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EDITORIAL OFFICE
Jin-Lei Wang, Director
Xiu-Xia Song, Vice Director
World Journal of Nephrology
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
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REVIEW

Nephropathy in dietary hyperoxaluria: A potentially preventable acute or chronic kidney disease

Robert H Glew, Yijuan Sun, Bruce L Horowitz, Konstantin N Konstantinov, Marc Barry, Joanna R Fair, Larry Massie, Antonios H Tzamaloukas

Robert H Glew, Department of Surgery, University of New Mexico School of Medicine, Albuquerque, NM 87131, United States
Yijuan Sun, Antonios H Tzamaloukas, Renal Section, Raymond G Murphy Veterans Affairs (VA) Medical Center and Department of Medicine, University of New Mexico School of Medicine, Albuquerque, NM 87108, United States
Bruce L Horowitz, Division of Nephrology, Department of Medicine, University of New Mexico School of Medicine, Albuquerque, NM 87131, United States
Konstantin N Konstantinov, Rheumatology Section, Raymond G Murphy VA Medical Center and Department of Medicine, University of New Mexico School of Medicine, Albuquerque, NM 87108, United States
Marc Barry, Department of Pathology, University of New Mexico School of Medicine, Albuquerque, NM 87131, United States
Joanna R Fair, Radiology Service, Raymond G Murphy VA Medical Center and Department of Radiology, University of New Mexico School of Medicine, Albuquerque, NM 87108, United States
Larry Massie, Pathology Section, Raymond G Murphy VA Medical Center and Department of Pathology, University of New Mexico School of Medicine, Albuquerque, NM 87108, United States
Author contributions: Glew RH contributed the section on biochemistry, endogenous production and excretion of oxalate, including the bibliographic search of these sections and made repeatedly extensive and critical revisions of the manuscript; Sun Y and Horowitz BL assisted in the conception of the work, including the bibliographic search and made critical revisions of the manuscript; Konstantinov KN was responsible for the section on pathophysiology including the bibliographic search; Barry M and Massie L are responsible for the section on Pathology; Fair JR is responsible for the section on imaging; Tzamaloukas AH conceived this work, wrote parts of the report, provided a substantial part of references and revised critically the report.
Correspondence to: Antonios H Tzamaloukas, MD, Renal Section, Raymond G Murphy VA Medical Center and Department of Medicine, University of New Mexico School of Medicine, 1501 San Pedro SE, Albuquerque, NM 87108, United States. antonios.tzamaloukas@va.gov
Telephone: +1-505-2651711 Fax: +1-505-2566443

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Abstract

Hyperoxaluria can cause not only nephrolithiasis and nephrocalcinosis, but also renal parenchymal disease histologically characterized by deposition of calcium oxalate crystals throughout the renal parenchyma, profound tubular damage and interstitial inflammation and fibrosis. Hyperoxaluric nephropathy presents clinically as acute or chronic renal failure that may progress to end-stage renal disease (ESRD). This sequence of events, well recognized in the past in primary and enteric hyperoxalurias, has also been documented in a few cases of dietary hyperoxaluria. Estimates of oxalate intake in patients with chronic dietary hyperoxaluria who developed chronic kidney disease or ESRD were comparable to the reported average oxalate content of the diets of certain populations worldwide, thus raising the question whether dietary hyperoxaluria is a primary cause of ESRD in these regions. Studies addressing this question have the potential of improving population health and should be undertaken, alongside ongoing studies which are yielding fresh insights into the mechanisms of intestinal absorption and renal excretion of oxalate, and into the mechanisms of development of oxalate-induced renal parenchymal disease. Novel preventive and therapeutic strategies for treating all types of hyperoxaluria are expected to develop from these studies.

Key words: Dietary hyperoxaluria; Chronic oxalate nephropathy; Acute oxalate nephropathy; Acute tubular necrosis; Interstitial nephritis; Nephrocalcinosis; Calcium oxalate nephrolithiasis; Oxalate transporters;

Inflammasomes

Core tip: Chronic nephropathy secondary to dietary hyperoxaluria has been reported in a limited number of patients. Dietary oxalate intake in these patients was lower than the average intake in certain parts of the world. This raises the question whether dietary hyperoxaluria has been a neglected cause of chronic kidney disease. This question along with recent findings elucidating the pathogenesis of oxalate nephropathy calls for further research in epidemiology, prevention and treatment of hyperoxaluria.

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INTRODUCTION

Oxaluria has been extensively studied in the context of nephrolithiasis[1-15]. While hyperoxaluria from various causes represents a definitive risk for calcium oxalate nephrolithiasis[1,2], lacking is convincing epidemiological evidence that oxaluria is a risk factor for idiopathic renal stone formation[9,10]. In addition to nephrolithiasis, hyperoxaluria can also cause nephrocalcinosis involving the renal cortex, the renal medulla, or both[16-21], acute kidney injury (AKI) and chronic kidney disease (CKD). Oxaluria has two sources: oxalate formed endogenously from metabolism of its precursors and oxalate absorbed from the gastrointestinal tract. Increased rate of formation or increased rate of absorption of oxalate can lead to hyperoxaluria. The principal aim of this review is to address various aspects of hyperoxaluric AKI and CKD with emphasis on nephropathy secondary to high dietary intake of oxalate. This topic was selected because of its potential epidemiologic importance. In addition, interest to the topic is enhanced by important recent developments in the pathogenesis of hyperoxaluric CKD and the relative paucity of published information on renal parenchymal disease from dietary hyperoxaluria.

This review will analyze in sequence the biochemistry of oxalate and oxalate stones, the pathways of hepatic synthesis of oxalate, the gastrointestinal absorption and renal excretion of oxalate, the various types of hyperoxaluria with emphasis on the dietary variety, and the histologic types of oxalate nephropathy and their pathogenesis. The final section focuses on future research avenues that may illuminate the topic of dietary hyperoxaluria. The potential benefit from this research could be a reduction of the incidence of end-stage renal disease (ESRD)[22].

CHEMISTRY AND PROPERTIES OF OXALIC ACID AND OXALATE STONES

Oxalic acid is a two-carbon dicarboxylic acid (HOOC-COOH). For a long time it was thought that oxalate stones were comprised of mono- and di-hydrates of calcium oxalate, with some contribution from trihydrates. However, recent studies have led to a picture in which some non-oxalate preformed particle such as a crystal of uric acid, phosphate salts, drugs or drug metabolite act as the heterogeneous nucleus for formation of the oxalate calculus[23].

Oxalic acid is a moderately strong acid with pKa values of 1.23 and 4.19. In its full ionic form it is called oxalate. Whereas oxalic acid is relatively soluble in water (8700 mg/dL; pH 7, 20 ℃), calcium oxalate is three to four orders of magnitude less soluble (0.67 mg/dL; pH 7.0, 20 ℃) and crystallizes readily. By way of comparison, calcium urate is about 400-fold more soluble than calcium oxalate[24]. Oxalate also forms crystals with other polyvalent ions, including magnesium, ferrous iron and zinc. The water solubility (expressed as mg/dL) of these complexes at 18 ℃ to 20 ℃ is as follows: magnesium oxalate 70.0, ferrous oxalate 22.0 and zinc oxalate 0.79, respectively. The solubility of calcium oxalate increases slightly with increasing pH; however, hydrogen ion changes in the physiological range have only a small effect on calcium oxalate solubility.

Oxalic acid is a toxic substance. It is not known whether oxalic acid and oxalate are themselves toxic before they react with calcium to form calcium oxalate. Under normal circumstances the concentration of oxalate in the blood and urine depends on the content of oxalic acid in foods and on metabolic conversion of endogenous oxalate precursors largely by oxidative reactions. Furthermore, dietary factors and substances other than oxalic acid per se can influence the tendency for oxalate crystals to form; these factors include: the amino acids 4-hydroxyproline, serine and glycine, calcium, and possibly ascorbic acid and fructose.

EXOGENOUS SOURCES OF OXALIC ACID

In Nature oxalic acid occurs in the free form but more commonly as the salt of sodium, potassium, calcium, magnesium or iron. The oxalate content of dietary items consumed by several populations has been analyzed[6,25-31]. Widely consumed foods that are rich in preformed oxalic acid include vegetables, nuts, cocoa, tea, and fruits high in vitamin C. Red meats, fish, poultry, eggs and dairy products contain relatively small amounts of oxalic acid. Items in Western diets that significantly increase urinary oxalate excretion include spinach, rhubarb, beets, nuts, chocolate, tea, wheat bran, and strawberries[6]. The bioavailability of ingested oxalate is influenced by other ingested items[32]. Oxalate content of various diets, its relation to nephrolithiasis, and guide-

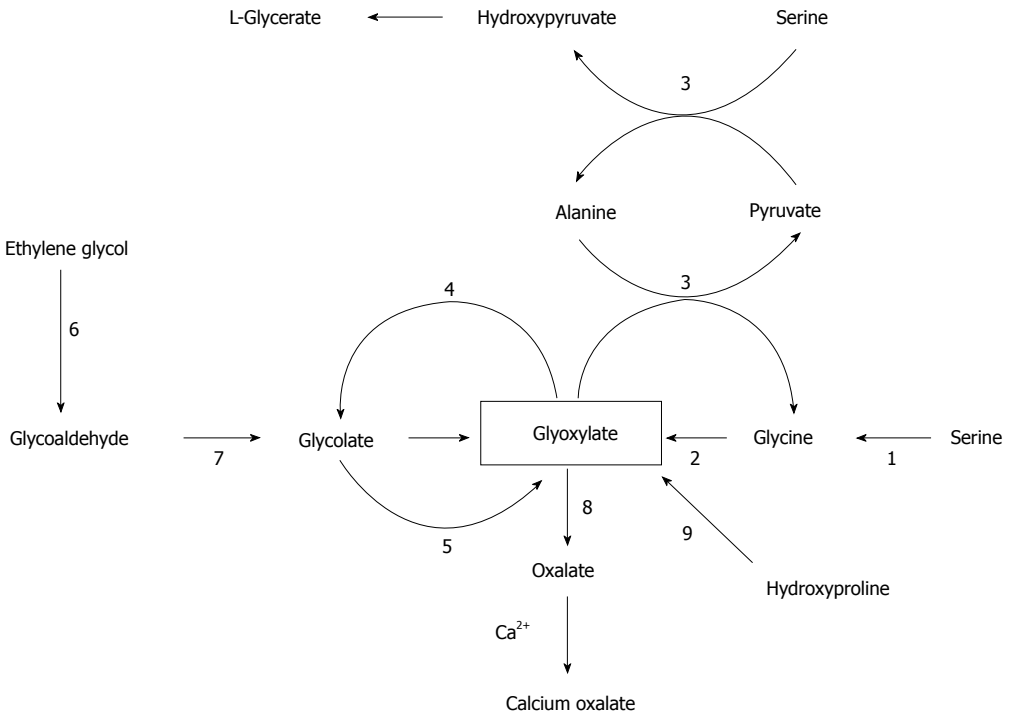

Figure 1 Biosynthesis of calcium oxalate. Glyoxylate is the main precursor of oxalate which combines spontaneously with calcium ions to form calcium oxalate. Names of enzymes: 1, serine hydroxymethyltransferase; 2, D-amino acid oxidase; 3, alanine:glyoxylate aminotransferase (AGT); 4, glyoxylate reductase-hydroxypyruvate reductase (GRHPR); 5, glycolate oxidase; 6, alcohol dehydrogenase; 7, aldehyde dehydrogenase; 8, lactate dehydrogenase; and 9, five enzyme-catalyzed reactions. PH1 results from mutations in AGT which is a hepatic peroxisomal enzyme. PH2 results from mutations in GRHPR which is a cytosolic enzyme found in several tissues, but primarily the liver. PH3 results from defects in the hepatic mitochondrial enzyme 4-hydroxy-2-oxoglutarate (HOG) aldolase which converts HOG and glyoxylate to pyruvate (reaction not shown), the last step in hydroxyproline catabolism. The reason why a deficiency of HOG aldolase activity increases oxalate production is obscure.

lines for oxalate intake have been reported[13-15,33-37]. One set of guidelines for prevention of nephrolithiasis proposed a maximal daily oxalate intake of 200 mg daily[33]. We found no epidemiological reports relating dietary oxalate intake to oxalate nephropathy and no guidelines for prevention of this nephropathy.

Table 1 shows estimates of dietary oxalate intake in six countries[13,35,36,38-42]. Oxalate intake varies greatly between countries and regions of the same country. For example, daily oxalate intake in Western diets ranges between 44 and 930 mg[13]. The seasonal variation of oxalate intake in a rural population in India is extreme (Table 1). Very high consumption of oxalate in the context of dietary intake can be comparable to some reported lethal doses of the compound. Although the average lethal dose (LD50) of oxalate was estimated at 375 mg/kg[43], or 26.3 g for a 70 kg person, much lower doses of oxalate can be lethal. An intravenous dose of 1.2 g of sodium oxalate, which is equivalent to 0.8 g of oxalate, was lethal in one reported case[44]. Of note also is that most studies cited in Table 1[13,35,36,39,40,42] as well as other large epidemiological studies[45] analyzed dietary oxalate intake to evaluate the risk of nephrolithiasis and no study addressed the risk of CKD from dietary hyperoxaluria.

SOURCES OF OXALIC ACID IN THE BODY

The body burden of oxalic acid has two sources, endogenous production in the liver and absorption from the gastrointestinal tract. The pathways of hepatic production and gastrointestinal absorption of oxalic acid are discussed below.

Hepatic production of oxalic acid

Oxalate is synthesized in the liver but is not metabolized further in humans. Oxalic acid produced by catabolism of ingested oxalate precursors by means of normal metabolic pathways contributes significantly to the body's burden of oxalate. Earlier reports estimated that only 10% of the urinary oxalate was derived from dietary oxalate, while the remaining 90% was derived equally from metabolism of other oxalate precursors, including ascorbic acid[46].

Figure 1 shows the metabolism of oxalate, with emphasis on the pathways of primary hyperoxaluria and of metabolism of ethylene glycol, which is a major cause of acute oxalate intoxication. The major precursors of oxalate under normal circumstances appear to be the amino acids hydroxyproline, glycine and serine (Figure 1). Glycine and serine are present in all food proteins. Oxalate is also the end-product of the metabolism of ingested ethylene glycol, the main component of antifreeze, which is encountered usually in the setting of attempted suicide. In order to facilitate understanding of the these endogenous pathways, it may be helpful to consult Figure 1 which relates the major two-and three-carbon compounds that are relevant to this discussion.

Table 1 Daily dietary oxalate intake in various countries and regions

Country-region	Subjects	Subject number	Oxalate intake (mg/24-h)	Ref.
Brazil, Sao Paolo	+Stones	70 (M:42, F:28)	98 ± 137[3]	[13]
	Healthy controls	41 (M:14, F:27)	108 ± 133[3]	
England	Hospital diet	Not reported	118	[38]
Germany	+Stones, ↑oxaluria	93 (M:73, F:20)	130 ± 181[3]	[39]
	+Stones, →oxaluria	93 (M:73, F:20)	101 ± 145[3]	
India, Rajasthan	Rural "common" diet	Not reported	78	[40]
	Rural rainy season	Not reported	2045	
	Urban, upper income	Not reported	606	
	Urban, lower income	Not reported	169	
	Hospital diet	Not reported	139	
India, Pune	Boys, upper income	100	193 (116-309)[4]	[41]
	Boys, lower income	100	169 (102-354)[4]	
	Girls, upper income	100	168 (115-209)[4]	
	Girls, lower income	100	133 (87-209)[4]	
Italy	Normal subjects[1]	12 (M:8, F:4)	335	[42]
	Normal subjects[2]	12 (M:8, F:4)	18	
United States, South	F, 50-79 yr, +Stones	1.179	330 ± 161[3]	[35]
	F, 50-79 yr. –Stones	1.179	345 ± 166[3]	
United States	M, +Stones	1.627	214 ± 117[3]	[36]
	M, -Stones	44.358	214 ± 121[3]	
	F, older, +Stones	1.414	184 ± 109[3]	
	F, older, -Stones	91.358	185 ± 112[3]	
	F, younger, +Stones	1.564	179 ± 121[3]	
	F, younger, -Stones	100.260	183 ± 121[3]	

[1]Diet containing fruits and vegetables; [2]Diet without fruits and vegetables; [3]Mean ± SD; [4]Mean (25^{th}-75^{th} percentile). +Stones: History of urinary stones; -Stones: Absence of history of urinary stones; M: Male; F: Female.

The key player in this story is glyoxylate: it is the nexus of pathways that lead to and away from oxalate.

Hydroxyproline is one of the most abundant amino acids in collagen. It is present in collagen-containing meat products, including gelatin, and is one of the most abundant proteins in the human body. In fact, collagen accounts for about 30% of total animal proteins and contains about 13% hydroxyproline[47]. Glyoxylate is the two-carbon end-product of hydroxyproline catabolism (pyruvate is the other product). The conversion of glyoxylate to oxalate is catalyzed by lactate dehydrogenase. Each day the human body turns over 2-3 g of collagen. In the process 240-420 mg of hydroxyproline are released with the concomitant production of 140-240 mg of glyoxylate[48].

Knight *et al*[48] demonstrated using healthy volunteers that daily ingestion of 30 g of collagen for three days increased glycolate and oxalate excretion by 43% and 5.3-fold, respectively. Glycolate is produced when glyoxylate is acted on by glyoxylate reductase which in the literature is also identified as hydroxypyruvate reductase and D-glycerate dehydrogenase. However, only 5% of the ingested hydroxyproline was recovered as glyoxylate plus oxalate, thereby indicating that most of the glyoxylate resulting from hydroxyproline catabolism was probably diverted to glycine synthesis in the reaction catalyzed by alanine:glyoxylate aminotransferase (AGT). The means of directing glyoxylate away from oxalate synthesis is the glyoxylate reductase reaction that converts glyoxylate into glycolate. Since oxalate is not oxidized to carbon dioxide and water or otherwise metabolized by humans, its only route of disposal is urinary excretion. Quantitatively, transamination of glycine and oxidation of glycine by D-amino acid oxidase are much less important than catabolism of hydroxyproline as sources of oxalate.

Since the metabolism of serine and glycine are so intimately linked in humans and because they are interconvertible, it is reasonable to expect that if one of these amino acids is metabolized to glyoxylate, the other too should be a precursor of glyoxylate, and that both should be sources of oxalate. Such is the case. The enzyme that catalyzes the serine-glycine interconversion is folate-dependent serine hydroxymethyl transferase. Another enzyme, namely D- amino acid oxidase, also converts glycine to glyoxylate.

Although the underlying metabolic link between ascorbic acid and oxalic acid is obscure, there is evidence that a high oral or intravenous intake of ascorbic acid can result in a moderate increase in urinary oxalic acid[8,39,49,50]. With regard to parenteral feeding, Robitaille *et al*[51] found that, on average, 80 mg of a 105 g infused dose of ascorbic acid was recovered as urinary oxalic acid in elderly adults with normal kidney function. Furthermore, intravenous ascorbic acid administration increased urinary oxalic acid excretion in a dose-dependent manner. These authors cautioned against high-dose infusions of ascorbic acid for individuals already at high risk of oxalate stones.

Epidemiologic studies that have addressed the relation between fructose intake and increased risk for oxalate stones have yielded conflicting results: however,

a large epidemiological study found a significant association between high consumption of fructose and risk of kidney stones[52]. On the other hand, studies of urinary oxalate excretion in humans administered high amounts of fructose orally[53] or intravenously[54] have produced equivalent results. A 2010 investigation of the relationship between fructose consumption and urinary oxalate in healthy subjects found that urinary excretion of oxalate and glyoxylate, which is a marker of oxalate synthesis, did not change when the fructose content of the diet was raised as high as 21% of calories[55]. A possible effect of fructose on the absorption of dietary oxalate or calcium excretion was not assessed in that study. Furthermore, lacking is evidence that humans metabolize fructose to oxalate. However, fructose could affect the serum oxalate level indirectly by affecting events in the gastrointestinal tract. For example, hyperabsorption of oxalate caused by a low intake of calcium for complexation with oxalate in the GI tract can exacerbate hyperoxaluria[39].

Gastrointestinal absorption of oxalate

The contribution of oxalate absorbed from the gastrointestinal tract to the total body burden of oxalate depends on the oxalate content of the diet. Recently, in a study of normal volunteers consuming diets with varying oxalate content, Holmes and associates[56] showed that oxalate excretion in urine depends significantly on the dietary oxalate intake. Dietary oxalate intake accounted for 24.4% of the urinary oxalate excretion when the diet contained 10 mg of oxalate per 2500 kcal. Urinary oxalate excretion and the percent of urinary oxalate derived from dietary oxalate increased progressively with progressive rises in dietary oxalate content, reached a value of 41.5% of the urine oxalate when the diet contained 250 mg of oxalate per 2500 kcal, and increased further to 52.6% of the urine oxalate when the diet contained both 250 mg of oxalate per 2500 kcal and a low calcium intake. In the same study, although urinary excretion of oxalate increased substantially with increasing oxalate intake, estimated fractional absorption of oxalate from the gastrointestinal tract decreased from 55.4% at the lowest oxalate intake to 5.8% at the highest intake and then increased to 9.7% at the highest oxalate intake combined with low calcium intake[56]. These findings are important in the context of dietary hyperoxaluria.

The functions involved in the disposition of dietary oxalate are exclusively absorption from the intestines and renal excretion[57]. In the intestines, oxalate is absorbed passively by means of a paracellular pathway. Whereas unbound oxalate is absorbable, oxalate salts of divalent cations such as calcium and magnesium are insoluble in water and therefore not absorbable. Oxalate transporters in the enteric[58,59] and renal epithelial cells have been identified and are discussed in some detail in the following subsection.

The magnitude of oxalate absorption is affected by various dietary substances and the gastrointestinal milieu. Dietary oxalate content is an important determinant of oxalate absorption that is particularly relevant to this review. The fact that urinary oxalate is derived from two sources, absorption of dietary oxalate and endogenously produced oxalate, complicates the study of oxalate absorption in the gastrointestinal tract. A reliable method for estimating oxalate absorption is by labelling oxalate with a stable carbon isotope (^{13}C), ingesting a known quantity of labelled oxalate, and measuring the fractional (or percent) excretion of the labelled oxalate in the urine[60,61]. The method assumes that absorbed oxalate is excreted exclusively in the urine. In one study conducted in normal subjects, oxalate absorption was evaluated by this method when total dietary intake of oxalate was low (63 mg daily) and high (600 mg daily). Mean daily urine oxalate was 25 mg at the low oxalate intake and 43 mg at the high intake, while the percent absorption of ingested oxalate increased from 7.9% at the lower intake to 14.7% at the higher oxalate intake[62].

The dietary content of certain divalent cations has clinically important effects on oxalate absorption. High dietary contents of calcium[63-65] and magnesium[66] inhibit oxalate absorption. The mechanism of this inhibition is formation of insoluble and poorly absorbable oxalate salts of these two divalent cations when they are in abundance in the enteric lumen. Fatty acids have an opposite effect from divalent cations on oxalate absorption. High intake of the 20-carbon polyunsaturated fatty acid arachidonic acid was shown to be associated with increased urinary excretion of oxalate[67]. Fatty acids bind bivalent cations, thereby decreasing the latter's availability for binding oxalate in the intestinal lumen. This effect of fatty acids on oxalate absorption also has clinical implications (see below).

Several anaerobic bacteria, including *Oxalobacter formigenes, Eubacterium lentum, Enterococcus faecalis* and *Lactobacillus acidofilus*, metabolize oxalate in the gut[68]. Administration of probiotics containing one or more of these bacteria to healthy subjects and, particularly, subjects with high baseline levels of oxalate absorption, decreases oxalate absorption[68,69]. Conditions that are known to affect oxalate absorption include the pH of the intestinal fluids and intestinal transit time[62]. Whether these conditions have clinical significance or not is unclear.

RENAL EXCRETION OF OXALATE

Oxalate is eliminated almost exclusively by the kidneys. In two studies involving subjects with normal renal function, more than 90% of injected radiolabelled oxalate was recovered in the urine[70,71]. Circulating oxalate is almost 100% ultrafilterable and it is filtered in the glomeruli[72] and excreted in the proximal tubules[73,74]. The basolateral membrane of proximal tubular cells contains a transporter, SLC26A1 that exchanges oxalate for bicarbonate or sulfate[75]. Exchangers of the SLC26 family, including SLC26A6, SLC26A7, SLC26A8, and SLC26A9, have been identified on the plasma membrane of cells

that transport oxalate[76,77]. The SLC26A6 transporter has also been localized to the brush border of proximal tubular cells[78]. Holmes and Assimos hypothesized that increases in plasma concentration of oxalate activate the basolateral SLC26A1 transporter which facilitates entry of oxalate into proximal tubular cells, which is then followed by oxalate efflux into the tubular lumen[79]. Tubular secretion of oxalate may have clinical significance. One study found enhanced tubular secretion of oxalate in hyperoxaluric patients compared to controls with normal oxalate excretion[4].

Oxalate transfer in the enteric epithelial cells gut is similar to that in the renal tubular cells. Oxalate transfer through the enteric tight junction is driven by a lumen-to blood concentration gradient and by water absorption. Soluble oxalate is secreted back into the enteric lumen through SLC26A1 and SLC26A6. SLC26A1 is located in the basolateral membrane and transfers oxalate from the paracellular space to the intracellular compartment. SLC26A6 is located in the apical membrane and returns oxalate to the enteric lumen. The transfer of oxalate through the anion transporters back into the enteric lumen modulates the absorption of this toxic compound[59].

In renal failure, oxalate excretion decreases roughly in proportion to the decrease in renal function and serum oxalate concentration increases[80]. As a compensatory mechanism, elimination of oxalate through the gastrointestinal tract is increased in renal failure[81,82]. A study by Hatch and colleagues provided evidence that the increased intestinal excretion of oxalate in renal failure is mediated, at least in part, by angiotensin Ⅱ[83]. Renal failure, therefore, is one condition in which oxalate is not eliminated in its entirety by the kidneys. Diuresis and body size are two factors that affect urinary oxalate excretion. In normal subjects, oxalate elimination in the urine increases in parallel to urinary flow rate[84,85]. The clinical significance of this finding is obscure because urinary oxalate concentration decreases in parallel as urinary flow increases[85]. Large body size is associated with a high urinary oxalate excretion rate[86,87]. This finding is clinically relevant because obesity is a risk factor for nephrolithiasis[88]. Finally, urinary oxalate excretion shows seasonal variations[89] that can have clinical importance.

CLINICAL TYPES OF HYPEROXALURIA

Hyperoxaluria can result from excessive endogenous production of oxalate, excessive absorption of dietary oxalate, excessive dietary or parenteral intake of oxalate, or a combination of these processes. Four main categories of hyperoxaluria are recognized: primary hyperoxaluria, absorptive or intestinal hyperoxaluria, idiopathic mild hyperoxaluria and dietary hyperoxaluria.

Primary hyperoxaluria

Primary hyperoxaluria (PH) consists of a family of autosomal recessive inherited disorders characterized by endogenous overproduction of oxalate[90-94]. Mutations in three enzymes involved in oxalate synthesis lead to three distinct PH subtypes, PH1[95], PH2[96,97] and PH3[98-100].

PH1 accounts for about 80% of all PH cases. PH1 results from mutations in the hepatic peroxisomal enzyme AGT[93-95]. The gene encoding AGT (AGTX) is located on chromosome 2q37.3[91]. AGT is pyridoxal-5-phosphate dependent[93,94] and catalyzes the transamination of glyoxylate to glycine[94,95]. PH1 mutations result in in accumulation of glyoxylate and excessive production of oxalate and glycolate[94]. Figure 1 illustrates these relationships.

As of 2013, 178 different AGT mutations had been discovered[94]. Phenotypes vary from nephrocalcinosis, failure to thrive and advanced renal failure in early childhood to recurrent or even occasional nephrolithiasis in adulthood[96,97]. As renal failure progresses, high plasma levels of oxalate result in supersaturation and precipitation of calcium oxalate crystals in various organs (oxalosis). Blood vessel walls, bones, joints, retinae, skin, bone marrow, cardiac tissue and the nervous system are sites affected in oxalosis[90-95]. Life-threatening clinical manifestations accompany the deposition of oxalate crystals in vital organs[97].

The diagnosis of PH1 is assisted by finding elevated levels of oxalate and glycolate in the urine. It should be noted, however, that approximately one quarter of subjects with PH1 do not have elevated glycolate levels in the urine[95]. Renal failure consistently decreases urinary oxalate excretion which can cause diagnostic problems[90]. In the past, liver biopsy for assessment of AGT activity was required for the diagnosis of PH1. Nowadays, however, the diagnosis relies on molecular genetic testing including DNA sequencing, deletion/duplication analysis and targeted mutation analysis[95].

The management of PH1 follows some of the same principles of management of urinary stones in general. Fluid intake to ensure large urinary volumes is recommended for patients without advanced renal failure. Calcium supplements and other measures to reduce gastrointestinal absorption of oxalate have limited effectiveness in treating PH. Potassium citrate or, in cases of advanced renal failure, sodium citrate may reduce the tendency to form stones[95]. Pyridoxine administration reduces oxalate formation in 10% to 30% of the patients with PH1[91]. Effectiveness of pyridoxine has been linked to the AGT genotypes Gly170R and Phe152Ile, which are associated with some residual activity of the enzyme[91,94]. Combined liver-kidney transplantation is the method of choice for PH1 patients with advanced renal failure[95].

PH2 is found in about 10% of the PH cases. PH2 results from mutations of the cytosolic enzyme glyoxylate reductase/hydroxypyruvate reductase (GRHPR)[94,96]. The gene for GRHPR is located on in chromosome 9p13.2[94]. GRHPR is present in tissues throughout the body and catalyzes the conversion of glyoxylate to glycolate and hydroxypyruvate to D-glycerate[94]. Reduced or absent GRHPR activity leads to increased availability of lactate and hydroxypyruvate for conversion to oxa-

Table 2 Surgical procedures and medical conditions associated with enteric hyperoxaluria

Surgical conditions	Medical gastrointestinal conditions	Other medical/surgical conditions	Drugs
Jejunoileal bypass[106,108,110]	Crohn's disease[109,119]	Morbid obesity[112]	Orlistat[130,131]
Roux-en-y gastric bypass[111,113]	Diabetic gastroenteropathy[115,116]	Cystic fibrosis[122,123]	Octreotide[132]
Small bowel resection[108,109]	Sprue[117]	Organ transplants[124-129]	
Partial gastrectomy[108]	Primary biliary cirrhosis[109]		
Pancreatectomy[109]	Chronic pancreatitis[118]		
External biliary drainage[114]	Intestinal lymphangiectasia[120]		
	Clostridium difficile colitis[121]		

late and L-glycerate. Urinary excretion of high levels of L-glycerate is a characteristic of PH2[96]. Nephrolithiasis, nephrocalcinosis, end-stage renal failure and oxalosis in advanced renal failure are the clinical hallmarks of PH2[92,96]. The severity of these manifestations is less than in PH1: nephrocalcinosis is rare and end-stage renal failure develops later in life[92]. The diagnosis can be made by assay of GRHPR in blood mononuclear cells[97]. The treatment of PH2 is similar to that of PH1, with two exceptions: pyridoxine is not effective in PH2; and renal transplantation has been used for treatment of end-stage renal failure, while combined liver-kidney transplantation has not been used in PH2[96].

PH3 accounts for 2.5% of PH cases. PH3 results from mutation of the hepatic mitochondrial enzyme 4-hydroxy-2-oxoglutarate aldolase (HOGA1)[98,99]. HOGA1 catalyzes the last step in the conversion of hydroxyproline to oxalate. The chromosomal location of the gene responsible for PH3 is in 10q242[94]. The mechanism by which non-functioning mutations of HOGA1 lead to hyperoxaluria is an enigma. Intuitively, decreased HOGA1 activity should lead to decreased production of oxalate through the hydroxyproline pathway. A hypothesis for the pathogenesis of hyperoxaluria in PH3 was recently proposed by Belostotsky and associates[100]. These investigators identified a cytosolic 4-hydroxy-2-oxoglutarate aldolase distinct from mitochondrial HOGA1 in human hepatocytes. They speculated that individuals with PH3 accumulate 4-hydroxy-2-oxoglutarate in mitochondria and that following transfer of this compound into the cytosol it is converted to glyoxylate by the cytosolic aldolase[100]. Oxaluria is less marked in PH3 than in PH1 or PH2 and the clinical manifestations are less severe. Urolithiasis is the main clinical manifestation in PH3. Furthermore, nephrocalcinosis and renal failure are uncommon, and oxalosis has not been described in PH3[94].

Surveys of primary hyperoxaluria in various countries[101-105] have identified prolonged delays in the diagnosis of PH. Delays in the diagnosis have been observed also in enteric hyperoxaluria and could be present also in dietary hyperoxaluria (see Figure 2 below).

Enteric hyperoxaluria

Table 2 lists some of the conditions and surgical interventions in the gastrointestinal tract, including medical diseases of the gastrointestinal tract, medical or surgical conditions outside the gastrointestinal tract, and medications, that are associated with hyperoxaluria secondary to excessive intestinal absorption of oxalate[106-132]. A common characteristic of the conditions listed in Table 2 is the presence of steatorrhea with excessive amounts of fatty acids in the enteric lumen which bind divalent cations, especially calcium, thereby increasing the availability of the unbound oxalate for absorption[109]. In certain morbid conditions, such as cystic fibrosis, solid organ transplants or octreotide administration, frequent use of antibiotics causing alterations in the intestinal flora and lack of colonization by oxalate-consuming bacteria increases the availability of oxalate for absorption[109,122-129]. In recipients of organ transplants, use of anti-rejection drugs (*e.g.,* mycofenolate) that cause diarrhea and steatorrhea can contribute to hyperoxaluria[127].

Studies conducted more than 30 years ago documented that the colon was the primary site of oxalate absorption and suggested that an intact colon is necessary for the development of enteric hyperoxaluria[133,134]. However, enteric hyperoxaluria has also been noted in patients with partial colon resection[119]. In patients with enteric hyperoxaluria, diarrhea causes volume depletion and metabolic acidosis leading to low urinary pH and hypocitraturia. In conjunction with hyperoxaluria, these conditions facilitate precipitation of calcium oxalate in renal tissues and promote the development of renal stones, nephrocalcinosis and oxalate nephropathy[109]. In patients with primary hyperoxaluria, the renal failure that follows the development of nephrolithiasis, hydronephrosis, nephrocalcinosis and particularly parenchymal oxalate nephropathy is chronic. Enteric hyperoxaluria can cause new-onset acute renal failure (acute oxalate nephropathy)[121,124-126,129,130,132,135-140], acute renal failure superimposed on pre-existing chronic kidney disease[116,118], or chronic oxalate nephropathy[110,113,119,120,128].

Idiopathic (mild) hyperoxaluria

Idiopathic hyperoxaluria is a condition characterized by hyperoxaluria that is much less severe than primary on enteric hyperoxaluria and recurrent calcium oxalate stone formation[5,141,142]. This entity is encountered in subjects without any of the known types of enteric or primary hyperoxaluria. Increased synthesis, increased gastrointestinal absorption, or increased renal tubular secretion of oxalate are the only known mechanisms of hyperoxaluria. All three mechanisms have been implicated in idiopathic hyperoxaluria. Increased absorption of oxalate by patients with idiopathic hyperoxaluria, es-

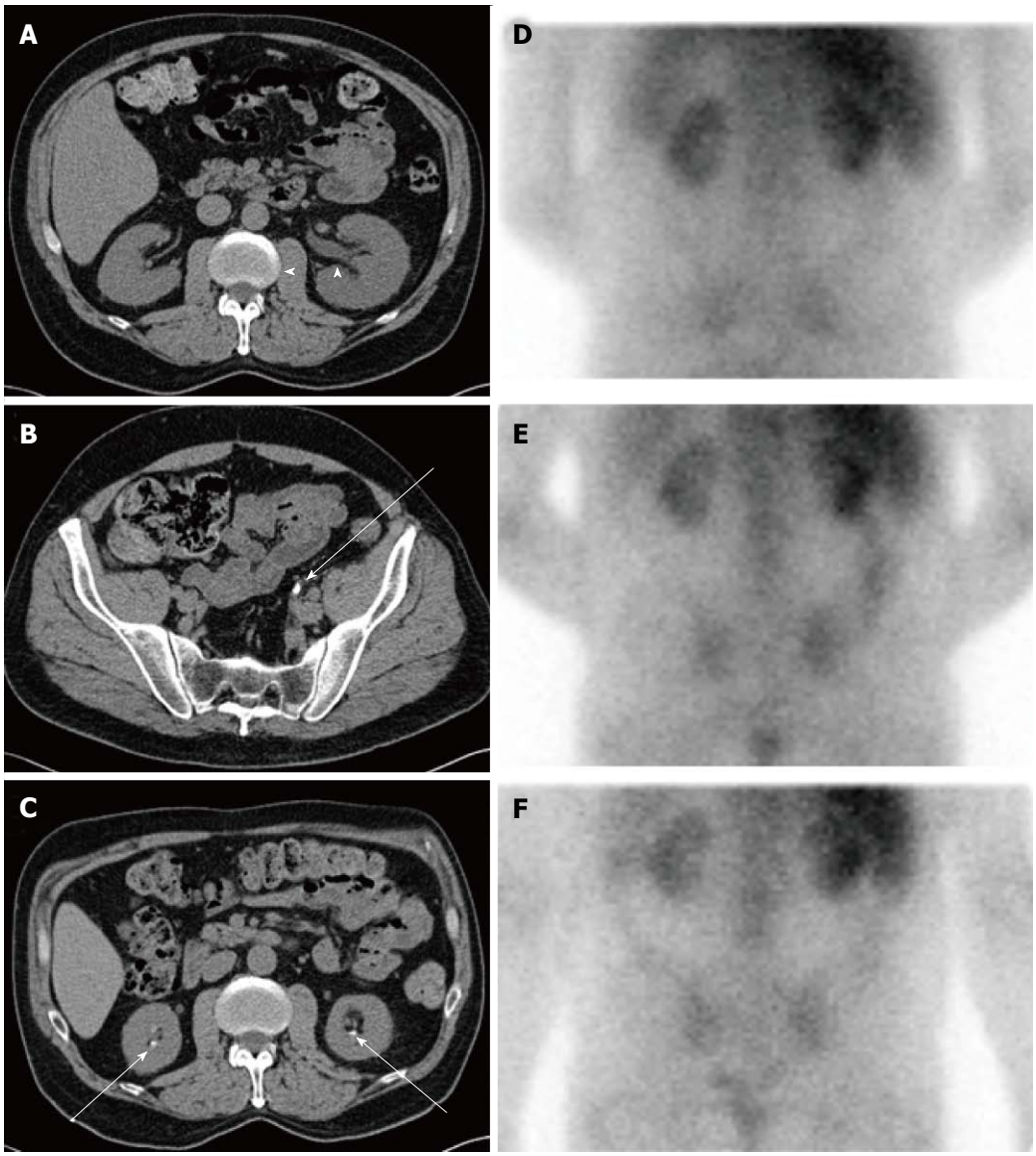

Figure 2 Sequential imaging studies of a not yet reported patient with chronic kidney disease from dietary hyperoxaluria. Axial computed tomography (CT) images obtained two years before the hyperoxaluria diagnosis show (A) mild left hydronephrosis (arrowheads) caused by (B) a left distal ureteral calculus (arrow). Axial CT image obtained around the time of the hyperoxaluria diagnosis shows (C) bilateral nephrolithiasis (arrows). Nuclear medicine gallium-67 citrate scan images were also obtained around the time of diagnosis, including (D) 4-, (E) 24-, and (F) 48 h after administration. These show abnormal, persistent bilateral renal activity at all time points, indicative of interstitial nephritis. Gallium scanning has classically been used to distinguish acute interstitial nephritis from acute tubular necrosis and other causes of acute renal failure[216-218]. In this patient chronic interstitial nephritis associated with hyperoxaluria led to this positive scan. The patient's diet for several years was based on nuts with estimated oxalate consumption $\geqslant$ 800 mg daily. During high oxalate intake, urine oxalate excretion was > 200 mg/24-h in several measurements obtained at serum creatinine levels > 3.5 mg/dL. After resumption of a diet low in oxalate and improvement of renal function to serum creatinine levels < 3.0 mg/dL, urine oxalate excretion decreased to normal levels.

pecially when the dietary content of calcium is low, has been reported[143-145]. In other studies in patients with the same entity, reduction of hyperoxaluria by large doses of pyridoxine was noted, suggesting that these subjects had excessive production of oxalate[146,147]. In another set of studies subjects with idiopathic hyperoxaluria developed higher levels of oxaluria than control subjects after ascorbate loads[148] or following meat ingestion[12,149]. This set of studies also pointed towards increased endogenous production of oxalate as the source of idiopathic hyperoxaluria. Finally, another study found enhanced tubular secretion in idiopathic hyperoxaluria[4]. Therefore, it is unclear whether idiopathic hyperoxaluria represents one or more types of hyperoxaluria. Further research is needed to clarify the mechanism(s) of hyperoxaluria in this particular condition.

Dietary hyperoxaluria

This section addresses dietary hyperoxaluria and hyperoxaluria secondary to medications or overdoses. The clinical and histological manifestations of these three categories of hyperoxaluria are similar. The reports of nephropathy from dietary hyperoxaluria, especially its chronic variety, are few and contain, in many instances,

Table 3 Reports of parenchymal renal disease induced by dietary hyperoxaluria

Ref.	Daily oxalate intake (mg), duration	Urine oxalate (mg/24 per hour)	Peak SCr (mg/dL)	Clinical diagnosis, course, outcome, final SCr (mg/dL)
150	310, many mo	16.6[1]	1.8	CKD with SCr 1.7-1.8
151	1880, 4 wk	34.2[2]		AKI on diabetic CKD. Progression to ESRD
152	2240-2800, 6 mo	-	8.08	CKD. Progression to ESRD
153a	9000, 4 d	60[3]	6.4	AKI, HDx10 days. SCr 0.9 in 6 wk
153b	4500, 5 d	-	9.3	AKI, HDx6 times. SCr 1.3 in 5 wk
153c	3600, NS	-	6	AKI, No HD. SCr 1.0 in 4 wk
153d	1800, NS	-	5.5	AKI, No HD. SCr 0.8 in 2 wk
153e	5400-6300, NS	-	12.3	AKI, HD. SCr 2.1 in 4 wk
153f	6300-7200, NS.	-	6.7	AKI, no HD. SCr 1.1 in 6 wk
153g	4500-5400, NS	-	9.8	AKI, HD. SCr 1.2 in 6 wk
153h	6300, NS	-	6.6	AKI, HD. SCr 1.1 in 4 wk
153i	2700-3600, NS	-	5.2	AKI, HD. SCr 0.8 in 2 wk
153j	7200 NS	-	10.4	AKI, HD. SCr 1.5 in 6 wk
154	1260, 6 wk	-	7.9	CKD on CKD from HTN. SCr 1.9 in 4 mo
155a	13120, once	7[4]	12	AKI, HDx2 times. SCr 1.3 in 1 yr
155b	9240, once	7[4]	11.7	AKI, no HD. SCr 1.3 in 4 mo
156	450-660, > 3 yr	-	6.9	CKD on other CKD, no HD. SCr 3.4 in 3 mo
157a	3725, once	-	-	AKI, no HD. Final SCr 1.1
157b	4360, once	-	6.3	AKI, no HD. Final SCr 1.1 NS
157c	7545, once	-	6.1	AKI, no HD. Final SCr 1.2
157d	1300, once	-	5.7	AKI, no HD. Final SCr 1.0
157e	2170, once	-	4.5	AKI, no HD. Final SCr 1.1
158	6830, once	-	16.4	AKI, no HD. SCr 0.9 mg/dL in 1 mo

[1]During recovery. SCr approximately 1.7-1.8 mg/dL; [2]Post-ingestion. SCr approximately 3.6 mg/dL; [3]During AKI. SCr approximately 6.4 mg/dL; [4]Post recovery. a,b,c,d,e,f,g,h,i,j,k in Ref. 153 and a,b,c,d,e in Ref. 157 represent the numerical sequence of the patients in these references (1st, 2nd, *etc*). SCr 1.3 mg/dL. SCr: Serum creatinine; AKI: Acute kidney injury; CKD: Chronic kidney disease; ESRD: End-stage renal disease; HD: Hemodialysis; NS: Not specified duration of intake.

incomplete information. Clinical and histological findings associated with the last two categories complete the picture of nephropathy in dietary hyperoxaluria.

Dietary hyperoxaluria should be differentiated from the other three categories of hyperoxaluria, since its treatment, which consists of reducing the dietary oxalate, is relatively simple. Elimination of the diagnostic option of primary hyperoxaluria may require genetic testing, but this is usually not required. A careful history should eliminate the possibility of enteric hyperoxaluria. Routine laboratory findings, such as normal serum albumin and electrolyte levels, may assist in eliminating this diagnosis. Differentiating between dietary and idiopathic hyperoxaluria can be difficult. Features establishing the diagnosis of dietary hyperoxaluria include: absence of primary or enteric hyperoxaluria; ingestion of large amounts of oxalate, usually found after the patient's oxalate-induced end organ damage has become manifest; documented hyperoxaluria associated with a high oxalate diet; and reduction of the oxaluria to within normal levels after normalization of the dietary oxalate. The evaluation of oxaluria is complicated in patients with impaired renal function, which, as noted earlier, decreases urinary oxalate excretion.

Dietary hyperoxaluria can cause renal disease and systemic oxalosis. Earlier studies focused mainly on the association between dietary hyperoxaluria and nephrolithiasis. A study by Neuhaus *et al*[11] established this association. More recently, several case reports of renal parenchymal disease manifested as either AKI or CKD[150-158] and oxalosis with primary neurological manifestations from dietary hyperoxaluria[159-163] have been published. Identified causes of dietary hyperoxaluria include ingestion of large amounts of the following: peanuts[150]; rhubarb[151]; Chaga mushroom powder[152]; *Irumban puli* (*Averrhoa bilimbi*), which is a fruit in the same family as star fruit[153]; juice made of celery, carrots, parsley, beets with greens, and spinach[154]; and, ingestion of star fruit (*Averrhoa carambola*), which has a very high content of oxalate[155-163]. Star fruit-induced oxalate nephropathy has also been investigated in experimental animals[164,165].

Table 3 shows estimates of oxalate intake and urinary excretion, type of clinical renal syndrome induced by oxalate (AKI *vs* CKD), peak serum creatinine concentration, whether dialysis was performed or not, and outcomes of patients with dietary hyperoxaluria-induced deterioration of renal function. The estimates of oxalate intake are approximations because estimates of the oxalate content of the same dietary item often vary widely[27,166-168]. We recorded in Table 3 either the oxalate intake reported in a study, or, if this intake was not reported directly, an estimate calculated from the amount of the dietary item consumed and the average oxalate content of this item.

Data regarding urinary oxalate excretion were missing from the majority of the published cases presented in Table 3. Even when urine oxalate excretion was reported, the findings were complicated by the presence of advanced renal failure, which, as noted above, decreases urinary oxalate excretion, or by the fact that oxalate excretion was measured in the recovery period after oxalate intake had been reduced. An elevation of urinary oxalate

excretion rate was reported only in one patient, who also had advanced renal failure[153]. Urinalysis findings varied: Proteinuria was absent in a few patients, modest in most patients, and as high as 3.7 gm/24 h in one patient who also had diabetes mellitus[151]. Hematuria and sterile pyuria were reported in several patients. Crystaluria was absent in several patients.

Oxalate nephropathy in subjects who briefly consumed food items containing very large amounts of oxalate tended to present as AKI, which was severe enough to require hemodialysis in some cases, but appeared to be reversible in all of them (Table 3). A few patients with chronic intake of oxalate at levels substantially lower than those causing AKI did develop CKD; their kidney function improved but did not normalize after reducing their dietary intake of oxalate[150,154,156].

The paucity of reported cases of chronic nephropathy secondary to dietary hyperoxaluria and of measurement of urinary oxalate in those cases led us to investigate other clinical states of temporary hyperoxaluria caused by excessive intake or formation of oxalate. These states include intake of ascorbic acid, drugs containing oxalate and intoxication with ethylene glycol.

As in dietary hyperoxaluria, excessive intake of ascorbate was initially linked to an increased risk of nephrolithiasis[169,170]. Recently, renal parenchymal disease from oxalate nephropathy causing AKI or CKD has been reported in patients with excessive oral[171-178] or parenteral[179-183] intake of ascorbate. An elevated urinary oxalate excretion rate at the time of ingestion of large amounts of ascorbate and decrease in oxaluria to within or close to its normal range was reported in several cases[171,172,175,179]. Severe AKI was present in most cases[171,173,174,179-183]. Several of these patients required hemodialysis for various periods of time and recovery of renal function was complete[171,174,179-183] or partial[173]. CKD was noted in four patients[175-178]. These patients were ingesting ascorbate chronically but usually in quantities substantially lower than the amounts of ascorbate that cause AKI. Two of these patients developed ESRD[176, 178] and one of them died[178].

Many cases of severe AKI after accidental or suicidal ingestion of oxalate[184,185] or ethylene glycol[186-198] have been reported. AKI had a protracted course in many of these patients and in most instances dialysis was required. Patients with severe ethylene glycol poisoning had significant mortality, especially in decades past[186]. Renal function did not return in several patients with AKI, although some did recover completely. Hyperoxaluria and calcium oxalate nephrolithiasis[199] or oxalate nephropathy with AKI or CKD were reported with the use of two medications used as vasodilators, namely pyridoxilate[200,201] and Praxilene[202-204]. Pyridoxilate is a combination of glyoxylate with pyridoxine. Pyridoxine was intended to redirect glycine formation away from glyoxylate. Nevertheless, at least a portion of the administered glyoxylate was still metabolized to oxalate. Praxilene's common name is naftidrofyryl oxalate. When this salt dissociates in the body oxalate is released. Finally, hyperoxaluria and oxalate nephropathy has been seen with the use of the anesthetic agent, methoxyfluorane[205]. The clinical and histologic features of drug-induced hyperoxaluria have been studied more extensively than those of dietary hyperoxaluria.

Urinary oxalate excretion rates differ between oxaluric states and can provide clues for the differential diagnosis between these states[95]. Table 4 summarizes reported daily rates of urinary excretion of oxalate in various clinical states. The table includes only representative studies for all types of hyperoxaluria, except dietary hyperoxaluria. For this last category of hyperoxaluria, we included in Table 4 all the reports providing measurements of oxalate excretion in patients with oxalate nephropathy that we could find. The degree of renal function has a major impact on urinary oxalate excretion. Primary hyperoxaluria, particularly PH1, is associated with very high rates of urine oxalate excretion[90,95,98,99]. However, even in primary hyperoxaluria, the renal oxalate excretion rate was within the normal range in patients with advanced renal failure[90,99]. Oxalate excretion rates in enteric hyperoxaluria depend on dietary oxalate content; the rate is generally less than in the primary variety, but can be within the range seen in primary hyperoxalurias[1,109,118,206].

Reported excretion rates of oxalate are comparable in idiopathic[35,39,95,206] and dietary[95,150,151,153] hyperoxaluria and substantially lower than in the primary varieties of hyperoxaluria. However, the degree of renal failure differs greatly between the reports of idiopathic and those of dietary hyperoxaluria. Determination of oxaluria in subjects with the dietary variety was usually performed in patients with AKI or advanced CKD whereas idiopathic hyperoxaluria was studied in the context of nephrolithiasis. The urinary oxalate excretion rate of patients with dietary hyperoxaluria may be in the range of subjects with the idiopathic variety (see the legend of Figure 2). Daily urinary oxalate excretion rates exceeding 90 mg (1 mmol) were considered primary or enteric hyperoxaluria[95]. We suggest that dietary hyperoxaluria can also cause oxalate excretion rates similar to those observed in primary hyperoxaluria.

RENAL PATHOLOGY AND PATHOPHYSIOLOGY IN HYPEROXALURIA

The chronic histologic lesions in the kidneys are indistinguishable between all categories of hyperoxaluria. Histologic lesions are also indistinguishable between AKI cases of enteric hyperoxaluria[115,121,125,126] and AKI cases of hyperoxaluria that have dietary, toxic or pharmacologic causes. Hyperoxaluric renal parenchymal disease is classified as a crystalline nephropathy[207], because it is widely acknowledged that oxalate injury to renal tissues begins with the deposition of abundant calcium oxalate crystals[208] in the lumen of renal tubules, the renal interstitium, and the walls of the renal vessels in all categories of hyperoxaluria[90,209-211].

Table 4 Daily urinary oxalate excretion in various hyperoxaluric states

Oxaluric state	Urinary oxalate, mg/24-h
Normal range	< 45, < 30[1]
PH1	> 90[95], > 63[94], 25-492[90], 26-530[99]
PH2	> 42[95], 44-520[99]
PH3	80-194[98], 35-120[99]
Enteric	> 90[95], 30-110[11], 63 ± 13[2], 130[109], 52-92[118], 77 ± 44[123], 48-90[206]
Oral ascorbic acid	98[171], 37[172], 84[175]
Parenteral ascorbic acid	76[179], 100[180], 176[181], 88[182]
Ethylene glycol	29[190], 10[195]
Methoxyfluorane	96-480[205]
Idiopathic	< 63[95], 56 ± 15[39], 38-50[206], 48[207]
Dietary	< 54[95], 16.6[150], 34.2[151], 60[153]

Oxalate excretion is presented as a single number representing the mean or median of the study (not specified in several studies), range (interquartile range in reference 120), or mean ± SD. For patients with two or more sequential measurements of urinary oxalate excretion rate, the Table reports the highest oxalate excretion. [1]Pediatric values. PH1: Primary hyperoxaluria, type 1; PH2: Primary hyperoxaluria type 2; PH3: Primary hyperoxaluria type 3.

Although finding calcium oxalate crystals in kidney biopsy specimens is necessary for the diagnosis of oxalate nephropathy, it is not a specific finding. Oxalate crystals are found in the kidneys in all conditions that elevate the plasma oxalate level. Principal among these conditions are all types of acute and chronic renal failure[212].

Extensive tubular damage with epithelial necrosis and tubular dilatation is the second cardinal characteristic of both acute and chronic oxalate nephropathy, while the involvement of glomeruli is inconsistent. The histologic features of renal tubules in hyperoxaluric AKI have the characteristics of acute tubular necrosis[115,121,151,153,158,159,164,171,174,195,213]. Changes in the renal interstitium are the other histologic characteristic of oxalate nephropathy. Profound interstitial fibrosis is present in chronic cases of oxalate nephropathy[90]. Tubulointerstitial nephritis with interstitial collection of mononuclear cells is a prominent characteristic of both chronic[90] and acute[175] cases of oxalate nephropathy. In some instances, interstitial nephritis takes the form of granuloma[150,214]. Oxalate-induced AKI may[157,164] or may not[153,155] exhibit interstitial nephritis in addition to acute tubular necrosis. Features of acute tubular injury, namely tubular simplification, flattening of tubular epithelial cells and dilatation of the tubular lumen are the earliest histological changes observed in kidneys of animals with experimental dietary acute oxalate nephropathy[165]. In addition to the kidneys, calcium oxalate crystals can be found in bone, skin, vessels and joints in patients with oxalosis[215]. Radiological and histologic features of nephropathy in a patient with dietary hyperoxaluria are shown in Figures 2 and 3 respectively.

The initial event in the development of oxalate nephropathy is the formation of calcium oxalate crystals in the lumen of proximal tubules[219]. Details of the mechanism of crystal formation, which have been reviewed extensively in the literature on stone formation, are outside the scope of this report. Randall's plaque (apatite collections in the interstitium of the papillae) was noticed in abundance in several hyperoxaluric states and may play a role in stone formation[220].

Adhesion of calcium oxalate crystals to the surface of tubular epithelial cells follows formation of the crystals. The mechanisms of adhesion have been extensively studied recently[221-227]. Coating with urine proteins, facilitated by low urinary pH, was shown to reduce the attachment of calcium oxalate crystals to renal inner medullary epithelial cells[221]. Calcium oxalate binding proteins that promote oxalate nephropathy have also been identified. Calcium oxalate monohydrate binding protein, one of these promoters, was shown to be upregulated by oxalate-induced oxidative stress[223]. A dual role was suggested for osteopontin, which inhibits calcium oxalate crystal formation and tubular retention[222], but also increases adhesion of these crystals to carboxylate ions that would promote oxalate-induced renal disease[225]. Prostaglandin E2 inhibits binding of calcium oxalate crystals to renal epithelial cells[224,226]. In a recent report, 26 oxalate-binding proteins were identified the kidney[227]. Further studies are needed to clarify the role of each of these proteins in oxalate-induced renal disease.

Evidence of the direct toxicity of supraphysiologic concentrations of oxalate to renal tubular cells was found in studies using cultured cells[228]. Both inhibition of cell proliferation and apoptosis have been identified as mechanisms of this nephrotoxicity. Studies in epithelial, endothelial and interstitial renal cell cultures found that exposure to sodium oxalate leads to reduced cell survival through inhibition of cell proliferation[229]. Evidence of oxalate-induced toxicity to renal cells was provided by finding increased levels of protein and mRNA of kidney injury molecule-1 in both human cell cultures and experimental animals[230]. In experimental animals hyperoxaluria increased production of TNF-α, FAS and FAS ligand, and apoptosis[231].

Research involving the mechanisms of innate immunity has shed considerable light on the molecular mediators and histologic features of oxalate nephropathy[232-243]. A role for toll-like receptors, NOD-like receptors and inflammasomes in AKI secondary to ischemia and sepsis has been documented[232]. A growing body of evidence has given inflammasomes a central place in our understanding of complex diseases (*e.g.*, metabolic syndromes, carcinogenesis) and physiological processes (*e.g.*, regulation of intestinal microbiome) and has identified them as important players of the intracellular surveillance system. Recent emphasis was also placed on the role of inflammasomes in various renal disease categories, including crystalline nephropathies[233].

Inflammasomes are part of the innate immune system. As their name suggests, inflammasomes represent large multimolecular cytosolic complexes that assemble into a platform for the activation of pro-inflammatory caspase 1[234-236]. Inflammasomes are important mediators

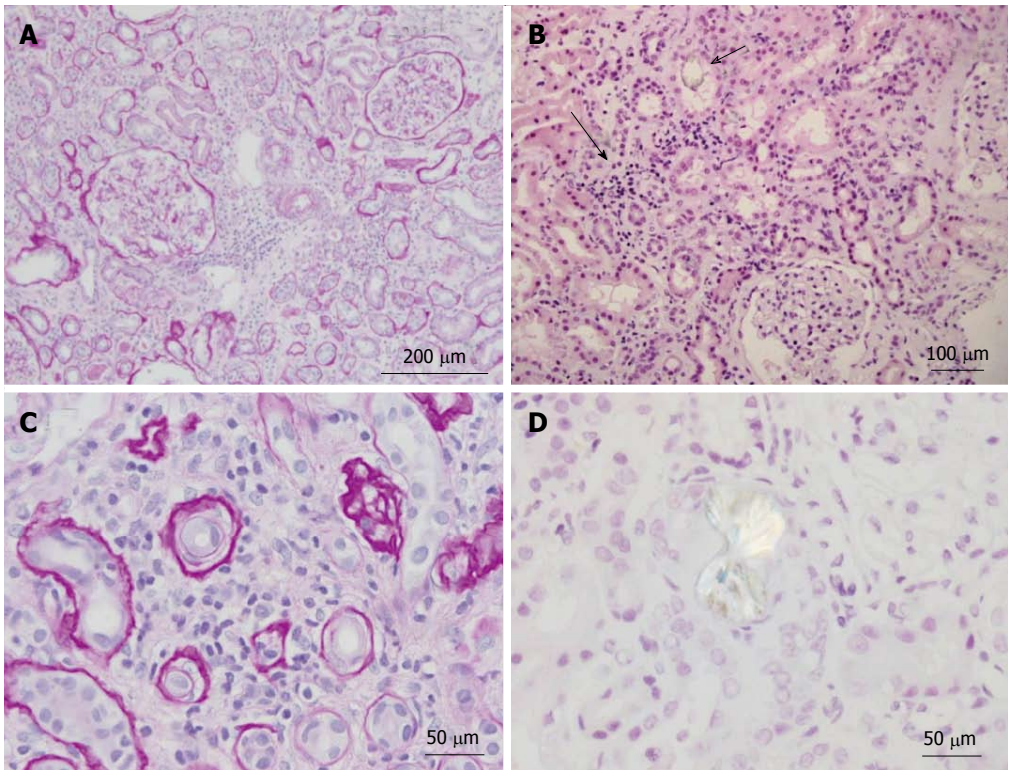

Figure 3 Renal histology in the patient depicted in Figure 2. A: Low power view of kidney showing two complete glomeruli and expansion of the interstitium by lymphocytes and edema. Periodic acid-Schiff (PAS) stain highlights the basement membranes of the tubules and Bowman's capsule. PAS stain; B: Low power view of renal parenchyma showing tubulointerstitial nephritis (solid arrow) and oxalate crystal within tubule (open arrow). H and E stain; C: High power view showing interstitium expanded by lymphocytic infiltrates and tubular atrophy. PAS stain; D: High power view of calcium oxalate crystal under polarized light. H and E stain.

of apoptosis, interstitial inflammation and fibrosis in various types of renal disease[237,238]. Of great importance in the context of oxalate nephropathy is the nucleotide-binding domain, leucine-rich repeat inflammasome (NALP3 or NLRP3). When activated, NALP3 proteins oligomerize and form a protein complex with caspase-1. This process activates caspase 1 which cleaves the inactive precursors of IL-1β and IL-18 to generate active cytokines that promote inflammation. The NALP3 inflammasome has been implicated in the molecular mechanism of nephropathy caused by urate crystals[239]. More recent studies detail the functional significance of the inflammasome and the IL-1β/IL-18 axis as an important factor in interstitial inflammation and fibrosis, as well as progression of renal failure, in oxalate nephropathy[240-242] and other kidney diseases[243]. In experimental models, genetic deletions of antagonists of the NALP3 inflammasome pathway have decreased the severity of oxalate nephropathy[240-242].

MANAGEMENT OF NEPHROPATHY IN ACQUIRED HYPEROXALURIAS

The general principles of management of oxalate-related nephropathies are the same in all categories of acquired hyperoxaluric nephropathy and include a diet low in oxalate and relatively high in calcium, fluid intake exceeding 1.5 L per m^2 body surface area per day, treatment with probiotics containing oxalate degrading bacteria, and medications to increase urinary solubility of crystals (*e.g.*, potassium citrate)[244]. Studies on the effect of probiotics on oxaluria have produced conflicting results. Intake of probiotics led to significant reduction of oxaluria in some studies[245,246], but had no effect on oxaluria in several other studies[247-249].

Specific measures targeted to the mechanism of hypercalciuria can be effective in patients with enteric hypercalciuria[244,250]. It is possible that probiotics may be useful in certain categories of patients with enteric hyperoxaluria, in particular, those who have altered enteric flora because of protracted courses of antibiotics, but this will require further study. A study by Toblli *et al*[251] reported that the angiotensin-converting enzyme inhibitor enalapril had a protective effect on the formation of tubulointerstitial lesions in rats fed ethylene glycol. Studies in humans with hyperoxaluria are needed to determine the effectiveness of this drug. Further studies are also needed to objectively assess the effectiveness of traditional herbal medications used for prevention or treatment of renal stones[252,253].

FUTURE RESEARCH

Our main reason for undertaking this review was to underscore the need for epidemiologic, biochemical and histologic studies of the effects of dietary hyperoxaluria on the development of CKD and end-stage renal disease (ESRD) across the globe. Occasional intake of nutrition-

al foods high in oxalate has been advocated[254]. While doing so may have merit, neither the highest "safe" dose of oxalate nor whether this dose differs between individuals has been determined. However, the main concern is not with brief ingestion of a relatively high dose of oxalate, but instead with the effects of chronic ingestion of high doses of oxalate on renal function, which is common in several parts of the world (Table 1). Interestingly, several patients with documented CKD due to chronic dietary hyperoxaluria had ingested amounts of oxalate comparable to or even lower than the average values reported in certain parts of the world (Tables 1 and 3). Difficulties and delays with the recognition of hyperoxaluria as the cause of CKD and ESRD have been documented, even for the primary hyperoxalurias[101,103,105,255], where early appearance of symptoms and renal failure, oxalosis and a family history of recurrent nephrolithiasis, renal failure and oxalosis should lead one to the diagnosis. That retention of oxalate in patients with CKD from any etiology may result in renal deposition of calcium oxalate, secondary deterioration of the renal function and systemic toxicities has been recognized[256]. However, in a recent comprehensive review excessive dietary oxalate intake was not listed among the primary risk factors for CKD[257]. Appropriate studies in populations with high dietary oxalate intake have the potential to reduce the rates of CKD and ESRD by simple dietetic interventions (*e.g.*, fluid intake, leaching of oxalate by soaking). Such studies should be encouraged.

Related to the need of studying the effects of oxalate intake on the development of CKD in various areas of the globe is the need to continue performing studies on genetic influences on oxalate absorption and excretion. Clinical and epidemiologic studies suggested that genetic influences can affect oxalate absorption and excretion[254,258-261]. Ongoing studies of genetic differences in intestinal and renal oxalate transporters[262-266] and of factors related to calcium metabolism[267] have the potential of leading to novel preventive and therapeutic modalities.

