outcome. Renal replacement therapy where required was done in form of hemodialysis only. Institutional review board was consulted to grant permission to compile and publish the data. Personal identification of individual patients not revealed. Informed consent as routine taken from all patients reaching to emergency of this hospital.

RESULTS

Between January 1990 and May 2016, 184 patients with AKI secondary to poisons were brought to SIUT emergency. Male to female ratio was 1.02:1, while mean age was 24.37 ± 8.30 (median 22 years). Distribution of patients brought with different poisons is given in Table 1, while Tables 2 and 3 highlight on major presenting symptoms and clinical and laboratory parameters of these patients. The majority of patients were brought here due to marked decline in urine output and uremic symptoms. Urinalysis is available in 121/184 (65.76%) patients and dipstick revealed 1-2+ protein in 69/121 urine samples while 21 and 11 showed 3+ and 4+ proteins. Numerous red blood cells per high power field were seen in 95/121 urine samples. Renal biopsy was available from 13 patients and the most common finding was acute tubular necrosis found in 11 biopsy samples. Pigment cast in tubules were seen in 6 biopsies. Tubulo interstitial involvement along with ATN was seen 2 biopsies, and in isolation one sample had cast along with TIN (biopsy from patient with methanol poisoning). One biopsy revealed acute cortical necrosis (ACN). Renal replacement therapy was required in 96% patients soon after arrival. Outcome of patients from different groups is given in Table 4.

DISCUSSION

We have previously published a series of patients developing AKI after PPD^[3] poisoning. The current study includes those cases as well as further cases from PPD and in addition AKI, as a result of exposure to other poisons. Poisoning with PPD has increased over last 6-7 years in our country, especially in the province of Sindh where this institution (SIUT) is located, and we are continuously receiving patients with AKI developed after toxic rhabdomyolysis as a result of ingestion of PPD. Measures for public awareness in the form of editorials, letters to the editors of local newspapers and local television channels have been made but so far no decline in use of poison has been observed. Contributing factors such as easy availability and low cost also remain unchanged.

Methanol is a substance which usually ingested in large groups on special occasions as entertainment by people in the low socio economic stratum. Annually, a large number of deaths are reported with methanol ingestion in groups^[22], survivors developing AKI are brought to SIUT and are included here in this study. Elevated levels of creatinine kinase indicate rhabdomyolysis as a cause of

Table 2 Presenting symptoms (n = 184)

Symptom	Frequency (%)	Mostly with substance
Oligoanuria	93	All groups except phenobarbitone
Vomiting	90	All groups
Hematuria/cola color urine	86	PPD, CuSO ₄ , Paraquat
Massive facial/neck swelling ± difficulty in swallowing	74	PPD
Hemetemesis	16	CuSO ₄ , OP, Paraquat, boiler water
Altered level of consciousness	16	Methanol, phenobarbitones, benzodiazepines, OP
Temporary loss of vision	2.17	Methanol

PPD: Paraphenylene diamine; OP: Organo phosphorus.

Table 3 Laboratory and other parameters on presentation in different groups (median values and ranges given)

Paramet	PPD (n = 135)	Methanol (n = 8)	CuSO ₄ (n = 5)	OP (n = 5)	Paraquat (n = 5)	Others (n = 26)
DOI	4 (1-28)	5 (1-15)	4 (2-5)	5 (2-6)	3 (1-5)	5 (1-25)
Hb, g/dL	11.95 (2.5-21.5)	13.7 (9-19.5)	5.5 (2-9.9)	10.3 (6.7-13.4)	8 (6.3-11)	11.5 (7.6-15.6)
Plt, × 10 ⁹ /L	234 (59-603)	285.5 (58-610)	303 (101-687)	114 (98-121)	90 (47-213)	211.5 (10-910)
Urea, mg/dL	183 (69-496)	123.5 (47-329)	282 (108-384)	234 (114-367)	224 (197-338)	213.5 (65-483)
Creat, mg/dL	7.81 (3-25.15)	5.25 (2-13.79)	10.3 (7.1-10.8)	9 (3.9-14.71)	9.9 (4.7-13.4)	10.25 (2.9-24.49)
K, meq/L	5.8 (2-9.3)	5.85 (2.7-7.9)	5.4 (3.4-6.8)	5.9 (3.7-6.9)	6 (5.5-6.8)	4.4 (1.9-6.9)
LDH, U/L	4785 (236-29130)	486 (95-4000)	11223 (974-13245)	2349 (891-3448)	1429 (756-6432)	1169 (179-4635)
CK, U/L	115989 (54-1998000)	115220 (387-228300)	Available for one patient only	699 (126-1012)	NA	806 (32-98720)
AST, U/L	2024 (15-17380)	136 (46-1748)	48 (34-425)	167 (78-557)	209 (88-456)	70.5 (3-771)
ALT, U/L	975 (13-6310)	104 (59-766)	34 (23-150)	112 (34-316)	101 (72-338)	36 (10-1036)
HD (ses rq)	4 (1-13)	1.5 (1-6)	3 (1-12)	2 (1-3)	2 (1-5)	2 (1-10)
HD done in	131/135	8/8	5/5	4/5 (one died before starting HD)	5/5	23/26

DOI: Days of insult; Hb: Hemoglobin; plt: Platelet; K: Potassium; LDH: Lactate dehydrogenase; CK: Creatinine phosphokinase; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; HD: Hemodialysis; ses rq: Sessions required; PPD: Paraphenylene diamine; OP: Organo phosphorus.

Table 4 Outcome in different groups (n = 184)

Outcome	PPD (n = 135)	Methanol (n = 8)	CuSO ₄ (n = 5)	OP (n = 5)	Paraquat (n = 5)	Others (n = 26)
Complete recovery	108	5	3	2	1	14
Partial recovery and lost follow-up	6	1	0	0	0	4
Left against advice during acute phase	2	0	0	0	0	1
Died	19	2	2	3	4	7

PPD: Paraphenylene diamine; OP: Organo phosphorus.

AKI in these patients.

CuSO₄ intoxication causing AKI reported by Chugh *et al*^[23] from India about 40 years ago. This substance is also easily available at low cost and used for both suicidal and homicidal purposes. Hemolysis is a common pathological feature and ATN is seen on renal histology. In our series renal biopsy was done in one patient and showed ATN with pigments, but in those days we were not doing markers for pigments (which we have started doing during last decade). Another study from our neighboring country, India, reports different poisons leading to hemodialysis requirement. This series studied over a period of 17 years reports 19 cases of AKI after CuSO₄ poisoning. Our patients with CuSO₄ poisoning revealed features of hemolysis with low hemoglobin, raised LDH, serum potassium and hyperbilirubinemia, which is in agreement with previously published studies.

Our patients with paraquat poisoning showed worst prognosis where 4 out of 5 died within 60 h of reaching

the hospital, one even before starting the dialysis. One who survived from this group later recovered renal function. Paraquat ingestion could be intentional or after occupational exposure. In 3 of our patients it was intentional while remaining 2 were exposed accidentally.

Published studies from Pakistan report benzodiazepines, mega doses of antidepressants and organophosphorus compounds utilized for self harm^[24]. Some of our patients has taken a combination of substances and most of these were with intention of self harm. All 3 patients of our series with phenobarbitone over dosage were brought unconscious with Glasgow Coma scale of 3. One of them died while the other two recovered very early, only 2 sessions of hemodialysis were required in each.

We have 4 patients in our series with poisoning from tartaric acid, a substance very commonly used as a food additive in our country, mainly to make food sour. Large amount of the powdered form of the substance

was taken by 3 patients for self harm and in one the substance was given by in-laws. Literature search has not revealed renal damage with the substance, but our findings on renal biopsy in two of these patients revealed ATN.

AKI as a result of acetic acid poisoning has been reported in 34 patients in a study published from Serbia, where they have treated these patients with peritoneal dialysis. Most of the patients were oligoanuric. Ten patients died in this series. The most frequent complications were oesophagitis, bleeding, mediastinitis, pneumonia and acute abdomen^[25]. In our series there was only one patient who developed AKI after acetic acid poisoning. This patient was a young male, who developed excessive vomiting and abdominal pain after ingestion, but showed rapid renal recovery.

Datura poisoning though used in our part of world as a homicidal agent, was used accidentally by two of our patients in the current series. Both developed anuric renal failure though they recovered required a bit prolonged dialysis (6 and 10 sessions).

Use of boiler water in one of our patient led to severe hemolysis and anuria. This patient died on the next day after reaching this hospital. Arsenic was taken by one of the patients for a sexually transmitted disease. He developed gastro intestinal symptoms, fever and paraplegia along with deafness after taking the substance, was anuric when brought to us with advanced uremia and deranged liver functions. He died after having 5 sessions of plasma exchange and 7 sessions of hemodialysis.

At this institution, we do renal biopsy as a policy in cases of AKI which have a suggestive history of glomerular disease or reveal protein on urine dipstick 3-4, or show delay in recovery. In the current series of patients biopsy samples were taken from 13. In 11 there was ATN, and on further breakdown we found ATN with pigment in 7 and ATN with TIN in 2. One biopsy revealed TIN with casts in tubular lumina and tubular damage; this was from a patient with methanol poisoning. One biopsy revealed ACN this biopsy was from a young patient who was living in bachelor's hostel and ingested a substance that was probably glycol along with multiple tablets of Xanax (benzodiazepines). In this series, his case was categorized under multiple substances.

Some of the patients brought into the emergency of SIUT with AKI and suspicion of poisoning were not included in this series as the patient or the family were reluctant to disclose the actual history though their course of management remained the same as for others. As mentioned earlier we have also not included AKI resulting from snake bite and scorpion stings in this series as these have been published separately^[26,27].

Limitations

The majority of patients exposed to poisons are dealt with general medical wards by internists or at small medical setups by family physicians. Because of this, the detection of renal involvement was delayed in many patients in this series, thus many patients reached us

when the time for taking beneficial measures had already elapsed.

Furthermore, most of patients cannot describe the amount of substance taken and thus it is difficult to comment on the amount of substance that can cause renal damage or could be fatal.

In conclusion, this study reveals possibility of renal involvement and AKI with ingestion of different poisonous substances, which usually have other uses and are thus frequently available. In developing countries like Pakistan money is another considerable factor. Most of the poisonous substances described here were both easily available and inexpensive. We believe that our results could be valuable for physicians in general and nephrologists in particular in managing such cases in emergency.

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COMMENTS

Background

Human exposure to paraphenylene diamine (PPD) is primarily through hair dyes and fortified "henna" which is used for tattooing. Occupational exposure is through photocopying and printing inks, black rubber, lithography plates, etc. Poisoning with PPD can cause oro-pharyngeal and gastrointestinal symptoms, hepatic involvement and later neurological involvement. Acute kidney injury (AKI) was reported in some cases. Developing AKI after PPD poisoning were also reported. It is a constituent of many commercially available industrial solvents and of poorly adulterated alcoholic beverages, in Pakistan called as "katchi sharab".

Research frontiers

Toxicity with ingestion of methanol, which is more often in larger groups of people, remains a common problem in many parts of the developing world, especially among members of lower socioeconomic classes. AKI may be associated with other signs of severity in methanol poisoning, but it is almost always reversible in survivors. The pathophysiology of AKI developing after methanol poisoning is multifactorial but ultimately leads to acute tubular necrosis.

Innovations and breakthroughs

This study reveals possibility of renal involvement and AKI with ingestion of different poisonous substances, which usually have other uses and are thus frequently available. In developing countries like Pakistan money is another considerable factor. Most of the poisonous substances described here were both easily available and inexpensive.

Applications

The results could be valuable for physicians in general and nephrologists in particular in managing such cases in emergency.

Peer-review

The draft could be interesting for the nephrologist. It is potentially interesting as a data base for consultation.

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Fluid overload as a major target in management of cardiorenal syndrome: Implications for the practice of peritoneal dialysis

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Abstract

Congestion is an integral component of cardiorenal syndrome and portends an adverse impact on the outcomes. Recent studies suggest that congestion has the ability of

modulating the interactions between the kidney and the heart in this setting. Peritoneal dialysis (PD) is a home-based therapeutic modality that is not only offered to patients with end-stage renal disease to provide solute clearance and ultrafiltration, but it has also been used in patients with refractory heart failure and fluid overload to help optimize volume status. Several uncontrolled studies and case series have so far evaluated the role of PD in management of hypervolemia for patients with heart failure. They have generally reported favorable results in this setting. However, the data on the outcomes of patients with end-stage renal disease and concomitant heart failure is mixed, and the proposed theoretical advantages of PD might not translate into improved clinical endpoints. Congestion is prevalent in this patient population and has a significant effect on their survival. As studies suggest that a significant subset of patients with end-stage renal disease who receive PD therapy are hypervolemic, suboptimal management of congestion could at least in part explain these conflicting results. PD is a highly flexible therapeutic modality and the choice of techniques, regimens, and solutions can affect its ability for optimization of fluid status. This article provides an overview of the currently available data on the role and clinical relevance of congestion in patients with cardiorenal syndrome and reviews potential options to enhance decongestion in these patients.

Key words: Heart failure; Peritoneal dialysis; Congestion; Cardiorenal syndrome

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Core tip: Congestion has been recognized as a dynamic state capable of modulating the interactions between the heart and the kidney in patients with cardiorenal syndrome. Optimization of volume status could significantly affect the outcomes of patients treated with peritoneal dialysis (PD) patients for end-stage renal disease and

pre-existing heart failure. Since PD is a highly modifiable therapeutic modality, it is conceivable that a regimen customized to the clinical characteristics and needs of the patients could improve their outcomes through efficient decongestion and optimization of volume status.

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INTRODUCTION

Heart failure (HF) is a public health problem due to its increasing prevalence, associated morbidity, high mortality, and a remarkable financial burden on the healthcare system. Prevalence of HF increases with age; it is currently one of the most common chronic conditions with a lifetime prevalence reaching 20%-33% in the United States^[1]. Despite advancements in diagnosis and treatment, the HF population is expected to expand to more than 8 million by 2030 due to the increase in the proportion of aging population as well as the improving number of patients surviving ischemic events^[2].

Congestion is the hallmark of HF, is the primary reason for hospitalization of these patients, and can contribute to HF progression^[3]. Renal dysfunction is a prevalent clinical finding in HF and portends an untoward impact on potential management options, course, and outcome. The population of patients presenting with both heart failure and chronic kidney disease [*i.e.*, cardiorenal syndrome (CRS)] is large and steadily growing^[3,4]. The pathophysiology of HF is complex as there exist a multitude of mechanisms by which the heart and the kidneys interact in the setting of cardiac dysfunction. Congestion can directly affect the interactions between the kidney and the heart in CRS^[4]. Indeed, several studies have so far highlighted the clinical significance of congestion, rather than renal dysfunction, as the primary driver of the adverse outcomes in patients with CRS. For example, in a study on 594 patients with acute HF, patients with concomitant congestion and deterioration in renal function had the worst outcomes while worsening kidney function alone (without lingering congestion) showed no adverse impact^[5]. Similarly, in a study on HF patients who were admitted to the hospital for congestion, those with hemoconcentration (proxy for decongestion) presented more often with deterioration in renal function but their outcome (*i.e.*, time to death) was still significantly improved compared to those who did not experience hemoconcentration during their hospitalization^[6].

FLUID OVERLOAD IN CRS

In chronic CRS, the maladaptive mechanisms involved in HF, whether in the form of low forward flow or high backward pressure, could ultimately result in diminished water and sodium excretion, lingering venous congestion, endothelial cell activation, systemic inflammation, and progressive deterioration in renal function to the point of renal failure and end-stage renal disease (ESRD)^[7]. In a subset of patients with HF, reduced cardiac output and fluid redistribution result in decreased renal perfusion. The aberrant compensatory mechanisms such as activation of the sympathetic nervous system, renin-angiotensin-aldosterone axis, and arginine vasopressin lead to enhanced renal water and sodium absorption in an effort to preserve renal perfusion, transglomerular pressure, and glomerular filtration rate. However, at long term, these mechanisms could induce deleterious effects on the heart and the kidney by promoting fibrosis, apoptosis, oxidative stress, activation of inflammatory mechanisms, and ventricular remodeling^[8,9]. A number of studies have also found an association between high venous pressures and deterioration in renal function that could be even stronger than the impact of arterial blood pressure or cardiac index on renal function^[10,11]. Increased pressure along renal veins is thought to reduce the net pressure gradient across the glomerulus leading to a decrease in glomerular filtration rate, diminished renal excretion of water and sodium, and progressively worsening congestion^[10].

Hence, systemic congestion is a key target in management of these patients, and its relief is considered a treatment success. Control of congestion not only is associated with improvement in clinical outcomes and reduction in the rate of hospitalization, but could also prevent progression of kidney disease associated with renal venous congestion^[12].

While high dose intravenous diuretics remain the cornerstone of decongestive therapy in patients with acute HF and acute CRS, extracorporeal ultrafiltration has recently re-emerged as a potential alternative in this setting with a number of proposed advantages such as effective and predictable fluid removal, efficient sodium extraction, and reduction in the rate of re-hospitalization^[13,14]. In the setting of chronic CRS, the studies have mainly focused on improving cardiac function, whether through medications or devices. The currently available pharmacologic options for decongestion are limited to diuretics that have been in use for several decades as well as the newly marketed neprilysin inhibitors^[15]. However, the use of diuretics in HF remains largely empirical, with potential disadvantages and untoward effects such as variable dose-response rate and diuretic resistance^[16]. Moreover, a number of practical aspects of their use such as concomitant administration of loop and distal diuretics

remain elusive, and an association between high doses of loop diuretics and adverse outcomes has also been proposed by observational studies^[17].

Peritoneal dialysis (PD) represents an intriguing home-based therapeutic option that provides the possibility of continuous, gentle, and customized removal of excess fluid and sodium in patients with HF who commonly present with various degrees of renal dysfunction. Herein, we explore the studies on the role of PD in management of CRS in two subsets of CRS patients separately; those non-ESRD patients with concomitant HF and chronic kidney disease (CKD) in whom PD is primarily used as an ultrafiltration modality for relief of refractory congestion rather than solute clearance, and those patients with HF and concomitant ESRD who have selected PD as a modality for chronic renal replacement therapy.

CKD and HF

Several studies so far have evaluated the role of PD in patients with chronic CRS and refractory volume overload in whom renal dysfunction is not severe enough to necessitate dialysis therapy for clearance of solutes. These trials have in general reported favorable outcomes. In a prospective single-center study including 118 patients with severe HF [New York Heart Association (NYHA) class III and IV], Koch *et al*^[18] evaluated the impact of intermittent automated PD (APD) therapy performed at least three times per week for 12 h per session. Mean baseline creatinine clearance was 19.2 mL/min and the patients were followed for slightly more than a year. The clinical symptoms of HF improved after starting PD as evidenced by improvement in the NYHA class at 6 mo, and fluid overload was also significantly reduced as shown by reduction in body weight from 78.7 to 74.7 kg ($P < 0.001$). In another prospective study, PD therapy was used for management of 25 patients with HF (NYHA class III/IV), CKD, persistent fluid overload, and at least two previous hospitalizations for acute HF^[19]. The mean daily peritoneal ultrafiltration was 679 mL; PD was associated with significant improvement in the Minnesota Living With Heart Failure Questionnaire and NYHA class at 6 and 24 wk. An 84% reduction in the number of hospitalized days for acute HF was also observed. Later, Courivaud *et al*^[20] published the largest study to-date in this field that included 126 patients with refractory HF. The mean estimated glomerular filtration rate was 33.5 mL/min per 1.73 m² and the mean duration on PD was 16 mo. During the first year of PD therapy, left ventricular ejection fraction improved significantly (38% at baseline vs 42% at 1 year, $P = 0.001$). The striking observation of the study was that PD therapy was associated with a 90% reduction in the duration of HF-related hospitalization (3.3 d/patient-month before PD vs 0.3 d/patient-month after PD, $P < 0.0001$). Recently, a meta-analysis of the studies on the use of PD in refractory HF reported that PD was associated with a significant decline in hospitalization

days and improvement in cardiac function defined by left ventricular ejection fraction and NYHA class^[21]. Since congestion is the primary reason for hospitalization of patients with HF, the improvement in the hospitalization of these patients implies better management of fluid overload by PD. It can also have an important impact on the cost related to inpatient care of these patients. Overall, the currently available data suggest that PD is a clinically-relevant therapeutic option for removal of fluid in patients with chronic CRS who present with persistent congestion despite optimal medical therapy. Finally, it is notable that the favorable results of these studies are evident despite typical use of PD as the “last resort” for patients refractory to conventional therapies.

The studies on the role of PD in chronic CRS have three major limitations: Lack of a reasonably matched control group, relatively short follow-up periods, and the possibility of a publication bias. A major concern regarding the use of PD in this patient population has long been that its morbidity might replace that of HF. In modern practice, with an acceptably low incidence of PD-related complications, this concern appears to be less relevant. Moreover, those studies that assessed the quality of life of the patients reported significant improvement after initiation of PD^[22]. Concerning the impact on survival, there is no conclusive evidence to this date to suggest that PD could indeed alter the natural course of the disease state although there have been reports of improvement in cardiac function^[20].

ESRD and HF

For those CRS patients in whom renal dysfunction progresses to ESRD, fluid removal can be achieved through either hemodialysis (extracorporeal ultrafiltration) or PD (intracorporeal ultrafiltration). A number of advantages have been proposed for PD in this setting such as gentle and continuous fluid and solute removal being less likely to exacerbate neurohormonal activation as well as better preservation of residual renal function^[23-25]. Importantly, it has been shown that patients undergoing fluid removal by hemodialysis experience myocardial stunning (*i.e.*, persistent left ventricular dysfunction due to repeated transient demand myocardial ischemia) even in the absence of angiographically significant coronary artery disease^[26]. Myocardial stunning at long run can lead to progression of HF *via* development of fixed systolic dysfunction^[27]. It has been shown that PD is not associated with myocardial stunning and hence would be less likely to lead to progression of HF in ESRD patients^[28].

Despite theoretical advantages of PD therapy in patients with ESRD and HF, studies have so far yielded conflicting results. Panday *et al*^[29] retrospectively compared the outcomes of 139 ESRD patients with concomitant HF, and reported no difference in 2-year mortality, cardiac outcomes, or hospitalization between PD and hemodialysis. Two large registry-based studies on ESRD population (one from United States and one from France) found that PD can be associated

with an even increased risk of mortality compared to hemodialysis in HF patients while these two modalities are associated with similar outcomes in ESRD patients without HF^[30,31]. Similarly, in a study on National Health Insurance Research Database in Taiwan including more than 35000 patients, Wang *et al*^[32] reported that PD was associated with inferior survival in ESRD patients with concomitant HF. It is not clear whether these findings are related to unexplored underlying mechanisms, the interplay of a number of well-known factors [e.g., difficulty in management of volume status in ESRD patients with reduced residual renal function (RRF)], or could possibly reflect the inherent limitations of the registry-based data analysis (e.g., treatment-by-indication bias). On the other hand, in a registry study from Lombardy in Italy, Locatelli *et al.* reported that the risk of *de novo* cardiovascular disease (HF and coronary artery disease) was similar between hemodialysis and PD^[33]. More recently, a study based on Taiwanese national registry including more than 45000 patients with ESRD found that the risk of *de novo* HF in patients receiving hemodialysis is 29% higher than those undergoing PD therapy (CI: 1.13-1.47, $P < 0.001$) although the advantage seemed to disappear over time^[34,35].

Despite the fact that the data is mixed, altogether they imply that the impact of PD as a dialysis modality on the outcomes of ESRD patients with “pre-existing HF” might be different from those without HF.

VOLUME STATUS IN ESRD - FOCUS ON PD

Fluid overload is a prevalent finding in patients with renal dysfunction and is associated with adverse cardiovascular outcomes^[36,37]. Recently, a multicenter study on more than 1000 incident PD patients revealed that fluid overload is present already at baseline when they start PD therapy^[38]. Using bioimpedance spectroscopy, the investigators found that the median fluid overload was 2 L, and less than half of the patients (38.7%) were indeed euvoletic; 25.1% of the patient population also had HF. Unfortunately, initiation of PD therapy does not seem to markedly improve fluid overload in patients with ESRD; congestion appears to remain a prevalent problem in a subset of PD population. For example, in the multicenter cross sectional European Body Composition Monitoring (EuroBCM) study that included 639 patients receiving PD therapy (mean time on PD 32.6 mo), only 40% were found to be euvoletic^[39]. Extracellular fluid volume expansion in PD patients has been shown to be directly associated with increase in inflammatory markers, an established underlying mechanism for deterioration in cardiac function^[40,41]. This could in part explain the unexpected outcomes of ESRD patients with pre-existing HF who choose PD for renal replacement therapy.

In recent years, there has been a renewed interest in the concept of optimization of fluid status in patients receiving renal replacement therapy due to the recognition of its significant impact on survival^[42,43]. Overhydration is associated with hypertension, left ventricular hypertrophy, and increased mortality in PD patients^[44]. Moreover, high serum levels of pro-B type natriuretic peptide (BNP), a surrogate for fluid overload, is an independent predictor of mortality in these patients^[45]. To examine whether fluid overload *per se* is associated with poor outcomes in PD population or it merely reflects potential untoward effects of other comorbidities such as HF, Jotterand Drepper *et al*^[46] studied 54 prevalent PD patients and found that overhydration was a strong and independent predictor of mortality after adjustment for cardiac function (relative hazard of 7.8). Similarly, in a study on 529 PD patients, O'Lone *et al*^[47] found that overhydration measured by bioimpedance spectroscopy is an independent predictor of mortality.

HYDRATION STATUS AND RESIDUAL RENAL FUNCTION

Since RRF has been reported to be associated with reduced mortality in PD patients, preservation of RRF has become one of the major goals in management of patients receiving PD therapy^[48]. The apparent importance of RRF is likely a proxy for adequate volume control in these patients. Since intravascular volume depletion could lead to a loss of RRF, it has been suggested that PD patients should avoid intravascular volume depletion and preferably be maintained hypervolemic to help preserve RRF. However, in an interesting study on 237 ESRD patients, McCafferty *et al*^[49] showed that extracellular volume expansion measured by bioimpedance did not have any association with preservation of RRF. Moreover, correction of severe overhydration does not seem to result in a significant drop in RRF^[50]. Therefore, based on currently available data, overhydration in the setting of PD therapy could increase the risk of cardiac dysfunction and adverse outcomes without an apparent beneficial impact on preservation of RRF.

VOLUME STATUS VS SOLUTE CLEARANCE

The clinical relevance of fluid overload and its impact on the outcomes in the setting of PD is to the point that euvoemia is likely to be even more important than small solute clearance as a marker of dialysis adequacy because fluid overload, but not small solute clearance, could predict outcomes^[45,51]. In the landmark Canada-United States study that included 601 PD patients, urine volume superseded renal small solute clearance as a predictor of mortality; every 250 mL increment in urine

volume was associated with a 36% reduction in the risk of death^[48]. In an interesting study on 125 PD patients, Ateş *et al*^[52] showed that total sodium and fluid removal were independent factors affecting survival while Kt/V_{urea} and total creatinine clearance were not. Similarly, in the European Automated Peritoneal Dialysis Outcome Study, the survival of 177 anuric patients who were treated with PD was associated with baseline ultrafiltration, but not with clearance of creatinine or membrane permeability status^[53].

DECONGESTION: SODIUM VS WATER

The common pathway for several maladaptive mechanisms involved in the development of HF is aberrancy in renal excretion of sodium with resultant extracellular fluid expansion. Since sodium is the main determinant of extracellular fluid volume, any therapeutic modality with greater ability for extraction of sodium will be advantageous in the setting of HF and volume overload. In a landmark study on vasopressin antagonists, addition of a vasopressin receptor antagonist to standard therapy of HF (with subsequent enhanced sodium-free water excretion) failed to reduce all-cause mortality, cardiovascular death, or re-hospitalization despite significant decongestion, highlighting the paramount role of sodium removal in this setting^[54]. When applying therapeutic modalities for management of fluid overload, this distinction should be taken into consideration. In the PD therapy, during the first 60–90 min of the intraperitoneal dwell of the dextrose-containing PD solution, rapid transport of solute-free water takes place across the aquaporins while the remaining solute-rich water moves much more slowly through the small pores of the peritoneal membrane. Hence, the initial dissociation between the rate of water and sodium transport into the peritoneal cavity results in an early drop in the concentration of dialysate sodium, called sodium sieving. The slow diffusive movement of sodium continues and, if the dwell is long enough, the concentration of sodium in the dialysate will eventually approach that of serum. These mechanistic considerations should be accounted for when PD therapy is offered to ESRD patients with HF as there seem to be significant variations in the ability of this therapy for fluid and sodium removal based on the techniques as well as the regimens that are selected.

DECONGESTION: CAPD VS APD

The concept of sodium sieving is clinically relevant in that shorter dwells, such as those typically achieved with APD, might not provide enough time for adequate extraction of sodium; they could mainly result in removal of sodium-free water and lead to reduced net sodium removal and progressive congestion at long run. Longer dwells, such as those typically provided by continuous ambulatory peritoneal dialysis (CAPD), might be advantageous in the setting where sodium

removal is the primary target (*i.e.*, patients with HF and volume overload). In a study on 141 PD patients, sodium removal was found to be significantly greater in those receiving CAPD compared to APD group, and switching techniques from CAPD to APD led to significant reduction in sodium removal^[55]. In another study, BNP (a surrogate for volume status) and left ventricular mass were reported to be significantly higher in the APD patients compared with CAPD^[56]. It should however be noted that several other factors such as the PD solutions and the regimens as well as the clinical characteristics and dietary habits of the patients can affect these results. For example, in a study on 158 prevalent PD patients (90 CAPD, 68 APD), Davison *et al*^[57] used bioimpedance spectroscopy to assess and compare the hydration status of the patients. They reported no difference between APD and CAPD with regard to the ratio of extracellular fluid volume to total body water. Mean total daily removal of sodium was 109 mmol for patients on CAPD and 130 mmol for APD ($P = 0.23$). Among CAPD patients, 41% had a sodium removal of less than 100 mmol/d compared to 33.8% in the APD group ($P = 0.36$). Blood pressure was also similar in the two groups. The results of this study can be in part explained by the fact that nearly 80% of the APD patients were on icodextrin for their long daytime dwell (hence improving fluid management), and also the number of nocturnal exchanges were decreased (*i.e.*, allowing for longer dwells and less sodium sieving).

ENHANCING SODIUM REMOVAL

Since sodium concentration of most conventional PD solutions (*i.e.*, 132 mmol/L) is close to that of serum, sodium removal is mainly convective; diffusion does not typically play an important role in this setting. In an attempt to improve sodium extraction through increased diffusion gradient, a number of studies have evaluated the impact of low-sodium PD solutions on various endpoints. For example, in a recent randomized controlled trial on 108 patients, Rutkowski *et al*^[58] used PD solution containing 125 mmol/L of sodium and compared it with the control group. They found that low-sodium solution could significantly increase sodium removal (by 1.1 g/d, $P < 0.001$) and improve blood pressure control. Although low-sodium solutions can prove helpful in specific settings and select patients (*i.e.*, those with HF), their widespread use is hindered by a number of factors such as reduced osmolality of the solution and consequent decrease in ultrafiltration thus offsetting their benefit.

APD, once used mainly for patients who were rapid transporters, has become the modality of choice by many patients and physicians in the developed countries due to it being not only convenient and adaptable to the lifestyle of patients but also modifiable to fit a wide range of clinical characteristics and needs. In the United States, more than 70% of patients are treated with this technique^[59]. As previously mentioned,

there is concern with regard to the ability of APD to adequately extract sodium and to address congestion in these patients. There are a number of strategies that are based on the mechanisms of water and solute transport in PD and can potentially improve fluid and sodium extraction by APD. This could be of special importance in specific clinical settings such as HF where decongestion, rather than clearance, is the primary target of this therapy. Decreasing the number of nocturnal cycles could increase the dwell time hence reducing sodium sieving. This is likely to improve sodium removal and, if the patient is on low sodium diet, could provide negative or even sodium balance especially through concomitant use of loop diuretics for those with significant RRF. Adding an exchange in the evening for select APD patients (*i.e.*, those with slow peritoneal transport characteristics) could also ensure adequate small solute clearance while further increasing sodium removal. Use of icodextrin, a high molecular weight glucose polymer developed specifically for use as an alternative osmotic agent to dextrose during the once-daily long-dwell exchange, allows for sustained fluid removal and optimization of volume status due to reduced back diffusion^[60]. Icodextrin has the advantage that it does not activate aquaporins; all the ultrafiltration takes place at the intercellular small pores where sodium fluxes with water (*i.e.*, no sodium sieving). This process allows for more efficient sodium removal compared to an equal volume of ultrafiltration with a dextrose-based solution. Therefore, icodextrin could prove helpful in clinical settings such as HF where enhanced sodium removal is of particular importance. In a multicenter randomized controlled trial on 50 PD patients with urine volume of less than 750 mL/d and high solute transport, Davies *et al*^[61] reported an average increase of 61.7 mmol in daily sodium removal and an average increase of 399 mL in ultrafiltration in patients receiving icodextrin instead of a glucose-based solution. Basile *et al*^[62] reported their experience with the use of icodextrin (1 to 2 exchanges a night) in patients with end-stage HF and severe volume overload over a follow up period of 2 years. After starting PD, the patients experienced a significant decrease in their mean weight by 11.3 kg ($P < 0.007$), an increase in urine output (from 587 to 1700 mL/d, $P < 0.003$), and significant reduction in the number of days hospitalized for HF (from 4.4 to 0.7 d/mo, $P < 0.04$). Therefore, the initial results with the use of icodextrin seem to be promising. A combination of the above-mentioned strategies (simultaneous or successive) could be used to enhance effective sodium removal by APD and help further improve patients' volume status. Whether these approaches would translate to better outcomes is to be determined by future studies.

CONCLUSION

While lingering congestion remains an unresolved issue in a significant subset of patients with CRS, PD therapy

has been offered as a clinically-relevant alternative to conventional therapies for optimization of volume. In those patients who present with ESRD and pre-existing HF, there is mixed data with regard to the role of PD therapy and its impact on survival. Whether this is related to suboptimal management of overhydration or other factors remains elusive. Optimization of volume status appears to be at least as important as providing clearance in patients receiving PD therapy, and sodium removal plays an integral role in this regard especially in those with concomitant HF. Clinicians could take advantage of the known strategies to enhance extraction of sodium-rich effluent in these patients. Future studies are needed to assess whether these methods would indeed lead to improvement of the outcomes.

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Causal relationship between hypoalbuminemia and acute kidney injury

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Abstract

Our meta-analysis published in 2010 provided evidence that low levels of serum albumin (hypoalbuminemia) are a significant independent predictor of acute kidney injury (AKI) and death following AKI. Since then, a large volume of additional data from observational clinical studies has been published further evaluating the relationship between serum albumin and AKI occurrence. This is an updated review of the literature to re-evaluate the hypothesis that hypoalbuminemia is independently associated with increased AKI risk. Eligible studies published from September 2009 to December 2016 were sought in PubMed (MEDLINE) and forty-three were retained, the great majority being retrospective observational cohort studies. These included a total of about 68000 subjects across a diverse range of settings, predominantly cardiac surgery and acute coronary interventions, infectious diseases, transplant surgery, and cancer. Appraisal of this latest data set served to conclusively corroborate and confirm our earlier hypothesis that lower serum albumin is an independent predictor both of AKI and death after AKI, across a range of clinical scenarios. The body of evidence indicates that hypoalbuminemia may causally contribute to development of AKI. Furthermore, administration of human albumin solution has the potential to prevent AKI; a randomized, controlled study provides evidence that correcting hypoalbuminemia may be renal-protective. Therefore, measurement of serum albumin to diagnose hypoalbuminemia may help identify high-risk patients who may benefit from treatment with exogenous human albumin. Multi-center, prospective, randomized, interventional studies are warranted, along with basic research to define the mechanisms through

which albumin affords nephroprotection.

Key words: Acute kidney injury; Acute renal failure; Hypoalbuminemia; Mortality; Prevention

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Core tip: The relationship between hypoalbuminemia and acute kidney injury (AKI)-related morbidity/mortality is now confirmed. This association is consistently evident in a wealth of observational studies conducted across a wide range of clinical settings, and suggests a causal link. Prospective studies adequately powered to assess severe AKI, mortality and causality are needed, as is evaluation of the trigger and appropriate target serum levels and albumin dose necessary to confer renal protection. Basic research is also warranted to define the mechanisms through which albumin affords nephroprotection. Serum albumin should be measured to identify patients with increased AKI risk who may benefit from treatment correcting underlying hypoalbuminemia.

Wiedermann CJ, Wiedermann W, Joannidis M. Causal relationship between hypoalbuminemia and acute kidney injury. *World J Nephrol* 2017; 6(4): 176-187 Available from: URL: <http://www.wjgnet.com/2220-6124/full/v6/i4/176.htm> DOI: <http://dx.doi.org/10.5527/wjn.v6.i4.176>

INTRODUCTION

Acute kidney injury (AKI), formerly referred to as acute renal failure (ARF), is a syndrome in which kidney function deteriorates rapidly over a period of hours or days. It is characterized by increased serum creatinine level (of ≥ 0.3 mg/dL in 48 h and/or 1.5-fold within 7 d) and decreased urine output. The staging system for AKI has evolved from the risk, injury, failure, loss of kidney function, and end-stage kidney disease (RIFLE) criteria, to the acute kidney injury network (AKIN) scheme, and most recently to the Kidney Disease Improving Global Outcomes (KDIGO) score (for a review of AKI diagnosis, see^[1]).

AKI is an acute systemic disease with major consequences for other organs besides the kidney, and is associated with significant short-term effects (e.g., fluid, electrolyte, and acid-base abnormalities, uremic toxin accumulation, cytokine elevation, systemic inflammation) and long-term adverse outcomes (e.g., myocardial infarction, chronic kidney disease, end-stage renal disease, mortality)^[2,3]. Need for dialysis and transplantation are increased, as is length of hospital stay^[4,5].

AKI is recognized as a major global health problem, with increasing incidence in both high- and low-income nations, and high associated healthcare costs^[6,7]. It is a common disorder encountered in multiple settings,

occurring in 21% of hospital admissions worldwide and in more than 13 million people each year^[5], especially critically ill patients^[1], where incidence rates well above 50% were reported in the recent prospective AKI-EPI study^[8]. The International Society of Nephrology's Oby25 initiative sets out a framework to eradicate preventable death from AKI by 2025 based on the 5 Rs: Risk, Recognition, Response, Renal Support, and Rehabilitation^[5].

The etiology of AKI includes community-acquired causes (common in developing countries), such as infections (malaria, dengue, gastroenteritis, pneumonia), acute glomerular disease, underlying chronic disease (kidney, cardiac, diabetes), and trauma, as well as hospital-acquired causes (especially in industrialized nations), such as surgery, hemorrhage, infection, septic shock, drug toxicity, and underlying chronic disease (reviewed in^[7]). The pathogenesis of AKI is multifactorial and several risk factors have been identified, both modifiable (e.g., dehydration, intravascular volume depletion, hypotension, anemia, hypoxia, body mass index) and non-modifiable (e.g., age, sex, prior invasive procedures, high-risk surgery, and comorbid disorders such as cancer and lung, liver or gastrointestinal disease)^[5,9].