Future research should also include enzymologic and protein-structure studies aimed at identifying potential drugs that would either promote reductive metabolism of glyoxylate, the immediate precursor of oxalate, or inhibit oxidative enzyme-catalyzed reactions that increase oxalate production, for example the LDH reaction. Inhibiting LDH activity would reduce oxalate production and increase the levels of calcium glyoxylate and calcium glycolate which are 3 to 4 orders of magnitude more soluble in water than calcium oxalate. This approach is analogous to the treatment of gout where allopurinol inhibits xanthine oxidase activity, thereby reducing uric acid production and increasing the levels of much more water soluble xanthine oxidase substrates (*e.g.*, hypoxanthine). The inflammasome NLP3 is an emerging potential target for new drug development NLP3[268].

CONCLUSION

Hyperoxaluria, regardless of its mechanism, can cause not only nephrolithiasis and nephrocalcinosis, but also AKI, CKD and ESRD. Research to verify or reject the hypothesis that chronic dietary hyperoxaluria is underrecognized as a cause of CKD and ESRD, particularly in global areas with high dietary oxalate consumption, has the potential of improving health, well-being and economy in these areas. This research should be combined with research on the genetics of oxalate transport, oxalate-induced mechanisms of disease and development of medications affecting these processes.

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REVIEW

Why do young people with chronic kidney disease die early?

Shankar Kumar, Richard Bogle, Debasish Banerjee

Shankar Kumar, Medical School, St George's, University of London, SW17 0RE London, United Kingdom
Richard Bogle, Department of Cardiology, St George's Hospital NHS Trust, SW17 0QT London, United Kingdom
Richard Bogle, Department of Cardiology, Epsom and St Helier University Hospitals, NHS Trust, SW17 0QT London, United Kingdom
Debasish Banerjee, Renal and Transplantation Unit, St George's Hospital NHS Trust, SW17 0QT London, United Kingdom
Author contributions: All authors contributed to this paper.
Correspondence to: Dr. Debasish Banerjee, MD, FRCP, FASN, Consultant Nephrologist and Reader, Renal and Transplantation Unit, St George's Hospital NHS Trust, Blackshaw Rd, SW17 0QT London, United Kingdom. debasish.banerjee@stgeorges.nhs.uk
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Abstract

Cardiovascular disease poses the greatest risk of premature death seen among patients with chronic kidney disease (CKD). Up to 50% of mortality risk in the dialysis population is attributable to cardiovascular disease and the largest relative excess mortality is observed in younger patients. In early CKD, occlusive thrombotic coronary disease is common, but those who survive to reach end-stage renal failure requiring dialysis are more prone to sudden death attributable mostly to sudden arrhythmic events and heart failure related to left ventricular hypertrophy, coronary vascular calcification and electrolyte disturbances. In this review, we discuss the basis of the interaction of traditional risk factors for cardiovascular disease with various pathological processes such as endothelial dysfunction, oxidative stress, low grade chronic inflammation, neurohormonal changes and vascular calcification and stiffness which account for the structural and functional cardiac changes that predispose to excess morbidity and mortality in young people with CKD.

Key words: Chronic kidney disease; Cardiovascular mortality; Cardiorenal syndrome; Endothelial dysfunction; Vascular calcification and stiffness

Core tip: In this review, we set out to summarise current opinion based on extensive scientific research that might explain the reasons for the disproportionately high death rate in chronic kidney disease and dialysis patients. The cardiovascular "phenotype" that poses increased risk to patients with chronic kidney disease (CKD) changes with progression of kidney dysfunction. Macrovascular disease is more important in early CKD whereas microvascular processes play an increasing role with worsening kidney disease.

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EPIDEMIOLOGY

People with chronic kidney disease (CKD) are at higher mortality risk compared with the general population[1,2]. End-stage renal disease is associated with highest mortality despite modern renal replacement therapy and pharmacological interventions. Mortality risk among individuals starting haemodialysis is greatest in the first 120 d, accounting for 27.5 deaths per 100 person-years and, thereafter, the annual mortality rate is around 20%[3,4]. Furthermore, around 9% of deaths in the first 3 years after commencing dialysis are in the 20-54 years age group[5]. Findings from the United Kingdom Renal Registry indicate that a person commencing dialysis aged 25-29 years has a median life expectancy of only 18.5 years, 33 years less than someone in the same age group in the general population without CKD[6]. Similarly,

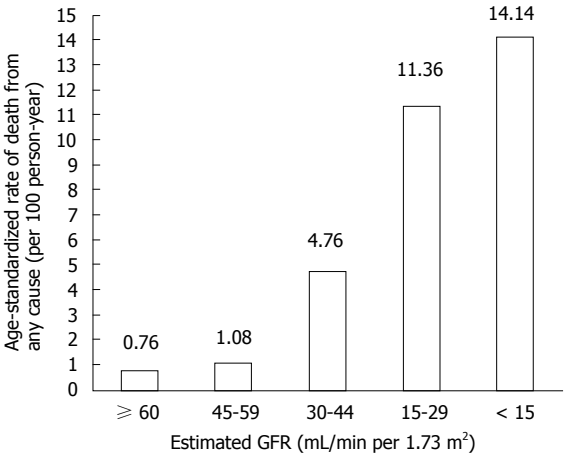

Figure 1 All-cause mortality and its relationship to worsening chronic kidney disease. After Go AS 2004[1].

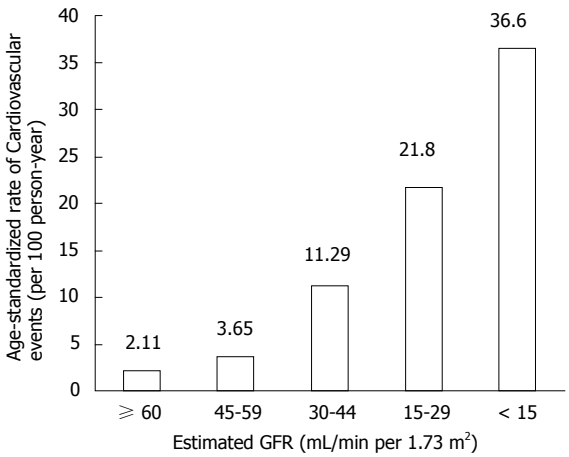

Figure 2 Cardiovascular event rates according to chronic kidney disease stage. After Go AS 2004[1].

patients aged 65-74 years, which is the commonest age group starting dialysis reported in the European Renal registry, can expect to live 5 years, about 50% less than those in the same age group in the general population[5].

The leading cause for this observed excess morbidity and mortality in end-stage renal disease is cardiovascular disease which accounts for 40%-50% of deaths[5,7-9]. In absolute terms, patients receiving dialysis have a 10-20 fold increased risk of cardiovascular death than do age and sex-matched controls in the general population. For younger dialysis patients, below 45 years of age, cardiac mortality is even higher, exceeding 100 times. After kidney transplantation, the risk is reduced but remains at 3-5 times that in the general population[7,10].

Of the non-cardiovascular causes of death in advanced renal failure, infection and malignancy are most important, accounting for approximately 15% and 8%, respectively, in the first 3 years of dialysis treatment[5,11]. Over this period of time, 10% of mortality due to infection was recorded in younger adults (20-54 years age group) and a similar percentage was attributed to malignancy. Vascular catheter-associated blood-borne infection often due to recurrent Staphylococcus aureus[12-15] and pneumonia[16] are the main causes. The high incidence of infections and inflammation in dialysis patients is related to disturbances in innate and adaptive immune mechanisms[17]. In particular, renal insufficiency is associated with down-regulation of toll-like receptors leading to sub-optimal stimulation of the innate immune system.

Non-adherence to haemodialysis and dietary restriction especially of high potassium-containing food, and excessive interdialytic fluid weight gain leading to congestive cardiomyopathy, are all contributory risk factors of premature death, especially in young dialysis patients[18]. The number refusing treatment or committing suicide is also not insignificant[5]. Treatment by peritoneal dialysis confers survival advantage over haemodialysis, at least in the first few years, before risk equalises[19,20]. Nevertheless, cardiovascular disease still poses the greatest risk in peritoneal dialysis (PD) patients[21,22]. This patient group shares similar cardiovascular risk factors to haemodialysis patients but they typically gain more weight (due to the high glucose load and insulin resistance) and demonstrate higher levels of chronic inflammation in response to exposure to non-physiological peritoneal dialysis fluid and episodes of peritonitis[21]. However, relatively little randomised trial data is available pertaining to cardiovascular risk factors/outcome in peritoneal dialysis patients and so much of the discussion below relates to haemodialysis patients.

CARDIORENAL SYNDROME

Large population studies have indicated that all stages of CKD predispose to premature death from cardiovascular and other causes, and is not restricted to those on dialysis[1]. Go and colleagues' landmark study demonstrated that the age standardised mortality rate from any cause increased in a step-wise manner, independent of known risk factors (Figure 1). Even in cases of moderate renal insufficiency (eGFR 45-59 mL/min), the risk of death was 8% higher per 100 person years than in the general population without kidney impairment. Thereafter, this study indicated that the risk increased exponentially with declining eGFR, exceeding 11 times risk in CKD stage 4. Similarly, when considering age-standardised rate of cardiovascular events, there was a significant increase in events with progressive renal insufficiency (Figure 2). With mild degrees of renal impairment (eGFR > 60 mL/min), the rate of coronary events was 2.11 per 100 person years greater than the general population with no kidney impairment, rising to 21.8 times the risk with CKD stage 4.

Most striking was the adjusted hazard ratio for death from any cause found to be 20% greater in CKD stage 3a and a 40% increase of having a coronary event, rising to 590% and 340% at CKD stage 5, respectively (Table 1). This study confirmed the findings of many longitudinal studies since the 1970s that had shown that patients with advanced CKD died from cardiovascular causes[23,24], and

Table 1 Adjusted hazard ratio for death from any cause and cardiovascular events in 1120295 adults according to estimated glomerular filtration rate

Estimated GFR (mL/min per 1.73 m^2)	Death from any cause	Any Cardiovascular event
⩾ 60	1	1
45-59	1.2 (1.1-1.2)	1.4 (1.4-1.5)
30-44	1.8 (1.7-1.9)	2.0 (1.9-2.1)
15-29	3.2 (3.1-3.4)	2.8 (2.6-2.9)
< 15	5.9 (5.4-6.5)	3.4 (3.1-3.8)

Adjusted hazard ratio with 95%confidence intervals given in parentheses. Data adjusted for age, gender, presence or absence of prior coronary heart disease, prior chronic heart failure, prior ischaemic stroke or ischaemic attack, prior peripheral arterial disease, diabetes mellitus, hypertension, dyslipidaemia, cancer, liver disease, chronic lung disease. After Go *et al*[1], 2004.

has been substantiated by a recent study[20]. Recognition that cardiovascular disease is a major threat to patients with CKD and, conversely, renal dysfunction is prevalent in patients with cardiac disease, indicating a poorer prognosis, led to adoption of the term, *cardio-renal syndrome*. Ronco *et al*[25] published their widely adopted classification to highlight this crucial interaction.

The bidirectional effect of heart failure and kidney failure is a key concept in the cardiorenal syndrome[26]. In the context of a failing heart due to pump failure, pressor systems (the sympathetic nervous system and renin-angiotensin-aldosterone axis) are activated to maintain the haemodynamic status quo[26,27]. Increased glomerular filtration pressure, achieved by efferent vasoconstriction helps to maintain glomerular filtration rate in low-output states, but the increased vascular resistance decreases kidney perfusion. Over time, this causes tubular hypoxic damage, renal cell apoptosis and replacement fibrosis, which leads to loss of nephron mass and to progressive renal dysfunction. Conversely, as chronic kidney disease progresses, the sympathetic nervous system is overactivated as a result of renal ischaemia, raised angiotensin Ⅱ levels and suppression of nitric oxide, causing hypertension, left ventricular hypertrophy and progressive left ventricular dilatation. Cardiac myocyte dysfunction and fibrosis, so-called "CKD cardiomyopathy", is believed to be the predominant pathophysiological mechanism. This may be compounded by salt and water overload caused by raised angiotensin Ⅱ levels leading to elevated central venous pressure and organ congestion.

TRADITIONAL AND NON-TRADITIONAL RISK FACTORS FOR CARDIOVASCULAR DISEASE

Patients with cardiovascular disease and those with CKD share many 'traditional' risk factors for atheromatous plaque formation, such as hypertension, dyslipidaemia, diabetes mellitus, obesity and smoking, but it is increasingly recognised that these factors fail to account fully for the disproportionate increase in cardiovascular mortality risk in CKD compared to the general population[8,23,24,28]. In addition, evidence based treatment strategies such as the use of statins for treating hyperlipidaemia in type 2 diabetic patients which have reduced morbidity and mortality significantly[29], appear less effective in diabetic patients requiring dialysis[30]. Changes unique to CKD are the progressive accumulation of uraemic toxins, electrolyte abnormalities, metabolic acidosis, sympathetic nervous system and renin angiotensin aldosterone system activation, and volume overload that result in structural and functional abnormalities of the heart, termed uraemic cardiomyopathy[31].

Non-traditional risk factors include endothelial dysfunction, elevated plasma homocysteine, increased levels of inflammatory factors and oxidative stress, abnormal apolipoprotein levels, enhanced coagulability, albuminuria, increased arterial calcification and arterial stiffness, anaemia, and left ventricular hypertrophy[8,23,24,32]. Whether and how these and other, as yet unidentified, factors contribute to morbidity and mortality is not entirely clear, but is the subject of on-going research. In this review, we discuss current knowledge about emerging non-traditional risk factors and their complex interaction.

ENDOTHELIAL DYSFUNCTION

Endothelial dysfunction is considered to be one of the first mechanisms involved in the development of atherosclerosis[33]. In CKD, endothelial dysfunction has been defined by increased levels of von Willebrand factor, reduced nitric oxide levels (NO) and over expression of inflammatory cytokines and C-reactive protein (CRP)[34]. An excess of pro-inflammatory over anti-inflammatory cytokines has been reported in early atherosclerotic lesions as lipid particles accumulate[33]. Microalbuminuria, a marker of early kidney disease, in both diabetic and non-diabetic patients, correlates with altered endothelial function. NO levels decline with progressive kidney disease so that reduced vasodilatory activity contributes to the increased risk of developing hypertension[34]. Schiffrin and colleagues suggested that the combination of impaired endothelial function, low grade inflammation, and dyslipidaemia may interact to promote accelerated atherogenesis and progressive renal disease[32].

In health, endothelium-derived nitric oxide is an important anti-atherogenic molecule. Circulating NO levels fall as asymmetric dimethylarginine (ADMA) levels rise[34,35]. This competitive inhibitor of nitric oxide synthase (NOS) also blocks the entry of L-arginine into cells to reduce NO synthesis[36]. ADMA is excreted by the kidneys or metabolized by dimethylarginine dimethylaminohydrolases (DDAH) and this pathway is attractive as a potential modulator of the NOS system in dialysis patients. Plasma ADMA concentrations increase with deteriorating kidney function, and the highest levels are found in dialysis patients[34]. ADMA levels are raised in elderly hypertensive patients and are strongly predictive of acute

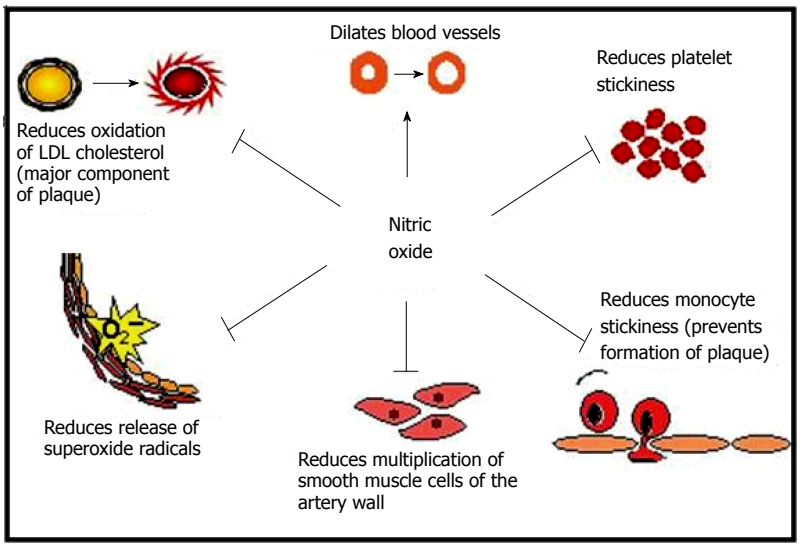

Figure 3 The physiological roles of nitric oxide on endothelial function.

coronary events and increased cardiovascular mortality risk in CKD[35,37-39].

The beneficial properties of NO are shown in Figure 3. Through NO inhibition, ADMA indirectly promotes vasoconstriction, raises blood pressure, impairs endothelium-dependent relaxation, and promotes platelet adhesion and aggregation and smooth muscle cell replication. It favours the release of superoxide radicals, formation of peroxynitrite and tyrosine nitration which cause vascular endothelial damage[40]. ADMA accumulation in CKD promotes atherogenesis and end-organ damage through sustained hypertension and other mechanisms[35]. In CKD, left ventricular hypertrophy, which is associated with premature death, may be a consequence of hypertension, partly triggered through prolonged inhibition of nitric oxide synthase. L-arginine supplementation should theoretically abrogate the effects of ADMA, but not all studies have found improvements in endothelial function[35]. One possible explanation is that chronically sustained high levels of ADMA induce irreversible vascular damage. There may be other mechanisms of action of ADMA other than NOS inhibition, yet to be identified, and not influenced by L-arginine supplementation. In an experimental model, DDAH activity of endothelial cells was decreased by almost half when incubated with oxidized LDL or TNF-α, and similar findings were observed in rabbits fed a high cholesterol diet[41]. These findings indicate that lipoproteins or cytokines may increase endothelial production of ADMA by reducing DDAH activity. This may be an important mechanism whereby local release and accumulation of intracellular ADMA inhibits NOS in hyperlipidaemia. The precise balance of pro and anti-inflammatory mediators present in the cellular milieu is likely to result in a variable overall effect which is directed towards or away from increased risk of atherosclerosis and atherothrombosis.

HYPERHOMOCYSTEINAEMIA

Many studies have shown an association between elevated levels of homocysteine and increased risk of cardiovascular events, stroke and peripheral vascular disease in the general population[42]. High levels of homocysteine contribute to endothelial dysfunction, oxidative damage and thrombosis[42-45]. Patients with declining kidney function accumulate homocysteine due to decreased metabolism by the kidneys[43,46]. In one study, the finding of elevated homocysteine and fibrinogen levels in CKD was thought to account for 38% of the attributable mortality risk, whereas individuals with CKD and low homocysteine levels (< 10 μmol/L) had mortality rates similar to those with normal renal function[43]. Stuhlinger *et al*[45] have proposed that homocysteine exerts its atherogenic activity by indirectly suppressing NO production, through inhibition of dimethylarginine dimethylaminohydrolases (DDAH) that metabolise ADMA. Homocysteine is not obtained from the diet, but is synthesized from the amino acid, methionine. Homocysteine can be recycled back into methionine and deficiencies of the vitamins folic acid, pyridoxine (B_6), or cyanocobalamin (B_{12}) can lead to high homocysteine levels. Supplementation with these vitamins lowers homocysteine levels but has not been associated with a significant reduction in cardiovascular events[42]. However, fortification of grain products with folic acid in the United States since 1998 has seen a decrease in stroke incidence which, at least in part, is thought to be due to lower homocysteine levels in the population[44]. A recent meta-analysis failed to demonstrate a significant decrease in the risk for cardiovascular events, stroke and all-cause mortality among a CKD population[47]. Hyperhomocysteinaemia may be a marker rather than a direct cause of CVD[46].

EPIDEMIOLOGICAL LINKS BETWEEN ALBUMINURIA AND CARDIOVASCULAR EVENTS

Microalbuminuria refers to albumin excretion of be-

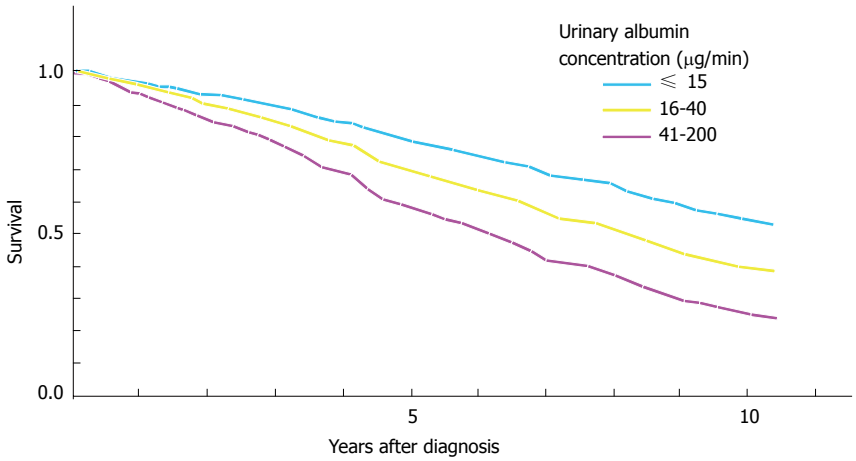

Figure 4 Microalbuminuria as a risk factor for death in type 2 diabetes. Reproduced from Schmitz *et al*[49], 1988.

tween 30 and 300 mg in the urine over 24 h (20-200 μg/min) that derives from a glomerular or tubular abnormality in primary kidney disorders, or it may reflect a generalised increase in vascular permeability due to vascular endothelial dysfunction[8]. Microalbuminuria, most commonly seen in diabetes mellitus and hypertension, signifies risk of progressive renal impairment and predates any fall in eGFR[52]. In a prospective study over 7 years, the degree of microalbuminuria in diabetic patients was found to correlate strongly with cardiovascular events and mortality[48]. Microalbuminuria was found to be a stronger predictor of cardiovascular outcomes than smoking, hypertension and raised serum cholesterol, in men who had no pre-existing cardiovascular disease. This was one of many studies that confirmed the early findings of Schmitz *et al*[49] (Figure 4). Diabetic patients were divided into 3 groups, entering the study with microalbuminuria of less than 15 μg/min, 16-40 μg/min and 41-200 μg/min. At 10 years, the overall mortality was 58%, caused by CVD or stroke with a further 3% dying from end-stage renal failure. 10-year survival was 55% and 25% in the < 15 μg/min and 41-200 μg/min microalbuminuria patient groups.

In diabetic patients, the development of microalbuminuria indicates microvascular disease which is associated with extracellular matrix expansion in the glomeruli of the kidney[50]. The natural history results in progressive glomerulosclerosis, increasing proteinuria, and chronic renal failure. But how does microalbuminuria, a marker of diabetic nephropathy, or a slightly reduced eGFR predict cardiovascular events and mortality before there is any evidence of overt coronary artery disease? Endothelial cell dysfunction seems to be the common pathophysiological pathway linking renal disease and CVD. Interplay between low-grade inflammation, elevated ADMA, increased circulating pro-inflammatory cytokines, dyslipidaemia, oxidative stress, sympathetic system over-activity and inappropriate activation of the renin angiotensin aldosterone system, is implicated for generalised endothelial cell dysfunction[51].

Large epidemiological studies have demonstrated that microalbuminuria in non-diabetic individuals is also associated with coronary, peripheral and cerebral vascular events[52]. Here again, the premise is that microalbuminuria is a marker of generalised endothelial cell dysfunction. Microalbuminuria is associated with increased transcapillary leakage of albumin and increased von Willebrand factor and other markers of endothelial dysfunction[50,51]. Inhibition of the renin-angiotensin-aldosterone system with either angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor antagonists (AT1 receptor antagonists) can reduce albuminuria in both diabetic and non-diabetic individuals, to slow down the progression of renal disease and provide cardioprotection[53]. The underlying pathophysiology relates to the ability of ACE-I and AT1 receptor blockers to lower intra-glomerular capillary pressure by decreasing efferent arteriolar pressure and the reduction in transglomerular pressure decreases albuminuria. These drug classes have reduced progression of diabetic renal disease by reversing microalbuminuria to normoalbuminuria. Further long-term epidemiological studies are necessary to define its extent and enduring impact. The heart outcomes and prevention evaluation study (HOPE) is one of many studies showing that the ACE inhibitors reduce the progression of albuminuria and, at the same time, are effective in decreasing cardiovascular mortality in both diabetic and non-diabetic patients with normal blood pressure[54]. The Irbesartan Diabetic Nephropathy Trial demonstrated concomitant reductions in urinary protein excretion and cardiovascular endpoints in hypertensive type 2 diabetic participants[55].

Proteinuria is widely accepted as an independent risk factor for cardiovascular morbidity and mortality. Microalbuminuria progressing to overt proteinuria confers increasing cardiovascular mortality risk and concomitant CKD is associated with worsening cardiovascular and all-cause mortality, acting as risk multipliers across the CKD continuum[1,56,57]. Only a minority of the stage 3-5 CKD population progress to end-stage dialysis-requiring disease, most succumbing to premature cardiovascular death. Proteinuria surpasses blood pressure and cholesterol as a predictor of adverse clinical outcome[58]. Furthermore, the same group reported that the risk of acute myocardial infarction in subjects with CKD and

proteinuria was similar to or exceeded the cardiovascular risk associated with diabetes mellitus[59]. The PREVEND study found a significant independent association between microalbuminuria and myocardial ischaemia found on ECG[60]. Microalbuminuria is accompanied by raised inflammatory markers such as CRP and a fall in adiponectin levels[61]. Endothelial dysfunction has been implicated in the aetiopathology linking proteinuria with ADMA[62]. Since the detection of subclinical atherosclerosis is difficult and approximately 50% of cardiac events arise from the rupture of a vulnerable plaque in non-occlusive coronary disease, it may be that microalbuminuria associated with endothelial dysfunction is also acting as a marker of subclinical atherosclerosis. In this respect, studies have demonstrated that microalbuminuria independently predicts an increased carotid artery intima-media thickness which is a marker of subclinical atherosclerosis[63].

INFLAMMATION, DYSLIPIDAEMIA, ADVANCED GLYCATION END-PRODUCTS AND OXIDATIVE STRESS

Systemic inflammation is fundamental to the development of atherosclerosis[33,64]. Inflammatory markers including CRP, fibrinogen, soluble adhesion molecules and pro-inflammatory cytokines correlate with the future development of CVD and risk of sudden death in the general population[65].

Progressive renal insufficiency is characterised by a chronic inflammatory state represented by higher concentrations of CRP, interleukin-6 (IL-6), tumour necrosis factor α (TNF-α) and fibrinogen, and with lower levels of albumin[66]. But disorders commonly associated with CKD such as diabetes and hypertension exhibit low grade inflammation long before there is evidence of renal damage, and in the absence of any discernable reduction in serum albumin concentration. Irrespective of the mechanisms that trigger inflammation, there is no doubt that chronic inflammation induces vascular injury, initiating accelerated atherosclerosis[64], which is more pronounced in the younger patient with CKD. The causes of inflammation in renal disease can be partly attributed to reduced clearance of pro-inflammatory cytokines such as IL-6 and TNF-α, to the production of reactive oxygen species and the contribution of co-morbid conditions such as diabetes mellitus and heart failure[23,32,67]. Accumulation of advanced glycation end-products (AGE), normally cleared by the kidneys, may be important in the generalised chronic inflammatory process[68,69]. It has been established that AGEs are naturally formed in all tissues as part of ageing but at an increased rate in certain pathological processes such as diabetes and CKD[69]. Studies have demonstrated that up to 50% of patients with CKD have raised serum levels of CRP, fibrinogen, IL-1, IL-6, TNF-α, D-dimer and the soluble adhesion molecules E-selectin, VCAM-1 and ICAM-1[32,33], and research is focussed on the mechanisms of interaction that promote oxidative stress and atherosclerosis[64].

Correlation between raised serum CRP levels and future cardiovascular events in the general population is strong[65], but the association is more robust in CKD, in which it also closely predicts progression of kidney disease[67,70]. In a prospective study involving over 1000 dialysis patients with a median follow up of 2.5 years, 22% of patients died due to sudden cardiac death[71]. The highest third of high sensitivity CRP and IL-6 levels had twice the risk of sudden cardiac death. Moreover, those with a reduced serum albumin level had a 35% increased risk of suffering sudden cardiac death. IL-6 acts as a major stimulus for release of CRP by the liver. Ramkumar *et al*[72] identified increased production of IL-6 by intra-abdominal adipocytes, which provides a possible link between obesity and increased inflammation in CKD. In haemodialysis patients, other factors stimulating inflammation include repeated exposure to bio-incompatible dialysis membranes, exposure to foreign materials such as dialysis catheters and infection[23,32]. Infection in this group of patients is often subclinical being related to the presence of polytetrafluoroethylene (PTFE) central venous haemodialysis and peritoneal dialysis catheters.

Hyperfibrinogenaemia is observed with declining renal function and raised levels of this acute phase protein parallel those of other inflammatory markers. Hyperfibrinogenaemia predisposes to coronary thrombosis[72,73]. However, there is some uncertainty in defining the extent to which this factor contributes to overall mortality because fibrinogen is closely linked with other factors, such as dyslipidaemia[8].

Dyslipidaemia in CKD is a major factor in the inflammatory response and to atherosclerosis[74]. In health, high-density lipoprotein (HDL) cholesterol acts as an anti-atherogenic molecule in a number of ways. It reverses cholesterol transport, and has anti-thrombotic, anti-inflammatory and anti-oxidant properties, reducing oxidised LDL cholesterol[32,74]. It also promotes endothelial repair by decreasing the expression of adhesion molecules by vascular endothelial cells induced by cytokines[74]. HDL levels fall progressively as renal function declines, and the HDL cholesterol that is produced is dysfunctional. Figure 5 depicts the maturation of HDL and the protective effect of the apolipoprotein-A (apoA-I). In renal failure, apoA-I, synthesized by the liver, decreases so HDL cholesterol levels fall[32,74]. ApoA-I acts *via* ABCG1 taking up cholesterol from macrophages. The enzyme, lecithin-cholesterol acyltransferase (LCAT) esterifies cholesterol in the maturation of HDL cholesterol. The resulting HDL_3 isoform and, to a lesser extent HDL_2, are rich in anti-oxidative enzymes including paraoxonase 1 (PON 1). With progressive renal dysfunction, there is decreased LCAT activity and consequently less HDL. ApoA-I that normally comprises half of the proteins in HDL is replaced by serum amyloid A. This form of HDL cholesterol has a reduced ability to counteract the effects of oxidised LDL[75] and decreased

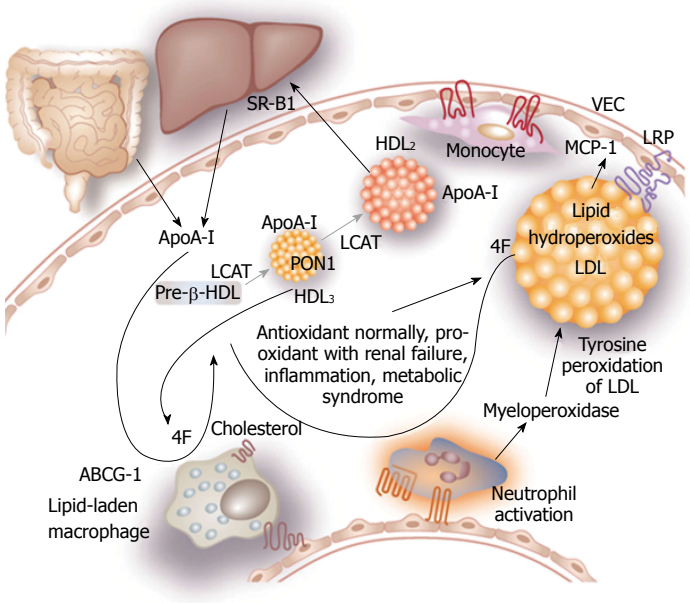

Figure 5 Maturation of high-density lipoprotein and the protective effect of apoA-I mimetic peptide 4F. (Apo)A-I: Apolipoprotein A-I; ABCG1: Adenosine triphosphate–binding cassette transporter G-1 protein; LCAT: Lecithin–cholesterol acyltransferase; SR-B1: Scavenger receptor B1; PON1: Paraoxonase-1; LRP: Lipoprotein-like receptor; VEC: Vascular endothelial cells; MCP-1: Monocyte chemoattractant protein-1; HDL: High-density lipoprotein. After Kaysen[74], 2009.

capacity to protect against cytokine action on vascular endothelium. Vaziri *et al*[76] showed that an apolipoprotein A-I mimetic peptide could reduce the effect of oxidised LDL on cultured aortic endothelial cells to produce the cytokine monocyte chemoattractant protein 1 (MCP-1), which may ultimately provide a therapeutic pathway to overcome dysfunctional HDL present in CKD (Figure 5).

Higher levels of LDL cholesterol and triglycerides are found with declining kidney function[8]. The impact on coronary artery disease is significantly greater than in the general population without renal impairment[8,74]. Accumulation of small dense atherogenic LDL cholesterol activates the renin-angiotensin-aldosterone system and also up-regulates the angiotensin type 1 receptor (AT_1). This increases the burden of oxidative stress and inflammation leading to endothelial dysfunction and atherosclerosis[32,33,75]. Not only does angiotensin Ⅱ cause hypertension (directly linked to atherosclerosis) but also activates vascular NADPH oxidase which induces superoxide anion generation (O_2^-). The superoxide anion inactivates nitric oxide which causes increased smooth muscle hypertrophy and proliferation, leading to hypertension and atherosclerosis[75].

Myeloperoxidase (MPO) is an enzyme present in leucocytes, particularly neutrophils, monocytes and tissue macrophages, which may play an important role in vascular injury and atherosclerosis in patients with advanced kidney disease[32]. Figure 5 shows how MPO promotes tyrosine peroxidation of LDL cholesterol. Leucocytes, which are activated in acute and chronic inflammation, secrete MPO into the blood which binds to vascular endothelium where it interferes with nitric oxide[74].

Lipoprotein a [Lp(a)] is a potent risk factor for CVD and serum levels increase progressively with declining renal function[8]. Lp(a) concentrations are highest in proteinuric states and fall after kidney transplantation.

Inflammation is a key component in the *malnutrition-inflammation-atherosclerosis* syndrome, observed across the spectrum of CKD, especially in young adults and is associated with substantial mortality[77]. Systemic inflammation, low serum HDL cholesterol and activation of angiotensin Ⅱ provide the rationale for use of anti-inflammatory agents such as aspirin, statins, angiotensin-converting enzyme inhibitors, angiotensin Ⅱ receptor blocking agents and antioxidants in combating endothelial dysfunction and atheroma[33,67,75].

SYMPATHETIC NERVOUS SYSTEM OVER-ACTIVITY, ANAEMIA AND LEFT VENTRICULAR HYPERTROPHY

Sympathetic nervous system over-activity in CKD is deleterious and results from renal ischaemia, raised angiotensin Ⅱ levels, and suppression of nitric oxide, causing hypertension, left ventricular hypertrophy and eventually left ventricular dilatation[24]. The prevalence of LVH was found to be 31% in those with GFR 25-49 mL/min and 45% in those with GFR < 25 mL/min[78]. There is evidence from epidemiological studies such as Framingham that LVH is independently associated with increased risk of fatal and non-fatal cardiovascular events[79]. ACE inhibitors and angiotensin Ⅱ receptor antagonists have been widely used to overcome sympathetic overdrive and to inhibit the renin angiotensin aldosterone system. However, a recent meta-analysis has demonstrated that although pharmacological intervention reduces LV mass it has no significant impact on reducing the risk of fatal and non-fatal cardiovascular events[80].

In the general population, LV dilatation and heart failure are generally the end result of end-organ damage sustained as a consequence of chronic hypertension and coronary atheroma. Although there is a higher prevalence of these conditions in young adult patients with CKD, cardiac myocyte death is accelerated by increased oxidative stress and anaemia[7,67,81]. Cardiac failure leads

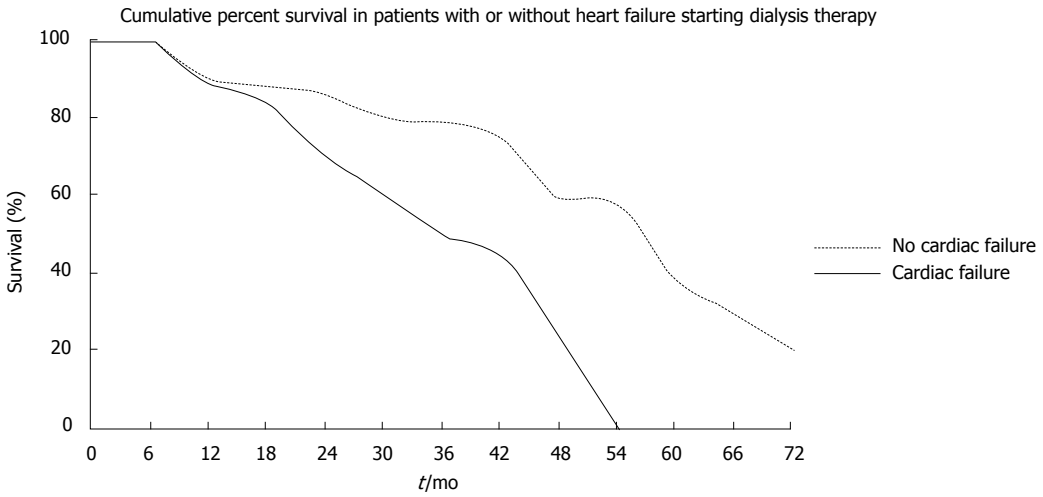

Figure 6 Premature death related to heart failure in haemodialysis. After Harnett *et al*[81], 1995.

to premature death (Figure 6)[81].

Anaemia appears in CKD stage 3 or 4 when erythropoietin production by the kidney diminishes[23]. If left untreated, the pathophysiological response is increased cardiac output, cardiomegaly, left ventricular structural abnormalities and, ultimately, congestive heart failure[24]. Correction of anaemia in CKD with erythropoietin results in regression of LVH and improved survival[23]. Timely intervention with iron and erythropoietin supplementation is important.

VASCULAR CALCIFICATION AND ARTERIAL STIFFNESS

Declining kidney function is associated with alterations in calcium and phosphorus metabolism that result in mineral bone disease (renal osteodystrophy), characterised by soft tissue and vascular calcification[82,83]. Secondary hyperparathyroidism, the physiological response aimed at correcting hyperphosphatemia by promoting phosphaturia, and vitamin D deficiency are both associated inflammation, vascular risk and cardiovascular mortality[83]. The situation is more complex with the discovery of fibroblast growth factor 23 (FGF-23) which is secreted by osteocytes. It acts as a phosphaturic hormone, inhibits production and secretion of parathyroid hormone, and reduces 1,25 vitamin D synthesis by interfering with vitamin D metabolism (Figure 7)[82]. α-Klotho is a hormone synthesised by the kidneys which seems to be essential for normal physiological functioning of FGF-23[84]. It is phosphaturic and may also have antioxidant and vasoprotective activity. As kidney function deteriorates, FGF-23 concentrations rise and early evidence indicates a strong association with left ventricular hypertrophy, independent of α-Klotho[85,86].

Coronary artery calcification is known to be important in the formation of atherosclerotic plaque[87]. Vascular calcification can take two forms, involving the tunica intima and media[82]. While it is not clear whether they follow a common pathogenesis, both are stimulated by CKD. Intimal calcifications develop in more than 80% of atherosclerotic plaques that occlude the vessel lumen causing ischaemia and myocardial necrosis[88]. Calcification of the tunica media involves smooth muscle cells and the elastic lamina[82,88,89], and is prevalent in more than 40% of patients with CKD stage 3B, who have accelerated coronary artery calcification[89]. Diabetic patients are particularly prone to calcific atheroma[32,67,89]. Calcification of the tunica media increases vascular rigidity and decreases compliance. Systolic hypertension occurs contributing to LVH. Increasing vascular calcification and stiffness, particularly of the aorta, measured by pulse-wave velocity has been shown to predict cardiovascular mortality in CKD patients[90,91].

Current theory suggests that tunica media calcification is an inflammatory process transforming vascular smooth muscle cells into osteoblast-like cells that express phosphorus transporter Pit-1 which concentrates calcium and phosphorus in an extracellular matrix that ultimately mineralises[87,92]. Vascular calcification is a complex process dependent upon the balance between promoters and inhibitors of calcification summarized in Table 2[87]. For example, a high calcium-phosphate product, raised parathyroid hormone levels and bone morphogenetic protein 2 (BMP-2) are pro calcific, whereas inhibitory factors include Fetuin-A, BMP-7, osteopontin, pyrophosphate and osteoprotegerin (OPG)[87,92].

Fetuin-A, produced by the liver, is a negative acute phase protein, its levels falling with rising CRP. Conversely, as CRP levels fall, fetuin-A levels may rise. This provides a link between inflammation and vascular calcification[93]. Matrix-Gla protein inhibits calcification of vascular smooth muscle and a negative correlation has been found with coronary artery calcification[32]. Osteoprotegerin regulates osteoclast activity and its deficiency has been associated with vascular calcification[82,87]. Osteoprotegerin deficiency is associated with increased mortality in dialysis patients[94]. Leptin is normally associated with nutritional state and satiety, but in the context of

Table 2 Promoters and inhibitors of vascular calcification

Promoters of vascular calcification	Inhibitors of vascular calcification
Traditional factors	Circulating inhibitors
Older age, male gender, hypertension, diabetes, smoking, high LDL cholesterol, low HDL cholesterol, genetic predisposition	Fetuin-A, bone morphogenetic protein-7, parathyroid hormone-related peptide, HDL cholesterol, magnesium,
Uraemia-related factors	
Uraemia, hyperphosphatemia, increased Ca x P product, exogenous vitamin D therapy, elevated parathyroid hormone level, duration of dialysis, calcium load and hypercalcaemia, chronic inflammation, warfarin, elevated leptin levels	Locally acting inhibitors Matrix Gla protein, α-klotho, osteopontin, pyrophosphate, osteoprotegerin, genetic predisposition

Adapted from Qunibi[87], 2005. HDL: High-density lipoprotein.

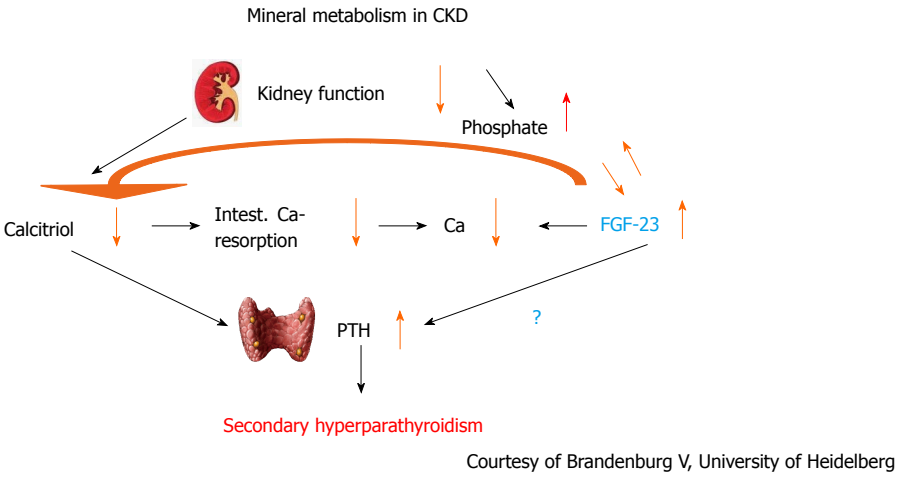

Figure 7 Interplay between calcium, phosphate, calcitriol and Fibroblast growth factor-23 in chronic kidney disease. FGF: Fibroblast growth factor; CKD: Chronic kidney disease.

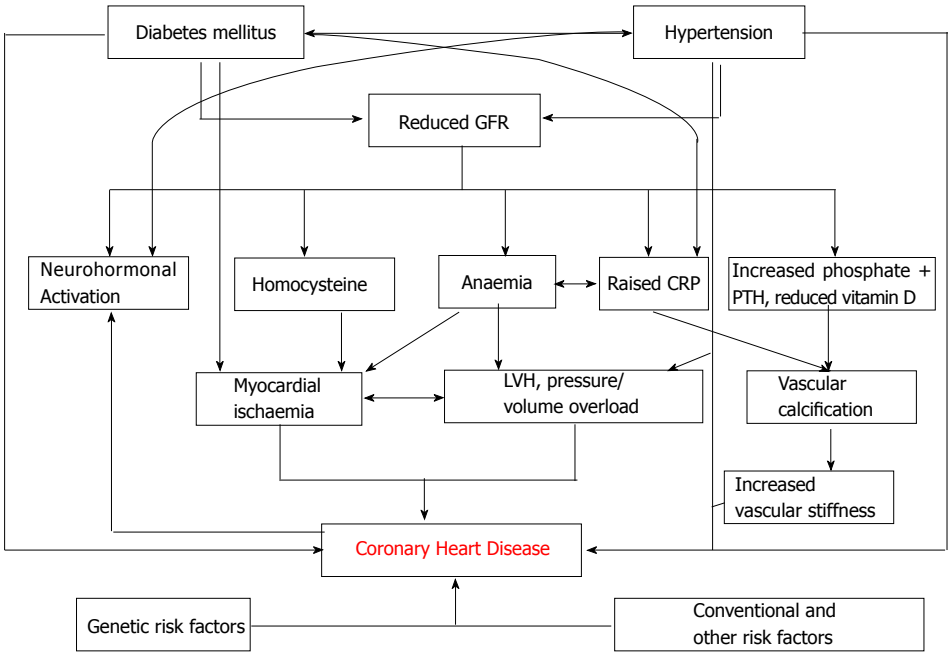

Figure 8 The association between chronic kidney disease and coronary heart disease. Adapted from Hage FG 2009[67].

renal failure, in which its levels are increased, it promotes calcification[87].

SUDDEN CARDIAC DEATH AND DIALYSIS

Dialysis patients have a 10-20 times increased risk of car-

diovascular death than do age and sex-matched controls in the general population[5,7-9], with the largest relative excess mortality seen in younger patients on dialysis. Sudden, unexpected death accounts for 25% of mortality on haemodialysis[95,96]. In most cases, acute coronary occlusion (the end-product of "accelerated atherosclerosis"), which was previously implicated[7], is not the underlying pathology. Instead, sudden cardiac death is explained by the composite effects of left ventricular hypertrophy caused by long-standing hypertension, left ventricular dilatation attributed to volume overload, chronic inflammation, over activation of the renin angiotensin aldosterone pathway, and increased propensity to ventricular dysrhythmias caused by electrolyte abnormalities[95-97].

The structural and functional abnormalities that occur through the interaction of numerous factors presented in this review, gives rise to stiff and non-compliant vasculature which has to negotiate myocardial ischaemia imposed by repeated haemodynamic stresses of haemodialysis therapy. Echocardiographic evaluation and positron emission tomography have shown that repeated haemodialysis adversely affects cardiac perfusion caused by transient myocardial stunning, but over time this leads to fixed regional myocardial wall abnormalities and fibrosis, culminating in heart failure and death[98,99]. In a recent pilot study, our group have demonstrated a possible relationship between endothelial dysfunction and the development of LVH in non-dialysis CKD patients[100]. The CRASH-ILR study is currently underway which is prospectively using implantable loop recorders in patients on haemodialysis to ascertain the frequency of cardiac arrhythmia. In an interim analysis of 18 patients monitored for 124 to 512 h there were 3 significant cardiac events including 1 bradyarrhythmia requiring pacing, 1 sudden cardiac death due to ventricular fibrillation and one onset of atrial tachycardia requiring anti-arrhythmic drug therapy. The final results of this study are awaited[101].

CONCLUSION

Cardiovascular disease is the most important cause for the high morbidity and mortality seen in patients with chronic kidney disease, especially younger people. Traditional risk factors play a major role, but coronary heart disease is somewhat different in CKD patients with increased contribution made by oxidative stress, low grade chronic inflammation and vascular calcification. The interaction of many of these pathophysiological processes is, if not unique to, most marked in CKD. Haemodialysis imparts the greatest mortality risk because of the challenges imposed on the heart by the repeated haemodynamic stresses that accelerate development of heart failure and dilated cardiomyopathy. Limited benefit of standard pharmacological interventions in the dialysis population emphasises the different pathophysiology which has evolved. The complexities of the association between chronic kidney disease and cardiovascular events are summarised in Figure 8. A better appreciation of the interplay and relative contribution of the various mechanisms discussed, along with new pathogenetic mechanisms yet to be discovered over the next few years, will enable new therapies to be developed. This will, hopefully, curb the excessive morbidity and mortality which seems to be particularly pronounced in young dialysis patients. Data from implantable loop recorders may give further insights to the precise events which result in sudden cardiac death and allow development of strategies to predict risk and reduce events.

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REVIEW

Cardiovascular co-morbidity in chronic kidney disease: Current knowledge and future research needs

Hudaifa Alani, Asad Tamimi, Nihad Tamimi

Hudaifa Alani, Broomfield Hospital, Mid Essex NHS Trust, CM1 7ET Chelmsford, United Kingdom
Asad Tamimi, University College London Hospital, NW1 2BU London, United Kingdom
Nihad Tamimi, Pfizer Worldwide Research and Development, Cambridge, MA 02139, United States
Author contributions: All authors contributed to this paper
Correspondence to: Dr. Nihad Tamimi, MBBS, MSc, FRCP, Pfizer Worldwide Research and Development, Pfizer Inc, 610 Main Street, Cambridge, MA 02139, United States. nihad.tamimi@pfizer.com
Telephone: +44-7811-368079
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Abstract

Chronic kidney disease (CKD) is recognised as a health concern globally and leads to high rates of morbidity, mortality and healthcare expenditure. CKD is itself an independent risk factor for unfavorable health outcomes that include cardiovascular disease (CVD). Coronary artery disease is the primary type of CVD in CKD patients and a significant cause of death among renal transplant patients. Traditional and non-traditional risk factors for CVD exist in patients with CKD. Traditional factors include smoking, hypertension, dyslipidemia and diabetes which are highly prevalent in CKD patients. Non-traditional risk factors of CKD are mainly uraemia-specific and increase in prevalence as kidney function declines. Some examples of uraemia-specific risk factors that have been well documented include low levels of haemoglobin, albuminuria, and abnormal bone and mineral metabolism. Therapeutic interventions targeted at more traditional risk factors which contribute to CVD, have not had the desired effect on lowering CVD events and mortality in those suffering with CKD. Future research is warranted to delineate clear evidence to the benefit of modifying non-traditional risk factors.

Key words: Cardiovascular disease; Chronic kidney disease; Risk factors; Inflammation

Core tip: Chronic kidney disease (CKD) has been recognised as a health concern globally and leads to high morbidity, mortality and healthcare expenditure. CKD is an independent risk factor for several different unfavourable outcomes including cardiovascular disease (CVD). Traditional and non-traditional risk factors for CVD exist in patients with CKD. Non-traditional risk factors of CKD are mainly uraemia-specific and include release of large levels of inflammatory and prothrombotic factors, low levels of haemoglobin, albuminuria, and abnormal bone and mineral metabolism. Future research is warranted to delineate clear evidence to the benefit of modifying non-traditional risk factors

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INTRODUCTION

CKD has become recognised as a key independent risk factor for several adverse health outcomes including cardiovascular disease (CVD). It is now increasingly apparent that individuals are more likely to die from cardiovascular disease than to develop end stage renal disease (ESRD)[1-3]. Initial evidence indicating a relationship between renal dysfunction and adverse cardiovascular events became apparent in those on dialysis, where the number of CVD deaths was found to be raised. Almost 50% of those suffering from established ESRD are un-

likely to survive a CVD event[2-5]. Compared to the age adjusted CVD mortality in the general populations this is approximately 15 to 30 times higher[4,6]. Although true across all ages it is particularly more profound in the 25-34 year age group, where a 500-fold increase in CVD mortality rate is found when comparing it to their counterparts in the general population[1].

Defining CKD

According to the Kidney Disease Improving Global Outcomes (KDIGO), CKD can be defined as either damage to kidneys or a glomerular filtration rate (GFR) of < 60 mL/min per 1.73 m^2 for a period of $\geqslant 3$ mo, with implications for health. Kidney damage can be defined by structural (detected by imaging) or functional abnormalities of the kidneys with or without a decrease in GFR. These may be apparent as either pathological irregularities or as indicators of kidney damage which include albuminuria > 30 mg/d, urine sediment abnormalities and electrolyte and other abnormalities secondary to tubular disorders.

Individuals with CKD are usually staged according to their GFR levels (Stage 1-5) and albuminuria category, with a higher stage representing lower GFR levels[7,8].

Traditional vs non-traditional risk factors

Traditional risk factors for atherosclerotic CVD are not enough to justify the significant upsurge in cardiovascular mortality seen amongst CKD patients and in particular ESRD. This has led to the suggestion that in patients with CKD two groups of CVD risk factors can be defined; traditional and non-traditional. Traditional factors are those described in the Framingham study[9] including hypertension, smoking, dyslipidemia and diabetes that are well known to contribute to the acceleration of the atherosclerotic process, and are highly prevalent in CKD patients[10]. Non-traditional risk factors of CKD increase in prevalence as kidney function declines. Some examples of such risk factors have been and includes, of large levels of inflammatory and prothrombotic factors, low levels of haemoglobin, albuminuria, and abnormal bone and mineral metabolism[4,11]. Some of these non-traditional risk factors will be discussed in more detail below (Figure 1).

CKD AND CARDIOVASCULAR OUTCOMES

Left ventricular hypertrophy and CKD

Echocardiographic studies report a high prevalence of left ventricular hypertrophy (LVH), systolic/diastolic dysfunction and ventricular dilatation (dilated cardiomyopathy) in patients with ESRD[12-15]. They are more strongly associated with an unfavourable prognosis than more established cardiovascular risk factors[14,16]. These structural and functional abnormalities can lead to sudden, presumed arrhythmic death and account for 50% of cardiovascular deaths in patients with ESRD[17-19].

LVH exists in 70% of patients starting dialysis and is an independent risk factor for cardiac death[12,13,20]. In a cross-sectional study by Stewart and colleagues, 296 non-diabetic renal disease patients underwent echocardiographic monitoring. The results showed that left ventricular mass was increased from even the earliest stages of renal disease (near-normal renal function). Eccentric LVH was found to be the prevalent pattern. The increase in LVH was progressive and 80% of those on renal replacement therapy were found to have LVH, with the concentric pattern being more dominant[19].

In an early study by Levin *et al*[21], 175 pre-dialysis patients underwent echocardiographic monitoring and had their left ventricular mass index (LVMI) assessed. The study demonstrated that the presence of LVH increases with progressive renal decline, reaching 45.2% in patients having severe renal impairment (CrCl < 25 mL/min)[21].

Paoletti *et al*[22] studied 244 non-diabetic pre-dialysis patients and found a greater prevalence, with LVH being associated with 51% in CKD stage 1 and 2 patients and 78% in CKD stages 3 to 5. In all studies - age, haemoglobin, systolic blood pressure and CrCl were found to be significantly different between those who either did or did not have LVH.

Coronary artery disease and CKD

Coronary artery disease (CAD) is one of the primary types of CVD in patients with CKD and is a major cause of death among renal transplant patients[23-27]. The prevalence varies from 24% in young patients without diabetes, to 85% in elderly haemodialysis patients with diabetes[28,29].

In earlier studies it was found that approximately 25%-40% of asymptomatic patients undergoing coronary angiography before their renal transplant exhibited evidence of significant stenosis (50%-70%) in one or more coronary arteries[30-32]. Furthermore, Liu and colleagues, showed that patients with CKD were found to have a 2.5 times higher chance of having 3-vessel disease compared with patients without CKD[33].

Kiyosue *et al*[27] studied the association found amongst renal dysfunction and the severity of CAD. It looked at 572 patients and graded severity according to how many stenotic coronary arteries were there and the estimated GFR (eGFR). More stenotic coronary arteries were present in the CKD group compared to other groups. Multivessel stenosis was also greater in the CKD group[27].

Whether or not CAD should be screened for and interventions offered for patients with advanced kidney disease remains a contentious issue. Coronary angiography remains the modality of choice for CAD investigation in CKD patients, however its invasiveness and associated risks in a group at risk of contrast-induced nephropathy, makes it unfavourable[34,35]. While other imaging modalities exist which are effective (CT coronary angiography, cardiovascular MRI), there are several factors including significant costs, adverse affects as well as technical difficulties that must be considered[36,37].

NON-TRADITIONAL RISK FACTORS

Anaemia

Anaemia is an anticipated consequence as renal function

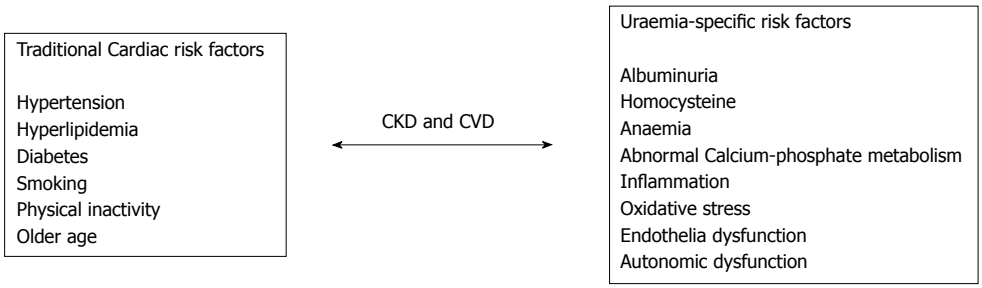

Figure 1 Traditional and non-traditional cardiovascular risk factors in chronic kidney disease[10,11]. CKD: Chronic kidney disease; CVD: Cardiovascular disease.

declines, and generally begins to develop before ESRD. The severity of anaemia however increases with declining kidney function[38,39]. There is a strong association between anaemia and cardiovascular complications. Specifically, anaemia is linked to LVH development, found in up to 74% of patients at the commencement of renal replacement therapy and is an independent predictor of consequent cardiac morbidity and mortality among patients with ESRD[12,13,21,40]. In an Observational study it was demonstrated that each 10 g/L drop in haemoglobin, leads to a 20%-40% increased risk of developing heart failure, LVH or mortality in those patients on long-term dialysis[41]. Interestingly sustained anaemia is often associated with eccentric hypertrophy, whereas hypertension is associated with concentric hypertrophy[21].

Physiologically, chronic anaemia leads to an increased cardiac output (CO) as a result of decreased afterload, an increase in preload and an increase in chronotropic/inotropic effects. This will eventually lead to ventricular dilation and LVH[42-44]. This chronic rise in CO eventually causes remodeling of the central elastic arteries of aorta or carotids. Subsequently it can result in enlargement of arteries and compensatory intima-media thickening, or arteriosclerosis. If either is present, they could be more directly correlated with future CVD risk (Figure 2)[44,45].

One of the first studies to demonstrate anaemia as an independent risk for CVD outcomes was carried out in the ARIC studies. It found anaemia to be associated with an adjusted hazard ratio of 1.41 for CVD in the entire cohort[46].

Jurkouitz *et al*[47] looked at 13329 patients and found a significant link between the haemoglobin (Hb) level and the serum creatinine (S-cr). In anaemic patients, a high S-cr level can result in the risk of coronary events rising by 2.7 fold when compared to a normal S-cr. This is independent of risk factors that include age, gender and race[47].

Levin *et al*[48] focused on the association between anaemia and LVH. 246 participants with a creatinine clearance of 25 to 75 mL/min (0.42 to 1.25 mL/s) underwent echocardiographic imaging done at baseline and 12 mo to specifically investigate LV growth. The results showed that each 0.5-g/dL (5-g/L) drop in Hb level led to a 32% increased odds of LV growth[48].

Further anaemia and echocardiographic studies carried out by Foley *et al*[41], demonstrated that each 1 g/dL drop in Hb was independently linked with the presence of left ventricular dilatation on repeat echocardiogram and the subsequent development of new/recurrent heart failure. Furthermore, every 1 g/dL drop in the haemoglobin level was independently linked with mortality when patients were on dialysis therapy[41].

Weiner *et al*[49] looked at the combination of both LVH and anaemia in patients at the earlier stages of renal dysfunction (eGFR 30-60), revealing that patients who had LVH as well as anaemia, had a risk of cardiac disease that increased by 4-fold compared with individuals who had neither anaemia nor LVH. However in those having LVH but no anaemia or anaemia but no LVH, the risk of CVD outcomes did not increase significantly[49].

The strong association between anaemia and cardiovascular complications has led to several studies investigating whether correction of haematocrit has any benefit on adverse cardiovascular outcomes. Besarab *et al*[50], looked at 1233 patients on haemodialysis with heart disease who were prescribed recombinant human erythropoietin (epoetin), looking at length of time till death or the first non-fatal myocardial infarction. Six hundred eighteen patients received sufficient doses to sustain a haematocrit of 42% and 615 to sustain a haematocrit of 30%. The study was halted due to the higher haematocrit target group having an almost significant mortality risk, and the fact that thrombotic vascular access events were also higher. No single unifying explanation was thought to be the cause[50].

The Cardiovascular Risk Reduction by Early Anaemia Treatment with Epoetin Beta (CREATE) trial looked at patients in the earlier stages of CKD (3 and 4) to try and achieve levels of normal; 130-150 g/L and low to normal; 105-115 g/L Hb. The normal Hb group was found to have an improved overall health and quality of life. LVMI was found in both groups to be stable, and thus treating the anaemia did not have an effect on the LVH progression[51]. This is supported by many other studies[52-54].

The Anaemia Working Group of European Renal Best Practice (ERBP) published a statement on its opinion of what Hb targets should be. Following results of the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) Study they maintained that Hb values of 11-12 g/dL should be targeted in CKD patients,

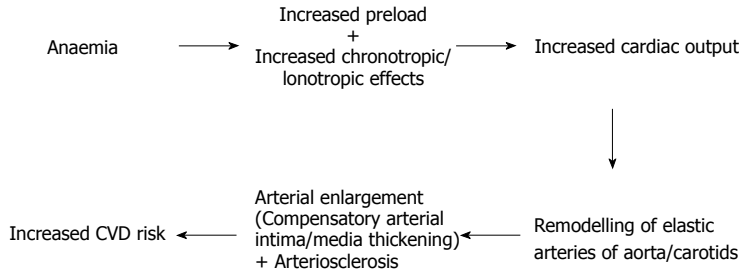

Figure 2 Physiological impact of chronic anaemia in chronic kidney disease. CVD: Cardiovascular disease.

and without deliberately aiming for targets above 13 g/dL[55,56].

Correcting the anaemia associated with ESRD with recombinant human erythropoietin (r-EPO)/ iron supplementation is essential, and results in significant improvements of Hb levels as well as a reduction in the need for blood transfusion requirements[57,58]. Recent literature however, suggests excess iron as well as contributing to arrhythmias and heart failure may also have a role to play in the development of vascular calcification[59,60].

A cross sectional study by Bagheri *et al*[61] looked at 337 patients to evaluate the importance of iron stores in the risk evaluation of atherosclerotic disease. All patients had an angiogram of the coronary artery, and the study revealed that the iron serum level was significantly more raised in the severe atherosclerosis group than in the normal group[61].

It is thought that one of the ways in which iron contributes to vascular calcification is by enhancing the oxidative stress process through the induction of reactive oxygen species. This subsequently activates molecular mechanisms that result in vascular calcification[60].

Drüeke *et al*[62] looked at the role of I.V. iron therapy in 79 dialysis patients. They concluded that iron therapy (at dose 1.5-2 g per year) can lead to arterial wall damage in the early stages of atherosclerosis[62]. This was later supported by Reis *et al*[63] who showed a significant relationship between ferritin, I.V. iron dosage and common carotid artery intima-media thickness in 60 dialysis patients[63].

Further research is required to assess the effect that iron has on arterial calcification, however the potential of iron to cause oxidant injury and CVD should not be disregarded.

Homocysteine

Homocysteine (HC) at high levels can be an independent risk factor for cardiovascular disease[64]. Levels of HC are elevated in renal failure and there is an inverse relationship between HC levels and GFR, such that more than 85% of patients on dialysis will experience a mild to moderate level of hyperhomocysteinemia[64,65].

The pathogenesis of hyperhomocysteinemia in renal dysfunction remains to be elucidated[64,66]. There is some evidence to suggest that high levels of homocysteine may be due to a reduced HC clearance and insufficient metabolism by less well functioning kidneys. However there is no direct evidence to support this[64].

Several epidemiological studies suggest that a high level of HC specifies a higher risk of CVD as well as stroke[67,68]. While the underlying mechanisms are yet to be defined, both *in vitro*/*vivo* studies suggest that production of potent reactive oxygen species (ROS) and decreased endothelial nitric oxide play a pivotal role. Thus high HC levels may facilitate oxidative damage at the vascular interface[69-71]. Other proposed mechanisms suggest that elevated HC causes proliferation of smooth muscle cells thus leading to increased oxidation of low-density lipoproteins[72]. Elevated HC is also associated with increased platelet aggregation and hence favouring a prothrombotic state[73]. This strongly links elevated levels of HC to the enhancement of atherosclerosis and other thrombotic events.