Hypoalbuminemia, or low levels of serum albumin (often defined as < 3.5 - 4.0 g/dL or ≤ 3.5 mmol/L), is a well-established risk factor for increased morbidity and mortality^[10] and has also been associated with an increased risk of AKI occurrence; it is modifiable by infusion of human albumin solution. Our systematic review and meta-analysis published in 2010 found evidence, from observational studies in surgical and ICU patients, that low serum albumin is a significant independent predictor of AKI [pooled odds ratio (OR) = 2.34, 95%CI: 1.74-3.14] and of death following AKI (pooled OR = 2.47, 95%CI: 1.51-4.05)^[9].

Since then, a large volume of additional clinical data has been published on hypoalbuminemia and AKI, across an expanded range of settings. Therefore, we performed an updated review of the literature to define the role of hypoalbuminemia and albumin administration in the development and prevention of AKI. Detailed discussion of the potential nephroprotective mechanisms of albumin is beyond the scope of the present review but was the subject of a separate review^[11].

RESEARCH

Literature was sourced by conducting a systematic search of the PubMed (MEDLINE) database using phrases and synonyms for "kidney injury", "albumin", "hypoalbuminemia" and "mortality" (Table 1). The search was limited to articles published from September 2009 to December 2016 (inclusive), i.e., since the end of the search period used in our 2010 systematic review^[9].

Only studies meeting the following selection criteria

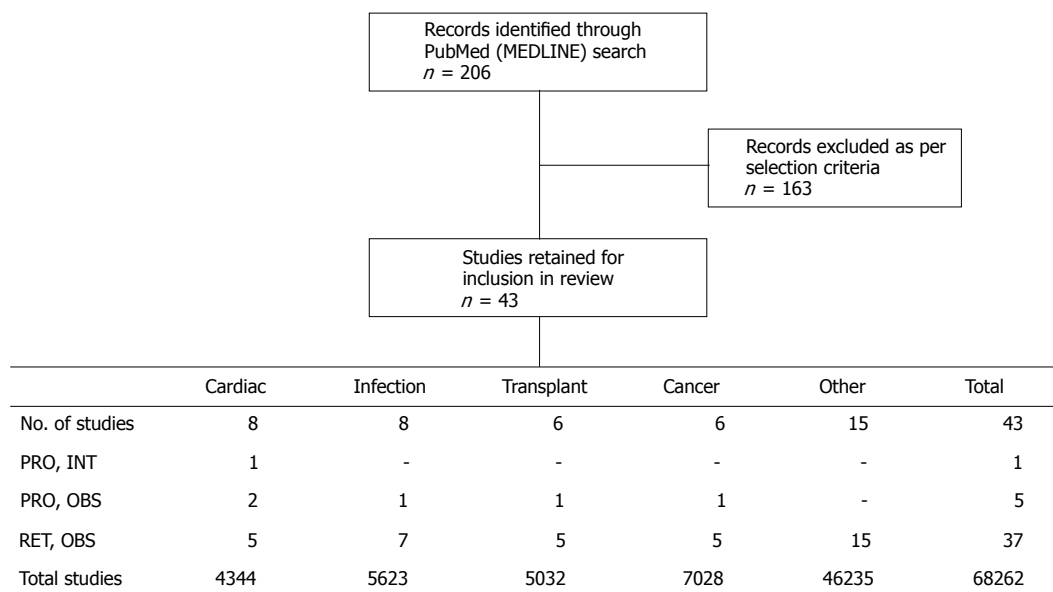


Figure 1 Flow diagram summarizing the literature screening and the designs and settings of the included studies. The numbers presented for the sizes of the data sets include control populations and do not represent only patients with acute kidney injury/acute renal failure and/or hypoalbuminemia. OBS: Observational; INT: Interventional; PRO: Prospective; RET: Retrospective.

Table 1 PubMed (MEDLINE) search strategy

- 1 Search: "acute kidney injury" OR AKI OR "acute renal failure" OR ARF
- 2 Search: mortality OR survival OR death
- 3 Search: "serum albumin" OR hypoalbuminemia* OR hypoalbuminaemia*
- 4 Filter: Publication date from 2009/09/01 to 2016/12/31
- 5 Search: #1 AND #2 AND #3 AND #4

The search was conducted without applying restrictions to language or publication type.

were retained for inclusion in the present review: Reported original data on associations between serum albumin levels (absolute levels, variously defined by authors as < 3.5 or < 3.0 or < 2.5 g/dL, or percentage prevalence of hypoalbuminemia) and the development of AKI (during the different observation periods, depending on the indication), or on mortality in patients with both AKI and hypoalbuminemia.

From included studies, data were extracted on clinical setting/population, study design and size, assessment of albumin levels/hypoalbuminemia, AKI occurrence/risk, and mortality (Tables 2-5).

INCLUDED STUDIES

Our search retrieved a total of 206 entries on PubMed (MEDLINE). The titles and abstracts of all hits were screened and research articles that did not report relevant data as stated in the selection criteria were discarded, along with any review/opinion articles. A total of 43 research articles were retained for inclusion in the present review (Figure 1). The great majority of these were retrospective in nature (37 of 43 studies), except

for a single interventional randomized controlled trial (RCT), conducted in off-pump coronary artery bypass (OPCAB) surgery, and five prospective observational studies: Two in cardiac settings, one in HIV-infected patients, one in liver transplant recipients, and one in patients with hepatocellular carcinoma (HCC) with ascites. In total, the data set comprises approximately 68000 patients across a range of clinical settings, as described and discussed below.

CARDIAC SURGERY AND ACUTE CORONARY INTERVENTIONS

AKI is a common complication following cardiac surgery, and is associated with significant morbidity, mortality, and hospital costs (reviewed in^[12]). We identified eight studies, involving more than 4000 subjects, which explored the role of albumin in AKI occurring after cardiac surgery or coronary intervention (Table 2).

In the only interventional drug study among the 43 retained articles, Lee *et al.*^[13] recently performed a single-center, randomized, parallel-arm, double-blind trial which evaluated the effects of exogenous 20% human albumin solution vs saline on the incidence of postoperative AKI in adult patients with hypoalbuminemia (< 4.0 g/dL) undergoing off-pump coronary artery bypass (OPCAB) surgery. Dose was 100, 200, or 300 mL immediately before surgery, stratified according to preoperative serum albumin level of 3.5-3.9, 3.0-3.4, or < 3.0 g/dL, respectively. In the saline group, rate of postoperative AKI (KDIGO-criteria patients) appeared to increase as postoperative serum albumin level decreased (29.5%, 31.1%, 41.7% for 3.5-3.9, 3.0-3.4, < 3.0 g/dL, respectively). The incidence of postoperative AKI (KDIGO criteria) was

Table 2 Included studies on cardiac surgery and acute coronary interventions

Ref.	Population/ setting	Study design	Overall study size	Albumin measurement	Hypoalbuminemia-related outcomes	
					AKI/ARF	Mortality
Lee <i>et al</i> ^[13]	OPCAB surgery	Prospective RCT	220	Postoperative albumin 3.5-3.9 <i>vs</i> < 3.0 g/dL	Increased rate: 29.5% <i>vs</i> 41.7%. AKI rate lower with albumin <i>vs</i> control (13.7% <i>vs</i> 25.7%; <i>P</i> = 0.048)	ND
Grodin <i>et al</i> ^[20]	Acute heart failure	Prospective, observational	456	Admission albumin level (continuous and stratified by median $\geq$ 3.5 g/dL)	NS	NS
Moguel-González <i>et al</i> ^[16]	Cardiac surgery	Prospective, observational, longitudinal	164	Preoperative albumin < 4.0 g/dL	Increased risk: OR = 3.852 (95%CI: 1.101-13.473; <i>P</i> = 0.063)	ND
Lee <i>et al</i> ^[14]	OPCAB surgery	Retrospective, observational, propensity score matching	1182 (incl. 323 matched pairs)	Preoperative albumin < 4.0 g/dL	Increased risk: OR = 1.83 (95%CI: 1.27-2.64); <i>P</i> = 0.001; propensity analysis: OR = 1.62, (95%CI: 1.12-2.35); <i>P</i> = 0.011	ND
Murat <i>et al</i> ^[21]	ACS and PCI	Retrospective, observational	890	Albumin level at hospitalization	Low albumin (3.52 g/dL <i>vs</i> 3.94 g/dL) predictive of CI-AKI: OR = 0.177 (95%CI: 0.080-0.392; <i>P</i> < 0.001)	ND
Kim <i>et al</i> ^[17]	Thoracic aorta repair with CPB	Retrospective, observational, propensity score matching	702 (incl. 183 matched pairs)	Preoperative albumin < 4.0 g/dL	Increased risk: OR = 2.50 (95%CI: 1.39-4.50; <i>P</i> = 0.002)	ND
Findik <i>et al</i> ^[15]	CAB surgery	Retrospective, observational	530	Preoperative albumin < 3.5 g/dL	Increased rate: OR = 1.661 (95%CI: 1.037-2.661); <i>P</i> = 0.035	ND
Go <i>et al</i> ^[19]	LVAD implantation	Retrospective, observational	200	< 2.5 g/dL (low) <i>vs</i> 2.5-3.5 g/dL (mid-range) <i>vs</i> > 3.5 g/dL (normal)	Increased ARF: 42.9% <i>vs</i> 16.5% <i>vs</i> 17.3%; <i>P</i> = 0.05	NS

ACS: Acute coronary syndromes; AKI: Acute kidney injury; ARF: Acute renal failure; CI-AKI: Contrast-induced acute kidney injury; CPB: Cardiopulmonary bypass; LVAD: Left ventricular assist device; ND: Not disclosed; NS: Not significant; OPCAB: Off-pump coronary artery bypass; OR: Odds ratio; PCS: Percutaneous coronary intervention; RCT: Randomized, controlled trial.

Table 3 Included studies on infectious diseases

Ref.	Population/ setting	Study design	Overall study size	Albumin measurement	Hypoalbuminemia-related outcomes	
					AKI/ARF	Mortality
Prakash <i>et al</i> ^[22]	HIV	Prospective, observational	3540	Albumin level at hospitalization	ND	2.14 g/dL in patients who died <i>vs</i> 3.2 g/dL in survivors; <i>P</i> < 0.001
Vannaphan <i>et al</i> ^[34]	Severe falciparum malaria	Retrospective, observational	915	Albumin < 3.5 g/dL	Associated with ARF (<i>P</i> < 0.001)	ND
Lee <i>et al</i> ^[39]	Acute viral hepatitis A	Retrospective, observational	391	Albumin < 3.0 g/dL	OR = 8.24 (95%CI: 2.53-26.86; <i>P</i> < 0.0001)	ND
Lee <i>et al</i> ^[35]	Scrub typhus	Retrospective, observational	246	Admission albumin < 3.0 g/dL <i>vs</i> $\geq$ 3.0 g/dL	Increased rate of non-oliguric ARF (40.4% <i>vs</i> 11.1%; <i>P</i> < 0.001)	ND
Mehra <i>et al</i> ^[40]	Dengue fever	Retrospective, observational	223	Admission Albumin level	Lower albumin (2.65 g/dL) in patients with <i>vs</i> without AKI (3.09 g/dL; <i>P</i> < 0.001)	ND
Vikrant <i>et al</i> ^[36]	Scrub typhus	Retrospective, observational	174	Admission albumin level	ND	2.4 g/dL in patients who died <i>vs</i> 2.9 g/dL in survivors; <i>P</i> < 0.001
Ceylan <i>et al</i> ^[41]	Antibiotic therapy	Retrospective, observational	112	Albumin level at start of colistin therapy	Lower albumin (2.4 g/dL <i>vs</i> 2.7 g/dL) predicts colistin-induced AKI: OR = 0.643 (95%CI: 0.415-0.994; <i>P</i> = 0.047)	ND
Trimarchi <i>et al</i> ^[37]	H1N1 pneumonia	Retrospective, observational	22	Albumin level at study inclusion	NS	ARF in 10 of 12 deaths: 1.82 g/dL in patients who died <i>vs</i> 2.61 g/dL in survivors; <i>P</i> < 0.01

AKI: Acute kidney injury; ARF: Acute renal failure; ND: Not disclosed; OR: Odds ratio; NS: Not significant.

lower in the albumin group compared with the saline group (17.6% *vs* 31.7%; *P* = 0.031). Multivariate

Table 4 Included studies on transplant surgery

Ref.	Population/ setting	Study design	Overall study size	Albumin measurement	Hypoalbuminemia-related outcomes	
					AKI/ARF	Mortality
Tinti <i>et al</i> ^[45]	Liver transplantation	Prospective, observational	24	Preoperative albumin level	Lower albumin (3.1 g/dL <i>vs</i> 3.7 g/dL) predictive of ARF (<i>P</i> = 0.02)	ND
Moore <i>et al</i> ^[48]	Renal transplantation	Retrospective, observational	2763	Albumin < 4.0 g/dL	Predictive of transplant failure: HR = 1.71 (95%CI: 1.18-2.49; <i>P</i> < 0.001)	ND
Sang <i>et al</i> ^[46]	LDLT	Retrospective, observational, propensity score matching	998 (incl. 249 matched pairs)	Albumin < 3.0 g/dL <i>vs</i> ≥ 3.0 g/dL before surgery	Albumin < 3.0 g/dL associated with increased AKI: OR = 0.42 (95%CI: 0.28-0.64; <i>P</i> < 0.001)	Survival rate lower with postoperative albumin < 3.0 g/dL (<i>P</i> = 0.02)
Park <i>et al</i> ^[47]	LDLT	Retrospective, observational	538	Preoperative albumin level	Albumin < 3.5 g/dL: OR = 1.76 (95%CI: 1.05-2.94; <i>P</i> = 0.032)	ND
Yang <i>et al</i> ^[49]	Renal transplantation	Retrospective, observational	375	Preoperative albumin < 3.5 g/dL <i>vs</i> 3.5-3.9 g/dL <i>vs</i> 4.0-4.4 g/dL <i>vs</i> ≥ 4.5 g/dL	Lowest risk of graft failure with ≥ 4.5 g/dL: HR = 0.536 (<i>P</i> = 0.029) <i>vs</i> < 3.5 g/dL	ND
Chen <i>et al</i> ^[44]	Liver transplantation	Retrospective, observational, matching	334 (incl. 118 matched pairs)	Preoperative albumin ≤ 3.5 g/dL	OR = 2.785 (95%CI: 1.427-5.434; <i>P</i> = 0.003); risk factor for posttransplantation AKI or ARF	ND

AKI: Acute kidney injury; ARF: Acute renal failure; HR: Hazard ratio; LDLT: Living donor liver transplantation; ND: Not disclosed; OR: Odds ratio.

Table 5 Included studies on cancer

Ref.	Population/ setting	Study design	Overall study size	Albumin measurement	Hypoalbuminemia-related outcomes	
					AKI/ARF	Mortality
Hsu <i>et al</i> ^[51]	HCC with ascites	Prospective, observational	591	Albumin < 3.3 g/dL	Independently associated with ARF: OR = 7.3 (95%CI: 1.47-35.7; <i>P</i> = 0.009)	ND
Kim <i>et al</i> ^[50]	Gastric cancer surgery	Retrospective, observational	4718	Preoperative albumin < 4.0 g/dL	Independent predictor of AKI: OR = 1.40 (95%CI: 1.11-1.77; <i>P</i> = 0.005)	ND
Mizuno <i>et al</i> ^[55]	Chemotherapy-induced hypotension	Retrospective, observational	972	Hypoalbuminemia defined as ≤ 3.5 g/dL	Associated with low BP: OR = 1.497 (95%CI: 1.070-2.095; <i>P</i> = 0.019). Low BP associated with AKI	ND
Lahoti <i>et al</i> ^[56]	AML or HR-MDS	Retrospective, observational	537	Albumin level at baseline (median 3.3 g/dL)	Hypoalbuminemia predictive of AKI: OR = 0.7 (95%CI: 0.5-0.99; <i>P</i> = 0.049)	ND
Haynes <i>et al</i> ^[57]	Multiple myeloma	Retrospective, observational	107	Albumin ≥ 3.5 g/dL <i>vs</i> < 3.5 g/dL	ND	Higher albumin predictive of survival: HR = 0.56 (95%CI: 0.35-0.91; <i>P</i> = 0.02)
Fischler <i>et al</i> ^[59]	Cancer	Retrospective, observational	103	Albumin level at start of CVVHDF	ND	Low albumin (median 2.5 g/dL <i>vs</i> 3.05 g/dL) associated with mortality: OR = 3.341 (95%CI: 1.229-9.077; <i>P</i> = 0.02)

AKI: Acute kidney injury; AML: Acute myelogenous leukemia; ARF: Acute renal failure; BP: Blood pressure; CVVHDF: Continuous venovenous hemodiafiltration; HCC: Hepatocellular carcinoma; HR: Hazard ratio; HR-MDS: High-risk myelodysplastic syndrome; ND: Not disclosed; OR: Odds ratio.

logistic regression revealed a renal-protective effect of albumin therapy (OR = 0.42, 95%CI: 0.21-0.83; *P* = 0.012). Administration of albumin increased urine output during surgery (median 550 mL *vs* 370 mL; *P* = 0.006). No differences were observed between the two groups in the incidence of severe AKI, need for renal replacement therapy (RRT), or mortality.

These findings are interesting for a number of reasons. First, the inverse relationship apparent between serum albumin level and postoperative AKI rate, in the setting of a randomized double-blind trial, provides the highest-quality and most compelling evidence yet that

serum albumin level is an independent driver of AKI risk. This corroborates an earlier retrospective analysis in 1182 consecutive adult patients undergoing OPCAB, conducted by the same group^[14]. Moreover, the data from Lee *et al*^[13] further underline the importance of the relationship between albumin level and renal health, as correction of hypoalbuminemia by exogenous albumin supplementation resulted in smaller increases in serum creatinine and conferred a degree of protection against AKI occurrence. That no significant treatment effect on severe AKI was observed (≥ KDIGO stage 2) might reflect an underpowered analysis due to the relatively

low sample size/event rate. Alternatively, either albumin supplementation is beneficial only in milder AKI, or the dosing regimen was insufficient.

Lee *et al.*^[13] did not investigate the mechanism(s) underlying the renal-protective effect they observed with albumin administration but speculated whether this might be attributable to augmentation of intravascular volume over correction of hypoalbuminemia. Indeed, both hemodynamic and pharmacodynamic mechanisms may contribute to the beneficial renal effects of albumin, supporting a possible causal link. Pharmacodynamic properties of human albumin with renal-protective potential include mitigation of nephrotoxicity of medications, restoration of balanced net fluid balance, protection against loss of glycocalyx, and maintenance of glomerular filtration (reviewed in^[11]). Further studies are needed to ascertain in which clinical indications such properties might be beneficial. In addition, data from large-scale RCTs are needed to define trigger and target levels and dosing for pre-emptive albumin therapy as a strategy for protecting against postoperative renal morbidity and mortality.

Whereas in the RCT performed by Lee *et al.*^[13] no differences were evident between the albumin and saline treatment groups with respect to subsequent need for RRT or mortality, precedent does exist for the impact of albumin level on both of these outcomes. Findik *et al.*^[15] recently performed a retrospective review of data collected prospectively from 530 adults with normal renal function who underwent isolated CAB surgery. Their analysis divided the patient population based on preoperative serum albumin level and found that RRT ($P = 0.018$) and death within 30 d (6.8% vs 2.4%; $P = 0.037$) after surgery were more frequent in the group with albumin < 3.5 g/dL. Mean duration of ventilatory support (7.9 h vs 11.4 h; $P = 0.001$), ICU stay (66.0 h vs 59.0 h; $P = 0.026$), and hospital stay (7.7 d vs 7.1 d; $P = 0.022$) were also greater in the lower albumin group.

Beyond CAB surgery, a prospective, observational, longitudinal study of 164 adult patients undergoing any type of elective cardiac surgery used univariate logistic regression analysis to identify low serum albumin (< 4 g/dL), among other variables [high preoperative blood urea nitrogen (BUN), creatinine, and uric acid], as a major risk factor for postoperative development of AKI^[16]. Similarly, Kim *et al.*^[17] also identified preoperative albumin level < 4.0 g/dL as an independent risk factor for AKI in 183 patients who underwent surgery on the thoracic aorta with cardiopulmonary bypass (CPB) and subsequently developed AKI, matched by propensity score with controls without AKI. The authors suggested that correction of preoperative hypoalbuminemia might protect against AKI in the studied population. However, when patients converted to CPB were included in the randomized analysis performed by Lee *et al.*^[13], the effect of albumin treatment was unclear. Further research is needed to evaluate the effects of exogenous albumin treatment in patients undergoing

cardiac surgery with CPB, though such studies will be complicated by the fact that CPB itself is associated with AKI and contributes to its pathogenesis (reviewed in^[18]).

In a single-center, retrospective review, Go *et al.*^[19] aimed to establish the impact of different serum albumin strata (< 2.5 g/dL, low; 2.5–3.5 g/dL, mid-range; > 3.5 g/dL, normal) on outcomes after left ventricular assist device (LVAD) implantation in 200 patients. Consistent with findings in cardiac surgery patients, lower albumin was associated with significantly increased rates of postoperative ARF (Table 2) and prolonged hospitalization (median 28.5 d vs 16 d vs 15.5 d; $P = 0.008$). Survival at 6 mo, 1 year, and 5 years appeared to reflect albumin levels (79%, 79%, 49% with low; 84%, 78%, 51% with mid-range; 94%, 88%, 60% with normal), though this trend was not statistically significant ($P = 0.22$). The authors concluded that hypoalbuminemia (in this case defined as < 2.5 g/dL) should not be considered a contraindication to LVAD candidacy, and called for more data on the utility of albumin levels for predicting morbidity and mortality after LVAD implantation.

Two studies reported data on albumin levels in patients undergoing acute coronary interventions. In a prospective, observational study of 456 acute heart failure patients undergoing decongestive therapy, no significant associations were found between serum albumin levels at admission and clinical outcomes, either short-term (worsening renal function, worsening heart failure, clinical decongestion by 72 h) or longer-term (60-d mortality, re-hospitalization, unscheduled emergency room visits)^[20]. The authors concluded that serum albumin levels might not be relevant in guiding decongestion strategies. They also acknowledged that their post-hoc analysis used a carefully selected cohort drawn from the DOSE-AHF and ROSE-AHF trials that were inadequately powered to detect clinical end points according to baseline albumin, and that their findings may not be generalizable. A separate study, by Murat *et al.*^[21], retrospectively looked at the impact of serum albumin levels on AKI occurrence in a cohort of 890 patients with acute coronary syndromes (ACS) treated with percutaneous coronary intervention (PCI). Serum albumin was inversely associated with AKI risk and, along with a number of other variables [age, female gender, creatinine kinase-myocardial band, and glomerular filtration rate (GFR)], was independently predictive of AKI occurrence. This was the first such report in ACS patients receiving PCI and requires confirmation by prospective, randomized trial. Nonetheless, these preliminary findings suggest that measurement of serum albumin, widely available and relatively inexpensive, should be included in the risk stratification of ACS patients before undergoing PCI.

INFECTIOUS DISEASES

Our review identified eight studies conducted across a total of more than 5500 subjects with infections and

data on albumin levels and renal injury (Table 3). The only prospective study was an observational analysis of AKI in HIV-seropositive adults^[22]. AKI was noted in 138/3540 (3.9%) patients and in most cases was AKIN stage II (42.1%) or III (48.5%). Mean serum albumin at baseline was 2.92 g/dL. Low serum albumin was one of few variables found to be significantly associated with death of HIV-infected patients following AKI. Prerenal factors (e.g., clinical/laboratory evidence of volume depletion or reduced renal blood flow), ischemic acute tubular necrosis (ATN), and sepsis were among the most frequent causes of AKI in this population. These observations are consistent with clinical trials suggesting efficacy and mortality benefit of albumin therapy for volume resuscitation in sepsis patients^[23-30], as well as mechanistic data indicating a role for albumin in preservation of renal tubular cells^[31-33].

The largest study on AKI occurrence in an infectious disease setting to be published during the review period was a 10-year retrospective analysis of AKI occurrence in 915 severe falciparum malaria patients^[34]. AKI is a major contributor to morbidity and mortality in severe malaria infection, and hypoalbuminemia (< 3.5 g/dL) was significantly more prevalent in patients with AKI (135/195; 69%) vs those without AKI (308/720; 43%). The authors concluded that although causality could not be deduced, correction of ARF risk factors such as hypoalbuminemia should be incorporated into the management of patients with severe malaria.

Two retrospective studies reported associations between serum albumin level and AKI outcomes in scrub typhus infection. Lee *et al*^[35] divided a population of 246 adults with scrub typhus into two groups based on serum albumin level. Their analysis revealed that serum albumin < 3.0 g/dL was closely related to AKI occurrence as well as various other complications (e.g., confusion, pulmonary edema, pleural effusion, arrhythmia), leading to longer mean hospital stay (additional 5.5 d) and higher direct hospital costs (additional United States \$1222). Whereas this study found no difference in mortality with lower vs higher albumin (overall deaths 9/246; 3.7%), a subsequent study by Vikrant *et al*^[36] did detect a difference. This later study was smaller overall than that conducted by Lee *et al*^[35] but provided a larger cohort of scrub typhus patients with AKI and substantially more deaths occurred (28/174; 16.1%), providing greater power to assess mortality. Mean serum albumin was 2.8 g/dL and hypoalbuminemia, again defined as < 3.0 g/dL, was present in 56.9% of study subjects. Serum albumin was significantly higher in survivors vs non-survivors (mean 2.9 g/dL vs 2.4 g/dL; $P = 0.001$).

An association between lower serum albumin and mortality has also been observed in critically compromised patients with H1N1 pneumonia. In a 2-mo, retrospective, ICU study, both hypoalbuminemia and AKI were significantly associated with death ($P < 0.01$), and serum albumin appeared to be lower in those with vs without AKI (1.95 g/dL vs 2.59 g/dL), though this

difference did not reach statistical significance in this small cohort ($n = 22$)^[37]. Larger, multivariate analysis is required to confirm these results. The authors suggested that rhabdomyolysis (life-threatening muscle disintegration) is likely to be the main pathophysiologic mechanism of renal dysfunction in this setting, and a separate study subsequently linked hypoalbuminemia with AKI in patients with severe rhabdomyolysis^[38].

Other reports on low serum albumin as a predictive factor for AKI include a chart review and multivariate analysis of data from 391 patients with acute viral hepatitis A^[39]. AKI was present in 45 (11.5%) patients, and the AKI group had significantly decreased albumin levels compared with the non-AKI group at presentation (mean 3.3 g/dL vs 3.8 g/dL; $P < 0.0001$) and at peak during illness (mean 2.7 g/dL vs 3.4 g/dL; $P < 0.0001$). Among 223 patients with dengue fever, AKI developed in 24 (10.8%) and was associated with lower serum albumin (2.65 g/dL vs 3.09 g/dL; $P < 0.001$)^[40]. Low serum albumin (median 2.4 g/dL vs 2.7 g/dL) has also been shown to be independently predictive of acute renal injury in patients receiving antibiotic therapy with colistin ($n = 112$)^[41], consistent with previous observations^[42,43].

TRANSPLANT SURGERY

Hypoalbuminemia is common before and after liver transplantation, especially in patients with cirrhosis^[44], and there is a growing body of research exploring the implications of this. Our searches retrieved six relevant studies (including > 5000 subjects) published since September 2009 that reported albumin levels in relation to AKI occurrence after transplantation (Table 4). Four of these were in the setting of liver transplantation (approximately 2000 subjects), while 2 studies focused on renal transplant recipients. All six studies were non-interventional and all except one were conducted retrospectively.

In the only prospective study, data on 24 patients were collected from health records before, during and after deceased donor orthotopic liver transplantation (OLT)^[45]. Reduced pre-OLT serum albumin level was found to be associated with ARF (RIFLE classification), whereas no other pre-OLT parameters (e.g., creatinine, GFR, serum sodium, serum bilirubin) were. Interestingly though, higher Model for End-Stage Liver Disease (MELD) score (mean 22 vs 18; $P = 0.02$) was also associated with AKI, leading the authors to speculate that the significance of hypoalbuminemia and higher MELD score as risk factors in this population might reflect the close relationship between renal and hepatic function in cirrhosis.

The largest of the three retrospective, observational studies assessing hypoalbuminemia in liver transplantation was a propensity score analysis of 998 consecutive living donor liver transplantation (LDLT) patients in a single center^[46]. This analysis aimed to ascertain the influence of early postoperative serum

albumin level on subsequent development of AKI. Serum albumin < 3.0 g/dL within 48 h postoperatively was identified by multivariate analysis as an independent risk factor for AKI (AKIN or RIFLE classification; Table 4), the first such report in the setting of LDLT. Furthermore, ICU ($P = 0.006$) and hospital ($P < 0.001$) stays were prolonged in the low albumin group and overall mortality was also higher ($P = 0.02$), making this one of the few studies retained from our literature review to report data associating serum albumin level with mortality. The findings of Sang *et al.*^[46] are consistent with an earlier, smaller retrospective study by Chen *et al.*^[44] in which multivariable analysis of 118 matched pairs of liver transplantation patients with/without postoperative renal injury demonstrated that preoperative hypoalbuminemia (≤ 3.5 g/dL) was strongly predictive of AKI within the first week after surgery. Similarly, Park *et al.*^[47] also identified by multivariate analysis that preoperative serum albumin < 3.5 g/dL was an independent, modifiable risk factor for AKI (RIFLE classification) in patients ($n = 538$) undergoing LDLT. Interestingly, the authors also identified MELD score > 20 as a significant risk factor for post-LDLT AKI (OR = 2.01, 95%CI: 1.17-3.44; $P = 0.011$), as in the study by Tinti *et al.*^[45], providing further evidence of renal-hepatic interactions in patients undergoing liver transplantation.

Notwithstanding the inherent limitations of retrospective, observational analysis, Sang *et al.*^[46] postulated that, when considering their results together with evidence accruing from other studies, hypoalbuminemia may be one of the major contributors to AKI development. Park *et al.*^[47] noted the reported nephroprotective capacity of albumin, through enhanced renal perfusion and reduced apoptosis/increased proliferation of renal tubular cells^[31-33]. However, they questioned whether exogenous augmentation of serum albumin could modify renal dysfunction within a short timeframe and reduce the risk of postoperative AKI. Sufficiently powered, prospective, interventional, randomized trials will be required to answer this question. Additional research will also be needed to further elucidate the mechanism(s) by which albumin can positively influence renal function, in LDLT surgery and other settings.

Fewer studies provide evidence on albumin levels in renal transplantation; however, these studies enrolled more subjects than those discussed above in the setting of liver transplantation. One large retrospective study, by Moore *et al.*^[48], analyzed data from 2763 adult kidney transplant recipients who were enrolled into the Long Term Efficacy and Safety Surveillance study and survived for ≥ 12 mo post transplantation. Multiple regression analysis revealed that hypoalbuminemia in the preceding 6 mo was independently associated with renal transplant failure, both in the death-censored analysis [< 3.5 g/dL, hazard ratio (HR) = 2.19, 95%CI: 1.58-3.05; $P < 0.001$] and overall (Table 4). Yang *et al.*^[49] also found a relationship between serum albumin level and likelihood of renal graft failure. In their single-

center study of 375 renal transplant recipients, the relative risk of graft failure was lowest in the group with highest serum albumin (≥ 4.5 g/dL) before transplantation. Chronic rejection (36.2%) and delayed graft function (12.8%) were most frequent in patients with albumin < 3.5 g/dL, though these results were not statistically significant. The authors concluded that hypoalbuminemia before kidney transplantation is associated with more serious complications and worse short- and long-term graft outcomes.

CANCER

An association between hypoalbuminemia and AKI morbidity/mortality has also been noted in cancer studies. We identified six relevant studies published during the search period, involving a total of more than 7000 patients, the majority of whom had gastric cancer^[50] (Table 5).

One of these studies was prospective ($n = 591$) and included data on incidence and risk factors of AKI in a subset of 87 patients with HCC with ascites undergoing transarterial chemoembolization (TACE) at a single center^[51]. Lower serum albumin was more common in HCC patients with vs without ascites (mean 3.2 g/dL vs 3.8 g/dL; $P < 0.001$). Furthermore, hypoalbuminemia (< 3.3 g/dL) occurred in 82% vs 38% of ascitic HCC patients who did ($n = 11$) vs did not ($n = 76$) develop AKI after TACE ($P = 0.009$). Logistic regression analysis among HCC patients with ascites found that hypoalbuminemia was the only risk factor independently predictive of post-TACE AKI. Based on earlier reports, the authors speculated whether nephroprotection by albumin might result from increased renal blood flow and GFR^[52], decreased changes in electrolyte and serum creatinine levels^[52], or plasma expansion^[53,54].

The largest retained study in cancer patients was a retrospective analysis of AKI occurrence after partial or total gastrectomy for gastric cancer ($n = 4718$)^[50]. Multivariate analysis identified hypoalbuminemia (< 4 g/dL), along with male gender, hypertension, chronic obstructive pulmonary disease, use of diuretics, vasopressors, or contrast agents, and packed red blood cell transfusions, as an independent predictor of postoperative AKI (Table 5). Prevalence of hypoalbuminemia tended to increase with severity of AKI (KDIGO staging). The authors acknowledged that the mechanisms through which hypoalbuminemia causes AKI are not fully understood, but noted that albumin plays a critical role in maintaining the integrity and function of renal tubular cells^[32,33].

Smaller retrospective studies also found significant associations between serum albumin level and AKI development in cancer settings. Mizuno *et al.*^[55] demonstrated significantly lower serum albumin in patients receiving cisplatin as first-line chemotherapy who had low ($n = 229$) vs normal ($n = 743$) blood pressure (mean 3.73 g/dL vs 3.87 g/dL; $P = 0.001$), suggesting that hypoalbuminemia associates with low blood pressure,

leading to renal hypoperfusion and thereby promoting ischemic AKI. Hypoalbuminemia was similarly associated with AKI in patients with acute myelogenous leukemia or high-risk myelodysplastic syndrome undergoing induction chemotherapy ($n = 537$; 187 with AKI)^[56]. In a 20-year, single-center, retrospective study of patients with multiple myeloma and acute severe renal failure ($n = 107$), serum albumin ≥ 3.5 g/dL was one of three factors (along with use of chemotherapy, and dialysis independence) found to be independently associated with survival^[57], though serum albumin is already incorporated into the International Staging System for multiple myeloma^[58]. A recent multivariate analysis of 103 consecutive ICU patients with cancer (any type) and AKI revealed low albumin level to be statistically associated with in-hospital mortality, leading to the conclusion that hypoalbuminemia (and presumably correction thereof) must be considered before initiating RRT in cancer patients^[59].

OTHER INDICATIONS

The majority of the recent studies generating data on hypoalbuminemia and AKI occurrence were conducted in the settings of cardiac/coronary interventions, infectious diseases, transplantation, or cancer, as described above. However, a further fifteen studies, all retrospective and observational in nature and involving a total of more than 46000 patients, also reported data on albumin levels and kidney outcomes, across numerous other patient populations.

By far the largest albumin data set among all of the literature retained for this review was a retrospective analysis of 37143 patients in the American College of Surgeons National Surgical Quality Improvement Program who underwent primary total knee arthroplasty (TKA) and had serum albumin data available^[60]. Mortality was higher in patients with albumin < 3.5 g/dL vs ≥ 3.5 g/dL (0.64% vs 0.15%; OR = 3.17, 95%CI: 1.58-6.35; $P = 0.001$), as were AKI (0.32% vs 0.06%, OR = 5.19, 95%CI: 1.96-13.73; $P = 0.001$) and a range of other major perioperative complications. The authors drew encouragement from these findings since hypoalbuminemia may be more easily modifiable than other risk factors (e.g., morbid obesity). Results from two subsequent studies also involving thousands of patients undergoing TKA (primary^[61] or revision^[62]) were consistent with these findings.

In a recent analysis of 408 patients with amyloidosis, serum albumin < 2.5 g/dL at admission was highly associated with requirement for RRT within 30 d of autologous stem cell transplantation ($P < 0.001$)^[63]. A smaller study in amyloidosis patients receiving high-dose melphalan with stem cell transplantation yielded similar results^[64]. Recent evidence in other clinical scenarios comes from isolated studies involving a total of more than 2500 patients. Hypoalbuminemia has been associated with AKI-related morbidity/mortality in patients with severe rhabdomyolysis^[38], pyogenic liver

abscess^[65], contrast-induced nephropathy^[66], hospital-acquired AKI^[67,68], and in critically ill patients requiring continuous RRT^[69], geriatric patients^[70-72], and those undergoing open ventral hernia repair^[73].

Taken together, the recent evidence discussed herein clearly demonstrates that hypoalbuminemia is an important consideration for AKI risk in a broad range of patients. However, each clinical scenario is multifactorial and presents its own complexities, and comorbidities that might also impact the development of AKI and thus be confounders in assessing the relative importance/contribution of serum albumin level in AKI. In diverse clinical settings there is a need for controlled, interventional studies to evaluate exogenous albumin therapy aimed at correcting hypoalbuminemia and reducing the risk of subsequent AKI, mortality, and other adverse outcomes. Also required will be mechanistic studies to define the pathways involved in nephroprotection by albumin.

LIMITATIONS

Limitations of this review include the fact that most of the included studies were observational with patient populations in the various clinical settings that are still quite heterogeneous. In addition definitions of AKI were often creatinine-dependent and based on different classification systems for AKI including RIFLE, AKIN, and KDIGO. As the systematic search of the literature was restricted to PubMed (MEDLINE), additional studies may be missing.

CONCLUSION

The association between hypoalbuminemia and development of AKI and subsequent morbidity/mortality can be regarded as confirmed. This robust association is consistently evident in a wealth of observational studies conducted across a wide range of clinical settings and involving tens of thousands of patients, and may be interpreted as an indication of a causal link.

Furthermore, a prospective RCT conducted in cardiac surgery patients, demonstrated for the first time that correction of low albumin level is associated with lower increase in creatinine, suggesting improved renal function with human albumin therapy and also supporting a causal link. These observations justify further interventional studies with albumin therapy, in cardiac surgery (including CPB) and other settings, such as transplantation other than liver or renal. Multi-center, prospective studies adequately powered to assess severe AKI, mortality and causality would be valuable, as would evaluation of the appropriate trigger and target serum levels and albumin dose necessary to confer renal protection. Basic research is also warranted to define the mechanisms through which albumin affords protection from renal injury. Moreover, because the development of AKI in high-risk patients is multifactorial, modification of a single risk factor might

not be sufficient for prevention. Therefore, further research is needed to advance our understanding of the combinatorial nature of AKI pathogenesis.

In the meantime, the large volume of data already available underscores the need to be alert to risk factors for AKI. Serum albumin level should be monitored to aid early identification of patients who may be at increased risk and who may stand to benefit from treatment to correct hypoalbuminemia.