Several trials have looked at the efficacy of HC-lowering treatments on clinical outcomes. Two major studies, Homocysteine study (HOST)[74] and Heart Outcomes Prevention Evaluation-2 (HOPE-2)[75] looked for any benefits in certain vitamins including; folic acid, vitamin B6 and vitamin B12 supplements on overall CVD risk and mortality. Both studies found no significant benefit on CVD risk or all-cause mortality. Therefore based on these trials, there is not much to support using HC-lowering interventions for preventing cardiovascular outcomes.

Calcium and calcium-phosphorus product

Dysfunction in the metabolism of minerals occurs early in CKD. As GFR levels decline, there is a decrease in serum calcium (Ca) levels while parathyroid hormone (PTH) and phosphate levels become elevated[76]. An elevated level of serum phosphorus is highly prevalent in ESRD patients, and is a significant and independent risk factor of all cause and cardiovascular mortality[77]. A study by Block *et al*[77] found that phosphate levels greater than 6.5 mg/dL were associated with a far greater mortality risk (27%) when compared with levels of between 2.4-6.5 mg/dL[77].

Further studies by Kestenbaum *et al*[78] demonstrated that PO4 levels > 3.5 mg/dL are linked with an increased risk of death that is significant. Furthermore, for every 0.323 mmol/L serum phosphate increase, there

was an increased risk of death by 23%[78].

In a study by Dhingra *et al*[79] it was suggested that even phosphate levels within the normal range can contribute to CVD in patients who have kidney function within the normal, to near-normal range. Furthermore phosphate levels above 1.1 mmol/L can increase the risk of CVD events by 55%, following adjustment for any traditional cardiovascular risk factors. The cholesterol and recurrent events study (CARE) enlisted 4159 patients who had a background of previous myocardial infarction concluded that there was a graded, independent relationship between baseline fasting serum phosphate level and the subsequent risk for all-cause mortality, the development of new heart failure, and coronary events[80].

Calcium-phosphate products are also associated with increased risk of cardiovascular morbidity and mortality in CKD patients. Ganesh *et al*[81] demonstrated that for every rise in serum calcium-phosphate product by 0.8 mmol2/l2, there was an increased sudden death risk of approximately 7% in those on long-term haemodialysis[81].

The underlying mechanism through which hyperphosphatemia and an increase in calcium-phosphate product leads to cardiovascular disease is not well established. One theory is that high phosphate levels exacerbate the atherosclerosis process by increased calcification and proliferation of smooth muscle[82].

Raggi *et al*[83] carried out a cross-sectional study of 205 patients on hemodialysis who had baseline electron-beam tomography (EBT) testing to evaluate both vascular/valvular calcification. The incidence and degree of valvular calcification was found to be remarkable with 45% of subjects having calcification of the mitral valve, and 34% having calcification of the aortic valve, compared with 3%-5% prevalence in the general population. More than 70% of patients had coronary artery calcification significant enough to be linked with a high risk of future MI and coronary death in the general population[83].

Goodman *et al*[84] screened for calcification using EBT in 39 young patients (age range 7 to 30 years of age) with ESRD on dialysis. It found evidence of coronary calcification in 14 of the 16 patients aged 20-30 years[84].

Current KDOQI guidelines advise that serum phosphate levels should be maintained at 0.8 mmol/L in stage 3-4 CKD and between 1.1 and 1.8 mmol/L in stage 5 CKD[8]. Several phosphate binders exist in the treatment of hyperphosphataemia, however the choice of binders is controversial.

Calcium-based binders have been shown in observational studies to be associated with arterial calcification[84,85]. Sevelamer is a non-absorbable agent that does not contain calcium and has been shown in a significant number of trials to be effective in lowering serum phosphate levels. It has also been shown to have beneficial effects on vascular calcification progression and bone disease[86].

Two large studies have compared Sevelamer with calcium-based binders. In the Renagel in New Dialysis (RIND) trial it found that calcium-based phosphate binders resulted in higher cases of mortality than compared to Sevelamer[87]. The Dialysis Clinical Outcomes Revisited (DCOR) study however showed that the difference in mortality was not significant. Conflicting results can be possibly explained by difference in patient population[88].

Albuminuria

Not only is albuminuria a marker of renal damage, it is also an independent risk factor for CVD and leads to an increase in all cause mortality in diabetics, those with hypertension and in relatively unselected or general populations[89-93].

In the Heart Outcomes Evaluation (HOPE) trial results showed that in those with or without diabetes, albuminuria of any level can be a risk factor for CVD events. It also found microalbuminuria to result in an increased risk of future stroke, myocardial infarctions and death in both diabetic and non-diabetics without CKD.

Additionally, for every increase in the albumin:creatinine ratio (ACR) by 0.4 mg/mmol, there was a 5.9% increase in the HR hazard ratio (HR) of major CVD outcomes[91].

The Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial studied 8206 patients in order to establish if the relationship between albuminuria and cardiovascular risk can be useful in predicting cardiovascular morbidity and mortality in hypertensive patients. It discovered that for every increase of the ACR by 10-fold, cardiovascular deaths increased up to 98% in non-diabetics without CKD[92].

These trials demonstrate that the relationship between albuminuria and experiencing a CV event is not entirely restricted to the microalbuminuria cut off range. The relationship between the ACR and CV disease can extend to at least as low as 0.5 mg/mmol and thus an ACR of 2.0 mg/mmol, the threshold for the screening of microalbuminuria may not be appropriate when considering the risk for CV outcomes[91,92].

Microalbuminuria has also been associated with several lipid abnormalities. In a study by Kahri *et al*[94], the lipid profiles in both those having microalbuminuria and normoalbuminuria were compared. It found that the high-density lipoproteins (HDL) that are known to be cardioprotective were 11.6-fold lower in microalbuminuric patients compared with normoalbuminuric patients[94].

The pathophysiology behind how microalbuminuria contributes to CVD remains to be fully understood, however studies suggest that microalbuminuria might reflect endothelial dysfunction[95,96]. As well as causing impaired arterial dilatory capacity[97], microalbuminuria has been shown to increase levels of several adhesion molecules including Von willeband factor (vWF), Vascu-

lar adhesion molecule-1, thrombomodulin, PAI-1, serum IV collagen and t-PA[87]. These all favour the formation of atherosclerosis[98].

ROLE OF INFLAMMATION, OXIDATIVE STRESS, HYPERTENSION AND URIC ACID

Inflammation

It is now well established that the incidence of acute-phase inflammation and oxidative stress in patients with ESRD is high, which are both significant contributors to a high degree of CVD morbidity and mortality[99-101]. Oberg *et al*[102] confirmed presence of increased oxidative stress and acute-phase inflammation in early and advanced stages of CKD (3-5) compared to healthy subjects. Renal insufficiency is associated with increased levels of several different inflammatory and pro-coagulant biomarkers, the main two being CRP and IL-6, which are strong predictors of all-cause mortality and cardiovascular outcomes in ESRD[103-105]. Elevation of these markers as well as fibrinogen, PAP, factor Ⅶ-Ⅷ, and D-dimer was apparent even in those who had no evidence of clinical or subclinical cardiovascular disease[106-108].

The extent to which GFR is related to biomarkers of inflammation is controversial. While one cross sectional study found that increased CRP was associated with decreased GFR, other studies have found serum CRP levels do not correlate with either GFR or disease progression[109].

A study by Friedman *et al*[110], which looked at both CRP and albumin in dialysis patients, found CRP to be a significant predictor of death and suggested that these patients need to have careful evaluation as well as monitoring irrespective of whether albumin concentration is in the normal range[111]. Evidence seems to suggest that CRP may also be responsible for numerous processes involved in propagating atherosclerosis, which includes plaque initiation, formation, and rupture[111].

Inflammatory and prothrombotic markers have been heavily linked with CVD and mortality in CKD patients. Shlipak *et al*[112] however, demonstrated that although CRP and IL-6 are linked with CVD, their collective impact on cardiovascular mortality is actually far less significant compared to the collective impact of the more traditional risk factors[112].

Oxidative stress

Numerous experimental studies have revealed that endothelium derived vasoactive mediator nitric oxide (NO) has a vital part to play in progressive kidney damage. Low levels of NO leads to endothelial cell injury and dysfunction, and plays a major role in potentiating atherosclerosis[113-115]. Animal studies in which NO synthase (NOS) was inhibited resulted in enhanced progression of the atherosclerotic process as well as causing impairment in the angiogenic response and loss of the capillary endothelium[116]. Endogenous NOS inhibitor, asymmetric dimethylarginine (ADMA) is thought to be significantly associated with the oxidative stress process through its inhibition of NO, and thus leading to endothelial dysfunction and vascular damage[117]. ADMA correlates with traditional and non-traditional risk factors, it is recognised as a strong indicator in atherosclerosis, and is a strong independent predictor of death and incident cardiovascular complications in both CKD and non-CKD patients[117-119].

In a cohort study of 131 patients with CKD, the correlation between levels of ADMA and the probability of progressing to ESRD and death was investigated. ADMA was found to be reliable in predicting event occurrence independently of other confounders, such as GFR, proteinuria and several others. Furthermore, ADMA was found to be inversely related to GFR and signifies an independent marker of risk for ESRD progression and mortality[117].

Several studies have looked at interventions in order to reduce the plasma levels of ADMA or its binding capability to NOS in an attempt to decrease any risk of CVD events in those suffering from CKD. Lerman *et al*[120] studied the effects of supplementing 26 patients with L-arginine, a precursor to NO in order determine its future therapeutic use. It found that following 6 mo of supplementation, it improved endothelium function in coronary vessels while also providing symptomatic relief and lowering levels of endothelin[120]. Further support of these results come from studies by Clarkson *et al*[121] who explained that L-arginine orally enhanced the peripheral endothelium-dependent dilation of hypercholesterolaemic patients, as well as Rector *et al*[122] who showed that L-arginine was helpful in heart failure subjects.

Other studies have looked at the antioxidant effects of acetylcysteine and Vitamin E. Both supplements have demonstrated a reduction in composite cardiovascular end points in haemodialysis patients[123,124].

Hypertension

Hypertension itself can act as a dominant risk factor for CVD in patients with CKD, and it is almost inevitable that CKD patients will have hypertension. The underlying mechanism considered most important in the elevation of blood pressure, is related to retention of sodium as well as stimulation of the renin-angiotensin system[125]. Sympathetic activation and elevated catecholamine release in CKD has also been linked[126,127]. Cardiac damage caused by hypertension in CKD patients is thought to be via LVH induction[128].

Two major studies have evaluated the relationship between renal function and mortality in hypertensive patients. In the Hypertension Detection and Follow-up Program Cooperative Group, 10490 patients where analysed to assess all-cause mortality. It demonstrated that in those who had a baseline creatinine of $\geqslant$ 1.7 mg/dL the mortality rate (8-year) was $\geqslant$ 3 times greater than that of all other patients[129].

The Hypertension Optimal Treatment (HOT) study supports these outcomes. They evaluated 18790 patients over 3.8 years, only 10% of whom had evidence of atherosclerotic plaques. It found that the relative risk for both mortality and CVD events was 1.65 and 1.58 respectively, in those with a GFR < 60 mL/min compared with those who had a GFR > 60 mL/min[130].

Despite strong evidence linking CVD mortality in hypertensive CKD patients, the ideal blood pressure (BP) targets in these patients remains a challenging area. The National Institute for Health and Clinical excellence (NICE) suggests that antihypertensive treatment be commenced in those < 80 years with declining renal function and hypertension-stage 1, to aim for a blood pressure of < 140 / 90 mmHg. The BP during haemodialysis/peritoneal dialysis period should not exceed > 160 mmHg[8,131]. However excessive BP lowering in these patients may prove to be detrimental due to the risk of exacerbating myocardial stunning[132-134]. There remains an insufficient number of RCT trials on optimum blood pressure control in CKD patients and it is important to address this issue.

Uric acid

While hyperuricemia is a well-recognised consequence of impaired renal function it is also linked with increasing hypertension risk, ESRD and unfavorable cardiovascular outcomes[135].

UA has been demonstrated as an independent risk factor for the onset of CKD, in a healthy population. Obermayer *et al*[136] reported that even with a modest rise in UA levels there was a two-fold increased risk of renal disease, whilst at 535 μmol/L or more the risk was threefold.

Sedaghat *et al*[137] further supported this theory. They analysed 2601 subjects aged > 55 years who where followed up over a 6.5 year period. They exhibited that for each 60 μmol/L rise of uric acid, there was a decline in the eGFR by 0.19 mL/min. In hypertensive patients the decline in eGFR was more profound[137].

The detrimental effects of hyperuricemia are also well documented in CVD. In the health professionals follow-up study hyperuricemia was found to increase CVD mortality even more than compared with those who already had established heart disease[138]. This was further supported by long-term data from the NHANES I study that demonstrated that there was a proportionate rise in CVD mortality with UA levels[139].

Studies have looked at the use of xanthine oxidase (XO) inhibitors (Allopurinol, Febuxostat), as potential treatment to prevent further renal deterioration and to provide a cardioprotective effect. In one meta-analyses, allopurinol was found to produce a small but yet significant reduction of both systolic/diastolic blood pressure. This is further supported by randomised controlled trials, where again a significant blood pressure drop is achieved with UA-lowering agents[140].

Rekhraj *et al*[141] demonstrated that treating patients with diagnosed LVH and ischaemic heart disease with high dose allopurinol (600 mg/d) for 9 mo, resulted in a reduction of the LVM and end systolic volume as well as improving endothelial function[141]. This modest reduction in LVM was shown in the LIFE study to reduce mortality and cardiovascular outcomes by 13%[142,143].

In the context of CKD, a study by Goicoechea *et al*[144] demonstrated that in those patients receiving allopurinol for 12 mo there was a diminution in the deterioration of kidney function or the need for dialysis compared to placebo. (143) In another study allopurinol reduced eGFR in patients with, established CKD (stage 3) independent of age, sex or diabetes. Adverse cardiovascular events were also found to be reduced[144].

FUTURE RESEARCH NEEDS

CKD is a major health concern globally and leads to high rates of morbidity, mortality and healthcare expenditure. Much of the morbidity and mortality associated with CKD is significantly attributable to cardiovascular outcomes. While we have tried to briefly analyse some of the current knowledge underlying the strong association between CKD and CV outcomes there still remains several non-traditional risk factors and pathophysiological mechanisms to be described.

Several markers have a clear association with current and subsequent CV outcomes including; reduced GFR, albuminuria, troponins, phosphate, vitamin D, FGF-23 and NT-proB-NP[145-152]. While these markers are present, there remains no routine screening for CVD in CKD patients, despite strong evidence supporting this. The screening and treatment of patients with abnormal markers cannot only reduce overall cardiovascular events and kidney failure, but could also prove to be cost effective.

Perhaps one reason for lack of implementation is due to the fact that these diagnostic screening tools are lacking in sensitivity and specificity to make them reliable, and are in need of more RCT-quality evidence in order to guide intervention.

Therapeutic interventions that aim at reducing traditional risk factors for CVD have not been shown to be effective at lowering the incidence of CVD events or mortality in those with CKD. More importantly, strategies in risk reduction have inadequately tackled non-traditional risk factors that have been exhibited as being essential in the progression of CVD. Furthermore there remains to be clear evidence with regards to the benefit of modifying these non-traditional risk factors.

In view of current knowledge it is perhaps favourable to investigate preventive strategies in early-stage chronic kidney disease and multifactorial interventions in late-stage chronic kidney disease.

Some of the excess CVD risk associated with CKD has been explained by a multifactorial range of myocardial and vascular insult including; uraemic cardiomyopathy, inflammation, oxidative stress, autonomic

dysfunction and endothelial dysfunction. However, it is very likely that there are as yet undiscovered factors, and inter-relationships, which are possibly of great significance.

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REVIEW

Preeclampsia from a renal point of view: Insides into disease models, biomarkers and therapy

Janina Müller-Deile, Mario Schiffer

Janina Müller-Deile, Mario Schiffer, Division of Nephrology and Hypertension, Department of Medicine, Hannover Medical School, 30625 Hannover, Germany
Author contributions: Müller-Deile J and Schiffer M solely contributed to this paper.
Correspondence to: Janina Müller-Deile, MD, Division of Nephrology and Hypertension, Department of Medicine, Hannover Medical School, Carl-Neuberg-Str. 1, 30625 Hannover, Germany. schiffer.mario@mh-hannover.de
Telephone: +49-51-15324708 Fax: +49-51-1552366
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Abstract

Proteinuria is a frequently detected symptom, found in 20% of pregnancies. A common reason for proteinuria in pregnancy is preeclampsia. To diagnose preeclampsia clinically and to get new insights into the pathophysiology of the disease it is at first essential to be familiar with conditions in normal pregnancy. Animal models and biomarkers can help to learn more about disease conditions and to find new treatment strategies. In this article we review the changes in kidney function during normal pregnancy and the differential diagnosis of proteinuria in pregnancy. We summarize different pathophysiological theories of preeclampsia with a special focus on the renal facets of the disease. We describe the current animal models and give a broad overview of different biomarkers that were reported to predict preeclampsia or have a prognostic value in preeclampsia cases. We end with a summary of treatment options for preeclampsia related symptoms including the use of plasmapheresis as a rescue therapy for so far refractory preeclampsia. Most of these novel biomarkers for preeclampsia are not yet implemented in clinical use. Therefore, we recommend using proteinuria (measured by UPC ratio) as a screening parameter for preeclampsia. Delivery is the only curative treatment for preeclampsia. In early preeclampsia the primary therapy goal is to prolong pregnancy until a state were the child has an acceptable chance of survival after delivery.

Key words: Preeclampsia; Pregnancy; Proteinuria; Biomarkers; Treatment

Core tip: This review summarises different pathophysiological theories of preeclampsia with a special focus on the renal facets of the disease. In this context current animal models are presented. The reader gets a broad overview about different biomarkers for preeclampsia. Furthermore, the article discusses treatment options for preeclampsia related symptoms including the use of plasmapheresis as a rescue therapy for so far refractory preeclampsia.

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INTRODUCTION

There are many physiological changes in the function of different organs during normal pregnancy. Changes in kidney function and low grade proteinuria are common findings in pregnancy. However, new onset of proteinuria is also one of the primary symptoms for the clinical diagnosis of preeclampsia[1]. To understand pathological conditions in pregnancy it is important to know the normal changes and also typical complications that may occur during pregnancy. In pregnancy the physician always treats two patients. What is required for treatment of the mother is not always beneficial for the child. Many drugs

are contraindicated in pregnancy or there is no data on their safety. We review the development of kidney function and proteinuria in pregnancy in general and then discuss preeclampsia in particular. This is likely the first review where all prevailing animal models for preeclampsia and all currently suggested markers for early detection of the disease are presented with special focus on the kidney. Further more, we give treatment strategies for preeclampsia and discuss controversial new methods for therapy refractory preeclampsia.

KIDNEY FUNCTION IN PREGNANCY

During a normal pregnancy kidneys increase in size and the kidney volume can enlarge up to 30%[2]. In pregnant women the ureter and the renal pelvis are frequently dilated which can lead to an increased risk for urinary tract infections and pyelonephritis. There are no renal histological changes due to pregnancy but higher urinary frequency, nocturia, dysuria, urgency and stress incontinence are common[3]. The glomerular filtration rate (GFR) rises by approximately 40% to 50% above baseline levels in pregnancy. Thus, a normal serum creatinine can actually reflect significant renal insufficiency in a pregnant woman. Equations like Modification of Diet in Renal Disease (MDRD) formula, Cockcroft-Gault formula and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula are usually used to estimate GFR but are not accurate during pregnancy. Smith *et al*[4] compared eGFR calculated using the MDRD formula with inulin clearance in 24 healthy women during and after pregnancy. They found that MDRD formula underestimated GFR by more than 40 mL/min during pregnancy. The Cockcroft-Gault formula, the MDRD formula and the CKD-EPI formulas were evaluated for their accuracy in preeclampsia by Alper *et al*[5] All of these equations were inaccurate in predicting GFR in preeclamptic women compared with creatinine clearance obtained from 24-h urine collections.

Cystatin-C does not seem to be a useful marker in pregnancy because it increases in the third trimester. This is thought to be due to changes in size and charge selectivity of the glomerular filtration barrier leading to decreased filtration of cystatin-C [6]. Increased placental production of cystatin-C may also play a role in the increased levels observed in late pregnancy[7]. In line with this Saxena *et al*[8] found that serum cystatin-C did not correlate with inulin clearance during pregnancy or postpartum. Therefore, the best method to determine the GFR in pregnancy is the mean of urea and creatinine clearance obtained from collected urine.

PROTEINURIA IN PREGNANCY

There are several methods used clinically to measure proteinuria. A dipstick test is the easiest method to quantify proteinuria, however, in a recent study the dipstick test in spot-urine over and underestimated proteinuria[9]. Another alternative to estimate proteinuria is the urine protein creatinine (UPC) ratio. A UPC-ratio above 700 mg/g creatinine predicts significant proteinuria while a UPC ratio of less than 150 mg/g creatinine is normal. Nevertheless, the UPC ratio has several disadvantages. It cannot detect changes in proteinuria over the course of the day or take into account orthostatic changes that can potentially cause relevant changes in proteinuria. Moreover, likely day-to-day biological variation of the UPC-ratio has to be considered and only relatively large changes indicate a reliable change in disease status[10]. Proteinuria is known to have a circadian rhythm so when samples for the calculation of UPC ratio are collected at a fixed time of the day UPC ratio can be an acceptable alternative for 24-h urine collections, especially in an outpatient setting[11]. UPC ratio was a reasonable "rule-out" test for detecting proteinuria of 0.3 g/d or more in hypertensive pregnancy[12], but normal UPC ratio cannot rule out mild preeclampsia[13].

Different cut-off values for UPC ratio have been suggested with different results. In one study a cut-off value of 220 mg/g creatinine predicted significant proteinuria with 87% sensitivity and 92.6% specificity[14]. According to another study random UPC ratio is helpful primarily when it is below 150 mg/g creatinine, in that proteinuria of more than 300 mg is unlikely below this threshold. The accuracy of this UPC ratio in predicting 300 mg of protein in 24-h urine collection in pregnant patients with suspected preeclampsia had a sensitivity ranged from 90%-99% and specificity ranged from 33%-65%[15]. In contrast to that UPC ratio and 24-h urine total protein level showed a poor correlation with negative predictive value of 47.5% and specificity of 55.8% in a study of 220 women by Durnwald *et al*[16] Nevertheless he same authors admit that UPD ratio can predict severe preeclampsia and thus can be used for rapid diagnosis of severe preeclampsia as the correlation of UPD ratio and 24-h proteinuria increases with the amount of proteinuria.

Therefore the gold standard for proteinuria is the 24-h urine collection. However, the 24-h urine collection is inconvenient for pregnant women, expensive and may be inaccurate due to insufficient collection. To address this problem and for validation of the results quantification of the urine creatinine excretion should be done. Urinary creatinine excretion should be between 15 and 20 mg/kg body weight if the collection was adequate.

Urinary protein excretion increases due to both increased glomerular filtration and increased permeability of the glomerular filtration barrier during normal pregnancy. Urinary protein excretion rises to about 180 to 200 mg/d in the third trimester of the pregnancy. In women with pre-existing proteinuria the rise in proteinuria is often higher and cannot be explained by increased GFR alone.

The majority of women with pre-existing glomerular disease have increased proteinuria during the course of their pregnancy and can develop nephrotic range

proteinuria in the third trimester. Nevertheless, the presence of nephrotic syndrome due to renal disease, in the absence of significant renal insufficiency or significant hypertension, does not seem to affect the natural course of renal disease or foetal survival[17]. *De novo* renal disease like lupus nephritis or renal diseases secondary to diabetes or hypertension are other possible causes of increased proteinuria in pregnant women. In addition a symptomatic urinary tract dilatation may also be associated with proteinuria in pregnancy[18]. Thus, the underlying reason for proteinuria in pregnancy is often clinically uncertain. Sometimes a definitive cause of renal disease can only be found histologically. The published evidence for the benefit of a kidney biopsy during pregnancy is heterogeneous and there are only a few reports of renal biopsies during pregnancy which were performed to determine the definite diagnosis of renal disease.

Packham *et al*[19] reported 111 renal biopsies performed before the 29th week of gestation where complications of the procedure were similar to those in the non-pregnant population. Day *et al*[20] showed that pregnancy itself does not increase the risk associated with a renal biopsy. In contrast to that, other investigators reported a significantly higher risk of complications for kidney biopsies in pregnancy, with a peak at around the 25th gestational week[21]. Some clinicians prescribe empirical therapy with steroids in nephrotic syndrome in pregnancy. However, diabetic nephropathy or amyloidosis may be exacerbated by steroid therapy. Lupus nephritis during pregnancy follows a variable course and the type and extent of renal lesions can only be assessed histologically. Patients with a biopsy-proven diagnosis of mesangial-proliferative lupus nephritis usually have a favourable prognosis. Diffuse proliferative lupus nephritis typically results in a decreased glomerular filtration rate, a poor prognosis and requires aggressive therapy. Renal biopsy for the diagnosis of glomerulonephritis or preeclampsia led to therapeutic changes in 66% of cases[21]. In general we would recommend waiting until postpartum before performing a renal biopsy unless an unexplained rapidly progressive loss of renal function or unexplained nephrotic range proteinuria occurs. Therapeutic options in pregnancy are given below.

PREECLAMPSIA

A common reason for increased proteinuria in pregnancy is preeclampsia. Preeclampsia affects 2%-8% of pregnancies and is defined as the combination of pregnancy induced hypertension and proteinuria[22]. Recently the American College of Obstetricians and Gynecologists removed proteinuria as an essential criterion for diagnosis of preeclampsia in 2013[23]. Therefore, it is possible that in recent studies 10% of women with clinical and/or histological manifestations of preeclampsia had no proteinuria[24].

It has been hypothesized that preeclampsia results from a reduction in uteroplacental perfusion which leads to uteroplacental ischemia. In the preeclamptic placenta trophoblasts do not develop normally and are unable to invade the myometrium effectively[25]. Specifically the placental tissue but not the foetus is involved in the development of preeclampsia, since preeclampsia also occurs in women with a hyaditiform mole[26-29]. Risk factors for preeclampsia include family history of preeclampsia, multiple gestation, nulliparity, obesity, older maternal age, molar pregnancies, diabetes mellitus, pre-existing hypertension, chronic renal disease and thrombotic vascular disease[30-33]. Paradoxically, smoking during pregnancy is associated with a reduced risk of preeclampsia[34,35]. Nicotine inhibition of thromboxane A2 production might explain this. However, it must be stated that smoking in general and especially during pregnancy has an increased health risk and is absolutely contraindicated.

Preeclampsia can cause small-for-gestational-age infancy, preterm delivery, hypoxic neurologic injury and foetal death. Perinatal mortality is approximately 10% and maternal mortality even occurs in 10% to 15%[36]. Maternal complications of preeclampsia include renal failure, eclampsia, HELLP syndrome (haemolysis, elevated liver enzymes, and thrombocytopenia), seizures, liver failure and stroke. In contrast to normal pregnancy where blood urea nitrogen (BUN) and creatinine decrease, preeclamptic women have BUN and creatinine levels similar to non-pregnant women due to reduced GFR and RPF.

Clinical signs of preeclampsia generally resolve spontaneously within 12 wk after delivery whereas proteinuria due to other renal disease does not. New-onset proteinuria after 20 wk of gestation together with new-onset hypertension is a strong indicator of preeclampsia. The severity of proteinuria does not correlate with the severity of preeclampsia and can even be absent in 10% of the cases[1,37,38]. However, a high UPC ratio in preeclamptic women is associated with a highly increased likelihood of adverse maternal outcomes[39].

In cases where information on the presence or absence of proteinuria in early pregnancy is lacking, the distinction between an underlying primary renal disease and preeclampsia can be very difficult. If *thrombotic thrombocytopenic purpura* occurs for the first time during pregnancy, it may mimic severe preeclampsia.

The timing of preeclampsia can also be atypical with onset before the 20th week of gestation or up to 4 wk postpartum. Thus, in some cases, the distinction between preeclampsia and other renal diseases in pregnancy can only be made in retrospect.

Postpartum preeclampsia is the occurrence of hypertension and proteinuria after delivery. Late postpartum eclampsia is an atypical form of eclampsia beginning between 48 h to 4 wk after delivery[40]. The incidence of postpartum preeclampsia is dependent on the population included in the study. In one 10-year retrospective case series it was 5.7%[41]. In the same analysis 15.9% of hypertensive or preeclamptic women in the postpartum period develop eclampsia.

Most patients with postpartum preeclampsia have no evidence of preeclampsia during pregnancy[42]. Hypertension is a common but not universal finding in postpartum preeclampsia. In postpartum preeclampsia proteinuria may occur less often than in preeclampsia during pregnancy[43]. Seizures are often more severe and refractory to treatment.

Persistence of trophoblasts is associated with the development of preeclampsia in gestational trophoblastic disease[28,29]. Even though found only on the microscopic level, trophoblastic, tissue was found in patients with postpartum preeclampsia and suggests that it causes the disease. Epstein *et al*[44] demonstrated that women with preeclampsia develop hypertension more often than their non-preeclamptic siblings.

ANIMAL MODELS FOR PREECLAMPSIA

A number of animal models have been proposed for preeclampsia but have some limitations. Mice have shallow trophoblast invasion and three trophoblast layers verses a single layer of trophoblasts of the human placenta in pregnancy. Therefore mice models are less useful for studying trophoblast invasion processes. In order to model reduced uterine perfusion pregnant rats undergo clipping of the aorta above the iliac bifurcation at day 14 of gestation[45]. There are also some mouse models of preeclampsia that employ manipulation of sFlt-1, VEGF 121[46], endothelin, endothelial nitric oxide synthase[47] or the renin-angiotensin system[48].

From a renal point of view the sFLT model is one of the most promising because it is the only one that shows glomerular endotheliosis as well as hypertension and proteinuria[49]. Karumanchi *et al*[50] created a rat model of preeclampsia by administration of a sFLT1-expressing adeno-virus. The administration of the sFLT1 by this vector resulted in a dose-dependent hypertension, proteinuria, and glomerular endotheliosis in pregnant rats[50]. As preeclampsia only occurs spontaneously in pregnant women, no animal model can completely mimic the entire pathogenesis of human preeclampsia and all animal models only reflect some limited aspects of the underlying disease. Thus, the definitive studies on preeclampsia must be clinical.

In the last few years many potentially useful biochemical markers have been proposed for the prediction and outcome of preeclampsia. The timeframe of diagnostic usefulness of these biomarkers to distinguish women at risk for preeclampsia from healthy pregnant women will be reviewed below.

BIOMARKERS IN PREECLAMPSIA

Autoantibodies

Gant *et al*[51] identified hypersensitivity to infused Angiotensin Ⅱ in preeclamptic patients. However, circulating levels of Angiotensin Ⅱ are not increased in preeclampsia[52]. Instead, immunoglobulins from preeclamptic women increased the beating rate of neonatal rat cardiomyocytes. These immunoglobulins contained Angiotensin Ⅱ type 1 (AT1) autoantibodies that stimulate the Angiotensin-receptor. The increased heartbeat rate could be blocked by treatment with losartan and it could be demonstrated that the autoantibodies bind to the second extracellular loop of the AT1 receptor[53]. AT1 agonistic autoantibodies are not only found in preeclampsia but also in antibody mediated kidney transplant rejection[54]. In kidney-transplant recipients who had severe allograft dysfunction without anti-HLA antibodies but detection of AT1 agonistic autoantibodies rejection was accompanied by accelerated hypertension and convulsions[55]. It is proposed that similar mechanisms might be involved in preeclampsia and refractory allograft rejection and it was found that one rejecting kidney-transplant recipient had had preeclampsia 16 years earlier[55].

Adrenomedullin

Pregnancy is associated with high concentrations of adrenomedullin in maternal and foetal blood and in the amniotic fluid[56]. Adrenomedullin has a potent and long-lasting hypotensive effect when injected intravenously in anaesthetised rats. Hata *et al*[57] measured circulating adrenomedullin concentrations in preeclampsia and normotensive pregnant women and showed that adrenomedullin concentrations are significantly lower in preeclamptic women.

Podocyturia

Renal involvement in preeclampsia can be at least partly explained by impaired podocyte function. Podocytes are the major source of VEGF in the glomerulus[58]. Podocyte-derived VEGF has paracrine functions on endothelial cells as well as autocrine functions on the podocytes themselves[58-60]. New data suggest that detection of podocyturia might serve as an early diagnostic marker for preeclampsia prior to the development of proteinuria and hypertension. Garovic *et al*[61] showed that podocyturia is present at delivery in women with preeclampsia. Podocyturia also had a significantly greater sensitivity and specificity for the subsequent diagnosis of preeclampsia than any single angiogenic marker or a combination thereof in the second trimester[62]. A strong correlation was found by Aita *et al*[63] between the number of podocytes lost in urine and blood pressure, but no correlation with proteinuria. Several markers have been used in different studies to detect podocyturia. Nevertheless, it is important to keep in mind that the expression of marker proteins does not allow a definite allocation of the involved glomerular cell types. De- or transdifferentiation and detachment of cells as well as changes in the urine milieu have a direct effect on marker protein expression. According to Skoberne *et al*[64], the urine markers most reliable for assessing disease activity of certain glomerular diseases are PDX- or CD68-positive cells.

mRNA

Recently, quantitative polymerase chain reaction for podocyte-specific markers was found to be a rapid meth-

od to detect preeclampsia. Significantly elevated mRNA levels of nephrin, podocin, and VEGF were detected in preeclamptic women compared with healthy controls[65].

Placental protein 13

Placental protein 13 (PP13) is a member of the galectin super family and is important for differentiation and proliferation. Than *et al*[66] found reduced PP13 mRNA levels in placentas obtained from patients with preeclampsia and HELLP syndrome in the first trimester compared to controls. Blood levels of PP13 mRNA were also significantly lower in preeclampsia compared to controls[67].

Pregnancy associated plasma protein-A

Pregnancy associated plasma protein-A (PAPP-A) is mainly produced by the placental trophoblasts. PAPP-A and PP13 serum levels were significantly lower in the first and second trimesters in women who developed preeclampsia[68]. First-trimester PAPP-A provided a prediction for preeclamspia when combined with uterine artery pulsatility measured by Doppler velocimetry[69].

Activin A and inhibin A

During the first trimester of pregnancy, the foeto-placental unit is the main source of circulating activin A and inhibin A. Activin A enhances *Follicle-stimulating hormone* (FSH) biosynthesis and secretion and is involved in the control of trophoblast cell differentiation in the first trimester. Inhibin A down regulates FSH synthesis and inhibits FSH secretion. Activin A seems to be a sensitive marker for the risk of later development of preeclampsia at 21-25 wk of gestation[70]. Inhibin A is thought to be more sensitive than activin A in predicting cases of early-onset preeclampsia at 15-19 wk of gestation[70].

P-selectin

P-selectin belongs to the group of cell adhesion molecules. It is expressed in granules of platelets and the Weibel-Palade bodies of endothelial cells and is involved in leukocyte-endothelial interactions. The P-selectin concentration was found to have a negative predictive value of almost 99% for preeclampsia. Mean plasma P-selectin concentrations were significantly elevated at 10-14 wk of gestation in women who later developed preeclampsia[71]. Wang *et al*[72] suggested that the increase in neutrophil-endothelial adhesion and activation seen in preeclampsia is at least in part due to up-regulation of P-selectin. This would be in line with the theory that preeclampsia reflects an excessive maternal inflammatory response to pregnancy[73].

Pentraxin 3

Another inflammatory molecule involved in preeclampsia is Pentraxin 3. It is expressed in response to inflammatory stimuli by endothelial cells, monocytes, macrophages and fibroblasts. Elevated maternal plasma levels of pentraxin 3 in preeclamptic in comparison to normal pregnancies could represent altered endothelial function[74,75]. The increase in maternal plasma develops from 11th to 13th week of gestation in women with subsequent preeclampsia[76].

Fibronectin

Maternal plasma fibronectin levels of patients with preeclampsia were significantly higher than those of healthy pregnant women[77]. Significant elevations in fibronectin levels with an extra type Ⅲ domain occurred in the first trimester before clinical evidence of preeclampsia. Fibronectin plays a major role in embryonic development, cell adhesion, growth, migration and differentiation.

Heat-shock proteins

Heat-shock proteins (Hsps) are highly conserved molecules that have chaperone functions. Circulating Hsps may also be cytoprotective, as exogenous Hsp70 increases the survival and protects from apoptosis in stressed arterial smooth muscle cells[78]. Fukushima *et al*[79] reported significantly higher Hsp70 serum levels in preeclampsia. Higher serum levels of Hsp70 were also found in patients with early onset of severe preeclampsia[80,81]. The difference in serum Hsp70 concentration between preeclamptic patients and the control group was statistically significant in each gestational age. Thus, Hsp70 might not only be a marker but also play a role in the pathogenesis of preeclampsia.

Fms-like tyrosine kinase 1/ placental growth factor

Gene expression profile studies identified the regulation of soluble fms-like tyrosine kinase 1 (sFlt-1) in preeclampsia. SFlt-1 binds and antagonises vascular endothelial growth factor (VEGF) and placental growth factor (PlGF).

The described functions of VEGF include induction of matrix metalloproteinases, regulation of angiogenesis, lymphangiogenesis and hematopoiesis and cell signalling. Serum concentration of sFlt-1 decreases from 8-12 wk to 16-20 wk of gestation, gradually increases at 26-30 wk of gestation and rapidly elevates at 35-39 wk of gestation in normal pregnancy[82].

SFlt1 concentrations increased gradually throughout pregnancy in women with preeclampsia and was significantly higher between 25 and 28 wk of gestation in women with preeclampsia than in women with normal pregnancies or isolated hypertension[83]. Of note, sFlt1 are high 5-6 wk prior to the onset of preeclampsia and correlate with the severity of disease[83-85]. In rats sFlt-1 infusion increased vascular and placental oxidative stress, decreased maternal circulating VEGF and NO and reduced foetal weight[85].

Serum concentration of PlGF increases gradually from 8 wk until 29-32 wk of gestation and then decreases at 33-40 wk of gestation in normal pregnancy[79]. PlGF levels in women who later developed preeclampsia were significant lower than those of controls from 13-16 wk of gestation until delivery[85]. As the change of PlGF occurs earlier than that of sFlt-1, it might be the better

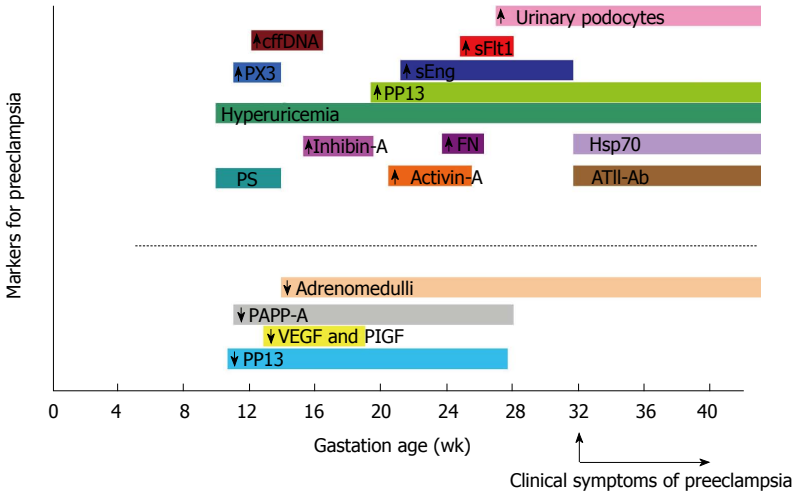

Figure 1 Treatment of preeclampsia. ATII-Ab: Angiotensin II type 1 autoantibodies; cffDNA: Cellfree fetal DNA; FN: Fibronectin; Hsp70: Heat-shock protein 70; PlGF: Placental growth factor; PAPP-A: Pregnancy associated plasma protein-A; PP13: Placental protein 13; sFlt-1: Fms-like tyrosine kinase 1; PS: Pselectin; PX3: Pentraxin-3; sEng: Soluble endoglin; VEGF: Vascular endothelial growth factor.

angiogenic factor for predicting preeclampsia. Serum sFlt-1 to PlGF ratio (sFLT-1/PIGF) was also suggested as screening parameter. An adenovirus-expressing sFlt-1 in rodents caused a clinical syndrome with glomerular endotheliosis, proteinuria, and hypertension[86]. Glomerular capillary endotheliosis is another typical lesion in preeclampsia.

Soluble endoglin

Serum levels of sEng in normal pregnancy are quite stable and slightly increase by 33-42 wk of gestation[87]. Placental endoglin is up-regulated in preeclampsia and released in the circulation. Rising levels of circulating soluble endoglin (sEng) herald the onset of preeclampsia. Women with higher sEng levels at 21 through 32 wk of gestation had an increased risk of preterm preeclampsia and an increased risk for a small-for-gestational-age infant[87].

Cellfree fetal DNA

Cellfree fetal DNA (cffDNA) is increased at 11-13 wk of gestation in pregnancies that experience preeclampsia[88]. Hypoxia within the intervillous space of the placenta leads to tissue oxidative stress and increases placental apoptosis and necrosis. This might be the cause of increased levels of cffDNA. Elevated cffDNA is not specific for preeclampsia and is also seen in other conditions associated with placental pathology[17].

Uric acid

Uric acid is the end product of purine metabolism in the liver. In normal pregnancy uric acid concentrations initially fall 25%-35% due to estrogens, expanded blood volume and increased glomerular filtration rate[89]. By term concentrations slowly rise to those observed in non-pregnant women. In contrast to that, uric acid levels increase at 10 wk of gestation and continue to rise until 48 h postpartum in preeclamptic women[90]. The increase in uric acid precedes the reduction in plasma volume in preeclampsia[91]. Uric acid may be protective during preeclampsia as an antioxidant, but is at the same time proinflammatory and contributes to endothelial dysfunction[92]. In a recent study the concentration of serum uric acid in preeclamptic women was associated with disease severity[93].

Nevertheless, lowering uric acid with probenacid had no effect on the degree of hypertension in preeclamptic women[94]. Another study with allopurinol showed no significant effects on the outcome of pregnancy in humans[95].

A summary of timed expression of these biomarkers in preeclampsia is given in Figure 1.

The optimal management of a pregnant woman with preeclampsia depends on gestational age and disease severity. Delivery is the only curative treatment for preeclampsia. Indicators for delivery in preeclampsia are given in Table 1 (modified from[22]).

The severity of the disease must always be weighed against the risks of infant prematurity. A mild preeclampsia at or beyond 37 wk should be delivered. In severe preeclampsia, induction of delivery should be considered after 34 wk of gestation. Prior to induction corticosteroids should be given to accelerate lung maturity. The prevention of seizures and adequate control of maternal blood pressure should also be of high priority. Maternal evaluation includes monitoring of blood pressure, urine output, cerebral status, epigastric status, tenderness or vaginal bleeding. Platelet count, liver enzymes and serum creatinine should be controlled closely. The target of blood pressure is between 140-160 mmHg systolic and 90-105 mmHg diastolic. The blood pressure should not be lowered under 140/90 mmHg to prevent insufficient utero-placental blood flow and reduced birth weight[96,97]. Foetal evaluation includes foetal heart rate monitoring, a biophysical profile, ultrasonographic assessment of foetal growth, amniotic fluid status and um-

Table 1 Indications for delivery in preeclampsia

Maternal	Foetal
Eclampsia	Severe foetal growth retardation
Shortness of breath, pulse oximetry of < 94% on room air, pulmonary oedema	severe oligohydramnios
AST or ALT > 2 times above normal	Foetal death
Uncontrolled severe hypertension	Repetitive late or variable foetal heart rate decelerations
Oliguria , serum creatinine level of ≥ 1.5 mg/d	Umbilical artery doppler imaging with reverse diastolic blood flow
Suspected abruptio placentae	
Persistent platelet count < 100000 /mm^3	

bilical artery doppler velocimetry.

Antihypertensives

Methyldopa, nifedipine, labetalol and hydralazine are the antihypertensives of choice for preeclampsia. Oral Methyldopa is suggested for mild to moderate hypertension in an outpatient with preeclampsia. Oral nifedipine is used for treatment of moderate or severe pregnancy hypertension in a dose of 10-20 mg every 4-6 h[98]. As a calcium channel blocker nifedipine acts on arteriolar smooth muscle cells and induces vasodilatation by blocking calcium entry into the cells. The side effects of nifedipine include tachycardia, palpitations and headaches. The calcium channel blockade with isradipine lowered the maternal mean arterial blood pressure in women with hypertension but not in women with proteinuria[99].

In hospital settings intravenous hydralazine (5-10 mg every 15-30 min) is commonly administered for hypertensive emergencies associated with pregnancies. Hydralazine is a direct peripheral arteriolar vasodilator. The most common adverse effect of hydralazine is the unpredictable hypotension. Other side effects are headache, nausea, maternal hypotension and vomiting. Labetalol is a selective alpha blocker and a nonselective beta blocker. The side effects of labetalol are dizziness, nausea and headaches. When the medications mentioned above have failed to lower blood pressure sodium nitroprusside may be given. Nitroprusside causes vasodilatation by the release of nitric oxide. Severe rebound hypertension may result. Therefore, nitroprusside should be reserved for use in postpartum care or just before the delivery because cyanide poisoning of the foetus is also a possible side effect.

Diuretics

Despite peripheral oedema, the intravascular volume is depleted in patients with preeclampsia. In contrast, pulmonary oedema can occur 48-72 h postpartum due to mobilization of extravascular fluid.

As preeclampsia is characterized by a reduction in circulating plasma volume diuretics are not generally recommended in preeclampsia. There are significant warnings against the use of thiazides during pregnancy like metabolic risks to the mother and fetus including hyponatremia, hypokalemia, thrombocytopenia, hyperglycemia.

Furthermore they may result in inhibition of labor and decrease placental perfusion in pregnany. Therefore we do not recommend the general use of diuretics in preeclampsia.

Nevertheless, the use of thiazide diuretics or loop diuretics is occasionally indicated for severe intractable or pulmonary oedema. The reduction of excessive oedema should be done slowly and under close supervision. There are no recommendations for dating, dosage or time for diuretics in this situation as it would be an individual symptom dependent and symptom guided therapy. We recommend to get written approval for the use of diuretics from the mother after detailed education on risks and side effects during pregnancy. Measures to respond to blood pressure drops must always be available and vital signs of the mother and foetus must be controlled continuously under diuretic treatment. This includes continuous electronic foetal heart rate monitoring and cardiovascular monitoring of the mother.

Antiepileptics

Magnesium sulfate is the drug of choice for the treatment and prevention of eclampcia. Magnesium sulphate more than halves the risk of eclampsia[100]. The Magpie-Trial compared magnesium sulphate with placebo for women with preeclampsia and found a preventive effect[101,102]. Therefore, prophylactic treatment with magnesium sulfate is indicated for all patients with severe preeclampsia. There is no consensus if patients with mild preeclampsia need magnesium prophylaxis. However, active seizures should be treated with an intravenous loading dose of 4 g magnesium sulphate over 5-10 min followed by an infusion of 1 g/h for 24 h. Seizures that are refractory to magnesium sulfate may be treated with lorazepam and phenytoin.

Antiplatelet therapy

There is an imbalance between thromboxane and prostacyclin production in preeclampsia. Thus, the use of low-dose aspirin in preeclampsia seems to be reasonable. Wallenburg *et al*[103] conducted the first prospective double-blind controlled trial using 60 mg aspirin per day for the treatment of women at risk for preeclampsia. Only two of the 23 treated women versus 12 of the 23 controls became preeclamptic. Supplementation of Aspirin at or before the 16th week of pregnancy reduced preterm preeclampsia without any effect on term preeclampsia[104]. In other studies low-dose aspirin had no

significant effect on the incidence of preeclampsia in the low-risk groups but was more beneficial in high-risk groups[105,106].

Plasmapheresis/ apheresis

The experience and safety of plasmapheresis (PE) in pregnancy is limited to case reports. In 1986 a successful use of plasmapheresis during pregnancy was reported in a patient with unusually fulminant, antibody-negative myasthenia gravis[107].

Another case report has suggested that PE may be a successful treatment for pregnant women with antiphospholipid syndrome[108]. PE was also successfully used in pregnant patients with acute fatty liver of pregnancy[109,110]. Additionally two cases of hypertriglyceridemia-induced acute pancreatitis during pregnancy and a case of a pregnant woman with Pemphigus vulgaris were successfully treated by PE[111,112]. Thrombocytopenia associated with microangiopathic disease in severe preeclampsia generally resolves within 3 to 4 d after delivery. It was suggested to use PE when thrombocytopenia persists beyond this time[113].

In preeclampsia a potentially useful approach of PE would be to subtract circulating autoantibodies from maternal circulation. In 1986 fourteen cases of PE with fresh frozen plasma for maternal indications in selected cases of preeclampsia and eclampsia were reviewed with promising results[114]. In contrast, PE did not prolong pregnancy in preterm preeclampsia in a report by Martin *et al*[115]. In another report, plasma exchange was commenced at 23, 26 and 29 wk of gestation in preeclamptic women and continued until delivery. Here preeclamptic signs regressed and renal function stabilised. One baby with severe hyaline membrane disease died but the others were delivered in good health[116].

Like PE with fresh frozen plasma heparin-mediated extracorporeal low-density lipoprotein precipitation has been attempted in preeclampsia[117]. Pregnancies were prolonged for 3 to 49 d in 9 very preterm preeclamptic women by the use of this apheresis.

Thadhani *et al*[118] hypothesized that a selective adsorption column would create a concentration gradient and augment the removal of sFlt1. They treated 5 women with very preterm preeclampsia with dextran sulfate cellulose apheresis. This treatment reduced circulating sFlt-1 levels and proteinuria in a dose-dependent manner and stabilized blood pressure without apparent adverse events. Dextran sulfate cellulose apheresis was able to reduce sFlt-1 plasma levels by 20%-30%. Pregnancy was continued for 15 d with the use of two apheresis and for 23 d with four apherese sessions[118].

Maternal blood pressure was stable and was not markedly decreased after apheresis. However, antihypertensive medications were stopped before treatments and saline infusions were given during treatments. Three patients with postpartum HELLP syndrome and persistent thrombocytopenia were treated with PE with prompt resolution of their diseas[113]. There is no animal model for plasmapheresis at the meantime. Therefore the only way to get more experience on this filed is the clinical use in selected patients.

Taken together single cases indicate that PE seems to be a treatment with low risk during pregnancy and could be a promising treatment option for otherwise refractory preeclampsia. We recommend only use this therapy in specialized centers with first class experience on the filed and with written consent of the mother after detailed education about the risks and experimental status of this therapy.

Albumin substitution

Serum albumin levels of preeclamptic women are often even below 10 g/L. Thus, one can suggest albumin substitution in preeclampsia. Albumin infusions increased serum albumin and colloid osmotic pressure values in preeclampsia[119].

However, daily albumin infusions did not lower blood pressure and was unable to stabilise renal function. Albumin substitution was also associated with higher foetal mortality[120]. Therefore, we do not recommend using albumin substitution in preeclampsia.

Uterine curettage

Uterine curettage immediately after delivery accelerates the recovery of severe preeclampsia[121]. This operation was also successfully used in single cases of postpartum preeclampsia[122,123]. Due to the fact that even microscopic level of trophoplastic tissue can perpetuate preeclampsia uterine curettage should be done after delivery.

CONCLUSION

We reviewed the literature with a focus on proteinuria during pregnancy and preeclampsia. Several new diagnostic markers for preeclampsia were presented. Most of these are not yet implemented in clinical use and several are only used in studies or experimental conditions. Therefore, we recommend using proteinuria as a screening parameter for preeclampsia. The first screening should be UPC ratio. If the UPC ratio is below 150 mg/g total proteinuria is unlikely to be more than 300 mg/d and needs no further investigation at that time. For a UPC ratio greater than 150 mg/g we suggest performing a full 24-h urine protein collection as a second diagnostic tool for confirming accurate results. If a new onset of proteinuria greater than 300 mg/d together with hypertension and/or general oedema occurs after the 20th week of gestation the diagnosis of preeclampsia can be made. Atypical presentation must always be kept in mind. We presented different therapeutic options for preeclampsia.

Delivery is the only curative treatment for preeclampsia. In early preeclampsia the primary therapy goal is to prolong pregnancy until a state were the child has an acceptable chance of survival after delivery. In the mean time close maternal and foetal monitoring and evaluation

is necessary. We presented therapeutic options to treat hypertention, oedema and seizures during this period.

Plasmapheresis is not a common treatment strategy in preeclampsia but could be considered as rescue therapy in otherwise therapy refractory cases.

When performing PE in preeclampsia measures to respond to blood pressure drops must always be available and vital signs must be controlled during and after the entire session. This includes continuous electronic foetal heart rate monitoring and cardiovascular monitoring of the mother. Eventually, antihypertensives must be paused before and/or after PE. In general after the 34th week of gestation delivery is the better choice of treatment for both mother and child.

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We searched PubMed for articles with the keywords "preeclampsia AND animal models", "treatment of preeclampsia", "proteinuria in pregnancy", "treatment of preeclampsia", "markers for preeclampsia", "podocyturia", "physiological changes in pregnancy", "plasmapheresis in pregnancy". We also searched the bibliographies of the articles retrieved for further relevant references.

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REVIEW

Acute kidney injury due to bilateral ureteral obstruction in children

Daniele Bianchi, Giuseppe Vespasiani, Pierluigi Bove

Daniele Bianchi, Giuseppe Vespasiani, Pierluigi Bove, Department of Urology, Policlinico Tor Vergata, Viale Oxford, 00100 Rome, Italy
Author contributions: All authors contributed to the manuscript.
Correspondence to: Daniele Bianchi, MD, Department of Urology, Policlinico Tor Vergata, Viale Oxford, 81, 00100 Rome, Italy. danielebianchimail@yahoo.it
Telephone: +39-62-0902977 Fax: +39-62-0902975
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Abstract

Bilateral ureteral obstruction in children is a rare condition arising from several medical or surgical pictures. It needs to be promptly suspected in order to attempt a quick renal function recovery. In this paper we concentrated on uncommon causes of obstruction, with the aim of giving a summary of such multiple, rare and heterogeneous conditions joint together by the common denominator of sudden bilateral ureteral obstruction, difficult to be suspected at times. Conversely, typical and well-known diseases have been just run over. We considered pediatric cases of ureteral obstruction presenting as bilateral, along with some cases which truly appeared as single-sided, because of their potential bilateral presentation. We performed a review of the literature by a search on PubMed, CrossRef Metadata Search, internet and reference lists of single articles updated to May 2014, with no time limits in the past. Given that we deal with rare conditions, we decided to include also papers in non-English languages, published with an English abstract. For the sake of clearness, we divided our research results into 8 categories: (1) urolithiasis; (2) congenital urinary tract malformations; (3) immuno-rheumatologic causes of ureteral obstruction; (4) ureteral localization of infections; (5) other systemic infective causes of ureteral obstructions; (6) neoplastic intrinsic ureteral obstructions; (7) extrinsic ureteral obstructions; and (8) iatrogenic trigonal obstruction or inflammation. Of course, different pathogenic mechanisms underlay those clinical pictures, partly well-known and partly not completely understood.

Key words: Acute kidney injury; Bilateral ureteral obstruction; Hydronephrosis; Anuria; Pediatrics; Ureteral stenting; Henoch-Schönlein purpura; Tuberculosis; Masses; Congenital malformations

Core tip: Bilateral ureteral obstruction in children is a rare condition related to several medical or surgical pictures. It needs to be promptly suspected in order to attempt a quick renal function recovery. It is a rare event, but to be kept in mind. We identified many potential causes grouped as follows: (1) urolithiasis; (2) congenital urinary tract malformations; (3) immuno-rheumatologic causes of ureteral obstruction; (4) ureteral localization of infections; (5) other systemic infective causes of ureteral obstruction; (6) neoplastic intrinsic ureteral obstructions; (7) extrinsic ureteral obstructions; and (8) iatrogenic trigonal obstruction or inflammation.

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INTRODUCTION

The definition of acute kidney injury (AKI) has been deeply changing over the last decade, starting off with adult patients[1] and followed by a still debated extension to children[2-4], with some new biomarkers for AKI early detection proposed[5,6].

In particular, AKI in children has been widely discussed in several reviews and meta-analysis[2,3,7], including

some papers focused on AKI in newborns[8] and very preterm infants[9], while some articles concentrated on kidney injury due to urinary tract obstruction[10-13], especially on nephrolithiasis, which accounts for up to 30% of AKI in pediatrics[10].

Aim

Aim of the present paper is to give a diagnostic overview of rare or very rare causes of pediatric AKI due to sudden bilateral ureteral obstruction, which can be related to lots of different conditions - either medical or surgical - and needs to be promptly suspected in order to attempt a quick renal function recovery.

We decided not to focus on typical and well-known diseases, which have been just run over in this paper, while we intended to concentrate on uncommon pictures, with the aim of giving a summary of such multiple, rare and heterogeneous conditions joint together by the common denominator of sudden bilateral ureteral obstruction, which appears difficult to be suspected at times.

Thus, our purpose was to provide a sort of companion to causes of bilateral or potentially bilateral ureteral obstruction in pediatrics, given the lack of such a paper in the literature. We did not address the issue of different imaging modalities - for example, see Riccabona[12] about - and we just outlined some therapeutic aspects, with no intention of a systematic analysis.

Research

We performed a review of the literature by a search on PubMed, CrossRef Metadata Search, internet and reference lists of single articles updated to May 2014, with no time limits in the past. Given that we deal with rare conditions, we decided to include also papers in non-English languages, published with an English abstract.

We considered pediatric cases of ureteral obstruction presenting as bilateral, along with some cases which truly appeared as unilateral, but still at risk of bilateral involvement.

For the sake of clearness, we divided our research results into 8 categories: (1) urolithiasis; (2) congenital urinary tract malformations; (3) immuno-rheumatologic causes of ureteral obstruction; (4) ureteral localization of infections; (5) other systemic infective causes of ureteral obstruction; (6) neoplastic intrinsic ureteral obstructions; (7) extrinsic ureteral obstructions; and (8) iatrogenic trigonal obstruction or inflammation. Categories are summarized in Table 1.

UROLITHIASIS

Urolithiasis is generally considered a relatively rare disease in children, with some peaks of incidence in Turkey, some South Asian, African and South American countries[14].

Overall, kidney stone disease is considered to affect boys and girls equally[15] accounting for 1:1000-1:7600 hospital admissions in the United States of America, even if some studies pointed out a male prevalence in the first decade and a female prevalence during the second decade of life[11,15].

Causes of urolithiasis in children

A systematic review of urolithiasis goes beyond the scope of this paper, but some aspects can be of interest in our topic.

It has been evaluated that in some European countries, 75% of stones in children are composed of organic matrix and struvite, mostly sustained by Proteus infection or urinary tract anomalies[14].

Anyway, according to the underlying condition, we could consider systemic/genetic diseases and medical treatment-related conditions, according to Valentini *et al*[11].

Among systemic diseases, cystic fibrosis and inflammatory bowel diseases are considered risky conditions for stone formation because they result in intestinal calcium chelation, thus freeing up an exceeding amount of unbounded oxalate, which can be absorbed from the intestinal tract, finally becoming available for stone formation[11].

As well, spinal cord injuries and spina bifida have been traditionally considered potential causes of stone disease because a neurogenic bladder - usually seen in these conditions - is associated with a higher risk of struvite stones, although more recently some metabolic studies showed that calcium phosphate stones are becoming more frequent, with a minor incidence of struvite calculi, probably due to the better bladder care achieved by clean self-catheterization[11].

Some genetic aspects concern primary hyperoxaluria, classified in type-1 and type-2, which can lead to an early onset of disease with nephrocalcinosis and kidney injury, more clinically relevant in type-1 form.

Other conditions include tubular disorders such as cystinuria, which has been postulated as responsible for 3% of renal stones in one pediatric study[16]. This autosomal recessive disorder finally causes an increased excretion of the amino-acids cystine, ornithine, lysine and arginine because of a proximal tubular defect.

Other genetic disorders include the X-linked Dent disease, the Lesch-Nyhan syndrome and the extremely rare 2,8-dihydroxyadeninuria[11].

Clinical presentation

It has been pointed out that stone disease in children may present as flank/abdominal pain or hematuria, similarly to adults[11], even if urolithiasis in infants may mimic an intestinal colic[14].

To our knowledge, no studies investigated the real incidence of bilateral ureteral obstruction in urolithiasis among pediatric population.

CONGENITAL URINARY TRACT MALFORMATIONS

Lots of congenital urinary tract malformations can lead

Table 1 Causes of bilateral or potentially bilateral ureteral obstruction in children

Categories of disease	Single entities or underlying causes
Urolithiasis	Idiopathic
	Neurologic disease
	Metabolic and genetic disorder
	Inflammatory bowel disease
Congenital urinary tract malformations	Obstructive megaureter
	Uretero-pelvic junction obstruction
	Duplicated collecting system
	Horseshoe kidney and other anomalies
Immuno-rheumatologic diseases	Necrotizing vasculitis
	Periarteritis nodosa
	Kawasaki disease
	Henoch-Schönlein purpura
	Eosinophilic ureteritis
Ureteral localization of infections	Fungal infections
	Viral infections
	Bacterial infections
	Tubercular infections
Other systemic infections	Rotavirus
Neoplastic intrinsic ureteral obstructions	Fibroepithelial polyps, ureteritis cystica, malignant neoplasms
Extrinsic ureteral obstructions	Abdomino-pelvic masses
	Familial adenomatous polyposis
	Retroperitoneal fibrosis
Iatrogenic trigonal obstruction/inflammation	Device-induced obstruction
	Bulking agents for vesico-ureteral reflux
	Obstruction after appendectomy

to kidney injury, including uretero-pelvic junction obstruction, obstructive megaureter, vesico-ureteral reflux and posterior urethral valves.

Anyway, functional impairment may be graded and slowly progressive[13]. With regard to the purpose of the present review, we remember that megaureter can be characterized by transient or permanent urine flow impairment, above all if secondary to structural or functional obstruction of the distal ureter[17].

In a retrospective paper about obstructed megaureters in early infancy, 5 infants out of 47 between years 1963-1987 had a solitary kidney and one of them presented with anuria, while 7 out of the 47 patients had bilateral megaureter[18].

In the literature, just one case of bilaterally duplicated collecting systems with obstructing ureteral stones has been described in an adult patient[19], along with one case of pediatric bilateral ureteral reflux at the distal part in a bilaterally duplicated collecting system in a 5-year-old girl presenting with repeated urinary tract infections[20].

By the way, also retrocaval ureter can lead to ureteral obstruction and it can often be associated with other major anomalies (see Lopez Gonzalez *et al*[21] for a bibliographic review).

Moreover, ureteropelvic obstruction can be related to horseshoe kidney, extrarenal pelvis, transverse valves of periureteral junction and other congenital anomalies[22,23], both isolated or in genetic syndromes[24,25].

As a general rule, congenital urinary tract malformations should always be considered in case of hydronephrosis, both in children and young adults, as they can be asymptomatic for many years, giving signs in adolescence or adulthood.

IMMUNO-RHEUMATOLOGIC CAUSES OF URETERAL OBSTRUCTION

Stenosing ureteritis secondary to rheumatologic diseases is a rare condition, difficult to be estimated exactly because of the lack of papers about.

We found the description about a case of necrotizing vasculitis with ureteral involvement in a 12-year-old girl[26] firstly admitted to the hospital when she was aged 2 years because of arthritis, fever and growth retardation, successfully treated by aspirin and penicillin and then being healthy until the age of 8, when she had a bronchial asthma episode. A subsequent arthritis manifestation occurred at the age of 11, treated by penicillin and naproxene. At the age of 12 she presented with fever, legs ulcers, abdominal crisis, bronchial asthma, sinusal arrhythmia. Radiologic findings showed bilateral ureteral strictures and a skin biopsy revealed necrotizing vasculitis of medium-sized arteries.

The girl was successfully treated by prednisone and azathioprine.

In the literature, we found a couple of descriptions of ureteral involvement during periarteritis nodosa in a 13-year-age girl[27] and a 6-year-age boy[28], the latter treated by steroids.

To our knowledge, just one case has been published reporting on left ureteral obstruction in a 7-year-age boy affected by Kawasaki disease, who finally underwent excision of a left upper third ureteral stricture, with left-

dismembered pyeloplasty[29].

Henoch-Schönlein purpura is a common systemic vasculitic condition of which the majority of cases occur in pediatrics[30].

Urinary tract involvement in Henoch-Schönlein purpura usually concerns the kidney, with a focal proliferative glomerulonephritis occurring in 20%-90% of cases[30].

Ureteral obstruction secondary to Henoch-Schönlein purpura is rare, with 14 cases described in the literature. Most patients were treated by medical therapy, while two by surgery.

One of them underwent total bilateral ureteral replacement using ileal segment, but progressed to end-stage renal disease because of reflux along the graft, thus radical excision of the ileal graft and both native kidneys was performed in order to eradicate any infectious process before immuno-suppression therapy[31].

The other one was a boy aged 7 years, who underwent multiple conservative surgical treatments for two years, including bilateral nephrostomic tubes and ureterocalycostomies along with a left dismembered pyeloplasty, which appeared to be successful at the beginning but were then complicated by infections and worsening of renal function[30]. Finally, a left nephrectomy was performed and two and a half years after the onset of disease, the boy remained tube-free without hydronephrosis recurrence on the right, with no further hospital readmissions required[30].

Eosinophilic ureteritis is a rare disease with imaging presentation similar to ureteral tumors[32], leading to ureteral stricture due to mural involvement, with secondary hydronephrosis[33].

Even though it may be associated with hypersensitivity to bacteria, parasites, food and drugs, the etiopathogenic mechanism is not completely clear[34] and peripheral eosinophilia is not a constant finding[35]. In a paper, filariasis has been proposed as a possible triggering etiology of bilateral upper ureteric strictures in a 54-year-old man, as the patient had a previous history of cellulitis with epididymitis and came from an endemic area[35].

Up to 1991 just one case of eosinophilic ureteritis in children had been published[33], describing a 3-year-old boy with bilateral ureteral obstruction.

To our knowledge, no further cases of pediatric eosinophilic ureteritis have been described in the literature, while cases of eosinophilic cystitis have been reported, with some pathological aspects still debated[33].

Some molecular details of murine ureteritis causing obstructive uropathy with hydronephrosis have been investigated[34], providing a novel molecular pathogenesis for elucidating causes of aseptic inflammation in human upper urinary tract.

URETERAL LOCALIZATION OF INFECTIONS

Fungal infections

Systemic candidiasis with possible renal localization is uncommon in neonates and infants[36], although it is a well-documented entity in several special conditions, such as intensive care in premature newborns[37], prolonged antibiotic therapy, intravenous lines and immunocompromised patients[36].

The management of renal obstructive candidiasis is challenging and not well summarized over the past decades[38]. In a review[39], the clinical course and management of 35 neonates and infants were considered, with prematurity, broad spectrum antibiotics, prolonged hospital stay and the use of intravascular catheters resulted as predisposing factors. Among the other ones, candidemia and withholding antifungal therapy were poor prognostic factors.

After year 2011, some more cases of candidiasis in newborns have been described in the literature[40-43], with no standardized treatment at the moment[44]. Of course, transplant recipients must be considered at high risk for opportunistic pathogens[45,46] and obstructive anuria due to fungal bezoars has been described[47].

Therapeutic options range between medical drugs such as amphotericine-B or fluconazole and surgical treatment, consisting of nephrostomy or retrograde stenting along with irrigation by streptokinase as required, until open surgery if needed[43].

Viral infections

Viral infections can represent severe complications in immunocompromised patients. Among them, BK-virus has been related to hemorrhagic cystitis in bone marrow transplant recipients[48-50] or to pyelonephritis and ureteral stenosis in renal transplant recipients[51].

Also adenovirus infections are postulated as causes of urologic complications in bone marrow transplantation, mainly consisting of hemorrhagic cystitis[52], moreover obstructive pyelonephritis treated by double-J ureteral stenting has also been described[53].

Management of viral infections, including Epstein-Barr, cytomegalovirus etc, is a challenging problem in both hematopoietic and solid organs transplantation[54-56].

As to the purpose of this paper, we cite a case of late onset hemorrhagic cystitis and ureteritis induced by cytomegalovirus after kidney transplantation[57].

Bacterial infections

Although syphilis, toxoplasmosis and candidiasis are recognized as causes of infections leading to kidney injury in newborns[8], in the literature we found just one case describing a *Pseudomonas aeruginosa* infection with bilateral ureteral involvement[58]. It concerned a 14-mo-old male diagnosed with an acute lymphocytic leukemia, who showed bilateral ureteral obstruction caused by purulent debris from *Pseudomonas*, with a subsequent anuria. The Authors reported it was not possible to insert a ureteric catheter on the left side, while a right retrograde pyelogram revealed a medial deviation of the right ureter with no chance of further upward progression. An irrigation was performed and the patient became polyuric after the procedure, with a renal function recovery two days after

the cystoscopy, along with ciprofloxacin administration[58].

Tubercular infection

Tubercular infection is endemic in some geographic areas and genitourinary tract involvement is quite common[59].

In a paper based on a retrospective study over 13 years in a single Indian centre, Singh *et al*[59] identified ureteral involvement in 27.35% out of 117 patients with genitourinary tubercular disease.

In a Russian paper[60], the Authors analyzed 158 patients with active nephrotuberculosis, identifying 24 without obstructive uropathy, 70 with upper ureter obstruction and 64 with lower ureter obstruction. Bilateral involvement was recorded in 75% of patients. Unfortunately, just an English abstract was available in our research, so we do not know the amount of pediatric patients involved.

Other isolated cases have been published, including major surgical reconstructive treatment in one of them[61,62] and one case of primary papillary mucinous adenocarcinoma of the ureter mimicking genitourinary tuberculosis in a 54-year-old man[63].

In our opinion, tubercular infections could be suspected according to the geographic origin of the patient, although actual worldwide travelling habits should invite physicians to be cautious anytime.

OTHER SYSTEMIC INFECTIVE CAUSES OF URETERAL OBSTRUCTION

Rotavirus infections are the most common cause of severe diarrhea in infants and young children worldwide[64]. In a clinical paper, Ashida *et al*[64] retrospectively described 21 cases of gastroenteritis in Japanese children with acute post-renal failure due to ureteral obstruction from bilateral stones.

The patients were 18 boys and 3 girls, with a median age of 1.3 years, ranging between 0.4 and 3 years, while the median duration between the onset of oliguria and that of *Rotavirus* gastroenteritis was 6.7 d, ranging from 3 to 16 d.

The Authors highlighted that all the children were under 3 years old, many of them had hyperuricemia and the stones mainly consisted of ammonium acid urate. Some causes have been considered as possibly responsible for such stones, including a laxative-like mechanism related to water loss or fluctuations in urinary acidity, which in another paper[65] has been recognized to play a role in ammonium acid uric stones formation.

In our opinion, more studies are advocated to clear this entity.

Moreover, we found a paper published in 1991[66] describing about 4 cases of children aged between 14 mo and 13 years, including a 3-year-old girl, who presented with oligo-anuria and either flank pain or fluid retention. Three of them had a profuse vomiting and diarrhea in the previous days, with the forth one revealing a familial history of renal calculi. All the patients showed an evidence of crystalline sludge in their lower ureters.

Dehydration was postulated as a primary predisposing factor, even if three of them had an underlying crystalluria, two had a raised excretion of uric acid and one of cystine.

NEOPLASTIC INTRINSIC URETERAL OBSTRUCTIONS

Benign neoplasms

Fibroepithelial polyps are the most common ureteral benign neoplasms[67], although this mesodermal tumor rarely occurs in children[68].

It usually arises along the proximal ureter and is more common in boys, with presenting signs consisting of hematuria or flank pain due to urinary obstruction. Nevertheless, cases of single polyp with mid-ureter[69] or distal ureter[70] localization have been described, with one case prolapsing into the bladder, thus mimicking a bladder tumor[71].

Overall, in the literature we found some 40 cases of pediatric patients affected by ureteral polyps[72,73], with bilateral obstruction described in at least 5 cases, the first one in 1990[67,74-77].

Surgical management of such cases is not standardized, with some polyps treated by ureteroscopic procedures and other ones by segmental resection of the ureter[76,67]. A concomitant ureteropelvic obstruction underwent pyeloplasty, even if more studies are advocated about multiple metachronous polyps recurring after laparoscopic or robotic pyeloplasty[72].

A differential diagnosis is required between ureteral polyps and ureteritis cystic[78], which has been reported as a cause of ureteral obstruction in some cases[79-81], bilaterally in one of them[80].

Malignant neoplasms

Among malignant neoplasms, we should rapidly consider a collection of rare cases which truly presented as a single-side ureteral involvement.

A paper investigated the extension of Wilms' tumor into the ureter[82] and 45 children out of the Wilms' Tumor Study Group database showed ureteral involvement, with hydronephrosis identified in 12 and non-function of the kidney in another 8. Tumor was right-sided in 26 and left-sided in 19.

In the literature, we found a case of 17-year-old girl[83] and of a 12 year-old boy[84] with Ewing's sarcoma/neuroectodermal tumor with unilateral ureteral localization, both presenting with nausea, vomiting, hematuria and abdominal pain.

One case has been described of a 4-year-old girl presenting with an embryonal rhabdomyosarcoma, botryoid variant, arising within the left ureter[85].

Ureteral localization of lymphoma was identified in one adult in a clinico-pathological study of 40 cases of

genitourinary tract lymphomas, with the two pediatric cases involving kidney and testis[86]. Another paper reported a case of penile lymphoma in a 4-year-old boy[87].

An isolated case of bilateral ureteral obstruction due to lymphoma has been described in an adult[88]. To our knowledge, no cases of pediatric lymphomas with ureteral localization have been published.

EXTRINSIC URETERAL OBSTRUCTIONS

Abdomino-pelvic masses

Urinary obstruction secondary to malignant pelvic tumors is a well-known condition in adult patients[89].

In a paper published in 2004, Meir *et al*[90] retrospectively investigated about the same condition among the records of two major children's hospitals, identifying 17 patients affected by upper urinary tract obstruction - 9 boys and 8 girls - with a median age of 5.7 years, ranging between 0 and 12. The most represented tumor was rhabdomyosarcoma, followed by lymphoma, and the urinary obstruction was bilateral in 11 cases. Most of them were treated by ureteral retrograde stenting or nephrostomy, with just some cases deferred to major surgery.

In another paper, Alexander *et al*[91] ascertained the incidence and outcome of hydronephrosis in children affected by abdominal (non-renal) or pelvic tumors. They reviewed 366 patients from a database between 1995 and 2009, finding out 66 cases - 39 female and 27 male - of upper urinary obstruction due to a compression by the tumor or by surgery/radiotherapy, with a median age of 5.1 years. Out of those 66 cases, 35 were bilateral. The most represented tumor was neuroblastoma, followed by immature teratoma and rhabdomyosarcoma. For further details about histotypes involved, see Meir *et al*[90] and Alexander *et al*[91].

Mucinous cistoadenoma of the ovary is a rare neoplasm in pediatric age[92], with 20 cases described in the literature. Most of them presented late as an abdominal mass, with urinary outflow obstruction due to bilateral distal ureter compression, eventually leading to renal failure[92].

Mesenteric and omental cysts are considered as rare intra-abdominal lesions, with an incidence of about 1 per 105000 admissions to general hospitals, ranging in age from in-utero to 18 years[93]. They can lead to hydronephrosis because of compression, as described about an abdominal cyst causing anuria in a newborn girl[94], for example.

A single case of mesenteric cyst in a neonate responsible for not only obstructive uropathy but also secondary type-1 hyperaldosteronism has been described in the literature[95]. It concerned a 9-d-old female neonate who presented with lethargy, refusal to feed and anuria over the previous 2 d. An ultrasound scan revealed a round mass in the inferior abdomen, compressing both ureters and leading to bilateral hydronephrosis. The case was treated by subtotal surgical excision of the cyst.

The autosomal-dominant inherited disorder neurofibromatosis type-1 rarely involves the genito-urinary tract, but some pediatric cases of obstruction and hydronephrosis or bladder involvement have been described[96-102], with at least one needing ureterocutaneostomy[103].

Cases of bilateral ureteral obstruction have been described both in adults and children due to traumatic pelvic hematoma and increased retroperitoneal pressure, in the so-called acute pelvic compartment syndrome[104].

Familial adenomatous polyposis

Intra-abdominal desmoid disease is one fearful condition related to familial adenomatous polyposis (FAP), potentially causing ureteric obstruction. Joyce *et al*[105] retrospectively investigated the incidence of ureteric obstruction among patients with desmoids disease from the FAP registry within the Sanford R. Weiss Center for Inherited Colorectal Neoplasia[105] and they sorted out that 30 patients out of the 107 with desmoids disease presented with ureteral obstruction, which was bilateral in 13. The median age of first colonic surgery was 21 years, ranging between 11 and 60. Most patients were treated by endoscopic retrograde ureteral stenting or percutaneous nephrostomy, while 4 cases underwent nephrectomy, 1 ureteric resection and reimplantation and 1 ureterolysis.

A preceding Asian paper reports on two patients affected by the same condition, with a review of 14 previous cases in the literature[106].

Retroperitoneal fibrosis

Retroperitoneal fibrosis is considered a rare entity in childhood[107], with 26 cases published[107-109], one of whom associated to lymphoma[110].

IATROGENIC TRIGONAL OBSTRUCTION OR INFLAMMATION

Device-induced obstruction

In the literature, we found 2 cases of anuria secondary to balloon catheters in children, described in a paper published in 1977[111].

The first one was a 17-mo-old girl affected by spastic neurogenic bladder, presenting with a 16-Fr Foley catheter with an 8-mL balloon, placed to manage a vesicocutaneous fistula developed after bilateral ureterovesical reimplantation. The catheter was patent and when it was removed the urine output restored.

The second case concerns a 7-d-old male newborn who underwent a transurethral resection of posterior urethral valves, presenting with an 8-Fr Foley catheter with a 3-mL balloon via a perineal urethrostomy. The catheter was found to be patent and by deflating the balloon diuresis was restored. Of course, those complications are less likely to occur with current pediatric devices.

Endoscopic procedures

Patients undergoing minimally invasive endoscopic peri-

ureteral injection of bulking agents for vesicoureteral reflux are potentially at risk of hydronephrosis[112,113], but those situations are well-known and such patients are deferred to a urologic follow-up after the procedure[114].

Bilateral ureteral obstruction after appendectomy

Known surgical complications leading to ureteral damage goes beyond the scope of this paper, while in the literature there are some cases reporting on bilateral ureteral obstruction as a rare complication after appendectomy in pediatrics, not related to direct surgical ureteral damage.

The last report found on PubMed, with a review of the literature, dates back to 2005[115] when the Authors described a case of anuria in a 11-year-old boy, 5 d after surgery for a perforated appendix. At ultrasound examination some echogenic "plugs" were found in the distal portion of both ureters, with no abscess at an abdomino-pelvic computed tomography.

During a cystoscopy a bladder base inflammation was revealed, so the patient was treated by bilateral ureteric stenting, with a prompt recover of diuresis and renal function.

In the review of the literature, the Authors found out 15 similar cases, curiously all boys aged 6-15 years[115].

An edematous process has been postulated as possibly triggered by a localized peritoneal reaction to intraoperative bacterial contamination, with boys more susceptible because their appendix is located closer to the bladder, while in girls internal genitals are situated between the appendix and the bladder[116].

In our opinion, such mechanism can be considered as an attractive pathogenesis explanation, although we do not know if an inadequate fluid replacement therapy could play a role, above all in cases with underlying predisposing factors to urolithiasis. More studies would be necessary, including a focus on metabolic disorders in patients presenting with such condition.

Personally, we observed a case of a 16-year-old boy with similar presentation after appendectomy, who was diagnosed with bilateral ureteric stones successfully drained during ureteric bilateral catheterization. He was suggested to undergo a metabolic panel but the patient was lost at follow-up.

CONCLUSION

Bilateral ureteral obstruction in pediatric population is a rare condition and can be related to either medical or surgical underlying causes, thus it is not possible to identify a common etiology.

With regard to pathogenetic mechanisms, some aspects remain unclear, in particular: (1) more studies are advocated to clarify ureteral obstruction secondary to severe diarrhea after *Rotavirus* infection; (2) ureteritis in immuno-rheumatologic diseases is not a completely clear event, although murine models elucidated some details; (3) multiple metachronous polyps recurring after laparoscopic or robotic pyeloplasty should be further investigated; and (4) sudden ureteral obstruction secondary to appendectomy could be related to dehydration, although in our opinion further studies would be necessary to highlight critical points and to evaluate metabolic aspects.

As a recommendation for clinical practice, a possible ureteral obstruction should be investigated in patients presenting with any picture described in this paper.

An abdominal ultrasound scan could be a simple, first-line diagnostic tool useful in the evaluation of hydronephrosis in most patients.

Treatment of ureteral obstruction deeply varies according to the underlying condition, with some cases successfully managed by drugs and other ones requiring surgery.

Surgical procedures often consist of ureteroscopy, ureteral stenting or nephrostomic tubes, with some cases deferred to major surgery for ureteral resection and reimplantation. Nephrectomy can be an option in patients presenting with advanced infections, particularly if recurrent, inveterate or in those needing an immunosuppression therapy for their underlying condition.

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REVIEW

Retrograde intrarenal surgery in pediatric patients

Berkan Resorlu, Eyup Burak Sancak, Mustafa Resorlu, Murat Tolga Gulpinar, Gurhan Adam, Alpaslan Akbas, Huseyin Ozdemir

Berkan Resorlu, Eyup Burak Sancak, Murat Tolga Gulpinar, Alpaslan Akbas, Department of Urology, Canakkale Onsekiz Mart University, Faculty of Medicine, 17100 Canakkale, Turkey
Mustafa Resorlu, Gurhan Adam, Huseyin Ozdemir, Department of Radiology, Canakkale Onsekiz Mart University, Faculty of Medicine, 17100 Canakkale, Turkey
Author contributions: Resorlu B, Sancak EB and Resorlu M wrote the manuscript; Adam G, Akbas A and Gulpinar MT designed the manuscript and provided materials; Ozdemir H were involved in editing the manuscript.
Correspondence to: Berkan Resorlu, MD, Department of Urology, Canakkale Onsekiz Mart University, Faculty of Medicine, Terzioglu Yerleskesi, Barbaros Mh, 17100 Canakkale, Turkey. drberkan79@gmail.com
Telephone: +90-533-6897268 Fax: +90-286-2180393
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Abstract

Urinary tract stone disease is seen at a level of 1%-2% in childhood (< 18 years). In recent years, however, there has been a marked increased in pediatric stone disease, particularly in adolescence. A carbohydrate- and salt-heavy diet and a more sedentary lifestyle are implicated in this increase. Although stone disease is rare in childhood, its presence is frequently associated with metabolic or anatomical disorders or infectious conditions, for which reason there is a high possibility of post-therapeutic recurrence. Factors such as a high possibility of recurrence and increasing incidence further enhance the importance of minimally invasive therapeutic options in children, with their expectations of a long life. In children in whom active stone removal is decided on, the way to achieve the highest level of success with the least morbidity is to select the most appropriate treatment modality. Thanks to today's advanced technology, renal stones that were once treated only by surgery can now be treated with minimally invasive techniques, from invasion of the urinary system in an antegrade (percutaneous nephrolithotomy) or retrograde (retrograde intrarenal surgery) manner or shock wave lithotripsy to laparoscopic stone surgery. This compilation study examined studies involving the RIRS procedure, the latest minimally invasive technique, in children and compared the results of those studies with those from other techniques.

Key words: Percutaneous nephrolithotomy; Pediatric; Renal stone; Retrograde intrarenal surgery; Shockwave lithotripsy

Core tip: In the last two decades, technological advancement of instruments have changed the treatment options of renal stone disease. Today retrograde intrarenal surgery may represent an alternative treatment modality to shock wave lithotripsy and percutaneous nephrolithotomy, with acceptable efficacy and low morbidity in pediatric patients.

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RETROGRADE INTRARENAL SURGERY IN CHILDREN

Treatment of urinary stone disease in pediatric patients is a challenging problem[1-5]. Although the indications employed in treatment selection in children are regarded as the same as those for adults, children respond particularly well to shock wave lithotripsy (SWL)[6]. The fact that developing kidney tissue transmits shock waves better and that spontaneous passage is comparatively

easier in children than in adults both play a role in this rapid response. SWL, which began being applied in the 1980s with the principle of the use of high-energy shock waves, represents a milestone in the treatment of stone disease in children[7].

Gofrit *et al*[8] compared the results of pediatric and adult patients administered SWL for renal stones larger than 10 mm, and reported stone-free status levels of 95% in children and 78.9% in adults. Similar results were obtained from many subsequent studies. In a recent randomized prospective study Mokhles *et al*[9] compared the outcome of retrograde intrarenal surgery (RIRS) and SWL for stones 10 to 20 mm in preschool age children. They found that the overall stone-free rate was 93% and 96% for SWL and RIRS groups, respectively. SWL is therefore recommended as the first treatment option in children with stones of up to 20 mm (approximately 300 mm^2) in modern guidelines[10]. However, the fact that the procedure usually requires general anesthesia in children, the need for general anesthesia in repeat sessions, concerns over the possibility of long-term renal scarring, hypercalciuria, hypertension or chronic renal insufficiency and some stones (cysteine stones, *etc*.) not responding to the technique represent concerns over its use in children[10,11].

Technological advances in recent years has permitted the miniaturization of endoscopic devices, as a result of which percutaneous nephrolithotomy (PNL) has become the first treatment option for stones larger than 2 cm in children[11]. Although the procedure was initially performed with adult-type devices, Jackman *et al*[12] described a "mini-perc" technique using a 7 Fr rigid cystoscope and 11 Fr vascular access. They emphasized that a smaller tract will lead to less tissue and nephron injury and that this is more significant in pediatric patients with small and delicate kidneys, citing the example of a 24 Fr access sheath used in an infant being equivalent to 72 Fr in an adult.

Desai *et al*[13] reported that intraoperative hemorrhage occurring during PNL is related to the number and diameter of tracts, for which reason tract diameter should not exceed 22 Fr. In the majority of subsequent pediatric PNL series, the risk of intraoperative complications has been shown to decrease with use of small-size instruments[11,14]. Indeed, new PNL modifications aimed at reducing complication levels still further, such as tubeless PNL, ultramini-PNL and micro-perc, have been described[15-17]. However, despite all these modifications and high success rates, major complications such as neighboring organ injury, severe hemorrhage and urosepsis are still reported at levels of up to 10%, and the debate over whether the procedure is truly non-invasive continues[18,19].

RIRS is a comparatively new concept in pediatric patients. Before embarking on the details of this method in children, it will be useful to briefly review the stages by which it arrived at its present-day position. Use of this technique for treating renal stones was first described in 1983, by Huffman *et al*[20], when a large stone located in the renal pelvis was broken with the help of a ureteroscope with a rigid rod-lens structure and an ultrasonic lithotripter. Although the authors maintain that stones in the upper ureter and renal pelvis can be effectively and safely treated using small caliber rigid devices, the technique as it stands has not achieved popularity, due to its low success rate and high level of complications. Retrograde treatment of renal stones has been able to enter into widespread use only with the development years later of flexible ureteroscopes (f-URS) possessing fiberoptic technology and retrieval instruments with a nitinol structure and the simultaneous entry into use of Ho:YAG laser in intracorporeal lithotripsy[21].

Following the first description of the pediatric ureteroscopy (URS) by Ritchey *et al*[22] in 1998, the development of URS decelerated due to concerns over existing instruments not being of suitable sizes for children, the inadequacy of optic imaging systems and development of complications post-URS in child patients, such as ischemia, injury, perforation, stricture and vesicoureteral reflux, and this delayed the use of RIRS in this patient population[22,23]. However, the development in subsequent years of more resistant and finer (< 8 Fr) ureteroscopes and auxiliary nitinol instruments, the improvement of optic system quality, the entry into use of Ho:YAG laser and, parallel, to all these technological advances, an increase in surgeon experience with flexible URS led to the technique also starting to be used in child patients.

The first wide series on the subject of pediatric RIRS was published by Cannon *et al*[24] in 2007. Twenty-one child patients (13 girls, 8 boys) administered RIRS due to lower pole renal stone and with a mean stone size of 12 mm were included in that study. After a mean 11 mo of follow-up, stone-free status was achieved at a level of 76%, and no intra- or postoperative complications were reported in any patient. Passive dilatation was applied using preoperative stent in 38% of patients, while a ureteral access sheath was used in 43% (Table 1). However, the upper age limit was set at 20 (mean 15.1) in that publication reporting a pediatric series and a great many cases were postpubertal (67%) patients.

A 100-case series was published by Smaldone *et al*[25] in that same year. Although 37% of the stones in that series were intrarenal (renal pelvis 6%, upper pole 10% and lower pole 17%). Mean stone size was 8.3 mm and mean patient age was 13.2 years, with 49% of cases being prepubertal children. Passive dilation was applied in 54% of cases, ureteral active dilatation with a coaxial dilator to 70% and ureteral access sheath to 24%. Stone-free status was achieved in 91% of patients, while ureteral perforation developed in 5 and ureteral reimplantation was required due to stricture in the late period in one. However, no correlation was reported in that study between the complications that developed and use of ureteral access sheath or ureteral dilation.

In a study from 2008, Tanaka *et al*[26] published the

Table 1 Outcomes of pediatric retrograde intrarenal surgery procedures in published series

Ref.	Patient No.	Mean age, yr	Mean stone size (mm)	Passive dilation	Active dilation	Ureteral access sheat	Success	Complications
Cannon *et al*[24]	21	15.2 (1-20)	12 (± 5.9)	38%	81%	43%	76%	0%
Smaldone *et al*[25]	100	13.2 (± 5.4)	8.3 (± 5.3)	54%	70%	24%	91%	Ureteral stricture (1%) Ureteral perforation (5%)
Tanaka *et al*[26]	50	7.9 (1.2-13)	8 (1-16)	56%	35%	48%	58%	0%
Kim *et al*[23]	167	5.2 (1-18)	6.1 (3-24)	57%	-	?	99%	0%
Unsal *et al*[27]	16	4.2 (0-7)	11.5 (8-17)	37.50%	29.40%	17.60%	88%	Ureteral perforation (n = 1)
Erkut *et al*[28]	65	4.3 (0-7)	14 (7-30)	-	100%	100%	93%	27% complication rate
Abu Ghazaleh *et al*[29]	56	8.2 (6-14)	12 (9-15)	100%	-	-	100%	Urinary infection (n = 3) Hematuria (n = 1)
Resorlu *et al*[30]	95	9.4 (0-17)	18 (10-30)	?	18.90%	63.10%	85%	% 8.4 complications

results from 50 pediatric patients with a mean age of 7.9 (1.2-13.6 years) and receiving RIRS due to renal stone. Mean stone size was 8 mm (1-16) mm; 58% of cases remained stone-free at long-term follow-up with a single procedure, while an additional procedure was required in 36%. Success rate was correlated with stone size (P = 0.005), while additional procedure requirement was correlated with both stone dimension (P = 0.002) and patient age (P = 0.04). However, the text refers to procedures being performed for stones as small as 1 mm.

Kim *et al*[23] reported the experience with flexible URS of the Philadelphia Children's Hospital, announcing the results of 170 procedures performed on 167 pediatric patients with a mean age of 62.4 mo (range, 3-218). Mean stone dimension was 6.1 mm (range, 3-24), with stones in 60% of cases being intrarenally located (28% upper ureter stone, 12% upper ureter stone). Access to the ureter could not be established in 57% of patients, for which reason a stent was inserted and left to passive dilatation. Ureteral access sheath was only used in cases with a heavy stone burden or receiving passive dilatation, although no level of use was cited. Following surgery lasting a mean 107 min (range, 72-196), 100% of patients with stones smaller than 10 mm achieved stone-free status, and 97% of those with stones larger than 10 mm. No intra- or postoperative complications were reported in this series.

Unsal *et al*[27] examined the reliability of this procedure in pre-school children, evaluating 16 child patients with a mean age of 4.2 years (range, 10 mo-7 years). Mean stone dimension was 11.5 mm (range, 8-17); 37.5% of patients received double-j stent (passive dilatation), active dilatation was performed on 29.4%, and ureteral access sheath was used in 17.6%. One hundred percent of patients with stones smaller than 10 mm and 81% of those with larger stones achieved stone-free status. Ureteral perforation developed during ureteral dilatation in one case. That study showed that RIRS can successfully be used in infants aged under 1 year, describing the youngest (10 mo) case treated using the procedure in the literature. Subsequently, Erkurt *et al*[28] showed with a wider case series that the procedure can be safely used in pre-school age children. In that study, a ureteral access sheath was used in each case, and complication rates of 27% and stone-free status of 93% were reported.

In a study evaluating the efficacy of RIRS in prepubertal children Abu Ghazaleh *et al*[29] reported the results from 56 children (age 6-14) with stones less than 15 mm in size. Pre-procedural passive dilatation was performed in all cases, and electrohydraulic lithotripsy was used for stone breaking. At the end of 34-mo follow up, 100% stone-free status was reported and no intraoperative complication developed, although urinary infection was reported in 3 patients in the postoperative period and macroscopic hematuria in one. The use of a lithotripsy technique that has been abandoned due to high complication levels, each patient being subjected twice to anesthesia with the application of passive dilatation and stones inside the renal pelvis being broken with rigid URS represent question marks in that study, despite such high success rates.

In a multi-center comparative analysis (Table 2), Resorlu *et al*[30] compared the outcomes of patients with renal stones 10-30 mm in size treated with mini-perc (n = 106) or RIRS (n = 95). Stone-free status levels were 84% for RIRS and 86% for mini-perc, while complication levels were 8.4% for RIRS and 17% for mini-perc. All complications in both groups were minor (Clavien Ⅰ-Ⅱ), and no major complications (Clavien Ⅲ-Ⅳ) were observed. However, transfusion requirement at a level of 6% was reported in the mini-perc group. In addition, exposure to fluoroscopy, length of surgery and length of hospital stay were all lower in the RIRS group. Although RIRS appears to offer more advantages than mini-perc, when preoperative factors were assessed, there was a significant difference between the two groups in terms of stone size (23.7 mm *vs* 14.3 mm), and this was cited as a significant limitation in the text. When the groups

Table 2 Comparison of percutaneous nephrolithotomy and retrograde intrarenal surgery data in a recent study by Resorlu *et al*[30] *n* (%)

	PNL	RIRS
No. patients	106 (52.7)	95 (47.3)
Mean fluoroscopy time ± SD (s)	113.7 ± 36.6	33.2 ± 14.6
Mean operative time ± SD (min)	76.3 ± 21.2	42.1 ± 15.3
Mean hospitalization time ± SD (d)	3.1 ± 1.2	1.7 ± 0.6
Initial stone-free rate	91 (85.8)	80 (84.2)
Stones ⩾ 20 mm	78/93 (83.9)	4/8 (50.0)
Stones < 20 mm	13/13 (100)	76/87 (87.3)
Final stone-free rate	100 (94.3)	88 (92.6)
Minor (Clavien Ⅰ-Ⅱ) complications	18 (17.0)	8 (8.4)
Major (Clavien Ⅲ-Ⅳ) complications	-	-
Blood transfusion rate	7 (6.6)	-

PNL: Percutaneous nephrolithotomy; RIRS: Retrograde intrarenal surgery.

were compared again in terms of stone size, success rates of 87% in the RIRS group and 100% in the mini-perc group were obtained in stones of 1-2 cm, and 50% in the RIRS group and 84% in the mini-perc group in stones of 2-3 cm. The success rate of RIRS falls markedly when stone size exceeds 2 cm. In the light of these results, the authors reported that RIRS is superior to mini-perc in stones less than 2 cm in size, but that mini-perc has a better success rate with larger stones, and that RIRS can represent an alternative to it.

As technology has advanced, thinner and more resistant ureteroscopes and lithotripters with a greater deflection capacity and image quality have been developed[31]. This has made it easier to break stones at all points in the kidney. In the light of all these advances and increasing experience, the success rate of RIRS has increased and indications for use have widened, and it has now assumed a place together with SWL and PNL methods among treatment options for renal stones in children.

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REVIEW

Prostatic surgery associated acute kidney injury

Elerson Carlos Costalonga, Verônica Torres Costa e Silva, Renato Caires, James Hung, Luis Yu, Emmanuel A Burdmann

Elerson Carlos Costalonga, Verônica Torres Costa e Silva, Renato Caires, James Hung, Luis Yu, Emmanuel A Burdmann, Department of Nephrology, Cancer Institute of São Paulo, University of São Paulo Medical School, São Paulo 01246-000, Brazil
Luis Yu, Emmanuel A Burdmann, Division of Nephrology, University of São Paulo Medical School, São Paulo 01246-903, Brazil
Author contributions: Costalonga EC, Costa e Silva VT, Caires R, Hung J, Yu L and Burdmann EA contributed equally to this work.
Correspondence to: Elerson Carlos Costalonga, MD, Department of Nephrology, Cancer Institute of Sao Paulo, University of Sao Paulo Medical School, Av Dr Arnaldo 251, 2o Andar (Porta 2), São Paulo 01246-000, SP, Brazil. elersonc@yahoo.com.br
Telephone: +55-11-38932332 Fax: +55-11-30882267
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Abstract

Acute kidney injury (AKI) is associated with extended hospital stays, high risks of in-hospital and long-term mortality, and increased risk of incident and progressive chronic kidney disease. Patients with urological diseases are a high-risk group for AKI owing to the coexistence of obstructive uropathy, older age, and preexistent chronic kidney disease. Nonetheless, precise data on the incidence and outcomes of postoperative AKI in urological procedures are lacking. Benign prostatic hyperplasia and prostate cancer are common diagnoses in older men and are frequently treated with surgical procedures. Whereas severe AKI after prostate surgery in general appears to be unusual, AKI associated with transurethral resection of the prostate (TURP) syndrome and with rhabdomyolysis (RM) after radical prostatectomy have been frequently described. The purpose of this review is to discuss the current knowledge regarding the epidemiology, risk factors, outcomes, prevention, and treatment of AKI associated with prostatic surgery. The mechanisms of TURP syndrome and RM following prostatic surgeries will be emphasized.

Key words: Acute kidney injury; Prostatic hyperplasia; Prostate cancer; Transurethral resection of the prostate; Prostatectomy; Rhabdomyolysis

Core tip: Postoperative acute kidney injury has a significant effect on patient outcomes and has been associated with longer hospital stays, high risks of in-hospital and long-term mortality. Urology patients are a high-risk group for acute kidney injury (AKI) because of the common occurrences of obstructive uropathy, older age, and chronic kidney disease, as well as postoperative complications. The purpose of this review is to discuss the current knowledge regarding the epidemiology, risk factors, outcomes, prevention, and treatment of AKI associated with prostatic surgery.

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INTRODUCTION

Prostatic diseases are associated with morbidity and mortality in elderly men. Benign prostatic hyperplasia (BPH) is the fourth most common diagnosis in older men[1]. Meanwhile, in developing countries, prostate cancer (PCa) is the most common solid neoplasm, and it is the currently second-leading cause of cancer mortality for men. Beyond conservative medical therapy, the surgical approach remains an important step for the treatment of these diseases[2].

A number of surgical techniques have been devel-

Table 1 Surgical approach to the treatment of benign prostatic hyperplasia and prostate cancer

Benign prostatic hyperplasia
Transurethral resection
Open simple prostatectomy
Electrovaporization
Laser prostatectomy
Holmium laser enucleation
GreenLight™ laser vaporization
Transurethral incision
Transurethral needle ablation
Prostate cancer
Radical Prostatectomy
Open (retropubic or perineal)
Minimally invasive
Laparoscopic
Robot-assisted

oped over the years to treat prostate diseases (Table 1). In recent decades, new surgical methods for treating BPH and PCa have been developed, such as laser- and robot-assisted prostatectomy. Although these procedures have been associated with lower postoperative complication rates in some studies, their efficacy and long-term robustness remain to be proven. At present, the gold-standard treatments for PCa and BPH are still open radical prostatectomy (ORP) and transurethral resection of the prostate (TURP), respectively[2].

In surgical patients, outcomes are strictly dependent on the occurrence of complications. Urology patients are a high-risk group for acute kidney injury (AKI) because of the common occurrences of obstructive uropathy, older age, and CKD, as well as bleeding and urinary obstruction, that sometimes follow the surgery. However, precise data on the incidence and outcomes of postoperative AKI in urological procedures are lacking[3].

Observational studies that compared different surgical approaches to treating prostatic diseases rarely monitored AKI as a relevant early postoperative complication. For instance, in a prospective multicenter analysis of the postoperative complications of 10654 patients subjected to transurethral prostatic surgery for BPH, no AKI case was reported[4]. Similarly, in a prospective observational study of 280 patients subjected to laparoscopic (LSP) or open simple prostatectomy (OSP) for BPH, three patients developed AKI (defined as a 50% rise above the patient's baseline serum creatinine level)[5]. Moreover, Marmiroli *et al*[6] studied the postoperative outcomes of 100 patients ⩾ 75 years old who had undergone TURP or OSP for BPH and found an incidence of 1% of AKI that required dialysis in this high-risk population. As is the case with the literature on BPH, AKI seems to be infrequently or underreported in patients undergoing ORP for PCa. Recently, one large retrospective analysis, including more than 77000 patients, examined outcomes after robot-assisted radical prostatectomy (RARP) and ORP, and AKI was not cited as a major complication[7].

Based on the available literature, episodes of severe AKI after prostate surgery appear to be unusual. Because the current recommended Kidney Disease Improving Global Outcomes (KDIGO) AKI definitions[8] (Table 2) have never been employed in this situation, acute subclinical serum creatinine (SCr) increases have never been systematically monitored across prostatic surgery outcome studies, and the exact incidence of AKI cannot be determined. However, AKI secondary to TURP syndrome has been consistently described[9,10]. Furthermore, a number of small case studies and case reports of rhabdomyolysis (RM)-associated-AKI after radical prostatectomy have also been published[11-13].

Table 2 Kidney disease improving global outcomes acute kidney injury definitions

AKI is defined as any of the following
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; or
Urine volume < 0.5 mL/kg per hour for 6 h

AKI: Acute kidney injury.

This review outlines AKI associated with prostatic surgery, emphasizing the mechanisms of TURP syndrome and RM following prostatic surgeries. The surveillance, prevention and treatment of these complications will also be addressed.

TURP AND AKI

TURP requires the use of an irrigating fluid to expand the operating field and to wash away debris and blood. TURP syndrome is a clinical complication caused by the systemic absorption of the irrigating fluid and is characterized by a combination of hyponatremia and fluid overload, causing potential damage to the cardiovascular, renal and nervous systems[14,15].

The incidence of TURP syndrome ranges from 1.0% to 8% of reported TURPs and appears to be decreasing in recent years[16,17]. Mortality rates are generally between 0.2% to 0.8%, but rates as high as 25% can occur if severe TURP syndrome develops[10,18].

TURP syndrome can be defined as sodium of 125 mEq/L or less after TURP with two or more circulatory and/or neurological symptoms[19]. However, no universal defining criteria have been adopted by all centers, and not all studies have used clear definitions of TURP syndrome. Of note, the definition and severity of kidney dysfunction are not always detailed in TURP syndrome, and no studies have used the definition proposed by the most recently updated Kidney Disease Improving Global Outcomes (KDIGO) AKI guidelines. Similarly, there are scant data on late prognoses because few studies have reported on outcomes more than three to six months after the event. In particular, the incidence of CKD resulting from TURP syndrome is unknown. Many aspects of TURP syndrome are still unclear, and its overall burden is not completely determined.

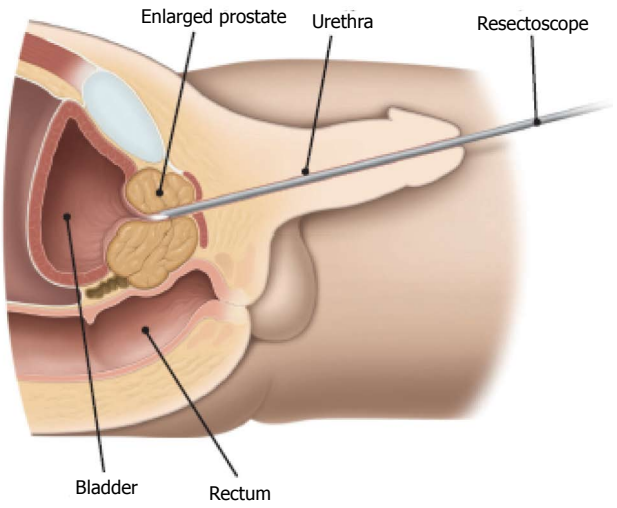

Figure 1 Surgery through the urethra. Courtesy of the European Association of Urology.

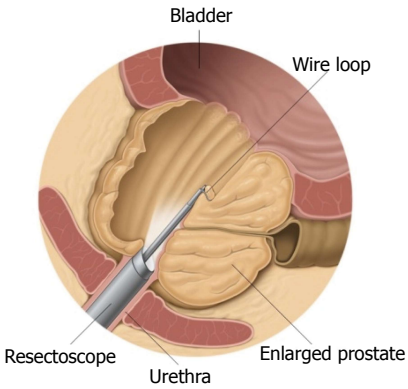

Figure 2 The resectoscope removes parts of the prostate tissue during transurethral resection of the prostate. Courtesy of the European Association of Urology.

RISK FACTORS

Although important differences appears according to the compositions of the irrigation fluids, the most important risk factor for TURP syndrome is the amount of fluid absorbed, which can vary from < 300 to 3000 mL[20]. After the absorption of 1.0 mL of fluid, serum sodium reduction is approximately 6 to 8 mEq/L, and it can achieve 20 mEq/L after absorption of 3.0 L[21]. The rate of fluid absorption is most likely also an important risk factor, and absorption in excess of 200 to 300 mL per 10 min is more frequently related to hyponatremia[22]. The risk of the TURP syndrome is higher in the presence of bleeding, longer resection times, higher absorption of irrigating fluid and prostate size larger than 45 g[23]. Smoking is a factor known to be associated with the increased risk of TURP syndrome , but the malignancy does not seem to be associated with the increased risk[24].

FLUID ABSORPTION MECHANISM

In TURP, a resectoscope loaded with a diathermy loop is introduced into the bladder to resect prostatic tissue (Figures 1 and 2). TURP typically takes 60 min, and approximately 10 to 20 liters of irrigating fluid are generally required. During TURP, irrigation pressure is regulated to achieve 60 mmHg, a much higher threshold than that for physiological intravesical pressure, which peaks at 25 mmHg during micturition[25]. When prostate tissue is resected, veins may be severed, and irrigating fluid can be rapidly absorbed into the vascular system. Intravenous fluid absorption begins when the fluid pressure exceeds the prostate venous pressure by approximately 12.5 mmHg[26], and it rarely ceases once it begins[20]. Most of the fluid absorption takes place during the second half of the resection when the resectoscope approaches the vein plexus, reaching larger vessels, and an extended area for fluid influx is opened[20]. Herein, small amounts of fluid are always absorbed during TURP, and absorption in excess of one liter has been reported to occur in 5%-20% of procedures[27,28]. Extravasation can occur after instrumental damage of the prostatic capsule or the bladder wall during TURP, which occurs in at least 10% of surgeries (Figure 3). The fluid pressure must only exceed an intra-abdominal pressure of approximately 3.72 mmHg for extravasation to occur, and several liters of irrigating fluid will be rapidly deposited in the periprostatic, retroperitoneal or intraperitoneal spaces[29]. The fluid is absorbed by lymphatic drainage, a slower process than vascular intake, which can translate into a delayed reduction in serum sodium compared with classic intravascular absorption. Extravasation contributes to TURP syndrome development in approximately 20% of cases[30].

IRRIGATION FLUID PHYSIOPATHOLOGY

An ideal irrigating fluid should be isotonic, nonhemolytic, electrically inert, nontoxic when absorbed, not metabolized, and transparent; should not influence blood osmolality; should be rapidly excreted; and should not cause significant expansion of extracellular fluid volume. However, no such solution exists; each irrigating fluid has particular physicochemical and pharmacokinetic characteristics and each comes with its own potential complications.

Distilled water

Distilled water (D.W.) was the first irrigating fluid used in TURP surgeries and is still often used because of its advantages: clear visual field, absence of electric conductivity, volume of distribution equal to the body's full water content, and lower cost[31,32]. After the description of cases of hemolytic AKI[33,34], iso- or hypo-osmolar nonhemolytic solutions other than D.W. were introduced to overcome this issue. D.W. continues to be used, but it should be restricted to laser TURP or to procedures that are expected to be short and performed by very skilled surgeons with all precautions taken to avoid the risk of

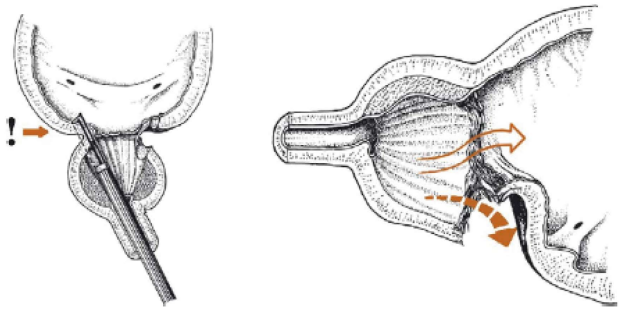

Figure 3 Division of the bladder neck with subsequent extraperitoneal extravasation. From Rassweiler *et al*[28].

TURP syndrome[32].

Glycine

Glycine (Gly) is a neutral, nonessential amino acid, used as an irrigating fluid solute since 1949. A 1.5% Gly solution is commonly used in TURP because it is nonconductive, hypo-osmotic (osmolality of approximately 200 mOsm/L), and nonhemolytic and it provides good optical visibility[35]. This amino acid spreads through intracellular compartments, creating osmotic water movement into cells, which gradually increases serum sodium and minimizes the risk of severe hyponatremia. However, Gly presents some drawbacks and is commonly associated with TURP syndrome. It has cardiotoxic properties, and can cause serious visual disturbances due to retina damage[36]. Hyper-ammoniemic encephalopathy[37] and hyperoxaluria have been associated with Gly metabolites[38].

Sorbitol solutions

Solutions based in sorbitol are frequently used in the United States of America as irrigating fluids, typically in the concentration range of 2.2% to 3% and frequently in association with mannitol[39]. Sorbitol is non-electrolytic, has an osmolality of approximately 180 mOsm/L, and clears rapidly from the plasma after its transformation to fructose and glucose by liver cells. Sorbitol is considered a safe irrigating fluid and is associated with low rates of TURP syndrome.

Mannitol

Mannitol is frequently used as an irrigating fluid in concentrations of 3% or 5% solution (osmolalities of 175 and 275 mmOsm/L, respectively)[40]. Mannitol is nonconductive and nonhemolytic and gives a satisfactory visual operating field. Mannitol is excreted unchanged in the urine, promoting osmotic, electrolyte-free diuresis, which could help to increase serum sodium concentration. Mannitol is considered a suitable irrigating fluid that is associated with low rates of TURP syndrome.

Physiologic saline

Saline solution cannot be used as an irrigating fluid during the standard prostatic resection because its dissipates the electrical current of bipolar resectoscope, therefore preventing both cutting and coagulation. Normal saline (0.9%) osmolality is approximately 300 mOsm/L, which makes it the most suitable irrigation fluid for TURP. Very few cases of TURP syndrome have been described with this solution. Fluid overload is more likely during the absorption of normal saline solution due to the higher volume expansion[41]. In addition, the excessive sodium chloride infusion can cause hyperchloremic acidosis.

CLINICAL AND LABORATORY PRESENTATION

TURP syndrome occurs from 15 min to 24 h after prostate resection. The incidence and severity of TURP syndrome symptoms increase progressively as more solution is absorbed. When the threshold of 3.0 L is exceeded[10], the symptoms are severely impaired.

Some symptoms may be noticed in the intraoperative period. Vague, nonspecific symptoms may occur such as the sense of being unwell[27], transitory feeling of burning, accompanied by nausea, restlessness and headache. Neurologic events are more frequently observed when glycine solutions are used and in patients with decreases in serum sodium of 10 mEq/L or more[42]. Focal or generalized seizures and altered mental states can occur. This is generally associated with irrigant absorption levels as high as 2.0 to 3.0 L. Brain stem herniation, persistent brain injury and death have also been reported[43]. Visual disturbances, including transitory blindness have been observed, mostly related to glycine solution[36].

Patients may develop both hypervolemic and hypovolemic complications. Bradycardia and hypotension at the end of the operation, or immediately after, are often early signs suggesting TURP syndrome[44]. Shortness of breath and pulmonary edema can occur in surgeries where mild/less severe bleeding is observed[45]. Chest pain and hypertension have also been observed in 5% of the patients, particularly when more than 1 L is absorbed[46]. Small elevations in cardiac enzymes can occur, especially when Gly solution is used[47].

Most patients subjected to TURP are elderly with coexisting diseases, reduced functional heart and kidney reserves and less capacity to endure stress[48]. CKD patients are also at exacerbated risk for TURP syndrome[15]. AKI has been reported in TURP syndrome patients; it is typically oliguric and can be observed as early as the first postoperative day. Bilen *et al*[9] assessed a group of 439 patients who had undergone TURP using mostly distilled water as the irrigating fluid. AKI defined as an increase in postoperative SCr > 1 mg/dL occurred in 16 (3.64%) of the patients.

Severe TURP syndrome, defined by a drop in serum sodium concentration to < 120 mEq/L, is a rare but well-described event in the specialized literature, characteristically reported when more than 3.0 L of irrigating fluid are absorbed[49]. A review of 24 severe

cases in which Gly 1.5% was used as the irrigating fluid demonstrated neurological complaints in 92%, cardiovascular signs in 54%, visual disturbances in 42%, and gastrointestinal symptoms in 25% of these patients, with a mortality rate of 25%. AKI is observed in more than 50% of cases of severe TURP syndrome, sometimes requiring renal replacement therapy (RRT)[50].

Hyponatremia (< 135 mEq/L), a hallmark of the syndrome, is seen in nearly all patients, and it is more frequently observed at the end of surgery (or one to two hours subsequent)[51]. Hyponatremia might be transitory and could go undetected if serum sodium is assessed more than three hours after surgery completion. Although most irrigating fluids are hypo-osmolar (approximately 200 mOsmol/L), compared with normal serum osmolality (approximately 290 mOsm/L), hypo-osmolality in TURP syndrome is less pronounced than that observed in other hyponatremia etiologies because the solute contents of irrigating fluids (Gly, sorbitol, mannitol) prevent large osmolality reductions[52]. In TURP syndrome, serum osmolar gaps reflect the concentrations of the infused/absorbed irrigants and can achieve 30 to 60 mOsm/kg[53]. Herein, serum osmolality should be measured in all TURP syndrome patients.

PATHOPHYSIOLOGY

Hemodynamics

The rapid volume expansion which can reach up to 200 mL/min can cause hypertension and reflex bradycardia. Hypertension coupled with hyponatremia can trigger pulmonary edema and hypovolemia due to net water flux from the intravascular space into the pulmonary interstitium[54]. In sequence, a major hypokinetic hemodynamic phase ensues, distinguished by low cardiac output, hypovolemia and hypotension[44,55].

Natriuresis has been highlighted as a key element in promoting dilutional hyponatremic shock and explains why hypovolemic hypotension persists despite the administration of large amounts of fluid. The osmotic diuresis leads to sodium losses and occurs when the renal reabsorption mechanisms are either overwhelmed (Gly) or absent (mannitol)[56]. The capacity of the kidneys to control the urine's composition is then undermined, and a number of small solutes, including amino acids and sodium, are ultimately lost from the body.

Other factors that contribute to the hemodynamic changeover include metabolic acidosis[57], acute hypothermia[58], release of endotoxins into the bloodstream[59], and depression of the heart conductivity system[47].

Central nervous system

Even moderate osmolality reduction could result in a fluid influx into the cerebral space, leading to brain edema[59,60]. Other factors that contribute to central nervous system impairment in TURP syndrome, such as the very low serum sodium concentration itself, are Gly toxicity and the accumulation of its metabolic derivates (ammonia, serine, and/or glyoxylate)[37,61].

Renal disease

AKI following TURP has been reported since 1947, and a variety of mechanisms have been proposed for its development[62,63]. When sterile water was used for irrigation, intravascular hemolysis was thought to be the principal insult[64]. Hemolysis takes place in the blood as well as in the bladder, where hemolyzed blood is absorbed. In both cases, hemoglobinuria develops and renal injury occurs through a number of pathways. Heme proteins have powerful oxidant effect, it can trigger renal vasoconstriction[65] and under acidic conditions, precipitate with Tamm-Horsfall proteins contributing to tubule obstruction. Hemolysis should be investigated in all AKI events after TURP[34] although these events have become rare with the observed change to other irrigating fluids, and other pathogenic mechanisms have been described.

Hyponatremia-associated RM resulting in AKI has been reported as a complication following TURP in a small number of cases[66]. After a number of hours, muscle cellular swelling induced by hyponatremia will peak because of the potassium outflux from the muscle cells into the extracellular fluid. Hyponatremia also reduces the concentration gradient for sodium entry into the muscle cells, resulting in a decreased outward flux of calcium, which leads to increased intracellular calcium[67] destroying the cell structure[68]. At this point, all patients with AKI-related TURP syndrome should be screened for RM.

It has been suggested that "hemodynamic" acute tubular necrosis is an important cause of AKI in some patients after TURP. Hypotension coupled with osmotic diuresis results in ischemic kidney episodes[69]. Another possible mechanism is sudden kidney cell swelling as a result of acute hypo-osmolality, similar to the development of central nervous system edema[70].

More recently, Kim *et al*[71] described three cases of AKI after laser vaporization of the prostate using distilled water as the irrigating fluid. All patients developed significant hyponatremia, and two of them required RRT[71]. Histological findings were tubular cell necrosis and Tamm-Horsfall protein stasis with regurgitation into the Bowman capsule accompanied by an amount of eosinophilic interstitial infiltrate. Special staining for hemoglobin and myoglobin had negative results, and there was no histologic evidence of ischemic damage. Hyponatremia and hemodynamic mechanisms could not be ruled out, but this scenario strongly suggested direct damage to the tubular epithelium by urinary stasis and the backflow of the irrigating fluid, hemoglobin, and prostate secretions resulting from high intravesical pressure. This report suggests transient vesicoureteral reflux as a new pathogenic mechanism of kidney injury in TURP syndrome, although this has yet to be confirmed by other studies[71].

The physiopathology of renal injury in TURP syndrome is complex, multifactorial and not completely un-

derstood. It is most likely that one or more of a number of mechanisms are implicated.

PREVENTION

Prostate gland size and operative time

There are no definitive data establishing an operative time threshold beyond which excessive fluid is absorbed, but after one hour of surgery, the risk increases significantly[72], and after that point, the patient´s overall status, the volume of fluid absorbed, and the anticipated time to completion should be reassessed[73]. For patients with large glands and expected long procedures, it is advised that bipolar TURP or other low-risk techniques be used.

Fluid bag height

Fluid is infused using the force of gravity (elevating the infusion bag to different heights) or by inflating a large blood pressure cuff around the infusion bag. Placing the irrigating fluid bag at 60 cm above the operating table has been advised to avoid fluid absorption. Nevertheless, two studies including almost 600 patients did not demonstrate conclusive benefits in higher fluid bag[74,75].

Intraprostatic vasopressin injection

Transrectal intraprostatic vasopressin (IPVP) injected at the operating site is considered to vasoconstrict intraprostatic vessels and reduce blood loss and fluid absorption during TURP[76]. IPVP appears to be effective and could be used in patients with large prostates or when fluids associated with higher incidence of TURP syndrome such as Gly and D.W. are used.

Low-pressure irrigation

Irrigating fluid absorption is less pronounced when TURP is performed under low pressure. A number of measures to maintaining low intra-bladder pressure has been used, such as suprapubic catheterization, intermittent drainage of the irrigating fluid and continuous flow resection[77].

Bipolar TURP

Bipolar resection of the prostate utilizes a specialized resectoscope loop that incorporates both the active and the return electrodes. The bipolar loop resects, coagulates, vaporizes and transects the tissue. Because the bipolar resectoscope uses a 0.9% sodium chloride solution as the irrigation fluid, the risk of TURP syndrome is eliminated, allowing for longer and safer resections[78]. Omar *et al*[79] recently published a systematic review and meta-analysis comparing bipolar and monopolar TURP. The study comprised 24 trials, and no case of TURP syndrome was observed in the bipolar group. Therefore, bipolar TURP is a safe procedure that is suitable for high-risk patients such as CKD patients and those with large glands.

Laser and vaporization prostatectomy vs TURP syndrome

Photoselective vaporization of the prostate (PVP) and other laser techniques are novel procedures that promote effective hemostasis with nearly bloodless removal of prostate tissue and minimal absorption of irrigating fluid[80]. PVP can use normal saline as the irrigating fluid, and laser therapies have been reported to successfully treat patients with very large prostates (> 100 g) and those with ongoing oral anticoagulation[71].

Trans-operatory monitoring of fluid absorption

A key aspect to preventing the development of TURP syndrome is monitoring the fluid absorption during the endoscopic surgery. A number of alternatives have been attempted to achieve this goal. Volumetric fluid balance, the difference between the amount of irrigating fluid used and the output volume, is the most commonly used technique to estimate fluid absorption. However, other variables such as bleeding, irrigant leakage, urinary output (diuresis), and blood dilution make this a comparatively unreliable tool[81]. Although it has limitations, volumetric fluid balance is simple, noninvasive, and inexpensive, and it should be performed in every surgery.

The gravimetric method is often used and requires that the surgery take place on a bed-scale. The method relies on the supposition that increases in the body weight are generated by fluid absorption. Bleeding and intravenous infusions must be considered in recordings, that must be carried out when the bladder is empty[82].

To minimize the risk of hyponatremia, an intraoperative approach based on the amount of absorbed fluid is suggested[27]. If more than 1.0 L of fluid is estimated to be absorbed, the surgical team should temporarily halt the procedure, fluid inflow should cease and serum sodium should be measured. If mental and cardiovascular status are maintained, surgery can be resumed for as short a period as possible. If more than 2.0 L of fluid were absorbed, hemorrhage points should be coagulated and the procedure should be terminated. Serum sodium concentration and mental status should be closely monitored.

MANAGEMENT AND TREATMENT OF TURP SYNDROME

The urologic surgeon and the anesthetist should be aware of the development of TURP syndrome. Asymptomatic and stable patients should be kept under observation. Specific treatment is not required, particularly if sodium reduction is below 5 mEq/L. In these cases, if renal function is adequate, excretion of the excess water and metabolism of the infused solute will rapidly correct the hyponatremia[83]. There is no specific treatment for the visual symptoms of Gly intoxication, and even blindness is typically resolved in 24 h without the need for specific treatment[84].

Hypertonic saline is indicated to replace the excreted sodium in symptomatic patients with marked hyponatremia, particularly those who have substantially reduced serum osmolality or a cerebral edema[85]. Hypertonic

saline in a 3% solution can be given as a 100 mL bolus at 10-min intervals or continuously infused (approximately 1.0 L in 12 h). Rapid correction of hyponatremia is most likely safe following TURP because of the extremely short duration of hyponatremia and the restricted time for cerebral adaptations. A reasonable and safe strategy is to increase the serum sodium concentration to up to 12 mEq/L in the first 24 h. Furosemide may be used to reverse the fluid overload, although furosemide increases natriuresis and hyponatremia, further reducing plasma volume and increasing the cellular edema[86,87]. Furosemide should not be routinely given in TURP patients in the absence of fluid overload.

Hemodialysis will rapidly correct hyponatremia, osmotic derangements, and volume expansion and remove the non-electrolyte solute and its toxic metabolites (Gly, sorbitol, mannitol). It has been used in symptomatic patients with severe renal disease and in patients with severe neurologic symptoms and marked hyponatremia[53].

In the case of important fluid extravasation and large fluid collections, it might be necessary to carry out a open surgical drainage by percutaneous drainage[88].

ANESTHESIA AND TURP SURGERY

For years, spinal anesthesia was considered the anesthetic technique of choice for TURP. Spinal anesthesia is considered to reduce the risk of pulmonary edema, to decrease bleeding risk and to allow a prompt diagnosis of neurologic symptoms[89]. However, spinal anesthesia reduces central venous pressure, affecting prostate venous pressure, which could result in greater absorption of the irrigating fluid[89]. During general anesthesia, the detection of TURP syndrome may be more difficult, based on afterward changes in blood pressure and electrocardiographic abnormalities[89]. In fact, the best anesthetic technique for TURP procedures has not yet determined.

RADICAL PROSTATECTOMY AND RHABDOMYOLYSIS

Radical prostatectomy is the main surgical treatment for PCa. Radical retropubic prostatectomy (RRP) is performed with patients in the supine position, while in radical perineal prostatectomy (RPP), patients are placed in an exaggerated lithotomy position[90]. More recently LSP and RARP have been developed, and these minimally invasive procedures are replacing open radical prostatectomy in some countries[2].

The first description of position-induced RM with subsequent AKI after a knee-chest position was in 1953 by Gordon[91]. Renal failure following radical prostatectomy is uncommon, and the incidence of subclinical RM following this procedure is currently unknown[90]. In a recent retrospective study of 175699 patients subjected to robotic or non-robotic radical prostatectomy, the incidence of RM was 0.08%[92]. In a prospective study of 60 patients undergoing RARP and lymph node dissection with prolonged positioning in a steep Trendelenburg position, Mattei *et al*[93] demonstrated that ten patients developed RM (serum creatine kinase > 5000 IU/L). Although AKI following radical prostatectomy appears to be rare, there are a number of case reports that suggest RM secondary to an exaggerated lithotomy position as a cause of AKI in this setting[90,94-96].

AKI associated with myoglobinuria is an important complication of RM[97]. After glomerular filtration, myoglobin is uptake by the tubule epithelial cell through endocytic pathways and is metabolized. The precise mechanisms leading to the glomerular filtration rate impairment are unclear, however some evidence suggests that hypovolemia, vasoconstriction, intraluminal cast formation, oxidative stress and direct heme-induced cytotoxicity are all responsible for kidney injury.

RM after the exaggerated lithotomy position during surgery is usually due the intraoperative development of lower extremity compartment syndrome or from muscle breakdown in the back and gluteal regions[90]. Improperly positioned or inadequately padded patients are prone to ischemia-reperfusion injury from excessive compression. Compartment syndrome was reported in 93% of 46 patients with position-related RM associated with AKI[96]. The lower extremities were most often involved (50%), with muscle swelling and ache being the presenting symptoms[96]. Lithotomy and chest-knee position were the most frequent postures in these patients[96]. Fortunately, compartment syndrome is a rare complication of radical prostatectomy surgery[92].

Rhabdomyolysis associated with prostatectomy prevention and management

To prevent RM associated with surgical position, all pressure points should be protected, including paying special attention to the shoulders, back, and sacrum[90]. The vascular status of the patient's lower extremity should be evaluated with a preoperative vascular examination, and repositioning the lower extremities every two hours could improve perfusion and avoid the occurrence of injury[90]. Some investigators have suggested noninvasive or invasive intraoperative monitoring to assess for impending limb compartment syndrome[94]. Others have recommended obtaining preoperative CPK levels, levels every two hours intraoperatively and levels six to eighteen hours postoperatively if the procedure is expected to be prolonged[11], especially in high-risk groups[93].

An approach to the extensive management of RM was published elsewhere[97]. The approach to RM after prostatectomy is not different from that in other settings. Early and aggressive intravascular volume expansion with crystalloids to restore kidney blood flow and increase urine flow is the cornerstone intervention for preventing and treating AKI. Intravenous fluids should be initiated ideally within the first 6 h after muscle injury, at a rate that maintains a urine output of 300 mL/h or more in adults, for at least the first 24 h[98]. There

Table 3 Suggestions for the prevention and management of transurethral resection of prostate syndrome

Preoperative
Estimate GFR using the CKD-EPI equation
Identify patient risk factors: large prostate gland (> 45 g), heart disease, CKD, and smoking
Advise bipolar TURP or laser techniques for high-risk patients
Intraoperative
Avoid D.W. and glycine as irrigating fluids. Sorbitol and mannitol are good options. Physiologic saline is a safe choice when feasible
Maintain low-pressure irrigation
Consider the use of intra-prostatic vasopressin injection in high-risk patients
Alert surgical team when surgery exceeds one hour
Monitor the volume of absorbed fluid. Consider aborting the procedure if the absorbed volume exceeds 1.0 L and suspend surgery if absorbed volume exceeds 2000 mL
Both spinal and general anesthesia are adequate
Avoid hypotension and central venous pressure reduction and closely monitor the vital signs
Post-operative
Assess serum sodium and serum creatinine in all patients in the immediate postoperative period
Apply KDIGO AKI definitions to AKI diagnosis
If TURP syndrome is diagnosed, initiate medical treatment:
Assess serum osmolality
Maintain asymptomatic and mildly symptomatic patients under close observation
Initiate hypertonic saline 3% infusion in symptomatic patients with marked hyponatremia, reduced osmolality and cerebral edema
Restrict diuretic use to treat fluid overload
If AKI occurs, test for hemolysis and rhabdomyolysis
Consider hemodialysis in symptomatic patients with severe renal disease
Patients that developed AKI should be followed and eGFR equations must be used to identify CKD

AKI: Acute kidney injury; CKD: Chronic kidney disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; D.W.: Distilled water; GFR: Glomerular filtration rate; KDIGO: Kidney disease improving global outcomes; TURP: Transurethral resection of prostate.

is insufficient evidence to support the routine use of bicarbonate-containing fluids, mannitol, or loop diuretics. Hyperkalemia and compartment syndrome are other complications that should be closely surveyed, early diagnosed, and effectively treated.

NEPHROLOGY CONSULTATION

Preoperative nephrology consultation might identify clinical risk factors such as CKD or other comorbidities. To accurate diagnosis and stage CKD we suggest the CKD Epidemiology Collaboration (CKD-EPI) equation. The CKD-EPI equation was published in 2009 and intended to be more generalizable across various clinical settings[99].