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Basic Study

Tesevatinib ameliorates progression of polycystic kidney disease in rodent models of autosomal recessive polycystic kidney disease

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Abstract

AIM

To investigate the therapeutic potential of tesevatinib (TSV), a unique multi-kinase inhibitor currently in Phase II clinical trials for autosomal dominant polycystic kidney disease (ADPKD), in well-defined rodent models of autosomal recessive polycystic kidney disease (ARPKD).

METHODS

We administered TSV in daily doses of 7.5 and 15 mg/kg per day by I.P. to the well characterized bpk model of polycystic kidney disease starting at postnatal day

(PN) 4 through PN21 to assess efficacy and toxicity in neonatal mice during postnatal development and still undergoing renal maturation. We administered TSV by oral gavage in the same doses to the orthologous PCK model (from PN30 to PN90) to assess efficacy and toxicity in animals where developmental processes are complete. The following parameters were assessed: Body weight, total kidney weight; kidney weight to body weight ratios; and morphometric determination of a cystic index and a measure of hepatic disease. Renal function was assessed by: Serum BUN; creatinine; and a 12 h urinary concentrating ability. Validation of reported targets including the level of angiogenesis and inhibition of angiogenesis (active VEGFR2/KDR) was assessed by Western analysis.

RESULTS

This study demonstrates that: (1) *in vivo* pharmacological inhibition of multiple kinase cascades with TSV reduced phosphorylation of key mediators of cystogenesis: EGFR, ErbB2, c-Src and KDR; and (2) this reduction of kinase activity resulted in significant reduction of renal and biliary disease in both bpk and PCK models of ARPKD. The amelioration of disease by TSV was not associated with any apparent toxicity.

CONCLUSION

The data supports the hypothesis that this multi-kinase inhibitor TSV may provide an effective clinical therapy for human ARPKD.

Key words: Autosomal recessive; Autosomal dominant; Polycystic kidney disease; Therapy; Kinase inhibition; Multi-kinase inhibitor; Phosphorylation; Renal cysts; Biliary; G-protein coupled receptor

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Core tip: This study examined the effect of a multi-kinase inhibitor, tesevatinib (TSV) on cyst development and growth in rodent models of autosomal recessive polycystic kidney disease (ARPKD). Tesevatinib which targets epidermal growth factor receptors, Src and KDR is currently in clinical trials for autosomal dominant polycystic kidney disease (ADPKD) and given the molecular and cellular interactions of the ADPKD and ARPKD genes and proteins we sought to determine if TSV would ameliorate ARPKD. TSV was tested in two well described models of ARPKD, the BPK a phenocopy, and an orthologous rat model of ARPKD, the PCK. Of particular interest was the effect of TSV's inhibition of VEGFR2 or KDR during early post-natal development and renal maturation.

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INTRODUCTION

Renal cystic diseases encompass a broad group of disorders with variable phenotypic expression. The term polycystic kidney disease (PKD) explicitly refers to two genetically defined renal cystic diseases: Autosomal recessive polycystic kidney disease (ARPKD) and autosomal dominant polycystic kidney disease (ADPKD).

ARPKD (OMIM 263200) belongs to a group of congenital hepatorenal fibrocystic diseases characterized by dual renal and hepatic involvement^[1-5]. ARPKD has an incidence estimated at 1/20000 to 1/40000 with a wide spectrum of phenotypic expression^[2,4-6]. ARPKD occurs as the result of a mutations in a single gene, polycystic kidney and hepatic disease 1 (*PKHD1*)^[7,8]; encodes a protein called fibrocystin or polyductin (FPC)^[9,10]; and is commonly diagnosed *in utero* through early childhood^[2,3,5].

ADPKD is generally an adult-onset multisystem disorder, characterized by bilateral renal cysts, vascular abnormalities including intracranial aneurysms, and cysts in other organs including the liver. ADPKD is increasingly diagnosed in childhood and adolescents^[2,11]. Substantial variability in the severity of renal disease and other extrarenal manifestations occurs even within the same family. ADPKD is more common than ARPKD with an incidence of estimated at 1 in 600 and 1 in 1000 live births^[12]. ADPKD is a heterogenetic disorder caused by mutations in either the *PKD1* gene (85%) (OMIM173900) encoding the protein polycystin 1 (PC1), or in the *PKD2* gene (15%) (OMIM173910), encoding polycystin 2 (PC2). The recent report of a third ADPKD gene has been reported but it represents a very small number of ADPKD patients that did not map to PKD1 or PKD2 locus^[13]. ADPKD is characterized by the progressive development and expansion of fluid-filled cysts derived from renal tubule epithelia and typically leads to ESRD by late middle age^[14,15].

Clinically, a significant overlap of symptoms between ARPKD and ADPKD has been observed in children. Recent investigations at the cellular and molecular level provide compelling rationale for this clinical observation as ARPKD and ADPKD share many common pathophysiological features^[2,5,16]. Such studies reveal: (1) PKHD1, PKD1 and PKD2 proteins are expressed in multimeric "cystoprotein" complexes at specific locations within epithelial cells^[5,17-19]; (2) complex interactions between all three genes and their protein products occur at a molecular and cellular level^[15,20-23]; (3) cyst formation not only requires a PKD mutation but also requires simultaneous cell proliferation; (4) cyst development in both ARPKD and ADPKD begins *in utero*^[24-26]; and (5) clinical manifestations of both disorders are seen in newborns, children, and adolescents^[3,5,27-30]. These findings suggest that therapeutic interventions at an early stage of disease may provide the best opportunity for beneficial long-term clinical outcomes for patients with PKD^[3,5,31].

Cyst initiation and expansion are complex pheno-

mena comprised of multiple interacting processes. The precise mechanisms leading to enlarged cystic kidneys and liver abnormalities are unclear. However, various cellular defects have been identified that are common to cystic renal epithelia in both ARPKD and ADPKD. These include: (1) abnormalities of expression, function and polarity of one or more members of the epidermal growth factor (EGF) family of receptors and ligands [the (EGFR)-axis]; (2) abnormal activity of c-Src (pp60c-Src); decreased intracellular calcium leading to aberrant intracellular cAMP signaling; (3) abnormal structure and/or function of the primary cilia; (4) alterations in cell-cell, and cell-matrix interactions; and (5) activation of interstitial macrophages leading to progressive fibrosis.

Tesevatinib (TSV, previously been known as XL7647, XL647, PRIM-001 and KD-019) is a unique multi-kinase inhibitor that is being utilized in a phase II clinical trial for treatment of ADPKD (<https://ClinicalTrials.gov/ADPKD:NCT01559363>)^[32,33]. The basis of this therapeutic approach is that the use of a multi-kinase inhibitor provides "combination therapy" targeting multiple abnormal signal transduction events in PKD. TSV is a particularly appealing candidate for therapy due to its inhibition profile of c-Src (pp60c-Src) which decreases activity of both the EGFR axis and cAMP pathways^[34] as well as its inhibition of KDR that will target abnormal angiogenesis necessary for cyst growth.

MATERIALS AND METHODS

Animal models

All animal experiments were conducted in accordance with policies of the NIH Guide for the Care and Use of Laboratory Animals and the Institutional Animal Care and Use Committee of the Medical College of Wisconsin.

The BALB/c-^(Bicc1/Bicc1) model

The BALB/c-^(Bicc1/Bicc1) (BPK) model, a murine phenocopy of ARPKD, has been extensively characterized^[35-37]. Affected animals die at postnatal day (PN) 23 (average) with a range of PN-21 to PN-25. Extrarenal manifestations include biliary ductal ectasia (BDE). BPK animals were identified utilizing a PCR based genotyping method that has been described in detail^[38]. BALB/c wildtype (WT) controls were utilized in all experiments.

Both WT and cystic (bpc) male mice were administered the HCL salt of TSV, by intraperitoneal (IP) injections at 7.5 and 15 mg/kg per day starting at PN4. Kidney and liver (left lobe) tissues were harvested at PN-21, 2 h following the last dose, and assessed for the following: Body weight; total kidney weight (TKW); kidney weight to body weight (KW/BW) ratios; morphometric determination of a cystic index (CI); target validation was confirmed by western analysis; and renal function was assessed by determining serum BUN; creatinine (CR); and urinary concentrating ability

(UCA).

A colony of bpc animals have been inbred in the Avner laboratory since 1991 without significant phenotypic drift.

PCK rat model

The PCK rat is an orthologous model of human ARPKD characterized by slowly progressing renal cyst formation, impairment of renal function and development of congenital hepatic fibrosis. The PCK arose from a spontaneous mutation in the rat homolog of human PKHD1 in a Sprague Dawley colony in Japan at the Education and Research Center of Animal Models for Human Diseases of Fujita Health University and subsequently transferred to Charles River United States^[10,39].

Similar to human disease, previous reports in PCK rats have demonstrated an increased renal expression of active ErbB2 (pY1221/1222)^[34], active c-Src (pY418)^[34,40] and hepatic sensitivity to EGFR inhibition^[41]. Therefore, the PCK is a valuable orthologous model for testing therapeutic intervention in ARPKD.

Male PCK and Sprague Dawley controls were administered TSV daily by oral gavage, from PN30 to PN90 (61 doses). Similar to the bpc, PCK and SD kidney and liver (left lobe) tissues were harvested two hours following the final dose and assessed for the following parameters: Body weight; total kidney weight (TKW); KW/BW ratios; morphometric determination of a CI; target validation by western analysis; and renal function was assessed by determining serum BUN; CR; and UCA.

A colony of PCK and SD animals has been maintained at the Medical College of Wisconsin 2004 without significant phenotypic drift.

TSV

TSV (formerly named XL7647, XL647, PRIM-001 and KD-019) is an orally bioavailable compound with a MW of 663.59 g/mole. TSV is a 4-anilinoquinazoline bearing an octahydro-cyclopentapyrrol substituted methoxy group at the C-7 position. It is a mono-*p*-toluenesulfonic acid salt with a MW of 663.59 g/m. Data from pharmacodynamics *in vivo* experiments show that inhibition spectrum of TSV includes key tyrosine kinases (EGFR, HER2/ErbB2, c-Src) that promote epithelial cell proliferation and VEGFR2/KDR which promotes angiogenesis and/or neovascularization^[32,33].

TSV preparation and administration

Compound solutions EtOH:PEG 400:distilled water (5:45:50) were prepared under sterile conditions at concentrations of 5 mg/mL (for 7.5 mg/kg per day dose) or 10 mg/mL (for 15 mg/kg per day dose) to keep injection volumes equivalent despite the different dosing levels. Solutions were prepared in vehicle and stored at 4 °C for 3 d. Solutions were made fresh every 4 d.

BPK (cystic) and BALB/c (wild-type control) litter-

mates received TSV at 7.5 or 15 mg/kg per day by intraperitoneal (*i.p.*) injections. This dosage was based on company supplied pharmacologic and pharmacokinetic data of TSV treatment in mice and preliminary dose-response studies (data not shown). Animals were treated from PN4 to PN21 (18 doses). Kidney and liver were routinely harvested at P21 (2 h post last injection) and heart, spleen, pancreas, stomach, and thymus were periodically harvested at PN21 to evaluate possible toxicity of vehicle or TSV. Both BALB/c and bpk animals were divided into four groups each for testing and analysis. These groups included: (1) untreated or sham wildtype control; (2) wildtype treated with vehicle only; (3) wildtype treated with TSV at 7.5 mg/kg per day; (4) wildtype treated with TSV at 15 mg/kg per day; (5) untreated or sham cystic (bpk); (6) vehicle treated bpk; (7) TSV treated bpk at 7.5 mg/kg per day beginning at PN4 to PN21; and (8) bpk treated with TSV at 15 mg/kg per day beginning at PN4 to PN21.

PCK treatment

SD and PCK males were administered TSV by oral gavage from PN30 to PN90. SD sham, vehicle treated and TSV treated at 7.5 and 15 mg/kg per day along with the same groups of PCK animals were examined. Two hours following the last dose, renal and the left lobe of the liver were routinely harvested at P90 (2 h post last substitute dose for injection). Heart, spleen, pancreas, stomach, and thymus were periodically harvested at PN90 to evaluate possible toxicity of vehicle or TSV. The same parameters evaluated in bpk were assessed in the PCK. First urine samples were collected in metabolic cages after 88 d to assess UCA after 12 h without water. TSV treatment of PCK animals resulted in significant improvement of all assessed parameters compared to untreated PCK without evidence of toxicity or detrimental effects of KDR inhibition.

Western analysis

Control and cystic kidneys were first chopped in RIPA buffer supplemented with protease and phosphatase inhibitors (RIPA⁺), to minimize the contribution of cyst fluid protein to the total cellular protein. Tissue lysates were then extracted in fresh RIPA⁺ as previously described^[34] and were adjusted to an equal amount of protein (1.5 mg) (determined by BCA assay, Pierce, Rockford, IL, United States) per milliliter based on the least concentrated sample.

For Western analysis, 30 µg of the original tissue lysate (after volume adjustment), were denatured with 5 × sample buffer; and subjected to SDS-PAGE on 4% to 20% gradient gels, and were transferred onto membrane by Western blotting. The levels of total protein and active (phosphorylated) proteins were determined using specific primary antibodies, followed by peroxidase-conjugated appropriate secondary antibody and visualized by ECL (GE Healthcare Bio-Sciences Corp, Piscataway, NJ,

United States). Transfer efficiency and molecular weight determinations were performed with Rainbow[®] MW markers (GE Healthcare Bio-Sciences Corp, Piscataway, NJ, United States). Bands were semi-quantitatively compared using NIH Image 1.62. The densitometry value of wildtype untreated control was arbitrarily set at 1 and the densitometry of the other bands was compared to this value. Both Westerns and respective densitometry data shown are representative of three independent experiments with reproducible findings.

Antibodies

Rabbit polyclonal antibody to pan Src (#2108), p-Src (#2101), EGFR (#4267), p-EGFR (pY1068) (#3777), ERK1/2 (#4695), p-ERK1/2 (#4376), KDR (#9698, #2472), p-KDR (#3770), and β-actin (#3700) were purchased from Cell Signaling Technology (Beverly, MA, United States). Mouse anti-rat (#550300) and rat anti-mouse (#553708) CD-31 (PECAM1) (#550300) was purchased from BD Biosciences (San Jose CA, United States) and anti-mouse CD-31 (ab28364), ErbB2 (ab16901), and p-ErbB2 (ab131102) was purchased from Abcam Inc. (Cambridge, MA, United States) and used to probe Western blots. A rabbit polyclonal to β-actin (ab8227) was used to monitor protein loading of Westerns.

Histology, immunohistology, and determination of segmental nephron cyst localization

All kidney and liver tissues were fixed in 4.0% paraformaldehyde in phosphate buffer (pH = 7.4) for 30 min at 4 °C, dehydrated and embedded in paraffin. Segmental nephron cyst localization and collecting tubule (CT) CI were quantitated in each experimental group by combining morphometric analysis with light microscopy and immunohistology as previously described^[34,35,37,42].

Kidney weight/body weight ratio and renal CI

At P21, or PN90 control and cystic, treated and untreated animals were given the last dose weight, as were both excised kidneys. Total kidney weights to body weight ratios were calculated. The degree of CT cyst formation was quantitatively assessed by segment specific morphometric analysis as previously described^[34,37,42] and expressed as the CI (see below). Cyst localization was determined by segment-specific lectin binding using Dolichos biflorus agglutinin (DBA) as a marker for CTs and Lotus tetragonolobus agglutinin (LTA) as a marker for proximal tubules^[34,37,42]. For each treatment group, a CT CI was determined on 5 to 6 affected pups.

The CI is a model specific means to assess the degree of disease burden or progression based on the natural progression of the renal disease and hepatic disease (BDE in bpk) and (LW/BW in PCK) In the bpk, the CI and BDE index are on a scale of 1 to 5 based on the disease burden normally present at PNO, 5, 10, 15,

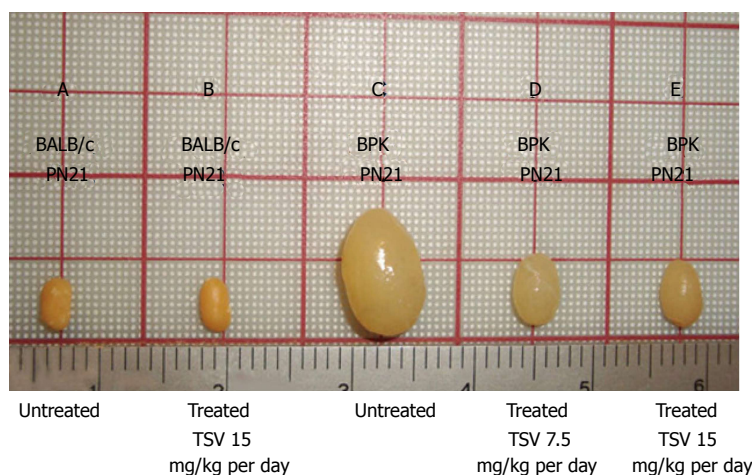


Figure 1 Tesevatinib treatment in the BPK model of autosomal recessive polycystic kidney disease. Compared to wild-type BALB/c control kidneys (A) at PN21, BPK cystic kidneys (C) are extremely enlarged by PN21. TSV treatment resulted in a dose-dependent reduction in the overall kidney size at doses of 7.5 mg/kg per day (D) and 15 mg/kg per day (E) when compared to PN21 BPK untreated cystic kidneys (C). Treatment of wildtype BALB/c with 15 mg/kg per day (B) did not result in significant reduction of overall kidney size when compared to untreated BALB/c kidneys (A). This correlates directly with the total kidney weight (TKW) of each group listed in Table 1. Further, the morphology of wildtype TVS treated kidneys seen in Figure 2A shows no obvious signs of toxicity (Treatment interval: PN4-PN21). TSV: Tesevatinib.

and 20. The renal index in bpk measures the number and size of PT and CT cysts and the BDE (also a 1-5 scale) is based on the number of abnormal portal triads in the left lobe of the liver that is seen during the natural progression in the bpk.

The PCK CI is on a scale of 1 to 10 based on the number and size of cystic lesions seen at 15 d intervals beginning at PN15 and ending at PN150. Since all cysts occur in CT segments the number and size of these lesions are evaluated. The hepatic lesions in the PCK are biliary cysts and all are affected to varying degrees so we use a simple LW/BW ratio to assess hepatic disease progression.

The kidney and left lobe of the liver in bpk and kidney in PCK is embedded medulla side down and a minimum of 3, 4 $\mu\text{mol/L}$ thick sections at depths 100 μm s apart (25 sections) are evaluated as previously described^[34,37,42].

Analysis of renal function and UCA

Animals were deprived of water for 12 h prior to collection of urine samples for determination of UCA. Urinary concentrating was determined by freeze point using a freezing point osmometer (Multi-Osmette; Model 2430, Precision Instruments Inc).

Blood samples were obtained by cardiac puncture for serum BUN and CR measurements. Serum BUN and CR was determined on an automated clinical chemistry analyzer as previously described^[37].

Statistical analysis

The significance of differences between experimental groups was determined by a one-way analysis of variance. Results are expressed as means $\pm$ SD.

RESULTS

BPK

The *in vivo* activity of TSV was evaluated in the bpk mouse, a phenocopy of ARPKD based on the dual organ abnormalities seen in this model. It is a rapidly progressing model that results in ESRD and death by PN

24. The rapid progression simulates the clinical course of severe ARPKD presenting in newborns. The bpk model provides a relatively rapid means of assessing the *in vivo* efficacy of a potential therapeutic compound. Given the reported activity of TSV against the vascular endothelial growth factor receptor 2 (VEGFR2 or KDR), the bpk model is also a good model to evaluate the inhibition of angiogenesis inhibition during postnatal cystic kidney development.

Both wildtype (WT) ($\text{BALB/c}^{(Bicc+/Bicc+)}$) and cystic (bpk) ($\text{bpk}^{(Bicc-/Bicc-)}$) mice were administered the HCL salt of TSV, by intraperitoneal (IP) injections at 7.5 and 15 mg/kg per day starting at PN4. At PN21 the animals were weighted for the last time and kidney and liver tissues were harvested 2 h following the last injection of TSV. The following parameters were assessed: body weight, total kidney weight (TKW); KW/BW ratios; and morphometric determination of a CI. Renal function was assessed by: Serum BUN; CR; and a 12 h UCA. Validation of reported targets including the level of angiogenesis and inhibition of angiogenesis (active VEGFR2/KDR) was assessed by Western analysis. TSV treatment of bpk mice resulted in significant improvement of all assessed parameters compared to untreated or vehicle treated cystic animals without significant changes in body weight, evidence of toxicity or detrimental effects of the inhibition of KDR (Table 1).

Figure 1 reveals that TSV administration to bpk animals from PN4 to PN21 (18 doses) results in a dose dependent reduction in whole kidney size when compared to untreated bpk cystic kidneys. The change in whole kidney size is also reflected in the dose dependent significant decrease in TKW from 2.03 ± 0.28 g in untreated bpk (column E, Table 1) to 1.59 ± 0.19 g ($P < 0.001$) and 1.21 ± 0.10 g ($P < 0.001$) with TSV at 7.5 mg/kg per day (column G, Table 1) and 15 mg/kg per day (column H, Table 1) respectively.

The reduction in whole kidney size and TKW for bpk kidneys is associated with markedly improved renal morphology as shown in Figure 2. Accordingly, the CI was significantly reduced by treatment as seen in Table 1.

The CI index was reduced by 25% in bpk mice from

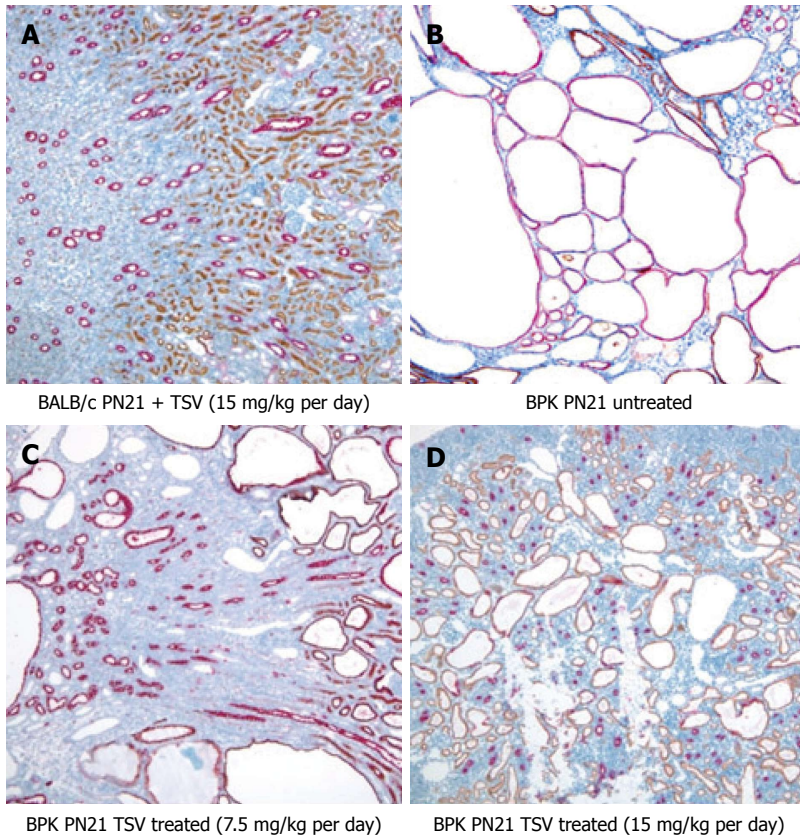


Figure 2 Renal morphology of tesevatinib-treated BPK kidneys. Immuno-histological analysis of BPK kidneys reveals a marked decrease in the size and number of collecting tubule cysts (stained red) following treatment with TSV at 7.5 mg/kg per day (C) and 15 mg/kg per day (D) when compared to the untreated cystic kidneys (B). Treatment of control BALB/c kidneys with TSV at 15 mg/kg per day (A) demonstrated no obvious histological abnormalities (Nephron segment-specific lectin binding of lotus tetragonolabus agglutinin shows proximal tubules in brown, and binding of dolichus biflorus agglutinin shows collecting tubules in red). TSV: Tesevatinib.

Table 1 BPK summary data

	WT PN-21 Sham <i>n</i> = 22	WT PN-21 VEH <i>n</i> = 10	WT PN-21 TSV 7.5 <i>n</i> = 10	WT PN-21 TSV 15 <i>n</i> = 10	BPK PN-21 Sham <i>n</i> = 17	BPK PN-21 VEH <i>n</i> = 12	BPK PN-21 TSV 7.5 <i>n</i> = 10	BPK PN-21 TSV 15 <i>n</i> = 14
BW (g)	10.31 ± 0.55	10.76 ± 0.72	10.57 ± 0.80	10.10 ± 0.29	10.46 ± 0.60	10.29 ± 0.45	10.50 ± 0.96	10.11 ± 0.50
TKW (g)	0.15 ± 0.01	0.16 ± 0.02	0.141 ± 0.02	0.13 ± 0.01	2.03 ± 0.28	2.01 ± 0.22	1.59 ± 0.19 ^a	1.21 ± 0.09 ^{f,e}
KW/BW (%)	1.41 ± 0.10	1.50 ± 0.12	1.33 ± 0.08	1.25 ± 0.09	19.32 ± 1.71	19.57 ± 1.62	15.12 ± 1.1 ^e	11.96 ± 1.22 ^{f,e}
CI	NA	NA	NA	NA	4.7 ± 0.50	4.8 ± 0.42	3.6 ± 0.52 ^e	2.50 ± 0.35 ^{f,e}
BUN (mg/dL)	19.25 ± 1.14	21.20 ± 1.99	18.60 ± 2.07	19.40 ± 1.5	108.3 ± 17.8	112 ± 23.3	63.6 ± 20.3 ^e	40.9 ± 13.7 ^{d,e}
Cr (mg/dL)	0.24 ± 0.05	0.29 ± 0.06	0.24 ± 0.05	0.28 ± 0.06	0.55 ± 0.14	0.58 ± 0.10	0.41 ± 0.1 ^b	0.28 ± 0.07 ^{c,e}
12 h UCA	1043 ± 35	1065 ± 52	1026 ± 39	1024 ± 27	465 ± 83	460 ± 92	581 ± 67 ^a	786 ± 185.2 ^{d,e}
BDE	NA	NA	NA	NA	4.8 ± 0.4	4.5 ± 0.5	3.70 ± 0.4 ^b	2.8 ± 0.4 ^{d,e}

^a*P* < 0.05, ^b*P* < 0.01, ^c*P* < 0.001 *vs* untreated (Sham) BPK; ^d*P* < 0.05, ^e*P* < 0.01, ^f*P* < 0.001 *vs* BPK TSV treatment at 7.5. CI: Cystic index; UCA: Urinary concentration ability at 12 h; BDE: Biliary ductal ectasia; KW/BW: Kidney weight to body weight; NA: Not applicable; TKW: Total kidney weight.

4.80 ± 0.4 to 3.60 ± 0.52 (*P* < 0.001) treated with TSV at 7.5 mg/kg per day and by 48% (2.5 ± 0.5, *P* < 0.001) in BPK mice treated with TSV at 15 mg/kg per day compared to untreated bpk kidneys (Table 1).

The morphology of bpk kidney and liver shown in Figures 2 and 3 respectively, demonstrates a dose dependent reduction in the progression of disease in both kidney and liver respectively. The red labelled CTs cysts in PN21 untreated bpk animals (Figure 2B) are very large with little normal parenchyma in between. TSV treatment reduces the number and size of the CT cysts in kidneys treated with TSV at 7.5 mg/kg per day (Figure 2C) and 15 mg/kg per day (Figure 2D). Kidneys shown in Figure 2C and D reveal LTA labelled proximal tubule cysts (brown) that are indicative of a “younger” PKD disease course as previously described^[34,35,43]. The

improved morphology with TSV treatment correlates with the reduced whole kidney size (Figure 1) as well as with the reduced TKW, CI and BDE index in Table 1.

All morphometric measures of renal disease and liver abnormalities associated with ARPKD, as well as all renal functional parameters improved in a dose dependent manner in bpk with TSV administration. In the bpk, at PN21 this included an improvement in: BUN of 41% (*P* < 0.001) and 62% (*P* < 0.001); serum CR improved 25.5% (*P* < 0.01) and 49% (*P* < 0.001); and the UCA improved by 25% (*P* < 0.05) and 69.4% (*P* < 0.001) with 7.5 and 15 mg/kg per day respectively as seen in Table 1.

There was also a marked change in biliary ductal ectasia (BDE) with TSV treatment as assessed by histological evaluation of hepatic morphology in the bpk

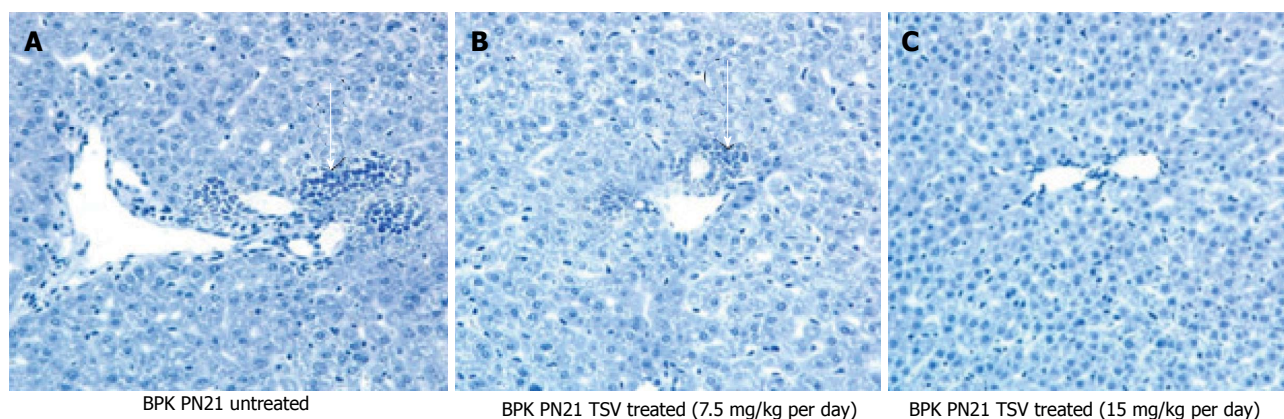


Figure 3 Liver morphology of tesevatinib-treated BPK mice. Histological analysis of hematoxylin stained BPK livers reveals a marked decrease in the biliary ductal ectasia (arrow) following treatment with TSV at 7.5 mg/kg per day (B) (arrow) and 15 mg/kg per day (C) when compared to untreated BPK livers (A) (Treatment interval: PN4-PN21).

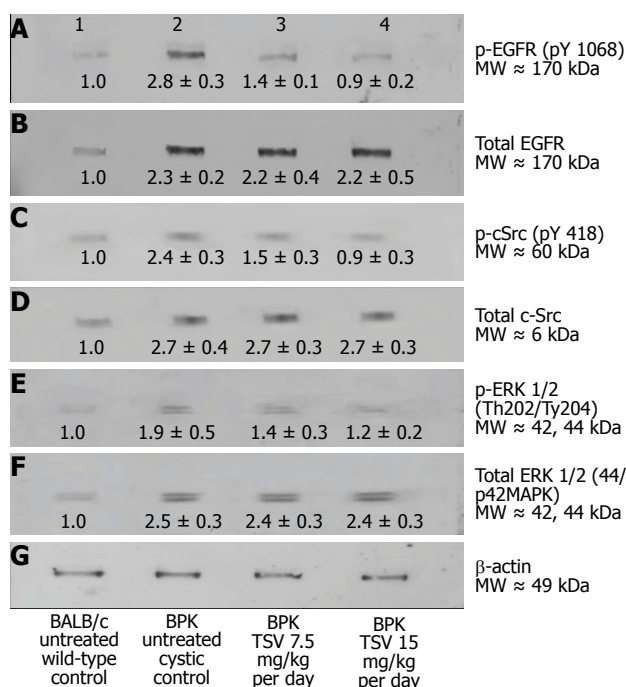


Figure 4 Target validation in BPK. Western analysis of the MAPK pathway activity of EGFR (p-EGFR), cSrc (pSrc), and ERK1/2 (p-ERK 1/2) reveals that BPK cystic kidneys have significantly increased levels of active or phosphorylated p-EGFR (A2), pSrc (C2) and ERK1/2 (E2) compared to wild-type BALB/c control levels in lanes (A1, C1 and E1) respectively. TSV treatment at 7.5 or 15 mg/kg per day resulted in a dose dependent reduction in the phosphorylation or activity of p-EGFR (A3 and A4), and p-Src (C3 and C4) that correlated directly to a reduction in the activity of ERK1/2 (p-ERK1/2: E3 and E4). The reduced level of phosphorylated proteins occurred without changes in the level of total EGFR (B2, B3 and B4), total Src (D2, D3 and D4) or total ERK1/2 (F2, F3 and F4). The numbers below the band in each lane represents the average ± SD ($n = 3$) of the relative density of each band when normalized to the wildtype BALB/c control value arbitrarily set at 1.

(Figure 3 and Table 1). BDE at PN21 of TSV treated cystic mice (Table 1) was significantly reduced by 25% from 4.80 ± 0.50 to 3.70 ± 0.40 ($P < 0.01$) with 7.5 mg/kg per day and was furthered reduced by 42% to 2.80 ± 0.40 ($P < 0.001$) with TSV treatment at 15 mg/kg per day.

Treatment of BALB/c wildtype control animals showed no statistical difference in any assessed parameters including renal function at 7.5 or 15 mg/kg per day dose when compared to untreated wildtype animals. The morphology of both the kidney (Figure 2A) and liver (Figure 3A) at the 15 mg/kg per day dose and the lack of change in renal function (Table 1) at either dose indicated no obvious signs of toxicity with TSV administration.

Kinase target validation was assessed in the bpk kidneys treated with TSV. As seen in the Western blots of Figure 4, TSV targeted the kinases previously shown to play a role in proliferation and cystic disease in renal epithelia. The use of TSV resulted in a significantly reduced phosphorylation level of EGFR (Figure 4A3, and 4A4), c-Src (Figure 4C3 and 4C4) and ERK1/2 (Figure 4E3 and 4E4). For these key kinases, TSV treatment of 15 mg/kg per day resulted in phosphorylation levels similar to untreated control kidneys (Figure 4, lanes A4, C4 and E4 compared to wildtype control levels as seen in Figure 4 lane 1 of panel A, C and E).

An obvious consideration with the potential use of TSV in pediatric patients is deleterious side effects due to disruption of developmentally critical proteins. A particular concern is the effect of TSV on angiogenesis. The inhibition of KDR or VEGFR2 ideally would not cause a reduction in activity of the receptor much below wildtype levels where inhibition of angiogenesis would likely have significant detrimental effects on normal kidney development. The rapidly progressive bpk was used to evaluate the inhibitory effect of KDR during postnatal development.

To investigate the level of angiogenesis inhibition we measured the change in VEGFR2 (KDR) activity in bpk (Figure 5). As Figure 5 shows, the amount of active p-KDR in TSV-treated kidneys at 15 mg/kg per day is not significantly different from the level of untreated wild type controls. The expression data of CD-31 or PECAM-1, an endothelial cell protein reveal a decreased expression in TSV treated bpk cystic kidneys. These data demonstrate

Table 2 PCK summary data

	SD PN-90 Sham <i>n</i> = 12	SD PN-90 VEH <i>n</i> = 10	SD PN-90 7.5 mg/kg per day <i>n</i> = 8	SD PN-90 15 mg/kg per day <i>n</i> = 8	PCK PN-90 Sham <i>n</i> = 10	PCK PN-90 VEH <i>n</i> = 12	PCK PN-90 7.5 mg/kg per day <i>n</i> = 10	PCK PN-90 15 mg/kg per day <i>n</i> = 12
BW (g)	375.9 ± 12.1	380 ± 19.46	375 ± 23.23	377 ± 13.31	434 ± 16.6	417.8 ± 21.0	413.4 ± 18.7	406.0 ± 18.5
TKW (g)	3.63 ± 0.46	3.70 ± 0.22	3.71 ± 0.16	3.85 ± 0.32	8.02 ± 0.32	7.54 ± 0.52	6.21 ± 0.44 ^e	5.06 ± 0.43 ^{e,f}
KW/BW (%)	0.96 ± 0.10	0.97 ± 0.04	0.99 ± 0.6	0.91 ± 0.33	1.84 ± 0.09	1.81 ± 0.05	1.50 ± 0.11 ^b	1.18 ± 0.1 ^{c,e}
CI	NA	NA	NA	NA	7.44 ± 0.8	7.0 ± 0.6	5.3 ± 1.0 ^e	3.8 ± 0.9 ^{d,e}
BUN (mg/dL)	21.17 ± 1.2	22.40 ± 1.6	23.50 ± 1.7	23.6 ± 1.9	49.2 ± 12.7	48.88 ± 15.3	36.40 ± 4.4 ^b	24.17 ± 8.7 ^{c,e}
Cr (mg/d)	0.33 ± 0.08	0.34 ± 0.12	0.36 ± 0.05	0.34 ± 0.08	0.67 ± 0.1	0.66 ± 0.12	0.51 ± 0.08 ^b	0.38 ± 0.07 ^{c,e}
UCA 12 h	2778 ± 159	2983 ± 421	2749 ± 63.1	2712 ± 113	1390 ± 221.9	1448 ± 236	2196 ± 169 ^e	2630 ± 214 ^{d,e}
LW/BW (%)	4.3 ± 0.47	4.2 ± 0.7	4.13 ± 0.57	4.00 ± 0.65	6.02 ± 0.35	6.08 ± 0.42	5.40 ± 0.21 ^b	4.92 ± 0.27 ^{c,e}

^a*P* < 0.05, ^b*P* < 0.01, ^c*P* < 0.001 *vs* untreated (Sham) PCK; ^d*P* < 0.05, ^e*P* < 0.01; ^f*P* < 0.001 *vs* TSV treatment at 7.5. CI: Cystic index; UCA: Urinary concentration ability at 12 h; LW/BW: Measure of cyst burden; KW/BW: Kidney weight to body weight; TKW: Total kidney weight.