TURP syndrome and RM after prostatectomy are generally diagnosed and treated by anesthesiologists and urologists. Nephrologists are typically called only in the most severe cases, which require RRT. Nephrologists should be aware of the risk factors, physiopathology, clinical picture and treatment strategies of TURP syndrome and RM after prostatectomy. An active role of nephrologists in the whole procedure could improve the care of those patients. Nephrologists would be an important add for early identification and treatment of AKI, electrolytes abnormalities, fluid overload, and previous chronic kidney dysfunction.

Although the limitations in the quality of published evidence preclude firm recommendations in this field, some suggestions on preventive and management strategies are depicted in Tables 3 and 4.

CONCLUSION

Severe AKI appears to be a rare event after prostate surgery. However, it is a hazardous surgical complication that increases the risk of permanent kidney damage or death. Because mild SCr elevations were not systematically monitored across the majority of the available studies, the exact incidence of AKI is underdetermined. Studies using the current definitions of AKI are very necessary for providing a better understanding of AKI risk factors and the influence of AKI on patient outcomes after prostate surgeries. Preoperative nephrology consultation might be helpful to better assess kidney function and the presence of other risk factors for AKI, allowing for adequately planning the surgical technique and reinforcing preventive strategies. Affected patients should be followed to assess long-term prognosis and CKD development.

In the last years, several studies about urinary and serum biomarkers for the diagnosis and prognostication of AKI have been published[100,101]. The question that arises is which biomarker is a reliable differential diagnostic tool under which circumstances. As hematuria and need of bladder irrigation are common after prostatic surgeries, the urinary biomarkers might be less suitable in this setting. Further research in this field is warranted before biomarkers can be introduced in the clinical practice.

The available data suggest TURP syndrome as the main mechanism for AKI following prostatic surgery. The absorption of 1-2 L of irrigating fluid occurs in 5%-10% of patients and results in easily overlooked mild TURP syndrome. Fortunately, TURP syndrome inci-

Table 4 Suggestions for the prevention and management of surgical position-related rhabdomyolysis

Preoperative
Identify patient risk factors: obesity, hypovolemia, diabetes mellitus, hypertension, chronic kidney disease, peripheral vascular disease, expected surgery time longer than 5 h
The vascular status of the patient's lower extremity should be carefully assessed with a well-documented preoperative vascular examination
The patient´s volume status should be evaluated
Intraoperative
Ensure correct patient positioning and protect all pressure points
Monitor lower extremities and vascular status
Reposition lower extremities every two hours
Adequate fluid reposition, avoiding hypovolemia
Monitor serum potassium levels
Appropriate operative time, completing the procedure as quickly as possible
Post-operative
Assess serum-CK and SCr 6 h and 18 h postoperatively in high-risk patients
Closely check serum creatinine, potassium levels, and acid-base disorders
Apply KDIGO AKI definitions to AKI diagnosis
Monitor signs of compartmental syndrome and consider fasciotomy if present
If RM syndrome is diagnosed, initiate medical treatment:
Initiate aggressive early fluid repletion;
Treat acid-base and electrolyte abnormalities;
Consider early RRT

CK: Creatine kinase; KDIGO: Kidney disease improving global outcomes; RM: Rhabdomyolysis; RRT: Renal replacement therapy; SCr: Serum creatinine. AKI: Acute kidney injury.

dence appears to be declining because of the use of laser surgery techniques and bipolar circuitry, together with the systematic institution of routine precautions to minimize the risk of TURP syndrome development (*e.g.*, low-pressure irrigation, monitoring the extent of absorption and surgery length). TURP syndrome pathophysiology is complex, multifactorial and not completely understood. The pathogenic mechanisms postulated for AKI development include acute hemolysis, renal interstitial edema, ischemic tubular injury, RM and reflux nephropathy resulting from the absorption of irrigating fluid, dilutional hyponatremia and high intra-bladder pressure. A variety of different irrigating fluids are available, but studies in animals, volunteers and patients show that glycine solution should be avoided. Treatment of symptomatic hyponatremia should be based on the administration of hypertonic saline rather than of diuretics. RRT might be necessary in severe AKI.

RM-induced AKI after radical prostatectomy has also been described in a small number of case reports. These reports identified a number of risk factors, such as exaggerated lithotomy position, preexisting CKD, obesity, and surgery longer than 5 h. In patients at high risk for AKI, every effort should be made to ensure correct positioning during surgery. Early diagnosis of RM and aggressive volemic expansion are the keys to the patient's successful recovery.

It is important for nephrologists to know the main aspects of the physiopathology, clinical presentation, treatment and particular characteristics of AKI in the context of prostate surgery. Close collaboration with the urologist and anesthesiology staff is extremely important to allow for the adoption of preventive measures and to detect any earlier, elusive clinical presentations of AKI.

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REVIEW

Metabolic syndrome and chronic kidney disease: Current status and future directions

GV Ramesh Prasad

GV Ramesh Prasad, Department of Medicine, University of Toronto, Ontario M5C 2T2, Canada
Author contributions: Prasad GVR contributed to this paper.
Correspondence to: GV Ramesh Prasad, MBBS, MSc, FRCP(C), FACP, FASN, Associate Professor of Medicine, University of Toronto, 61 Queen Street East, 9th Floor, Toronto, Ontario M5C 2T2, Canada. prasadr@smh.ca
Telephone: +1-416-8673722 Fax: +1-416-8673709
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Abstract

Metabolic syndrome (MetS) is a term used to denote a combination of selected, widely prevalent cardiovascular disease (CVD)-related risk factors. Despite the ambiguous definition of MetS, it has been clearly associated with chronic kidney disease markers including reduced glomerular filtration rate, proteinuria and/or microalbuminuria, and histopathological markers such as tubular atrophy and interstitial fibrosis. However, the etiological role of MetS in chronic kidney disease (CKD) is less clear. The relationship between MetS and CKD is complex and bidirectional, and so is best understood when CKD is viewed as a common progressive illness along the course of which MetS, another common disease, may intervene and contribute. Possible mechanisms of renal injury include insulin resistance and oxidative stress, increased proinflammatory cytokine production, increased connective tissue growth and profibrotic factor production, increased microvascular injury, and renal ischemia. MetS also portends a higher CVD risk at all stages of CKD from early renal insufficiency to end-stage renal disease. Clinical interventions for MetS in the presence of CKD should include a combination of weight reduction, appropriate dietary modification and increase physical activity, plus targeting of individual CVD-related risk factors such as dysglycemia, hypertension, and dyslipidemia while conforming to relevant national societal guidelines.

Key words: Metabolic syndrome; Cardiovascular disease; Diabetes; Dialysis; Hyperlipidemia; Hypertension; Microalbuminuria; Obesity; Progression

Core tip: Metabolic syndrome is associated with chronic kidney disease but its role in chronic kidney disease incidence and progression has not been established. When both these conditions are present, management should be targeted to individual risk factors for kidney disease progression and cardiovascular disease.

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INTRODUCTION

Metabolic syndrome (MetS), previously called "syndrome X" is a term in popular use for the past quarter century, having first been described in 1988 by Reaven[1] to denote a combination of selected, widely prevalent cardiovascular disease (CVD)-related risk factors. Although the general principle behind using the MetS concept is to denote an increased CVD or diabetes risk, the MetS definition itself is ambiguous though the inclusion of different criteria and assigning them different levels of importance[2-6]. Furthermore, some MetS definitions have been revised over the years, leading to the multiple definitions in current use[2-6]. The four most common definitions are summarized in Table 1. Nonetheless, the general concept is that a MetS patient will have some combination of conditions, among which are insulin resistance or hyperglycemia, dyslipidemia, hypertension, and obesity. Identifying such combinations should add meaningfully to the long-term clinical management of

Table 1 Criteria in definitions of the metabolic syndrome[2-6]

Definition and its criteria	Values
World Health Organization 1998	
Insulin resistance	Type 2 diabetes mellitus or impaired fasting glucose (> 100 mg/dL per 5.6 mmol/L) or impaired glucose tolerance
Plus two of the following:	
Abdominal obesity	Waist-to-hip ratio > 0.9 in men or > 0.85 in women or BMI > 30 kg/m^2
Triglycerides and/or HDL cholesterol	> 150 mg/dL (1.7 mmol/L) and/or < 35 mg/dL (0.9 mmol/L) in men and < 39 mg/dL (1.0 mmol/L) in women respectively
Blood pressure	⩾ 140 mmHg systolic; ⩾ 90 mmHg diastolic
Microalbuminuria	Urine albumin ⩾ 20 μg/min or albumin-to-creatinine ratio ⩾ 30 mg/g
American Heart Association/National Heart, Lung, and Blood Institute (2004)	
Any three of the following:	
Waist circumference	> 102 cm in men and > 88 cm in women
Triglycerides	⩾ 150 mg/dL (1.7 mmol/L)
HDL cholesterol	< 40 mg/dL (1.03 mmol/L) in men and < 50 mg/dL (1.29 mmol/L) in women
Blood pressure	≥ 130 mmHg systolic; ≥ 85 mmHg diastolic
Fasting glucose	⩾ 100 mg/dL (5.6 mmol/L)
International Diabetes Federation 2005	
Central obesity based on ethnicity	Waist circumference for Europeans > 94 cm in men and 80 cm in women; South Asians, Chinese, and Japanese > 90 cm in men and > 80 cm in women; ethnic South and Central Americans use South Asian data; for sub-Saharan Africans and Eastern Mediterranean and Middle East (Arab) populations use European data. Can be assumed if BMI > 30 kg/m^2
Plus two of the following:	
Triglycerides	⩾ 150 mg/dL (1.7 mmol/L)
HDL cholesterol	< 40 mg/dL (1.03 mmol/L) in men and < 50 mg/dL (1.29 mmol/L) in women
Blood pressure	⩾ 130 mmHg systolic; ⩾ 85 mmHg diastolic; treatment of previously diagnosed hypertension
Fasting glucose	⩾ 100 mg/dL (5.6 mmol/L), in which case oral glucose tolerance test is recommended
Harmonized (Consensus) Definition incorporating IDF and AHA/NHLBI definitions (2009)	
Any three of the following:	
Waist circumference	According to population and country-specific definitions
Triglycerides	⩾ 150 mg/dL (1.7 mmol/L)
HDL cholesterol	< 40 mg/dL (1.03 mmol/L) in men and < 50 mg/dL (1.29 mmol/L) in women
Blood pressure	⩾ 130 mmHg systolic; ⩾ 85 mmHg diastolic
Fasting glucose	⩾ 100 mg/dL (5.6 mmol/L) or use of medication

IDF: International Diabetes Federation; AHA/NHLBI: American Heart Association/National Heart, Lung, and Blood Institute.

MetS.

MetS is known to be with increased CVD risk in the general population[7,8]. It has also been associated with incident overt type 2 diabetes[9,10], in those previously without diabetes contributing to their MetS definition. Other MetS associations include non-alcoholic fatty liver disease[11], and hyperuricemia[12]. In addition, the association of MetS with chronic kidney disease (CKD) is receiving increased attention in selected populations[13-15]. CKD however is also a long-term illness, just like MetS, and often progresses over many years from mild reductions in glomerular filtration rate to more advanced preuremic states and eventual renal replacement therapy. CKD is asymptomatic until very late in its course, when symptoms such as fatigue, nausea and anorexia, itching, cramping and muscle twitching, and edema occur. The relationship between MetS and CKD is typically approached as snapshots in isolation during each CKD stage. The major purpose of this review is to approach the MetS-CKD relationship from the standpoint of each stage as points along the CKD spectrum where the diagnosis of MetS may be raised. This may help to better determine whether MetS is either in fact part of the etiology of CKD, the end result of risk factors common to both MetS and CKD, or a completely unrelated entity.

METABOLIC SYNDROME AS AN ASSOCIATION WITH CKD

Many studies associate MetS with CKD. This is perhaps the lowest level of evidence for causation. Each component of MetS has been associated with both CKD incidence and progression. MetS and CKD share a complex, bidirectional relationship. Obesity is associated with CKD[16-18]. Both obesity and CKD are increasing in prevalence, at least in the United States[19]. The earliest stages of CKD are typically missed because of its asymptomatic nature and lack of screening in annual physical examinations. It is therefore difficult to assemble sufficiently large cohorts known to be without CKD based on the appropriate baseline data and then follow them over a sufficient length of time in order to determine whether they have developed early (*i.e.*, stages I or II) CKD or not. This will require measurements of renal function in the normal range that tools such as the Modification

Table 2 Renal associations of metabolic syndrome

Renal outcome	Ref.
eGFR < 60/mL/min per 1.73 m^2	[15,19]
Proteinuria and/or microalbuminuria	[13,22,23,29,30]
Histopathological abnormalities (tubular atrophy, interstitial fibrosis, arterial sclerosis)	[31]
Ultrasound abnormalities (increased intra-renal resistive indices)	[32]

of Diet in Renal Disease (MDRD) equations[20] were not designed to handle.

A meta-analysis of eleven studies[13,14,21-29] of 30146 subjects reported that MetS was associated with development of an estimated GFR (eGFR) < 60 mL/min per 1.73 m^2, (Stage Ⅲ CKD) with odds ratio (OR) 1.55 (95%CI: 1.34-1.80)[19]. Many of these studies specifically excluded those with diabetes[21,22,26-28], which is not only a potential component of MetS, but a major cause of CKD. Not included also was a study[15] from the National Health and Nutrition Examination Survey (NHANES Ⅲ) database of 7800 subjects followed for 21 years, who having had normal renal function at baseline, were found to have an OR of 2.6 (95%CI: 1.68-4.03) for CKD if MetS was present. These authors[15] also determined a relationship between the number of MetS components present and risk. Sometimes, surrogate markers of CKD such as microalbuminuria or proteinuria are used instead[13,22-23,29] using varying definitions for both protein loss and MetS[19]. A small number of studies showed an increase in albumin or protein excretion associated with MetS[19]. Another study from the NHANES database also showed an increase in microalbuminuria with MetS[30].

Despite the large number of such associative studies between MetS and CKD, causality remains unproven[19]. The time-to-onset of both MetS and CKD are equally difficult to determine. Since individual components of MetS are prone to fluctuating values and are sensitive to unmeasured lifestyle modifications, medication effects, or acute illness, it is possible that some proportion of subjects experience change with respect to their MetS status overall during follow-up. Similar changes may occur with eGFR and a CKD diagnosis that is based on arbitrary eGFR cut-offs. Over-simplification of MetS criteria (such as using only body mass index (BMI) while ignoring waist and hip circumference, or systematically ignoring ethnicity), further limits making firm conclusions about associations. Obesity and CKD are increasing in prevalence[19] and this could obfuscate the relationship between two common disease entities. Investigation at the level of the individual subject may help shed light on the association of MetS with CKD.

A histopathology-based cross-sectional report of 146 patients undergoing nephrectomy showed a higher prevalence of CKD features, including global as well as segmental glomerulosclerosis in those with MetS. Other features noted included a higher prevalence of tubular atrophy, interstitial fibrosis, and arterial sclerosis[31]. Loss of renal function post-nephrectomy was more pronounced[31], but sequential biopsy studies are of course not feasible. Another approach is to study intra-renal hemodynamics by ultrasound, wherein renal parenchymal damage in MetS may be reflected by increased intra-renal resistive indices[32]. These novel studies may help us progress beyond making simple associations, but will need prospective evaluation in larger numbers of patients for validation. A summary of important renal associations with MetS is provided in Table 2.

METABOLIC SYNDROME AS AN ETIOLOGY OF CKD

More convincing than association alone would be a mechanistic explanation for MetS as a cause for CKD. The search for mechanisms is essential to remove the "black boxes" that exist along any proposed causal pathway between MetS and CKD. It may be all one linear mechanism that leads from MetS to CKD, or it may equally likely be a number of distinct but inter-dependent mechanisms set in motion by MetS and operating simultaneously to result in significant renal impairment. The mechanisms leading to MetS may also be the same ones causing CKD. In this context, there may be a "perfect storm" of multiple risk factors including insulin resistance, inflammation, abnormal lipid metabolism, and hypertension leading to increased expression of profibrotic factors[33]. Finally, we still cannot exclude chance associations between two otherwise common diseases.

Insulin resistance may be the most important MetS-related etiological factor for CKD. Insulin is an anti-inflammatory hormone. Insulin resistance, which is typical of type 2 diabetes, leads to inflammation, leading to oxidative stress and renal insufficiency[34]. Raised insulin levels stimulate insulin-like growth factor 1 (IGF-1) production, which increases connective tissue growth factor, thus causing fibrosis in the diabetic state[35]. Furthermore, and possibly independently, obesity may lead to increased secretion by adipose tissue of pro-inflammatory cytokines such as leptin, interleukin-6, and tumor necrosis factor-alpha (TNF-α)[36]. Leptin may lead to increased intra-renal expression of transforming growth factor-beta (TGF-β), leading to glomerulosclerosis[37]. It may also promote type IV collagen production[38,39]. TNF-α may lead to the production of reactive oxygen species (ROS) that can in turn lead to renal endothelial cell dysfunction, mesangial expansion and fibrosis[40]. Anti-inflammatory hormones like adiponectin may be reduced[36,41], contributing to insulin resistance as well. Adiponectin deficiency is associated with vascular intima thickening and smooth muscle cell proliferation[42]. Its vascular effects may even be independent of insulin sensitivity[43], and so may extend to CKD. Obesity also leads to increased glomerular volume, podocyte hypertrophy, and mesangial matrix expansion preceding CKD[44]. Triglycerides and free fatty acids may themselves be nephrotoxic by

Table 3 Potential mechanisms of chronic kidney disease in metabolic syndrome

Mechanism	Ref.
Oxidative stress	[34,40]
Increased pro-inflammatory cytokines (leptin, interleukin 6, tumor necrosis factor α)	[36]
Increased connective tissue growth and/or fibrosis factors (connective tissue growth factor, transforming growth factor β, type Ⅳ collagen)	[35,37-39]
Increased glomerular volume and podocyte hypertrophy	[44]
Triglyceride- and free-fatty acid induced injury	45
Increased ischemia and microvascular injury (angiotensin Ⅱ)	[46,47]
Hyperuricemia	[48,49]

promoting pro-inflammatory cytokine production[45]. In association with hypertension, another MetS component, angiotensin Ⅱ stimulates ROS production, in turn decreasing nitric oxide synthase production and causing renal microvascular injury, ischemia, and tubulointerstitial damage[46,47]. Dissecting out the relative contribution of insulin resistance, obesity, and hypertension to these findings versus the composite of MetS however is difficult. In this regard, the presence of early arterial hyalinosis[31] which is more typical of diabetes but not MetS, may point towards MetS being a distinct risk factor for CKD independent of its individual components. One more somewhat provocative hypothesis is that hyperuricemia, not a "traditional" MetS component but associated with MetS[12], is a promoter of CKD through the inhibition of nitric oxide production[48] or even recurrent nephrolithiasis[49]. Another limitation to be pointed is that most mechanistic explanations have been derived from animal models, and so their importance in human patients with MetS and CKD, with their different lifespans and disease profiles remains to be demonstrated. A summary list of possible mechanisms for CKD in MetS is shown in Table 3. Studies mostly support the direction of the relationship to be from MetS to CKD and not vice versa, but this is unconfirmed.

METABOLIC SYNDROME AND PROGRESSIVE CKD

Once CKD is identified, with the understanding that the definition is somewhat arbitrary, monitoring progression becomes more straightforward. Several population-based studies have identified MetS with CKD progression. Once stage Ⅲ or Ⅳ CKD has been reached, the presence of MetS has been associated with a hazard ratio of 1.33 (95%CI: 1.08-1.64) for end-stage renal disease (ESRD) over a follow-up period of just 2-3 years in a cohort of over 15000 patients[50]. In particular, impaired glucose metabolism, hypertriglyceridemia, and hypertension were associated with an increased risk of ESRD. Similarly, an incremental increase in insulin resistance was associated with a greater rate of decline in renal function in a cohort of elderly patients with CKD[51]. On the other hand, it was demonstrated that the relationship of MetS to CKD may not be constant over the progression through CKD stages. In the later stages of CKD, MetS as a risk factor for progression may become less important[52], perhaps because CKD itself leads to rapid progression in a form of vicious circularity. Also, greater attention may be paid to MetS in the later stages of CKD, so that its impact becomes less prominent. Another study showed that even though MetS was associated with albuminuria, the effect of MetS on CKD progression was independent of this[53]. This is controversial however, since proteinuria is a known risk factor for CKD progression to ESRD and is also a component of some MetS definitions. Despite the greater than 30% risk with MetS, adjustment for proteinuria attenuated the risk for development of a composite endpoint of significant decrease in GFR, ESRD, or death in the African American Study of Kidney Disease and Hypertension trial[54].

The distinction between CKD incidence and progression may be arbitrary since renal insufficiency must first progress to the point where CKD is diagnosed at some threshold level of renal function. If the underlying progression is left unchecked however and the new pathophysiology of CKD becomes established, then the risk factors common to CKD and MetS combine to accelerate CKD progression. First, obesity-related glomerular hyperfiltration could combine with that induced by CKD itself, leading to accelerated glomerulosclerosis. Second, inflammation and oxidative stress are worsened in CKD[55]. Hypertension and hypertriglyceridemia are worsened[55], and insulin resistance may be promoted by the undernourished state that can be caused by CKD as well as lead to CKD[56,57]. This relationship is thus bidirectional. Third, this insulin resistance may combine with inflammation to cause "endoplasmic reticulum stress". According to this theory, misfolded proteins accumulate in the lumen of the endoplasmic reticulum, suppressing insulin secretion through phosphorylation of the insulin receptor substrate (IRS-1)[58]. Finally, insulin resistance also worsens renal hemodynamics through increasing sodium retention, and affecting the transport of other cations and anions[59]. Hypertension is worsened, leading to further renal damage. Similarly, the sympathetic nervous system is activated[60], leading to unfavorable renal hemodynamics, proteinuria, and ischemia. Proteinuria itself may lead to podocyte injury, and eventually lead to chronic tubulointerstitial injury, thereby worsening CKD[61]. Unless cardiovascular mortality intervenes, progression to ESRD may occur.

Role of cardiovascular disease in progression of metabolic syndrome-related CKD

Even mild CKD has been associated with increased CVD risk[62]. CVD mortality also increases with increasing serum creatinine concentrations[62]. Advanced CKD is also a high risk situation for cardiovascular events and mortality. In one study of stage Ⅳ or Ⅴ CKD patients, MetS was predictive of a composite of CVD mortality, acute coronary syndrome (ACS), revascularization, non-

fatal stroke, and amputation (hazard ratio 2.46, 95%CI: 1.17-5.18)[63]. In this study of 200 patients, intensive risk factor modification was not effective[63]. Coronary heart disease is promoted by the components of MetS. Patients with both MetS and CKD exhibit greater coronary artery plaque burden with higher lipid content, as demonstrated by intravascular ultrasound[64]. With renal insufficiency, myocardial infarction (MI) in the context of MetS is associated with higher mortality at one year[65]. In over 900 patients undergoing carotid revascularization where 14% had some degree of CKD, MetS increased the risk for stroke, MI, and death[66].

The patient with MetS and progressive CKD treads a dangerous path towards ESRD. Besides being simply associated with CKD, MetS may also lead to CKD through a variety of pathophysiological mechanisms. MetS may also lead to more rapid CKD once it is established. Both MetS and CKD in turn are associated with increased risk for CVD events, and when both occur together the effect may be additive. It stands to reason that ACS and MI are major contributors to all-cause mortality seen when these two common conditions are combined, regardless of whether MetS leads to CKD or both are independently acquired. Furthermore, it is likely that ACS and MI themselves lead to acute kidney injury and acceleration of CKD. This could happen as a result of acute shifts in effective intravascular volume or contrast exposure, for example. Increased mortality effectively prevents progression of CKD to ESRD, so it is reasonable to speculate that fewer patients with MetS will actually reach ESRD.

METABOLIC SYNDROME AND RENAL REPLACEMENT THERAPY

Many patients receiving hemodialysis (HD) also have MetS. The mortality rate is very high in the initial few months after HD initiation both in the United States[67] and worldwide[68]. A significant proportion of this mortality is attributable to CVD, related to existing cardiovascular comorbidities[69]. Therefore, patients with MetS starting chronic HD are at increased risk for major cardiovascular events and mortality. The prevalence of MetS is quite high (often exceeding 50%) in HD cohorts worldwide[70-72]. Interestingly, the presence of MetS has even been extended to their relatives[73]. Longer-term follow-up also indicates a higher incidence of cardiovascular events[74] and high rate of hospitalization[75]. Other co-morbid conditions may co-exist with MetS in HD patients. A higher prevalence of moderate-to-severe periodontal disease has been reported[76]. However, significant correlations were not noted in dialysis patients with reduced bone mineral density[77], quality of life[78], or mood[78].

Several pathophysiological mechanisms may be operational during hemodialysis that could further exacerbate the effects of MetS. Besides insulin resistance, hyperlipidemia, and hypertension carried over from the pre-dialysis phase of CKD, further inflammation and oxidative stress may result from dialysis treatment itself. There is a loss of antioxidants and increase in leukocyte activation during dialysis[79-82]. This may occur through loss of vital antioxidants through the hemodialysate, or reactions to semi-synthetic dialysis membranes, or both. Dialysis patients are also prone to infections further promoting inflammatory stress. Logistical difficulties in hemodialysis in obese patients, such as vascular access difficulties leading to suboptimal renal functional replacement may promote inflammation. Chronic volume expansion promotes worsening hypertension, further adding to morbidity. Insulin resistance, even in those without diabetes, may also lead to chronic malnutrition as part of an overall catabolic condition[83].

MetS has an impact on patients on peritoneal dialysis (PD) as well. When glucose-containing solutions are used there is systemic glucose absorption via the peritoneal membrane, leading to increased intra-abdominal fat[84] consistent with MetS. The increased glucose load increases serum LDL cholesterol and triglyceride concentrations, which when combined with hypertension and volume overload, may increase CVD[85]. MetS increases patient mortality on PD[86,87] and also decreases PD technique survival in patients on PD for at least three months[87]. Technique failure and subsequent conversion to HD is also a stressful state that can cause inflammation. MetS has been associated with an elevated white blood cell count and C-reactive protein level, independently of infection but consistent with inflammation[88]. MetS is also associated with lower circulating adiponectin levels in PD[89], and this may increase CVD risk.

TREATING THE METABOLIC SYNDROME IN THE PRESENCE OF CKD

There is an obvious clinical need to reduce CKD morbidity and mortality, and MetS seems to be an easily identified target for intervention. However, the approach is far from precise. Randomized clinical trials in CKD patients are few and are limited by small sample sizes. Renal outcomes are often not described as the primary outcomes. Studies of CKD prevention or progression require large numbers of patients followed over long periods of time to gather sufficient CVD or ESRD outcomes, and if MetS is added as an inclusion criterion, recruitment difficulties are exacerbated. There is a shortage of high quality randomized, controlled trials in nephrology generally[90]. Nonetheless, targeting MetS as a risk factor for CVD, for which CKD patients are at risk is certainly reasonable.

An initial approach should include some combination among weight reduction, dietary modification, and increased physical activity[91], preferably all three. A small clinical trial of 38 patients with MetS but without CKD, randomized to dietary weight loss, weight loss plus aerobic exercise, or no treatment was able to dem-

Table 4 Possible clinical interventions for metabolic syndrome in chronic kidney disease[a,b]

Clinical intervention	Ref.
Lifestyle modification: weight reduction, dietary adjustment (calorie and phosphate reduction), increased physical activity, and/or smoking cessation	[91-94]
Weight loss medication (orlistat) or surgery	[95,97]
Lipid-lowering medication (statins, fibrates)	[96,104,105]
Blood pressure-lowering medication (renin-angiotensin system antagonists)	[100]
Blood glucose-lowering medication (metformin, thiazolidinediones)	[102,103]

[a]It is recommended that individual national society guidelines be followed in the management of individual metabolic syndrome components; [b]Interventions are individualized and used in combination.

onstrate a relationship between weight loss, albuminuria reduction, and improvement in eGFR, augmented by exercise[92]. An observational analysis of PREMIER, a randomized trial of blood pressure lowering in obese subjects but again without CKD, showed a relationship between reduction in waist circumference and urinary albumin excretion[93]. A decrease in phosphate intake may be beneficial as well[93]. It is unclear if these results indicate an improvement in incipient renal disease, or an improvement in systemic endothelial dysfunction manifest as microalbuminuria. Achieving weight loss without a corresponding loss in muscle mass may be difficult to achieve in CKD, especially ESRD. In a sample of 2288 participants with CKD from the NHANES Ⅲ survey, regular physical activity but not diet was associated with decreased mortality[94]. Although unproven, it is likely that patients with both CKD and MetS will especially benefit. A multi-disciplinary approach that involves an exercise specialist to ensure regular physical activity and a dietician to achieve the goal of weight loss through reduced calorie intake, while avoiding malnutrition at the same time is preferable. Hospitalizations are likely to lead to setbacks. Smoking cessation has been associated with reduced mortality in CKD[94]. Measurement of waist circumference or the waist-to-hip ratio may allow for better compliance with existing MetS definitions[2-6] both for diagnosis and follow-up.

Both pharmacotherapy and surgical procedures for weight loss in patients with MetS have been explored. It is unclear if drugs prescribed for weight loss have significant adverse effects on renal function. Orlistat may be beneficial for MetS in the general population[95]. Fibrates on the other hand may worsen renal function[96], and could be harmful in patients with MetS and CKD. Pharmacotherapy needs to be combined with lifestyle modification in order to have significant effect, and would not be recommended in the absence of clinical trial data pertinent to CKD. Bariatric surgery has been shown to improve MetS parameters and also decrease mortality in the general population[97], and also reduce albuminuria[98]. However, the ability of CKD patients to recover from major surgery needs to be considered. Clinical trials in CKD patients are needed before this can be recommended.

Blood pressure control reduces CVD risk and CKD progression, and so relevant national guidelines for blood pressure targets and therapeutic agents should be followed depending on the presence or absence of CKD and/or diabetes, in the absence of specific guidelines for MetS patients. Thiazides may worsen MetS, perhaps through hyperuricemia, hypokalemia, and diabetes[99]. Renin-angiotensin system antagonists may prevent new-onset diabetes[100]. This may be considered for those with MetS who have not yet developed diabetes. MetS is associated with increased sympathetic activity, and so renal denervation has been considered when hypertension is part of MetS[101]. However, the value of this procedure for achieving sustained blood pressure reduction is controversial.

Management of dysglycemia requires special attention in the context of MetS. Metformin is associated with improved insulin resistance and endothelial function[102]. However, metformin is not used in more advanced CKD due to concerns surrounding lactic acidosis. Thiazolidinediones may also be considered[103], but their side effect profile deserves special attention. They may improve endothelial function as well as have anti-inflammatory effects[103]. Weight loss may also help improve glycemic control, but dietary conflicts among diabetes-related restrictions (such as carbohydrates) and CKD-related restrictions (potassium and phosphorus) may be especially problematic in MetS where total caloric intake must also be reduced and protein intake maintained. Specialized dietician input is again required.

Finally, the use of statins in MetS requires consideration. Statins may reduce proteinuria[104], either through improved endothelial function or reduction in systemic inflammation[104,105]. Success with statins in reducing cardiovascular events in ESRD[106] has been variable.

A summary of possible therapeutic interventions for MetS in the context of CKD is provided in Table 4. In the absence of firm data, relevant national guidelines should be followed for each individual cardiovascular or CKD-related risk factor.

CONCLUSION

At this point, it remains unclear whether MetS adds further cardiovascular risk to that conferred by CKD alone. Further research is first required to firmly establish the link between MetS and incidence of CKD in the first instance, and then between MetS and the progression of CKD. A single large, prospective clinical trial in human subjects that addresses both CKD incidence and progression in established CKD will help to provide the necessary justification for MetS intervention. However, the major clinical concern surrounding MetS is its association with CVD. A prospective clinical trial of intervention targeted to multiple MetS parameters in CKD would help address whether MetS is more than the sum of its parts in the context of CKD. Until then, we are

left with using surrogate markers such as proteinuria or microalbuminuria for both CKD and CVD. Statins, fibrates, and renin-angiotensin system antagonists allow for targeting specific MetS components including diabetes, hyperlipidemia, hypertension, and microalbuminuria. In combination with aggressive lifestyle modification, there is potential in the meantime for reducing MetS, CKD, and CVD mortality. Beneficial snapshot effects may be found in the literature for a particular intervention in one CKD sub-population and not another, such as in the case of statins. However, viewing CKD as a longitudinal construct allows for better understanding of the pathophysiology of CVD and CKD progression with MetS, and may thus allow for more rational therapeutic choices.

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REVIEW

Chronic kidney disease and erectile dysfunction

Etsu Suzuki, Hiroaki Nishimatsu, Shigeyoshi Oba, Masao Takahashi, Yukio Homma

Etsu Suzuki, Institute of Medical Science, St. Marianna University School of Medicine, Miyamae-ku, Kawasaki 216-8512, Japan
Hiroaki Nishimatsu, Yukio Homma, The Department of Urology, Faculty of Medicine, University of Tokyo, Bunkyo-ku, Tokyo 113-8655, Japan
Shigeyoshi Oba, Masao Takahashi, The Department of Internal Medicine, Faculty of Medicine, University of Tokyo, Bunkyo-ku, Tokyo 113-8655, Japan
Author contributions: All the authors solely contributed to this paper.
Correspondence to: Etsu Suzuki, MD, PhD, Institute of Medical Science, St. Marianna University School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki 216-8512, Japan. esuzuki-tky@umin.ac.jp
Telephone: +81-44-9778361 Fax: +81-44-977-8361
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Abstract

Erectile dysfunction (ED) is a common condition among male chronic kidney disease (CKD) patients. Its prevalence is estimated to be approximately 80% among these patients. It has been well established that the production of nitric oxide from the cavernous nerve and vascular endothelium and the subsequent production of cyclic GMP are critically important in initiating and maintaining erection. Factors affecting these pathways can induce ED. The etiology of ED in CKD patients is multifactorial. Factors including abnormalities in gonadal-pituitary system, disturbance in autonomic nervous system, endothelial dysfunction, anemia (and erythropoietin deficiency), secondary hyperparathyroidism, drugs, zinc deficiency, and psychological problems are implicated in the occurrence of ED. An improvement of general conditions is the first step of treatment. Sufficient dialysis and adequate nutritional intake are necessary. In addition, control of anemia and secondary hyperparathyroidism is required. Changes of drugs that potentially affect erectile function may be necessary. Further, zinc supplementation may be necessary when zinc deficiency is suspected. Phosphodiesterase type 5 inhibitors (PDE5Is) are commonly used for treating ED in CKD patients, and their efficacy was confirmed by many studies. Testosterone replacement therapy in addition to PDE5Is may be useful, particularly for CKD patients with hypogonadism. Renal transplantation may restore erectile function. ED is an early marker of cardiovascular disease (CVD), which it frequently precedes; therefore, it is crucial to examine the presence of ED in CKD patients not only for the improvement of the quality of life but also for the prevention of CVD attack.

Key words: Erectile dysfunction; Chronic kidney disease; Nitric oxide; Phosphodiesterase type 5; Testosterone

Core tip: Erectile dysfunction (ED) is a common condition in chronic kidney disease (CKD) patients. The etiology is multifactorial. Phosphodiesterase type 5 inhibitors are commonly used for the initial treatment. ED has gained attention as an early marker for cardiovascular disease (CVD), which it frequently precedes. Therefore, it is pivotal to examine the presence of ED in CKD patients not only for the improvement of quality of life but also for the prevention of CVD attack. The pathophysiology of erection, which most nephrologists are not familiar with, is also discussed.

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INTRODUCTION

Erectile dysfunction (ED) is defined as an inability to

attain and/or maintain penile erection sufficient for satisfactory sexual performance. It is now a common condition and approximately 150 million males worldwide are estimated to suffer from ED[1]. The prevalence of ED in 2025 is projected to be approximately 300 million worldwide[2]. It is well known that age, metabolic disorders (hypertension, diabetes, and hyperlipidemia), and smoking are major risk factors for ED. Recently, chronic kidney disease (CKD) has also gained attention as a risk factor for ED. Although CKD causes sexual dysfunction in both genders, this review article focuses on the role of CKD in the development of ED. We discuss the etiology and treatment of ED in CKD patients.

PREVALENCE OF ED IN CKD PATIENTS

The prevalence of ED in the United States male population aged > 50 years (Participants: 31,742 men, age 53-90 years) was reported to be 33%[3], whereas that in the Turkish male population aged > 40 years (Participants: 2158 men) was 69.2%[4]. However, the prevalence was 36% when mild ED cases were excluded. Navaneethan *et al*[5] reported in their meta-analysis study that the prevalence of ED in CKD patients was 70% on average. Furthermore, Mesquita *et al*[6] reported that the prevalence of ED in CKD outpatients with stages 3, 4, and 5 was 72.3%, 81.5%, and 85.7%, respectively. Nassir reported that the prevalence of ED in patients just entering dialysis programs was 82.7%[7]. Thus, it is observed that ED frequently occurs in CKD patients.

BLOOD SUPPLY TO THE PENIS

The blood supply to the penis originates predominantly from the internal pudendal artery, which branches into the penile artery. The penile artery then branches into the cavernous arteries. The cavernous artery enters the cavernous body and subsequently divides into many branches called the helicine arteries, which open into the cavernous sinuses. Blood in the cavernous sinuses is drained by the subtunical veins that form the venous plexuses just beneath the tunica albuginea and then returns to the circulation *via* 3 sets of veins; the superficial, intermediate and deep veins.

PATHOPHYSIOLOGY OF PENILE ERECTION

Penile erection and detumescence are regulated by relaxation and contraction, respectively, of the smooth muscle located in the arteries and the cavernous body. In the flaccid state, the sympathetic nervous system is dominant, and the arterial and corporal smooth muscle is tonically contracted. As a result, only a minimal amount of blood flows through the cavernous artery into the cavernous body. After sexual stimulation, parasympathetic activity causes a decrease in the peripheral resistance due to vasodilatation, and the blood flow through the cavernous and helicine arteries increases. The intracavernous pressure increases without any increase in the systemic pressure. In the full erectile state, increased blood volume in the cavernous body and the following compression of the subtunical drainage veins against the rigid tunica albuginea lead to a reduction in the venous outflow (referred to as the veno-occlusive mechanism), and therefore, high intracavernous pressure is maintained. However, when the corporal smooth muscle is unable to relax sufficiently and/or the corporal tissue loses its normal compliance, the increased intracavernous pressure during erection cannot adequately compress the subtunical veins, resulting in the leakage of blood out of the cavernous body during erection. This is a major cause of ED and is referred to as the corporal veno-occlusive dysfunction (CVOD). CVOD occurs when the smooth muscle content decreases and/or when the collagen content increases in the cavernous body[8]. Therefore, the ratio of the smooth muscle content to the collagen content in the cavernous body decreases in CVOD.

REGULATION OF PENILE SMOOTH MUSCLE CONTRACTION

Detumescence of the penis is predominantly mediated by adrenergic nerve terminals whose neurotransmitter, norepinephrine, activates adrenergic receptors on the penile smooth muscle. The contraction of penile arteries and trabecular smooth muscle is largely mediated by α-1 adrenergic receptors[9,10]. Other vasoconstrictors including endothelin-1, prostaglandin F2α, thromboxane A2 and angiotensin II are also implicated in the contraction of smooth muscle in the penis[11-13].

REGULATION OF PENILE SMOOTH MUSCLE RELAXATION

Dilatation of the cavernous artery and helicine arteries is the first event in the development of an erection. The blood flow and pressure increase in the cavernous sinuses, and subsequently, smooth muscles surrounding the trabeculae relax, resulting in further expansion and accumulation of blood in the cavernous body. It is now well established that nitric oxide (NO) plays a pivotal role in the initiation and maintenance of erection. NO acts through the stimulation of the soluble guanylate cyclase, which mediates the subsequent formation of cyclic-GMP (cGMP). cGMP activates protein kinase G (PKG), and PKG is implicated in the relaxation of smooth muscle. cGMP is inactivated by phosphodiesterase type 5 (PDE5), which is predominantly located in the cavernous smooth muscle and is the target of PDE5 inhibitors (PDE5Is) such as sildenafil and vardenafil. NO synthase (NOS) uses the amino acid L-arginine and molecular oxygen to produce NO. Three distinct isoforms of NOS have been identified. Two constitutive forms, neuronal NOS (nNOS) and endothelial NOS (eNOS), are present in the

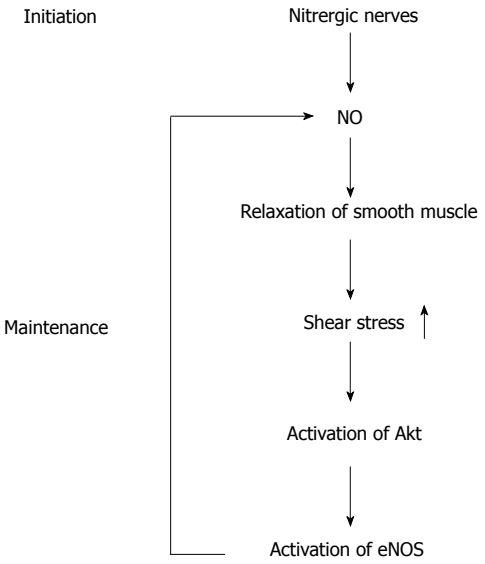

Figure 1 Nitric oxide is critically implicated in the initiation and maintenance of penile erection. NO: Nitric oxide; eNOS: Endothelial nitric oxide synthase.

nervous system and vascular endothelial cells, respectively. A third isoform, inducible NOS (iNOS) is expressed in a variety of cells in response to inflammatory mediators and bacterial products. The isoforms nNOS and eNOS are expressed in the autonomic nerves and endothelium of the penis, respectively[14-17]. Under physiological conditions, iNOS is not expressed in the penis. Postganglionic parasympathetic nerves, which express nNOS and release NO as a cotransmitter with acetylcholine, are now termed nitrergic nerves[17,18]. The stimulation of the cavernous nerve activates nitrergic nerve fibers and elicits NO release at the nerve terminals, which causes relaxation of penile smooth muscle. The functional role of NO released from the nitrergic nerve termini during the relaxation of penile smooth muscle has been demonstrated in many studies in which penile erection induced by stimulation of the cavernous nerves or the spinal cord can be inhibited by NOS inhibitors[14,19-21]. The role of eNOS in erection has also been studied. One possibility was that acetylcholine released from postganglionic cholinergic nerves evoked the release of NO from the endothelium to induce endothelium-dependent relaxation of the penile smooth muscle. However, atropine, a competitive inhibitor of the muscarinic effect of acetylcholine, did not inhibit cavernous nerve-induced penile erection[14]. Furthermore, neurogenic relaxation of the cavernous body does not require a functional endothelium[22,23], suggesting that acetylcholine-induced endothelium-dependent relaxation of the smooth muscle is not required for cavernous nerve-induced penile erection. A second possibility was the activation of eNOS by shear stress. During erection, an increased blood flow on the luminal surface of the penile artery and cavernous sinuses can cause shear stress, which may lead to the activation of protein kinase Akt (also known as Protein kinase B) and subsequent phosphorylation and activation of eNOS, facilitating NO release from the endothelium. Hurt *et al*[24] demonstrated that both electrical stimulation of the cavernous nerve and direct intracavernosal injection of a vasorelaxant drug, papaverine, caused a rapid increase in the phosphorylation and activation of Akt and eNOS. The authors also showed that penile erection elicited by papaverine is significantly reduced in eNOS gene knockout mice. They proposed a model in which the rapid, brief activation of nNOS initiates the erectile response, whereas Akt-dependent phosphorylation and activation of eNOS are necessary for sustained NO production and maximal erection (Figure 1).

POSSIBLE CAUSES OF ED IN CKD PATIENTS

Most studies in this field have been performed using dialysis patients and renal transplant recipients. Little data exist on the etiology and treatment of ED in CKD patients before entering a dialysis program.

Hormonal abnormalities

Chronic renal failure (CRF) is associated with impaired spermatogenesis, and it often results in infertility[25]. In addition, testes develop endocrine dysfunction. Total and free testosterone levels are typically reduced, although the binding capacity and concentration of sex hormone-binding globulin are normal[26-28]. Serum luteinizing hormone (LH) level increases in CRF patients, and testosterone secretion in response to acute administration of human chorionic gonadotropin (HCG), a compound with LH-like actions, shows a blunted response, suggesting that the testosterone-producing Leydig cells have low responsiveness to LH and that this is the primary cause of low testosterone levels in CRF[29]. Interestingly, a factor capable of blocking the LH receptor *in vitro* has been identified in uremic serum, providing an explanation for the blunted response of Leydig cells to infusion of HCG. This blocking activity is inversely correlated with GFR and almost disappears after renal transplantation[30]. In addition, follicle-stimulating hormone (FSH) secretion increases in men with CRF. FSH release from the pituitary gland is negatively regulated by inhibin, a peptide product of Sertoli cells that are located in the convoluted seminiferous tubules. FSH concentration appears to increase in uremic patients because of the damage to seminiferous tubules, resulting in the suppression of inhibit production[31].

Testosterone is required not only for libido but also for the maintenance of the normal morphology and function of the penis. Testosterone deficiency leads to the loss of smooth muscle in the cavernous body and its replacement with collagen fibers[32,33]. This may result in CVOD. It has also been demonstrated that the activity of nNOS and PDE5 are positively regulated by testosterone[32].

Elevated plasma prolactin levels are commonly found in CRF[34]. Increased production is the main cause because the kidney plays little, if any, role in its catabolism. Secondary hyperparathyroidism may be implicated in the increased prolactin secretion in CRF because an infusion

of parathyroid hormone (PTH) in healthy men enhances prolactin release[35]. Depletion of zinc reserves may also play a role in uremic hyperprolactinemia[36]. Hyperprolactinemia induces the loss of libido and low serum testosterone levels[37], which may cause ED.

Endothelial dysfunction

It is now well known that CKD is a risk factor for cardiovascular disease (CVD)[38,39]. Endothelial dysfunction is an early marker of CVD, and has also been reported to occur in CKD patients[40-42]. In addition, endothelial dysfunction is a cause of ED, because NO production from the endothelium decreases in this state. Therefore, it is not surprising that ED frequently occurs in CKD patients. Furthermore, CKD patients often suffer from metabolic diseases such as hypertension, hyperlipidemia, and diabetes. Diabetes is a major cause of CKD. These metabolic diseases also cause endothelial dysfunction and are risk factors for ED. Therefore, in addition to the concomitant metabolic diseases, CKD *per se* appears, at least in some part, to cause ED via the induction of endothelial dysfunction.

Disturbance in the autonomic nervous system

Autonomic neuropathy occurs in end-stage renal disease and can be a cause of ED[43,44]. It is well known that autonomic neuropathy is a common complication of diabetes, and it can be a cause of ED in CKD patients.

Anemia and erythropoietin deficiency

Erythropoietin (Epo) has been widely used to treat anemia in uremic patients. Several reports have demonstrated that treatment with Epo improved erectile function in dialysis patients[45-47], suggesting that anemia and/or Epo deficiency are implicated in ED. The mechanism by which Epo restores erectile function remains unclear. Epo normalized the increased serum prolactin level in early studies[45,48], but this finding was not confirmed by other studies[49-51]. Moreover, Epo increased serum testosterone levels in some studies[51,52]; however, this finding was again not confirmed by other studies[45,46,49,50]. Allaf *et al*[53] examined the effects of Epo on the recovery of erectile function in a rat model of cavernous nerve injury and found that Epo restored erectile function. They also found that Epo stimulated axonal regeneration of the injured cavernous nerve. Therefore, Epo may stimulate the regeneration of the cavernous nerve. Epo reportedly has protective effects against ischemic damages *via* its anti-apoptotic activity[54-59]. Therefore, Epo may protect the cavernous body against injuries *via* its anti-apoptotic activity. Furthermore, the receptor for Epo is expressed on vascular endothelial cells (VECs) and Epo stimulates the proliferation and migration of VECs[60,61]. Epo is also capable of mobilizing endothelial progenitor cells (EPCs) from the bone marrow[62,63]. EPCs were originally isolated from human peripheral blood[64]. EPCs are progenitor cells whose differentiation potential is restricted to VECs. They were incorporated in the capillaries and small arteries of ischemic tissues *in vivo* and expressed markers for VECs such as CD31 when introduced into the circulation using a hindlimb ischemia model[64], suggesting their involvement in the stimulation of angiogenesis. Several studies have reported that the number of circulating EPCs decreased in ED patients[65-67]. These data suggest that Epo may restore erectile function *via* its proangiogenic activity. In summary, Epo has nerve-protective, anti-apoptotic, and proangiogenic activities, at least in animal models, and these activities may be implicated in Epo-induced restoration of erectile function. It is likely that Epo restores erectile function via interaction with its receptors on cells such as nerves and VECs rather than on red blood cells with a resultant improvement in anemia.

Vitamin D deficiency and secondary hyperparathyroidism

Although no conclusive data have been published, Massry *et al*[68] reported that a decline in serum PTH concentration by treatment with 1,25(OH)$_2$ vitamin D$_3$ correlated with the recovery of erectile function in dialysis patients. It was also reported that PTH administration increased serum prolactin concentration[35]. Therefore, it is possible that secondary hyperparathyroidism is implicated in erectile dysfunction in dialysis patients.

Drugs

Many drugs used for CKD patients potentially cause ED. Common examples are anti-hypertensive drugs including diuretics, agonists for α-2 adrenergic receptors, and beta-blockers. Other examples are cimetidine, tricyclic antidepressants, and metoclopramide.

Depression

The prevalence of depression among dialysis patients has been estimated to be 20%-30%[69-71]. Several studies demonstrated that depression is an independent risk factor for ED[72,73].

Zinc deficiency

Several reports demonstrated that oral zinc supplementation restored erectile function, which was associated with an increase in serum testosterone concentration[74,75]; however, some negative effects of zinc supplementation on erectile function were also reported[76]. Possible causes of ED in CKD patients are summarized in Table 1.

ED AS AN EARLY MARKER FOR CVD

Because of the high prevalence of ED among CVD patients, ED was traditionally regarded as a secondary complication of CVD. Recently, ED has gained attention as an early marker of CVD, because ED often precedes the occurrence of CVD. The Prostate Cancer Prevention Trial was a prospective, randomized, and placebo-controlled trial to assess whether finasteride decreased the prevalence of prostate cancer[77]. Finasteride is an

Table 1 Possible causes of erectile dysfunction in chronic kidney disease patients

Abnormalities in the gonadal and pituitary systems
Testosterone↓
LH↑, FSH↑
Prolactin↑
Endothelial dysfunction
Hypertension, diabetes, hyperlipidemia
Autonomic neuropathy
Anemia (Erythropoietin↓)
Secondary hyperparathyroidism
Drugs
Diuretics
Agonists for α-2 adrenergic receptors and b-blockers
Cimetidine
Tricyclic antidepressants
Depression
Zinc deficiency

LH: Luteinizing hormone; FSH: Follicle-stimulating hormone.

inhibitor of 5α-reductase, and inhibits the conversion of testosterone to dihydrotestosterone, which is the primary androgen in the prostate. Participants were regularly monitored for overall health, including cardiovascular events and sexual function. Data from 9457 men randomized to the placebo group in this trial were analyzed to assess the hypothesis that ED is an early marker of patients with occult CVD[78]. At entry to the study, 8063 (85%) men had no CVD; of these men, 3816 (47%) patients reported some level of ED. Among the 4247 men without ED at study entry, 2420 men (57%) reported an incident ED after 5 years, and this incidence increased to 65% at 7 years. Incidents of ED were significantly associated with subsequent angina, myocardial infarction, or stroke; hazard ratio after adjustment was 1.25. Several other studies also confirmed this finding that ED often precedes the onset of CVD[79-81]. Furthermore, ED has been recognized as an early marker for silent coronary artery disease (CAD). Gazzaruso *et al*[82] examined the prevalence of ED in 133 uncomplicated type 2 diabetic men with angiographically verified silent CAD and in 127 diabetic men without myocardial ischemia[82]. The groups were comparable for age and diabetes duration. The prevalence of ED was significantly higher in patients with silent CAD than in those without silent CAD (33.8% *vs* 4.7%, $P = 0.000$). Significant risk factors for silent CAD were identified using multiple logistic regression analysis. These risk factors included ED, apolipoprotein (a) polymorphism, smoking, microalbuminuria, HDL, and LDL. Interestingly, among these risk factors, ED was the strongest predictor of silent CAD (odds ratio 14.8). García-Malpartida *et al*[83] also examined the association between ED and silent myocardial ischemia (SMI) in 154 type 2 diabetic patients without a clinical evidence of CVD and demonstrated that ED was significantly associated with SMI (18.1% in patients with ED *vs* 4.1% in patients without ED, $P = 0.018$). Therefore, ED should be examined carefully in CKD patients not only for the improvement of their quality of life but also for the prevention of CVD.

TREATMENT

Sufficient dialysis and adequate nutritional intake are necessary to improve the general condition of uremic patients. In addition, control of anemia using Epo and control of secondary hyperparathyroidism using phosphate binders, an active form of vitamin D and/or cinacalcet hydrochloride are required. Zinc supplementation may be necessary when zinc deficiency is suspected. If a psychological problem is suspected, psychotherapy and/or antidepressant medications may be necessary.

PDE5Is

PDE5Is are inhibitors of PDE5 and suppress the degradation of cGMP, thereby stimulating the relaxation of smooth muscle in the cavernous body. Many studies have demonstrated the efficacy of PDE5Is for the treatment of ED in dialysis patients and in renal transplant recipients[84-90]. Although headache, flushing, and dyspepsia are the most common adverse effects[91], PDE5Is were well tolerated among dialysis patients in these studies. Among PDE5Is, sildenafil without dose adjustment has been used to treat ED in dialysis patients in several studies. However, it may be safer to start with half the dose (25 mg) and subsequently increase it up to 100 mg, depending on the patients' responses. Special care should be taken when PDE5Is are administered to patients with cardiovascular or hepatic diseases.

Testosterone replacement therapy

Although testosterone replacement therapy is generally effective for patients with low circulating levels of testosterone when causes of ED are other than CKD, the administration of testosterone to uremic men usually fails to restore libido or potency, despite increased testosterone levels[92,93]. However, one pilot study demonstrated that treatment with testosterone gel improved erectile function in hypogonadal hemodialysis patients[94]. Testosterone stimulates an increase in NO production and degradation of cGMP, because it reportedly increases the activities of nNOS and PDE5 simultaneously[32,95,96]. Thus, the stimulatory effect of testosterone on NO production may be negated by its stimulatory effect on PDE5 activity. In this regard, combination therapy of testosterone and PDE5Is may be more effective than treatment with either testosterone or PDE5Is alone. Indeed, several reports demonstrated the efficacy of combination therapy on erectile function in hypogonadal men who did not respond to PDE5Is[97-100]. The efficacy of the combination therapy was also reported in dialysis patients and renal transplant recipients[101]. However, a recent randomized, double-blind, placebo-controlled trial did not show a significant effect of the addition of testosterone to sildenafil therapy on erectile function[102]. Therefore, the efficacy of the combination therapy is still controversial.

Other treatments for ED

Other options for the treatment of ED include injecting prostaglandin E1 into the shaft of the penis, vacuum constriction devices and constriction bands, and penile prostheses. These treatments are beyond the scope of this review, and have not been discussed in detail.

EFFECT OF RENAL TRANSPLANTATION ON ERECTILE FUNCTION

It is well recognized that dialysis therapy does not improve sexual function[103,104]. Several reports demonstrated the improvement of erectile function after renal transplantation[104-106]. Nassir performed a prospective study in which the erectile function of 52 patients undergoing dialysis therapy was analyzed before and after renal transplantation[104]. No improvement of erectile function was observed in patients during dialysis therapy, whereas renal transplantation significantly improved erectile function. Akbari *et al*[107] examined the effect of renal transplantation on sperm quality and sex hormone levels. The authors found that sperm motility significantly improved, although morphology and sperm count did not change significantly. They also found that the level of testosterone significantly increased, whereas levels of FSH, LH and prolactin significantly decreased after renal transplantation. Furthermore, erectile function was compared between patients on dialysis therapy and renal transplant recipients in several studies, and erectile function was reportedly better in renal transplant recipients[108-110]. However, ED is still common in renal transplant recipients (approximately 50%)[111,112], and the prevention of the occurrence of CVD seems necessary in these patients to maintain erectile function[113,114].

STUDY LIMITATIONS

Most studies on this topic collect information from patients on dialysis therapy and renal transplant recipients. Little reliable data exist with regard to the prevalence, etiology, and treatment of ED in CKD patients before starting dialysis therapy. Future studies are required to elucidate these points.

CONCLUSION

ED is a very common disease in CKD patients, and it is a multifactorial disease whose causes include hormonal, metabolic, nutritional, and psychological factors. PDE5Is are commonly used during treatment. Testosterone replacement therapy together with PDE5Is may be useful, particularly for CKD patients with hypogonadism. Renal transplantation may restore erectile function, particularly for young patients. ED is an early marker for CVD and it precedes the occurrence of CVD; therefore, ED should be examined carefully in CKD patients to avoid occurrence of CVD.

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REVIEW

Searching for a treatment for Alport syndrome using mouse models

Kan Katayama, Shinsuke Nomura, Karl Tryggvason, Masaaki Ito

Kan Katayama, Shinsuke Nomura, Masaaki Ito, Department of Cardiology and Nephrology, Mie University Graduate School of Medicine, Tsu, Mie 514-8507, Japan
Kan Katayama, Karl Tryggvason, Division of Matrix Biology, Department of Medical Biochemistry and Biophysics, Karolinska Institute, Stockholm S-17177, Sweden
Author contributions: Katayama K, Nomura S, Tryggvason K and Ito M contributed to writing this paper.
Correspondence to: Kan Katayama, MD, PhD, Department of Cardiology and Nephrology, Mie University Graduate School of Medicine, 2-174 Edobashi, Tsu, Mie 514-8507, Japan. katayamk@clin.medic.mie-u.ac.jp
Telephone: +81-59-2321111
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Abstract

Alport syndrome (AS) is a hereditary nephritis caused by mutations in COL4A3, COL4A4 or COL4A5 encoding the type IV collagen α3, α4, and α5 chains, which are major components of the glomerular basement membrane. About 20 years have passed since COL4A3, COL4A4, and COL4A5 were identified and the first Alport mouse model was developed using a knockout approach. The phenotype of Alport mice is similar to that of Alport patients, including characteristic thickening and splitting of the glomerular basement membrane. Alport mice have been widely used to study the pathogenesis of AS and to develop effective therapies. In this review, the newer therapies for AS, such as pharmacological interventions, genetic approaches and stem cell therapies, are discussed. Although some stem cell therapies have been demonstrated to slow the renal disease progression in Alport mice, these therapies demand continual refinement as research advances. In terms of the pharmacological drugs, angiotensin-converting enzyme inhibitors have been shown to be effective in Alport mice. Novel therapies that can provide a better outcome or lead to a cure are still awaited.

Key words: Alport syndrome; Angiotensin-converting enzyme; Genetic; Hereditary nephritis; Pharmacological; Renal injury; Stem cell therapy

Core tip: There is currently no curative treatment for Alport syndrome, a progressive hereditary nephritis. However, many drugs have been demonstrated to slow the progression of renal injury in Alport mouse models. Alport mice treated with vasopeptidase inhibitors or angiotensin-converting enzyme inhibitors showed a more than two-fold longer survival than untreated Alport mice. A human clinical trial of an angiotensin-converting enzyme inhibitor is currently in progress. Genetic approaches have been used to elucidate the pathogenesis of this progressive renal disease. Stem cell therapies were also attempted, with some beneficial effects; however, they need to be improved before being tested in clinical trials.

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INTRODUCTION

Alport syndrome (AS) is characterized by a classic triad of renal injury, sensorineural deafness and ocular abnormalities[1]. The disease frequency of AS is about 1:5000[2]. AS begins with asymptomatic microscopic hematuria, progresses to characteristic thinning, thickening and splitting of the glomerular basement membrane (GBM), and finally leads to end-stage renal failure[3]. The causative genes of this syndrome are COL4A3, COL4A4 and COL4A5, which are associated with two types of

disease: X-linked and autosomal. The X-linked type of AS is caused by mutations in COL4A5[4], while the autosomal type of AS is caused by mutations in COL4A3 or COL4A4[5,6]. COL4A3, COL4A4 and COL4A5 encode the type Ⅳ collagen α3, α4 and α5 chains, respectively. Since the type Ⅳ collagen α3, α4 and α5 chains are major structural components of the GBM, AS is a type Ⅳ collagen disease.

The purpose of this review is to summarize the current knowledge that has been obtained using mouse models of Alport syndrome.

PATHOGENESIS

At the molecular level, there are only three triple-helical protomers, α1.α1.α2, α3.α4.α5 and α5.α5.α6, in type Ⅳ collagens[7]. The non-collagenous domain (NC1) at the carboxyl terminus of these protomers joins them to each other to make the suprastructure of the GBM. The α1/α1/α2, α1/α2/α5/α6 and α3/α4/α5 heterohexamers were identified by digesting the NC1 hexamer from human glomeruli with bacterial collagenase[7]. Interestingly, the α3/α4/α5 heterohexamer consists of one α4-α4 homodimer and two α3-α5 heterodimers, while the α1/α1/α2 heterohexamer consists of two α1-α1 homodimers and one α2-α2 homodimer, and the α1/α2/α5/α6 heterohexamer consists of two α1-α5 heterodimers and one α2-α6 heterodimer[7]. The α3 (Ⅳ) and α4 (Ⅳ) chains have to accompany the α5 (Ⅳ) chain, and the α3/α4/α5 heterohexamer consists of compositions of $(\alpha3)_2(\alpha4)_2(\alpha5)_2$[7]. NC1 domains were also demonstrated to contain recognition sequences to form α1.α1.α2 (Ⅳ) and α3.α4.α5 (Ⅳ) networks[8].

There is a developmental switch from α1 and α2 (Ⅳ) chains to α3, α4 and α5 (Ⅳ) chains; the GBM from capillary loop stage contains α3, α4 and α5 (Ⅳ) chains, as well as α1 and α2 (Ⅳ) chains, while the GBM at the comma- and S-shaped stages contains only α1 and α2 (Ⅳ) chains[9,10]. In mature glomeruli, the GBM is mainly composed of α3, α4, and α5 (Ⅳ) chains. While only the distal tubular basement membranes (TBMs) were positive for the α3, α4 and α5 (Ⅳ) chains in humans, nearly the full range of TBMs in the mouse are positive for the α3, α4 and α5 (Ⅳ) chains[9].

GBM in X-linked AS patients consists of only α1 and α2 (Ⅳ) chains because the developmental switch does not occur[10]. The loss of the α5 (Ⅳ) chain leads to the loss of all three chains (α3, α4 and α5 (Ⅳ) chains) in the GBM because of the defective assembly of triple-helical α3.α4.α5 (Ⅳ) protomers[11]. This abnormal GBM in X-linked AS patients is more susceptible to proteolysis by bacterial collagenase, cathepsin B, cathepsin G and *Pseudomonas* elastase than that in normal humans[10], because the collagenous domain of α1.α1.α2 (Ⅳ) protomers contains fewer disulfide cross-links than do α3.α4.α5 (Ⅳ) protomers[11].

Interestingly, AS patients with 5' glycine mutations have a later onset of end-stage renal failure than those with 3' glycine mutations, which is compatible with the fact that type Ⅳ collagen assembly starts from the NC1 domain at the carboxyl terminus[12,13].

By generating two hybrid kidneys that contained wild endothelial cells and COL4A3 -/- podocytes or COL4A3 -/- endothelial cells and wild podocytes, type Ⅳ collagen α3, α4 and α5 chains proved to be originally produced specifically by podocytes in the kidney[14], thus suggesting that AS is podocyte-associated disease.

Table 1 Mouse models of Alport syndrome

Gene	Mutation	Ref.
ARAS		
COL4A3	exon 48	[15]
COL4A3	exon 48-50	[16]
COL4A3-COL4A4	COL4A3 exon 2-COL4A4 exon 12	[17]
COL4A4	exon 30	[18]
XLAS		
COL4A5	exon 1	[19]

ARAS: Autosomal recessive Alport syndrome; XLAS: X-linked Alport syndrome.

MOUSE MODELS OF ALPORT SYNDROME

There were two COL4A3 knockout models reported in 1996. One model was generated by cloning a neomycin cassette into exon 48 of COL4A3[15]. The other model was generated by deleting three exons between exons 48 and 50 of COL4A3[16]. Both models aimed to disrupt exons in the NC1 domain, and the resulting phenotypes resembled those of autosomal recessive AS in human. The COL4DELTA3-4 model, which has a large deletion between exon 2 of COL4A3 and exon 12 of COL4A4, was also reported[17]. This mouse model was found because of the observation that there was unexpected renal disease in a transgenic line, and this model had a more severe type of AS than the above COL4A3 knockout models, because the expression of COL4A3 and COL4A4 mRNAs were not detected due to a lack of the intergene region of COL4A3-COL4A4. A new COL4A4 mouse model, which has a splice site mutation and skips exon 30 of Col4a4, was also recently reported[18]. Since this mutation does not cause a frame shift, this mouse model retains a mutant α4 (Ⅳ) chain in the GBM and represents a good new AS model.