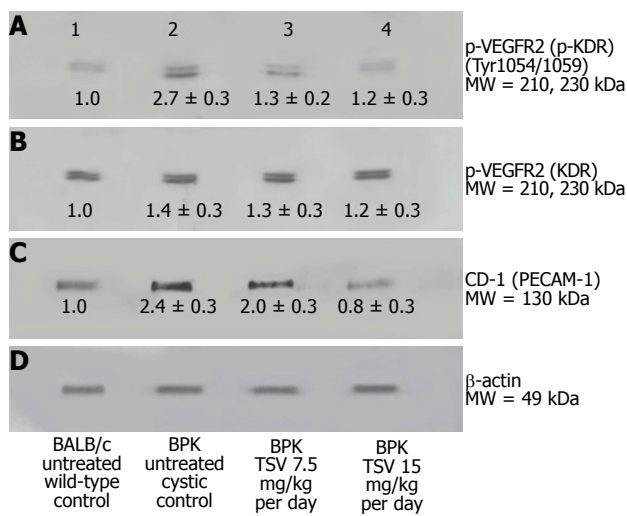


Figure 5 VEGFR2 (KDR) and CD-31 expression in BPK. Western analysis of the renal expression of VEGF2 (KDR) in BPK (B), and active (p-KDR) in BPK kidneys (A) demonstrate an increased phosphorylation of KDR in untreated cystic kidneys (2) compared to BALB/c untreated wildtype controls (A1). TSV treatment of BPK at 7.5 (A3) and 15 mg/kg per day (A4) respectively, reduced the level of p-KDR in a dose dependent manner to near normal (wildtype) levels. This reduced p-KDR correlated directly with expression levels of CD-31 shown in (C) which was also reduced in a dose dependent manner with TSV treatment. The numbers below the band in each lane represents the average ± SD of the relative density of each band when normalized to the wildtype BALB/c control value arbitrarily set at 1. D is the loading control. Each average represents a minimum of *n* = 3 individual westerns. These data are confirmed by the morphology of CD-1 stained BPK kidneys shown in Figure 6.

that inhibition of angiogenesis as assessed by p-KDR translated into a reduced expression of CD-31. As seen in Figure 6, the level of CD-31, is increased around cystic CT (6B) when compared to age-matched BALB/c animals (6A). It appears that TSV treatment eliminates abnormal peritubular CD-31 expression but still permits the robust expression of CD-31 in glomeruli (6C) of TSV treated bpk kidneys.

PCK

The orthologue of human ARPKD, the PCK, and Sprague Dawley wildtype controls were administered TSV by oral gavage from PN30 to PN90 and the same parameters assessed following TSV administration as in the bpk.

Figure 7 reveals that TSV administration to PCK animals from PN30 to PN90 (61 doses) results in a dose dependent reduction in whole kidney size when compared to untreated PCK. The change in whole kidney size is also reflected in the dose dependent significant decrease in TKW from 8.02 ± 0.32 g in untreated PCK to 6.21 ± 0.44 (*P* < 0.001) and 5.06 ± 0.43 g (*P* < 0.001) with TSV at 7.5 and 15 mg/kg per day respectively as shown in Table 2. The reduction in whole kidney size and TKW is associated with markedly improved renal morphology shown in Figure 8. Accordingly, the CI was significantly reduced by treatment as seen in Table 2. The improved renal morphology was mirrored by a dose dependant improvement in hepatic morphology as seen in Figure 9 which was reflected in a reduced LW/BW ratio listed in Table 2.

Results summarized in Table 2, demonstrate that compared to untreated PCK animals (*n* = 10), cystic animals treated with TSV showed an 18%, (*P* < 0.01) and 36% (*P* < 0.001) reduction in KW/BW ratio, reductions in CI of 29%, (*P* < 0.001) and 49%, (*P* < 0.001) and a 10% (*P* < 0.05) and 18% (*P* < 0.001) reduction in LW/BW ratios. There was a dose dependent improvement in KW/BW of 26% and CI of 28% with increased dosage from 7.5 to 15 mg/kg per day. Compared to untreated PCK animals, renal function parameters also demonstrated significant dose dependent improvement with TSV treatment. BUN levels decreased by 26% (*P* < 0.01), and 49% (*P* < 0.001), CR levels decreased by 24% (*P* < 0.01) and 43% (*P* < 0.001) while UCA improved by 36% (*P* < 0.001) and 47% (*P* < 0.001) following TSV treatment with 7.5 and 15 mg/kg per day respectively. Treatment of SD controls shows no significant differences in assessed parameters at either TSV dose.

The improvement in morphology and renal function correlates with target verification shown in Figure 10. The activity (phosphorylation) of ErbB2 (Figure 10A3 and A4) Src (Figure 10C3 and 10C4) ERK1/2 (Figure 10E3 and 10E4) are reduced in a dose dependent manner with treatment with TSV at 7.5 and 15 mg/kg per day respectively. Figure 11 demonstrates that TSV reduces pKDR levels which correlates with a reduced

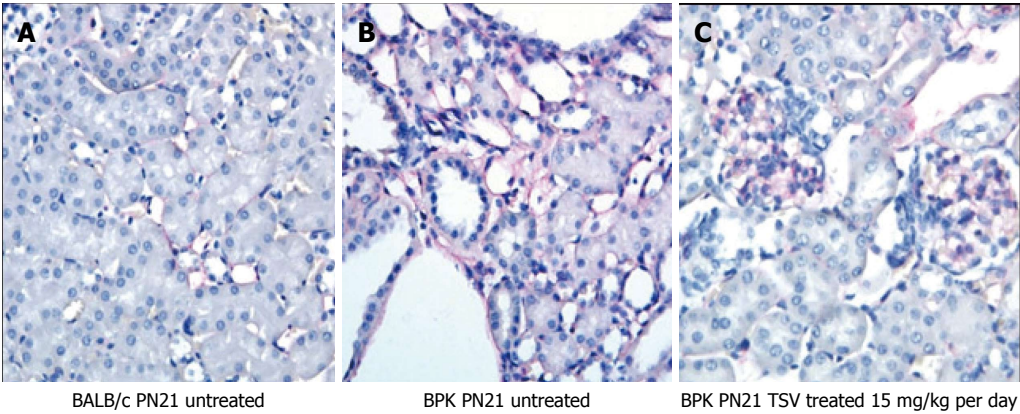


Figure 6 Immuno-histological analysis of CD-31 expression in testesevatinib-treated BPK kidneys. Expression of CD-31 (PECAM1) (red), a marker of endothelium, in PN21 wild-type BALB/c kidneys (A) reveals fine thin lines of endothelial elements that run along the nephrons. Untreated BPK kidneys (B) demonstrate prominent expression of CD-31 along the tubules and pronounced expression surrounding cystic lesions. TSV-treated cystic kidneys at 15 mg/kg per day (C) reveal a marked reduction in CD31 expression along the tubules to near normal levels but maintain robust glomerular staining of CD-31.

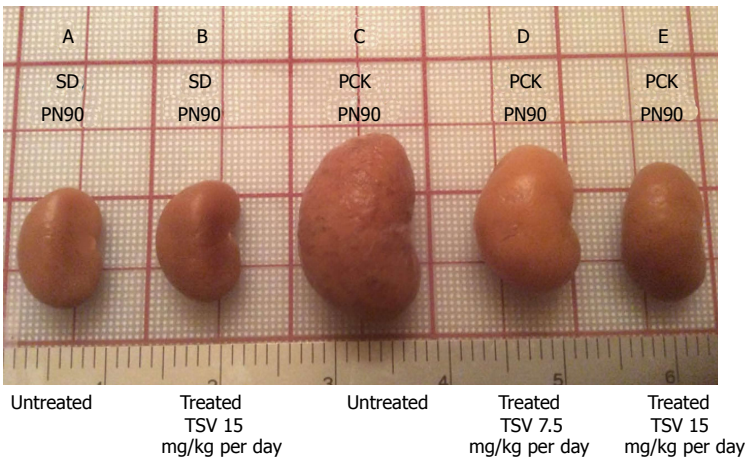


Figure 7 Testesevatinib treatment in the PCK model of autosomal recessive polycystic kidney disease. Compared to wild-type SD control kidneys (A) at PN90, PCK cystic kidneys (C) are significantly enlarged by PN90. TSV treatment results in a dose-dependent reduction in the overall kidney size at doses of 7.5 mg/kg per day (D) and 15 mg/kg per day (E) when compared to untreated PCK cystic kidneys at PN90 (C). Treatment of wildtype SD with 15 mg/kg per day did not result in significant reduction of overall kidney size (B) compared to untreated wildtype SD animals. This correlates directly with the total kidney weight (TKW) of each group listed in Table 2 (Treatment interval: PN30-PN90). TSV: Testesevatinib.

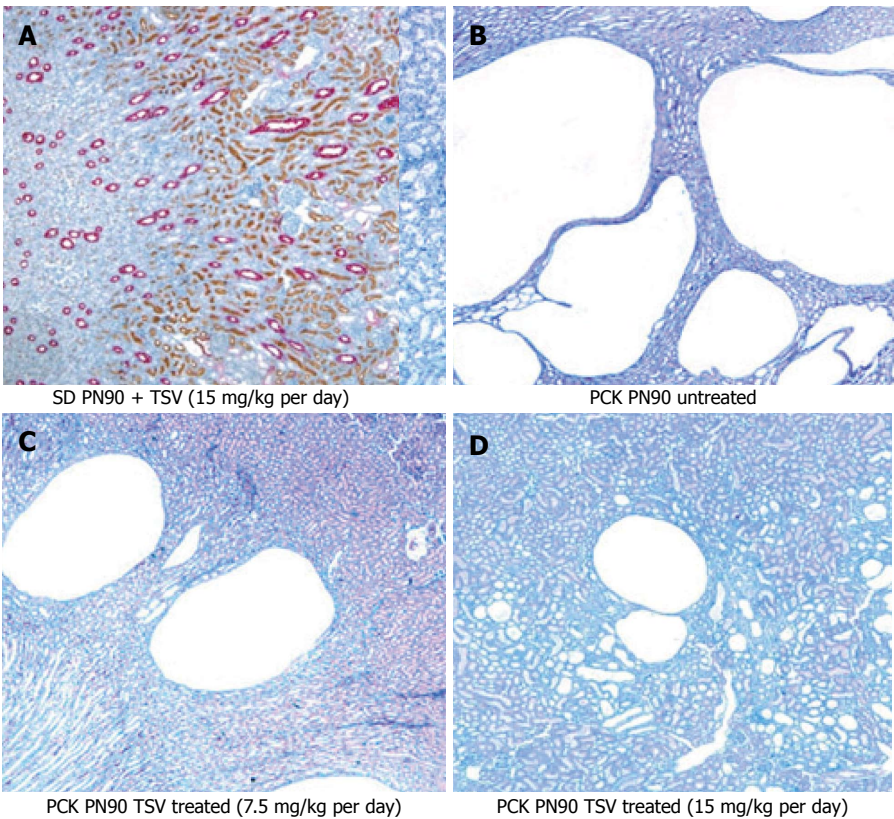


Figure 8 Renal morphology of testesevatinib-treated PCK kidneys. Histological analysis of HE stained PCK kidneys reveals a marked decrease in the size and number of collecting tubule cysts following treatment with TSV at 7.5 mg/kg per day (C) and 15 mg/kg per day (D) when compared to untreated cystic kidneys (B). Treatment of control Sprague Dawley kidneys at 15 mg/kg per day (A) revealed no histological abnormalities (Treatment Interval: PN30-PN90). TSV: Testesevatinib.

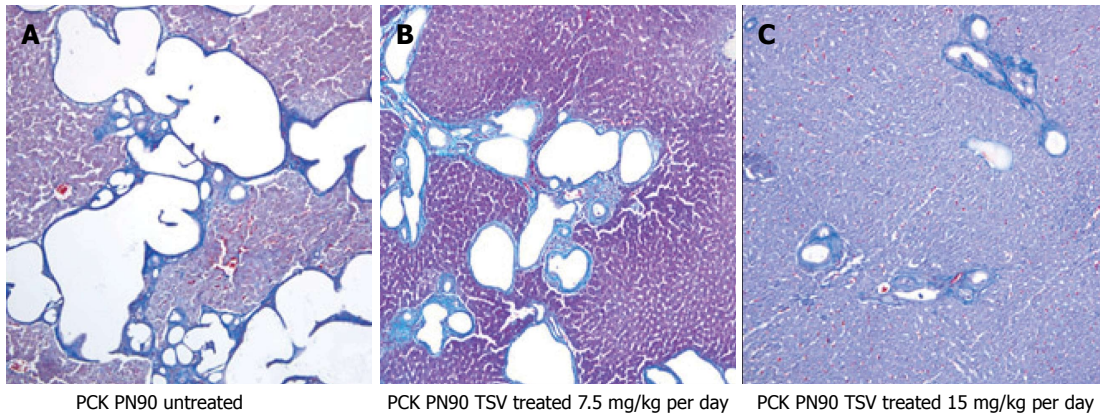


Figure 9 Liver morphology of tesevatinib-treated PCK mice. Histological analysis of PCK livers reveals a marked decrease in the size and number of biliary ductal cysts following treatment with tesevatinib at 7.5 mg/kg per day (B) and 15 mg/kg per day (C) when compared to untreated PCK livers (A) (Treatment interval: PN30-PN90).

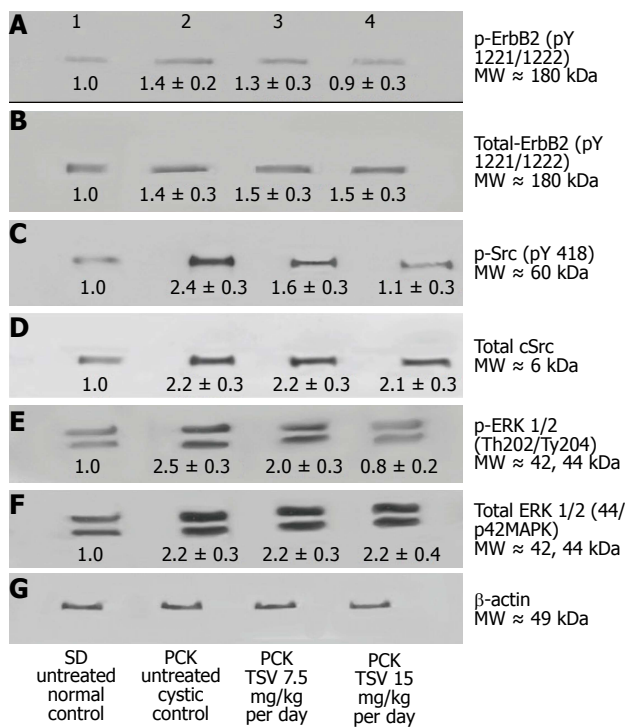


Figure 10 Target validation in BPK. Western analysis of the MAPK pathway activity of EGFR (p-EGFR), cSrc (pSrc), and ERK1/2 (p-ERK 1/2) reveals that BPK cystic kidneys have significantly increased levels of active or phosphorylated p-EGFR (A2), pSrc (C2) and ERK1/2 (E2) compared to wild-type BALB/c control levels in lanes (A1, C1 and E1) respectively. TSV treatment at 7.5 or 15 mg/kg per day resulted in a dose dependent reduction in the phosphorylation or activity of p-EGFR (A3 and A4), and p-Src (C3 and C4) that correlated directly to a reduction in the activity of ERK1/2 (p-ERK1/2: E3 and E4). The reduced level of phosphorylated proteins occurred without changes in the level of total EGFR (B2, B3 and B4), total Src (D2, D3 and D4) or total ERK1/2 (F2, F3 and F4). The numbers below the band in each lane represents the average ± SD ($n = 3$) of the relative density of each band when normalized to the wildtype BALB/c control value arbitrarily set at 1.

CD-31 level with TSV therapy.

Toxicology

Treatment of bpk mice and PCK rats with TSV demonstrated no apparent morphological evidence of renal

or hepatic toxicity, no compound-related deaths, and no microscopic changes in heart, spleen, stomach, pancreas or thymus with 7.5 mg/kg per day or 15 mg/kg per day dosing.

In sum, the use of TSV at 7.5 or 15 mg/kg per day results in a significant improvement in all assessed parameters compared to untreated or vehicle treated cystic animals in both bpk and PCK animals without obvious evidence of toxicity or detrimental effect of KDR inhibition.

DISCUSSION

A long-recognized clinical observation is the overlap of phenotypic features that at times leads to difficulty delineating ARPKD from ADPKD in pediatric patients^[3,5,16]. Data now reveal that the pathophysiology of the two diseases have significant overlap. Recent evidence revealed a complex set of interactions between PKHD1, PKD1 and PKD2 that occur both at the molecular and cellular level^[5,15,20-23]. Despite the identification of the causative genes responsible for ARPKD and ADPKD, the precise function of these genes and their protein products is still unclear.

This complexity, in part, is due in part to many novel attributes of the genes including: (1) the complexity of their protein structures; (2) the large size of *PKHD1* and *PKD1*; (3) the multiple transcripts produced by these genes; (4) the interaction of the PKD proteins; (5) the multiple intracellular sites of PKD protein localization; and (6) the participation of these proteins in a number of multimeric protein complexes^[5,17-19,44]. The lack of functional PC1, PC2 or fibrocystin is embryonically lethal, indicating that PKD begins *in utero*^[25]. ARPKD and ADPKD share common phenotypic abnormalities and intersecting signaling pathways whose disruption leads to cyst formation^[3,5,16,23,34]. Despite this rudimentary understanding, emerging molecular and cellular insights into the pathophysiology of PKD is beginning to translate into unique disease-specific, targeted therapies.

Previous work in our laboratory demonstrated that

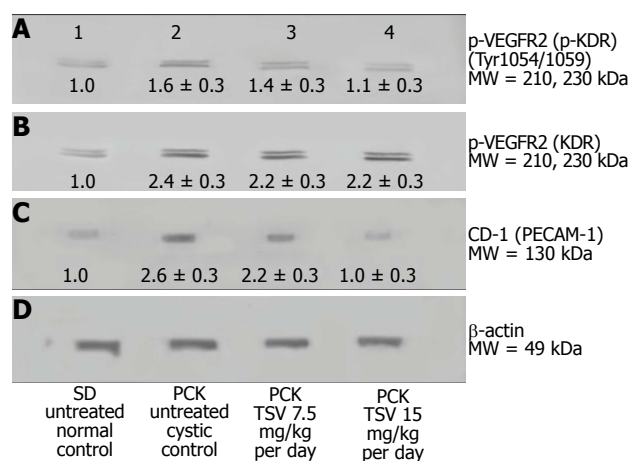


Figure 11 VEGFR2 (KDR) and CD-31 expression in PCK. Western analysis of the renal expression of VEGF2 (KDR) in PCK (B), and active (p-KDR) in PCK kidneys (A) demonstrate an increased phosphorylation of KDR in untreated cystic PCK kidneys (A2) compared to SD untreated wildtype controls (A1). TSV treatment of PCK at 7.5 (A3) and 15 mg/kg per day (A4) respectively, reduced the level of p-KDR in a dose dependent manner to near normal (wildtype) levels. This reduced p-KDR correlated directly with expression levels of CD-31 shown in C, which was also reduced in a dose dependent manner with TSV treatment. The numbers below the band in each lane represents the average $\pm$ SD of the relative density of each band when normalized to the wildtype SD control value arbitrarily set at 1. D is the loading control. Each average represents a minimum of $n = 3$ individual westerns.

the combination of therapies that inhibit both the epidermal growth factor receptor (EGFR) autophosphorylation and EGFR ligand availability provide a novel example of effective combination therapy in murine PKD^[37]. Extending this concept, we reasoned that identification of signaling intermediates which: (1) regulate multiple steps in a single pathophysiological pathway; in addition to acting as; and (2) an integration point for multiple signaling cascades may provide even greater benefit than EGFR combination therapy noted above. Key integration points for targeting to prevent disease progression include the activation of the EGFR axis, c-Src, and VEGFR2 by specific kinases^[3,34,40,45-50] and cAMP signaling^[51-53]. This led us to examine the potential of a novel multi-kinase inhibitor, TSV, in preventing progression of ARPKD.

Given the differences in route of administration, the speed of disease development and the fact that the measure of the disease burden in the kidney and liver are model specific make direct comparison of the results in bpk and PCK unreliable. It is also difficult to compare these results to other interventional therapies we have attempted in these models because we tested two doses only on the basis of recommendations from Kadmon. Never the less the current study demonstrates that TSV ameliorates the progression of renal cystic disease in two well characterized rodent models of ARPKD. Further, TSV's inhibition of the phosphorylation of c-Src, EGFR and ErbB2 led to significant reduction of MAPK activity (ERK 1/2 phosphorylation), and resultant cellular proliferation. In addition to amelioration of renal cystic disease, TSV also led to significant reduction in the biliary ductal abnormalities characteristic of ARPKD

in BPK and in the LW/BW ratios of PCK. The results of the current study also indicate that the use of a multi-kinase inhibitor that targets angiogenesis driven by KDR or VEGFR2 can be an effective and safe therapy during postnatal renal maturation and development.

Preliminary data from the ongoing phase II clinical trial of TSV (KD-019) for treatment of ADPKD (<https://ClinicalTrials.gov/ADPKD>: NCT01559363) presented at the American Society of Nephrology 2015 annual meeting reported: (1) QTc prolongation to ≥ 485 ms was seen in 2/8 pts treated with 100 mg/d; (2) The half-life in adults allowed for intermittent dosing which improved tolerability; (3) The most common AEs were those associated with EGFR kinase inhibition: Diarrhea; nausea; and acneiform rash; and (4) 50 mg/d appeared to be safe and well tolerated and additional patients were being enrolled at this dose to confirm the safety profile^[54].

On balance, these data suggest that TSV may be a safe and effective therapy for childhood ARPKD.

COMMENTS

Background

The study detailed here was designed to ascertain if a multi-kinase inhibitor "tesevatinib" would effectively slow the growth of renal cysts and reduce the loss of renal function in two well characterized models of autosomal recessive polycystic kidney disease (ARPKD). This compound targets the EGFR axis, cSrc and it inhibits angiogenesis by preventing phosphorylation of VEGFR2 (also called KDR). The bpk mouse was chosen to examine the effect of KDR inhibition on post-natal development and the orthologous PCK was chosen to examine the effect of oral dosing on inhibition of the target signaling pathways. Tesevatinib inhibit renal cyst growth in both models without overt signs of toxicity.

Research frontiers

This study demonstrated that there is indeed considerable overlap in the aberrant signaling cascades in ARPKD and autosomal dominant polycystic kidney disease (ADPKD). This raises the hope that the lessons learned from therapeutic interventions in ADPKD can be adapted for ARPKD patients.

Innovations and breakthroughs

The most exciting result of this study is that inhibition of angiogenesis, an important component of cyst growth, can now be added to arsenal to slow cyst growth when activity (phosphorylation) is cautiously reduced to normal or wildtype levels. This inhibition with tesevatinib contributed to the amelioration of cyst growth without overt signs of toxicity even in early post-natal development.

Applications

The value of these results is that effective therapies developed and tested for ADPKD patients can be for use in ARPKD patients. A multi-kinase drug with multiple targets theoretically would reduce the amount of compound necessary to achieve equivalent results compared to amounts needed with single target drugs. This effectively reduces the exposure to the compounds and would result in reduced toxicity and potentially allow long term use of the therapeutic compound. This should accelerate the use of therapeutic compounds in clinical trials of ARPKD patients.

Terminology

The activity of a kinase refers to the phosphorylation state of the molecule. It generally means the target molecule becomes phosphorylated and this results in increased activity until it is de-phosphorylated by another molecule. A multi-kinase inhibitor is a compound that targets multiple signaling components simultaneously and can prevent phosphate from binding to and activating the signaling components thus rendering the molecule useless. This occurs

simultaneously and provides a means hitting two or more targets with a single compound.

Peer-review

This paper was well-written.

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Retrospective Study

Reproducibility of serial creatinine excretion measurements in peritoneal dialysis

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Institutional review board statement: This study was reviewed and approved by the Human Research Committee of the Raymond G. Murphy VA Medical Center.

Informed consent statement: Patients were not required to give informed consent to this retrospective study because the study used anonymous clinical data obtained to evaluate adequacy of dialytic treatment. Each patient has agreed to the dialytic treatment and the collection of the data used in the study. The institutional Human Research Committee approved the use of these data for this study without a signed informed consent.

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Abstract

AIM

To test whether muscle mass evaluated by creatinine excretion (EX_{Cr}) is maintained in patients with end-stage kidney disease (ESKD) treated by peritoneal dialysis (PD), we evaluated repeated measurements of EX_{Cr} in a PD population.

METHODS

One hundred and sixty-six PD patients (94 male, 72 female) receiving the same PD dose for the duration of the study (up to approximately 2.5 years) had repeated determinations of total (in urine plus spent dialysate) 24-h EX_{Cr} (EX_{Cr} T) to assess the adequacy of PD by creatinine clearance. All 166 patients had two EX_{Cr} T determinations, 84 of the 166 patients had three EX_{Cr} T determinations and 44 of the 166 patients had four EX_{Cr} T measurements. EX_{Cr} T values were compared using the paired *t* test in the patients who had two studies and by repeated measures ANOVA in those who were studied three or four times.

RESULTS

In patients who were studied twice, with the first and second EX_{Cr} T measurements performed at 9.2 ± 15.2 mo and 17.4 ± 15.8 mo after onset of PD, respectively, EX_{Cr} T did not differ between the first and second study. In patients studied three times and whose final assessment occurred 24.7 ± 16.3 mo after initiating PD, EX_{Cr} T did not differ between the first and second study, but was significantly lower in the third study compared to the first study. In patients who were studied four times and whose fourth measurement was taken 31.9 ± 16.8 mo after onset of PD, EX_{Cr} T did not differ between any of the studies. The average EX_{Cr} T value did not change significantly, with the exception of the third study in the patients studied thrice. However, repeated determinations of EX_{Cr} T in individuals showed substantial variability, with approximately 50% of the repeated determinations being higher or lower than the first determination by 15% or more.

CONCLUSION

The average value of EX_{Cr} T remains relatively constant for up to 2.5 years of follow-up in PD patients who adhere to the same PD schedule. However, repeated individual EX_{Cr} T values vary considerably in a large proportion of the patients. Further studies are needed to evaluate the clinical significance of varying EX_{Cr} T values and the stability of EX_{Cr} T beyond 2.5 years of PD follow-up.

Key words: Creatinine excretion; Peritoneal dialysis; Lean body mass; Muscle mass

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Core tip: Total creatinine excretion (EX_{Cr}) in urine and in the used peritoneal dialysis (PD) fluid is correlated with muscle mass and has been shown to predict survival and morbidity of patients on PD. This retrospective study

evaluated the long-term constancy of 24-h excretion of creatinine in urine and spent peritoneal dialysate from patients with end-stage kidney disease treated by PD. Over a period of 2.5 years, the average value of total EX_{Cr} in the study population did not change significantly. However, in individuals there was a substantial variation of repeated measurements of total EX_{Cr} above or below its initial value. Approximately half of those studied repeatedly exhibited total EX_{Cr} above or below its initial value. Further studies are needed to evaluate changes, both increase and decrease, of EX_{Cr} in PD patients and the constancy of EX_{Cr} in patients on PD for more than 2.5 years.

Xu Z, Murata GH, Sun Y, Glew RH, Qualls C, Vigil D, Servilla KS, Golper TA, Tzamaloukas AH. Reproducibility of serial creatinine excretion measurements in peritoneal dialysis. *World J Nephrol* 2017; 6(4): 201-208 Available from: URL: <http://www.wjgnet.com/2220-6124/full/v6/i4/201.htm> DOI: <http://dx.doi.org/10.5527/wjn.v6.i4.201>

INTRODUCTION

An elevated serum creatinine concentration ($[Cr]_s$) is a predictor of prolonged survival in patients undergoing chronic peritoneal dialysis (PD)^[1]. $[Cr]_s$ is largely a function of muscle mass and is widely regarded as a reliable indicator of somatic nutrition. Exercising muscles secrete a variety of myokines with beneficial effects on various organ systems, including anti-inflammatory effects^[2]. Physical inactivity leads to altered pattern of myocyte secretion promoting obesity and atherogenesis^[2]. Inactivity is prominent among patients treated by chronic dialysis. McIntyre *et al*^[3] reported a tendency to muscle mass depletion in this patient group. However, a significant limitation of $[Cr]_s$ as an indicator of somatic nutrition is reliance on this parameter as the sole determinant of muscle mass. In the steady state, which is defined as equal rates of creatinine production and elimination, $[Cr]_s$ has two physiological determinants, the rate of production of creatinine (P_{Cr}) which is a function of muscle mass, and the rate of removal of creatinine from body fluids, which is expressed as creatinine clearance (C_{Cr}). This relation is expressed as $[Cr]_s = P_{Cr}/C_{Cr}$. Consequently, variations in C_{Cr} in patients on PD can result in variations in $[Cr]_s$ that are unrelated to muscle mass^[4].

In the steady state, the total amount of creatinine excreted in spent PD dialysate plus urine over a certain time period (EX_{Cr} T) is in general a better index of muscle mass than $[Cr]_s$. Conditions in which EX_{Cr} T does not reflect muscle mass are addressed in the Discussion section of this report. EX_{Cr} T over 24 h has been proposed by Walser^[5] as an index of somatic nutrition in the general adult population and has been evaluated in PD populations. Whereas high EX_{Cr} T values are

associated with favorable outcomes, including survival and continued success of PD^[6,7], low values of $EX_{Cr} T$ are associated with a high risk of peritonitis and PD catheter-related infections^[8].

The lean body mass formula from creatinine production (LBM_{Cr}) in PD patients^[9] takes into account $EX_{Cr} T$ and creatinine eliminated through metabolic creatinine degradation (MCD), the second variable at a clearance of 0.038 L/kg^[10]. MCD per 24-h is calculated as $0.038 \times [Cr]_s$ (mg/mL) $\times 10 \times$ weight (kg). $EX_{Cr} T$ is invariably the larger of the two determinants of LBM_{Cr} . For example, in a 53-year old PD patient who weighs 70 kg and has a $[Cr]_s$ value of 9.5 mg/dL, estimated MCD rate will be 253 mg/24-h. Applying a PD population-specific formula predicting $EX_{Cr} T$ ^[11] to this illustrative example, average estimates of $EX_{Cr} T$, in mg/24-h, are 1062 if the patient is male and non-diabetic, 1023 if the patient is male and diabetic, 892 if the patient is female and non-diabetic and 852 if the patient is female and diabetic. High LBM_{Cr} values predict long survival of PD patients^[12-14].

The short-term reproducibility of $EX_{Cr} T$ in PD was studied by Lo and coauthors, who obtained two to four 24-h collections of urine and spent dialysate over a one-week interval from five patients undergoing PD^[15]. These authors reported maximal variations of $EX_{Cr} T$ from the mean ranging between 0.32% and 19.88%. The purpose of the present study was to investigate the reproducibility of $EX_{Cr} T$ in patients on long-term PD. Changes in renal function or peritoneal transport characteristics will change the amount of creatinine removed through each route. However, regardless of such changes steady state long-term constancy of $EX_{Cr} T$ is consistent with preservation of muscle mass in PD patients. In contrast, a progressive decrease in $EX_{Cr} T$ during PD would indicate progressive loss of muscle mass and deterioration of somatic nutrition.

MATERIALS AND METHODS

We analyzed creatinine excretion data collected during routine clearance measurements for assessment of the adequacy of PD. Patients included in this study were followed in Albuquerque during the years 1992 to 2002. Only patients in whom the prescribed dose of PD did not change during the observation period were included in the study. Approximately 40% of the patients were receiving continuous ambulatory peritoneal dialysis (CAPD) with four or five daily exchanges and 2.0-L or 2.5-L fill volume. The remaining patients received nocturnal automatic PD with 8-10 L fill volume plus one or two daytime PD exchanges with 2.0 L fill volume. Serum ($[Cr]_s$) at the study differed from the preceding or following monthly value by < 0.30 mg/dL in all patients. None of the patients were receiving drugs causing increased creatinine production (e.g., fenofibrate).

The focus of the study was on detecting a statistically significant decline in $EX_{Cr} T$. The minimal number of patients required to detect a 15% reduction

in $EX_{Cr} T$ over time was calculated by power analysis. For a simple power analysis, we considered repeated measurements at two points in time and assumed a correlation of 0.7 between these two samples and a standard deviation of $EX_{Cr} T$ equal to 450 mg/24-h (see Tables in Results). The power and α value of the study were set at 80% and 0.05 respectively.

Between the sequential clearance studies we compared the following variables: Urine volume (V_u), drain volume (V_d), weekly Kt/V urea, weekly C_{Cr} , serum urea nitrogen level (SUN), $[Cr]_s$, EX_{Cr} in urine ($EX_{Cr} U$), EX_{Cr} in dialysate ($EX_{Cr} D$), and total creatinine excretion in urine plus dialysate ($EX_{Cr} T$).

Statistical analysis

Results are reported as mean $\pm$ SD. Statistical comparisons were carried out using the two-tailed paired *t* test for patients with two clearance studies and the repeated measures ANOVA for patients who had three or four clearance studies. Statistical analysis was performed using SAS version 9.4.

RESULTS

Power analysis computed a minimal sample size of 37 patients for detecting a 15% decline in $EX_{Cr} T$. A total of 166 PD patients who had been subjected to at least two clearance studies comprised the initial study group. Among these patients, 84 patients had three clearance studies and 44 patients had four clearance studies. Small number of patients, eight or less, underwent five or more studies. Consequently, this study includes patients who had two, three and four clearance studies.

Table 1 summarizes relevant features of the patients included in the report. There were no significant differences between the three subgroups in terms of the age of patients at the onset of PD, percent of males and females or percent of patients with end-stage renal disease secondary to diabetic nephropathy.

Table 2 compares variables related to creatinine excretion in patients with two clearance studies. Between the first and second clearance study V_u , total Kt/V urea, total C_{Cr} , and $EX_{Cr} U$ decreased, $[Cr]_s$ and $EX_{Cr} D$ increased, while V_d , SUN and $EX_{Cr} T$ did not change significantly. Peritoneal C_{Cr} did not change while renal C_{Cr} decreased from the first to the second study. Average peritoneal ($C_{Cr} P$) and renal ($C_{Cr} R$) weekly C_{Cr} , expressed in L/1.73 m² throughout this report, values were as follows: $C_{Cr} P$ 48.7 in the first and 49.5 in the second study; $C_{Cr} R$ 29.1 in the first and 18.4 in the second study.

Table 3 compares variables in patients who were studied three times. V_u , total Kt/V urea, total C_{Cr} and $EX_{Cr} U$ decreased progressively from the first to the third measurement, while $EX_{Cr} T$ was significantly lower in the third study than in the first study. V_d and SUN did not change, while $[Cr]_s$ increased; however, the increasing trend in $EX_{Cr} D$ did not reach statistical significance. Peritoneal C_{Cr} did not change while renal

Table 1 Patient characteristics *n* (%)

	Two clearance studies	Three clearance studies	Four clearance studies
Patient number	166	84	44
Age at onset of peritoneal dialysis, yr	52 ± 15	51 ± 16	51 ± 18
Male	94 (56.6)	46 (54.8)	26 (59.1)
Female	72 (43.4)	38 (45.2)	18 (40.9)
Diabetic nephropathy	73 (44.0)	36 (42.9)	17 (38.6)

Table 2 Creatinine excretion in patients with two studies

Variable	1 st clearance study	2 nd clearance study	<i>P</i> value
PD duration, mo	9.2 ± 15.2	17.4 ± 15.8	
VU, L/24-h	0.54 ± 0.63	0.40 ± 0.53	< 0.001
VD, L/24-h	11.3 ± 3.2	12.1 ± 3.6	NS
Kt/V urea, weekly	2.30 ± 0.62	2.12 ± 0.03	0.003
C _{cr} , L/1.73 m ² , weekly	77.9 ± 32.1	67.9 ± 18.2	0.002
SUN, mg/dL	49.7 ± 15.1	49.4 ± 16.2	NS
[Cr] _s , mg/dL	9.1 ± 3.3	10.1 ± 3.4	0.001
EX _{cr} U, mg/24-h	406 ± 337	286 ± 350	0.003
EX _{cr} D, mg/24-h	680 ± 337	769 ± 390	< 0.001
EX _{cr} T, mg/24-h	1087 ± 470	1055 ± 421	NS

PD: Peritoneal dialysis; NS: Not significant; VU: Urine volume; VD: Drained volume of spent dialysate; Kt/V urea: Fractional urea clearance, weekly; C_{cr}: Weekly renal plus peritoneal creatinine clearance; SUN: Serum urea nitrogen; [Cr]_s: Serum creatinine concentration; EX_{cr} D: Creatinine excretion in spent dialysate; EX_{cr} U: Creatinine excretion in urine; EX_{cr} T: Total creatinine excretion in urine plus dialysate.

C_{cr} decreased progressively from the first to the third study. Average weekly C_{cr} P and C_{cr} R values were as follows: C_{cr} P 50.5 in the first, 48.2 in the second and 49.7 in the third study; C_{cr} R 28.8 in the first, 23.2 in the second and 18.3 L/1.73 m² in the third study.

Table 4 compares clearances and creatinine excretion parameters in patients who had four clearance studies. V_u, total Kt/V urea and total C_{cr} decreased progressively from the first to the fourth determination. EX_{cr} U decreased significantly between the first and third studies, but reached a stable mean between the third and fourth studies. [Cr]_s increased progressively from the first to the third study; however, the mean values were not different between in the third and fourth studies. V_D and SUN were essentially the same in the four studies. EX_{cr} D increased progressively from the first to the fourth study, whereas EX_{cr} T did not change significantly throughout the study. Peritoneal C_{cr} did not change while renal C_{cr} decreased progressively from the first to the fourth study. Average weekly C_{cr} P and C_{cr} R values were as follows: C_{cr} P 50.2 in the first, 47.4 in the second, 51.2 in the third and 49.7 in the fourth study; C_{cr} R 27.3 in the first, 23.0 in the second, 17.3 in the third and 16.4 L/1.73 m² in the fourth study.

Table 5 shows the results (number and percent) of the second, third and fourth studies where EX_{cr}

Table 3 Creatinine excretion in patients with three studies

Variable	1 st clearance study	2 nd clearance study	3 rd clearance study	<i>P</i> value
PD duration, mo	8.6 ± 7.8	16.8 ± 11.6	24.7 ± 16.3	
VU, L/24-h	0.58 ± 0.66	0.45 ± 0.59	0.38 ± 0.50	0.0001
VD, L/24-h	11.5 ± 4.0	11.8 ± 3.7	12.4 ± 3.7	NS
Kt/V urea, weekly	2.28 ± 0.65	2.14 ± 0.58	2.12 ± 0.63	0.0245
C _{cr} , L/1.73 m ² , weekly	79.3 ± 35.6	71.4 ± 27.8	68.0 ± 26.9	0.0335
SUN, mg/dL	50.4 ± 18.5	49.5 ± 17.9	49.2 ± 19.2	NS
[Cr] _s , mg/dL	9.5 ± 3.5	9.8 ± 3.4	10.1 ± 3.3	0.0066
EX _{cr} U, mg/24-h	418 ± 404	370 ± 425	286 ± 362	< 0.0001
EX _{cr} D, mg/24-h	731 ± 379	767 ± 396	779 ± 382	NS ¹
EX _{cr} T, mg/24-h	1149 ± 416	1137 ± 454	1065 ± 442	0.0087

¹Statistical trend (*P* = 0.0895). PD: Peritoneal dialysis; NS: Not significant; VU: Urine volume; VD: Drained volume of spent dialysate; Kt/V urea: Fractional urea clearance, weekly; C_{cr}: Weekly renal plus peritoneal creatinine clearance; SUN: Serum urea nitrogen; [Cr]_s: Serum creatinine concentration; EX_{cr} D: Creatinine excretion in spent dialysate; EX_{cr} U: Creatinine excretion in urine; EX_{cr} T: Total creatinine excretion in urine plus dialysate.

T differed from the EX_{cr} T of the first study by less than 15%. The same table also shows the number and percent of studies with EX_{cr} T higher or lower than the EX_{cr} T of the first study by 15% or more. In approximately half of the second, third and fourth studies EX_{cr} T differed from the first study by less than 15%. In 25.0%-33.3% of the patients, EX_{cr} T values in subsequent studies were higher than the EX_{cr} T value found in the first study by more than 15%. In 19.1%-21.1% of the patients, EX_{cr} T in subsequent studies was lower than the EX_{cr} T in the first study by more than 15%.

DISCUSSION

This study had two important findings: First the mean EX_{cr} T value did not change significantly in 2.5 years of follow-up of patients who were on the same PD schedule for the duration of the study, with the exception of a lower mean EX_{cr} T in the third study than in the first study in EX_{cr} data analyzed thrice. The constancy of the mean EX_{cr} T was maintained despite a progressive decrease in urinary volume, urinary C_{cr} and urinary EX_{cr}. Increases in peritoneal EX_{cr} associated with parallel rises in [Cr]_s offset the declines in renal EX_{cr}. Second, in about half of the patients, individual values of EX_{cr} T varied substantially in clearance studies following the initial study. These findings have important clinical implications.

The finding of unchanged EX_{cr} T suggests that the muscle mass of the average patient who remains on PD for 2.5 years is preserved. This observation points to stable creatinine production, and preserved muscle mass, as favorable predictors of outcomes of PD; however, this issue will require further investigation. The finding of great variation of individual EX_{cr} T values on repeated measurements should prompt investigation of the factors affecting EX_{cr} T in PD in addition to changes

Table 4 Creatinine excretion in patients with four clearance studies

Variable	1 st clearance study	2 nd clearance study	3 rd clearance study	4 th clearance study	P value
PD duration, mo	8.1 ± 12.6	16.5 ± 4.4	24.5 ± 16.3	31.9 ± 16.8	
VU, L/24-h	0.54 ± 0.55	0.41 ± 0.49	0.33 ± 0.40	0.29 ± 0.42	< 0.0001
VD, L/24-h	11.8 ± 3.9	12.2 ± 3.6	12.2 ± 3.5	12.5 ± 3.2	NS
Kt/V urea, weekly	2.27 ± 0.65	2.15 ± 0.56	2.13 ± 0.54	2.10 ± 0.55	0.0356
C _{Cr} , L/1.73 m ² , weekly	77.5 ± 29.7	70.4 ± 28.5	68.5 ± 25.7	66.1 ± 22.1	0.0238
SUN, mg/dL	49.8 ± 16.7	49.5 ± 15.4	49.2 ± 15.3	49.0 ± 13.5	NS
[Cr] _s , mg/dL	9.8 ± 3.6	10.2 ± 3.7	10.8 ± 3.8	10.8 ± 3.6	0.0009
EX _{Cr} U, mg/24-h	411 ± 438	382 ± 460	272 ± 345	282 ± 481	0.0011
EX _{Cr} D, mg/24-h	755 ± 406	788 ± 424	808 ± 438	853 ± 398	0.0021
EX _{Cr} T, mg/24-h	1166 ± 440	1170 ± 495	1080 ± 455	1135 ± 521	NS

PD: Peritoneal dialysis; NS: Not significant; VU: Urine volume; VD: Drained volume of spent dialysate; Kt/V urea: Fractional urea clearance, weekly; C_{Cr}: Weekly renal plus peritoneal creatinine clearance; SUN: Serum urea nitrogen; [Cr]_s: Serum creatinine concentration; EX_{Cr} D: Creatinine excretion in spent dialysate; EX_{Cr} U: Creatinine excretion in urine; EX_{Cr} T: Total creatinine excretion in urine plus dialysate.

Table 5 Number (percent) of studies with creatinine excretion deviating from baseline by < 15% and ≥ 15%

Study	< 15% from the 1 st study	≥ 15% above the 1 st study	≥ 15% below the 1 st study
Second	90 (54.2%)	41 (24.7%)	35 (21.1%)
Third	40 (47.6%)	28 (33.3%)	16 (19.1%)
Fourth	24 (54.5%)	11 (25.0%)	9 (20.5%)

in the muscle mass.

One factor that can affect EX_{Cr} T is a change in total C_{Cr}. Mitch and Walser computed a “metabolic” C_{Cr} equal to 0.038 L/kg per 24-h in patients with renal failure mediated primarily by creatinine elimination through the gastrointestinal tract^[16]. As [Cr]_s levels increase progressively in advancing renal failure, the amount of creatinine removed through the metabolic-route increases progressively with a concomitant decrease in the measured renal EX_{Cr}^[16].

Large increases in total C_{Cr} in PD patients lead in the steady state to drop in [Cr]_s and in creatinine removal by the “metabolic” route and increase in EX_{Cr} T. In a previous study, we noted an increase in EX_{Cr} T in PD patients whose measured total (peritoneal plus renal) C_{Cr} was increased, with proportional decrease in [Cr]_s, following prescribed increases in the PD dose^[17]. This was the reason for including in the present study only patients with unchanged PD schedules. No effect of the decrease in total C_{Cr} through loss of renal function on EX_{Cr} T was seen in this study even when total C_{Cr} decreased by 11.4 L/1.73 m² weekly, on the average, between the first and fourth measurements (Table 4). We suggest that the increase in the amount of creatinine removed by the metabolic route due to the rise in [Cr]_s between these two measurements was too small to be detected by our statistical analysis. On average, [Cr]_s rose by 1.0 mg/dL between the first and fourth clearance study (Table 4). With this degree of increase in [Cr]_s, the rise in the amount of creatinine removed through the metabolic route at a C_{Cr} of 0.038 L/kg per 24-h would be only 26.6 mg/24-h in an individual weighing 70 kg.

Creatinine is formed by non-enzymatic breakdown of creatine-phosphate. Variations in the rate of creatine-phosphate conversion to creatinine may cause changes in EX_{Cr} T that are independent of changes in muscle mass. Neuromuscular diseases^[18] and the stage of recovery from protein malnutrition^[19] are examples of conditions characterized by abnormal creatine metabolism which leads to dissociation between creatinine production and muscle mass. In addition, neuromuscular diseases affect creatinine production and excretion through their effect on muscle mass homeostasis. The loss of muscle mass secondary to chronic neuromuscular disease is one of the major causes of decreases in creatinine production and EX_{Cr} T. Acute muscular disease, (e.g., rhabdomyolysis) however, increases creatinine production. Rhabdomyolysis can result from disease, poisons and medications exemplified by lipid-lowering agents^[20]. Other conditions causing increases in creatinine production and EX_{Cr} T include pregnancy^[21], consumption of meat and intense exercise^[22].

Circumstances that raise EX_{Cr} T without affecting creatinine production include errors in the collection of urine and spent dialysate and the presence of a non-steady state. Non-steady state following a rapid rise in C_{Cr} will increase EX_{Cr} T and decrease [Cr]_s. A hemodialysis session represents such a non-steady state condition. PD patients, who are non-compliant with their PD prescription and resume the prescribed PD schedule on the day of a clearance study will manifest a similar non-steady state. A high value of measured EX_{Cr} T over the EX_{Cr} T predicted by the Cockcroft-Gault formula^[23] (M/P_{Cr}) was proposed as a means of identifying non-compliance in PD^[24]. Although some

studies supported the use of the M/P_{Cr} ratio as a means of detecting PD non-compliance^[25,26], several reports confirmed that the sensitivity of this test is poor^[27-32]. Nevertheless, noncompliance will invariably increase EX_{Cr} T on the first day of resumption of the prescribed PD schedule^[28] and can be an important cause of the variation of EX_{Cr} T.

Conditions that can potentially lead to low EX_{Cr} T values include decreased production of creatinine, urine and dialysate collection errors, and intercurrent acute illnesses. This last category has not been studied adequately in PD patients. In acute illness, creatinine production could be temporally increased because of muscle disease or decreased because of loss of muscle mass. In one study, PD-associated peritonitis with routine course resulted in a 2.3% drop in body weight and 7.8% drop in $[Cr]_s$, while peritonitis with a protracted course resulted in a 7.2% drop in body weight and 25.0% drop in $[Cr]_s$ ^[33]. These findings suggest a loss of muscle mass proportional to the duration of peritonitis. However, an increase in peritoneal C_{Cr} secondary to peritoneal membrane inflammation could also cause a drop in $[Cr]_s$. EX_{Cr} data, which would allow differentiation between a rise in C_{Cr} and a loss of muscle mass as the cause of the decrease in $[Cr]_s$ were not provided in this study. The effects of acute illness on EX_{Cr} in PD will need further studies.

A final consequence of all the aforementioned influences on EX_{Cr} T is their effect on the estimation of LBM_{Cr} . Two studies reported agreement between LBM_{Cr} and estimation of lean body mass by research methodologies^[34,35]. Another study suggested that determination of lean body mass as LBM_{Cr} has advantages over its determination by bioimpedance or dual energy X-ray absorptiometry in overhydrated PD patients^[36]. However, several studies have reported substantial differences between LBM_{Cr} and other methods used to assess muscle mass and between LBM_{Cr} and other indices of nutrition in PD patients^[35,37-42]. Nevertheless, one of these studies did support the monitoring of EX_{Cr} T as a means of assessing changes in muscle mass^[37].

Our study has limitations: First, selection bias could have led to the finding of stable creatinine excretion with stable patients remaining on PD for longer time. Related to this limitation, clinical information and data on other indices of nutrition associated with the observed changes in EX_{Cr} T were not available for analysis. Second, the data available to us do not allow us to address whether any of the known determinants of creatinine excretion in patients treated by PD (body weight, age, gender, and diabetic status) can predict a decrease or increase in their EX_{Cr} T. Finally, monitoring of EX_{Cr} T beyond 2.5 years after initiation of PD was not performed because of the small number of such subjects. Future studies should address these limitations.

In conclusion, average EX_{Cr} T remains stable for up to 2.5 years in patients who are maintained on the

same PD schedule, despite a progressive loss of residual renal function which causes a progressive decline in urinary flow rate, C_{Cr} and EX_{Cr} . This finding suggests that the muscle mass of the average patient who remains on PD during this same time period is preserved. However, many patients exhibit substantial variability of EX_{Cr} T in sequential measurements. Both increases and decreases in EX_{Cr} T of individual patients managed by PD call for a systematic search for the conditions responsible for these changes. Further studies are also needed to evaluate the stability of EX_{Cr} T beyond 2.5 years of PD and the potential associations of changes in EX_{Cr} T with clinical outcomes and other indices of nutrition.

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COMMENTS

Background

In the steady state, defined as equal rates of production and removal, creatinine excretion reflects muscle mass. Loss of muscle mass has adverse effects on the outcomes of patients with chronic diseases, including patients with end-stage kidney disease treated by peritoneal dialysis (PD). High levels of creatinine excretion are associated with favorable outcomes in this patient population. The prevalence of adverse influences (*e.g.*, inactivity, chronic inflammatory state) in PD populations suggests loss of muscle mass in long-term PD. Repeated measurement of creatinine excretion in patients on long-term PD, which represents a steady state, provide a means of monitoring muscle mass.

Research frontiers

Muscle mass can be evaluated by several research methods. These methods require expenses and added expertise of the research personnel and, therefore, are not suitable for routine monitoring of PD populations.

Innovations and breakthroughs

Repeated measuring of total excretion of creatinine in spent peritoneal dialysate and urine offers a way of monitoring muscle mass in PD patients. Creatinine excretion measurements have been performed as part of monitoring adequacy of azotemic indices removal in PD. Comparison of subsequent creatinine excretion measurements to the first measurement, as used in this study, is simple and does not require added expenses.

Applications

The methodology explored in this report is appropriate for monitoring patients on long-term PD and for evaluating interventions (*e.g.*, exercise, diet) directed towards preserving or improving muscle mass in these patients.

Terminology

The following abbreviations express the technique for monitoring creatinine excretion in PD: EX_{Cr} U = urinary creatinine excretion, mg/24-h; EX_{Cr} D = creatinine excretion in spent peritoneal dialysate, mg/24h; EX_{Cr} T = EX_{Cr} U + EX_{Cr} D.

Peer-review

In this manuscript, the authors describe the reproducibility of serial creatinine excretion measurements in PD patients. They concluded that the average total creatinine excretion in urine plus dialysate (EX_{Cr} T) remains stable for up to 2.5

years in patients who are maintained on the same PD schedule, despite the progressive loss of residual renal function which causes a progressive decline in the urinary flow rate, renal plus peritoneal creatinine clearance (Ccr), and creatinine excretion (EXcr). They also suggested that the muscle mass was preserved in the average patient who remained on PD during this time period. This paper is clinically interesting.

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Observational Study

Exercise-induced albuminuria and circadian blood pressure abnormalities in type 2 diabetes

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Abstract

AIM

To investigate the relationship between circadian variations in blood pressure (BP) and albuminuria at rest, and during exercise in non-hypertensive type 2 diabetes (T2D) patients.

METHODS

We conducted a cross-sectional study in well controlled T2D patients, non-hypertensive, without clinical proteinuria and normal creatinine clearance. In each participant, we recorded the BP using ambulatory blood

pressure monitoring (ABPM) for 24-h, and albuminuria at rest and after a standardized treadmill exercise.

RESULTS

We enrolled 27 type 2 patients with a median age of 52; and a mean duration of diabetes and HbA1c of 3.6 ± 0.8 years and $6.3\% \pm 0.5\%$ respectively. Using a 24-h ABPM, we recorded a mean diurnal systolic blood pressure (SBP) of 128 ± 17 mmHg *vs* nocturnal of 123 ± 19 mmHg ($P = 0.004$), and mean diurnal diastolic blood pressure (DBP) of 83 ± 11 mmHg *vs* nocturnal 78 ± 14 mmHg ($P = 0.002$). There was a significant difference between albuminuria at rest [median = 23 mg, interquartile range (IQR) = 10-51] and after exercise (median = 35 mg, IQR = 23-80, $P < 0.001$). Patients with exercise induced albuminuria had an increase in nocturnal BP values on all three components (128 mmHg *vs* 110 mmHg, $P = 0.03$ for SBP; 83 mmHg *vs* 66 mmHg, $P = 0.04$; 106 *vs* 83 , $P = 0.02$ for mean arterial pressure), as well as albuminuric patients at rest. Moreover, exercise induced albuminuria detect a less increase in nocturnal DBP (83 *vs* 86 , $P = 0.03$) than resting albuminuria.

CONCLUSION

Exercise induced albuminuria is associated with an increase in nocturnal BP values in T2D patients.

Key words: Albuminuria; Ambulatory measurement of blood pressure; Exercise; Type 2 diabetes mellitus

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Core tip: Many studies have reported association between abnormalities in ambulatory blood pressure monitoring (ABPM) and albuminuria at rest, or the link between exercise induced albuminuria and future development of microalbuminuria. However, the relationship between exercise-induced albuminuria and nocturnal abnormalities of BP on ABPM have not been investigate. The current study aimed to investigate the potential relationship between exercise-induced albuminuria and circadian variations in BP in a sub-Saharan type 2 diabetes population. We found that exercise-induced albuminuria is associated with less important nocturnal abnormalities of BP than resting albuminuria suggesting that exercise-induced albuminuria be used to detect early abnormalities of nighttime BP.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is the leading cause

of chronic kidney disease (CKD) worldwide^[1,2]. It represents with hypertension - the most common cause of end-stage renal disease (ESRD); affecting at least one-third of patients starting chronic dialysis worldwide, and represents the main cause of mortality in diabetes patients^[3]. Early detection and intervention in diabetic nephropathy can help to slow loss in renal function, prevent complications, and decrease cardiovascular events; thereby improving survival and quality of life in T2DM patients^[3]. As the global incidence of T2D continues to rise, controlling diabetic nephropathy is becoming a health priority. Fifty years ago, the development of assays for detection of microalbuminuria (MA) revolutionized diabetes management. Microalbuminuria, also called moderate albuminuria (urinary albumin excretion ≥ 30 mg/24 h but less than 300 mg/24 h), measured at rest became the earliest marker of diabetic nephropathy, and was thought to predict overt diabetic nephropathy in 80% of patients^[4]. However, recent evidence have shown that only 30% of patients with microalbuminuria will develop overt diabetic nephropathy^[5]. Moreover, screening with albumin excretion rate alone would miss 20% of progressive disease^[6]. These evidences suggest that a need for methods for early detection of diabetic nephropathy. Physiologically, it is well known that patients with subclinical nocturnal blood pressure (BP) abnormalities are prone to renal insult and hence at risk of developing microalbuminuria^[7]. So, non-dipping nocturnal BP pattern defined as a less than 10% decrease in nocturnal BP, increase the risk of organ damage such as microalbuminuria^[7]. In the other hand, exercise-induced albuminuria has been proposed as a long term predictive factor of overt diabetic nephropathy, but there is still a dearth of evidence on its usefulness in routine screening^[8]. We sought to explore a possible relationship between resting and exercise-induced albuminuria, and circadian variations in BP levels on 24-h ambulatory blood pressure monitoring (ABPM).

MATERIALS AND METHODS

Setting and study population

This study was carried out at the National Obesity Center of the Yaoundé Central Hospital, a reference diabetes center in this area. Eligible participants were: Type 2 diabetics, according to the WHO definition^[9]; without clinical proteinuria (≤ 30 mg/dL), with clinical BP less than 140/90 mmHg, HbA1c less than 7%, an estimated glomerular filtration rate (eGFR) ≥ 60 mL/min per square meter using the MDRD formula which was found to be the most accurate formula for sub-Saharan African diabetic patients^[10]. We excluded patients working during the night, those receiving drugs for hypertension or any other drugs able to modify albuminuria, patients with contraindication to exercise or presenting signs of urinary tract infection. Patients having a fever and pregnant women were also

excluded. All patient included were on oral anti-diabetic treatment.

Study design and duration: This was a cross sectional study conducted from February to June 2015 a period of five months.

Procedure and investigations

This study was conducted to investigate the relationship between exercise-induced albuminuria and early diabetic nephropathy assessed by nocturnal elevation of ABPM. To this end, albuminuria was measured at rest for microalbuminuria, and after a moderate and standardized exercise for exercise induced albuminuria. Then comparison between patients were planned to shows that exercise induced albuminuria is similar or even higher to microalbuminuria at rest for the detection of abnormal nocturnal BP patterns.

All the patients attending the clinic were assessed, and eligible patients were invited to participate to the study. The procedure was comprised of an inclusion visit and three exploratory visits. Within the two weeks following an information visit, a careful clinical exam including BP measurement, urinary dipstick exam, and resting electrocardiogram were performed on eligible patients. The sample size was estimated using Withley *et al*^[11] formula: $n = (2/d^2) \times Cp, \text{ power}$.

The primary outcome was a significant difference of at least 10 mmHg of SBP and/or DBP in patients having exercise induced albuminuria. The standardized difference for BP in T2DM patients used was set at 10 mmHg (UKPDS). Considering $\alpha = 5\%$ and $\beta = 10\%$, with a statistical power of 90%, the minimal size was 11 patients.

The standardized difference, $d = (\text{expected difference})/(\text{standard deviation})$: $D = 10/10 = 1$.

$N = (2/d^2) \times Cp, \text{ power}$ where $Cp, \text{ power}$ is a constant defined by the chosen value of the statistical power and the value p . This constant is available in statistical tables^[11] $C_{0.05, 90\%} = 10.5$.

Thus the minimum size of the sample is: $n = 2/(1^2) \times 10.5$.

$n = 10.5$ rounded to 11 subjects.

To improve statistical power, we increased the study sample at 30 patients. Patients were screened clinically for eligibility with three clinical BP measurements, a urinary dipstick, resting electrocardiogram and a blood sample for creatinine estimation and creatinine clearance calculation. Of the 30 eligible patients invited, 3 were excluded because they had signs of urinary tract infection on dipstick.

Participants were invited to arrive at the hospital between 8:00 and 10:00 am for all exploratory visits. On arrival, participants were maintained in a sitting position for at least five minutes before BP measurement. Three serial BP measurements taken in the sitting position were obtained from non-dominant arm placed at the level of the heart, using adults cuffs (32-42 cm) adapted to an automated

sphygmomanometer Omron HEM-705 CP (Omron Corporation, Tokyo, Japan). The average of the three measurements was used for all analyses. Weight was measured in light clothed subjects to the nearest 0.5 kg with a mechanical scale, while height was measured in an upright position to the nearest 0.5 cm. The body mass index (BMI in kg/m^2) was calculated as $\text{weight (kg)} / [\text{height (m)} \times \text{height (m)}]$. Waist circumference was measured horizontally, midway between the lower rib margin and the iliac crest with a measuring tape. Macro or clinical albuminuria was assessed by dipstick of spot urine, and considered positive for at least 1+ ($< 30 \text{ mg}/\text{dL}$). Electrocardiography was done with the CardiMax FX-7302 electrocardiograph (Fukuda Den Shi, Tokyo, Japan).

Twenty-four hours BP measurement

Twenty-four hour BP was measured by a portable, light weight monitor device i-mapa CE 004 1.1 TM (High-tech Medical St Louis, Paris). The purpose of the examination and practical modalities including: the measurement procedure and related constraints were explained to the participants. The device was then connected to an adult cuff, tested and calibrated. The practical procedure consisted of two major steps.

Programming the measurement over 24 h with patient information:

For this purpose, demographic information and anthropometric measurements were entered into the i-mapa software, and then the medical history was recorded, allowing us to have an electronic medical record of the patient. Then a measurement protocol was selected from those proposed by the software and a 24-h measurement cycle was activated.

Installation of the measurement monitor on the patient:

Then, the standard cuff was placed around the patient's arm 2.5 cm above the antecubital dimple in direct contact with the skin and the case fixed at the level of the waist. The patient performs some movements to ensure comfort. After the patient had put on his clothes, a manual measurement was made, which enabled the selected measurement protocol to start and ensure functionality of the device. Thereafter, the patient returned to his daily activities with instructions concerning the handling of the device, and a paper where he/her was thought to notice all particular activity during the day such as medication taken with the hour, any important emotional or physical changing (diary) and the appointment was made the next day at the same time. The patient brought us back the monitor 24 h later. Once arrived, the device was turned off and unplugged. The measurements made were then transferred to a computer using a Bluetooth key enabling communication between the software and the monitor.

Reading the 24-h measurement: Readings were obtained automatically at 15-mn intervals during the

day time define from 07:00 to 22:00 and twice an hour from 22:00 to 07:00. This interval was set using a fix clock time but control with a personal diary for each patient.

The protocol used for physical exertion was set up by our research team. It consisted of a simple step at a constant speed of 1 m/s for 30 min with a slope set at 5% with the aim of achieving a sub-maximal physical effort, resulting in a rise in the heart rate to 50%-70% of the patient's maximum HR. For each participant, a complete emptying of the bladder was performed 10 min prior to exercise. In the preceding days, he was recommended to continue to carry out his usual activities, avoid moderate to vigorous physical activity 48 h before the start of each phase of investigations, namely: Jogging, rapid walking for 1 h, and also avoid taking medications that may modify the evaluated parameters such as angiotensin converting enzyme inhibitors.

The exercise was carried out under medical supervision. For this phase, the volunteer was invited to the exploration room of our research laboratory to the National Obesity Center of the Yaoundé central hospital between 08:00 and 10:00 in the morning. Upon arrival, blood glucose was performed; the data sheet was revisited and updated. The patient was driven and installed in the exercise room. The treadmill was then switched on with accessories such as the heart rate monitor. A urine and blood sample was collected at rest and preserved before the beginning of the exercise. The patient was then placed on the treadmill after having installed the heart rate monitor on the chest, the electrodes of the heart being in direct contact with the skin and safety belt installation. Continuous heart rate (HR) recording allowed us to ensure that the patient remained within the limits set for our study 50%-70% of maximal HR. At the end of the exercise, the patient was placed in an armchair to recover and received water for rehydration and to promote diuresis.

Urinary albumin excretion was calculate using albumin to creatinine ratio to reduce effect of urinary concentration after exercise on albuminuria and expressed in mg/g. First void urine collection was used for rest albuminuria and a random sample urine was collected within the 30 mn following physical exercise to measure exercise-induced albuminuria. Retinopathy was assessed by fundoscopy and creatinine measured using modified Jaffe kinetic reaction with colorimetric methods. Albuminuria was measured by turbidimetry and others biochemical parameters using an automatic spectrophotometer.

Statistical analysis

Data acquisition was done by Epi-data3.1 software and statistical analysis was performed using Statistical Package for Social Science (SPSS) version 21.0 for Windows (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, version 21.0. Armonk, NY: IBM Corp.) and Stata 12.0 software. Continuous variables

are expressed as median (interquartile range = IQR) or mean $\pm$ SD where appropriate, and categorical variables as count (percentage). The Spearman rank coefficient was used to test correlations. The χ^2 test, Mann-Whitney rank sum test were used to test associations between qualitative variables and difference between two respectively. A P value < 0.05 was considered statistically significant.

RESULTS

General characteristics

We included 27 patients (18 males) with a median age of 52 (IQR = 36-56) years, a mean duration of diabetes of 3.6 ± 0.8 years and a mean HbA1c of $6.3\% \pm 0.5\%$. Twenty four hours ABPM recorded a mean diurnal systolic blood pressure (SBP) of 128 ± 17 mmHg vs nocturnal of 123 ± 19 mmHg ($P = 0.004$), and mean diurnal diastolic blood pressure (DBP) of 83 ± 11 mmHg vs nocturnal DBP 78 ± 14 mmHg ($P = 0.002$) for a mean day vs night difference of 05 mmHg for SBP and 05 mmHg for DBP. Four/Twenty-seven of patients had diabetic retinopathy.

BP profile in groups with different albuminuria

Our population study was divided three times in two subgroups, according to albuminuria before and after exercise, these groups were subsequently compared pairs. These comparisons are illustrated in Tables 1, 2 and 3. They included clinical and ABPM findings in order to compare possible differences on BP profile associate with albuminuria.

The first two groups compared were patients with albuminuria at rest vs patients without resting albuminuria (Table 1). We found that patients with albuminuria at rest had more elevated DBP on clinical measure than non-albuminuric patients at rest (89 mmHg vs 77 mmHg, $P = 0.04$). Using ABPM, there was a marked increase in all component of nocturnal BP (130 mmHg vs 115 mmHg, $P = 0.06$ for SBP; 86 mmHg vs 72 mmHg for DBP, $P = 0.02$; and 107 vs 90, $P = 0.03$ for mean arterial BP).

The 2nd comparison concerned patients presenting with exercise-induced albuminuria and those without albuminuria after exercise (Table 2). This revealed that patients with exercise-induced albuminuria had an increase in nocturnal BP values on all three components [128 mmHg vs 110 mmHg, $P = 0.03$ for SBP; 83 mmHg vs 66 mmHg, $P = 0.04$; 106 vs 83, $P = 0.02$ for mean arterial pressure (MAP)].

The last comparison was made between patients presenting albuminuria only after exercise and those with albuminuria at rest (Table 3). Since patients with exercise-induced albuminuria had elevated night time BP values compared to those with albuminuria at rest, we sought to determine if exercise induced albuminuria is associated with a particular abnormality in BP profile. We found that patients with exercise induced albuminuria had slightly lower BP values

Table 1 Comparison between non albuminuric patients at rest and albuminuric patients at rest

Variables	Normoalb0	Microalb0	P value
Frequencies	19	8	/
Age	52 (40-56)	48 (34-56)	0.56
BMI (kg/m ²)	25.4 (23.1-28.5)	26.1 (24-31.6)	0.62
Waist circumference	92 (87-96)	93 (84-97)	0.99
SBP (mmHg)	122 (112-133)	137 (122-142)	0.68
DBP (mmHg)	77 (73-87)	89 (79-99)	0.04
HbA1c (%)	6.6 (5.9-7.0)	6.2 (6-7)	0.99
eGFR (mL/min)	93 (77-104)	89 (70-104)	0.52
ACR at rest	13.5 (8.6-21.9)	75.3 (46-94.1)	0.0001
Exercise induced ACR	29.2 (20.5-33.3)	92.3 (56.3-128.7)	0.0001

ACR: Albumin to creatinin ratio; BMI: Body mass index; eGFR: Estimated glomerular filtration rate; DBP: Diastolic blood pressure; SBP: Systolic blood pressure; Normoalb0: Patients without microalbuminuria at rest; Microalb0: Patients with microalbuminuria at rest.

Table 2 Comparison non-albuminuric patients after exercise and exercise induced albuminuric patients

Variables	Normoalb30	Microalb30	P value
Frequencies	11	16	/
Diurnal SBP	117 (112-133)	132 (125-136)	0.71
Nocturnal SBP	110 (98-125)	128 (122-138)	0.03
24 h SBP	116 (109-131)	132 (124-136)	0.05
Diurnal DBP	78 (76-85)	85 (80-92)	0.19
Nocturnal DBP	66 (59-82)	83 (74-89)	0.044
24 h DBP	76 (72-84)	85 (78-89)	0.11
Diurnal MAP	93 (89-107)	107 (102-112)	0.05
Nocturnal MAP	83 (77-102)	106 (99-110)	0.02
24 h MAP	89 (85-105)	108 (99-112)	0.03

DBP: Diastolic blood pressure; MAP: Mean arterial blood pressure; SBP: Systolic blood pressure; Normoalb30: Patients without microalbuminuria after 30 min of exercise; Microalb30: Patients with microalbuminuria after 30 min of exercise.

on clinical measure (130/87 mmHg vs 137/89 mmHg, $P = 0.08$). However, on ABPM, exercise induced albuminuria was associated with a slight and significant decrease in nocturnal DBP (83 mmHg vs 86 mmHg, $P = 0.03$) and a rise of percentage of abnormal SBP value ($P = 0.01$). Apart from the aforementioned abnormalities, both groups were similar in other parameters. Nevertheless, both groups had an increase in BP value compare to the rest of population.

BP profile with ABPM

Using ABPM, the mean BP of our population study was 128 ± 17 mmHg vs 124 ± 19 mmHg and 127 ± 17 mmHg (P day vs night = 0.004) for systolic day time, night time and 24 h values respectively; and 84 ± 11 mmHg vs 79 ± 14 mmHg and 83 ± 12 mmHg for diastolic component.

ABPM vs resting albuminuria and ABPM vs exercise-induced albuminuria

Correlation done between albuminuria and different components of BP on a sample population showed that

Table 3 Comparison between albuminuric patients at rest and exercise-induced albuminuric patients

Variables	Microalb0	Microalb30	P value
Frequencies	8	8	
Diurnal SBP	131 (126-136)	132 (125-136)	0.95
Nocturnal SBP	130 (126-138)	128 (122-138)	0.38
24 h SBP	133 (126-135)	132 (124-136)	0.60
Diurnal DBP	85 (83-93)	85 (80-92)	0.22
Nocturnal DBP	86 (80-92)	83 (74-89)	0.03
24 h DBP	86 (83-93)	85 (78-89)	0.11
Diurnal MAP	107 (104-111)	107 (102-112)	0.77
Nocturnal MAP	107 (102-112)	106 (99-110)	0.14
24 h MAP	107 (104-110)	108 (99-112)	0.68

MAP: Mean arterial blood pressure; DBP: Diastolic blood pressure; SBP: Systolic blood pressure; Microalb0: Patients with microalbuminuria at rest; Microalb30: Patients with microalbuminuria only after 30 min of exercise.

albuminuria at rest is weakly correlated with 24 h MAP ($r^2 = 0.11$, $P = 0.09$; Figure 1A), 24 h DBP ($r^2 = 0.13$, $P = 0.08$; Figure 1B) and nocturnal DBP ($r^2 = 0.13$, $P = 0.08$; Figure 1C). On the other hand, exercise induced albuminuria correlated better with 24-h mean arterial blood pressure (MAP) ($r^2 = 0.13$, $P = 0.07$; Figure 2A), night time DBP ($r^2 = 0.12$, $P = 0.09$; Figure 2B) and nocturnal MAP ($r^2 = 0.12$, $P = 0.09$; Figure 2C).

DISCUSSION

This study was carried out to investigate a relationship between urinary albumin excretion during exercise and circadian variations in BP. We found an average drop of 3.1% during the night with a high proportion of non-dippers (20/27 or 74%) in our study population, with a blunted nighttime BP. The proportion of non-dippers is higher than those of others study on type 2 diabetic population^[12]. The increase of non-dippers in our study could be due to the tendency of having elevated nocturnal BP in black subject as described by Hebert *et al*^[13] in 1996. So, the non-dipper profile could be more common in black populations. On the other hand, the high frequency of non-dipper status found in our study may reflect an incipient nephropathy in our population of diabetic patients without proteinuria. Since the reduction of nighttime dipping BP is consider as an earlier sign of diabetic nephropathy in diabetic patients with normal BP.

Patients were subsequently separated according to their urinary albumin excretion at rest and during exercise. Firstly, we compared albuminuric and non albuminuric patients at rest, and found that patients with albuminuria at rest exhibited more BP abnormalities compared to those without albuminuria. This include an elevated clinical DBP on clinical measure suggesting that albuminuria at rest is consistent with a slight elevation of clinical BP more marked on the diastolic component. Using ABPM, there was an increase in all diastolic components of BP (diurnal, nocturnal and mean arterial) as well as nocturnal SBP and nocturnal mean MAP in

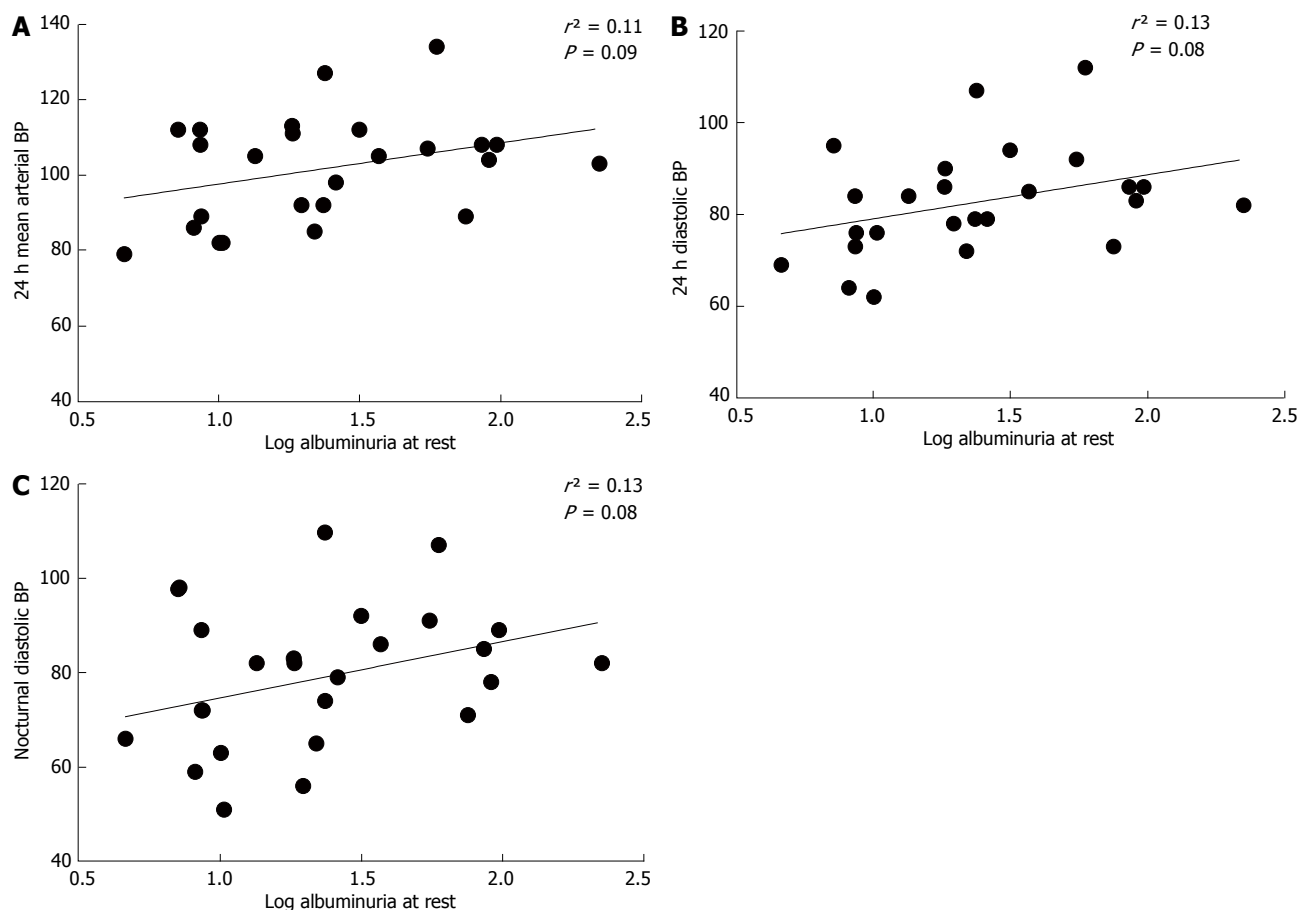


Figure 1 Correlation between albuminuria at rest and diastolic blood pressure. A: Correlation between albuminuria at rest and 24 h MAP; B: Correlation between albuminuria at rest and 24 h diastolic BP; C: Correlation between albuminuria at rest and nocturnal diastolic BP. MAP: Mean arterial blood pressure; BP: Blood pressure.

albuminuric patients at rest. These data are consistent with those found in literature where albuminuria at rest is associated with abnormal patterns of nocturnal BP^[13-15]. However, our study highlights the fact that this increase in nocturnal BP is more marked on diastolic component of BP. Therefore, clinical and nocturnal DBP must be checked and managed meticulously in T2D patients to detect even a slight elevation or a moderate rise in baseline DBP comparing with precedent measures. This is to ensure early detection of these patients, thereby improve their management to prevent diabetic nephropathy.

Secondly, we compared the BP of patients exhibiting exercise induced albuminuria at rest and during exercise with those without this abnormality on clinical measure and using ABPM. We found that, though there was no difference in SBP and DBP on clinical measure, but ABPM detected an increase in nocturnal BP including night time SBP, DBP as well as nocturnal MAP. This important finding supports and confirms our research hypothesis stipulating that exercise induced albuminuria is associated with abnormal circadian BP profile particularly abnormalities in night time BP pattern.

Finally, we compared patients exhibiting exercise induced albuminuria without resting albuminuria to those having albuminuria at rest in order to check if

there is a difference between BP profiles of these two groups of patients. Comparing with non-albuminuric patients, these two groups had elevated BP values. However, patients with moderate resting albuminuria tend to have a higher BP values than those presenting only exercise-induced albuminuria. This association could be of importance since mild variations in nocturnal BP has been associated with renal injuries in T2D patients. Our findings are consistent with the fact that exercise induced albuminuria is associated with the same abnormalities in BP profile as albuminuria at rest, and therefore could be useful in management of T2D patients to detect the same patients with blunted nighttime BP. Nevertheless, there is an urgent need for longitudinal studies to verify this hypothesis. Moreover, exercise induced albuminuria could be associated with very subtle variations in circadian BP.