Regarding the X-linked type, a COL4A5 knockout model was generated by making a nonsense mutation in exon 1 of COL4A5, and this has made the analysis of female carriers easier[19]. These five mouse models are summarized in Table 1.

The COL4A3 -/- mice have been the most commonly used as a mouse model of AS in experimental studies. This is partly because the survival of COL4A3 -/- mice is less variable than that of COL4A5 -/- mice[15,16,19]. Interestingly, the survival of COL4A3 -/- mice is influenced by the genetic background; being 66 d on a 129X1/SvJ background compared to 194 d on a

Table 2 The efficacy of pharmacological drugs in COL4A3 -/- mice

Drug	Survival (d)	Efficacy
Vasopeptidase inhibitor[22]	172	(+++)
ACE inhibitor[23]	150	(+++)
ARB[24]	98	(++)
HMG-CoA reductase inhibitor[26]	91	(++)
CCR1 inhibitor[27]	86	(+)
TNF-alpha antagonist[29]	81	(+)
Renin inhibitor[30]	78	(+)
Vitamin D analog[31]	75	(+)
Untreated (129SvJ background)	71	

ACE: Angiotensin converting enzyme; ARB: Angiotensin-II receptor blocker; CCR1: Chemokine (CC motif) receptor 1; HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme A; TNF: Tumor necrosis factor.

C57BL/6J background[20]. A linkage analysis of quantitative trait loci identified three markers on chromosome 9 and one marker on chromosome 16 that were suggested to be modifier genes. In this regard, it is important to use appropriate control littermates for all experiments. Although the 129 genetic background is good enough to assess the efficacy of new therapies in AS, the C57 genetic background might be better for assessing the long-term effects of new therapies.

The big difference between COL4A3 -/- mice and COL4A5 -/- mice is the existence of the α5 (IV) chain in the GBM of COL4A3 -/- mice[21]. Of note, the expression level of the α5 (IV) chain is more prominent in mice with a C57 genetic background than in those with a 129 genetic background[21]. To assess the efficacy of regeneration therapy in COL4A3 -/- mice, it is recommended that the α3 and α4 (IV) chains, not the α5 (IV) chain, should be used.

PHARMACOLOGICAL INTERVENTIONS

A vasopeptidase inhibitor, AVE7688, extended the lifespan of COL4A3 -/- mice dramatically, and it is the most effective drug against COL4A3 -/- mice identified so far[22]. The various drugs that have shown efficacy in treating COL4A3 -/- mice are summarized in Table 2.

An angiotensin-converting enzyme (ACE) inhibitor, Ramipril, was demonstrated to be effective for treating COL4A3 -/- mice[23]. Notably, early initiation of ACE inhibitor treatment was associated with a longer survival time, and this indicated that the ACE inhibitor had a renoprotective effect in the COL4A3 -/- mice, regardless of its impact on the blood pressure.

Moreover, Gross *et al*[24] compared the antifibrotic effects between an ACE inhibitor and an angiotensin receptor blocker (ARB), which was also known to be an angiotensin receptor 1 antagonist. Although both drugs prolonged the survival of COL4A3 -/- mice, the ACE inhibitor was much more effective than the ARB. Treatment with an ACE inhibitor reduced the transforming growth factor-beta 1 (TGF-β1) and connective tissue growth factor (CTGF) levels more effectively than did treatment with an ARB, which might explain the different effects between ACE inhibitors and ARBs, because TGF-β1 was demonstrated to be associated with renal disease progression in COL4A3 -/- mice[25].

A 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase inhibitor, which was originally used for the treatment of hypercholesterolemia, showed an antifibrotic effect in COL4A3 -/- mice, because it prolonged the survival by inhibiting the activation of fibrotic markers[26]. Interestingly, late initiation of treatment with the HMG-CoA reductase inhibitor at week 7 prolonged the survival of the mice from 71.3 to 90.5 d, while late initiation of ACE inhibitor treatment did not[23].

A chemokine receptor 1 antagonist, BX471, prolonged the survival of COL4A3 -/- mice by preventing interstitial macrophage recruitment[27]. That study showed the involvement of chemokines in the renal fibrosis of COL4A3 -/- mice. However, Ccl2 blockade did not prolong the survival of COL4A3 -/- mice even though it reduced the number of renal macrophages[28].

A tumor necrosis factor alpha antagonist prolonged the survival of COL4A3 -/- mice by decreasing podocyte apoptosis[29]. Aliskiren, a direct renin inhibitor, prolonged the survival of COL4A3 -/- mice by 18% by downregulating both TGF-β1 and CTGF in the kidney[30]. The combination of paricalcitol with an ACE inhibitor led to longer survival than the combination of calcitriol with the ACE inhibitor, which indicated that the different analogs of the active form of vitamin D exert different effects[31].

A matrix metalloproteinase (MMP) -2, -3, and -9 inhibitor cocktail prolonged the survival of COL4A3 -/- mice if it was administered before the onset of proteinuria[32]. In contrast, late administration of the inhibitor cocktail after the onset of proteinuria aggravated the renal disease of COL4A3 -/- mice, which was associated with increased interstitial fibrosis. This dual effect might explain why MMPs played a pathogenic role in the early stage, although they played a protective role in the late stage of disease in COL4A3 -/- mice[32]. MMP-12, also known as macrophage metalloelastase, was upregulated in the podocytes of Alport mice, and a MMP inhibitor, MMI270, which blocks MMP-2, -3, -9, -12 and -14, prolonged the survival of COL4A3 -/- mice from eight to 10 wk, while treatment with a MMP inhibitor that blocked MMP-2, -3 and -9 did not[33]. The authors of that study also showed that a CC chemokine receptor 2 antagonist, propagermanium, also prolonged the survival of COL4A3 -/- mice from eight to 11 wk.

At present, an ACE inhibitor has been reported to be the most effective treatment in humans[34]. A vasopeptidase inhibitor might be considered as the next candidate, since this drug led to the longest survival in COL4A3 -/- mice (Table 2).

GENETIC APPROACHES

TGF-β1 is involved in the progression of renal disease in COL4A3 -/- mice[25]. TGF-β1 was found to be sig-

nificantly upregulated after the onset of proteinuria. TGF-β1 and integrin α1β1 were found to affect distinct pathways in the pathogenesis of COL4A3 -/- mice[35]. While TGF-β1 inhibition prevented the thickening of the GBM, the deletion of integrin α1β1 diminished the foot process effacement of podocytes. Treatment with a combination of these approaches prolonged the survival of Alport mice. Recently, the same group showed that integrin α1 deletion in COL4A3 -/- mice decreased the mesangial invasion into the capillary loops of glomeruli[36]. Integrin α2 deletion in COL4A3 -/- mice prolonged the survival by 20% on a C57Bl6 background[37].

The deletion of discoidin domain receptor 1 (DDR1) in COL4A3 -/- mice prolonged the survival from 64.3 to 94.2 d[38]. Since DDR1 is expressed in podocytes, these results again showed the importance of podocyte involvement in the pathogenesis of AS.

Uterine sensitization-associated gene-1 (USAG-1) deletion in COL4A3 -/- mice improved the renal phenotype and improved the survival[39]. This result was compatible with the finding that recombinant human bone morphogenetic protein-7 (BMP-7) had a protective effect in COL4A3 -/- mice[40], because USAG-1 is known to counteract BMP-7 and is normally expressed in the distal tubules of the kidney[41]. Interestingly, they found that USAG-1 was also expressed in the macula densa, and showed the possibility of crosstalk between the macula densa and extraglomerular mesangial cells[39].

Although MMPs had been thought to be involved in the damage to the GBM in COL4A3 -/- mice, MMP-9 deletion did not affect the progression of renal disease in these mice[42]. Three MMPs; MMP-2, -3, and -9, were genetically ablated in COL4A3 -/- mice, and compensatory upregulation was shown among these MMPs[32]. Therefore, broad-spectrum MMP inhibition is likely required for any effects associated with the MMPs.

A mouse line which had a yeast artificial chromosome including COL4A3 and COL4A4 was generated, and this transgene could rescue the phenotype of COL4A3 -/- mice[43]. Although the expression level of the COL4A3 and COL4A4 transgenes were about 20% of the levels of COL4A3 and COL4A4 in a wild type mouse, the human α3 and α4 (IV) chains could assemble with the mouse α5 (IV) chain. This finding is very interesting, because the amino acid sequence homology of the α3 and α4 (IV) chains between the human and mouse, which are 79% and 78%, respectively, still allows for the formation of triple-helical α3.α4.α5 (IV) protomers.

The expression of an inducible human/mouse chimeric COL4A3 transgene after birth prolonged the lifespan of COL4A3 -/- mice by expressing α3, α4 and α5 (IV) chains in the GBM[44]. Notably, expression of the inducible transgene after three weeks of age could still rescue the phenotype of COL4A3 -/- mice, and the α3.α4.α5 (IV) protomers could integrate into the damaged GBM that was comprised by mainly a α1.α1.α2 network.

STEM CELL THERAPIES

There have been two reports that showed the efficacy of wild-type bone marrow transplantation (BMT) against the renal injury in COL4A3 -/- mice[45,46]. Prodromidi *et al*[45] reported that the blood urea nitrogen (BUN) and serum creatinine (Cr) levels were significantly improved in COL4A3 -/- mice that received wild-type (WT) bone marrow compared to those that received COL4A3 knockout (KO) mouse bone marrow (Table 3). The renal histopathology showed significant improvement of the glomerular injury and tubulointerstitial fibrosis in the WT to KO transplanted mice than in the KO to KO transplanted mice. Moreover, the α3 (IV) chain could be detected partially by immunofluorescence, but not in a Western blot analysis. Sugimoto *et al*[46] reported similar results (Table 3). They also showed that the BUN, Cr, and renal histopathology were significantly improved in the COL4A3 -/- mice that received 21-wk WT bone marrow than did the mice that received KO mouse bone marrow. An immunofluorescence study showed patchy staining of the α3 (IV) chain in the GBM of WT to KO transplanted mice. These two reports shared a common findings that BMT after irradiation from WT to COL4A3 -/- mice dramatically improved the renal injury even though the expression level of the α3 (IV) chain was very low. Neither group examined the survival after BMT as an absolute evaluation marker, so it is unclear whether the BMT could prolong the survival of the mice.

We also reported the results of BMT after irradiation in COL4A3 -/- mice[47]. In contrast to the previous two reports, the BUN, Cr, renal histopathology and survival were significantly improved in both WT to KO and KO to KO mice compared to the untreated KO mice, but there were no significant differences between the WT to KO and KO to KO mice (Table 3). The de novo expression of the α3 (IV) chain could not be detected in the WT to KO mice by immunofluorescence and Western blot analyses. However, wild type COL4A3 mRNA could be identified in the WT to KO, not in the KO to KO, mice by reverse transcription polymerase chain reaction. In fact, fewer than 1% of the podocytes were donor-derived when BMT was performed in a mouse model of mesangial sclerosis[48]. Since KO bone marrow had similar effects as WT bone marrow in the COL4A3 -/- mice, the effect of irradiation itself was examined at sublethal doses. Surprisingly, a sublethal dose of irradiation without subsequent BMT improved the survival of COL4A3 -/- mice. This suggests that the renal injury of COL4A3 -/- mice was improved by the irradiation, not by the BMT. The mechanism by which irradiation improved the survival remains to be clarified, since radiation exposure induces numerous effects.

Another group reported that multipotent mesenchymal stromal cells (MSCs) could not prolong the survival of COL4A3 -/- mice although they improved the interstitial fibrosis by producing vascular endothelial growth

Table 3 The effects of bone marrow transplantation therapy in COL4A3 -/- mice

	Prodromidi *et al*[45]		Sugimot *et al*[46]		Katayama *et al*[47]	
	WT -> KO	KO -> KO	WT -> KO	KO -> KO	WT -> KO	KO -> KO
α3 (IV) IF	+	-	+	-	-	-
α3 (IV) WB	no data	no data	+	-	-	-
Col4a3 mRNA	+	-	+	-	+	-
BUN and Cr	improved	no change	improved	no change	improved	improved
Renal pathology	improved	no change	improved	no change	improved	improved
Survival (d)	no data	no data	no data	no data	125	135

WT: Wild-type; KO: Knockout; IF: Immunofluorescence; WB: Western blot; BUN: Blood urea nitrogen; Cr: Creatinine.

factor[49]. MSCs in the kidney that transdifferentiated into renal cells could not be identified.

However, wild-type bone marrow cells were also shown to prolong the survival of unirradiated COL4A3 -/- mice[50]. Surprisingly, wild-type blood transfusion, as well as the injection of undifferentiated mouse embryonic stem cells, improved the renal function of unirradiated COL4A3 -/- mice, with the appearance of the *de novo* expression of the α3 (IV) chain in the GBM. Although these data confirmed that cell-based therapies could be effective, there was a large discrepancy between the expression patterns of the α3 and α5 (IV) chains: the expression of the α3 (IV) chain was patchy, while that of the α5 (IV) chain was linear. There might be an unknown association between the small amount of *de novo* α3 (IV) chains and the renal improvement of COL4A3 -/- mice that received WT bone marrow. Of interest, a single injection of amniotic fluid stem cells was recently shown to prolong the survival of COL4A5 -/- mice without *de novo* expression of α5 (IV) chains[51].

CONCLUSION

At present, there is no treatment available that can cure AS, and symptomatic renal protective therapies are currently the mainstay of treatment for AS. During the search for a treatment in Alport mice, ACE inhibitors were found to be the most promising therapeutic drugs as first-line therapy. This is a good example of the benefits of mouse studies, because this has led to a double-blind, randomized, placebo-controlled, multicenter EARLY PRO-TECT Alport trial[52]. BMT therapy is also promising, but is still controversial, given the fact that BMT itself is invasive[53]. Other therapeutic agents that have been proven effective in AS mouse models should be considered as the next options for clinical trials in patients with AS.

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MINIREVIEWS

Role of insulin resistance in uric acid nephrolithiasis

Hanhan Li, Dane E Klett, Raymond Littleton, Jack S Elder, Jesse D Sammon

Hanhan Li, Dane E Klett, Raymond Littleton, Jack S Elder, Jesse D Sammon, VUI Center for Outcomes Research Analytics and Evaluation, Henry Ford Health System, Detroit, MI 48202, United States

Author contributions: Li H and Klett DE drafted and finalized the manuscript; Elder JS, Littleton R and Sammon JD critically revised manuscript.

Correspondence to: Jesse D Sammon, DO, VUI Center for Outcomes Research Analytics and Evaluation, Henry Ford Health System, 2799 W. Grand Boulevard, Detroit, MI 48202, United States. jsammon79@gmail.com

Telephone: +1-207-6927167 Fax: +1-313-9164352
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Abstract

Metabolic syndrome has been implicated in the pathogenesis of uric acid stones. Although not completely understood, its role is supported by many studies demonstrating increased prevalence of uric acid stones in patients with metabolic syndrome and in particular insulin resistance, a major component of metabolic syndrome. This review presents epidemiologic studies demonstrating the association between metabolic syndrome and nephrolithiasis in general as well as the relationship between insulin resistance and uric acid stone formation, in particular. We also review studies that explore the pathophysiologic relationship between insulin resistance and uric acid nephrolithiasis.

Key words: Nephrolithiasis; Kidney calculi; Uric acid; Insulin resistance; Metabolic syndrome

Core tip: Increasing awareness of the association between prevalence of metabolic syndrome and uric acid nephrolithiasis has caused a closer examination into modifiable risk factors for stone recurrence. The mechanism behind this association is thought to be due to decreased ammoniagenesis as caused by insulin resistance in the proximal tubule of the kidney. The presence or recurrence of uric acid stones should prompt the physician to look for traits of metabolic syndrome. Further studies into this causal relationship may provide additional medical interventions to decrease incident stones.

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INTRODUCTION

In the United State, the prevalence of kidney stones has risen since 1976 and was estimated to be 8.8% in 2010[1,2]. The magnitude of this problem is exacerbated by a recurrence rate as high as 50% within 5 years[3]. The prevalence of kidney stones is largely dependent on many un-modifiable patient factors including gender, ethnicity, and geography[1]. However, a growing interest in the relationship between modifiable risk factors such as obesity, diabetes mellitus (DM) and metabolic syndrome (MetS) has developed in light of the increasing prevalence of these conditions[4].

The majority of kidney stones are calcium-based with uric acid (UA) nephrolithiasis comprising only 10% of calculi in the overall stone-forming population[5]. However, UA stones disproportionally affect certain cohorts. Among obese patients, UA nephrolithiasis accounts for up to 63% of the stone burden[6].

The central role insulin resistance appears to play in UA stone formation has been the subject of much research and debate. The exploration of this important relationship is the purpose of the current review. We first present epidemiologic studies that demonstrate the link between MetS and nephrolithiasis in general. We then

Table 1 Insulin resistance and kidney stone formation

Ref.	Type	Year	*n*	Study population	Relevant variables	Conclusion
Taylor *et al*[8]	Prospective	2005	241623	Health professionals from 3 different study cohorts starting as early as 1980	Patient reported BMI, waist circumference, and incidence of nephrolithiasis	Obesity, weight gain, and waist circumference are positively associated with renal stone disease
Taylor *et al*[7]	Cross-sectional	2005	220478	Health professionals	Patient reported incidence of diabetes and kidney stones	Patients with DM have higher relative risk of having stones Patients with kidney stones were more likely to develop DM
Rendina *et al*[27]	Cross-Sectional, single institution	2009	2132	Consecutive Caucasian inpatients in a single Italian hospital	AHA/NHLBI criteria for MetS diagnosis, kidney stones diagnosed on US	MetS, specifically HTN and obesity (in females) is significantly associated with US evidence of kidney stones
Chang *et al*[28]	Prospective, single institution	2011	3872	South Korean workers participating in comprehensive health exam from 2002-2009	National Cholesterol Education Program's Third Adult Treatment Panel criteria for MetS diagnosis, kidney stone diagnosed on US	MetS is significantly associated with acidified urine and increased risk of kidney stones MetS overtime as well as each additional MetS trait predicted development of kidney stones
Kabeya *et al*[9]	Cross-Sectional, single institution	2012	2717	Japanese patients undergoing MetS screening	Fasting serum insulin, FPG, HbA1c, US for diagnosis of kidney stone	Glycemic control may be in independent risk factor for kidney stones. The number of MetS traits is positively associated with kidney stone risk, specifically, patients with all 5 traits are at a 2.7 x increased risk of kidney stones compared to those with 2 traits
Kohjimoto *et al*[29]	Cross-Sectional	2013	11555	Japanese survey	MetS traits, incident kidney stones – multiple and recurrent	Increasing number of MetS traits increased stone burden

IR: Insulin resistance; HA/NHLBI: Heart Association/National Heart, Lung, and Blood Institute criteria; FPG: Fasting plasma glucose; MetS: Metabolic syndrome; DM: Diabetes mellitus; UA: Uric acid.

highlight studies examining the increased prevalence of UA stones in patients with insulin resistance. Finally we review of currently accepted pathophysiologic mechanisms that support the role of insulin resistance in UA stone formation.

METABOLIC SYNDROME AND NEPHROLITHIASIS

MetS comprises traits of insulin resistance (IR), obesity, hypertension (HTN), and hyperlipidemia. Multiple studies demonstrate that MetS and its constituent components are associated with increased risk of kidney stones (Table 1).

One of the largest studies to examine the link between components of MetS and nephrolithiasis was by Taylor *et al*[7] who reported a cross-sectional analysis of three large national patient surveys: Nurses Health Study I, Nurses Health Study Ⅱ, and Health Professionals Follow-Up Study. This investigation included over 200000 health professional males and female nurses responding to surveys administered every 2 years with an age range of 25 to 75 years of age. The study concluded that diabetes mellitus type Ⅱ (DM) was significantly associated with kidney stone formation with a relative risk of 1.38 in older women, 1.67 in younger women, and 1.31 in men as compared to non-diabetic patients after controlling for age, body-weight index (BMI), thiazide use, and diet. Additionally, they reported that among patients with kidney stones, the relative risk of developing diabetes was 1.33 in older women, 1.48 in younger women, and 1.49 in men as compared to patients without nephrolithiasis. In a separate analysis of these data, Taylor *et al*[8] reported that obesity, weight gain, and waist circumference were risk factors for incident kidney stones. Together, these studies support the underlying connection between the main components of MetS and kidney stones. While the conclusions of these studies are strengthened by the very large size of the study cohort, the analysis is likely biased by the use of self-reported outcomes in these datasets.

In another large study, Kabeya *et al*[9] showed a significant association between certain traits of MetS and kidney stone formation in 2717 healthy Japanese individuals. Traits significantly associated with increased risk of kidney stone formation included glucose intolerance (fasting plasma glucose ⩾ 100 mg/dL, OR 1.53) and HTN (Systolic ⩾ 130 mmHg, Diastolic ⩾ 85 mmHg, OR 1.42). In addition, they demonstrated a dose-dependent relationship between metabolic syndrome traits and kidney stone formation. The odds of patients with three or more traits of MetS [abdominal obesity, glucose intolerance, HTN, hypertriglyceridemia, and/or low high density lipoprotein (HDL) developing kidney stones was 1.48 times higher than those without these traits. This association was not shown for patients with two or fewer traits of MetS. This finding is especially important as a dose dependent response suggests a causal link between MetS and kidney stones. Although this study provides robust evidence for this association, it was limited by inclusion of a single Japanese population, reducing generalizability to other at risk populations. In addition, the cross-sectional study design confounds the temporal relationship between kidney stone formation and MetS.

Table 2 Insulin resistance and uric acid stone formation

Ref.	Type	Year	*n*	Study population	Relevant variables	Conclusion
Lieske *et al*[30]	Retrospective, Case Control, single county in Minnesota	2006	7122	Known stone former *vs* Control	Stone analysis, metabolic evaluation	DM, obesity, and HTN are associated with the development of kidney stones. DM is significantly associated with UA stone formation
Daudon *et al*[10]	Cross-sectional	2006	2464	DM *vs* Non-DM stone formers	Stone analysis, BMI, clinical and lab data in a subset of stone formers	DM is associated with a higher overall frequency of kidney stones, specifically, UA. UA stone formation can reflect IR and patients should be evaluated for MetS and/or DM if UA stones are diagnosed.
Akman *et al*[11]	Retrospective, single institution	2012	146	MetS *vs* Non-MetS undergoing PCNL	Kidney stone analysis, imaging for initial/recurrent kidney stone diagnosis, baseline blood chemistry and urinalysis	Patients with MetS have a higher frequency of UA stones (21.9% *vs* 4.1%) and a higher rate of all stone recurrence following PCNL
Cho *et al*[12]	Retrospective, three institutions	2012	712	MetS *vs* Non-MetS undergoing endourologic intervention for stones	Stone analysis, metabolic data, International Diabetes Federation definition for MetS	MetS, specifically the traits of impaired fasting glucose and hypertriglyceridemia, is significantly associated with UA stone formation, but calcium based stones remain most common in this group
Kadlec *et al*[31]	Retrospective, single institution	2012	590	All stone formers undergoing endourologic intervention	Stone analysis, MetS factors (presence of obesity, DM, HTN, and HL)	DM and HTN, components of MetS, are significantly associated with UA containing stones
Stansbridge *et al*[32]	Retrospective, single institution	2013	1504	UA stone formers *vs* Non-UA	24H urine, stone analysis, relevant underlying diagnoses, including DM	UA containing stones are increased in DM, but calcium containing stones are still the most common in DM
Inci *et al*[33]	Case-control, single institution	2012	99	Control *vs* Stone formers (substratified by stone type)	Stone analysis, metabolic evaluation	BMI and Hyperlipidemia, two major traits of IR/MetS, are significantly associated with calcium and UA stone formation
Zhou *et al*[34]	Retrospective, single institution	2013	269	UA stone formers *vs* Non-UA stone formers undergoing PCNL	CT for visceral fat area measuremen, stone analysis, metabolic evaluation	HTN and visceral fat area, two traits highly associated with IR/MetS, are independent risk factors associated with UA stone formation

IR: Insulin resistance; MetS: Metabolic syndrome; DM: Diabetes Mellitus; UA: Uric acid; HTN: Hypertension; PCNL: Percutaneous nephrolithotomy.

INSULIN RESISTANCE INCREASES RISK OF URIC ACID NEPHROLITHIASIS

Because different types of kidney stones have a tendency to form in different urine milieus, there has been substantial interest in studying the link between insulin resistance and UA stone formation. Low urine pH is a factor of both insulin resistance and UA stone formation; it has therefore been hypothesized that MetS should favor the formation of UA stones[10]. Multiple studies performed stone analyses in order to query the relationship between insulin resistance and specific kidney stone type (Table 2). In a study of 2464 kidney stone formers, Daudon *et al*[10] found that in patients with DM, UA stones accounted for 35.7% of all stones while only 11% in non-diabetic patients, $P < 0.0001$. The authors recommended that patients with UA stones should be evaluated for insulin resistance or MetS as the prevalence of DM in the UA stone population (27.8%) was significantly higher than the prevalence of DM in the population forming other stone types (6.9%).

Other studies have also demonstrated increased odds of UA stones in patients with MetS. In particular, Akman *et al*[11] found UA stones to be significantly more common in patients with MetS compared to patients without MetS (21.9% *vs* 4.1%, $P < 0.001$) in a group of 146 stone formers. Furthermore, the authors suggested that patients with MetS may be more susceptible to UA stone recurrence. In their study a trend toward higher recurrence of UA stone formation was demonstrated in patients with MetS as compared to patients without MetS (42.9% *vs* 0%, $P = 0.51$). Although a statistically significant association was not found, the study may have been underpowered to detect a difference. Therefore, a relationship between MetS and UA stone recurrence may exist, and further study is required.

In a separate study of UA stone formation in MetS, Cho *et al*[12] showed that MetS was an independent risk factor for UA stone. In an analysis of individual MetS traits, a direct relationship between UA stone and MetS traits was uncovered: as the number of MetS traits increased, the risk for UA stones increased (10.2% in patients with one MetS trait and as high as 30.4% with four components). These studies are limited by their use of cross-sectional or retrospective designs. Nevertheless, the relationship between UA stones and MetS established by these studies should prompt physicians to evaluate patients presenting with UA stones for underlying insulin resistance and related comorbidities.

Table 3 Pathophysiologic relationship between insulin resistance and uric acid stone formation

Ref.	Study Type	Year	*N*	Study population	Outcomes	Conclusion
Facchini *et al*[13]	Cross-sectional, single institution	1991	36	Healthy volunteers with varying degrees of IR	24H urine (pH, UA), UA clearance, steady-state plasma glucose, metabolic evaluation	As IR increases serum UA increases and urinary UA clearance decreases. Thus, serum UA concentration may be considered an additional trait of MetS
Cappuccio *et al*[14]	Cross-sectional, single institution	1993	568	Factory volunteers	Fasting spot urine (UA), fractional excreation of Na+, fasting blood analysis	The higher the serum UA level, the greater the amount of renal Na+ reabsorption. This phenomenon is consistent with hyperinsulinemia, and possibly IR, as insulin is known to increase renal sodium reabsorption
Pak *et al*[15]	Retrospective, single institution	2001	56	UAF *vs* matched control with diet control	24H urine	UA stone formers have increased serum UA, decreased fractional excretion of urinary UA, and decreased urinary pH
Sakhaee *et al*[16]	Prospective, single institution	2002	70	Healthy *vs* stone formers (UA *vs* Calcium *vs* Mixed) with diet control	24H urine (pH, NH4+), fasting glucose	UA stone formers are more likely to have IR/DM. UA stone formation occurs due to impaired NH4+ excretion and urine acidification. Acid loading further decreases urinary pH in these patients as compared to non-UA stone formers/Controls
Abate *et al*[17]	Prospective, single institution	2004	68	Stone free patients *vs* UA stone formers with diet control	24H urine (pH, NH4+), glucose disposal rate	Acute hyperinsulinemia leads to elevated urinary pH and NH4+ excretion in normal insulin-sensitive subjects. Alternatively, IR is associated with low urinary pH and impaired NH4+ excretion and could be renal manifestations of IR causing UA stone formation
Maalouf *et al*[23]	Cross-sectional, single institution	2007	148	MetS *vs* No MetS (all stone free)	24H urine (pH, NH4+), Homeostasis model for IR, metabolic evaluation	Acidic urine is a feature of MetS and is associated with the degree of IR. As MetS traits increase, urine pH decreases
Bobulescu *et al*[24]	Prospective, single institution	2013	35	Matched patients with and without UA stones, match non-stone forming diabetic controls	24H urine, urinary ammonium excretion	Both uric acid non-diabetic patients as well as DM non-stone forming patients had lower urinary pH as compared to matched non-stone forming non-diabetic controls
Cameron *et al*[25]	Prospective, single institution	2011	19	UA stone formers *vs* normal controls with diet control	24H urine, diurnal urinary pH	UA stone formers had decreased urinary pH with increased undissociated UA secretion compared to normal controls

IR: Insulin resistance; DM: Diabetes mellitus; UA: Uric acid; MetS: Metabolic syndrome.

PATHOPHYSIOLOGY OF URIC ACID STONE FORMATION IN PATIENTS WITH INSULIN RESISTANCE

The pathophysiologic basis for UA stone formation in patients with insulin resistance has been widely studied and a summary of important articles on this subject can be found in Table 3. Surprisingly, UA stone formation in insulin resistance does not depend on the presence of more UA in the urine. In fact, several studies revealed that insulin resistance decreases UA clearance[13,14]. This finding suggests that another causal mechanism may be responsible for UA nephrolithiasis in patients with insulin resistance. Clinically, UA stone formers have low urinary pH. Pak *et al*[15] studied 56 pure and mixed UA stone formers and 68 control subjects, patients were instructed to consume a calorie restricted diet and maintain high fluid intake. They showed that UA stone formers had higher serum UA levels but lower urinary UA levels. Nonetheless, urinary pH was 5.34 in UA stone formers compared to 6.17 in control subjects. This study suggests that it may be low urine pH rather than elevated urine UA levels that plays a critical role in UA stone formation.

In 2002, Sakhaee *et al*[16] published a key study revealing a defect in urinary ammoniagenesis among UA stone formers. After equilibrating to a control diet, UA stone formers demonstrated lower urinary pH and decreased urinary ammonium excretion as compared to normal controls and calcium stone formers. Furthermore, after patients were given an acidic load, pure and mixed UA stone formers experienced a greater degree of urine acidification when compared to both normal controls and calcium stone formers. These findings suggest that although diet has a strong impact on stone formation, patients forming UA stones may be at a particular disadvantage relative to their calcium stone forming peers at any level of diet acidity.

Given the above findings, it is reasonable to ask what is unique about UA stone formers that could cause this defect in urinary acid handling. Abate *et al*[17] revealed that insulin resistance is a driver of low urinary ammonium and pH. UA stone formers and healthy volunteers underwent a study in which they were maintained at a steady state diet and were given controlled doses of insulin (hyperinsulinemic-euglycemic procedure). Baseline 24-h urine collection revealed evidence of lower urinary pH, lower citrate excretion, higher net acid excretion and lower ammonium excretion in the UA stone formers. This suggests that the acid that is secreted is not being buffered adequately by ammonium. They also noted

(though not statistically significant) that UA stone formers with progressively lower urine pH tended to have lower glucose disposal rates (insulin resistance).

The specific mechanism for urinary acidification has been suggested by several novel vitro studies. Insulin receptors are expressed in the renal tubular epithelium, and insulin stimulates the renal tubular sodium-hydrogen exchanger (Na^+/H^+ exchanger) to increase reabsorption of hydrogen[18,19]. The activation and up-regulation of the Na^+/H^+ exchanger by insulin promotes ionic trapping of ammonia in the renal tubule; hydrogen ions become bound to ammonia, which is converted to ammonium and is unable to exit the lumen of the renal tubule[20-22]. Resistance to insulin thereby results in decreased buffering capacity for urinary acidification due to decreased ammonia secretion.

The critical relationship between MetS and urine acidification has been supported by Maalouf *et al*[23] who showed that non-stone formers with MetS had decreasing urinary pH with increasing number of MetS traits. Their work supports the theory that insulin resistance plays a role in renal acid handling causing decreased ammoniagenesis thereby increasing risk of UA stone formation.

Though insulin resistance appears to be playing a significant role in UA stone formation, not all DM patients go on to develop UA stones. This principle was explored by Bobulescu *et al*[24], who prospectively studied BMI-matched non-diabetic pure UA stones formers, diabetic non-stone formers and non-stone forming non-diabetic control patients. Their results demonstrated that both non-diabetic UA stone formers as well as diabetic non-stone forming patients have decreased urinary pH as compared to matched non-diabetic non-stone forming controls. However, non-diabetic patients with UA stones have impaired ability to secrete ammonium after acid loading as compared to diabetic and non-diabetic control patients without nephrolithiasis[24]. This suggests that while insulin resistance plays a role in UA stone formation, additional derangements may occur in these UA stone formers as compared to non-stone formers with DM.

Another salient and surprising feature of studies examining 24-h urine chemistries in UA stone formers *vs* non-stone formers is a frequent absence of difference in urine chemistries. Cameron *et al*[25] discovered a significant diurnal variation in urine acidification occurring in UA stone formers. This intermittent elevation urinary acid levels lead to transiently lower urine pH, allowing for the precipitation of UA, despite a relatively normal 24-h urine chemistry.

MANAGEMENT RECOMMENDATIONS

Currently the American Urologic Association guidelines recommend metabolic testing for recurrent stone formers and high-risk stone patients[26]. This work-up includes an initial 24-h urine chemistry followed by repeat testing if stones recur or after initiation of therapy. For patients with UA stones, fluid intake should be sufficient for 2.5 liters of urine output and dietary changes aimed at limiting animal protein a key driver of urinary acid levels. Additionally potassium citrate should be recommended to alkalinize the urine (increase urine pH) in an effort to decrease recurrence of UA stones. Nevertheless, these management guidelines do not address the underlying mechanism responsible for UA stone formation in insulin resistance. Further research targeting the defects in ammoniagenesis in insulin resistance may yield novel therapies for this challenging clinical problem.

CONCLUSION

This review explores the relationship between UA nephrolithiasis and insulin resistance. Several epidemiologic studies identify the association between insulin resistance and kidney stones, specifically UA stones. The mechanism underlying this association relates to the importance of renal insulin receptors in acid handling. Insulin resistance results in impaired excretion of urinary ammonia leading to lower urinary pH. Ultimately, these conditions induce UA precipitation out of the urine, leading to the formation of UA stones. As one of the key components of metabolic syndrome, insulin resistance should be suspected in patients with recurrent UA nephrolithiasis, and attention should be directed to the other components of metabolic syndrome, including hypertension, dyslipidemia, and obesity.

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MINIREVIEWS

Ureteroscopy and stones: Current status and future expectations

Anna E Wright, Nicholas J Rukin, Bhaskar K Somani

Anna E Wright, Nicholas J Rukin, Department of Urology, New Cross Hospital, Wolverhampton WV10 0QP, United Kingdom
Bhaskar K Somani, Department of Urology, University Hospital Southampton NHS Trust, Southampton SO16 6YD, United Kingdom
Author contributions: Wright AE, Rukin NJ and Somani BK solely contributed to this paper.
Correspondence to: Bhaskar K Somani, Honorary Senior Lecturer, Consultant Urological Surgeon (Stone Lead), Department of Urology, University Hospital Southampton NHS Trust, Tremona Rd, Southampton SO16 6YD, United Kingdom. bhaskarsomani@yahoo.com
Telephone: +44-23-80795273 Fax: +44-23-80795272
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Abstract

Urolithaisis is becoming an ever increasing urological, nephrological and primary care problem. With a lifetime prevalence approaching 10% and increasing morbidity due to stone disease, the role of ureteroscopy and stone removal is becoming more important. We discuss the current status of stone disease and review the ever increasing role that ureteroscopy has to play in its management. We discuss technological advances that have been made in stone management and give you an overview of when, how and why ureteroscopy is the most common treatment option for stone management. We touch on the role of robotic ureteroscopy and the future of ureteroscopy in the next 10 years.

Key words: Ureteroscopy; Techniques; Ureteral stones; Calculi; Treatment; Advances

Core tip: This manuscript demonstrates the advent, technical progression and modern use of ureteroscopy for stone disease. It begins with a brief epidemiology of renal stone disease, technological advances in flexible ureteroscope, use of laser for stone disease and the different types of surgical options available. We also share the current evidence of ureteroscopy for stone treatment in obesity, pregnancy, pediatrics and patients with bleeding diathesis and large renal stones. In the end we discuss what the future holds for ureteroscopy including an insight into robotic ureteroscopy.

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INTRODUCTION

With an increasingly ageing population, rising obesity, poor dietary habits and lack of adequate fluid intake we are seeing a rise in the incidence of renal and ureteric calculi[1-9]. This directly effects patient morbidity and places an ever increasing demand on healthcare resources. The concept of urinary stones is not new, indeed "cutting for the stone" was one of the classic three operations described more than 2000 years ago. It is somewhat ironic now, that endourological surgeons rarely "cut for the stone", but more "fish out" the stone with ureteroscopy (URS). Without doubt, the technological advances over the last 30 years has revolutionised our current management of urinary tract stone disease. We aim to highlight the importance of stone disease and take you through the important technological changes, discuss current concepts in stone management, explain what is new in ureteroscopy and touch on the future of ureteroscopy in the management of stone disease.

EPIDEMIOLOGY OF STONE DISEASE

Urolithiasis is a major clinical and economic burden for modern healthcare systems[10]. International epidemiological data suggest that the prevalence of stone disease is increasing[11]; with a rise in lifetime prevalence between 7%-12%. The mean age of patients with upper tract stones has remained constant at 49 years, although there has been an alarming increase of 19% in the number of children diagnosed[11]. The ever increasing prevalence of stone disease has a direct effect on healthcare resources, with the number of URS performed for stone disease increasing by 127% over the last 10 year period 2000-2010[11].

The rising prevalence of stone disease is multifactorial, but poor dietary habits and fluid intake, increasing levels of obesity and "metabolic syndrome" may further increase stone-related clinical episodes[12,13]. This emphasises the importance of education and lifestyle adaptations in attempting to prevent stone formation for at risk groups and the critical role of secondary prevention for those who have already suffered with stones.

TECHNOLOGICAL ADVANCES IN URETEROSCOPY

The use of URS has dramatically increased over the last 30 years mainly due to the rapid speed of technological advances. Since the advent of the first recorded URS in 1912[14]; the past century has seen a continued development of the ureteroscope alongside diversification of its use. Evaluation of the urinary tract was initially explored with specula, next came urethroscopy with dilatations of the urethra using knives and wax instruments[15]. The prototype endoscope, the "Lichtleiter", was introduced back in 1806 by Phillip Bozzini, and consisted of a hollow tube transmitting candlelight *via* a mirror[15]. This enabled the first true endoscopic operation in 1853 when Desormeaux extracted a urethral papilloma through the endoscope[15]. Further modifications to the endoscope were introduced by the dermatologist Grunfield of Vienna, who developed an endoscopic loop threader and scissor forceps allowing the first endoscopic bladder papilloma excision in 1881. The step from idea to realisation of endoscopic surgery was difficult and protracted. Bozzini *et al* ideas from the early 1800's were well ahead of their time. They were considerably hindered by the technical capabilities of the nineteenth century engineering, which resulted in clumsy and heavy instruments. In parallel with the development of the cystoscope there was continuing advancements in the endoscopic light source. A system of mirrors and lens' were introduced alongside candlelight to transmit light through a hollow tube; this idea was superseded by fibre-optic technology utilising the principle of internal reflection permitting the "bending" of light within flexible glass[16]. These principle and understanding lead onto the development of the first rigid ureteroscope in 1980. This was developed by Perez-Castro in collaboration with Karl Storz, incorporating a separate working and optic channel. These developments allowed the art of ureteroscopy to flourish and develop over the last 35 years[17].

The development of electrohydraulic and ultrasonic lithotripsy soon followed, enabling the fragmentation of ureteric stones[17]. Flexible tip ureteroscopes were introduced in 1983[16], and the modern digital scopes soon followed. Modern digital flexible ureteroscopes consists of a fiberoptic lens, with a single cable electronically transferring the image detected at the tip of a scope to the image display on a monitor ("Chip to tip" technology). Digital and conventional (fibre-optic) flexible ureteroscopes have seen a dramatic improvement in ergonomics, with lighter scopes and improved manoeuvrability[18]. The advent of digital images has resulted in improved resolution and colour discrimination, as well as significantly reduced operative times[16,19-21]. Figure 1 demonstrates the modern flexible ureterorenoscopes that we use in clinical practice today.

Despite improvements in scope technology, one still needs to fragment and/or remove the stone once visualised. Stones are commonly fragmented with a holmium laser (Light Amplification by Stimulated Emission of Radiation). Albert Einstein and Satyendranath Bose proposed the concept of lasers, but lasers were initially seen as a great invention with no obvious use. With time and hard work by laser pioneers, we now cannot imagine a world in which we don't use lasers. Indeed, the role of the Holmium laser in the management of renal tract stones has resulted in many stones in the urinary tract have been accessible to treatment in a minimally invasive fashion. Laser offers the surgeon a safe, effective method of stone fragmentation. One real benefit is the fact that laser can be manoeuvred around bends, enabling it to be used throughout the kidney. The lithotripter, although a useful adjuvant for ureteroscopy, has its limitations including stone retropulsion back into the kidney. The lithotripter is still commonly used for percutaneous nephrolithotomy surgery (PCNL), where larger stones can be fragmented quickly, without the need to manoeuvre around each calyx.

SURGICAL MANAGEMENT OF STONE DISEASE

Traditionally ureteric and renal stones were managed by open surgical techniques, and it was not until the 1980s and the advent of the Dormier H3 lithotriptor that shock wave lithotripsy (SWL) became common place[16]. SWL offered a relatively minimally invasive treatment option for patients, with acceptable outcomes in terms of stone free rates (SFR)[22]. With the advent of minimally invasive surgery, particularly URS, SWL treatment numbers are falling. Recent United Kingdom, American and Australian data clearly demonstrate dramatically rising rates of ureteroscopy, which far exceed small rises in

Figure 1 Flexible ureterorenoscope.

the use of SWL[1,11,23].

Current American and European Urology Association Stone guidelines summarise the current evidence based treatment for stone management based on stone size and location[24]. The size and location of the stone are the most important factors in determining which treatment options are most suitable, but individual surgeon's treatment preference is important in making treatment decisions for each treated stone.

The position of the stone in the ureter directly reflects in the success of the procedure. More distal stone have higher success rates when treated with rigid ureteroscopy, compared to the more proximal stones[24]. Indeed proximal stones can fall back into the kidney, therefore they often require a concurrent flexible ureteroscopy to achieve good stone free rates. Current guidelines recommend ureteroscopy, over other treatments including SWL, for the majority of ureteric stones[24].

In terms of stone size conservative management may be appropriate for smaller stones; 95% of stones up to 4 mm pass within 40 d[25]. Current recommendations advise the use of PCNL over URS and laser for larger more complex stones. The recommended size of stone treated by URS is increasing with each new update of stone guidelines, with the current size value of 20 mm and above favouring a percutaneous approach to treatment (PCNL)[24]. Despite this there is very good clinical evidence[26] for using URS for stones greater than 20 mm in size, with 94% deemed stone free after a mean number of 1.6 URS treatments. This data is comparable, and arguably better, than standard PCNL treatment with reduced morbidity and shorter length of hospital stay[27].

Stones greater than 2 cm often require planned two stage URS procedures to achieve complete stone clearance[28]. Although this necessitates staged procedures, it may be a worthwhile sacrifice in view of nephron preservation and the low complication rate[29]. This is not an insignificant consideration when treating an ever-increasing co-morbid patient. A comparison of the available treatment modalities, in terms of advantages, disadvantages and contraindications is summarised in Table 1.

URETEROSCOPY IN THE CURRENT ERA

Technological advances in the design and size of the ureteroscopes has enabled easier access to the kidney and ureters *via* the urethra, removing the need for any surgical incision. With rigid and flexible URS nearly all areas in the urinary tract can be readily accessed, with stunning high quality digital optics providing very accurate assessment of stones and mucosal lesions. One of the main benefits of URS is that there are minimal contra-indications for the procedure. A general anaesthetic is often required, but upper tract access with spinal or local anaesthetic can be achieved[30]. The only real contraindication would be a ureteric stricture preventing successful ureteric access and scope passage[24]. Fluoroscopy is required during URS, but radiation exposure can be reduced with careful consideration of when and how much fluoroscopy is needed. The benefits of URS are clearly evident in the literature, with low complication rates, high SFR, and short length of stay[26,28].

As with any procedure complications can happen, but the reported complication rates are relatively low[29,31]. The overall complication rate for URS is approximately 3.5%; which are mostly minor. Probably the most feared complication of ureteroscopy is ureteral avulsion, however it is rare (< 1%). Common complication include mucosal or ureteric injury (1.5%-1.7%), post-operative fever (1.8%), urosepsis, haematuria, ureteral stricture (0.1%) and persistent vesicoureteric reflux (0.1%)[29,32]. Due to its minimally invasive nature, URS can be performed as a day case procedure. This has obvious benefits for hospital finances, as well as patient satisfaction levels[11].

In recent years the role of URS has expanded, particularly with reference to an increasingly obese population, during pregnancy, bleeding diathesis and paediatric stone disease. With obesity rates at an all-time high[12,13] and the association of kidney stones in such patients, these groups can often be difficult to manage. The anaesthetic risk can be significantly increased and other treatment such as SWL or PCNL are often less successful[33]. Ureteroscopy is often ideal for such patients, as their renal tract can be readily be accessed[34]. Indeed, currently guidelines recommend URS as the most promising therapeutic option in obese patients[24].

Pregnancy offers a unique situation in terms of urinary stones disease. A cascade of metabolic changes occurs during pregnancy that may be associated with an increased likelihood of stone formation, particularly in the second and third trimester[35,36]. Whenever possible, conservative treatment of stones are encouraged. If complications do develop, URS can offer a minimally invasive treatment option for patients and hopefully avoid the need for long term urinary diversion with either a stent or nephrostomy tube[37,38]. A recent systematic review suggests that URS is a safe and effective procedure that can be used as the first line surgical management of

Table 1 Advantages and disadvantages of different techniques[24]

	Contra-Indications	Advantages	Disadvantages
Percutaneous nephrolithotomy	Pregnancy, potential malignant kidney tumour, tumour in access tract area, atypical bowel interposition	Large renal and staghorn stones Able to remove large fragments Quicker large stone fragmentation and removal	Needs renal puncture plus dilatation Renal bleeding +/- embolisation Patient positioning (often prone) Requires a general anaesthetic (with risk in prone ventilation) Multiple days inpatient stay
Shock wave lithotripsy	Infection, pregnancy, arterial aneurysm, bleeding diatheses, distal ureteric obstruction	Non-invasive treatment Out-patient treatment No anaesthetic needed	Lower success rates Renal colic (secondary stone fragments) Steinstrasse May need multiple treatments Success rates less for lower calyx stones
Ureteroscopy	None	No incisions Day case procedure Can be used in pregnancy, obese and patients not suitable for prone position	Might require 2 operations for stone clearance May need a ureteric stent post op Ureteric avulsion/strictures Requires a general anaesthetic

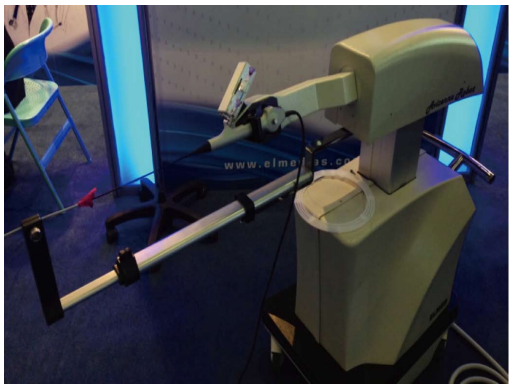

Figure 2 Robotic ureteroscopy.

symptomatic stones during pregnancy[36].

Patient with bleeding diathesis are at significantly increased risk of complications with treatments including SWL, PCNL, laparoscopic or open surgery[39-42]. For such patients, URS offers a safe and effective treatment modality. With ever increasing use of anticoagulation, based on risk assessment, these patients are an at-risk group and can be very difficult to manage surgically[24,43]. In term of URS and anticoagulation the literature is limited. A critical analysis of the published literature has shown good SFR with minimal complications when performing URS whilst the patient remains on anticoagulation. One worries about the rate of bleeding, but the combined data on URS reports a relatively low figure of 4% minor bleeding whilst on anticoagulation[44].

Childhood urolithiasis is becoming more prevalent, with a significant number of patients experiencing their first stone episode in childhood[24]. Such patients present diagnostic and treatment dilemmas, particularly their suitability for treatment due to their organ size. Traditionally the majority of these patients were treated with SWL, with reported SFR of approximately 80%[45]. With smaller calibre scopes and improved scope instrumentation such as smaller baskets and laser fibres, the role for URS has slowly increased. A recent systematic review has demonstrated SFR of up to 93% can be achieved with URS in a paediatric population[45].

FUTURE ADVANCES IN URETEROSCOPY

The future of URS is one of massive technological advances. With ever decreasing scope size, better optics and new device coming to market no corner of the urinary tract is inaccessible or unsuitable for access with URS. Ever more complex patients, with a plethora of medical problem are now becoming increasingly appropriate for URS.

Robotic surgery has recently entered the field of urology, particularly with reference to prostate, bladder and renal cancer treatment. URS has also had the robotic treatment, with the introduction of robotic flexible ureteroscopy. This "Robot" offers the surgeon the ability to control their flexible ureteroscope and laser fibre via the comfort of a robotic console. Figure 2 demonstrates this robotic device. The main robotic station holds the flexible ureteroscope whilst the surgeon controls the URS via a console and joystick devices. With only a few prototypes in clinical use and the procedure in its infancy this is a large area for future clinical development. Initial results are interesting; with the biggest benefit seeming to favour surgeon ergonomics rather than SFR[46]. Long term outcome data is awaited with anticipation.

Another area of future interest is the use of peptide-coated iron oxide-based microparticles[47]. These microparticles selectively adhere to calcium stone fragments enabling quicker retrieval of intraoperative stone fragments with the aid of a magnetic device, when compared to standard stone removal[47]. URS is without doubt an attractive area for technical innovation; where new advances have a huge potential to improve outcome and SFR.

CONCLUSION

With an ever-increasing prevalence of stone disease

careful consideration needs to be given to meet future demand. A large area of attention needs to be placed on primary and secondary stone prevention, with simple but effective patient education and lifestyle interventions.

In terms of URS, the future is one of great excitement. Larger stones, more complex patients, paediatric patients, pregnancy, bleeding diathesis and the obese are becoming more suitable than ever for minimally invasive URS. With the advent of future technological advances, the boundaries of what is achievable will be further expanded. Robotic is entering the playing field and is potentially the next big development in URS. The next 10 years is one of great excitement in URS and is likely to further transform of our current treatment strategies for the management of stone disease.

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MINIREVIEWS

Clinical audit, a valuable tool to improve quality of care: General methodology and applications in nephrology

Pasquale Esposito, Antonio Dal Canton

Pasquale Esposito, Antonio Dal Canton, Unit of Nephrology, Dialysis and Transplantation, Fondazione IRCCS Policlinico San Matteo and University of Pavia, 27100 Pavia, Italy
Author contributions: Esposito P and Dal Canton A contributed to this paper in: (1) conception and design, acquisition, analysis and interpretation of data; and (2) drafting the article and revising it critically for important intellectual content; all authors approved this version to be published.
Correspondence to: Pasquale Esposito, MD, PhD, Unit of Nephrology, Dialysis and Transplantation, Fondazione IRCCS Policlinico San Matteo and University of Pavia, Piazzale Golgi 19, 27100 Pavia,
Italy. pasqualeesposito@hotmail.com
Telephone: +39-03-82503883 Fax: +39-03-82503883
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Abstract

Evaluation and improvement of quality of care provided to the patients are of crucial importance in the daily clinical practice and in the health policy planning and financing. Different tools have been developed, including incident analysis, health technology assessment and clinical audit. The clinical audit consist of measuring a clinical outcome or a process, against well-defined standards set on the principles of evidence-based medicine in order to identify the changes needed to improve the quality of care. In particular, patients suffering from chronic renal diseases, present many problems that have been set as topics for clinical audit projects, such as hypertension, anaemia and mineral metabolism management. Although the results of these studies have been encouraging, demonstrating the effectiveness of audit, overall the present evidence is not clearly in favour of clinical audit. These findings call attention to the need to further studies to validate this methodology in different operating scenarios. This review examines the principle of clinical audit, focusing on experiences performed in nephrology settings.

Key words: Clinical audit; Evidence-based medicine; Quality improvement; Nephrology; Hemodialysis

Core tip: Clinical audit is a part of the continuous quality improvement process. It consists in measuring a clinical outcome or a process against well-defined standards, established using the principles of evidence-based medicine. The comparison between clinical practice and standards leads to the formulation of strategies, in order to improve daily care quality. This review examines the basis of clinical audit and the data about the efficacy of this methodology, focusing on nephrology issues. We think that clinical audit could offer to the modern Nephrologists a useful tool to monitor and advance their clinical practice.

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INTRODUCTION

"Audit" is a Latin word, and the verb *audio* ('hear') indicates both active listening and the action of investigation and interrogation of the judiciary. Transferred to the English vocabulary "audit" takes on a meaning of "an official inspection of an organization's accounts, typically by an independent body"[1].

The term is nowadays widely used in different settings (economic, business, *etc.*) referring to procedures aiming to ensure that the activities carried out for a purpose are consistent and effective for the achievement of objectives. Clinical (or medical) audits are part of the continuous quality improvement process that focus on

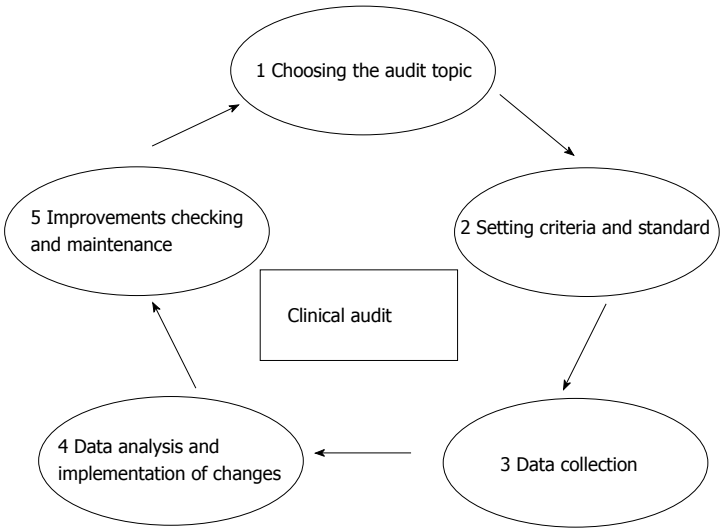

Figure 1 Clinical audit cycle.

specific issues or aspects of health care and clinical practice.

They consist of measuring a clinical outcome or a process, against well-defined standards set on the principles of evidence-based medicine. Aim of the audit is to highlight the discrepancies between actual practice and standard in order to identify the changes needed to improve the quality of care. A peculiar characteristic of the clinical audit is the "professionalism" of the initiative, which is expressed by some typical ingredients: clinical specific competence of the participants, the confidentiality of the results, the object strongly connected to the "quality" of professionals. From a methodological point of view, clinical audit consists of a "quality loop" (Figure 1): once chosen a topic and set shared and measurable criteria and standards, current clinical practice is evaluated, especially in terms of process or outcome, and suggestions for improvement are developed and applied, and then the cycle can begin again[2]. The audit should not be confused with data collection activities (*i.e.*, benchmarking) or clinical research: the latter, in fact, aims to define the characteristics of good practice on a unknown land, while the audit compares the current practice against well-defined and established standards[3]. The final aim of the clinical audit is always improving the care provided to the patient.

This achievement may be reach through different actions: (1) Increase the culture of clinicians; (2) Solve a problem; (3) Reduce the variability of professional conduct (standardize); and (4) Reduce the gap between theoretical standards and real life.

PRINCIPLES OF THE CLINICAL AUDIT

Step 1: Preparing for the audit

Good preparation is crucial for the success of an audit project.

The key elements to design valuable clinical audits are: choosing the topic, defining a clear purpose and providing the necessary organisation in terms of audit staff and resources.

The first step that must be accomplished in designing a clinical audit is to identify the topic (Table 1). The topic of the audit can be loosely identified in clinical practice and may relate to the adequacy of a care process or that of the results[4]. An audited theme should have specific characteristics: it should be of great clinical importance, of easy collection and analysis, and source of important consequences. The personnel involved in the audit have a key role in setting priorities among clinical problems to deal with. By choosing a suitable theme various aspects should be considered.

In particular, it would be a good choice to face a problem that involves the clinician in terms of: (1) High volumes of work; (2) High costs in terms of health and/or economic; (3) High risk; (4) High variability; (5) High complexity; and (6) High innovation.

Rare events, such as complex clinical cases or sporadic adverse events, are not an appropriate topic for a clinical audit, and should be analysed with more adequate methodologies (*i.e.,* Root Case Analysis)[5]. Once the topic has been selected, the purpose of the project must be defined, so that a proper audit methodology can be chosen and designed.

The aim of an audit project could include the implementation of new processes (for example laboratory protocols, surgical procedures, *etc.*) and/or the improvement of current strategies[6].

Moreover, before beginning a clinical audit, organisations should clearly declare the resources allocated to support the project management (data collection, hardware and software required) and for the training of the clinical staff, including education on clinical audit techniques, facilitation and data management[7,8].

Regarding the audit project team, it is advisable that it be customised for the specific audit project, with team members providing many of the skills needed. For example, if the topic of the audit is the management of vascular access in patients undergoing haemodialysis, it will be useful to include nephrologists, vascular surgeons

Table 1 Factors to consider in the decision on a topic for a clinical audit

For the choice of an appropriate theme for a clinical audit, assess that:
The problem to be audited has an important impact in terms of costs, resources, or risk
There is some strong scientific evidence available (guidelines, systematic reviews)
The improvements made on the subject in question can be easily evaluated and source of important clinical/organisational consequence.

and dialysis nurses in the audit team[9].

Step 2: Selection of indicators, criteria and standards and definition of intervention strategies

Once the preliminary issues of the audit have been defined, the next step is to set the standards, which the current clinical practice will be compared to. At this point, it is important to clarify some definitions: (1) Indicator: a variable that allows to describe complex phenomena and to measure changes in relation to defined criteria, in order to guide the decisions aiming at obtaining or maintaining the changes. It can be expressed as absolute number, percentage, rate, or average; (2) Criterion: it is a definable and measurable aspect of health care that describes its quality. The audit criteria are explicit statements that define an outcome to be measured. In a clinical audit, it is a declaration of what should happen on the basis of good practice, and it should be evidence-based[10]; and (3) Standard: it is the standard of care to be achieved for each specific criterion, usually expressed as a percentage. It represents the threshold of acceptability, that is, the value that defines the upper or lower limit, so that the quality of care is considered to be appropriate[11]. Some indicators are so important that the standards must be achieved in 100% of patients (*e.g.*, use of masks during the dressing of central venous catheters), but in general it is sufficient to meet the standard in a lower percentage (for example, in 80% of patients)[4].

The choice of criteria and standards is one of the most critical points in the design of a clinical audit and it requires the collaboration of all participants in the audit. Indeed, the quality of care provided (*i.e.*, the final result of the audit) will be evaluated just on the basis of a comparison with these parameters.

The sources where criteria and standards can be drawn from may be: international guidelines, scientific literature, expert consensus, data obtained by other health care facilities and personal case studies[12-14]. The stronger the evidence taken as a reference will be, the more the results of the comparison with daily clinical practice will be reliable. However, to design an effective clinical audit, it is important that the standard and criteria be shared with colleagues prior to the review of the collected data, since they should not be object of rearrangement in the course of verification, nor be changed retrospectively, in the light of the findings derived from the audit itself.

Finally, the audit team should also define the intervention strategies to be implemented in case of important discrepancies between standards and actual clinical practice. These strategies should be discussed, shared, clear and easy feasible according to a structured algorithm.

Step 3: Data collection

In clinical audit data can be collected prospectively or retrospectively[15]. Taking into consideration past clinical documentation, the latter method is certainly faster, but often the quality of the collected information is not optimal.

Perspective audits are more expensive in terms of time, but they allow a more accurate design, while offering a more realistic description of the current clinical practice. Before proceeding with data collection, it is necessary to carefully plan the variables to be recorded, and define the type of analysis to be conducted on the collected data. These points are important to prevent the collection of useless data or, conversely, the lack of essential information. A specific-designed form or a database should be arranged to collect patient records[16].

Moreover, it may be appropriate to carry out a sampling (preferably using randomized methods) if there is a very large number of patients to be examined, also in relation to the degree of confidence that one wants to achieve and the resources actually available (time, money, personnel)[17].

Collected data can be quantitative or qualitative, such as interviews, questionnaires or comments and data sources can be various, including medical records, results of biochemical and instrumental evaluations and/or other different archives[18,19]. The medical record is certainly the main source of information, but it is often incomplete. In this regard, highlighting the inadequacies of data management, already in the preliminary phase of data collection, the audit improves the existing information flow. Finally, it is worth pointing out that in every moment of data collection and analysis, patient privacy must be protected, making the information collected anonymous and explaining the reasons for the data collection, in case of direct involvement of patients themselves[20].

Step 4: Comparison of collected data with the standards and development of corrective actions

This is the central phase of clinical audit. In this phase, the team of professionals interested in the audit analyses the data and compares them with the pre-set standards. It is important to note that the critical nature of this moment lies in the fact that the professionals involved in the audit process can interpret the audit as an inspection of their clinical activity, thus becoming, unconsciously, an obstacle to an effective data analysis (Table 2)[21].

Table 2 Facilitating factors and barriers for effective clinical audit

Facilitating factors	Obstacles
Clarity of design and data collection	Not clear objectives and planning
Good planning	Lack of resources-heavy workload
Organisation support	Lack of clarity on the method
Dedicated staff	Lack of organizational support
Collective analysis of the results	Unwillingness to change

For this reason, the meeting where the results of the audit will be discussed must be carefully prepared, paying particular attention to all aspects of communication and social skills[22,23].

Moreover, these contents must be pre-emptively shared with those who have proposed the audit. From the comparison of actual data with the theoretical standards different results might emerge, and the standard could be reached or not. In the event that the standard is not met, it should be assessed whether or not there is the possibility of a real improvement. In fact, if the data are not in line with the standards but they are sufficiently close, one might decide that any further improvement is difficult to achieve, and therefore it would be useful to invest resources in the assessment of other problems. In the case there is a significant difference between information gleaned from the clinical documentation and standards, collegial discussion should highlight the barriers to the achievement of the standard[24]. Afterwards, audit methodology requires that the audit team elaborate intervention strategies and recommendations, according to the indications preliminarily set[25]. Such advices or recommendations should take into account organizational factors (in terms of economic resources, timing, dedicated staff) and the context in which the audit takes place. For this reason it is imperative that the developed recommendations be clear, explicit and shared[26]. The mere dissemination of educational materials, such as guidelines, has little effect if they are not accompanied by selected methods of implementation, such as training seminars or discussions among peers[27].

Instead, in case the results obtained from the audit can be considered satisfactory, it is equally indispensable to provide a form of monitoring. Finally, all the findings drawn from data analysis and the subsequent discussion, including strategies to implement change, should be reported in a detailed account to be distributed to all participants of the audit, as feedback and reminder of the work done.

Step 5: Check and maintenance of improvements

The audit cycle ends with the stage of verification and monitoring of implemented strategies[2,4].

Indeed, it is essential for a proper process of clinical audit to schedule periodic verifications of the effects of the changes introduced. It would be advisable to use a data collection and an organizational strategy similar to that used for the previous analysis, so that the results are comparable.

If it emerges that the objectives have not been achieved and the plan of improvements was not effective or sufficient, it could be necessary to make changes to planned strategies.

However, also in case of success, a monitoring plan should be equally scheduled in order to maintain the improvements made.

EFFICACY OF THE CLINICAL AUDIT

There is conflicting evidence on the effectiveness of clinical audit[28]. A systematic review of the Cochrane Study Group has considered 140 studies in which clinical audit and the corresponding feedback were tested alone or in comparison to other types of interventions (meetings, distribution of printed materials, *etc.*). In the studies included in this review, the results produced by the audit were widely variable, from a negative to a very positive effect. When the audit was effective, the effects generally ranged from small to moderate. The review concluded that the relative effectiveness of an audit is likely to be greater when baseline adherence to recommended practice is low and when feedback is carried out with greater intensity[29]. Therefore, at the moment, scientific evidence does not provide clear support about the real effectiveness of clinical audit. This finding could be a starting point to design studies and analyses to validate clinical audit in different operating contexts[30].