Albuminuria at rest had a positive but weak correlation with nighttime DBP and 24 h BP, sustaining the fact that an increase in 24 h BP is associated with an elevation in albuminuria at rest which could be a marker of renal deterioration^[16]. Therefore, an increase in nighttime DBP and/or 24 h DBP could be associated with greater kidney damage in diabetic patients without hypertension. These results corroborate with those Rossing in 1993^[17]. Similarly, exercise induced

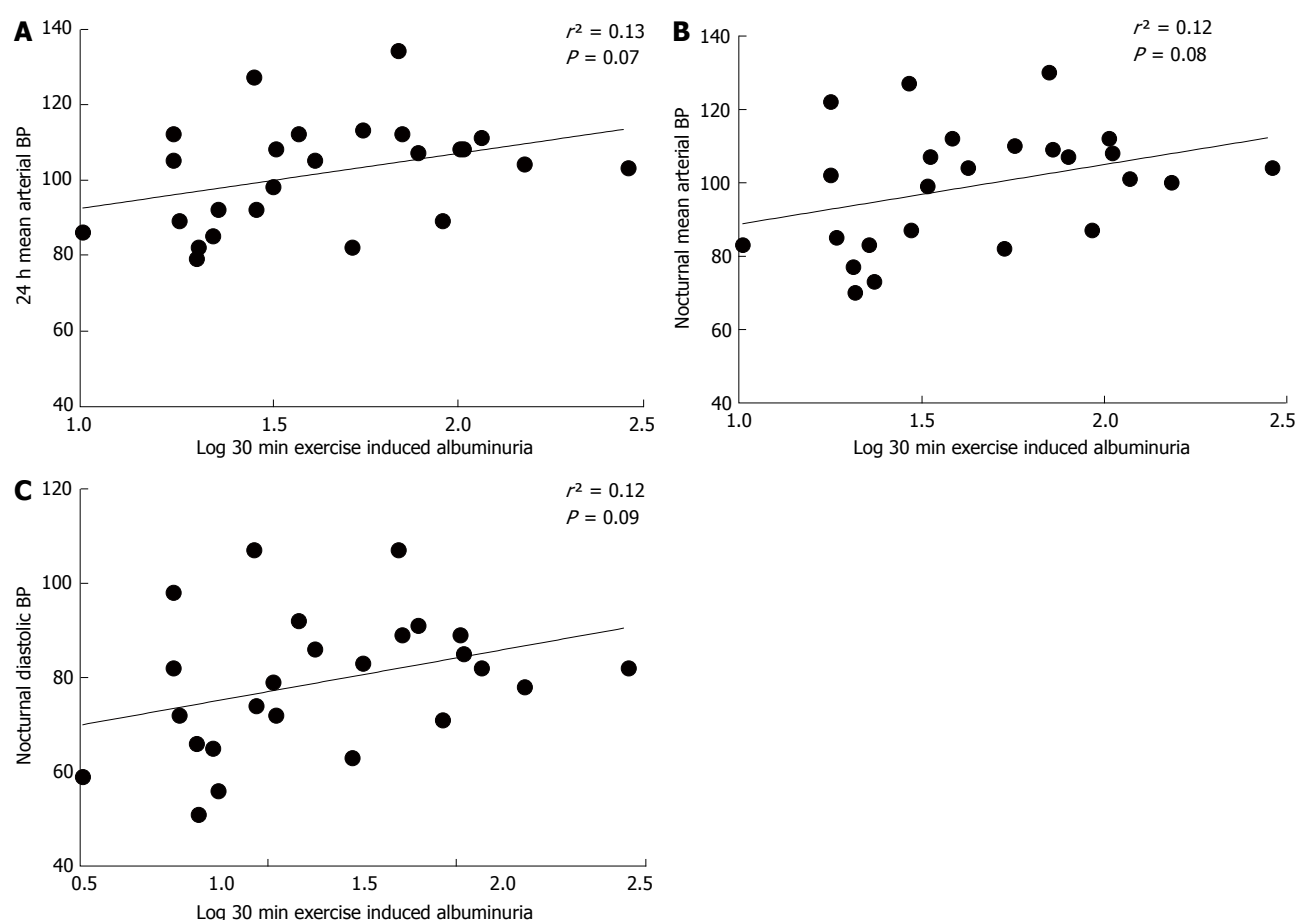


Figure 2 Correlation between exercise-induced albuminuria and diastolic blood pressure. A: Correlation between exercise induced albuminuria and 24 h MAP; B: Correlation between exercise induced albuminuria; C: Correlation between exercise albuminuria. MAP: Mean arterial blood pressure; BP: Blood pressure.

albuminuria correlated better, and positively, with night DBP and 24 h MAP. Thus, exercise induced albuminuria is correlated with the same characteristics as albuminuria at rest.

There was a strong positive correlation between albuminuria at rest and during exercise albuminuria ($r = 0.7$ and $P < 0.001$). This suggests that patients with a greater resting albuminuria therefore tend to have a higher albuminuria after exercise. Considering the fact that albuminuria at rest is a marker of incipient diabetic nephropathy, this suggests that exercise induced albuminuria would be greater in case of pre-existing renal impairment^[18]. This hypothesis is supported by physiology, since it is known that subclinical lesions can be unmasked even by moderate physical exercise^[8]. The results obtained in this study shows a significant proportion of abnormal circadian BP profile in patients with T2D, considered normotensive on clinic-based measurements.

Study strengths and limitations

This study presents some limitations related to the study design. Since this is a cross-sectional study, the predictive value of these abnormalities needs to be evaluated with prospective studies. This could bring more evidence and basic arguments to recommend management of T2D patients presenting exercise-

induced albuminuria. This study depicts the importance of ABPM in the management of diabetic patients, due to its efficacy in detecting abnormalities in BP values, which is a better predictor of renal damage compared with clinic-based BP measurements. We also found that exercise induced albuminuria discriminate the same patients as resting albuminuria stressing the need to revisit importance of exercise-induced albuminuria in the earlier diagnosis and management of T2D patients. This will require prospective studies in order to evaluate the predictive capacity of exercise induced albuminuria on nighttime BP abnormalities what have not been done yet to date.

Conclusion

Exercise-induced albuminuria is associated with nocturnal blood pressure abnormalities in T2D patients and could discriminate patients with more precocious increase of nighttime blood pressure than albuminuria at rest.

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COMMENTS

Background

Exercise induced albuminuria has long been proposed as early marker of diabetes nephropathy but was not approved due to lack of evidence and clinical importance. Nocturnal blood pressure abnormalities and represent an early marker diabetes kidney disease.

Research frontiers

A relation between nocturnal blood pressure abnormalities detected by ambulatory blood pressure monitoring (ABPM) and exercise-induced albuminuria would be of great importance since this will suggest that the latter can serve as earlier marker of diabetes nephropathy.

Innovations and breakthroughs

Most of studies conducted to determine the clinical importance of exercise-induced albuminuria have been done in type 1 diabetes individuals and has compared it only to albuminuria at rest. This study shows an association between nocturnal blood pressure abnormalities and exercise-induced albuminuria suggesting that it could be useful to discriminate type 2 diabetes (T2D) individuals with early renal diabetes kidney disease. As the best of our knowledge, this study is the first reporting this association in T2D patients who represent more than 90% of diabetes patients worldwide.

Applications

Economically, the separate or combined use of ABPM, and exercise induced albuminuria in assessing diabetic patients clinically normotensive, for the detection of subclinical diabetic nephropathy lesions could represent a significant gain in health spending by its low cost compared to new markers currently in test and would significantly reduce health care spending. Indeed, by allowing very early detection of subclinical renal damage, they would allow a more prompt and early treatment, increasing the chances of controlling the disease and slow its progression to end-stage renal disease (ESRD) and chronic kidney disease. This would be a significant reduction in costs for health systems today face a real inflation of the prevalence of ESRD and dialysis diabetes-related admissions.

Terminology

Albuminuria: Presence of albuminuria in urine which is a marker of renal damage; Microalbuminuria or moderate albuminuria: Urinary albumin excretion ≥ 30 mg/24 h or 30 mg/g with albumin to creatinin ratio; Exercise-induced albuminuria: Increase or presence of urinary albumin excretion after an exercise.

Peer-review

Well done important information supporting the view that patients regarded as not afflicted with diabetic nephropathy may indeed be progressing towards renal damage that is preventable if treated before diabetic nephropathy progresses to a 24 h disorder.

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Severe cyclophosphamide-related hyponatremia in a patient with acute glomerulonephritis

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Abstract

Cyclophosphamide is frequently used to treat cancer, auto-immune and renal diseases, such as rapidly progressive glomerulonephritis. Its side effects are well-known, including bone marrow depression, infections, alopecia, sterility, bladder malignancy and hemorrhagic cystitis. Moreover, in some cases cyclophosphamide use has been related to the onset of hyponatremia, by development of a syndrome of inappropriate antidiuresis. Indeed, severe hyponatremia has been previously reported in patients treated with high-dose or moderate-dose of intravenous cyclophosphamide, while only few cases have been reported in patients treated with low dose. Here, we discuss a case of a syndrome of inappropriate antidiuresis followed to a single low-dose of intravenous cyclophosphamide in a patient with a histological diagnosis of acute glomerulonephritis, presenting as acute kidney injury. After cyclophosphamide administration (500 mg IV), while renal function gradually improved, the patient developed confusion and headache. Laboratory examinations showed serum sodium concentration dropped to 122 mmol per liter associated with an elevated urinary osmolality of 199 mOsm/kg, while common causes of acute hyponatremia were excluded. He was successfully treated with water restriction and hypertonic saline solution infusion with the resolution of the electrolyte disorder. This case, together with the previous ones already reported, highlights that electrolyte profile should be strictly monitored in patients undergoing cyclophosphamide therapy in order to early recognize the potentially life-threatening complications of acute water retention.

Key words: Hyponatremia; Cyclophosphamide; Syndrome

of inappropriate antidiuresis; Glomerulonephritis; Hypertonic solutions; Antidiuretic hormone; Urine osmolality

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Core tip: The syndrome of inappropriate antidiuresis (SIAD) is a disorder of sodium and water balance characterized by hypotonic hyponatremia and impaired urinary dilution in the absence of renal disease or any non-osmotic stimulus known to release anti-diuretic hormone. It may be caused by several conditions including infections, neoplasms and use of some medications, such as antipsychotics, antidepressant and immunosuppressive drugs. Here, we report the clinical course of a case of SIAD attributed to administration of a single low-dose of intravenous cyclophosphamide in a patient with an acute glomerulonephritis.

Esposito P, Domenech MV, Serpieri N, Calatroni M, Massa I, Avella A, La Porta E, Estienne L, Caramella E, Rampino T. Severe cyclophosphamide-related hyponatremia in a patient with acute glomerulonephritis. *World J Nephrol* 2017; 6(4): 217-220 Available from: URL: <http://www.wjgnet.com/2220-6124/full/v6/i4/217.htm> DOI: <http://dx.doi.org/10.5527/wjn.v6.i4.217>

INTRODUCTION

Hyponatremia is the most frequent electrolyte disorder, being potentially a marker of different underlying diseases or a cause of morbidity itself.

Clinical manifestations vary from asymptomatic forms to severe neurological alterations, in dependence of hyponatremia severity, progression rate and intra- to extracellular osmotic gradient entity. Differential diagnosis is often challenging, since it includes diseases, which, in view of similar clinical pictures, have very different pathophysiological bases, such as syndrome of inappropriate antidiuresis (SIAD), cerebral/renal salt wasting syndrome (C/RSWS) and endocrine syndromes^[1].

SIAD is a disorder of sodium and water balance characterized by hypotonic hyponatremia and impaired urinary dilution in the absence of renal disease or any identifiable non-osmotic stimulus known to release antidiuretic hormone (ADH). SIAD may be itself caused by different conditions, including infections, neoplasms and use of several medications, such as antipsychotics, antidepressant^[2] and immunosuppressive drugs^[3].

Here, we report the clinical course of a rare case of SIAD attributed to cyclophosphamide (CYC) administration in a patient with a proliferative glomerulonephritis.

CASE REPORT

A 56-year-old man was referred to our Nephrology Department for rapidly decline of glomerular filtration

rate (GFR), proteinuria and haematuria.

He presented a history of hypertension, chronic kidney disease (with a stable serum creatinine of 158 mmol/L, estimated GFR 40 mL/min per 1.73 m² CKD-EPI), Crohn disease, psychiatric disorder in treatment with selective serotonin reuptake inhibitors (SSRIs) and normal pressure hydrocephalus with ventriculo-peritoneal shunt.

At the admission, the patient presented a well-controlled blood pressure (17.3/10 kPa) and significant peripheral oedema. Laboratory examinations showed: serum creatinine 290 mmol/L (corresponding to an estimated GFR of 19 mL/min per 1.73 m²), urea 47 mmol/L, sodium 137 mmol/L, potassium 3.69 mmol/L, serum albumin 30 g/L, cholesterol 3.93 mmol/L and triglycerides 2.19 mmol/L.

Urinalysis showed microhematuria, while quantitative proteinuria was 2.26 g/24 h. Autoimmunity evaluation, which included ANA, ENA, ANCA, C3 and C4, resulted negative.

So, in order to better elucidate the causes of renal disorder, we performed a percutaneous renal biopsy. Histological examination showed glomeruli with mesangial expansion and endocapillary hypercellularity due mostly by neutrophils infiltration with some karyorrhectic bodies, fibrinoid necrosis of small arterioles, and fibrocellular crescents (Figure 1). There was also moderate tubular atrophy within massive protein droplets, and moderate interstitial fibrosis. Immunofluorescence analysis did not show immune deposits, while electronic microscopy was not performed. So, considering clinical and histological findings our final diagnosis was rapidly progressive glomerulonephritis secondary to ANCA-negative pauci-immune crescentic glomerulonephritis.

At the time of biopsy pharmacological treatments included intravenous diuretics (furosemide 125 mg/d), antihypertensive drugs and SSRI. After the renal biopsy, also in consideration of the further deterioration of renal function (serum creatinine till 343 mmol/L), intravenous methylprednisolone was administered at the dose of 500 mg for three days followed by oral steroid at the initial dose of 1 mg/kg per day. In addition, the induction therapy was completed with a single dose of 500 mg of intravenous CYC (8 mg/kg). To minimize the risk of haemorrhagic cystitis, saline solution was infused 2 h before the cyclophosphamide administration. In the following days, while renal function gradually improved, patient clinical conditions worsened with development of confusion and headache. Laboratory examinations showed serum sodium 122 mmol/L, serum osmolality 261 mOsm/kg, urinary osmolality 199 mOsm/kg, and serum creatinine 202 mmol/L. Symptomatic hypotonic hyponatremia was further confirmed in the subsequent controls, so that fluid restriction and hypertonic saline solution (at initial concentration of 3%) treatment were initiated, while SSRIs were gradually withdrawn. In the following days, serum sodium progressively improved and we were able to reduce infusive therapy, also to

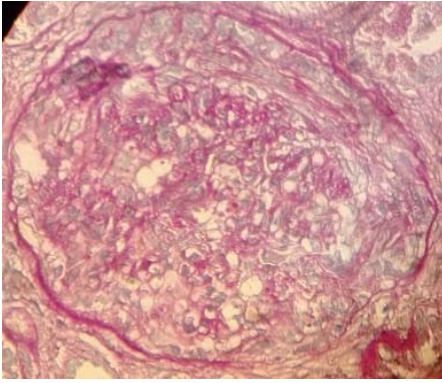


Figure 1 Histological examination showed glomeruli with mesangial expansion and endocapillary hypercellularity with some karyorrhectic bodies, fibrinoid necrosis of small arterioles, and fibrocellular crescents (as shown in the figure-PAS, x 400).

prevent the increase of oedema (Figure 2).

To establish the pathogenesis of the acute hyponatremia we investigated thyroid and adrenal functions, which resulted normal and performed a whole-body CT scan that ruled out pulmonary or cerebral complications. Therefore, in absence of further evidence and considering the temporal relationship between CYC infusion and onset of hyponatremia, the fact that diuretic and psychiatric therapy were unchanged and the presence of hypotonic hyponatremia with impaired urinary dilution we established a diagnosis of CYC-related syndrome of inappropriate anti-diuresis (SIAD)^[3]. So, in order to prevent other hyponatremia episodes further cyclophosphamide administration was avoided.

DISCUSSION

Cyclophosphamide is an alkylating agent used in the treatment of malignant and autoimmune diseases. Its well-known side effects include bone marrow depression, infections, alopecia, sterility, bladder malignancy and haemorrhagic cystitis. Hyponatremia due to SIAD has been infrequently described and it is considered a rare adverse effect related to CYC use. Indeed, until now severe hyponatremia has been reported only in few patients treated with high-dose (30-40 mg/kg)^[4,5] and moderate-dose (20-30 mg/kg) of intravenous cyclophosphamide, while even less were the cases of hyponatremia occurred in patients treated with low dose^[6-8]. Different underlying mechanisms have been proposed to explain the onset of water retention and SIAD after CYC administration. They can act either stimulating ADH release or accentuating its renal effects, finally causing hyponatremia^[9]. Harlow *et al.*^[10] demonstrated in a patient who received high dose of cyclophosphamide, the loss of Herring bodies and degranulation of various hypothalamic neurosecretory organelles, leading to the inappropriate secretion of ADH. It has been also demonstrated a direct effect of an alkylating metabolite of CYC on

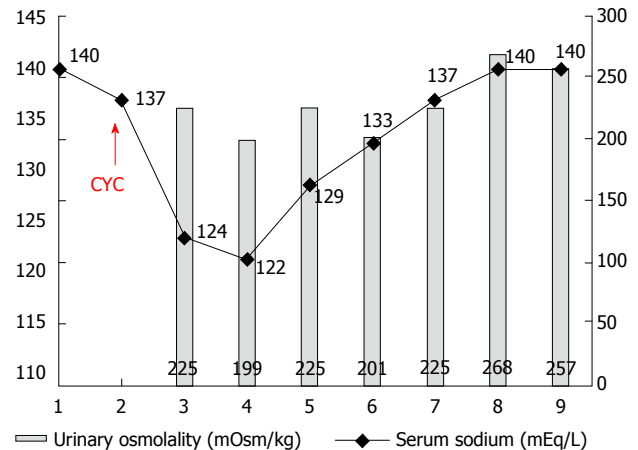


Figure 2 Time trend of serum sodium concentration and urinary osmolality following cyclophosphamide administration. During days 3 and 4 the urinary osmolality was inappropriately high considering the hyponatremia. In days 5 to 9 the urinary dilution capacity was re-established.

the kidney resulting in enhanced permeability of the distal tubules to water^[11]. Moreover, CYC might cause hyponatremia by up-regulating expression of the ADH receptor V2R and aquaporin 2 (AQP2) through the suppression of interleukin-1 and tumor necrosis factor- α , which generally act as negative regulators of V2R expression^[12]. In addition, recently Kim *et al.*^[13] demonstrated in experimental models (rat and inner medullary collecting cell cultures) that CYC could also induce V2R activation and AQP2 expression in the absence of ADH stimulation.

Actually, in our case the patient presented several predisposing factors that could have caused water retention, such as renal failure, the continuative use of SSRI and the normal pressure hydrocephalus; but the temporal association with the administration of CYC makes plausible its role in the development of the severe hyponatremia, also considering that prior to CYC treatment, he had normal serum electrolytes and did not present nausea or vomiting. Moreover, our case has common features with other reports in which hyponatremia was induced by intravenous cyclophosphamide. Hyponatremia usually occurs 12-48 h after the administration of cyclophosphamide, and returns to normal in few days.

In conclusion, we think that our case, together with the previous ones already reported, underlined the need to be aware of the potentially life-threatening complications of water intoxication when intravenous pulse cyclophosphamide is applied, especially in patients with other concomitant risk factors. Therefore, we strongly suggest checking electrolytes before and after CYC administration.

COMMENTS

Case characteristics

A patient with an acute glomerulonephritis who developed an acute symptomatic

hyponatremia after treatment with cyclophosphamide.

Clinical diagnosis

Acute Hyponatremia secondary to development of syndrome of inappropriate antidiuresis related to the administration of cyclophosphamide.

Differential diagnosis

Other causes of acute hyponatremia: Cancers, infections, hypovolemia, use of diuretics.

Laboratory diagnosis

Hypotonic hyponatremia associated with impaired urinary dilution.

Imaging diagnosis

CT to exclude cerebral or pulmonary disorders.

Pathological diagnosis

Renal biopsy proving the presence of an acute ANCA-negative pauci-immune crescentic glomerulonephritis.

Treatment

Water restriction, hypertonic saline solution infusion.

Related reports

Previous cases of hyponatremia in patients treated with different doses of intravenous cyclophosphamide.

Experiences and lessons

It is necessary to carefully monitor electrolyte and water balance before and after cyclophosphamide administration.

Peer-review

This case report is well-written and has interesting information.

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Podocytopia: Potential applications and current limitations

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Abstract

Chronic kidney disease is a prevalent condition that affects millions of people worldwide and is a major risk factor of cardiovascular morbidity and mortality. The main diseases that lead to chronic kidney disease are frequent entities as diabetes mellitus, hypertension and glomerulopathies. One of the clinical markers of kidney disease progression is proteinuria. Moreover, the histological hallmark of kidney disease is sclerosis, located both in the glomerular

and in the interstitial compartments. Glomerulosclerosis underscores an irreversible lesion that is clinically accompanied by proteinuria. In this regard, proteinuria and glomerular sclerosis are linked by the cell that has been conserved phylogenetically not only to prevent the loss of proteins in the urine, but also to maintain the health of the glomerular filtration barrier: The podocyte. It can then be concluded that the link between proteinuria, kidney disease progression and chronic kidney disease is mainly related to the podocyte. What is this situation due to? The podocyte is unable to proliferate under normal conditions, and a complex molecular machinery exists to avoid its detachment and eventual loss. When the loss of podocytes in the urine, or podocytopia, is taking place and its glomerular absolute number decreased, glomerulosclerosis is the predominant histological feature in a kidney biopsy. Therefore, tissular podocyte shortage is the cause of proteinuria and chronic kidney disease. In this regard, podocytopia has been demonstrated to precede proteinuria, showing that the clinical management of proteinuria cannot be considered an early intervention. The identification of urinary podocytes could be an additional tool to be considered by nephrologists to assess the activity of glomerulopathies, for follow-up purposes and also to unravel the pathophysiology of podocyte detachment in order to tailor the therapy of glomerular diseases more appropriately.

Key words: Podocyte; Podocytopia; Glomerulopathy; Chronic kidney disease; Proteinuria

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Core tip: Podocytes are cells that do not proliferate under normal conditions. Their loss in the urine, a process known as podocytopia, antedates proteinuria. When the number of podocytes per glomerulus is less than 80%, glomerulosclerosis is triggered and if not stopped, it will eventually lead to chronic kidney failure and end-stage kidney disease. A prompt and standardized assessment of podocytopia should lead to better results related to glomerular disease outcomes.

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INTRODUCTION

The podocyte is a well-differentiated cell that forms the glomerular filtration barrier together with the glomerular basement membrane and the adjacent fenestrated endothelial cell. Among the main functions of podocytes, two of them arise as the most relevant: Podocytes not only offer an efficient structural support to the capillary loop in order to assure the constant filtration of plasma, but podocytes also impede the loss of proteins in the urine during the constant process of plasma filtration^[1]. Podocytes perform their functions attached to the glomerular basement membrane, of which they synthesize most of its components and maintain its normal structure. Located in Bowman's space, they perform their functions facing a constant counterstream flow of plasma. This situation implies that in order to remain in their place, under normal circumstances they can eventually undergo mitosis but cannot undergo cytokinesis. This phenomenon results in maladapted binucleated podocytes^[2]. Therefore, an efficient machinery is settled in order to avoid the loss of podocytes in the urine, a phenomenon denominated podocyuria^[3].

When podocytes are lost, the glomerular basement membrane becomes denuded and proteins start to leak to Bowman's space and enter the lumen of the proximal tubule. Therefore, neighbour podocytes are to extend their foot processes in order to cover the denuded area^[3]. When the number of podocytes become critical, matrix expansion and glomerulosclerosis start to take place^[4,5]. It appears that glomerulosclerosis starts to occur when the loss of podocytes per glomerulus is approximately between 20% and 40%. Above this number, the glomerulus starts the point of no return and is destined to obliteration. It is well known that when the number of glomeruli is less than 50%, renal insufficiency ensues^[4,5]. This means that the decreased number of podocytes is followed by proteinuria, a marker of progression of chronic kidney disease and associated with cardiovascular morbidity and mortality^[6]. In summary, a prompt diagnosis of podocyuria, a better management of this situation, and more efficacious pathophysiologically-based therapeutic interventions should lead to a decrease in chronic kidney disease progression and in the prevalence of end-stage renal disease.

PODOCYTE

The podocyte mass is small compared of the entire kidney mass. It is highly differentiated and as such,

does not undergo cellular division. It forms part of the glomerular filtration barrier, together with the glomerular basement membrane and the adjacent fenestrated endothelium^[1-3,7]. They contain a large cell body, with prominent nucleus and nucleolus, and a rich Golgi apparatus and endoplasmic reticulum, engaged in the large number of unique proteins they synthesize. Podocytes possess numerous foot processes that interdigitate with neighbouring ones. Adjacent foot processes form the slit diaphragms, structures that determine the quality of the filtered plasma flow^[1-3]. They accomplish many functions, highly preserved among species.

Podocytes are coated by a sialic acid-rich polyanionic glycocalix mainly composed of podocalyxin and among its many functions contributes to the impediment of albumin filtration^[8]. Considering the fact that the normal serum albumin concentration is between 3.5 and 5 g/dL, and that approximately 200 L of blood are being filtered every day, then podocytes efficiently cope with the task of avoiding the daily urinary loss of 9 kilograms of albumin. Podocytes also contribute with the synthesis of the major number of components of the glomerular basement membrane, as collagen type IV, and to its maintenance^[1,7]. They also secrete vascular endothelial growth factor (VEGF) in a paracrine fashion, which is critical for the formation of fenestrae in the capillary endothelium, increasing the amount of filtered plasma^[9]. Podocytes also contain toll-like receptors, as well as receptors for complement and for the Fc portion of immunoglobulins, therefore behaving as antigen presenting cells^[10].

Within the cell body and the primary cell processes, microtubules and intermediate filaments dominate, while within the foot processes, longitudinally bundles of microfilaments are encountered. Actin, myosin, and α -actinin are associated with these bundles^[11,12]. A chain of proteins containing vinculin and talin then link the actin filaments through integrins to fibronectin and laminin located in the glomerular basement membrane (Figure 1). The cytoskeleton of podocytes and its interaction to the glomerular basement membrane is responsible not only for the fixation of the cell to the matrix, but also for the regulation of the capillary width, a critical factor that will determine the glomerular filtration rate.

Podocytes contain a large number of proteins that exert many functions (Figure 1). For example, podocytes secrete the proteins and constituents of the slit diaphragm, and a histological and physiological unit exists between the slit diaphragm and the adjacent foot processes. As podocytes contain an important contractile machinery, their relaxation and contraction determine not only the width of the slit diaphragm, but also the kind of filtered molecules. Many proteins play this role, as actin, α -actinin 4, and synaptopodin^[13]. This network of contractile proteins exert their function due to their link to surface cellular proteins located next to or on the cytoplasmic membrane. Actin is in active

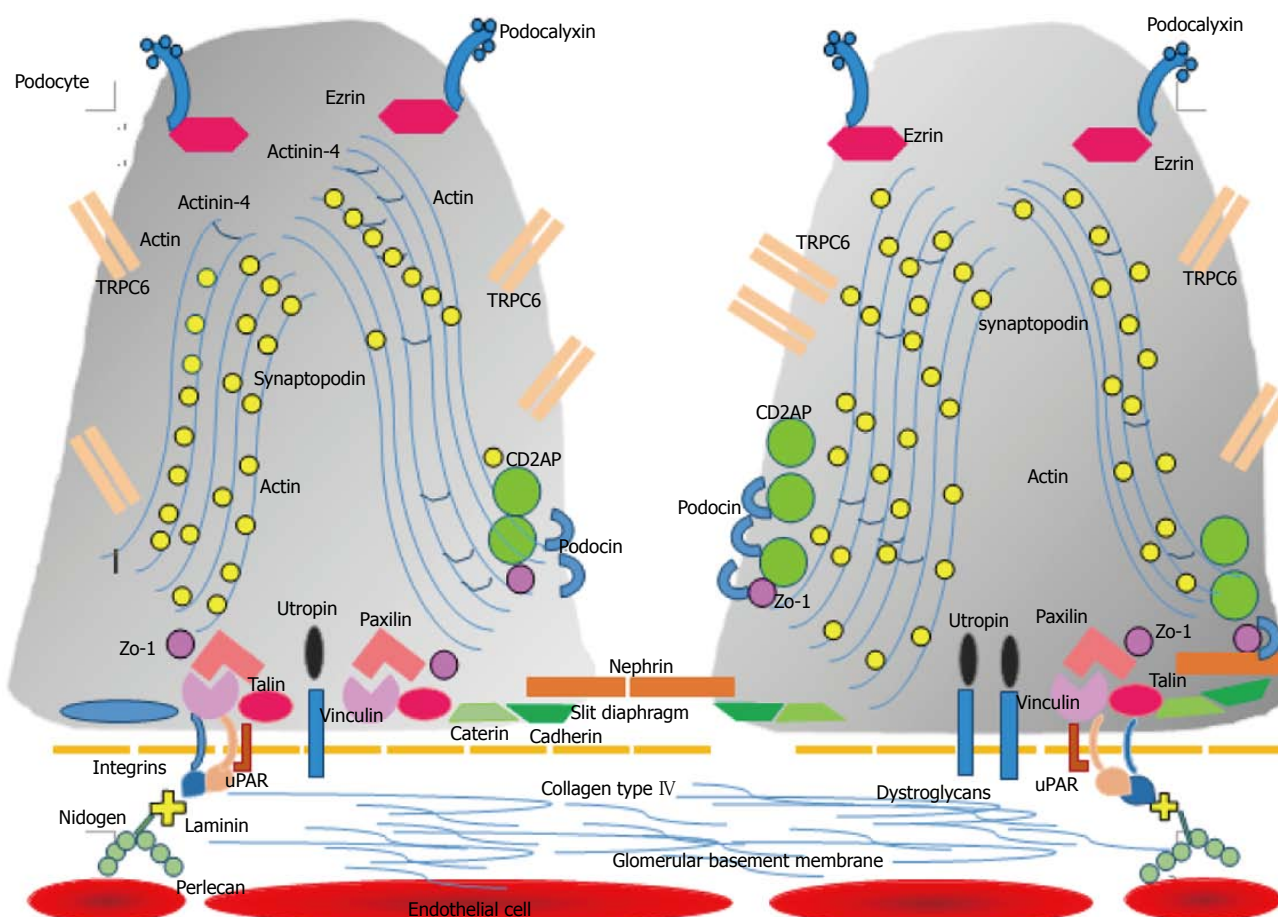


Figure 1 Glomerular filtration barrier. The podocyte with two of its many foot processes are attached to the glomerular basement membrane forming the slit diaphragm. Some components of these structures are illustrated. The fenestrated endothelium is depicted next to the basement membrane. TRPC6: Transient receptor potential cation channel 6; uPAR: Urokinase-type plasminogen activator receptor.

connection with CD2AP (CD2-associated protein), a regulatory protein that translates the information that podocin, a protein located in the foot process that also forms part of the slit diaphragm with nephrin^[14]. Actin also receives the information that calcium channels receive from the outside, like TRPC6 (ion-channel protein transient receptor potential cation channel 6)^[15]. Podocalyxin is a glycoprotein located on the cell surface that contributes to the negative charge of the cell surface and also acts as a receptor^[8]. Finally, actin is determined to relax or contract depending on the information that may come from the basal side of the cell, especially that concerned with the glomerular basement membrane and the endothelial cell. This is undertaken mainly by its interaction with urokinase-type plasminogen activator receptor (uPAR), which in turn operates with certain integrins^[16]. These integrins anchor podocytes to the glomerular basement membrane. When the assemblage between uPAR and integrins $\alpha V\beta 3$ or $\alpha 3\beta 1$ become activated, then actin is determined to contract. The intensity and duration of this interaction jeopardizes the attachment of the podocyte to the glomerular basement membrane. At this initial stage, foot processes efface and lose their fine digitations and the capacity to retain albumin from being lost in the urine, in order to stay attached to the surrounding

matrix^[11,12]. This podocyte stress is also expressed by its lower capacity to secrete the necessary amount of proteins to achieve the normal functions of the cell, and also in the lower quality of these synthesized molecules, a process known as granular endoplasmic reticulum stress^[17].

MECHANISMS OF PODOCYTE DETACHMENT

As podocytes adhere to the glomerular basement membrane by their processes, the detachment of a podocyte occurs in several stages. Podocytes begin to lose their foot processes connections, while others are still anchored to the glomerular basement membrane. It is important to note that when a podocyte is damaged, the adjacent ones start to follow the same structural and functional process^[18]. Concerning focal detachments, it does not necessarily imply that the cell will undergo a detachment, or that it will irreversibly undertake a process of disconnection from the basement membrane. Partial detachments are usually reversible to a certain degree^[11,12].

During the process of detachment, podocytes regularly display shape modifications, foot process

effacement being the hallmark at this stage. The vast majority of these cells appear to be viable with normal morphology and organelle distribution in the cell body^[2,11,12]. However, Voguelman *et al* have encountered that in addition to the viable detached podocytes, apoptosis occurred in approximately 50% of the cells^[2]. In this regard, Kriz *et al*^[11,12] state that this discrepancy lies on the method employed to assess podocyuria. In any case, when a podocyte detaches, contiguous podocytes commence to build links among themselves, forming a new interconnected net. According to Kriz, binucleate cells can be encountered, confirming previous observations reporting binucleated urinary podocytes^[11,19,20]. Detachment is frequently reported to occur in podocytes with effaced foot processes.

A particular kind of detachment affects podocytes that are located at the opening of Bowman's capsule to the proximal tubule (tubular pole). This is the zone where the highest flow velocities of filtrate have been recorded. Such podocytes are in extreme danger of being lost by detachment. Of note, and opposed to what occurs with podocytes located elsewhere in the glomerulus, just podocytes protruding into the urinary pore have been encountered to display foot process effacement. Therefore, foot process effacements could be the result of a cell reaction secondary to mechanical stress that antedates and may herald a potential detachment. Podocytes found in the process of detachment employing transmission electron micrograph images of experimental models are viable and show foot process effacement. In this setting, these findings may confirm that a foot process effacement precedes detachment. The intricate and complex organization of the cytoskeleton associated with foot process effacements is in conflict with the usual thought that this morphological feature is just a reflection of certain cell injury. Foot process effacement is reversible, even when widespread. Thus, it appears to represent a specific, reactive phenotype of the podocyte, which may facilitate the attachment the glomerular basement membrane and may decrease the risk of detachment, at least transiently. Foot process effacement not always results in success, as indicated by the widespread presence of urinary podocytes in virtually all sorts of glomerular disorders, either primary or secondary^[3,11].

As mentioned, podocytes attach *via* integrins to the glomerular basement membrane. uPAR is dispensable for normal renal function but required for podocyte motility in cell culture and for the development of foot process effacement and proteinuria *in vivo*^[16]. Therefore, the upregulated expression of uPAR on podocytes occur under pathologic conditions. These effects of uPAR as drivers of podocyte contraction and foot process effacement are independent of its major ligand urokinase or uPA, but require the activation of $\alpha V\beta 3$ -integrin within lipid rafts and $\alpha V\beta 3$ -integrin-mediated binding to high-affinity ligands such as vitronectin^[21].

Noteworthy, one of the agonists of uPAR, uPA, converts plasminogen to plasmin. Plasmin is involved not only as a fibrinolytic factor, but also acts in fibrotic processes, stimulating water and sodium reabsorption *via* distal tubule ENa⁺ channels activation^[22]. In nephrotic urines, plasmin is elevated due to the upregulated action of uPA, and its receptor uPAR is highly expressed in urinary podocytes^[21,22]. These findings suggest that uPAR is involved in podocyte detachment, probably *via* activation of $\alpha V\beta 3$ -integrin^[16,23,24]. Employing immunofluorescent microscopy, we have demonstrated that in patients with IgA nephropathy and Fabry disease, uPAR is present in the cytoplasm of urinary podocytes. In the case of IgA nephropathy, the number of uPAR⁺ detached podocyte is significantly higher than controls and in patients with glomerular sclerotic lesions compared to those without (M1E0S1T0 vs M1E0S0T0 according to Oxford classification)^[24]. Moreover, by western blot analysis as well as by PCR techniques we have confirmed the presence of elevated concentrations of uPAR in Fabry podocytes^[23]. In this disease, we have found that urinary uPAR⁺ podocytes are significantly higher in those without therapy^[23]. Finally, in Fabry subjects increased levels of urinary $\alpha V\beta 3$ -integrins have been encountered^[25]. In this regard, our group suggested that a probable pathway of podocyte detachment under pathological conditions is *via* the interaction between uPAR and $\alpha V\beta 3$ -integrins. This pathway may not be exclusive to one glomerulopathy, while more than one pathway could also be involved in one glomerular disease^[23].

METHODS OF DIAGNOSIS OF PODOCYTURIA

In order to avoid the deterioration of the urine, we collect a fresh three-hour retained urine on site and this sample is immediately processed as previously described^[26]. Podocyuria can be diagnosed in different ways with different methods. Urinary podocytes can be identified with colorimetric qualitative methods, as immunohistochemistry or with immunofluorescence^[26,27] (Figure 2). Different podocyte proteins can be targeted with monoclonal antibodies and consequently identified with the proper microscopy method employed^[28]. Podocytes can also be identified by polymerase chain reaction (PCR), employing primers that belong to the different podocyte proteins. With this technique, one can quantify the levels of a certain specific podocyte protein in glomerular disorders^[29]. Podocytes can also be identified by flow cytometry^[29].

Our group is now studying the identification of three different kind of podocyte proteins (synaptopodin, uPAR and podocalyxin) in urinary podocytes by immunofluorescence, in parallel with their mRNA correlate detected by PCR and with flow cytometry studies. All these methods of diagnosis are not already employed as routine diagnostic tools, have not been standardized,

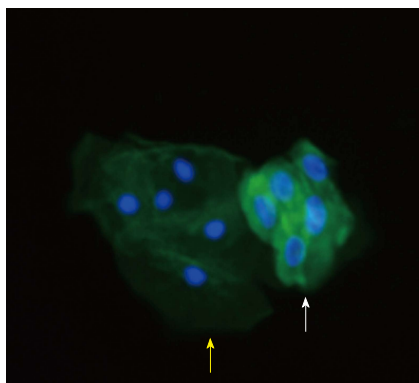


Figure 2 A cluster of podocytes diagnosed by immunofluorescence in a patient with Fabry disease are shown to the right (white arrow). Synaptopodin has been employed as the targeted podocyte protein. Tubular cells are also seen to the left of the image (yellow arrow). Green color stands for cytoplasmic synaptopodin, while blue color discloses cellular nuclei $\times 400$.

are to be validated, and are expensive, among other limitations, as discussed below. At the present time, we believe that the main usefulness of studying podocyuria is to unveil the different mechanisms of podocyte injury and detachment. Finally, with respect to the number of podocytes collected in a urine sample, and in agreement with other authors, we believe expressing the number of podocytes per gram of urinary creatinine confers a qualitative common nominator for correction purposes.

SEARCH FOR PODOCYTURIA: POTENTIALITY

Interestingly, podocyuria is also a physiologic process^[26,30]. This statement may partially explain why human beings lose renal function as they age. However, considering the fact that glomerulosclerosis and glomerulus obliteration is a consequence of tissular depletion, the finding of podocytes in the urine above control levels heralds a grim outcome if no intervention is followed by. In this regard, one can state that glomerulosclerosis and most cases of chronic kidney disease are caused by podocyte depletion.

In the adult human kidney, it is estimated that approximately 500 podocytes populate each glomerular tuft, and their turnover rate is very slow^[2,4]. As mentioned, it has been demonstrated that when a glomerulus loses between 20%-40% of its podocyte content (around 100-200 podocytes), it renders itself to sclerosis and obliteration^[2,4,5]. According to histologic observations, this podocyte loss could be uneven as to the distribution of glomerular structures, being more frequently found at the sub-capsular area, where obliterated glomeruli are encountered in kidney tissue due to non-glomerular diseases. Moreover, if the loss of 100-200 podocytes can lead to one obliterated glomerulus, in one year around 1460 glomeruli would be lost, and 14600 in 10 years-time, again in normal conditions. However, in the aged general population this

intriguing reality that shows a continuous physiological loss of this non-substitutable cell is not accompanied by severe proteinuria. On the other hand, renal function decline is the rule in the normal aging process. This could be due to the expansion of neighbouring podocytes covering the denuded glomerular basement membrane and tempering the degree of albumin filtration. Another provoking explanation could be- as mentioned above- the replacement of these podocytes by local pluripotential cells located in the parietal compartment of Bowman's capsule^[31]. Some parietal epithelial cells express stem cell markers as CD24 and CD133, and may act as renal progenitor cells. As they approach the vascular pole, they gradually lose these stem cell markers, acquire podocyte specific markers, and may migrate onto the glomerular basement membrane^[31]. The ability of the podocyte to migrate within the glomerular tuft has been elegantly demonstrated using time lapse fluorescence microscopy^[32].

However, not all replacement podocytes are derived from resident renal cells. Transplant studies in which male recipients received female kidney allografts, have demonstrated the presence of podocytes derived from the recipient male in approximately 50% of cells, suggesting a bone marrow derived stem cell source^[33]. Moreover, parietal epithelial cells express podocyte markers in several experimental models of glomerulonephritis^[34]. This phenotype switching may also portend adverse consequences for the glomerulus, possibly contributing to the development of adhesions and scars between the glomerular tuft and Bowman's basement membrane. Although some *in vitro* reports have identified these cells, no proven *in vivo* documentation has been published yet. If there is a lack of coverage, ballooning of the capillary loop ensues, synechial attachment of denuded areas to Bowman's capsule follows and focal and segmental glomerulosclerosis develops^[3,11,12].

Noteworthy, some aspects of physiologic podocyte turn over and substitution deserve to be mentioned. There is converging evidence from experimental and clinical data suggesting that adult stem cells within Bowman's capsule can rescue some of this loss^[31,35]. Glomerular epithelial stem cells generate podocytes during kidney growth and regenerate podocytes after injury, thus explaining why various glomerular disorders undergo remission occasionally. This regenerative process, however, is often inadequate because of inefficient proliferative responses by glomerular epithelial stem cells with aging or in the setting of focal segmental glomerulosclerosis. Alternatively, an excessive proliferative response by glomerular epithelial stem cells after podocyte injury can generate new lesions such as extracapillary crescentic glomerulonephritis or collapsing glomerulopathies. In addition, glomerular epithelial stem cells display a different regenerative potential at distinct stages of life, exhibiting the highest regenerative potential through adolescence^[36], which might explain why glomerular disorders have a better

prognosis during childhood whereas focal and segmental glomerulosclerosis is more frequent at an older age^[31,35].

Pharmacological targeted at podocyte detachment mechanisms could decrease the progression and consequently the prevalence of chronic kidney diseases^[16]. Once a kidney disorder in general or a glomerular disease in particular is diagnosed, a baseline level of podocyturia may prove to be useful, as a complement to the routine parameters to assess renal function and injury, such as proteinuria, hematuria, serum creatinine and glomerular filtration rate. Once therapy is started, a longitudinal profile of podocyturia could contribute to assess the case. However, a decrease in the amount of podocyturia could imply two completely different stages in a certain disease, as previously suggested. In an initial stage of a clinical setting, the amount of podocyturia could be low, and as it progresses, the amount would increase up to a point of no return, when the absolute number of cells would start to decrease due to the disease process itself and not to an improvement of the disease. In this regard, at the initial stages, a low podocyte count would be accompanied by a normal or higher glomerular filtration rate than at a more advanced stage. The same applies for proteinuria, nil or low at initial stages, and comparatively higher at later stages^[26]. Podocyturia has been assessed in a wide variety of glomerulopathies, as well as in transplantation and in entities where the glomerulus is not primarily affected, as in polycystic kidney disease^[26,27,29,30,37,38].

Podocyturia is ideally employed in hereditary kidney disorders like Alport of Fabry disease^[26,38,39]. In these settings, an index case is usually identified and properly studied and eventually treated. However, certain relatives with apparent no clinical renal involvement, who basically present with normal renal function, no proteinuria and later proven to carry the corresponding mutation, are identified as subjects with silent subclinical kidney involvement, as they present with higher and covert podocyturia load when compared to controls^[26,38,39]. Wickman *et al*^[30] have studied the degree of podocyturia in several glomerulopathies as membranous nephropathy, IgA nephropathy, lupus nephritis, diabetic nephropathy, rapidly progressive glomerulonephritis, severe hypertension, among others. They have shown that there was a significant relationship between proteinuria and podocyturia detachment mainly in advanced diabetic nephropathy, in progressors and in active lupus nephritis or IgA nephropathy. They also demonstrated a significant correlation between the degree of podocyturia and proteinuria for all clinic patients, suggesting that proteinuria is a consequence of glomerular dysfunction. Despite proteinuria is a non-specific marker of glomerular and kidney injury, they concluded that proteinuria would persist despite effective therapies that reduce the rate of podocyte detachment and that podocyte detachment is not only related to proteinuria, but it also determines the progression process and can provide useful additional information to the nephrologist to guide response to treatment and risk for progression in the clinic^[30].

However, as mentioned above, our group suggests that the correlation between podocyturia and proteinuria depends on the stage at which the process is approached. Once the mass of podocytes is low, podocyturia would decrease in contrast to a climb in proteinuria and a parallel decline in kidney function^[26]. In addition, podocyturia has been widely studied in preeclampsia. The main conclusion is that podocyturia can be employed as a diagnostic tool of preeclampsia among high risk patients, and correlates with the severity of the clinical case^[27]. Finally, we have just published an acute case of early-diagnosed IgA nephropathy with copious podocyturia that significantly decreased with immunosuppression and amiloride was associated with a decrease in proteinuria and an improvement in kidney function^[40].

In this regard, we have reported that in several glomerular diseases the addition of amiloride contributed to the decrease in the degree of podocyturia, probably due to its interaction with uPAR, and consequently with the attachment of podocytes to the glomerular basement membrane *via* integrins, as explained above^[16,23,38-41]. Zhang *et al*^[41] have shown that amiloride reduces uPAR expression, inhibits uPAR mRNA and protein synthesis in podocytes. Noteworthy, uPAR is highly expressed on cell the surface of diseased podocytes, but only scarcely on normal podocytes.

Early interventions in this asymptomatic cohort could lead to better clinical outcomes. We also believe that the study of the different podocyte proteins, particularly in each glomerulopathy, would contribute to unveil the triggered pathophysiologic mechanisms of podocyte detachment. Finally, as mentioned previously, we propose that due to the lack of biomarkers to assess kidney diseases, podocyturia ought to be a field to explore and to be standardized and validated for routine assessment of patients.

SEARCH FOR PODOCYTURIA: LIMITATIONS

Many limitations arise when the limitations are to be discussed. The available methods to study podocyturia are time-consuming, expensive, and laborious. They also require not only of certain type of microscopes, but also of trained professionals. Molecular biology methods also require the proper reactants and antibodies, mounted laboratories and adequate technology.

Podocytes are frequently lost in clusters and erratic. This intermittent loss of podocytes in the urine may oblige physician to perform serial analyses of repeated urine samples to correctly evaluate the case. Moreover, probably different populations of podocytes could be identified, depending on the predominant proteins expressed at different stages of the disease or even at the same stage. In this regard, a set of different antibodies targeted to several proteins would be ideal to perform. Our group is now undertaking the study

of proteins that belong to different cell compartments: Glycocalix, cytoplasm and basal side of podocytes.

Another important limitation is that unless proteinuria, microhematuria or an unexplained decline in renal function appear, then a kidney covert disease would not be suspected. Thus, podocyuria would be useful in clinical grounds when employed routinely for screening purposes in any patient. Urine is to be collected preferentially on site and processed without delays, in order to avoid the deterioration of the sample and the destruction of cells. The methods to assess podocyuria have not been validated yet. Finally, the cost of the study of loss podocytes is another major determinant that at this times positions this method in the research field and not also in the clinical ground.

CONCLUSION

Podocytes are highly differentiated cells unable to undergo cell division under normal conditions. Despite podocyuria exists as a physiologic phenomenon in the general population, any insult received by the podocyte either directly or indirectly, would trigger contractile mechanisms in order to retain them attached to the glomerular basement membrane, despite losing the function of avoiding the loss of protein in the urine. Under pathological situations, podocytes upregulate the synthesis of uPAR, which then couples with integrins to activate the contractile podocyte apparatus that eventually leads to podocyte detachment. Podocyte loss precedes proteinuria and loss of renal function at initial stages of kidney diseases, particularly glomerulopathies. Podocyuria has been employed as a diagnostic tool in a wide variety of glomerular disorders. Unravelling the mechanisms of podocyte detachment may lead to targeted therapeutic interventions that could delay the progression of chronic kidney diseases, as shown by the decrease of podocyte loss when amiloride is employed.

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Retrospective Study

Prevalence and outcome of acute kidney injury, as defined by the new Kidney Disease Improving Global Outcomes guideline, in very low birth weight infants

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Abstract

AIM

To evaluate the prevalence, risk factors and outcome of acute kidney injury (AKI) in very low birth weight (VLBW) infants.

METHODS

In this retrospective study of VLBW infants, we analyzed the prevalence of AKI, as defined by changes in serum creatinine and urine output, associated risk factors and outcomes.

RESULTS

A total of 293 VLBW infants (mean gestational age 28.7 wk) were included, of whom 109 weighed less than 1000 g at birth. The overall prevalence of AKI was 11.6% (22% in infants with a birth weight under 1000 g and 5.4% those heavier). A total of 19 (55%) affected infants died, with a mortality rate of 58% in infant less than 1000 g and 50% in those heavier. After adjusting for confounding variables, only necrotizing enterocolitis (NEC) remained associated with AKI, with odds ratio of 4.9 (95%CI: 1.9-18.6). Blood pressure and glomerular filtration rate (GFR) were not different between affected infants and the others upon discharge from hospital. A normal GFR was documented in all affected infants at one year of age.

CONCLUSION

Using Kidney Disease Improving Global Outcomes definition of AKI, it occurred in over 10% of VLBW infants,

more commonly in infants with lower birth weight. NEC was an independent associated risk factor. Renal function, as defined by GFR, was normal in all surviving affected infants 10 to 12 mo later.

Key words: Newborn; Case-control; Risk factors; Acute renal failure; Mortality; Kidney Disease Improving Global Outcomes

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Core tip: Our study is the first study from United Arab Emirates, dealing with neonatal acute kidney injury (AKI); After using many different definition in reporting AKI in the past, Kidney Disease Improving Global Outcomes started a new definition trying to stage AKI into different stages; Retrospectively our study is using this definition and apply it to all infants admitted to our unite to identify the incidence and risk factors associated with AKI in different gestational age; Our study revealed that extreme premature babies are more susceptible to AKI and this disease is linked to other neonatal morbidities like Necrotizing Enter colitis, sepsis and can predict higher mortality.

Al Malla M, Varghese NV, AlAbdullatif M, Narchi H, Khassawneh M. Prevalence and outcome of acute kidney injury, as defined by the new Kidney Disease Improving Global Outcomes guideline, in very low birth weight infants. *World J Nephrol* 2017; 6(5): 229-235 Available from: URL: <http://www.wjgnet.com/2220-6124/full/v6/i5/229.htm> DOI: <http://dx.doi.org/10.5527/wjn.v6.i5.229>

INTRODUCTION

At birth the kidneys receive 2.5% to 4% of the cardiac output which subsequently increases to 6%, 10%, 15%, at 24 h, one week and six weeks of age respectively^[1,2]. Similarly, the glomerular filtration rate (GFR) improves steadily over the first few months of life, reaching adult level by the age of two years^[3,4]. Preterm infants are more likely to develop acute kidney injury (AKI) as they usually require intensive care admission, are more prone to develop sepsis and hypotension, in addition to being administered potentially nephrotoxic medications^[5]. AKI is defined as a decline in kidney function that includes fluid imbalance and electrolytes disturbances with elevated waste products^[6]. Although serum creatinine (SCr) measurement is commonly used to evaluate kidney function, it unfortunately remains a suboptimal test for kidney injury^[5]. This is because a significant loss of kidney function must occur before SCr starts to rise^[3]. Furthermore, as in first few days of life the infant's SCr concentration directly reflects his mother's, baseline neonatal SCr level cannot easily be defined during that period^[7].

Over the last two decades, AKI has been studied in different age group, including neonates^[8]. It has been

shown to be common in the neonatal period, especially among preterm infants, but also in term infants with birth asphyxia or those requiring extracorporeal membrane oxygenation (ECMO) therapy^[9,10]. In very low birth weight (VLBW) neonates, the reported incidence of AKI varied between 12% and 39%, with a mortality rate reaching up to 70%^[11-13]. Risk factors associated with it include essentially pre-renal causes^[12], VLBW^[14], prematurity^[14], low Apgar scores^[15], sepsis^[16,17], hypotension requiring inotropic support^[12,17,18], patent ductus arteriosus (PDA)^[15], necrotizing enterocolitis (NEC)^[12,17], surgery^[17], cerebral insult^[17] or exposure to nephrotoxic medications such as vancomycin, gentamicin or ibuprofen^[15].

Most reports, however, were retrospective single-center studies, with small sample size and using various definitions of AKI. Recently, a simplified definition, staging neonatal AKI into three stages (mild, moderate, and severe) and relying on changes in SCr and urine output, has been developed by the Kidney Disease Improving Global Outcomes (KDIGO)^[19]. With this new definition, studies are now needed to validate this definition and its staging system to predict mortality and morbidity. In addition, very little has been published on neonatal AKI in this part of the world.

This study aims, therefore, to retrospectively ascertain the incidence of AKI in VLBW infants admitted to a tertiary neonatal intensive care unit between 2013 and 2015, using the new KDIGO definition. Associated risk factors and outcomes of infants with and without AKI will be evaluated.

MATERIALS AND METHODS

This is a retrospective case-control study on AKI in a cohort of VLBW infants.

Inclusion criteria

VLBW infants admitted to a 41-bed tertiary neonatal intensive care unit (NICU) in Al Ain, United Arab Emirates during a three-year period (between January 1st, 2013-December 31st, 2015) were included.

Exclusion criteria

These included infants with congenital renal disorder or who died in first 24 h of life without enough time to assess kidney function.

Data collection

Data file was retrospectively collected from the patients' electronic medical record and included: Demographic data (gestational age, birth weight, gender, nationality), maternal age, prenatal exposure to corticosteroid, mode of delivery, occurrence of AKI, associated risk factors (hypotension, need for inotropic medication, intraventricular haemorrhage (IVH), NEC, PDA, duration of mechanical ventilation, sepsis, surgery, placement of umbilical arterial catheter, postnatal medications such as corticosteroids, ibuprofen, dopamine, antibiotics such as gentamycin, vancomycin, urine output if documented,

Table 1 Characteristics of the 293 studied infants, *n* (%) unless stated otherwise

Males	142 (48)
Birth weight (g): median (range)	1130 (450-1860)
Gestational age (mean, SD)	28.7 (2.8)
Mode of delivery	
Vaginal delivery	53 (18)
Cesarean section	240 (82)
Maternal steroids	217 (74)
Intraventricular hemorrhage	
Grade 1	16 (5)
Grade 2	10 (3)
Grade 3	13 (5)
Grade 4	16 (5)
Periventricular leukomalacia	12 (4)
Necrotizing enterocolitis	30 (10)
Patent ductus arteriosus	
Tiny	34 (11)
Moderate	39 (13)
Large	25 (8)
Sepsis	
Clinical sepsis	61 (21)
Sepsis with normotension	24 (8)
Sepsis with hypotension	26 (9)
Duration of mechanical ventilation (d): median (range)	3 (1-410)
Surgery required	22 (7)
Inotrope use	59 (20)
Ibuprofen use	63 (21)
Vancomycin use	84 (29)
Gentamycin use	203 (69)
Post natal Steroids use	38 (13)
Umbilical arterial catheter use	158 (54)
Oliguria	
< 0.5 mL/kg per hour for 6 h	3 (1)
< 0.3 mL/kg per hour for 24 h	10 (3)
Hypotension	58 (20)
Normal saline intravenous bolus	50 (17)
Furosemide	12 (4)
Duration of hospital stay (d): median (range)	49 (1-480)
Acute kidney injury	
Stage 1	6 (2)
Stage 2	12 (4)
Stage 3	16 (5)
Mortality	46 (17)

hypotension, estimated GFR calculated during the peak of creatinine rise, therapy with loop diuretics, normal saline bolus infusions, mean blood pressure and SCr at the time of discharge. Outcome data included survival and duration of hospitalization, follow up at 12 mo of age with calculation of the estimated GFR.

AKI was defined using KDIGO criteria in neonates^[5,19]. Both, changes in SCr value or urine output were identified for each patient in order to classify the degree of AKI. GFR was calculated with the Schwartz formula using the highest SCr concentration at the time of AKI diagnosis^[4]. Sepsis was defined by a positive blood culture. Clinical sepsis was defined when a symptomatic infant had no growth in the blood culture but had elevated serum C reactive protein (CRP) concentration, or leukopenia, or leucocytosis, or an elevated immature to total neutrophils (IT) ratio and received at least seven days of antibiotics^[20]. Necrotising enterocolitis was

Table 2 Stages of acute kidney injury in 34 infants by birth weight *n* (%)

AKI stages	Birth weight		Total <i>n</i> = 293
	≥ 1000 g <i>n</i> = 184	< 1000 g <i>n</i> = 109	
1	2 (1.0)	4 (3.7)	6 (2.0)
2	3 (1.6)	9 (8.2)	12 (4.1)
3	5 (2.7)	11 (10.1)	16 (5.4)
Total	10 (5.4)	24 (22.0)	34 (11.6)

AKI: Acute kidney injury.

defined according to Bell's criteria^[21] and intra ventricular haemorrhage according to Papile's classification^[22].

The study was approved by the institutional research review board. Statistical analysis was done by a professional biostatistician. The normality of continuous variables was checked with the Shapiro-Wilk *W* test (only the gestational age had a normal distribution). Normally distributed variables were reported as mean and SD and the others as median value and range. AKI prevalence was reported as mean with 95% confidence intervals (CI).

Patient with AKI (cases) were compared with those without AKI (controls). In the univariate analysis, the comparison of the normally distributed continuous variables was conducted with the Analysis of Variance test (ANOVA) and those with non-normal distribution with the Kruskal-Wallis test. Proportions were compared with the χ^2 test and the Fisher exact test was used for small proportions. For all statistical analysis, significance was defined by a 2-tailed *P* < 0.05.

All factors associated in the univariate model with AKI or mortality of any cause with a *P*-value < 0.1 were subsequently entered in a logistic regression model. In that model, only the associations with a *P*-value < 0.05 were considered statistically significant and their odds ratio (OR) with 95%CI were calculated.

RESULTS

A total of 304 patients were included in this study. Eleven patients were excluded due to missing data or congenital renal anomalies or because they died in first 24 h of life. The remaining 293 infants were included in the analysis. Their general characteristics are detailed in Table 1. Some data were missing from a few children.

A total of 34 infants met the definition of AKI, of whom 13 (38%) were diagnosed using urine output criteria. The calculated overall prevalence of AKI was 11.6% (95%CI: 8.1-15.8). In infants with a birth weight under 1000 g, AKI had a prevalence of 22% (95%CI: 14.6-30.9) and in those over 1000 g it was 5.4% (95%CI: 2.6-9.7). The prevalence of the different stages of AKI by age is shown in Table 2 and Figure 1. All stages were more prevalent with lower birth weight. Furthermore, while the prevalence of all AKI stages was the same in infants over 1000 g, the more severe

Table 3 Patients with or without acute kidney injury, *n* (%) unless stated otherwise

	No AKI <i>n</i> = 259	Stage 1 AKI <i>n</i> = 6	Stage 2 AKI <i>n</i> = 12	Stage 3 AKI <i>n</i> = 16	Univariate analysis <i>P</i> value	Multivariate analysis ⁴ <i>P</i> value
Males	122 (47)	4 (67)	7 (58)	9 (56)	0.6 ¹	NS
Birth weight (g): mean (SD)	1130 (267)	976 (271)	791 (257)	850 (253)	< 0.001 ²	NS
Gestational age (wk): median (range)	29.0 (22-35)	28.0 (23-32)	25.0 (23-30)	25.5 (23-38)	< 0.001 ³	NS
Mode of delivery					0.03 ¹	NS
Vaginal delivery	40 (15)	1 (17)	3 (25)	9 (56)		NS
Cesarean section	219 (84)	5 (83)	9 (75)	7 (43)		NS
Maternal steroids	193 (74)	5 (83)	8 (67)	11 (69)	0.9 ¹	NS
Intraventricular hemorrhage					< 0.001 ¹	NS
Grade 1	15 (6)	1 (16)	0 (0)	0 (0)		NS
Grade 2	8 (3)	1 (16)	0 (0)	1 (6)		NS
Grade 3	9 (3)	1 (16)	1 (8)	2 (13)		NS
Grade 4	9 (4)	0 (0)	1 (8)	6 (40)		NS
Necrotizing enterocolitis	16 (6)	1 (16)	6 (50)	7 (43)	< 0.001 ¹	0.001
Patent ductus arteriosus					0.03 ¹	NS
Tiny	29 (11)	1 (16)	1 (8)	3 (18)		NS
Moderate	32 (12)	0 (0)	3 (25)	4 (25)		NS
Large	19 (7)	1 (16)	3 (25)	2 (12)		NS
Sepsis					< 0.001 ¹	NS
Clinical sepsis	45 (17)	3 (50)	6 (50)	7 (43)		NS
Sepsis with normotension	22 (8)	1 (16)	0 (0)	1 (6)		NS
Sepsis with hypotension	14 (5)	1 (16)	6 (50)	5 (31)		NS
Duration of mechanical ventilation (d): median (range)	2 (1-160)	3.5 (1-29)	17.5 (7-71)	13 (2-262)	< 0.001 ³	NS
Surgery required	11 (4)	1 (16)	4 (33)	6 (37)	< 0.001 ¹	NS
Inotrope use	37 (14)	2 (33)	8 (66)	12 (75)	< 0.001 ¹	NS
Ibuprofen use	51 (19)	1 (16)	7 (58)	4 (25)	0.01 ¹	NS
Vancomycin use	59 (22)	3 (50)	10 (83)	12 (75)	< 0.001 ¹	NS
Gentamycin use	173 (66)	5 (83)	11 (91)	14 (87)	0.08 ¹	NS
Steroids use	24 (9)	1 (16)	6 (50)	7 (43)	< 0.001 ¹	NS
Umbilical arterial catheter use	129 (49)	5 (83)	8 (66)	16 (100)	< 0.001 ¹	NS
Oliguria					< 0.001 ¹	NS
< 0.5 mL/kg per hour for 6 h	0 (0)	0 (0)	1 (8)	2 (12)		NS
< 0.3 mL/kg per hour for 24 h	0 (0)	1 (16)	3 (25)	6 (37)		NS
Hypotension	35 (13)	2 (33)	9 (75)	12 (75)	< 0.001 ¹	NS
Normal saline intravenous bolus	28 (10)	2 (33)	9 (75)	11 (68)	< 0.001 ¹	NS
Furosemide	4 (1)	1 (16)	3 (25)	4 (25)	< 0.001 ¹	NS
Duration of hospital stay in survivors (d): median (range)	52 (15-280)	64.5 (53-125)	74.5 (7-116)	116 (44-362)	0.02 ³	NS
Mortality	27 (10)	2 (33)	8 (66)	9 (56)	< 0.001 ¹	NS
Serum creatinine (μmol/L) on discharge: median (range)	44 (23)	64 (56)	93 (47)	133 (135)	< 0.001 ³	NS
Mean blood pressure (mmHg) on discharge: median (range)	55 (13)	48 (24)	38 (13)	41 (19)	< 0.001 ³	NS

¹χ² or Fisher exact test; ²Analysis of variance (ANOVA); ³Kruskal-Wallis test; ⁴Logistic regression. NS: Not significant; AKI: Acute kidney injury.

stages were more prevalent in those under 1000 g.

The univariate association of risk factors with AKI is shown in Table 3. Lower birth weight and gestational age, delivery by cesarean section, presence of IVH, NEC, PDA, sepsis, duration of mechanical ventilation, surgery, administration of inotropes, ibuprofen, vancomycin, corticosteroids, normal saline boluses, furosemide, insertion of an umbilical arterial catheter and hypotension were all significantly associated with the development of AKI. However, after adjustment for confounders in a multivariable regression model (Table 3), only NEC remained independently and significantly associated with the development of AKI, with odds ratio of 4.9 (95%CI: 1.9-18.6).

Table 4 shows the duration of hospital stay and the

mortality of any cause in the infants with AKI. Length of hospital stay was significantly longer in surviving infants with a developed AKI (*P* = 0.003). Mortality was significantly higher in infants under 1000 g than in heavier neonates and increased significantly in those who developed AKI in both weight groups (Table 4 and Figure 1). After adjusting for confounders in a multivariable regression model, the only factors significantly associated with mortality were the presence of AKI (OR = 4.4, 95%CI: 1.3-14.5, *P* = 0.01), NEC (OR = 3.1, 95%CI: 0.9-10.0, *P* = 0.05) and sepsis (OR = 19.5, 95%CI: 2.1-181.4, *P* = 0.009).

There was no significant difference in SCr or blood pressure between surviving affected infants and the others at discharge from hospital (Table 3). At one year

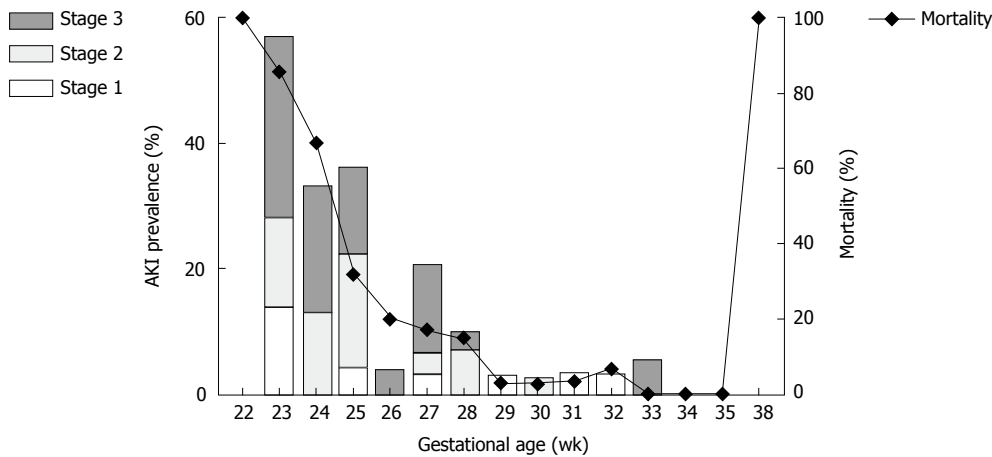


Figure 1 Prevalence of acute kidney injury stages and mortality of all causes (%) by birth weight in 293 low birth weight infants. AKI: Acute kidney injury.

Table 4 Outcomes, *n* (%) unless stated otherwise

	No AKI <i>n</i> = 259	Any stage AKI <i>n</i> = 34	<i>P</i> value
Length of stay in survivors: median (range)			
BW ≤ 1000 g (<i>n</i> = 108)	82 (37-280)	112 (7-362)	0.3 ²
BW > 1000 g (<i>n</i> = 184)	40 (15-149)	53 (35-137)	0.003 ²
Mortality of any cause			
BW ≤ 1000 g (<i>n</i> = 108)	18 (21)	14 (58)	< 0.001 ¹
BW > 1000 g (<i>n</i> = 184)	9 (5)	5 (50)	< 0.001 ¹

¹ χ^2 or Fisher exact test; ²Kruskal-Wallis test. Number of infants in birth weight categories is not identical in all outcomes as some data was missing. AKI: Acute kidney injury; BW: Birth weight.

of age, the mean (SD) GFR of the surviving affected infants was 80.7 (25.6) mL/min per 1.73 m², with a mean (SD) increase of 69.8 (28.4) mL/min per 1.73 m² since the diagnosis of AKI, with no child requiring renal replacement therapy. None of the surviving infants with AKI were given follow up appointment with a pediatric nephrologist at the time of discharge.

DISCUSSION

In this study, the prevalence of AKI using the new KDIGO definition was 11.6%. Applying the KDIGO criteria for defining stage one AKI in this cohort of 304 infants was challenging. The lack of measurement and documentation of hourly urine output, associated with the difficulty in having two SCr levels measured 48 h apart made the diagnosis of stage 1 AKI difficult to achieve. This may explain the lower prevalence of AKI in our series when compared to a previous report. Similar to another recent study using the new definition, our results confirmed that smaller infants are more likely to develop AKI stage 2 or 3, with also a higher mortality^[23].

Among the risk factors, only NEC was significantly

and independently associated with AKI. The development of NEC in an infant should alert the neonatologist to the increased risk of AKI with the need to closely monitor hemodynamics, kidney function and urine output. As the value of hemodynamic assessment in VLBW infants is based on unreliable interpretation of their vital signs, newer biomarkers, such as neutrophil gelatinase-associated lipocalin and serum cystatin C^[12,13,24,25], or non-invasive newer techniques such as near-infrared spectroscopy^[26] may aid in the early detection of AKI in these children at higher risk.

Although the duration of hospital stay was longer with increasing grades of AKI, the difference was not statistically significant. In infants weighing less than 1000 g, there was no difference between those who developed AKI of any grade and the others. This could be explained by their higher mortality rate, exceeding 58%. However, in surviving infants, hospital stay was significantly longer in neonates who developed AKI than those who did not. All the 19 surviving infants who had AKI in the neonatal period were followed for one year and had GFR in the normal range.

Weaknesses in this study included its retrospective design, with missing data on some infants. The relatively small sample size may have precluded the estimation of the association of AKI with some of the risk factors. In addition, the urine output KDIGO criterion to define AKI was difficult to obtain because the urine output was not documented on an hourly basis, but was only documented by the physicians whenever it exceeded 24 h. Similarly, the other KDIGO criterion to define AKI stage one (increase in SCr by 0.3 mg/dL in the previous 48 h) was not available for all infants as it was not clinically indicated before the onset of AKI.

AKI is common in VLBW infants, with a high mortality rate, and is significantly and independently associated with NEC. Despite the difficulty is recognizing grade one AKI because of the unavailability of some of the data, AKI staging using the KDIGO criteria is a strong predictor of mortality. A longer follow up of surviving VLBW infants with AKI is still required.

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COMMENTS

Background

Acute kidney injury (AKI) is defined as a decline in kidney function that includes fluid imbalance and electrolytes disturbances with elevated waste products. It is commonly reported in preterm infants and, recently, the Kidney Disease Improving Global Outcomes (KDIGO) has advocated a simplified definition of neonatal AKI, dividing it into three stages based on changes in serum creatinine and urine output. As more data is needed on the prevalence of that condition and its outcome in very low birth weight (VLBW) infants based on that new definition, the authors report recent experience in a tertiary neonatal intensive care unit. The authors report the prevalence of AKI, its associated risk factors and outcomes, including post-discharge follow up results of serum creatinine and blood pressure.

Research frontiers

Very little has been published on neonatal AKI in the Gulf region and only a limited number of studies in developed countries have tried to evaluate this new definition of AKI, with its validity in predicting the outcome of affected VLBW infants. Long term follow of these infants after discharge is also currently lacking. This study attempts to address these current limitations.

Innovations and breakthroughs

AKI was common in VLBW infants and carries a high mortality rate. It is significantly and independently associated with necrotizing enterocolitis (NEC). The new KDIGO AKI staging criteria strongly predict mortality. Blood pressure (BP) and glomerular filtration rate (GFR) were not different between surviving affected infants and the others upon discharge from hospital and all affected infants had a normal GFR up to one year of age.

Applications

AKI is common in VLBW infants and the new KDIGO definition strongly predicts mortality and long-term outcome. AKI is associated with other neonatal illness, especially NEC. Longer follow up studies of affected infants, including BP, are still required.

Peer-review

This is a very good manuscript facing with the new classification of AKI in infants according KDIGO.

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Observational Study

Restless legs syndrome is contributing to fatigue and low quality of life levels in hemodialysis patients

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Abstract

AIM

To examine whether hemodialysis (HD) patients with restless legs syndrome (RLS) are subjects of greater fatigue and impaired quality of life (QoL) compared to HD patients without RLS.

METHODS

Eighty five stable HD patients participated in this study. According to their RLS status, the patients were divided

into the RLS group ($n = 23$) and the non-RLS group ($n = 62$). QoL, fatigue, sleep quality, daily sleepiness and depression symptoms were assessed by using various questionnaires. Finally, biochemical parameters including iron, ferritin, hemoglobin, hematocrit and parathormone were assessed.

RESULTS

The HD patients with RLS scored worse in all the questionnaires used in the study ($P < 0.05$). The patients with RLS were more likely to receive the HD therapy on the morning shift, whilst 43.5% of the RLS patients reported to experience the RLS symptoms also during HD. The severity of RLS was correlated with fatigue, depression score and sleep quality ($P < 0.05$).

CONCLUSION

HD patients with RLS are subject to lower QoL related parameters and greater fatigue compared to HD patients without RLS. RLS should be successfully managed in order to improve the QoL of the sufferers.

Key words: Sleep quality; Depression; Secondary restless legs syndrome; Fatigue; Quality of life

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Core tip: Restless legs syndrome (RLS) is very common in patients receiving hemodialysis therapy. It seems that the hemodialysis patients who suffer also from RLS are subject of greater fatigue levels and they are experience even more impaired quality of life, sleep quality, daily sleepiness and depression symptoms compared to their free RLS counterparts.

Giannaki CD, Hadjigavriel M, Lazarou A, Michael A, Damianou L, Atmatzidis E, Stefanidis I, Hadjigeorgiou GM, Sakkas GK, Pantzaris M. Restless legs syndrome is contributing to fatigue and low quality of life levels in hemodialysis patients. *World J Nephrol* 2017; 6(5): 236-242 Available from: URL: <http://www.wjgnet.com/2220-6124/full/v6/i5/236.htm> DOI: <http://dx.doi.org/10.5527/wjn.v6.i5.236>

INTRODUCTION

Restless legs syndrome (RLS) (also called as Willis-Ekbom disease) is a sensory-motor sleep disorder which is very common in hemodialysis (HD) patients. It is called also as uremic RLS and it is affecting almost 30% of the HD population^[1].

According to the literature, the symptoms' severity of uremic RLS is worse compared to the idiopathic RLS^[2], whilst a number of studies highlight the negative effects of this extremely distressing sleep disorder on many aspects of the patient's quality of life (QoL), overall health and wellbeing^[1].

In particular, data derived mainly from cross-sectional studies reveal that the HD patients with RLS

experience significantly poorer sleep quality^[3], increased insomnia^[4] and motor activity during sleep^[5], higher depression symptoms^[6], increased anxiety levels^[7] and increased muscle atrophy^[6] compared to HD patients without RLS. Moreover, RLS motor and sensory symptoms may appear also during HD therapy^[8] inducing significant disturbance of the patient's rest and patience. Therefore is not surprising that the HD patients with RLS are characterized by even poorer QoL levels compared to HD patients without RLS^[1].

On the other hand, it is well known that the majority of the HD patients have significant levels of fatigue^[9]. Fatigue experienced by the HD patients has both mental and physical aspects and could significantly affect the QoL levels of this specific population^[10]. In the study by Jhamb *et al.*^[11], fatigue was independently associated, among others, with sleep quality and RLS.

The current study aimed to investigate potential differences in QoL, depression levels, sleep quality, fatigue and daily sleepiness status between HD patients with and without RLS. Taking into account the considerable negative effect of RLS on many physical and mental related parameters and especially on sleep, we hypothesize that the HD patients with RLS will present significantly greater fatigue and lower QoL levels compared to their free-RLS counterparts.

MATERIALS AND METHODS

Eighty-five out of 102 HD patients volunteer to participate in this study. Patients were recruited from the HD units of the General Hospitals of Larnaca and Limassol, Cyprus. After a brief discussion of the purpose of the study and the procedures to be followed, the patients who voluntarily agreed to participate to the study and gave written informed consent included in the cohort. Inclusion criteria were as follows: Being in HD therapy 3 times per week at least 3 mo and with stable clinical condition. Patients received the HD therapy with the morning shift either with the noon shift, both using hollow-fiber dialysers and bicarbonate buffer. Exclusion criteria included treatment with dopamine agonists prior to the study and cognitive inability to complete the various questionnaires.

RLS was diagnosed using the International RLS study group criteria^[12], whilst RLS severity was assessed by using the International RLS Severity Scale (IRLS)^[13]. Information related to when the first RLS symptoms appeared (before or after the institution of HD therapy), whether other members of the patients suffer also from RLS and whether the symptoms of RLS appear also during HD therapy were obtained also.

All patients provided a written consent for participation to the study, which conformed to the principles enumerated in the Helsinki Declaration of 1975. The study was approved by the National Bioethics Committee of Cyprus.