CLINICAL AUDIT IN NEPHROLOGY

Medical literature offers several studies on audits conducted in the field of clinical nephrology, especially in patients on haemodialysis (HD). The reported studies have evaluated different aspects of organizational management and clinical research, such as the problems associated with late referral, vascular access, the management of hypertension and anaemia[31-33]. A careful analysis of these studies shows that the research has been mainly focused on the comparison between data collected from several case studies and indications of the guidelines. Therefore, the majority of these studies lack in the processes of cyclicity and verification that, as aforesaid, are the distinctive and characteristic features of clinical audit. An example of a well-conducted audit has been reported in a paper of an Australian group that has performed an audit in order to assess the effect of a multi-disciplinary intervention on the choice of dialysis vascular access, aiming at reducing the use of central venous catheters[34]. The first data collection on 184 incident dialysis patients was useful to recognize the problems in limiting the use of arteriovenous fistula, such as communication difficulties with patients or organizational shortcomings. Then, basing on the difficulties identified, the audit team developed specific intervention strategies (*i.e.*, promotion of educational skills, facilitated access to the operating room, direct nurse involvement,

Table 3 Checklist for the planning and validation of a clinical audit

Item	Yes/ No
Promoting a clinical audit	The audit topic has been decided according to the needs of the working group.
	The objectives are clearly specified.
	Indicators, criteria and reference standards have been set according to literature, guidelines and/or the consensus among experts.
Design and planning	The audit has been organized in different stages and times, assigning specific responsibilities.
	Necessary resources have been allocated.
	The population/reference sample has been defined.
	Tools for data collection have been designed, preliminarily defining data management methods.
	The whole material has been proposed in advance to the participants.
Data collection	Those who participated in the preventive phase have been involved.
	The established phases have been met.
	Data have been correctly collected.
Data analysis	The results have been discussed with the participants to the audit and other interested parties.
Interventions	A structured strategy to implement changes has been defined.
	Written reports of the results have been made and sent to all the participants.
Checking the audit effectiveness	A check of the effectiveness of the changes introduced has been planned.
	The verification has been formally documented.

etc.), that resulted, 12 mo later, in a significant increase in the number of patients starting dialysis with an arteriovenous fistula (75% *vs* 56 % of control baseline, $P < 0.01$).

Many audit projects have been also focused on management of hypertension in HD patients and different aspects have been investigated, such as the role of sodium dialysate concentration and dialysate temperature in the determining blood pressure (BP) levels[35,36].

Interestingly, in a recent study we tested whether a clinical audit in se is effective in improving BP control in a population of patients on regular HD.

We studied 177 adult prevalent HD patients, recording data on factors affecting BP and anti-hypertensive drug regimen at months -1 (Pre), 0 (the date of the audit- Audit), and +1 and +6 after the audit.

Hypertensive patients were identified, cases were discussed and recommendations for improving BP management were recorded, and then returned to each physician as a reminder and a feedback of the audit process.

The interventions included the reduction of extracellular fluid volume in patients with fluid overload, use of interdialytic ambulatory blood pressure monitoring and bioimpedance, initiatives aimed to increase patient compliance and modulation of dialysis sodium content or temperature. Interestingly, the announcement of the audit by itself was associated with a decreased prevalence of hypertension (Pre 64.4% to Audit 58.7%) and a further decrease followed the audit (Post-1 51.1%, Post-6 47.6%, $P < 0.05$ *vs* Audit). Systolic BP in hypertensive patients also decreased (mean decrease was -8.5 and -14.1; $P = 0.007$ and $P < 0.001$ at Post-1 and Post-6), being also associated with a reduced number of drugs assumed, thus proving that clinical audit is an effective tool to improve BP control in HD patients[37].

Mineral metabolism disorders in Chronic Kidney Disease (CKD-MBD) are an example of a suitable topic for a clinical audit. Indeed, they are common in HD patients and are associated with a number of clinical symptoms and complications, including cardiovascular diseases[38].

However, although MBD in HD patients are the object of intense research activity, their prevention and treatment still remain unsatisfactory[39]. In this view, we performed two large multicentre audits aiming to enlighten the obstacles that hamper the successful control of MBD by a straightforward "patient-oriented" approach[40,41].

Overall, we collected information and discussed the cases of about 700 prevalent HD adult patients according to the audit methodology.

First of all, we confirmed the data regarding the difficulty to achieve therapeutic targets, showing that only 15%-20% of the evaluated patients presented Ca, P and PTH values simultaneously controlled[42].

Then, evaluating the factors related to unsatisfactory results, we found that low compliance with treatment was the major determinant of failure (43.5% of the cases).

However, we observed a discrepancy between the analysis of factors accounting for therapeutic failure and the interventions planned. In fact, while the low compliance was recognized as the main cause of therapeutic failure, most of the interventions were focused on pharmacological therapy. Consequently, six months after the audit we found that, against a significant increase in the amount of drugs prescribed, the control of MBD parameters did not improve.

Therefore, the results of the audit suggested that low compliance with treatments is a main but still neglected cause of failure in the achievement of MBD control in HD patients, while increase of drug administration, regardless the awareness to the compliance to the therapy, is insufficient to obtain an overall satisfactory rate of therapeutic success.

This finding is particularly important, since indicates that future therapeutic strategies, beyond the development of new drugs, should include the implementation of feasible educational programmes addressed to both

health personnel and patients. This kind of study shows the potentiality of a clinical audit that allows to effectively compare theoretical standards with daily clinical practice, providing suggestions to improve quality of care.

FUTURE APPLICATIONS

Audit methodology could be potentially extended to several other issues in the setting of clinical nephrology.

For example, it could be useful to evaluate the causes of treatment failure in patients undergoing peritoneal dialysis, such as to implement protocols to reduce the rate of central venous catheter-related infections. Moreover, clinical audit could be a feasible tool to solve organizational problems, such as the delays on the waiting list for kidney transplantation.

Finally, a clinical audit could be used to face more general topics, which may involve also renal patients, such as management of dyslipidaemia (for example, evaluating the appropriateness of statin prescription) and implementation of lifestyle change.

CONCLUSION

Quality control, and consequently the right allocation of resources, is becoming a central issue in the management of Health Care Systems. Several tools are deployed to provide a monitoring of the levels of care and improve its quality. Among them, clinical audit is one of the most popular and widespread. In the specific field of clinical nephrology, this method has proven its effectiveness in facing different problems, such as hypertension and mineral metabolism control. However, it still seems necessary to spread the understanding of clinical audit and promote its systematic application both nationally and locally, so that it can be part of the expertise of each health care provider, together with other quality improvement techniques. In Table 3 we present a checklist for the planning of a clinical audit.

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MINIREVIEWS

From crystalluria to kidney stones, some physicochemical aspects of calcium nephrolithiasis

Johannes M Baumann, Beat Affolter

Johannes M Baumann, Beat Affolter, Stone Research Center Viollier, CH-2502 Biel, Switzerland
Author contributions: Baumann JM and Affolter B solely contributed to this paper.
Correspondence to: Johannes M Baumann, MD, Professor, Stone Research Center, Viollier, Alpenstrasse 21A, CH-2502 Biel/Bienne, Switzerland. johannes.denise.baumann@bluewin.ch
Telephone: +41-32-3231010 Fax: +41-32-3231025
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Abstract

Nephrolithiasis seems to be the result of crystal formation, aggregation and retention in the kidney during crystalluria. These processes have to occur within the short urinary transit time through the kidney being in the order of few minutes. Recently much work was done on rather qualitative aspects of nephrolithiasis like genetics, metabolism and morphology. In this review we try to provide some quantitative information on urinary supersaturation with respect to stone minerals, especially Ca oxalate (CaOx), on the formation and aggregation of CaOx crystals and on crystal retention in the kidney. The paper is centered on idiopathic Ca nephrolithiasis being the most frequent stone disease with only partially known pathogenesis. New aspects of the role of urinary macromolecules in stone formation and of the mechanism of crystal aggregation are provided.

Key words: Calcium nephrolithiasis; Crystalluria; Crystal aggregation; Urinary macromolecules; Self aggregation

Core tip: The state of urinary saturation with respect to Ca salts is governed by pH, Ca and Ox concentration. Growth of calcium oxalate (CaOx) in urine is too slow that single crystals could acquire a size to be trapped in nephron. The aggregation (AGN) of CaOx in urine was lacking or severely delayed due to inhibition by urinary macromolecules (UM's). Albumin, after temporary adsorption on calcium phosphate, showed self aggregation and promoted AGN of CaOx. Self aggregated UM's probably overwhelm the electrostatic repulsion of crystals coated by negatively charged UM's. This mechanism may explain the effect of Randall's plaques.

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INTRODUCTION

Nephrolithiasis can be defined as the result of formation and retention of crystals within the kidneys[1] where during crystalluria stone formation mainly seems to occur by crystal aggregation (AGN)[2]. Urinary stones are large crystal aggregates being embedded in a proteinous matrix. During the last years much work was done with respect to genetic, metabolic and morphologic aspects of nephrolithiasis[3-6]. Crystallization of stone forming minerals often was studied in artificial solutions neglecting the important fact that in biological solutions like urine crystals are always coated by macromolecules which essentially influence results[7,8] and that crystallization being relevant for stone formation has to occur within urinary transit time through the kidney, being in the order of a few minutes[9,10]. In this review we try to give some quantitative information on crystal formation, growth, AGN and retention as they may occur in the kidney during stone formation. The paper is centered on idiopathic calcium oxalate (CaOx) nephrolithiasis being the most frequent stone disease[11]. To illustrate the different top-

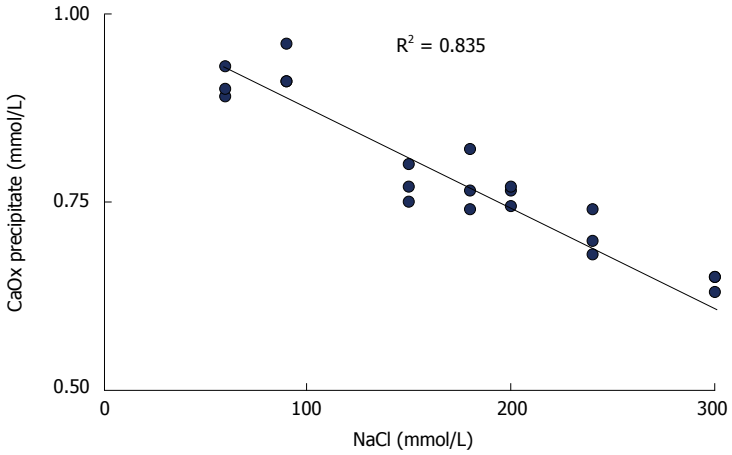

Figure 1 Influence of NaCl concentration on CaOx precipitation calculated from Ca decrease after the addition of 1.0 mmol/L sodium oxalate to aqueous solution of 1.5 mmol/L $CaCl_2$ buffered to pH 6.0 with 5 mmol/L sodium cacodylate.

ics, new figures were included which were drawn from own and only partially published experiments.

URINARY SUPERSATURATION WITH RESPECT TO STONE MINERALS, ESPECIALLY CAOX

The driving force for crystallization is urinary supersaturation which depends on the concentration of stone forming ions, their chelators, ionic strength and pH. Excessive excretion of Ca or Ox which almost exclusively can explain stone formation occurs in rare metabolic disorders like primary and secondary hyperoxaluria and some types of hypercalciuria[12]. In this review idiopathic Ca stone formation is addressed where not always and only relative mild forms of hypercalciuria or hyperoxaluria are found, which often are dependent from diet. After ingestion of a diet rich in Ox even in metabolic normal people an almost threefold increase of Ox excretion was observed[13]. To avoid dietary Ox excesses remains therefore essential in Ca stone metaphylaxis.

Urine is a complicated poly-ionic solution where multiple ions form various complexes between each other[14]. Some of these complexes like CaOx have an extremely poor solubility, precipitate already at a low concentration and -under special conditions being described below-form stones. In poly-ionic solutions the mobility and thus the activity of ions is reduced by the electrostatic forces exerted between the ions. Chemical reactions in solutions are therefore instead of ionic concentrations governed by ion activities (A, mol/L)[15]. A is calculated by the multiplication of the ion concentration (C) by an activity coefficient (f) as shown in equation (1). (f) can roughly be estimated by the ionic strength of the solution (I, mol/L).

(1) $A = f \bullet C$

In urine, ionic strength is mainly generated by sodium and chloride which are present in much higher concentrations than other compounds[16]. Increasing ionic strength decreases ion activities and thus supersaturation or the amount of substances which can be precipitated from supersaturated solutions. This is demonstrated by CaOx precipitation in solutions with constant Ca and Ox but increasing NaCl concentrations (Figure 1). Unfortunately, this effect cannot therapeutically be used because a high NaCl intake stimulates urinary Ca and reduces citrate excretion[17]. The high ionic strength in concentrated urine also does not protect from precipitation because the effect of decreasing ion activity is largely overwhelmed by the increase of supersaturation due to the increased ion concentrations[16]. A high diuresis remains therefore important for stone metaphylaxis.

Complex formation is schematically illustrated for CaOx by equation (2a). It is characterized by the reversible formation and dissociation of the soluble complex ($CaOx_S$) and by precipitation and dissolution processes between $CaOx_S$ and its crystalline precipitate ($CaOx_P$):

(2a) $Ca^{2+} + Ox^{2-} \leftrightarrow CaOx_S \leftrightarrow CaOx_P$

For each complex exists a dissociation constant (K_D, mol/L). It defines as shown in equation (2b) for CaOx the ratio between the mathematical product of free ion activities (A) in the solution and A of the solved complex:

(2b) $K_D = A_{Ca} \bullet A_{Ox}/A_{CaOxS}$

Since at a given temperature and with the precipitate in excess also the concentration of solved complexes is a constant (*e.g.*, 7.1 mg CaOx/L at 37 ℃). The status of complex forming ions in a solution can simply be expressed as activity product (AP).

In urine, multiple complexes are in competition to each other in reducing free ionic concentrations. Compounds which have a high tendency to form complexes with a high solubility are called chelators. Citrate is such a chelator which as shown in Figure 2 essentially reduces free Ca concentration (Ca^{2+}) and especially in patients with hypocitraturia has proofed to be efficient in stone metaphylaxis[18]. Contrary to other ions Ca^{2+} easily can be measured by Ca selective electrodes. Comparison of Ca^{2+} and total Ca in 20 urines showed a linear correlation with a chelation of 50%-70% of total urinary Ca being dependent from pH (Figure 3). A low pH or a high H^+ concentration respectively reduces by protonisation of phosphates and carboxyl groups the chemical

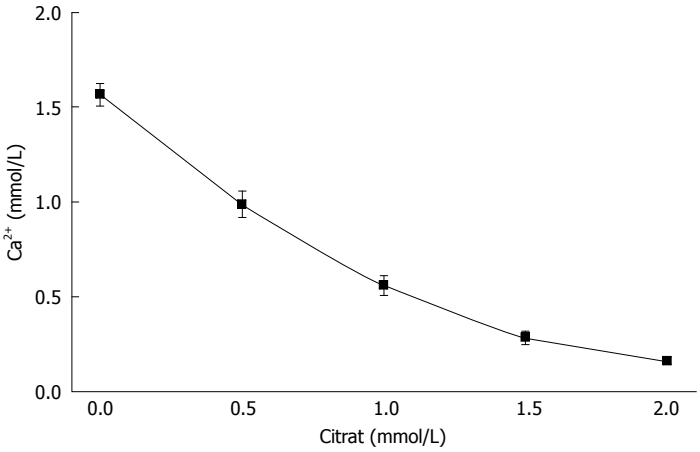

Figure 2 Influence of citrate concentration on free ionic Ca concentration (Ca^{2+}) in a solution like in Figure 1 but containing 100 mmol/L NaCl (mean ± SD, *n* = 5).

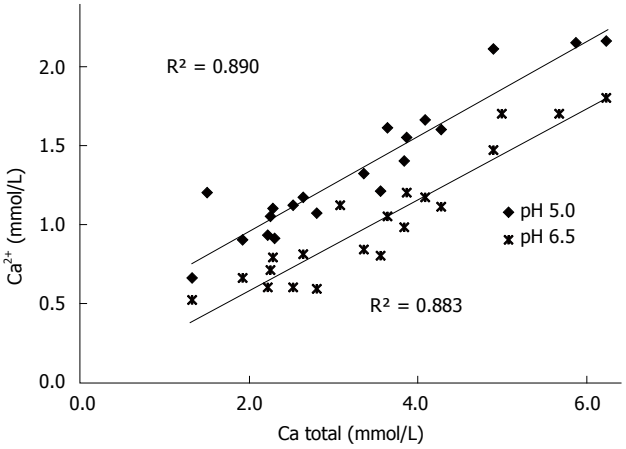

Figure 3 Correlation Ca^{2+} and total Ca concentration in 20 urines at pH 5.0 and 6.5.

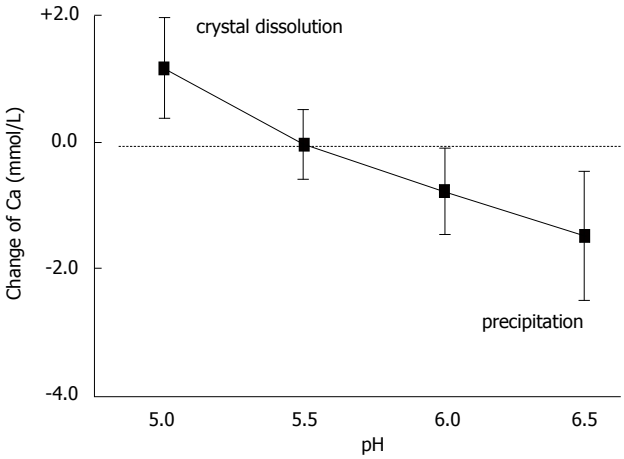

Figure 4 Influence of pH on solubility of hydroxyapatite demonstrated by the change of Ca concentration after equilibration of 20 urines with 10 mg/mL hydroxyapatite (mean ± SD).

valences of these compounds and thus their capacity of complex formation. This is demonstrated in Figure 3, where Ca chelation in urine was reduced and thus Ca^{2+} increased by lowering pH from 6.5 to 5.0. However, the most important effect of pH is observed with respect to phosphate. A high pH with its low H^+ concentration favors the formation of poorly soluble tertiary phosphates. This is demonstrated in experiments shown in Figure 4 where the change of Ca concentration was determined after equilibration of urine with hydroxyapatite (HAP, $Ca_{10}(PO_4)_6(OH)_2$). At an urinary pH above 5.5 the incubated HAP changed from dissolution to precipitation with a markedly decrease of urinary Ca. Struvite ($MgNH_4PO_4$) stones are exclusively found in alkaline urine where urease positive germs produce high concentrations of NH_4.

Due to all the various factors being involved, the state of urinary saturation with respect to stone minerals is difficult to determine. A generally accepted expression for this state is relative supersaturation (RS), the ratio of the products of ionic activities (AP) actually found in urine (e.g. $A_{Ca} \cdot A_{Ox}$) and the AP in the same urine being saturated with respect to the corresponding stone mineral (*e.g.,* CaOx)[15]. The latter AP is called solubility product (SP). An RS > 1.0 denotes supersaturation, an RS < 1.0 undersaturation. RS can be calculated by the sophisticated computer program Equil 93[14]. This program bases in its most extended version on the input of 15-23 chemical parameters and the calculation of about 100 complexes. Another approach is the calculation of an AP index from 5 parameters by equation (3) as demonstrated for CaOx[19]:

(3) $\text{AP index}_{CaOx} = 1.9 \cdot Ca^{0.84} \cdot Ox / Mg^{0.12} \cdot Cit^{0.22} \cdot \text{Urine-Vol.}^{1.03}$

The state of urinary saturation can also experimentally be determined by the calculation of a concentration product ratio (CPR) of stone forming ions before and after equilibration of urine with the corresponding stone forming mineral[20]. The comparison of CPR's and 6 chemical parameters measured in 76 urines of 19 idiopathic Ca stone patients showed only significant correlations between CaOx monohydrate saturation and Ox concentration ($P < 0.001$) and between brushite saturation and pH and Ca concentration ($P < 0.001$)[21]. Ca and Ox concentration and pH are thus the main parameters governing the state of urinary saturation with respect to stone forming Ca salts and which therapeutically can be influenced.

CRYSTAL FORMATION IN URINE

Stone minerals show as mentioned above at every state of saturation a bi-directional process of permanent precipitation and dissolution. With increasing supersaturation precipitation, which is also called crystal nucleation, prevails. However, low states of supersaturation do not have the energy to create stable particles and the precipitated crystal nuclei permanently dissolve[22]. To create stable particles a critical AP called formation product (FP) is mandatory which furnishes the energy being necessary to build up stable particle surfaces against surface tension. Supersaturation can thus be divided into two zones namely a labile zone above FP where crystal nucleation and growth occur and a metastable zone between FP and SP where already formed crystals grow without further nucleation. FP decreases with increasing incubation time, a fact that has to be taken in consideration in experiments simulating crystallization in the kidney with its short urinary transit times. Preexisting surfaces of solids where crystals can attach allow nucleation already in metastable supersaturated solutions. This special kind of nucleation is called heterogeneous nucleation.

Crystal nucleation and growth in urine are apart from supersaturation influenced by multiple urinary compounds called crystallization modulators[8]. These modulators comprise citrate, pyrophosphate, some glycosaminoglycans and a large group of proteins[23]. The most intensively studied and probably most important proteins are albumin, inter alpha inhibitor, nephrocalcin, osteopontin, prothrombin fragment 1 and Tamm Horsfall glycoprotein. Due to such modulators, often called inhibitors, crystallization processes in urine generally are decreased when compared to inhibitor free control solutions. Some substances can also act as nucleators. Despite of intensive research the role of all these compounds in stone formation could not definitively be clarified[24]. Studies in urine where all involved factors simultaneously are present are therefore of special interest.

Normal urine contains on average 4 mmol/L Ca and 0.4 mmol/L Ox and has a relative supersaturation (RS) of about 5[9], whereas for the spontaneous nucleation of CaOx an RS of 14 is mandatory[10]. In 60 urines of idiopathic stone patients and controls an Ox addition of 0.64 ± 0.11 mmol/L was necessary to induce CaOx crystallization without a difference between the two populations[7]. Such Ox concentrations are only achieved after excessive Ox ingestion[13]. Nevertheless, crystalluria is at least in some studies a frequent finding being generally more often found in urine of stone patients (9%-48%) than of healthy controls (2%-26%)[25]. Since urine often is only metastability supersaturated with respect to CaOx and storage and cooling have a minimal influence on CaOx formation[26], heterogenous nucleation seems to play an important role in crystalluria. Acid phospholipids accumulate Ca on cell membranes which thus become ideal nucleators for CaOx[23]. This heterogenous nucleation can occur by tubular cells in the kidney as well as by cellular debris in urine. Cellular material comprises about 50% of urinary deposits[27].

Nucleation and growth of CaOx can directly be followed in urine by measurement of the increase of optical density or the Ca decay after Ox addition[28]. Repeated measurement of the ionic Ca (Ca^{2+}) after different Ox additions to urine showed typical crystallization curves (Figure 5). being characterized by the half-life of Ca^{2+} decrease (h, min.) and by the ratio of Ca^{2+} decrease at time (t) and of total Ca^{2+} decrease at the end of crystallization (RD_t). RD_t can be calculated by equation (4a) from h, which is obtained by equation (4b) from Ox in urine after the Ox addition (Ox_i), a growth rate factor (g = 1.13 ± 0.36 mM^{-1} min^{-1}) and a factor for metastability (m = 0.60 ± 0.07 mmol/L).

(4a) $RD_t = t /(t + h)$

(4b) $h = 1 /g(Ox_i - m)$

Measurement of crystalluria by a coulter counter in freshly voided urine of stone patients and controls which was collected at 3 h intervals, showed after an oral Ox load single crystals with diameters on average of 6 μ and a maximum of 15 μ[10]. In the nephron at high urinary Ox concentrations (> 0.6 mmol/L) some nucleation can occur during a short time at the end of the descending limb of the loop of Henle but the main crystallization takes place at the end of collecting ducts[10]. The time for crystal nucleation and growth is therefore in the nephron about 1 min. For this time and a maximal Ox concentration of 0.9 mmol being assumed in idiopathic stone patients[9] a RD_t of 0.25 can be calculated. The size of the large single crystals obtained from bladder urine has therefore for the nephron to be reduced from 15 to 9.45 μ, which is far below the minimal internal diameter of 30 μ of renal collecting ducts[9]. The reduced crystal size (d) in the nephron was calculated basing on a reduction of an octahedron volume ($V = \sqrt{2}\, d^3/3$) of CaOx dihydrate crystals to 25%. This calculation shows that without AGN crystals seem to have only little chances to be mechanically trapped within renal tubules.

CRYSTAL AGGREGATION

Already in 1969 it was demonstrated that stone patients contrary to healthy controls especially after Ox ingestion have a tendency to excrete large crystal aggregates[29]. Such aggregates which can reach diameters up to 500 μ can obstruct collecting ducts and by further apposition of crystals can give raise to stone formation[12]. The growth of already existing stones can also be explained by aggregation (AGN)[2].

For AGN crystals have to collide. The natural driving forces for particle collision without shaking or stirring are diffusion by Brownian motion and sedimentation. The effect of these two forces recently was studied in the context of high physiological crystal concentrations, renal tubular and pelvic dimensions and urinary transit times in the kidney[30]. Crystals are even at the maximal

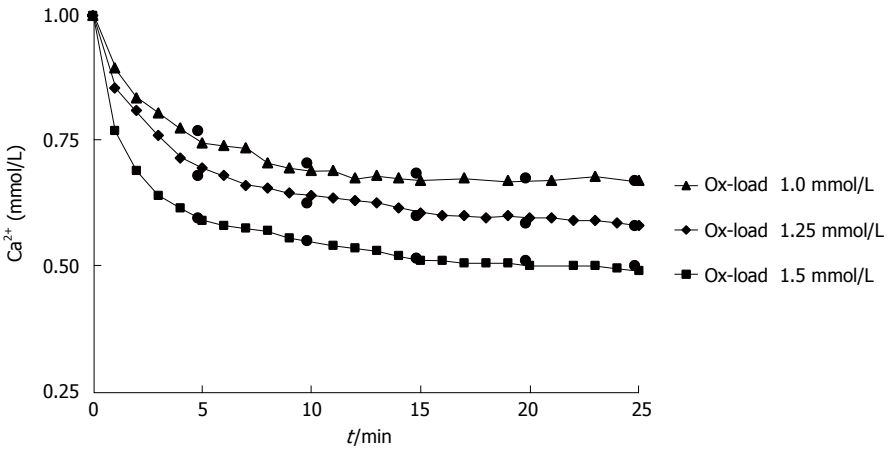

Figure 5 Decrease of Ca^{2+} in urine during observation time (*t*) after different Ox additions (1.0-1.5 mmol/L). Measured (triangle/diamond/square) and by RD_t (see text) calculated values (black circle).

concentration of 24000/cm^3 assumed in idiopathic Ca stone formers[9] on average in a distance of about 350 μ. Crystal motion by diffusion contrary to sedimentation is an undirected three- dimensional random process being only in the order of 10 μ/$min^{0.5}$. Crystal collision in the nephron by diffusion is therefore negligible and in the renal pelvis with a volume of 7 cm^3 may occur about 3 times per min. Collision of free floating single crystals by sedimentation is even more rare. It bases on differences in sedimentation rates due to differences in crystal sizes which in urine are too low for an efficient collision. However, sedimentation seems to be important for crystal accumulation on tubular walls where flow rate is slow due to fluid drag and on surfaces in the renal pelvic system where urinary transit time is prolonged. For collecting ducts being in a horizontal position a maximal accumulation of 1.3 crystals per min. was estimated. The accumulation of crystals on surfaces in the renal pelvic system by sedimentation (As, cm^{-2} $min.^{-1}$) can be calculated by equation (5) which contains the crystal concentration (C, cm^{-3}) and a sedimentation rate (vs, cm/min.).

(5) $As = C \bullet vs$

For maximal crystalluria of 24'000 crystals/cm^3 and a sedimentation rate of 0.026 cm/min. an accumulation of 624 crystals per cm^2 surface and min. can be calculated[30]. Crystal accumulation on kidney calcifications or stones seems to be an important mechanism in stone formation.

However, also with an important crystal accumulation on surfaces during crystalluria, for AGN crystals have to become attached to each other. In inorganic solutions this attachment generally is ascribed to an attraction by van der Waal forces being only effective at short distances of some 0.1 nm[31]. In biological fluids crystals are always surrounded by protein coats with a thickness of 10-30 nm[32]. These proteins have a negative electric charge of -15 to -30 mV which normally inhibits AGN by electrostatic repulsion of the identically charged particles[33]. From CaOx and CaP crystals being precipitated in urine six different proteins comprising albumin were isolated[34]. The composition of these proteins showed no difference whether they were precipitated from urine of stone patients or of controls. Inhibition of crystal AGN by urinary macromolecules (UM's) was demonstrated in various studies[23]. But a deficient urinary inhibitory activity in urine of stone patients could only be demonstrated in some studies[35-37] but not in all[38,39]. Examination of AGN often was performed in artificial solutions with the addition of an UM and of crystals which were previously produced in an inhibitor free medium.

However, the formation and AGN of CaOx can also be studied in urine by an oxalate titration with spectrophotometric follow of the crystallization process[7]. This is demonstrated in Figure 6A where after a critical Ox addition, which is a measure for metastability and was lower in a control solution (CS) than in urine, optical density (OD) steadily increased. The maximal OD which was reached at the end of titration and which mainly reflects particle concentration was lower in CS than in urine, where due to an inhibition of crystal growth more but smaller crystals were produced. After the end of Ox titration stirring was stopped and OD decrease reflecting particle sedimentation was followed during a further 30 min. In CS which in scanning microscopy performed at the end of Ox titration showed large crystal aggregates (Figure 6C), a rapid OD decrease immediately after the end of titration was observed, whereas in urine without AGN (Figure 6B) this rapid OD decrease was lacking or occurred with a delay of 15 and more minutes. Analysis of crystallization curves and scanning electron microscopy of crystal sediments revealed a good correlation between OD decrease and particle sizes[30]. Crystals produced by Ox titration showed in urine of 63% of healthy controls but only in urine of 33% of stone patients during 30 min observation time a complete inhibition of AGN ($P < 0.05$)[7]. In the remaining urine AGN occurred with a delay often being beyond urinary transit time through the kidney which is in the order of 15 min[40]. Most aggregates found in voided urine therefore seems to originate from crystal AGN in the urinary bladder. Since in ultrafiltrate of urine where urinary macromolecules (UM's) were retained on a 5 kD filter, AGN immediately occurred, inhibition of AGN could mainly be ascribed to the effect of UM's[41]. However, when UM's were isolated by a hemofilter procedure or

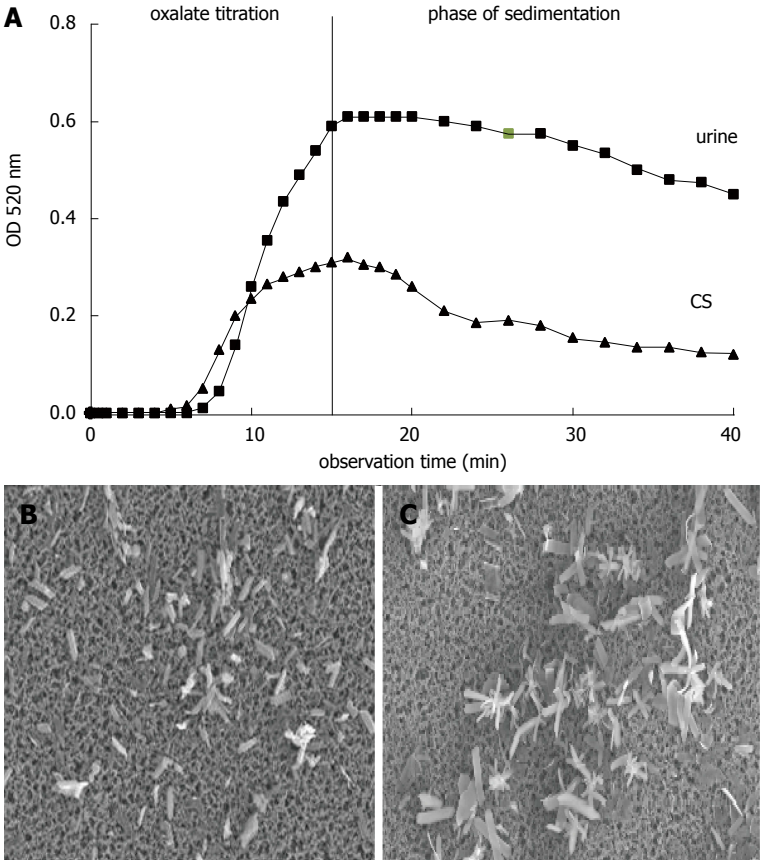

Figure 6 Ox titration. A: Spectrophotometric crystallization curve of Ox titration (0.1 mmol/min.) in urine and control solution (CS) both with pH 6.0, 100 mmol/L NaCl, initially 2 mmol/L Ca^{2+} and with total 1.5 mmol/L Ox addition by titration; B: Scanning microscopy of deposit on Millipore filter obtained at the end of Ox titration from urine and (C) from CS.

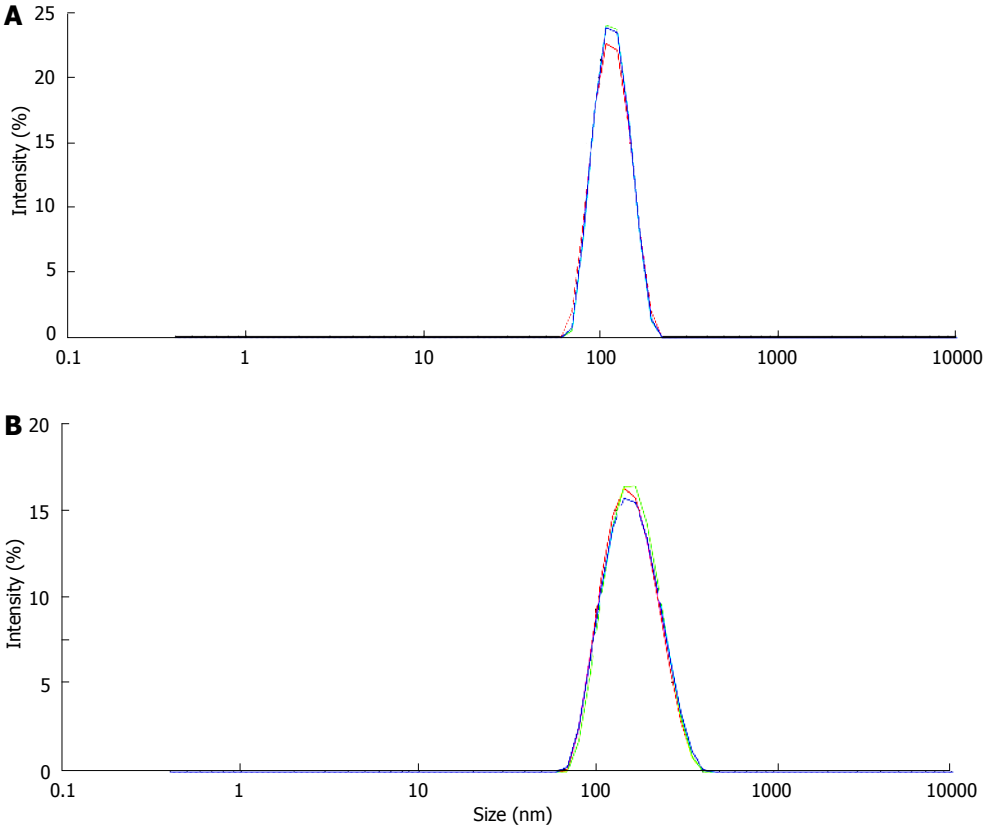

Figure 7 Particle size distribution in suspension of latex beads (size 100 nm, concentration 0.025%/mL) measured by a Zetasizer (A) in control solution, (B) in solution of urinary macromolecules obtained by CaP precipitation and dissolution of the precipitate.

by a CaP precipitation with dissolution of the sediment, AGN already occurred after a delay of about 7 min[33]. The same effect was observed after addition of hydroxyapatite crystals to urine[7]. A contact with surfaces even when temporary seems thus to destroy the inhibitory potential of UM's.

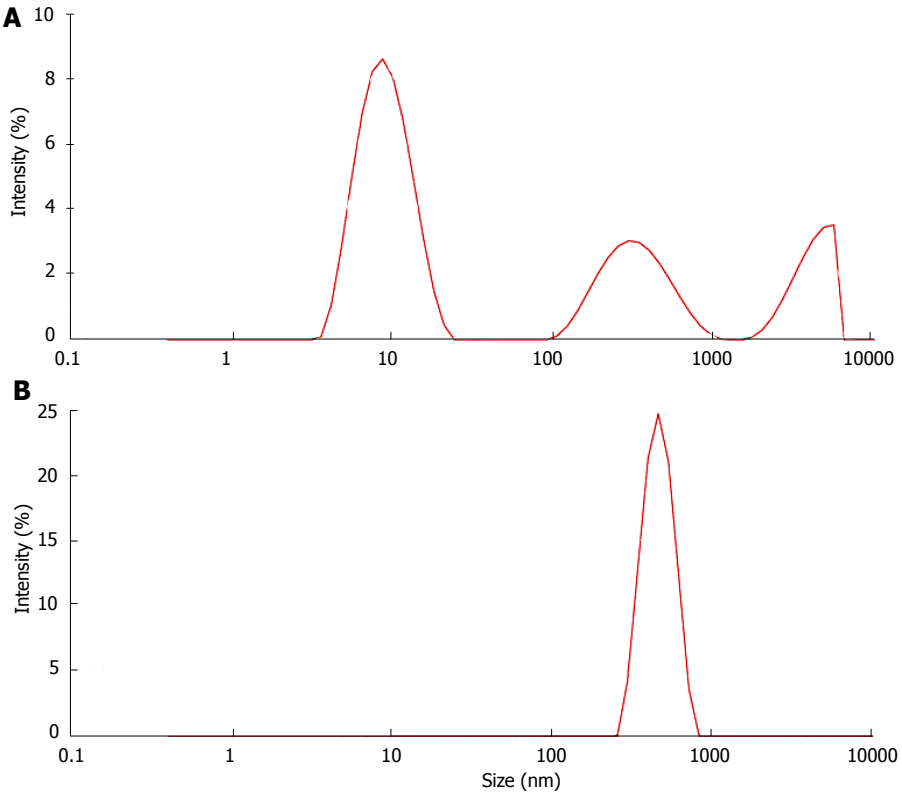

Figure 8 Particle size distribution (A) in albumin solution (AS, 20 μg/mL) and (B) in solution obtained from AS after CaP precipitation and dissolution of the precipitate (DPA).

UM's have a high and rather unspecific affinity to surfaces. As known from catheter incrustation they bind by hydrophobic forces even to latex. The adsorption of UM's on latex beads is demonstrated in Figure 7. Incubation in UM solution increased the maximal peak in particle size distribution of latex beads which was measured by a Zetasizer from 116 nm to 160 nm. Some UM's like albumin, osteopontin and Tamm Horsfall glycoprotein (THG) when concentrated are known to have a tendency to self AGN[23]. Self AGN turned THG from a potent inhibitor to a promoter of CaOx AGN[42]. Also polymers of albumin were found to be strong promoters of CaOx crystallization[43]. The tendency of albumin to self AGN is demonstrated in Figure 8 again by the measurement of particle size distribution with a Zetasizer. In an albumin solution apart of the main peak at 10 nm further peaks indicating albumin aggregates were found (Figure 8A). After CaP precipitation in the same solution and dissolution of the sediment where albumin temporary had been adsorbed to CaP crystals only one fraction of highly aggregated albumin with a peak at 480 nm was observed (Figure 8B). This highly aggregated albumin had, as shown in Figure 9, the same effect on CaOx crystallization curves as UM's isolated by hemofiltration or by CaP precipitation and as the addition of HAP to urine. Maximal OD after oxalate titration was diminished and already 7 min. after the end of titration a sharp OD decrease indicating CaOx AGN occurred. Temporary concentration of UM's by adsorption on surfaces seems thus to favor self AGN of UM's and to change their inhibitory potential with respect to the AGN of CaOx crystals.

The questions raises, how crystals aggregate despite of their electro-negative UM coats and electrostatic repulsion and how self AGN of UM's can favor crystal AGN. The answers to these questions are still speculative. Three different options for crystal attachment to each other are discussed: Incomplete isolation of crystals by protein coats , insufficient surface potential of coats and bridging between crystals by altered proteins. Scanning microscopy of crystal aggregates which were produced in protein solutions showed gaps in protein coats where crystals were in direct contact to each other[32]. But it could not be decided whether crystal coating had occurred before or after AGN. In other aggregates at points of crystal convergence large amorphous material was found suggesting crystal bridging by proteins.

The inhibition of crystallization processes by UM's is mainly attributed to anionic residues like carboxyglutamic acid[44,45], phosphate[46,47] and sialic acid[48,49] which have a high affinity to the Ca of crystals. Some of these anionic groups being responsible for the electro-negative charge of coated crystals were found to be reduced in UM's of stone patients. An insufficient crystal coating and electrostatic repulsion was therefore suggested to be responsible for AGN and stone formation. On the other hand it was shown that desialylation of Tamm Horsfall glycoprotein (THG) provoked self AGN of THG and AGN of CaOx crystals[49], effects which were also demonstrated in experiments performed with albumin (Figures 8 and 9). Desialylation reduces anionic domains and thus reinforces hydrophobic groups of THG being responsible for hydrophobic protein binding. This can favour not only self AGN of THG but also a bridging

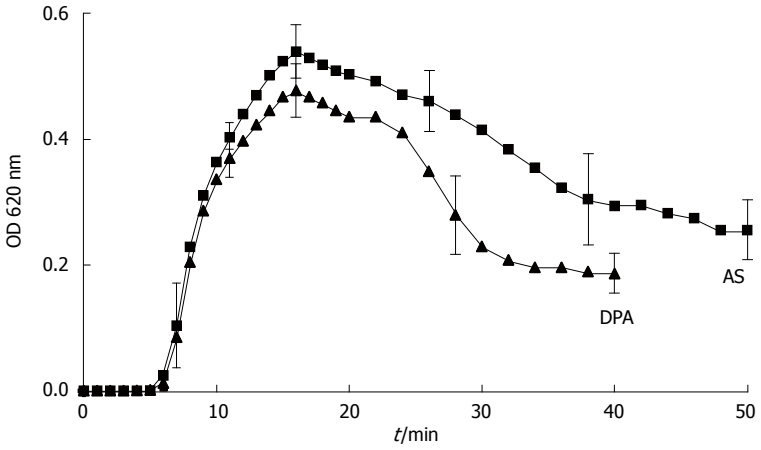

Figure 9 Spectrophotometric crystallization curve of Ox titration in AS and in DPA with pH 6.0, 100 mmol/L NaCl, initial 2.0 mmol/L Ca^{2+} and 1.5 m mmol/L Ox addition by titration. (Further details see Figure 8) (mean ± SD, *n* = 5).

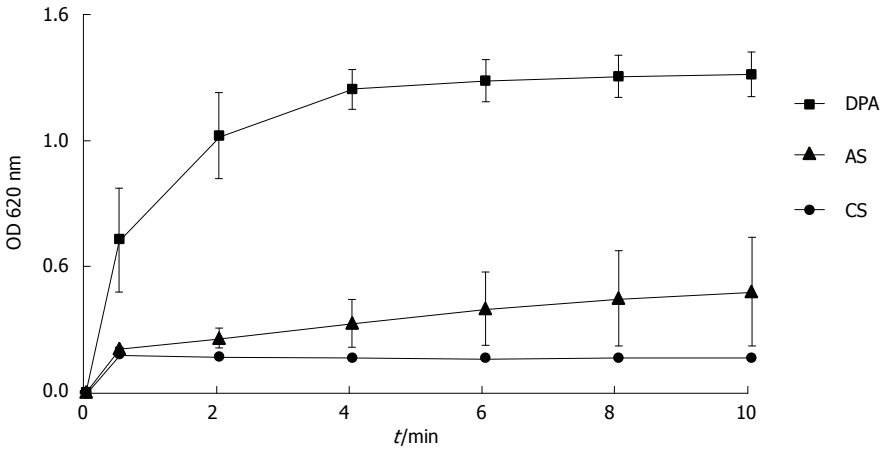

Figure 10 Increase of optical density of suspensions of latex beads reflecting increase of particle size by aggregation in control solution, in albumin solution and in aggreagted albumin. (Further details see Figure 8) (mean ± SD, *n* = 5). CS: Control solution.

function of THG between proteins of crystal coats. In electrolyte-containing solutions the electrostatic potential generated by electrically charged particles exponentially decreases with increasing distance from the particles[31]. Identically charged particles can therefore approach to each other to a critical distance of some nanometers where diffusion, sedimentation or mechanic forces like stirring or shaking are compensated by electrostatic repulsion. Large protein aggregates probably are able to bridge such zones of electrostatic repulsion.

Bridging and especially self AGN seem to be relative slow processes which could explain the delay of AGN observed in urine. In a spectrophotometer the velocity of albumin-induced AGN of latex beads can directly be followed by an OD increase which occurs in a linear correlation with the increase of latex aggregates[50]. Figure 10 shows that in the untreated albumin solution (AS) this increase was very slow whereas in a solution of aggregated albumin (DPA) latex-AGN was already complete within 4 minutes. Bridging of CaOx crystals with their irregular shape and large surface certainly takes more time than bridging of the small and spherical latex beads. In view of the delayed AGN of CaOx crystals in urine urinary transit time (UTT) through the kidney becomes a crucial factor for stone formation. In the nephron average UTT is about 3 min[10] and in the renal collecting system about 12 min[40]. These values were calculated for an urinary output of 1.5 L/24 h. Increasing diuresis which remains an important measure in stone metaphylaxis[51] essentially reduces UTT especially in the renal collecting system.

CRYSTAL AND STONE RETENTION IN THE KIDNEY

We showed that crystal growth at least in idiopathic stone patients generally is too slow for single crystals to be trapped in the upper urinary tract and that crystal AGN often is delayed beyond urinary transit time trough the kidney. Crystals are probably most often washed out by diuresis before AGN occurs. However, when CaOx crystals were produced in the presence of HAP crystals which were added to urine before Ox titration, AGN occurred as demonstrated in Figure 11 after about 7 min. Scanning microscopy of sediments showed that this AGN had occurred in narrow contact with the HAP crystals[52]. Tissue calcifications with HAP, after erosion to papillary surface seem therefore to be an ideal platform for a rapid attachment of urinary crystals. Randall developed already in 1937 the theory that Ca stones can start by CaOx growth initially fixed on papillary calcifications which are called Randall's plaques[53]. This mechanism allows crystal aggregates to grow to stones of a critical size where they can not anymore be washed out of the urinary tract by the urine flow. Systematic post-

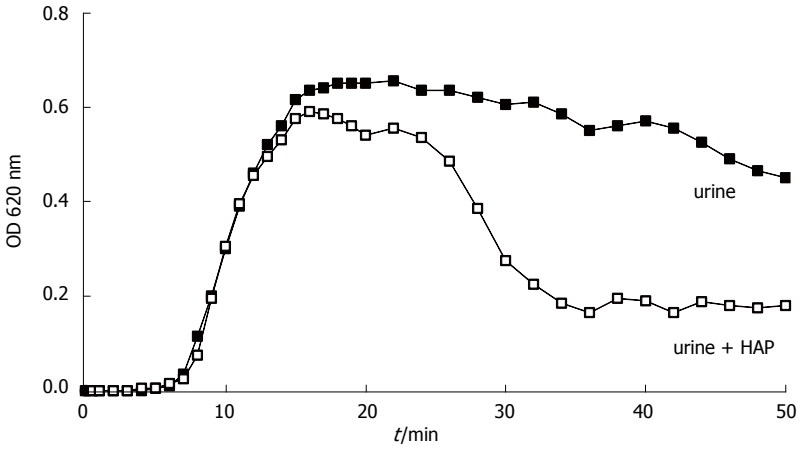

Figure 11 Spectrophotometric crystallization curve of Ox titration in urine without and with previous addition of 0.05 mg/L HAP.

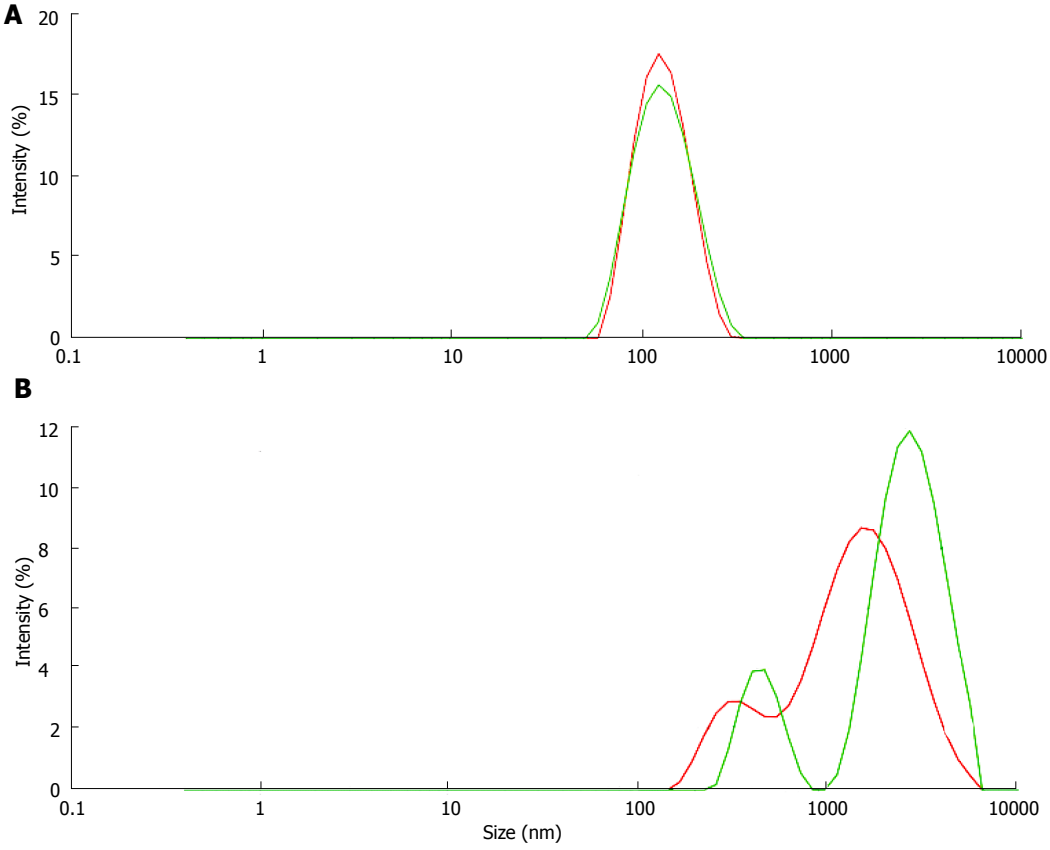

Figure 12 Particle size distribution of latex beads (A) at pH 6.0 and (B) at pH 5.0 in solution of urinary macromolecules obtained by CaP precipitation.

mortem examination of 100 kidneys revealed in 100% some calcifications but only in 7% stones[54]. Kidney calcifications are therefore not a singular cause of Ca stone formation. New endourologic methods allowing in vivo inspection of all renal papilla with the possibility of biopsies have brought new evidence for the role of Randall's plaques in idiopathic Ca stone formation[12,55]. CaOx stones found in calices often were attached to white plaques on the papilla containing amorphous hydroxyapatite within a protein matrix. Furthermore, most CaOx stones being endoscopically removed showed residual cores of apatite where they probably have been attached to the papilla.

Stone formation on Randall's plaques is complex and still poorly understood. Histological analysis with immunohistochemistry or infrared spectroscopy of Randall's plaques with an adherent stone showed that the plaques consisted of an osteopontin (OP) matrix with hydroxyapatite (HAP) deposits whereas the stone in addition to OP and HAP contained Tamm Horsfall glycoprotein (THG) and CaOx, the latter increasing with increasing distance from the plaque[12]. Stone formation thus seems to occur at the interface of HAP and CaOx crystals being embedded in proteins like OP and THG which both have a tendency to self AGN[23] and which in urine of some stone formers were found to have a deficiency in

acid groups[47,49]. A reduction of anionic groups reinforces as mentioned above hydrophobic activity of proteins and thus the tendency to self AGN and to the binding to hydrophobic domains of other proteins. AGN inhibition by anionic groups can indirectly be demonstrated studying the influence of pH on UM induced latex AGN (Figure 12). When latex beads with a diameter of about 100 nm were incubated at pH 6.0 in a UM solution obtained by the precipitation and dissolution of CaP in urine only a moderately increased particle size of 156 nm due to UM coating of the latex beads was observed (Figure 12A). The same procedure performed at pH 5.0 with a higher protonisation of anionic UM groups on the other hand produced a peak of particle intensity at 2400 nm showing a massive AGN (Figure 12B). Lowering pH from 6.0 to 5.0 reduced the surface potential of the latex beads being influenced by the anionic valence of the UM coats from -28 to -21 mV. An effect of pH on the activity of UM's and thus on AGN could be of interest from a therapeutic point of view and deserves further investigation.

CONCLUSION

It is astonishing that despite of the widespread occurrence of crystalluria and kidney calcifications not everybody produces stones. In stone patients without treatment average recurrence rate was only 1 stone within 8 years[56] and in 71% of patients stone residuals after percutaneous nephrolithotomy remained stable or even decreased during an observation time of 2-3 years[57]. The retention and growth of crystal aggregates in the kidney seems therefore only to occur under very special and rare conditions. Such conditions may be an extremely low diuresis with high concentrations of stone forming minerals and with a prolonged urinary transit time allowing crystal AGN already in the kidney and/or an extreme oxalate ingestion. Both conditions can produce an excessive crystalluria which can damage renal tubules and alter the production of UM's normally protecting from stone formation[23]. Which factors finally are decisive whether crystalluria provokes stone formation or crystalluria is a useful mechanism to eliminate heavy soluble substances with minimal water loss remains open to further research.

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MINIREVIEWS

T-cell ageing in end-stage renal disease patients: Assessment and clinical relevance

Ruud WJ Meijers, Michiel GH Betjes, Carla C Baan, Nicolle HR Litjens

Ruud WJ Meijers, Michiel GH Betjes, Carla C Baan, Nicolle HR Litjens, Department of Internal Medicine, Division of Nephrology and Transplantation, Erasmus Medical Centre, 3000 CA Rotterdam, The Netherlands
Author contributions: All authors contributed to this work.
Correspondence to: Ruud WJ Meijers, MSc, Department of Internal Medicine, Division of Nephrology and Transplantation, Erasmus Medical Centre, Room NA-523, PO Box 2040, 3000 CA Rotterdam, The Netherlands. r.meijers@erasmusmc.nl
Telephone: +31-10-7035421 Fax: +31-10-7044718
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Abstract

End-stage renal disease (ESRD) patients have a defective T-cell-mediated immune system which is related to excessive premature ageing of the T-cell compartment. This is likely to be caused by the uremia-associated pro-inflammatory milieu, created by loss of renal function. Therefore, ESRD patients are highly susceptible for infections, have an increased risk for virus-associated cancers, respond poorly to vaccination and have an increased risk for atherosclerotic diseases. Three ageing parameters can be used to assess an immunological T-cell age. First, thymic output can be determined by assessing the T-cell receptor excision circles-content together with CD31 expression within the naïve T cells. Second, the telomere length of T cells and third the T-cell differentiation status are also indicators of T-cell ageing. Analyses based on these parameters in ESRD patients revealed that the immunological T-cell age is increased by on average 20 years compared to the chronological age. After kidney transplantation (KTx) the aged T-cell phenotype persists although the pro-inflammatory milieu is diminished. This might be explained by epigenetic modifications at hematopoietic stem cells level. Assessment of an immunological T-cell age could be an important tool to identify KTx recipients who are at risk for allograft rejection or to prevent over-immunosuppression.

Key words: End-stage renal disease patients; Kidney transplantation; T-cell ageing; T-cell differentiation; Uremia

Core tip: The uremia-induced inflammatory environment in end-stage renal disease (ESRD) patients is associated with a prematurely aged T-cell compartment, resulting in defective T-cell-mediated immunity. ESRD patients are highly susceptible for infections, have an increased risk for virus-associated cancers, respond poorly to vaccination and have an increased risk for atherosclerotic diseases. Adequate renal replacement therapy in the form of kidney transplantation is able to diminish the uremic pro-inflammatory environment but unsuccessfully reverses the aged T-cell system. Assessment of T-cell ageing might be a tool to facilitate individualization of immunosuppressive regimes and prevent over-immunosuppression and its associated clinical complications in kidney transplant recipients.

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INTRODUCTION

Loss of renal function is strongly associated with a defective immune system which is known as uremia-associated immune deficiency[1-3]. Retention of uremic molecules and cytokines in end-stage renal disease (ESRD) patients are key mechanisms in generating oxidative stress and inflammation[2,4,5]. This creates a pro-

inflammatory environment in which both the innate (first line of defense, a-specific)[3,6-8] as well as the adaptive (specific) immune system are affected (Figure 1)[3,9,10].

T cells, members of the adaptive immune system, are the best-studied immune cells in ESRD patients and in the field of transplantation they are the main target of immunosuppressive medication[11]. The uremia-associated pro-inflammatory milieu causes T-cell defects associated with premature T-cell ageing when compared to healthy age-matched individuals (Figure 1)[12]. Analysis of the T-cell compartment in ESRD patients revealed that the immunological age of T cells is increased by 20 years compared to their chronological age (Figure 1)[12].

The dysfunctional immune system of ESRD patients has a substantial clinical impact on both the morbidity and mortality of ESRD patients. Patients are highly susceptible for infections[13,14], have an increased risk for virus-associated cancers[15], respond poorly to vaccination[16] and have an increased risk for atherosclerotic diseases[17,18].

In this review, the concept of uremia-associated age-related changes of T cells is highlighted focusing on the assessment of an immunological T-cell age, clinical implications and possible therapeutic options for ESRD patients.

CONCEPT OF T-CELL AGEING

With normal healthy ageing, the T-cell immune system ages as well[19]. Hematopoietic stem cells (HSCs), generated in the bone marrow, give rise to myeloid as well as lymphoid progenitor cells[20]. T cells are generated from the latter. With increasing age, HSCs are skewed towards myeloid-generating subsets at the expense of lymphoid-generating HSCs, resulting in a lower number of progenitor T cells. These progenitor T cells are further "educated" in the thymus in which naïve T cells will form specific receptors on their cell surface known as T-cell receptors (TCRs). With increasing age, the thymus involutes[21,22]. This process involves a decrease in tissue in combination with a loss of tissue organization with the net outcome that numbers of naïve T cells leaving the thymus, known as recent thymic emigrants (RTEs) are reduced. Involution of the thymus starts at birth and is accelerated during adolescence[23].

This explains the lymphopenic number in naive T cells with increasing age. Despite the fact that the naïve T-cell pool can also be maintained by homeostatic proliferation in which TCR triggering in combination with the cytokines Interleukin (IL)-7 and IL-15 expand T cells[24], the net effect is a diminished number of naïve T cells and the number of memory T cells in the peripheral blood of elderly individuals is preserved[25]. A relatively expanded number of naïve T cells by homeostatic proliferation results in a T-cell pool with a restricted TCR repertoire[24,26]. A diverse TCR repertoire is a necessary prerequisite for an adequate and effective T-cell response towards newly encountered antigens[27].

After encountering and activation by an antigen, a naïve T cell will proliferate and become a memory T cell. During physiological ageing the population of antigen-experienced memory T cells will increase and the majority of these cells will become highly differentiated. These cells are known to have an increase in pro-apoptotic markers[28] and loss in co-stimulatory molecule CD28[29,30]. CD28 plays an important role in the activation of T cells and a loss of CD28 can result in insufficient activation, shorter replicative lifespan and a higher toxicity[29]. Furthermore, highly differentiated cells are known to have a reduction in their telomere length[31].

A telomere is a region of repetitive nucleotides which is located at the end of each chromosome and prevents chromosomal instability. Loss of telomere length has been linked to an increased risk for tumor development and to T-cell ageing[32,33].

ASSESSING AN IMMUNOLOGICAL T-CELL AGE

A global assessment of the immunological age of the T-cell system can be performed by the analysis of three ageing parameters. During the formation of the T-cell receptor (TCR) in the thymus, DNA sequences in the TCR loci are deleted and circularized into episomal DNA molecules, so called single joint TCR excision circles (TREC), a process known as TCR rearrangement[34]. This TREC remains in the newly formed naïve T cells leaving the thymus. Upon replication of these cells in the periphery, the TREC is only transferred to one daughter cell resulting in a reduction of TRECs in the naïve daughter T cells. With an increasing age, the number of RTEs containing a TREC declines log linearity due to a lower thymic output of RTEs and an increase in proliferation of naïve T cells. The TREC content can be determined using a quantitative polymerase chain reaction (qPCR) method normalized to the single-copy albumin gene[34,35]. Next to the TREC content, these RTEs can be detected by measuring the expression of CD31 within the naïve T-cell pool[36,37]. In addition to the thymic output of T cells, the diversity of the TCR repertoire can be analyzed by sequencing in order to determine the loss of TCR specificities within the T-cell population and to assess the percentage of oligoclonal T cells[27,38]. Recently, a novel TREC assay in which the TCR diversity was combined with the TREC content to get quantitative insight into intra-thymic and post-thymic proliferative capacity of T cells and its alterations upon ageing[39].

As a second parameter for the assessment of an immunological T-cell age, the T-cell telomere length can be determined as a measurement for the proliferative history of a T-cell population[40]. A decline in telomere length is highly associated with an increased proliferative history. A commonly used method to assess a relative telomere length (RTL) is the fluorescent *in situ* hybridization (FISH) method[41,42]. During this procedure a labeled

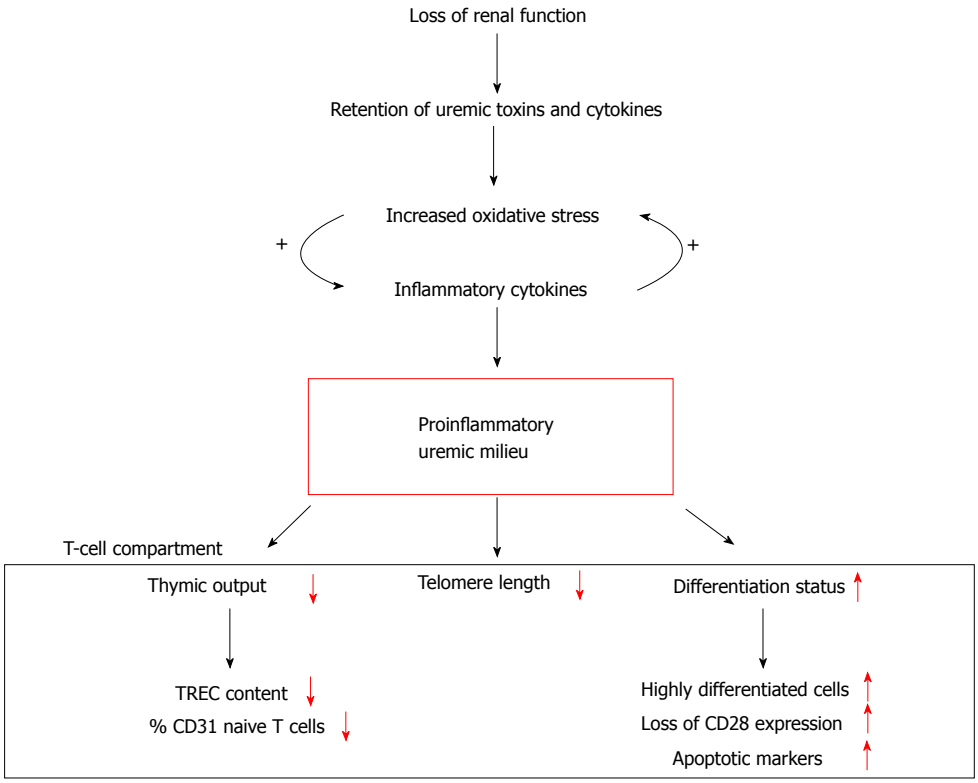

Figure 1 Schematic overview of the effects on the T-cell compartment caused by the uremia-induced pro-inflammatory milieu in end-stage renal disease patients. Loss in renal function creates a pro-inflammatory milieu by the retention of uremic toxins and cytokines which increases oxidative stress and the production of inflammatory cytokines. This pro-inflammatory uremic milieu is associated with premature T-cell ageing, which results in defective T-cell immunity. End-stage renal disease (ESRD) patients have a lower thymic output of naïve T cells which can be measured by the TCR excision circles (TREC) content and the percentage of CD31-expressing naïve T cells. Furthermore, ESRD patients have an expanded population of highly differentiated T cells with a loss in CD28 expression and an increase in apoptotic markers. Moreover, these expanded T cells have a high proliferative history causing a decline in telomere length which can be measured by the relative telomere length analysis.

peptide nucleic acid (PNA) probe binds to the telomere repeats which can be read-out by fluorescent microscopy or by fluorescence measurements using a flow cytometry (flow FISH). The RTL can be calculated by relating the intensity of the bound PNA probe to that of a T-cell lymphoblastic leukemia (1301 CCRF-CEM) cell-line, known for its long telomeres, as an internal control[41]. Inclusion of antibodies in this method makes it possible to analyze the telomere length in different T-cell populations (*i.e.,* $CD4^+$ and $CD8^+$ T cells)[2,41]. A limitation of this assay is the temperature (82 ℃) which is required for DNA annealing which makes the use of stable fluorochromes necessary[41,42]. Quantum dots (nanoparticles) were found to be highly fluorescent, bind to antibodies and have much better temperature stability. Quantum dots conjugated with antibodies directed to T-cell antigens were found to retain most of their fluorescence following the annealing step. The use of quantum dots can be a solution for the limitations in antibody use in the flow-FISH procedure and allows to assess a telomere length in different T-cell subsets within one assay[42].