Questionnaires

QoL levels were evaluated using the SF-36 question-

Table 1 Patient's characteristics presented as pool data and divided in two groups according to restless legs syndrome diagnosis

Variables	Patients pool data	RLS	Non-RLS	P value
<i>n</i>	85	23	62	-
Female/male	54/31	10/13	21/41	0.414 ¹
Age (yr)	67.3 ± 11.4	67.8 ± 9.6	67.1 ± 12.1	0.801
95%CI	64.8 to 69.8	63.6 to 73.0	64.1 to 70.2	
Weight (kg)	73.3 ± 15.9	77.3 ± 20.4	72.0 ± 14.1	0.205
95%CI		67.5 to 87.2	68.3 to 75.7	
Dialysis shift morning/noon	54/31	4/19	35/27	0.026 ¹
Years in hemodialysis	4.7 ± 5.1	5.2 ± 4.9	4.5 ± 5.2	0.592
95%CI	3.6 to 5.8	3.1 to 7.3	3.2 to 5.9	
IRLS score	-	21.8 ± 6.1	-	-
95%CI		19.1 to 24.5		
Iron (µg/dL)	44.7 ± 18.2	43.0 ± 16.6	45.4 ± 19.0	0.741
95%CI	38.2 to 51.2	30.2 to 55.7	37.3 to 53.4	
Ferritin (ng/mL)	514.4 ± 411.7	443.7 ± 356.5	547.4 ± 441.5	0.567
95%CI	344.4 to 684.3	145.6 to 741.8	320.4 to 774.6	
Hct	36.4 ± 5.3	33.9 ± 5.6	37.7 ± 4.9	0.111
95%CI	34.2 to 38.7	29.2 to 38.7	35.1 to 40.3	
Hb (g/dL)	11.1 ± 1.5	10.1 ± 1.6	11.4 ± 1.4	0.022
95%CI	10.5 to 11.6	8.9 to 11.3	10.8 to 12.0	
Parathormone (pmol/L)	4.9 ± 1.9	4.8 ± 1.7	4.9 ± 2.0	0.97
95%CI	4.2 to 5.5	3.6 to 6.1	4.0 to 5.8	
Albumin (g/dL)	3.6 ± 0.3	3.6 ± 0.3	3.6 ± 0.3	0.853
95%CI	3.5 to 3.8	3.4 to 3.9	3.5 to 3.8	
Diabetes (%)	30 (35.3)	9 (39.1)	21 (33.9)	0.765 ¹
Hypertension (%)	30 (35.3)	8 (34.8)	22 (35.5)	0.832 ¹

¹For categorical data a χ^2 test performed. All data are mean ± SD (95%CI). IRLS: International restless legs syndrome severity scale; Hct: Hematocrit; Hb: Hemoglobin.

naire^[14]. Fatigue levels were assessed by using the fatigue severity scale (FSS)^[15]. The patients' depression symptoms were assessed by using the self-rating depression scale developed by Zung^[16]. Daily sleepiness status was assessed by using the Epworth Sleepiness Scale (ESS)^[17]. Finally, the patients' subjective sleep quality was assessed by the Pittsburgh sleep quality index (PSQI)^[18].

Biochemical assessment

The patient's routine monthly laboratory results were recorded including iron (photometry), ferritin (spectrophotometry, Beckman Coulter AU 680 Chemistry Analyzer), hematocrit, haemoglobin [sodium lauryl sulfate (SLS) method], albumin (photometry) and parathormone (chemiluminescence, ARCHITECT assay, Abbott Laboratories, Wiesbaden, Germany). The biochemical analysis was performed at the clinical labs of the affiliated hospitals under standard hospital procedures.

Statistical analysis

The differences between the RLS and the non-RLS group in regards to the various variables were examined using independent samples *t* test. χ^2 tests were used in order to compare the two groups for categorical variables. The Pearson correlation test was used to assess the relationship between the examined variables. All data are presented as mean ± SD and the level of statistical significance was set at *P* < 0.05. All analyses were carried out using the SPSS Statistical Package version 19. The statistical review of the study was performed by

a biomedical statistician.

RESULTS

Twenty-three out of 84 patients (27%) were diagnosed to experience RLS symptoms, whilst 10 out of those 23 RLS patients reported to experience the RLS symptoms also during HD (43.5%). Only 2 patients reported that a member of their family experience also RLS symptoms (8.7%), whereas 3 patients reported to experience the RLS symptoms before the institution of the HD treatment (13%).

The patients' characteristics are presented in Table 1. The patients with RLS were found to have lower hemoglobin levels (*P* = 0.022) compared to the patients without RLS. In addition, the patients with RLS were more likely to receive the HD therapy on the morning shift (*P* = 0.026).

Depression, fatigue, daytime sleepiness and sleep quality data are presented in Table 2. QoL data are presented in Table 3. All the examined parameters were found to be significantly worse in the RLS patients compared to the free-RLS patients (*P* < 0.05). Finally, the IRLS score positively correlated with PSQI (*r* = 0.477, *P* = 0.025), depression score (*r* = 0.551, *P* = 0.010) and fatigue index (*r* = 0.582, *P* = 0.004).

DISCUSSION

The main finding of the current study is that the

Table 2 Depression, fatigue, daytime sleepiness and sleep quality data presented as pool data and divided in two groups according to restless legs syndrome diagnosis

Variables	Patients pool data	RLS	Non-RLS	P value
Pittsburgh sleep quality index	7.8 ± 5.1	13.9 ± 2.9	5.5 ± 3.6	0
95%CI	6.6 to 7.9	12.6 to 15.2	4.6 to 6.5	
Epworth sleepiness scale	4.3 ± 3.6	6.8 ± 4.3	3.4 ± 2.8	0
95%CI	3.5 to 5.1	4.9 to 8.7	2.6 to 4.1	
Zung depression scale	60.8 ± 7.1	58.0 ± 4.0	48.3 ± 6.1	0
95%CI	49.2 to 52.4	56.1 to 59.8	46.7 to 49.9	
Fatigue severity scale index	4.5 ± 1.2	5.8 ± 0.7	4.1 ± 1.1	0
95%CI	4.3 to 4.8	5.4 to 6.1	3.8 to 4.3	

All data are mean ± SD (95%CI). RLS: Restless legs syndrome.

Table 3 Quality of life data presented as pool data and divided in two groups according to restless legs syndrome diagnosis

Variables	Patients pool data	RLS	Non-RLS	P value
SF-36 MCS	55.3 ± 16.7	46.6 ± 15.4	58.5 ± 16.1	0.004
95%CI	51.6 to 59.0	39.8 to 53.5	54.3 to 62.7	
SF-36 PCS	51.8 ± 19.4	40.6 ± 18.1	56.1 ± 18.2	0.001
95%CI	47.5 to 56.1	32.5 to 48.6	51.2 to 60.8	
SF-36 total score	55.1 ± 18.8	45.5 ± 17.7	58.7 ± 18.1	0.004
95%CI	51.0 to 59.3	37.6 to 53.3	54.0 to 63.4	
Physical function	46.9 ± 29.1	38.4 ± 28.2	50.1 ± 29.1	0.107
95%CI	40.5 to 53.4	25.8 to 50.9	42.5 to 57.7	
Role physical	45.3 ± 42.4	28.4 ± 38.8	51.6 ± 42.2	0.027
95%CI	35.9 to 54.7	11.2 to 45.6	40.6 to 42.7	
Body pain	72.3 ± 23.1	63.9 ± 24.3	75.4 ± 22.0	0.045
95%CI	67.1 to 77.4	53.1 to 74.7	69.6 to 81.1	
General health	47.0 ± 16.4	37.1 ± 14.5	50.7 ± 15.6	0.001
95%CI	43.4 to 50.6	30.6 to 43.5	46.6 to 54.8	
Vitality	48.3 ± 16.1	36.1 ± 14.5	52.8 ± 14.2	0
95%CI	44.7 to 51.8	29.6 to 42.5	49.1 to 56.6	
Social functioning	71.8 ± 20.8	65.5 ± 21.7	74.1 ± 20.2	0.098
95%CI	67.2 to 76.4	55.9 to 75.1	68.9 to 79.4	
Mental health	52.2 ± 45.3	43.9 ± 47.5	55.3 ± 44.4	0.316
95%CI	42.2 to 62.3	22.8 to 65.0	43.7 to 66.9	
Reported health	57.1 ± 12.1	50.7 ± 10.7	59.5 ± 11.8	0.003
95%CI	54.4 to 59.8	45.9 to 55.4	56.4 to 62.6	

All data are mean ± SD (95%CI). SF-36: 36-Item Short Form Health Survey; MCS: Mental component score; PCS: Physical component score; RLS: Restless legs syndrome.

HD patients who suffer also from RLS are subject of greater fatigue levels and they are experience even more impaired QoL, sleep quality, daily sleepiness and depression symptoms compared to HD patients without RLS.

Many factors could contribute to the increased fatigue levels of the HD patients. Recent studies indicate sleep disorders as one of the major factors which may be responsible for the elevated fatigue levels of the HD patients^[10]. Interestingly, in line with our findings, RLS has been reported to associate with greater fatigue levels in patients on HD^[11].

RLS is a sleep disorder which is highly prevalent in the HD population^[11]. Approximately 27% of the studied patients were diagnosed to experience RLS symptoms; a prevalence which is in line with the published literature in the field^[11]. We should note that those are the first data regarding RLS from Cyprus.

In addition, approximately 43.5% of the RLS patients reported to experience the RLS symptoms during HD therapy, factor that may contribute to increase fatigability of the patients during their treatment. On the other hand, the findings of the current study reveal that the patients with RLS have significantly worse daily sleepiness status, in line with previous findings^[7,19]. Daily sleepiness has been shown to be associated with fatigue in patients receiving HD therapy^[11]. Finally, the data of the current study confirm the well known negative effect of uremic RLS on sleep quality^[1,4], whilst the severity of RLS was correlated with poor sleep quality.

Taking into consideration the fact that many HD patients experience elevated fatigue symptoms^[9,20] and the fact that RLS may contribute to even greater fatigue symptoms, successful management of RLS may help those patients to reduce among others also fatigue and

tiredness feelings. It is known that exercise training alone^[21-23] or in combination with dopamine agonists^[24] could ameliorate the severity of uremic RLS symptoms. On the other hand, evidence exists regarding the favorable effect of exercise training on fatigue levels of HD patients, however, RLS presence was not taken into consideration in these studies^[20]. It would be interesting in future studies to investigate the effects of chronic exercise training on fatigue levels in patients with uremic RLS.

Morning-shift HD was found to associated with RLS, in contrast with previous studies^[25,26], however, we should note that the association between the time of HD delivery and RLS is still controversial. In addition, hemoglobin levels observed to be significantly lower in the RLS group, confirming previous data^[27]. Notably, low haemoglobin levels may contribute to greater levels of fatigue in the HD population^[28]. However, we should note that many cross-sectional studies did not confirm an association between lower hemoglobin levels and RLS presence in HD patients^[6].

According to the literature, familial component appear to be high in idiopathic RLS^[29]. In contrast, familial component reported to be significantly lower in patients with uremic RLS compared to idiopathic RLS^[30]. In the current study, approximately 9% of the RLS patients reported that a member of their family experience also RLS symptoms, in line with previous data which reported similar prevalence^[30]. In addition, 13% of the RLS patients reported that they were experience the RLS symptoms before the start of the HD treatment, showing the association of renal disease and RLS. Interestingly, the RLS symptoms have been reported to ameliorated or disappeared after kidney transplantation^[31]. Moreover, no gender differences were found in regards to the RLS presence in our study, confirming previous studies^[32], and in contrast to others^[27].

Diabetes prevalence did not differ between groups. It is known that RLS has been linked to various diseases, including diabetes and hypertension^[33]. In the current study no such an association was found between RLS presence and diabetes and hypertension presence.

Depression score was found to be significantly worse in the patients with RLS compared to the patients without RLS, confirming previous studies the RLS group^[6,34]. Moreover, depression score was correlated with the severity of RLS. The depressing effect of RLS on various parameters which are known to affect fatigue levels in HD patients such as sleep, QoL and depression^[20,35] and the distressful nature of the syndrome itself may explain the higher depression score of the patients of the RLS group.

In conclusion, the findings of the current study confirm the negative effect of RLS on many aspects of QoL, including greater fatigue levels. Measures should be taken in order to manage the RLS symptoms and improve the QoL and general health of the patients with uremic RLS.

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COMMENTS

Background

Restless legs syndrome (RLS) (also called as Willis-Ekbom disease) is a sensory-motor sleep disorder which is very common in hemodialysis patients. Evidence reveals that RLS negatively affects various aspects of health and quality of life (QoL) in patients receiving hemodialysis (HD) therapy.

Research frontiers

It is well known that fatigue is one of the most common symptoms experienced by hemodialysis patients. However, it is not clear whether the hemodialysis patients who suffer also from RLS are subjects of greater fatigue levels compared to their free-RLS counterparts.

Innovations and breakthroughs

The main finding of the current study is that the hemodialysis patients who suffer also from RLS are subject of greater fatigue levels and they are experience even more impaired QoL, sleep quality, daily sleepiness and depression symptoms compared to hemodialysis patients without RLS. Those are the first published data regarding uremic RLS from Cyprus.

Applications

RLS could induce further impairments on various QoL and overall health parameters in patients receiving hemodialysis therapy. Given that almost 30% of the hemodialysis patients suffer from RLS, measures should be taken (pharmacological or non-pharmacological) in order to ameliorate the RLS symptoms and improve QoL and overall health of the hemodialysis patients.

Terminology

RLS characterized by an irresistible need to move the legs, usually accompanied by unpleasant sensations. The symptoms of RLS begin or worsen during periods of rest and inactivity (usually at night) resulting in a significant sleep disturbance. The urge to move or unpleasant sensations are partially or totally relieved by movement at least as long as the activity continues.

Peer-review

The paper is well-written.

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Abstract

Atypical hemolytic-uremic syndrome (aHUS) is a rare disease of complement dysregulation leading to thrombotic microangiopathy (TMA). Renal involvement and progression to end-stage renal disease are common in untreated patients. We report a 52-year-old female patient who presented with severe acute kidney injury, microangiopathic hemolytic anemia, and thrombocytopenia. She was managed with steroid, plasma exchange, and dialysis. Kidney biopsy shows TMA and renal cortical necrosis. Genetic analysis reveals heterozygous complement factor I (CFI) mutation. Eculizumab was initiated after 3 mo of presentation, continued for 9 mo, and stopped because of sustained hematologic remission, steady renal function, and cost issues. Despite this, the patient continued to be in hematologic remission and showed signs of renal recovery, and peritoneal dialysis was stopped 32 mo

after initiation. We report a case of aHUS due to CFI mutation, which, to the best of our knowledge, has not been reported before in Saudi Arabia. Our case illustrates the challenges related to the diagnosis and management of this condition, in which a high index of suspicion and prompt treatment are usually necessary.

Key words: Thrombotic microangiopathy; Atypical hemolytic-uremic syndrome; Complement factor I mutation

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Core tip: Atypical hemolytic-uremic syndrome (aHUS) is a rare disorder. In some cases, complement mutation can be identified. The most common cases involved mutations of genes for complement factor H and membrane co-factor protein, whereas rare cases were linked to complement factor I (CFI) mutation. We here describe the first case of aHUS due to CFI mutation in Saudi Arabia. Our case presented with interesting characteristics including late recovery of kidney failure from dialysis upon initiation of eculizumab and persistent hematologic and renal remissions despite discontinuation of eculizumab.

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INTRODUCTION

Thrombotic microangiopathy (TMA) is a life-threatening syndrome characterized by systemic microvascular occlusions, thrombocytopenia, microangiopathic hemolytic anemia, and renal or other end-organ damage^[1,2]. TMA may complicate several conditions, such as systemic infections, cancer, pregnancy complications, autoimmune diseases, organ transplantation, and severe hypertension^[1].

Atypical hemolytic-uremic syndrome (aHUS) is a rare, progressive, life-threatening form of TMA caused by a disorder in complement regulation, predominantly dysregulation of the complement alternative pathway^[3,4]. The underlying pathogenesis is complement gene mutations in the majority of patients and antibodies to complement factor H (CFH) in a smaller subset of patients (approximately 6%)^[5-7]. Several cases of aHUS had been reported at different age groups in association with mutations of genes for complement factor H (CFH)^[8-10], membrane co-factor protein (MCP)^[8,11], and complement factor I (CFI)^[8,12,13]. The most frequent mutation detected involves CFH (approximately 30%), then MCP (approximately 10%), and lastly CFI

(approximately 5%)^[12]. Although approximately 80% of patients present acutely with thrombocytopenia, microangiopathic hemolytic anemia, and renal impairment^[14,15], the onset may be more gradual in other patients^[16]. Because of systemic vascular involvement^[17], extrarenal manifestations occur in up to 48% of patients, with frequent neurologic and cardiovascular involvement^[6,18-20].

Untreated aHUS has been linked to high morbidity and mortality, with a 33%-40% risk of progression to end-stage renal disease (ESRD) or death during the first clinical manifestation^[6]. Patients treated with plasma exchange remains to have a poor prognosis, with up to 65% experiencing permanent renal damage, ESRD progression, or death within 1 year of diagnosis^[8].

The understanding of the disease pathogenesis, which involves activation of alternative complement pathway, resulting in the formation of membrane attack complex (MAC) C5b-9^[3], had contributed to the advances in treatment, which is eculizumab, a monoclonal IgG antibody that binds to C5 and prevents subsequent formation of terminal complement^[21]. Eculizumab has significantly decreased the risk of ESRD in adult patients with aHUS from 60%-70%^[6,14] to approximately 15%-20%^[22-24].

Globally, CFI mutation had been rarely reported in association with aHUS, and to our knowledge, this is the first case reported in Saudi Arabia. Our case highlights important challenges related to the diagnosis and treatment of this rare disorder.

CASE REPORT

Patient information and presentation

A 52-year-old Saudi female, with hypothyroidism on L-thyroxine, presented to the emergency department on November 25, 2012, complaining of continuous lower abdominal pain radiating to the left flank, passing clots with heavy menstrual bleeding, and dysuria for 1 mo. She used oral contraceptive pill for irregular menstrual bleeding 1 mo before, which she stopped 5 d before presentation. Basic laboratory investigations were unremarkable apart from leukocytosis (Table 1). The result of the pregnancy test, using serum β -hCG, was negative. Abdominal and pelvic ultrasound showed a mildly enlarged liver (18 cm), mildly enlarged spleen (12 cm), and a bulky uterus with thickened endometrial lining and left ovarian cysts with internal echoes, which were likely hemorrhagic cysts. Other structures were unremarkable. Abdominal and pelvic computed tomography (with intravenous contrast) was also remarkable for bulky uterus and left adnexal cyst. Appendicitis was ruled out, and she was given oral non-steroidal anti-inflammatory drug (ibuprofen 200 mg every 8 h, as needed) for pain control and oral antibiotics (ciprofloxacin 500 mg bid for 7 d) for suspicion of urinary tract infection and was discharged

Table 1 Laboratory investigations

Laboratory parameter	Before admission (Nov 25, 2012)	Day of admission (Nov 28, 2012)
Hematologic tests		
Complete blood count		
WBCs (normal, $4-10 \times 10^9/L$)	14.4	14.1
Hemoglobin (normal, 12-15 g/dL)	11.8	8.9
Platelets (normal, $150-400 \times 10^9/L$)	399	103
Coagulation profile (s)		
PT (normal, 11-14)	12	10
INR (normal, 0.9-1.2)	0.9	0.9
PTT (normal, 20-40)	24	29
Schistocytes on peripheral blood film	Not done	Yes
Serum biochemical tests		
Renal function tests (mmol/L)		
Sodium (normal, 135-145)	142	129
Potassium (normal, 3.5-5.5)	3.9	4.1
Bicarbonate (normal, 22-28)	15	11
Chloride (98-106)	110	99
Urea (normal, 2.1-7.1)	3.2	19
Creatinine (normal, 62-106)	54	773
Liver function tests		
Total bilirubin (normal, 5-20 mmol/L)	17.1	25.8
AST (normal, 0-40 U/L)	17	142
ALT (normal, 0-30 U/L)	18	240
ALP (normal, 40-129 U/L)	104	90
GGT (normal, 8-65 U/L)	21	18
Albumin (normal, 35-50 g/L)	42	29
LDH (normal, 140-280 U/L)	273	3377

PT: Prothrombin time; INR: International normalized ratio; PTT: Partial thromboplastin time; AST: Aspartate transaminase; ALT: Alanine transaminase; ALP: Alkaline phosphatase; GGT: γ -Glutamyltransferase; LDH: Lactate dehydrogenase.

home.

Three days later (November 28, 2012), she returned to the emergency department with similar complaints, along with nausea, vomiting, shortness of breath, and reduced urine output for 2 d. She had no fever, joint pain, hematuria, or diarrhea. A systemic review was otherwise unremarkable. She is a housewife and mother of five healthy kids. Family history was negative for any hematologic, rheumatologic, malignant, or familial disorders. There was no significant history of renal disease in the family. On examination, she was conscious and oriented but pale. She had no signs of respiratory distress. She was afebrile, with blood pressure of 149/70 mmHg and normal heart rate. She had bilateral lower limb edema and bruises over her abdomen and lower limbs. Abdominal palpation was tender on the left flank and lumbar areas. Examination of other systems was unremarkable. Laboratory investigations showed persistent leukocytosis, a newly developing anemia, thrombocytopenia, and acute derangement in renal and liver function tests (Table 1) (serum creatinine: 773 $\mu\text{mol/L}$; normal: 62-106 $\mu\text{mol/L}$; C-reactive protein: 239 mg/L; normal: 0.3-5.0 mg/L; erythrocyte sedimentation rate, 64 mm/h); lactic acid: 0.9 mmol/L, normal: 0.7-2.1 mmol/L). As shown in Table 1, the presence of anemia, thrombocytopenia with elevated total bilirubin, and lactate dehydrogenase (LDH) alerted the treatment team to observe for hemolysis. Peripheral blood smear

revealed significant schistocytes, whereas the result of the direct antiglobulin test was negative. Urinalysis was positive for protein, red blood cells, and leukoestrane and was negative for nitrite. Complement (C3 and C4) levels, autoantibody panel, antiphospholipid antibody panel, hepatitis serology, and tumor markers were all negative.

Clinical and management focus

Because of the presence of microangiopathic features and acute kidney injury, hemolytic-uremic syndrome/thrombotic thrombocytopenic purpura was considered, and she was started on hemodialysis along with daily plasma exchange and pulse steroid. Methylprednisolone was given for 3 d, and then oral prednisolone was started and then gradually tapered. She was treated for possible urinary tract infection with intravenous piperacillin-tazobactam 2.25 g every 8 h, and her vaginal bleeding was treated with medroxyprogesterone injections. Her platelet count improved with plasma exchange and steroids but started to decrease, and thus, diagnostic kidney biopsy was performed. The biopsy was complicated with left renal subcapsular hematoma and retroperitoneal bleeding. The bleeding was successfully controlled with embolization; however, the procedure also revealed bilateral renal vein thrombosis. During this bleeding episode, plasma exchange was intermittently stopped because of rapidly decreasing platelet count and increasing LDH,

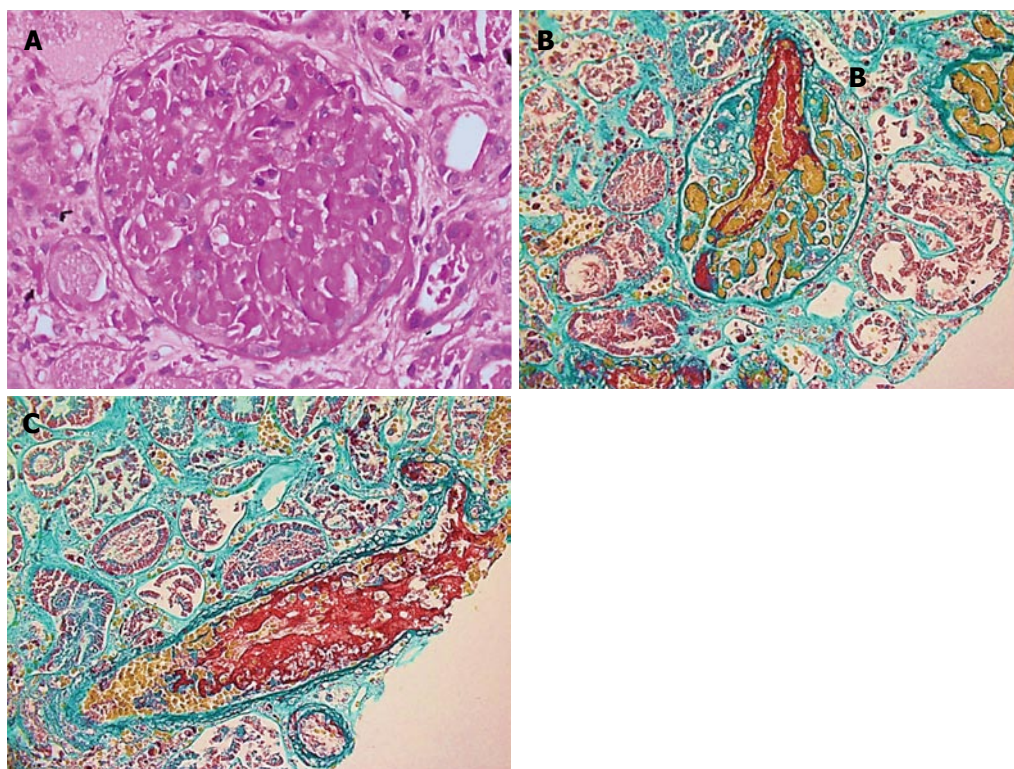


Figure 1 Finding of renal biopsy showed. A: A glomerulus with extensive fibrin thrombi involvement, obliterating the capillary loops (Periodic Acid-Schiff stain, original magnification $\times 400$); B: A glomerulus with an afferent arteriole with extensive red, fuchsinophilic material (fibrin) involvement (Masson trichrome stain, original magnification $\times 400$); C: A small arteriole with luminal fibrin staining red (fuchsinophilic) (Masson trichrome stain, original magnification $\times 400$).

which necessitated reinstitution of plasma exchange with fresh frozen plasma infusion. The dose of plasma exchange was increased from 1 to 1.5 plasma volumes daily.

Renal biopsy showed findings of renal cortical necrosis, TMA, and acute tubular necrosis (15 glomeruli, none with global sclerosis or significant tubular atrophy/interstitial fibrosis, arteriosclerosis, or hyaline arteriolosclerosis). Immunofluorescence was negative, and electron microscopy was negative for immune deposits, but it showed significant subendothelial widening with flocculent material and areas of organized structures resembling fibrin. There was foot process effacement involving short segments 10%-15% (Figure 1).

The patient also underwent endometrial bio-psy, which only showed necrotic decidua with no fetal elements. Bone marrow aspirate showed normocellular active bone marrow with trilineage hematopoiesis. Mammogram and bone scan results were unremarkable. For the hemodialysis and plasma exchange, a right internal jugular tunneled cuffed catheter was inserted; however, shortly after, she developed exit-site infection due to *Pseudomonas*, but it was successfully treated with ciprofloxacin. Despite plasma exchange, steroids, and antibiotics, the patient remained anuric, dependent on dialysis, and with fluctuating platelet count. Because of logistical reasons and the patient's preferences, she was shifted from hemodialysis to peritoneal dialysis

(PD). After control of bleeding and improvement of her platelet count, she was started on systemic anticoagulation using warfarin.

Diagnosis and treatment

The diagnosis of aHUS was considered because the patient had a refractory picture of TMA with renal failure. Treatment with eculizumab was decided, as it is the only FDA-approved drug for this disorder. Molecular genetic analysis of known genes for aHUS and related disorders by next-generation sequencing was performed. The result of the molecular testing showed that the patient carries a heterozygous CFI variant, c.944G > A (p.Arg315Lys), which was the possible cause of her disorder. During admission, because of the unavailability and high cost of eculizumab, she received 46 sessions of plasma exchange (once a day initially, then reduced to three times weekly, twice weekly, once weekly, and then every 2 wk). She received meningococcal vaccine. Eculizumab was started on March 1, 2013, with induction dose of 900 mg weekly for 4 wk, 1200 mg on week 5, and then maintenance dose of 1200 mg every 2 wk. She tolerated the treatment fairly well and her condition improved, and she was discharged on April 9, 2013. Eculizumab was continued in the outpatient setting until November 2013 and was stopped because of sustained hematologic remission, steady renal function, and cost issues.

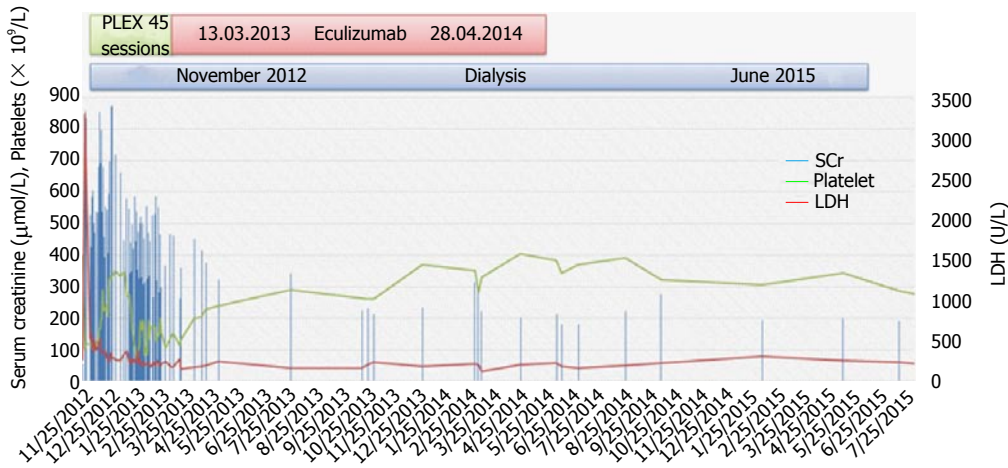


Figure 2 Serum creatinine levels did not improve despite plasma exchange, and hemodialysis was initiated. Lactate dehydrogenase levels improved with plasma exchange, whereas the platelets showed transient improvement under the plasma exchange treatment. Treatment with eculizumab induced a persistent improvement in platelet count. Continued eculizumab treatment resulted in late renal benefit, with dialysis withdrawn in June 2015. PLEX: Plasma exchange; Scr: Serum creatinine; LDH: Lactate dehydrogenase.

Follow-up and outcomes

In March 2014, she was admitted with PD-related peritonitis due to coagulase-negative *Staphylococcus aureus*, which responded to intraperitoneal vancomycin. Eculizumab was restarted. In April 2014, she remained anuric and dependent on dialysis, but she was in hematologic remission and eculizumab was discontinued due to cost issue. Systemic anticoagulation was also stopped, as she had completed more than 6 mo of treatment.

In June 2015, during routine follow-up in the PD clinic, she reported improving urine output, as she was oligoanuric until then, with normal platelet count and stable renal function [white blood cells (WBC): $4.6 \times 10^9/L$; hemoglobin: 11.6 g/dL; platelets: $248 \times 10^9/L$; urea: 3.6 mmol/L; creatinine: 174 $\mu\text{mol/L}$; 24-h urine collection creatinine clearance: 24 mL/min]. PD was stopped, and her kidney function remained stable with no uremic symptoms, and thus her PD catheter was removed. She was last seen in the clinic on February 2017 with no symptoms, and her laboratory investigations are as follows: WBC: $6.1 \times 10^9/L$; hemoglobin: 11.8 g/dL; platelets: $204 \times 10^9/L$; urea: 9.3 mmol/L; creatinine: 195 $\mu\text{mol/L}$; sodium: 141 mmol/L; potassium: 4.4 mmol/L; bicarbonate: 18 mmol/L; LDH 206 U/L. She continues to be healthy and in hematologic remission with stable kidney function without the need for dialysis, eculizumab, or anticoagulation. The course of events is summarized in Figure 2.

DISCUSSION

We reported a case of a middle-aged woman with aHUS due to rare CFI mutation presenting with severe acute kidney injury. She required dialysis and remained dialysis-dependent for 32 mo. Eculizumab treatment was associated with complete hematologic remission.

Interestingly, she is now off dialysis and continues to be in remission despite not taking eculizumab for more than 3 years. There are limitations and difficulties related to the management of this case. Most importantly, the time needed to confirm the diagnosis of complement factor mutation was significant due to lack of a laboratory facility for this test. In addition, eculizumab cost and availability was a limitation against prompt and continued use. Accordingly, these might have delayed the institution of appropriate treatment and impacted the clinical response and renal recovery.

The human complement cascade can be activated through three different pathways: The classical pathway, the lectin pathway, and the alternative pathway. CFH and MCP are regulatory proteins of the alternative pathway^[25]. Human CFI is a serine proteinase that cleaves the α chain of C3b and plays a key role in the inhibition of the alternative pathway amplification loop, which generates C3 convertase from C3b^[26]. Several familial and sporadic cases of aHUS were linked to mutations in these regulatory proteins of alternative pathway. Initially, the two complement alternative pathway proteins, CFH and MCP (CD46), have been identified to foster the development of aHUS^[10,27-30]. More recently, genetic analysis in patients with aHUS with no factor H mutation demonstrated presence of CFI mutations^[31]. In their novel description, Fremeaux-Bacchi *et al.*^[31] identified two heterozygous CFI mutations leading to a stop codon that are associated with functional deficiency in CFI. Later, more cases had been reported, and currently, CFI mutations account for 4%-10% of all cases of aHUS^[32]. The clinical outcomes are characterized by high rate of renal failure, end-stage renal disease (ESRD), post-kidney transplant recurrence, and graft loss.

In a report by Waters and Licht^[32,33] in 2010 and a previous cases series by Bell *et al.*^[33] in 1991, 33 cases of aHUS with complete or functional deficiency

of CFI were described. The age ranges from the time of birth to 57 years, with a mean age of 19 years. Using the varying follow-up data available and before the introduction of eculizumab, the following outcomes were noted among the 33 cases: Two deaths, 74% rate of ESRD, 48% of whom underwent kidney transplantation with a recurrence rate of 82% and very high rate of graft loss after recurrence (up to 100% after first graft). Re-transplantation is associated with recurrence. The response to immunotherapy including FFP infusion with or without plasma exchange was not consistent in cases where it was reported.

Similar to patients described in literature, our patient presented with severe renal failure requiring dialysis and had remained dependent on dialysis for 32 mo. With eculizumab introduction, she developed sustained hematologic remission and later recovered some kidney function and is currently off dialysis for 18 mo, with a serum creatinine level of approximately 200 $\mu\text{mol/L}$. Because of the unavailability and high cost of eculizumab, it was not provided for the past 3 years, but despite this, she remained in hematologic remission and off dialysis.

Cases with CFI mutation manifest increased susceptibility to infection with encapsulated organisms. Such susceptibility is linked to functional C3 deficiency as a result of uncontrolled activation of the alternative complement pathway^[34]. Our patient received meningococcal vaccine upon confirmation of the diagnosis of CFI mutation. She developed one episode of hemodialysis catheter-related exit-site *Pseudomonas* infection and one episode of PD-related staphylococcal peritonitis; however, apart from this, no exceptionally increased rate of infections with encapsulated organisms was noted. The susceptibility to infections in CFI mutations might be more prominent with complete CFI deficiency than with heterozygous mutation. Additionally, the late-age presentation and continued remission despite being off eculizumab in our patient may suggest a less severe genetic defect.

Similar to our patient, several cases of eculizumab discontinuation had been described. The largest case series reported the development of TMA in 5 (31%) of 16 patients following discontinuation^[35,36]. Those patients had received eculizumab for a median of 4.3 (range, 0.5-14.4) mo. In those 5 patients, relapse was identified, using regular home urine dipstick testing, within 6 mo of the last eculizumab dose. Eculizumab therapy was restarted, and it resulted in rapid improvement in serum creatinine levels and proteinuria.

In an attempt to address the possibility and safety of eculizumab discontinuation, Macia *et al.*^[37] studied the demographics, disease characteristics, and outcomes of aHUS cases in whom eculizumab was discontinued. The post-discontinuation follow-

up ranged from few days to 17 mo. According to the data collected from cases reports, TMA developed in 16 (31%) of 52 cases who discontinued the drug after multiple doses and in 4 (80%) of 5 cases who discontinued the drug after a single dose. TMA development was found to be higher with a single dose of eculizumab, and hence, current evidence does not support single-dose eculizumab.

According to the data collected from eculizumab clinical trials, TMA developed in 12 (20%) of 61 patients during a median post-discontinuation follow-up of 24 wk^[37]. The median time to TMA development was 13 (range, 4-127) wk. Three patients progressed to ESRD. The authors compared patients who experienced relapse ($n = 12$) to those who did not ($n = 49$) post-discontinuation across several demographic and disease characteristics. No particular trend to predict TMA development was noted with regard to sex, identified complement mutation or antibody, time from diagnosis to start of eculizumab, duration on eculizumab treatment, kidney function and dialysis (at the time of initial treatment and discontinuation), and kidney status (native versus transplant)^[37]. However, compared with patients who experienced no relapse, there was a trend to a lower median age (19.5 vs 27 years) and a higher proportion of CFH mutation (42% vs 18%) among those who experienced relapse. It had been noted that the use of functional tests of complement activity and measurement of complement proteins to predict development of TMA is of limited value^[37]. The authors concluded that the development of TMA following eculizumab discontinuation is unpredictable.

To our knowledge, this is the first case of aHUS due to heterozygous CFI variant c.944G > A (p.Arg315Lys) reported in Saudi Arabia. Several lessons can be learned from our case and similar cases. Although rarely reported, it is important to keep a high index of suspicion for such severe disease when acute kidney injury presents with unexplained microangiopathic anemia. In such presentations, the severity of renal disease, lack of significant neurologic symptoms, and absence of diarrhea make aHUS the likely clinical diagnosis. In addition, a renal benefit with discontinuation of dialysis was possible in our case despite relatively late initiation of eculizumab and prolonged period of dialysis-dependent kidney disease. Lastly, although eculizumab discontinuation was possible in our patient and seems to be safe in some other reported cases during the reported follow-up periods, predicting the risk of TMA development remains difficult. Therefore, informed decision-making requires a more comprehensive collection of data on eculizumab discontinuation and finding a more sensitive tool to monitor complement activation and disease activity.

ARTICLE HIGHLIGHTS

Case characteristics

A middle age woman who presented with acute kidney injury (AKI) and features of thrombotic microangiopathy (TMA).

Clinical diagnosis

TMA, most likely atypical hemolytic uremic syndrome.

Differential diagnosis

Causes of TMA with AKI: hemolytic uremic syndrome, thrombotic thrombocytopenic purpura (primary and secondary causes).

Laboratory diagnosis

Thrombocytopenia, elevated lactate dehydrogenase, schistocytes on peripheral blood film, acute kidney injury with normal coagulation profile and complement factor I mutation on genetic testing.

Imaging diagnosis

Computer tomography to exclude underlying malignancy as secondary causes.

Pathological diagnosis

Renal biopsy showing features of TMA with renal cortical necrosis, and acute tubular necrosis.

Treatment

Plasma exchange, dialysis and eculizumab.

Related reports

Previous cases of aHUS showing remission with initiation of eculizumab and maintenance of remission despite its discontinuation.

Term explanation

AKI: Acute kidney injury; aHUS: Atypical hemolytic uremic syndrome; CFH: Complement factor H; CFI: Complement factor I; MCP: Membrane co-factor protein; PLEX: Plasma exchange; TMA: Thrombotic microangiopathy; TTP: Thrombotic thrombocytopenic purpura.

Experiences and lessons

aHUS is a serious diagnosis that requires a high index of suspicion in cases presenting with unexplained AKI associated with microangiopathy. Renal benefit of eculizumab may be seen even with late initiation of the drug.

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