In addition to the telomere length, the activity of the telomerase can be measured. Telomerase is responsible for maintaining telomere length and the cellular replicative potential and an impaired activity of telomerase results attrition of telomeres[19]. Measuring the activity of telomerase gives additional information on the telomere shortening. This assay is based on the capacity of a test sample to amplify a telomere template[43].

The differentiation status of the T-cell compartment can be used as a third parameter to assess an immunological age. The increase in highly differentiated memory cells with increasing age can be determined by analysis of the phenotype of circulating T-cells using multicolor flowcytometry. Based on the expression of the chemokine (C-C motif) receptor 7 (CCR7), enabling cells to migrate to secondary lymphoid organs, and CD45RO, an isoform of the leukocyte common antigen expressed on memory T cells, a distinction within the memory T-cell compartment can be made. The different memory T cell subsets include Central Memory (CM) ($CCR7^+$ and $CD45RO^+$), able to home to secondary lymph nodes and producing mainly IL-2 which is necessary for the proliferation of T cells, Effector Memory (EM) ($CCR7^-$ and $CD45RO^+$), able to migrate to peripheral tissues exerting direct effector functions and terminally differentiated effector memory $CD45RA^+$ (EMRA) ($CCR7^-$ and $CD45RO^-$), which exert cytotoxic activities and are highly susceptibility to apoptosis[44]. Moreover, these terminally differentiated cells often lose the expression CD28 which makes them less dependent on co-stimulation to become activated[45]. In addition, CD57 can be measured

as a marker for highly differentiated memory T cells[12,46]. CD95 (FAS) and CD279 (known as programmed death receptor-1 (PD-1)) are both commonly used as pro-apoptotic markers[12,28,47].

AGED T-CELL SYSTEM IN ESRD PATIENTS

Based on the analyses of the T-cell ageing parameters, *i.e.*, assessment of TREC- content, relative telomere length and differentiation status we showed that the immunological age of ESRD patients is advanced by 20 years compared to their calendar age[12]. As compared to an age-matched healthy control, ESRD patients had a lower thymic output of naïve T cells, a decline in the T-cell telomere length and an increase in the differentiation status towards the terminally differentiated memory phenotype with a large number of CD28-negative (or CD28null) T cells (Figure 1)[12]. Progressive loss of renal function was highly correlated with a lack of IL-7, a loss of naïve T cells and an increase in terminally differentiated $CD8^+$ T cells[48]. The effects of renal replacement therapy (RRT) on the T-cell ageing parameters seemed to be small and were limited to the $CD8^+$ T-cell compartment of young ESRD patients[2]. The type of RRT did not influence the ageing parameters since both hemodialysis (HD) and peritoneal dialysis (PD) patients showed signs of an aged T-cell compartment[2]. Moreover, the duration of dialysis did not seem to influence the ageing parameters[49]. Furthermore, the type of underlying kidney disease was not related to any parameter of immunological ageing[2] indicating that the loss of renal function is the dominant factor for a decreased thymic output of naïve T cells and increased differentiation/proliferation of memory T cells.

Cytomegalovirus (CMV) is known to affect the T-cell compartment which closely resembles ageing[46,50-52]. Infection with the virus results in chronic latency and the effects of CMV on the T-cell compartment are relevant, since approximately 70% of the ESRD patients is infected with CMV[50]. In these patients, CMV was associated with an increased number of highly differentiated $CD4^+$ and $CD8^+$ T cells and a relatively small decline in $CD8^+$ T-cell telomere length[46,50,53]. The effects were restricted to the memory T-cell compartment since the thymic output of T cells was not affected. Therefore we concluded that CMV only affects the differentiation status of circulating T cells[46,50,53].

CLINICAL IMPLICATIONS OF AN AGED T-CELL COMPARTMENT

The uremia-associated prematurely aged T-cell immune system has a substantial clinical impact leading to an increased morbidity and mortality. ESRD patients are highly susceptible for infections which might further contribute to the pro-inflammatory milieu. For instance periodontitis, which is common in patients with chronic kidney disease (CKD), often leads to inflammation[54].

T cells of ESRD patients have an impaired production of IL-2 and the inadequate T-cell proliferative capacity results insufficient T-cell responses[55-57]. This in combination with low numbers of T cells results into inadequate T-cell responses directed to viruses and a decreased tumor surveillance which significantly increases the risk for virus-associated tumors[15,58]. Next to IL-2, in hemodialysis (HD) patients it was found that activated T cells have impaired responses to tumor necrosis factor (TNF)-α, implying a state of tachyphylaxis[59].

Following vaccination against hepatitis B, the formation of antigen-specific $CD4^+$ EM T cells is severely impaired in ESRD patients[56]. The poor development of IL-2 producing $CD4^+$ EM T cells in patients with ESRD was strongly associated with a low generation of antibodies towards hepatitis B antigens[56]. The inability to maintain protective antibody titers after T-cell dependent vaccinations[60,61] or after a natural infection[62,63] might be caused by a loss of antigen-specific T cells as a result of their increased susceptibility for apoptosis[12,47].

Furthermore, the loss in TCR diversity of naïve T cells due to a lower number of RTEs but an increase in proliferated naïve T cells is linked to a decreased efficiency of vaccination but also to an increased susceptibility for infections and cancers[26,64].

$CD4^+$ T cells lacking CD28 expression, are found to be highly cytotoxic as they produce large amounts of interferon (IFN)-γ and TNF-α and release granzyme-B and perforin upon activation. In several studies[17,65] it is shown that these cytotoxic cells are present in unstable atherosclerotic plaques and are associated with an increased risk for recurrence of both acute coronary events and ischemic stroke resulting in a higher mortality rate[66]. As confirmed in ESRD patients, high numbers $CD4^+$CD28null T cells is strongly associated with a history of cardiovascular diseases[17,18,65,67].

$CD8^+$CD28null T cells contain a subpopulation of cells possessing immunosuppressive capacities[68,69] and has therefore been linked to a decreased vaccination responsiveness of healthy individuals[70]. These immunosuppressive capacities also suggest that these cells could be important in preventing allograft rejection after kidney transplantation (KTx). Indeed, we recently demonstrated that patients with an expanded population of highly differentiated (EMRA) $CD8^+$CD28null T cells had a lower risk for allograft rejection after KTx[71]. Another explanations might be that $CD8^+$CD28null T cells represents clonal expansions of particular antigen-specific $CD8^+$ T cells that compete for immunologic space which is associated with reduction of T-cell diversity[72]. This might affect the diversity of alloreactive T-cells as well. Next to these highly differentiated $CD8^+$ T cells in KTx recipients, a high proportion of highly differentiated $CD4^+$ T cells was also linked to a lower risk for allograft rejection[73].

PREMATURE T-CELL AGEING AND KIDNEY TRANSPLANTATION

After KTx, the levels of pro-inflammatory proteins and oxidative stress decrease rapidly to levels that are comparable to healthy individuals[74]. Despite this, the uremia-associated prematurely aged T-cell immune system existed after KTx. (Meijers et al, 2014 submitted)

Immunosuppressive treatment affected the number of highly differentiated cells directly post-KTx. However after tapering the immunosuppressive medication, these highly differentiated T-cell numbers were restored to pre-KTx values. Furthermore, the telomere length of the T-cell compartment did not change and thymic function was not improved the first year post-KTx (Meijers *et al* 2014 submitted). Even after T-cell depleting immunosuppressive therapy [*i.e.*, rabbit antithymocyte globulin (rATG)] T cells are repopulating by homeostatic proliferation instead of a higher thymic output of naïve T cells[75,76]. Therefore, the uremia-associated immunological ageing seems stably imprinted in the T-cell system and not reversible by KTx.

Normal ageing is associated with, epigenetic changes in HSCs resulting in a shift in the balance towards myeloid precursors at the expense of the lymphoid ones[77,78]. Healthy ageing results in genetic alterations affecting T cells at developmental stages leading to phenotypic as well as functional changes[79]. In ESRD patients, uremia is able to cause epigenetic changes[80]. Young *et al*[81] 2012 found that methylation of the KLOTHO gene is initiated by oxidative stress in ESRD patients. KLOTHO deficient mice created a syndrome that resembles human ageing[82]. Although KTx reverses the uremic proinflammatory environment[74] it is unable to induce changes at the epigenetic level. The persistence of the aged T-cell phenotype post-KTx has several clinical implications as it may increase the risk for infections, malignancies and cardiovascular diseases in KTx recipients. T-cell lymphopenia has been associated with a high risk for infections and malignancies post-KTx[83,84].

Due to ageing of the T-cell compartment, elderly patients are more vulnerable for drugs toxicity, infections and malignancies caused by over-immunosuppression. In these patients, the incidence of virus-associated cancers is even higher post-KTx as it is pre-KTx[58,85]. Over-immunosuppression might be prevented after mapping the T-cell immune system of the transplant recipient[73,86] as T cells are the main target of immunosuppressive medication[11]. A study of Ducloux *et al*[87] in 2010 showed that prolonged $CD4^+$ T-cell lymphopenia after severe T-cell depletion by rATG is associated with an increased risk for infections and mortality post-KTx. High TREC values implying for a "younger" T-cell compartment pre-KTx, is associated with a better reconstitution of T-cell numbers after rATG and lower risk for infections and cancer post-KTx[87].

THERAPEUTIC OPTIONS TO REVERSE T-CELL AGEING

As mentioned earlier, RRT did not reduce T-cell ageing since no major differences between patients on dialysis and predialysis patients with respect to the T-cell ageing parameters were observed[2]. Adequately targeting the presence of the pro-inflammatory environment in ESRD patients by KTx[74] did not successfully reverse the aged T-cell immune system.

Another method to reduce the level of oxidative stress and inflammation in ESRD patients is targeting the transcription factor Nuclear factor-erythroid-2-related factor 2 (Nrf2) which is an important regulator of genes encoding antioxidant and detoxifying molecules[88]. Treatment with bardoxolone methyl, which is an activator of Nrf2 may attenuate T-cell ageing in ESRD patients[88]. However, treatment is restricted due to the increased risk of cardiovascular diseases after treatment with bardoxolone[89].

Another therapeutic option that might be able to improve T-cell function in ESRD patient is treatment with IL-7, a key cytokine for homeostatic proliferation of naïve T cells, that is reduced in patients causing a depletion of naïve T-cell pool[48,90]. The first human studies, in which IL-7 was administered, are promising since an increased naïve T-cell pool with a broader TCR repertoire diversity was found[38,91]. At present, IL-7 administration has not been tested in patients with ESRD.

CONCLUSION

Progressive loss of renal function creates a pro-inflammatory milieu which is highly associated with a dysfunctional immune system. This is a logical explanation for the increased vulnerability for infections, poor vaccination responses, high risk for malignancies and high risk for atherosclerotic diseases. Analysis of the T-cell system showed that ESRD patients have a prematurely aged T-cell compartment resulting in an impaired function. ESRD patients have a lower thymic output of naïve T cells, T cells have shorter telomeres and the T-cell compartment is shifted towards more differentiated T cells.

Therapeutic options to minimize morbidity and decrease mortality by improving or even fully reversing the aged T-cell phenotype are warranted. Although improvement of renal function by adequate renal replacement therapy in the form of KTx, which drastically decreases the uremia-associated pro-inflammatory milieu, the prematurely aged T-cell phenotype appeared to be irreversible. Therefore the aged T-cell immune system remains an important determinant of the dysfunctional immune system post-KTx. More research is necessary to fully understand the uremia-associated premature T-cell ageing phenomenon, also at earlier developmental stages of T-cells, to be able to successfully intervene and increase the life-span of ESRD patients.

Until today, all KTx recipients receive the same standard immunosuppressive therapy to prevent allograft rejection. Recently it was shown that the effect of calcineurin-inhibitors and rapamycin on peripheral blood mononuclear cells (PBMCs) was different between young and elderly individuals[92]. Assessing an immunological T-cell age using T-cell ageing parameters as described in this review, may guide clinicians in decision-making with respect to transplanting an ESRD patient or not, adjusting immunosuppression following KTx to minimize its long-term-associated adverse events.

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MINIREVIEWS

Nutcracker syndrome

Kaan Gulleroglu, Basak Gulleroglu, Esra Baskin

Kaan Gulleroglu, Esra Baskin, Department of Pediatric Nephrology, Baskent University, 06540 Ankara, Turkey
Basak Gulleroglu, Department of Radiology, Adana Numune Training and Research Hospital, 01123 Adana, Turkey
Author contributions: Gulleroglu K, Gulleroglu B and Baskin E contributed equally to this work; Gulleroglu K, Gulleroglu B and Baskin E analyzed the data; Gulleroglu K, Gulleroglu B and Baskin E wrote the paper.
Correspondence to: Kaan Gulleroglu, MD, Department of Pediatric Nephrology, Baskent University, 54. Cadde, No: 72/3, Bahcelievler, 06540 Ankara, Turkey. kaangulleroglu@yahoo.com
Telephone: +90-312-2234936 Fax: +90-312-2157597
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Abstract

The nutcracker phenomenon [left renal vein (LRV) entrapment syndrome] refers to compression of the LRV most commonly between abdominal aorta and superior mesenteric artery. Term of nutcracker syndrome (NCS) is used for patients with clinical symptoms associated with nutcracker anatomy. LRV entrapment divided into 2 types: anterior and posterior. Posterior and right-sided NCSs are rare conditions. The symptoms vary from asymptomatic hematuria to severe pelvic congestion. Symptoms include hematuria, orthostatic proteinuria, flank pain, abdominal pain, varicocele, dyspareunia, dysmenorrhea, fatigue and orthostatic intolerance. Existence of the clinical features constitutes a basis for the diagnosis. Several imaging methods such as Doppler ultrasonography, computed tomography angiography, magnetic resonance angiography and retrograde venography are used to diagnose NCS. The management of NCS depends upon the clinical presentation and the severity of the LRV hypertension. The treatment options are ranged from surveillance to nephrectomy. Treatment decision should be based on the severity of symptoms and their expected reversibility with regard to patient's age and the stage of the syndrome.

Key words: Nutcracker syndrome; Renal vein entrapment; Hematuria; Orthostatic proteinuria; Left renal vein hypertension

Core tip: The nutcracker phenomenon [left renal vein (LRV) entrapment syndrome] refers to compression of the LRV most commonly between abdominal aorta and superior mesenteric artery. Term of nutcracker syndrome (NCS) is used for patients with clinical symptoms associated with nutcracker anatomy. The symptoms vary from asymptomatic hematuria to severe pelvic congestion. The management of NCS depends upon the clinical presentation and the severity of the LRV hypertension.

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INTRODUCTION

The nutcracker phenomenon [left renal vein (LRV) entrapment syndrome] refers to compression of the LRV most commonly between abdominal aorta and superior mesenteric artery. This phenomenon is characterized by impeded outflow from the LRV into the inferior vena cava (IVC) due to extrinsic compression.

The terms nutcracker phenomenon and nutcracker syndrome (NCS) are sometimes used as synonym in the literature. Nutcracker phenomenon descript anatomic findings suggestive of nutcracker are present without clinical symptoms. Term of NCS is used for patients with clinical symptoms associated with nutcracker anatomy.

Diagnosis of NCS could be difficult for some reasons. It was thought to be a rare condition. Also in the

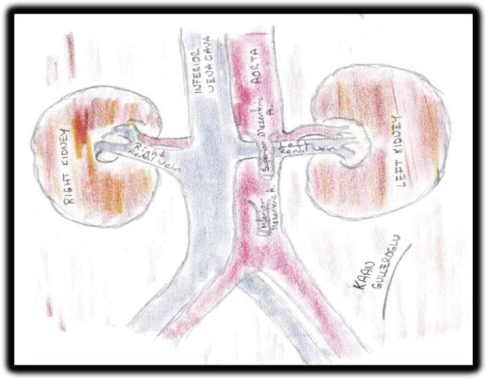

Figure 1 Anatomical configuration of nutcracker syndrome.

absence of clinical features it was necessitate a high suspicion. A noninvasive imaging must be followed by an invasive imaging for confirmation of the diagnosis.

ANATOMICAL CONFIGURATION AND PATHOPHYSIOLOGY

LRV entrapment divided into 2 types: anterior and posterior. Anterior NCS is the compression of a normally situated LRV by the abdominal aorta and the superior mesenteric artery (Figure 1). Posterior NCS is rare. It is presented with retroaortic LRV compressed usually between abdominal aorta and vertebral column. Other uncommon causes such as pancreatic neoplasm, paraaortic lymphadenopathy, retroperitoneal tumor, abdominal aortic aneurysm, overarching testicular artery, LRV duplication, and ectopic ventral right renal artery and strangulating fibrolymphatic tissue may play a role on the etiology of posterior NCS. Left renal ptosis, lordosis and decreased retroperitoneal and mesenteric fat tissue may cause to NCS[1-3].

Right-sided NCS is a more rare condition. Pregnancy is defining as a factor contributing to right-sided NCS by compression of large veins[1]. Left-sided IVC, hemiazygos continuation and persistent left superior vena cava combination is another rare cause of right NCS[4].

All of the anatomic mechanisms involved in renal vein compression are resulting with outflow obstruction leads to LRV hypertension with a measurable renocaval pressure gradient. The normal pressure gradient between the distal renal vein and IVC is < 1 mmHg. A renocaval pullback pressure gradient of ⩾ 2 mmHg is highly suggestive of a nutcracker phenomenon[5]. LRV hypertension is the underlying mechanism which may result in formation of varices and collaterals. Venous sinuses in the neighboring of renal calyces were taken in form by these varices and collaterals. Hematuria and proteinuria are the results of these venous sinuses[6].

DEMOGRAPHIC CHARACTERISTICS

Prevalence of NCP is unknown. NCP may be higher in female. Affected persons are ranging from children and adolescents to middle-aged and older people with seventh decade of life[7]. Most symptomatic patients are in their second and third decade of life and a second peak of NCS occurs in middle-aged women[8]. Coincidental cases in siblings have been reported, although NCP is not a hereditary phenomenon[9]. The rapid increase in body height and the maturation of the vertebral bodies during puberty is resulting with decrease in the angle between the superior mesenteric artery and aorta. A low body mass index has been shown to correlate positively with NCS[10].

CLINICAL FEATURES

Clinical features of patients with NCS are various. The symptoms vary from asymptomatic hematuria to severe pelvic congestion. Some patients have severe and persistent symptoms. Symptoms are aggravated by physical activity[7]. Symptoms include hematuria, orthostatic proteinuria, flank pain, abdominal pain, varicocele, dyspareunia, dysmenorrhea, fatigue and orthostatic intolerance[11-13]. The symptoms of autonomic dysfunction such as hypotension, syncope, and tachycardia could be seen but they are rare[14]. Henoch-Schönlein purpura, IgA, nephropathy, membranous nephropathy, and idiopathic hypercalciuria with nephrolithiasis associated with NCS have been reported[12,15].

NCS can differentiate clinically into 2 subtypes as follows: typical presentation (or renal presentation) and atypical presentation (or urologic presentation). Typical clinical presentation include hematuria (micro- to macrohematuria), orthostatic proteinuria with or without flank pain. Abdominal pain, varicocele, dyspareunia, dysmenorrhea, fatigue and orthostatic intolerance are the components of the atypical presentation (Table 1).

The most common symptom is hematuria. It is due to elevated LRV pressure resulting in the rupture of thin-walled septum between the varices and the collecting system in the renal fornix. Hematuria varies from micro- to macrohematuria. LRV is correspondent in this variation[14]. Isolated hematuria was reported 33.3% in children with NCS. Microhematuria is 4 times more common than macrohematuria[16].

Orthostatic proteinuria is another common symptom in NCS. The degree of proteinuria is variable. The incidence of orthostatic proteinuria is high during puberty. The mechanism of orthostatic proteinuria was not well understood yet. Changes of renal hemodynamic and the elevated levels of norepinephrine and angiotensin II were thought as the causes[17].

Pain is a result of the inflammatory cascade triggered by venous hypertension. Flank pain and abdominal pain are the consequences of that inflammatory process[1]. Left flank pain can be due also to urethral colic related to blood clots passing down to left ureter[7].

Varicocele affects 5.5%-9.5% of men and usually occurs on the left side. Development of varicocele is related with high LRV pressure and collateral circulation.

Table 1 Clinical features of the nutcracker syndrome

	Renal presentation	Urologic presentation
Hematuria	+	-
Orthostatic proteinuria	+	-
Flank pain	+	-
Abdominal pain	-	+
Varicocele	-	+
Dyspareunia	-	+
Dysmenorrhea	-	+
Fatigue	-	+
Orthostatic intolerance	-	+

Collateral veins could be demonstrated on pelvic and abdominal Doppler ultrasonography or venography[11].

DIAGNOSIS

Variations of normal anatomy must be considered before the diagnosis. Asymptomatic dilatation of LRV is frequently seen on ultrasonography or computed tomography, has been accepted as a finding of a normal variant[18]. NCS can exist without distended LRV. Normal flow also can exist in distended LRV[11]. Therefore, the first diagnostic need must be clinical examination. Existence of the clinical features constitutes a basis for the diagnosis. The presence of macroscopic or microscopic hematuria and proteinuria must evaluate. Urine analysis, urine phase contrast microscopy, urine culture and imaging of kidneys should be performed. Several imaging methods are used to diagnose NCS. Doppler ultrasonography, computed tomography angiography (CTA), magnetic resonance angiography (MRA) and retrograde venography are utilized.

Doppler ultrasonography can be used as the first diagnostic test in patients with suspected NCS. Length of the LRV is 6 to 10 cm and the average normal LRV diameter is 4 to 5 mm[7]. The normal pressure gradient between LRV and IVC is 1 mmHg or lower An elevated gradient > 3 mmHg between the LRV and the IVC can be used as a criteria of diagnosis for NCS[5]. Diameter of normal left gonadal vein is approximately 3 mm[19]. The normal superior mesenteric artery (SMA) originates behind the neck of the pancreas at the level of the first lumbar vertebra, and usually creates an acute angle at its origin from the aorta. Mean SMA angle is 51 ± 25° and mean SMA-aorta distance is 16 ± 6 mm in normal adults. Mean SMA angles in children are 45.8 ± 18.2° for boys and 45.3 ± 21.6° for girls. Mean SMA-aorta distances in children are 11.5 ± 5.3 mm for boys and 11.5 ± 4.5 mm for girls[20]. The standards of ultrasound diagnosis of NCS are descript by Zhang *et al*[21]: (1) the flow velocity of stenosis of the LRV in the supine position accelerates remarkably, and the acceleration, which is more than 100 cm/s, is more obvious after the patient has stood for 15 min; (2) the inner diameter ratio between ratio between the renal hilum and stenosis of the LRV in the supine position is > 3 and is > 5 after the patient has stood for 15 min[21]. Doppler ultrasonography has a sensitivity of 78% and a specificity of 100%[22]. However, in children the use of these criteria is limited because the smallest LRV sampling area and the largest Doppler angle than in adults[23].

CTA and MRA provide visualization of the anatomy. These tests can demonstrate the precise LRV compression point and/or prestenotic dilatation of the LRV together with perirenal and/or gonadal vein varices[24]. "Beak sign" is the abrupt narrowing of the LRV with a triangular shape at the aortomesenteric portion. It might be most useful finding among the various CT parameters, because it showed sensitivity 91.7% and specificity 88.9%[25]. MRA finding are similar to CT findings and MRA has the advantages of being less invasive with less amount of radiation than retrograde venography.

Retrograde venography is the gold standard for the diagnosis of NCS. It is not only confirming anatomic change, but also show a pressure gradient across the area of entrapment. Reflux of contrast into adrenal and gonadal veins from periureteral and perirenal venous collaterals, and pooling of contrast into the renal vein can be demonstrated[22]. Retrograde venography is the most informative method although it is an invasive test. It is not commonly performed in patients who have not severe symptoms.

Another invasive test such as cystoscopy may be helpful to identify hematuria from left ureteral origin. Notching from varicosities of the renal pelvis and ureters may be seen[26]. Cystoscopy is an indirect diagnostic method for NCS diagnosis.

TREATMENT

NCS is a type of spectral disease and varies in severity and symptoms, reflecting degrees of LRV compression, LRV hypertension and the compensatory stage related to the development of collaterals[11]. The management of NCS depends upon the clinical presentation and the severity of the LRV hypertension. The treatment options are ranged from surveillance to nephrectomy. Treatment decision should be based on the severity of symptoms and their expected reversibility with regard to patient's age and the stage of the syndrome[27]. Mild and tolerable symptoms can be followed conservatively. However, recurrent gross hematuria with anemia, severe flank pain, renal functional impairment, and inefficacy or aggravation of conservative treatment of the persistent orthostatic proteinuria after 24 mo of follow-up might require surgical treatment[18].

Spontaneous resolution by physical development during childhood is possible[18]. Conservative approach with observation during minimum 2 years without medication is the best option for patients younger than 18 years old. Seventy-five percent of patients with hematuria have complete resolution during this time[7]. Angiotensin inhibitors could be effective in patients with especially severe and prolonged orthostatic proteinuria[1].

Surgical procedures are used for treatment in patients with severe symptoms. Nephropexy, intravascular and

extravascular stent implantation, transposition of the LRV or SMA, gonadocaval bypass, renal autotransplantation and nephrectomy are surgical procedures.

Open surgical techniques for anterior NCS include LRV transposition, LRV transposition with patch venoplasty, patch venoplasty without LRV transposition, LRV transposition with saphenous vein cuff, gonadal vein transposition and saphenous vein bypass[28]. LRV transposition is the most frequent and most effective technique in which LRV is transposed distally to the IVC. The LRV is transected and re-anastomosed to the IVC in a more distal location and in a tension-free end-to-side fashion. LRV transposition with patch venoplasty is used in conditions as permanent distortion of the vein with prolonged compression of the LRV or overstretched LRV because of the prominent aorta. The great saphenous vein is used as a patch to augment the LRV-IVC confluence after transposition of the LRV. Patch venoplasty without LRV transposition technique is used when transposition is not favorable because of the short renal vein is short or it is not improve the external compression of the vein. In LRV transposition with saphenous vein cuff technique the saphenous vein is used to form a cuff extension to the LRV to create tension-free anastomosis. Decrease of pelvic congestion and decompression of LRV can be obtained by left gonadal vein transposition. Saphenous vein also can be used for the bypass of the decompressed segment of the LRV[28].

Anterior transposition of LRV is used for posterior variant of NCS. In this technique LRV is excised with a small rim of the caval wall, and transposed to IVC, in a proximal position, *via* anteaortic routing[29].

Surgical placement of an external stent to the LRV is another surgical approach to NCS [5]. Endovascular stenting is an alternative treatment option. It can be preferred to open surgery because of the long period of renal congestion, additional anastomoses and extensive dissection requirement of the open surgery. Thrombosis, stent migration, fracture and restenosis are the complications of the endovascular stenting but they are rare[30].

CONCLUSION

NCS is a type of spectral disease and varies in severity and symptoms. Variations of normal anatomy must be considered before the diagnosis. Existence of the clinical features constitutes a basis for the diagnosis. The management of NCS depends upon the clinical presentation and the severity of the LRV hypertension.

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MINIREVIEWS

Usefulness of hounsfield unit and density in the assessment and treatment of urinary stones

Adnan Gücük, Uğur Üyetürk

Adnan Gücük, Uğur Üyetürk, Department of Urology, Faculty of Medicine, Abant Izzet Baysal University, 14280 Bolu, Turkey
Author contributions: Gücük A performed majority of experiments and designed, wrote the manuscript; Üyetürk U provided vital reagent and analytical tools.
Correspondence to: Dr. Adnan Gücük, Associate Professor, Department of Urology, Faculty of Medicine, Abant Izzet Baysal University, Gölköy Kampüsü, 14280 Bolu, Turkey. gucukadnan@hotmail.com
Telephone: +90-505-6748193 Fax: +90-374-2534615
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Abstract

Computed tomography (CT) is widely used to examine stones in the urinary system. In addition to the size and location of the stone and the overall health of the kidney, CT can also assess the density of the stone in Hounsfield units (HU). The HU, or Hounsfield density, measured by CT, is related to the density of the tissue or stone. A number of studies have assessed the use of HU in urology. HUs have been used to predict the type and opacity of stones during diagnosis, and the efficacy has been assessed using methods including extracorporeal shock wave lithotripsy (ESWL), percutaneous nephrolithotomy (PCNL), ureterorenoscopic ureterolithotripsy (URSL), and medical expulsive treatment (MET). Previous studies have focused on the success rate of HU for predicting the type of stone and of ESWL treatment. Understanding the composition of the stone plays a key role in determining the most appropriate treatment modality. The most recent reports have suggested that the HU value and its variants facilitate prediction of stone composition. However, the inclusion of data regarding urine, such as pH and presence of crystals, increases the predictive accuracy. HUs, which now form part of the clinical guidelines, allow us to predict the success of ESWL; therefore, they should be taken into account when ESWL is considered as a treatment option. However, there are currently insufficient data available regarding the value of HU for assessing the efficacy of PCNL, URSL, and MET. Studies performed to date suggest that these values would make a significant contribution to the diagnosis and treatment of urinary system stones. However, more data are required to assess this further.

Key words: Hounsfield unit; Urinary stones

Core tip: Hounsfield units provide information not only for the diagnosis of urinary system tumors but also regarding a number of properties of urinary stones. Computed tomography is currently used most commonly to predict the type of stone and assess the potential efficacy of extracorporeal shock wave lithotripsy treatment. However, it might also assist urologists to decide which of percutaneous nephrolithotomy, ureterorenoscopic ureterolithotripsy, and medical expulsive treatment should be used to treat a patient.

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INTRODUCTION

In recent years, the use of helical non-contrast computed tomography (CT) in patients with urinary system stones has increased. Hounsfield units (HU), a parameter generated from standard CT, are related to the density of the stone or structure of interest.

Sir Godfrey Newbold Hounsfield first introduced

Table 1 Some critical hounsfield unit values in recent literature

	Ref.	Year	Hounsfield units	Affected parameters
Prediction of stones	Motley *et al*[4]	2001	Density < 76 /mm	Non-calcium stone
	Patel *et al*[5]	2009	Mean, 879 ± 230	Calcium oxalate monohydrate stone
			Mean, 844 ± 346	Apatite stone
			Mean, 550 ± 74	Cystine stone
	Spettel *et al*[7]	2013	< 500	Uric acid stone
Prediction of Radio-opacity	Chua *et al*[9]	2012	> 498.5	Radio-opaque stone
	Huang *et al*[10]	2009	> 800 (ureteral stones)	Radio-opaque
			< 200	Radiolucent
Predicting the success of ESWL	Hameed *et al*[15]	2013	> 1350	Low ESWL success
	El-Assmy *et al*[16]	2011	> 1000	Low ESWL success
	El-Assmy *et al*[17]	2013	≤ 600 and stone length ≤ 12 mm (in children)	High ESWL success
	Ouzaid *et al*[18]	2012	> 970	Low ESWL success
	Foda *et al*[19]	2013	> 934	Low ESWL success
Use in PNL	Gücük *et al*[20]	2012	< 677.5	Low PNL success
	Gücük *et al*[21]	2013	< 677.5	Increases success with flexible nephroscope use
Use in URS	Kim *et al*[22]	2014	Any	No effect
Medical expulsive treatment	Erturan *et al*[24]	2013	Any	No effect

ESWL: Extracorporeal shock wave lithotripsy.

the principle to quantify the amount of X-rays that pass through or are absorbed by tissues, and developed the resulting radiodensity scale. CT images are made up of pixels, each of which has a gray scale value from 1 (black) to 256 (white). This value corresponds to the amount of X-rays that pass through the structure, and can be measured and expressed in Hounsfield units (HU). HU have since been used to evaluate and quantify tissues and fluids. When the radiodensity of water is defined as 0, fat has a negative HU, and blood and other tissues have a positive HU. Using this method it is possible to differentiate 256 shades of gray that are indistinguishable to the naked eye[1].

HU can also be used to assess the CT density of urinary system stones. In recent years, this has become an important diagnostic tool, not only for predicting the type of stone but also for determining the appropriate mode of treatment. The aim of this review is to assess the various areas in which HU is used to diagnose and treat urinary system stones (Table 1).

THE ROLE OF HU IN PREDICTING THE TYPE OF STONE

Understanding the composition of urinary system stones is critical for determining the optimal mode of treatment. Urine pH, the presence of crystals, urease-positive bacteria in urine, plain radiographs, and a history of urinary stones have long been used to predict the composition of stones; recently, HU also was used for this purpose[2]. Mostafavi *et al*[3] performed an *in vitro* study and reported that stone composition could be predicted with high accuracy using HU. Motley *et al*[4] attempted to determine stone composition using HU density, calculated by dividing HU by the greatest transverse diameter of the stone (in mm), and suggested that HU density was more effective than HU alone. However, the authors also reported that neither HU value nor density was sufficient for determining stone composition *in vivo*[4].

Patel *et al*[5] investigated whether HU values could be used for differentiating among subtypes of calcium stones, and reported they were particularly useful for diagnosing calcium oxalate monohydrate and dihydrate stones. In a similar study, the authors reported that calcium stones could be identified with high accuracy using HU values, but that there was an overlap between the HU values of cystine and uric acid stones, making it difficult to differentiate these types of stones[6].

Spettel *et al*[7] designed an *in vivo* study to predict uric acid stones using urine pH and HU, and argued that using the two parameters together were more effective for predicting uric acid stones than either one alone. Specifically, for a stone > 4 mm a HU ≤ 500 and pH ≤ 5.5 had a positive predictive value of 90% for uric acid composition[7]. To elucidate whether the composition of struvite stones could be predicted using HU values, Marchini *et al*[8] reported that the HU values of pure and mixed struvite stones overlapped, and concluded that struvite stone composition could not be accurately predicted by HU.

Recent studies suggested that HU and their variants are useful for predicting the composition of stones. However, they were insufficient for certain types of stone; the use of urinary parameters improved the accuracy in such cases.

THE ROLE OF HU IN PREDICTING RADIO-OPACITY

Knowing the radio-opacity of urinary system stones affords significant information to urologists for selecting the appropriate treatment and imaging modality to use during follow-up. Nevertheless, the relationship between the range/threshold of the HU values of stones measured using CT and radio-opacity is poorly understood.

Identifying radiolucent stones using CT has the advantage of preventing unnecessary radiographies during follow-up, preventing exposure to radiation, lowering anxiety, and reducing costs. Chua *et al*[9] also assessed the predictive potential of the radio-opacity of stones identified using plain radiographs and HU values. They examined 184 cases, and calculated that 498.5 HU was the appropriate cut-off value for determining if a stone > 4 mm was radio-opaque or radiolucent, with 89.3% sensitivity and 87.3% specificity[9]. Huang *et al*[10] performed a study that also included ureteral stones, and reported that stones of HU > 800 were visible on plain radiographic images, whereas those with a density < 200 HU were not. Taken together, data assessing the relationship between HU values and radio-opacity suggested that the follow-up of certain groups of patients could be performed adequately using plain radiographs rather than repeated CT examinations, reducing the time, cost, and exposure to ionizing radiation.

THE ROLE OF HU IN PREDICTING THE SUCCESS OF EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY TREATMENT

Extracorporeal shock wave lithotripsy (ESWL) can successfully eliminate approximately 90% of renal stones in adults[11]. Successful ESWL depends on the type of lithotripter, and the localization, size, and hardness of the stone[12]. Many previous studies have investigated the relationship between CT parameters and successful ESWL. Data revealed that the energy of the shock wave needed for fragmentation was related to stone density, and that the higher the stone density, the stronger the shock wave energy needed to achieve fragmentation[13,14].

Hameed *et al*[15] reported that successful fragmentation using ESWL was decreased in stones with HU > 1350, which required application of more shock waves. El-Assmy *et al*[16] used the Hounsfield value of the stones to predict stone composition and density, and the fragmentation success using ESWL, and selected HU > 1000 as their cut off value. Another study of pediatric patients by the same group revealed that stones ⩽ 600 HU and ⩽ 12 mm in length were significant independent predictors of SWL success in children[17].

Ouzaid *et al*[18] performed a prospective study on 50 patients, and reported that a HU threshold of 970 was predictive of successful ESWL. Specifically, the stone-free rate was 96% and 38% with HU < 970 and > 970, respectively[18]. Foda *et al*[19] demonstrated that stone disintegration failed if the stone density was > 934 HU; therefore, they did not recommend ESWL in this group of patients.

Taken together, the available data suggest that the HU value, a parameter that is incorporated into clinical guidelines and enables prediction of successful ESWL, should be considered when making decisions regarding the use of ESWL.

THE ROLE OF HU IN PERCUTANEOUS NEPHROLITHOTOMY

Fluoroscopic imaging has been widely used during percutaneous nephrolithotomy (PCNL) operations to facilitate access to the collector system and renal anatomy, determine the placement of surgical tools, and identify and extract residual stones. The accurate assessment of post-operative residual stones significantly reduces morbidity. However, identifying residual stones using fluoroscopy depends largely on the size and opacity of the stone. In contrast, CT is an effective imaging tool for identifying all but indinavir stones. In addition, it allows the opacity of the stones to be quantified using HU. The HU value of stones affects the outcome of PCNL operations. Gücük *et al*[20] investigated the effects of certain parameters, including HU, on the outcome of 179 PCNL patients, and concluded that the HU value was an independent factor that affected the success of PCNL. Specifically, an HU value < 677.5 reduced the success of PCNL by 2.65-fold. The authors also reported a positive relationship between HU value and hemorrhage, and explained that this was associated with an increased frequency of endoscopic manipulation to extract residual stones. The identification of residual stones became easier with increasing HU value, and a higher HU value was also associated with increased renal trauma as a result of the higher energy required to breakdown stones[20]. The same group assessed the efficacy of routine flexible nephroscopic examination for identification and treatment of residual stones during PCNL operations, and reported that flexible nephroscopy was more effective in stones with low compared with high HU values. They suggested that this might be because flexible nephroscopy is used more commonly than fluoroscopy because stones with a low HU cannot be identified using fluoroscopy[21].

Although limited data are available regarding the association between HU and percutaneous nephrolithotomy, we conclude that consideration of HU values in patients scheduled for PCNL might assist selection of the appropriate treatment procedures and improve success rates.

THE ROLE OF HU IN URETEROSCOPIC LITHOTRIPSY

Ureteroscopic lithotripsy (URSL) is an important treatment modality for ureteral stones that is currently used for stones of all sizes present in any location within the ureter. The size and location of the stone are the prime factors that determine the success of URSL. However, it remains unclear whether HU is a determinant of URSL success. The only previous study of the relationship between HU value and URSL success was performed by Kim *et al*[22]. They examined the size, location, impaction, and HU value of stones using CT, as well as the effect of

these parameters on the success of URSL. Their results revealed that the HU value did not affect the success of treatment using URSL[22]. However, this study failed to assess several important parameters, such as the duration of the operation and of lithotripsy. As with ESWL, more energy might be needed and/or the procedure might be prolonged to fragment stones with a high HU using URSL. Therefore, further studies are required to elucidate whether higher energy and/or prolonged treatment are needed to successfully fragment stones with high HU values, and to identify any associated complications.

THE ROLE OF HU IN MEDICAL EXPULSIVE TREATMENT

Medical expulsive treatment (MET) is commonly used to facilitate the passage of ureteral stones in the absence of severe renal colic, infection, and obstruction. The spontaneous passage ratio can be as high as 98%, particularly in stones smaller than 5 mm. The most important factors that affect spontaneous passage are the size and location of the stone[23]. Erturhan *et al*[24] assessed the effect of HU value on the success of MET. This study, the only current report assessing this relationship, demonstrated that stones with a high HU would pass through the ureter slowly and with difficulty because of their compact structure. They compared two groups of stones with mean HU values of 625 and 507, and concluded that HU could not be used to predict the likelihood of success for MET[24]. However, that study included two groups in which the HU values were similar. As such, additional studies including stones with a wider range of HU values would make a significant contribution to current knowledge. Nevertheless, the available data suggest that HU values do not provide any additional benefit to MET.

CONCLUSION

Previous studies have revealed the benefit of HU values, parameters obtained from CT scans, on ESWL treatment and predicting the composition of urinary system stones. HU measurements now form part of the clinical guidelines because of the lower success rate of ESWL treatment of high HU stones[11]. Although HU is currently used most commonly during ESWL treatment and for prediction of stone composition, current data suggest that it could be used in other treatment modalities as our knowledge increases.

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MINIREVIEWS

Renal biopsy practice: What is the gold standard?

Soumeya Brachemi, Guillaume Bollée

Soumeya Brachemi, Guillaume Bollée, Division of Nephrology and Research Center of the Centre Hospitalier de l'Université de Montréal and Université de Montréal, Montréal QC H2L 4M1, Canada
Author contributions: Bollée G and Brachemi S equally contributed to the literature search, study design and writing of the article.
Correspondence to: Dr. Guillaume Bollée, Division of Nephrology and Research Center of the Centre Hospitalier de l'Université de Montréal and Université de Montréal, 1560 Sherbrooke Street East, Montréal QC H2L 4M1, Canada. guillaume.bollee.chum@ssss.gouv.qc.ca
Telephone: +1-514-8908000-26616 Fax: +1-514-4127831
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Abstract

Renal biopsy (RB) is useful for diagnosis and therapy guidance of renal diseases but incurs a risk of bleeding complications of variable severity, from transitory haematuria or asymptomatic hematoma to life-threatening hemorrhage. Several risk factors for complications after RB have been identified, including high blood pressure, age, decreased renal function, obesity, anemia, low platelet count and hemostasis disorders. These should be carefully assessed and, whenever possible, corrected before the procedure. The incidence of serious complications has become low with the use of automated biopsy devices and ultrasound guidance, which is currently the "gold standard" procedure for percutaneous RB. An outpatient biopsy may be considered in a carefully selected population with no risk factor for bleeding. However, controversies persist on the duration of observation after biopsy, especially for native kidney biopsy. Transjugular RB and laparoscopic RB represent reliable alternatives to conventional percutaneous biopsy in patients at high risk of bleeding, although some factors limit their use. This aim of this review is to summarize the issues of complications after RB, assessment of hemorrhagic risk factors, optimal biopsy procedure and strategies aimed to minimize the risk of bleeding.

Key words: Renal biopsy; Bleeding; Complications; Procedure

Core tip: Renal biopsy (RB) is useful for diagnosis, prognostic assessment and therapy guidance of various diseases affecting native kidneys or transplants. However, RB incurs a potential risk of bleeding complications of variable severity. This aim of this review is to summarize the issues of complications after RB, assessment of hemorrhagic risk factors, optimal biopsy procedure and strategies aimed to minimize the risk of bleeding.

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INTRODUCTION

Renal biopsy (RB) is often necessary for diagnosis, prognostic assessment and therapy guidance of various diseases affecting native and transplant kidneys. The final diagnosis differs from the main hypothesis in up to one third of cases[1]. Despite its necessity, RB incurs a potential risk of bleeding complications of variable severity, from transitory hematuria or asymptomatic hematoma to life-threatening hemorrhage[1-3]. Several studies identified risk factors for complications after RB[4-6]. However, controversies persist regarding the optimal assessment and management of bleeding risk. Two surveys, one conducted by the Society of Nephrology in France and another one in United Kingdom paediatric hospitals, highlighted significant variation in RB procedures[7,8]. Therefore, the gold standard for RB practice still re-

mains to be defined. We previously participated to the elaboration of consensual recommendations by the Society of Nephrology in France[8]. Optimizing procedures for RB may improve patient safety and may also provide some logistic benefits and save costs.

This review discusses the issue of complications after RB, optimal biopsy procedure, and strategies aimed to minimize the risk of bleeding. We only address biopsies for the investigation of medical kidney diseases, but not those performed for kidney tumors.

COMPLICATIONS AFTER PERCUTANEOUS RB

Several large prospective and retrospective studies provide an estimate of the frequency of complications after percutaneous RB[1-3,5,9-12]: (1) Death: < 0.1%; (2) Major bleeding requiring nephrectomy or surgical hemostasis: 0.1% to 0.5%; (3) Arteriovenous fistula requiring invasive intervention: 0.1% to 0.5%; (4) Blood transfusion requirement: 0.3% to 7.4%; (5) Uncomplicated hematoma: 10 to 90%; and (6) Transient macroscopic hematuria : 1% to 10%.

We recently published a series of 312 native kidney biopsies performed at our institution: 15% of patients developed a symptomatic hematoma, 5% macroscopic hematuria, 9% received a red blood cell transfusion and 1% required an angio-intervention[13].

The reported incidence of complications after RB varies in relation to numerous factors, including patient selection, definitions of complications, procedures, and monitoring protocols. Several studies were performed before the implement of ultrasound guidance and automated biopsy devices, which improved the safety and efficiency of RB procedures[4,9]. The rates of complications drawn from these reports may therefore not reflect the risk associated with RB performed nowadays.

Recent studies reported major bleeding and life-threatening complications in less than 0.1% of RB procedures[2,4]. Tøndel *et al*[12] recently published the largest report of RB complications: 9288 (715 children and 8573 adults) biopsies from the Norwegian kidney biopsy registry, the vast majority of which (99.7%) were guided by ultrasound. In this study, 0.9% of the patients needed blood transfusion, 0.2% required an invasive procedure (surgery or angiointervention), and 1.9% had a macroscopic hematuria[12].

The risk of bleeding complications appears lower for transplant than native kidney biopsie[14,15]. However, major complications can occur after transplant biopsy[16].

ASSESSMENT OF HEMORRHAGIC RISK FACTORS AND CONTRAINDICATIONS TO PERCUTANEOUS RB

An important step before RB is to search for factors increasing the risk of complications, particularly bleeding. Although there are no definitive ways to predict which patients will experience complications, several predisposing factors to bleeding have been identified, at times inconstantly.

High blood pressure, age, a decreased GFR, obesity, anemia, low platelet count and small center size (< 30 biopsies/year) are associated with an increased risk of bleeding[4-6,12,17-19]. Amyloidosis was reported to be associated with bleeding[4], although such association was not found in large study by Tøndel *el al*[12]. As discussed below, hemostasis disorders, anticoagulant or antiplatelet therapy, and certain anatomic conditions, may also contraindicate or complicate percutaneous RB.

A recent systematic review and meta-analysis of hemorrhagic complications after percutaneous native kidney biopsy using ultrasound guidance and automated spring-loaded biopsy device reviewed 34 publications and concluded that the predictors of erythrocyte transfusion were: the needle gauge (14 *vs* 16 or 18), sex (female), serum creatinine (⩾ 2 mg/dL), low hemoglobin prior biopsy (⩽ 12 g/dL) and acute kidney injury[18].

High blood pressure

Although high blood pressure is a well-recognized and modifiable risk factor of bleeding after RB[4,6,19], it is difficult to determine a cut-off level above which RB should not be performed. One study demonstrated a significant increase in the risk of bleeding when systolic blood pressure (SBP) was > 160 mmHg or diastolic blood pressure (DBP) was > 100 mmHg[6]. Some studies suggested that an upper limit value of 140/90 mmHg prior to an RB procedure would be appropriate to minimize this risk[4,6]. Interestingly, the risk of bleeding is increased in patients with a history of hypertension, irrespective of blood pressure at the time of biopsy[6]. It is possible that arteriolar hyalinosis associated with chronic hypertension limits the ability of vessels to contract following RB, regardless of the current blood pressure.

Hemostasis abnormalities

Screening for inherited or acquired hemostasis abnormalities relies on patient questioning, study of current and recent medications, and hemostatic tests. Even patients with mild bleeding disorders can bleed after surgery or invasive procedures[20]. In the general population, the most frequent mild bleeding disorders are Von Willebrand disease and platelet function disorders, each with an estimated frequency of up to 1%[21]. Thus, questioning patients about personal and familial bleeding history should not be neglected. However, our survey conducted in France highlighted that such information was not always assessed[8]. One issue may be that nephrologists are not familiar with this practice. The use of questionnaires prepared by hemostasis experts, such as the bleeding assessment tools[21] may be helpful to screen for inherited hemostasis abnormalities. However, these tools have not been validated in the setting of RB and cannot be used to predict bleeding after RB.

Careful examination of the list of current and recent medications, with a focus on anticoagulant and antiplatelet drugs, should be systematically performed before RB. The issue of RB in patients receiving anticoagulant or antiplatelet is discussed below.

It is universal practice to check blood cells count, prothrombin time and partial thromboplastin time before RB[8]. When a bleeding disorder is suspected based on a history of previous bleeding episodes, thrombopenia or abnormal hemostasis tests, thorough investigations should be carried out to determine whether percutaneous RB can be performed safely. It should be emphasized that hemostasis laboratory tests available do not reliably predict "uremic bleeding", which is the result of multifactorial alterations of hemostasis in a setting of chronic or acute renal failure[17]. Some nephrologists use bleeding time in an attempt to predict complications after RB, and some studies showed that a prolonged bleeding time was a risk factor for hemorrhagic complications[19]. However**,** the usefulness of this test is controversial. In the context of RB, several studies failed to demonstrate predictive value of the bleeding time for hemorrhagic complications[3,4,22,23]. It is now widely accepted that the bleeding time is not a good predictor of the risk of hemorrhage associated with surgical procedures and cannot reliably identify patients who have recently ingested antiplatelet agents; it is therefore no longer recommended as a routine preoperative test[24,25]. *Other laboratory* hemostasis tests have not been shown to improve prediction of bleeding after RB and are therefore not required.

RB in patient receiving anticoagulant or antiplatelet therapy

It is a standard of care to discontinue anti-platelet agents and non-steroidal inflammatory agents 5 to 7 d before an invasive procedure in order to reduce the risk of bleeding. However stopping an anti-platelet agent in a coronary patient can increase the risk of a thrombotic event[26], especially in patients with a high cardiovascular risk profile (extensive coronary disease, patients with recent stent placement: less than 6 wk after bare metal stent placement and less than 6 to 12 mo after drug eluting stent placement)[27,28]. In a cohort of 1358 consecutive patients admitted for a suspected acute coronary syndrome (ACS), 5% of those patients with a confirmed ACS had a history of coronary artery disease and had recently stopped their aspirin. The event happened after a mean of 11 d of aspirin cessation[29].

Some studies raised the possibility that withdrawal of antiplatelet therapy might not be mandatory before RB. In a retrospective study, the incidence of major hemorrhage after percutaneous RB was 1% (13/1270) in patients taking aspirin before RB, which was similar to the incidence of bleeding in patients not taking aspirin[30]. One important limitation of this study was that patients who stopped aspirin less than 10 d before RB, which is a common practice, were included in the "aspirin use" group. Additionally, the continuation of an anti-platelet agent was not identified as an increased risk factor of blood transfusion in a meta-analysis of 34 studies[18]. Mackinnon *et al*[31] reported 1120 RB from two different centers, in one, anti-platelets were stopped 5 d before the biopsy, whereas they were not discontinued in the other. There were no difference in the rate of major complications between the two centers but a significantly higher percentage of patients in the group still taking anti-platelet agents experienced a $\geqslant$ 1g/dL reduction in hemoglobin (23.5% *vs* 12.5%). The proportion of patients taking an anti-platelet agent was only specified for the elective biopsies (135 patients) where 75 had stopped the agents prior to biopsy whereas 60 patients were still taking an anti platelet agent (aspirin $n = 68$, clopidogrel $n = 7$) at the moment of the biopsy[31].

However, these studies about the safety of RB without cessation of aspirin have important limitations. In addition, the risk of bleeding associated with the continuation of other agents such as clopidogrel or newer agents like prasugrel or ticagrelor, is higher than the one with aspirin. It should be kept in mind that RB is a high bleeding risk procedure and, in our opinion, withdrawing anti-platelet agents before RB should be the standard of care in low-risk patients. It is therefore advisable to withhold these agents for 7 d before an elective kidney biopsy[32], and resume them 1 to 2 d after the biopsy. The management of patients at high risk of thrombotic events should be discussed with their cardiologist. The biopsy should be deferred if necessary or a transjugular biopsy, if available, should be considered.

Oral anticoagulant (anti-vitamin K) should be stopped 5 d before the biopsy and bridging with heparin should be considered in high and moderate risk patients. Oral anticoagulants should be resumed 12 to 24 h after the biopsy[28].

Although data are limited, platelet transfusion seems to be the best option in patients who are taking an anti-platelet agent and experience severe bleeding from a RB.

Solitary kidney and anatomic abnormalities

Renal ultrasound is usually performed in the assessment of kidney diseases and provides important information before RB about the size and morphology of kidneys. An anatomic or functional solitary native kidney is generally considered as a contraindication for RB, given the possibility that nephrectomy may be necessary in case of life-threatening bleeding. Complications requiring nephrectomy are however very rare and ultrasound-guided percutaneous RB with an automated biopsy device has been shown to be safe if contraindications, especially high blood pressure and abnormal haemostasis, are adressed. In three retrospective studies that included a total of 1955 ultrasound-guided percutaneous renal biopsies, only one case required nephrectomy[2-4]. Some authors advocated that otherwise uncomplicated adult patients with a solitary kidney might be considered for percutaneous biopsy[5]. Despite these reassuring data, un-

dertaking a solitary kidney biopsy remains an important decision that should be made only after carefully thinking about whether the RB result is likely to have important therapeutic implications.

Anatomic abnormalities of the kidney (congenital malformations, cysts, atrophy, hydronephrosis...) or blood vessels (arteriovenous fistula, aneurysm, microaneurysm...) can make RB difficult to perform. Such abnormalities have to be carefully characterized using appropriate imaging techniques in order to determine the risk and feasibility of the biopsy.

PREVENTION OF BLEEDING BEFORE RB

As it is for any invasive procedure, correction of coagulopathy is mandatory before RB. The platelet count threshold at which a RB can be safely conducted is not clear. Most platelet count thresholds for invasive procedure are based on weak observational evidence. For most major surgery, other than ocular and neurologic, platelet transfusion are considered if the platelet count is below 50000/microL[33]. It is not clear if this can be applied to RB. Many nephrologists consider RB contraindicated if platelet count is < 100000/microL, which seems more prudent. Of course, optimal methods for raising platelet count depend on the underlying condition.

In the setting of renal disease, the risk of bleeding can result from dysfunctional platelets resulting from uremia. Indeed, uremic bleeding is a well-known complication of renal failure. The exact underlying mechanisms remain largely unknown, but seem to be multifactorial. The pathophysiology of uremic bleeding and evidence based treatment recommendations were the subject of a review by Hedges *et al*[17]. Many factors contribute to platelet dysfunction including anemia, dysfunctional von Willebrand factor, platelet membrane abnormalities, uremic toxins inhibiting platelet aggregation, and increased prostacyclin and nitric oxide levels, which are strong anti-platelet aggregating factors[17]. Correction of anemia, deamino-8-D-arginine vasopressin (DDAVP), estrogens and cryoprecipitate have been shown to improve "uremic bleeding".

Desmopressin (DDAVP) is probably the most common agent used to treat or prevent bleeding in uremic patients. DDAVP improves hemostasis by releasing factor VIII from storage sites. DDAVP can reverse uremic platelet dysfunction rapidly (approximately within one hour of IV injection) for a short period of time (around 24 h)[17].

Several studies demonstrated that recombinant erythropoietin treatment prevents bleeding caused by uremic platelet dysfunction if the hematocrit is increased to more than 30%. Recombinant erythropoietin was shown to improve primary hemostasis in uremia through an increase of hematocrit but also through an effect on platelet function[17,34,35].

Several studies showed that intravenous conjugated estrogens can safely and effectively improve uremic platelet dysfunction and clinical bleeding. Intra-venous conjugated oestrogens improve bleeding time with a maximum effect at 5 to 7 d, lasting from 14 to 21 d[17].

Finally, cryoprecipitate is another therapeutic option in the setting of active uremic bleeding or in patients with high risk of bleeding[17,36]. Cryoprecipitate is prepared from plasma and contains fibrinogen, von Willebrand factor, factor Ⅷ and factor XⅢ. It has a rapid onset of action (around 1 h) and its effect lasts approximately 24 to 36 h.

The impact of dialysis on uremic bleeding is unsure. Studies are old, and the effect on platelet function and coagulation is inconstant.

In all, the evidence supporting recommendations for the prevention or treatment of uremic bleeding is limited, especially in the context of RB. Despite the absence of robust evidence, it may be prudent to avoid undertaking RB when the hematocrit is lower than 30%, and to consider DDAVP or oestrogens before RB when the glomerular filtration rate is lower than 30 mL/min per 1.73m^2, as suggested by some authors[37].

PROCEDURES FOR PERCUTANEOUS RB

Well-trained nephrologists can perform RB as well as radiologists[38,39]. Automated biopsy guns have superseded Tru-cut needles and are probably used in most centers[8]. Several studies suggested that 14-18G needles are appropriate for percutaneous RB[3,15,40]. The use of an automated biopsy gun in combination with real-time ultrasound guidance was reported to provide adequate samples in nearly 99% of cases, with severe hemorrhagic complications occurring in less than 0.1%. This method can be considered the gold standard[2,4]. The use of bedside ultrasound to assess the location and depth of the kidneys was reported as a reliable alternative to real-time guidance[39]. In some instances, especially in obese patients, it may be necessary to perform RB under guidance by CT-scan instead of ultrasound.

ALTERNATIVES TO PERCUTANEOUS RB

Transjugular RB has been reported to be a safe and reliable alternative to conventional percutaneous RB in patients with obesity[41] or those at risk for bleeding, including high-risk patients with coagulopathy and thrombocytopenia[42-44]. In these studies, transjugular RB provided diagnostic yield and safety similar to those of percutaneous approach. However, in most countries, the use of transjugular RB is limited to a few centers because of the necessity of skilled interventional radiologists.

Laparoscopic RB has also been reported as an alternative for patients in whom percutaneous approach was not feasible or was contraindicated, because of obesity, solitary kidney, anticoagulation or coagulopathy, or failed percutaneous biopsy[45,46]. However the number of patients included in these studies was limited and no study has compared the safety of percutaneous, transjugular

Table 1 Studies evaluating the safety of short observation time (< 24 h) after a percutaneous renal biopsy of native kidney

Study	Complications: minor/major	Timing of complications
Whittier *et al*[22] Retrospective 750 patients	6.6% minor complications 6.4% major complications (79% blood transfusion)	38 (42%) complications ⩽ 4 h post RB 61 (67%) complications ⩽ 8 h post RB 77 (85%) complications ⩽ 12 h post RB 81 (89%) complications ⩽ 24 h post RB
Lin *et al*[56] Retrospective 147 inpatients 183 outpatients	19.7% hematoma 6.4% macroscopic hematuria 0.9% pain No difference between in and out patients	2 outpatient admission (blood transfusion) all complications occurred within observation time of 6 h
Maya *et al*[57] Prospective *N* = 100	13% asymptomatic hematoma No major complications	All complications occured within 8 h of observation time 4% extended 24 h observation for decrease hematocrit
Margaryan *et al*[53] Retrospective, *N* = 146	Bleeding 2.8% Gross hematuria 1.4% Transfusion 0.69%, intervention 0	Hospital admission 5.6%, no late complications. Observation time 4-6 h
Jiang *et al*[52] Retrospective *N* = 475	6.9% minor complications 1.3% (6 patients) had major complications (transfusion or interventional radiology)	Median time for minor complications 2.5 h, 4/33 after 6 h 4/6 major complications occurred within 4 h, 1/6 at 12 h and 1/6 beyond 48 h
Carrington *et al*[50] Retrospective *N* = 192	3.6% (*n* = 7) immediate complications related to bleeding, 2/7 required blood transfusion and embolisation	All complications occurred within observation period of 8 h
McMahon *et al*[31] Prospective *N* = 105, low risk	11% required admission for complications (11/12 minor, 1 major complication)	9/12 during the observation time (5 h) 1 at 48 h (macroscopic hematuria), 2 at 5 d (AVF, hematoma)
Simard-Meilleur *et al*[13] Retrospective 164 inpatients 148 outpatients	15% symptomatic hematoma (pain, drop of more than 10 g/l Hb, gross hematuria, hypotension), 9% RBC transfusion, 1% angio-intervention	100% outpatient complications occurred during observation time (8 h)
Korbet *et al*[19] Prospective 1055 patients	Minor complications 8.1% Major complications 6.6%	57% of all complications occurred within 4 h, 72% within 8 h, 85% within 12 h and 89% within 24 h

RB: Renal biopsy.

and laparoscopic RB in patients at high risk for bleeding. In addition, when considering these procedures, one should carefully contemplate the risk of general anesthesia, perioperative risk and recovery time.

SURVEILLANCE AFTER RB

After RB, patients have to be monitored closely for the occurrence of complicatons such as gross hematuria, flank pain, hypotension and acute renal obstruction.

The standard practice after RB has traditionally been to observe the patient overnight, as suggested by early studies[47]. In our French survey, almost all nephrologists observed patients for at least 24 h after a native kidney biopsy[8]. However, controversies have emerged regarding the optimal duration of observation after RB and it has been proposed that patients be discharged after 6-8 h of observation[48,49]. Performing RB as an outpatient procedure offers several advantages but raises the concern of missing late complications. Whittier *et al*[22] reported a large series of 750 native kidney biopsies in adults. In this study, 13% patients developed biopsy-related complications; minor complications occurred in 6.6% and major complications (most requiring a blood transfusion) occurred in 6.4% patients. Around 30% of the patients had a biopsy performed using a manual biopsy device. The analysis of the timing of complications showed that 89% of complications were identified within 24 h after RB, and that an observation period less than 8 hours missed 33% of complications. On the contrary, several smaller studies suggested that outpatient observation time of 6 to 8 h is safe (Table 1)[13,19,49-57]. Most of outpatients in these studies were selected as low risk. Considering this, an outpatient biopsy may be an option in a carefully selected population with no risk factor.

Renal transplant biopsies are routinely performed as an outpatient procedure in some centers. In our survey in France, approximately 25% of nephrologists performed transplant biopsies with observation times limited to 4-8 h[8]. In a multicentric study by Furness *et al*[58] on 2127 protocol transplant biopsies, only 9 (0.42%) severe complications occurred, all presenting within four hours after biopsy. In another study, no severe complications were observed after 251 protocol transplant biopsies[59]. Therefore, an observation time of 4-8 h after a transplant biopsy appears to be a relatively safe practice, at least in patients without risk factors for bleeding.

Some protocols use a routine renal ultrasound or measurement of hemoglobin or hematocrit control before discharge, in addition to clinical monitoring. Systematic ultrasound reveals perirenal hematoma in 40%-90% of procedures[11,60]. Arteriovenous fistula may be detected in 10% of RB, but they usually disappear

spontaneously after a few months[61,62]. In biopsies that are otherwise uncomplicated with an asymptomatic course, hematomas are usually small (< 3 cm)[48,63]. These hematomas are almost always asymptomatic, and such a finding usually occurs without therapeutic consequence. In a study that evaluated the use of renal ultrasound one hour post-RB, the presence of a hematoma was poorly predictive of complications[63]. The absence of a hematoma was predictive of an uncomplicated course in after RB[63]. However, a period of observation is required after RB, even in the absence of hematoma right after the biopsy. Early routine repeat imaging is therefore of limited usefulness and is not necessary in patients otherwise asymptomatic.

The use of a hemoglobin or hematocrit measurement after a RB as a predictor of bleeding is controversial. Systematic hemoglobin monitoring was shown to be of little value in detecting complications after RB in one study[22], although in another study, a direct relationship was found between the change of hematocrit at 6 h and the hematocrit at 24 h following a RB, suggesting that the absence of fall at 6 h makes a significant fall of hematocrit at 24 h unlikely[64].

CONCLUSION

The RB is an indispensable tool to establish the diagnosis and management of kidney diseases. Although the overall incidence of serious complications is low, risk factors for bleeding must be carefully assessed and, whenever possible, corrected before the procedure. If contraindications, especially high blood pressure and hemostasis abnormalities, are respected, percutaneous RB with an automated biopsy device and ultrasound guidance is safe for the vast majority of patients. Some controversies remain regarding the optimal duration of observation and the possibility to perform RB as an outpatient procedure. To address these issues, further studies are warranted to improve our ability to predict and stratify the risk of bleeding.

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MINIREVIEWS

Regulatory roles of nitric oxide and angiotensin II on renal tubular transport

Shoko Horita, Motonobu Nakamura, Ayumi Shirai, Osamu Yamazaki, Nobuhiko Satoh, Masashi Suzuki, George Seki

Shoko Horita, Motonobu Nakamura, Ayumi Shirai, Osamu Yamazaki, Nobuhiko Satoh, Masashi Suzuki, George Seki, Department of Internal Medicine, The University of Tokyo, Tokyo 113-0033, Japan
Author contributions: All authors contributed to this paper.
Correspondence to: George Seki, MD, Department of Internal Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan. georgeseki-tky@umin.ac.jp
Telephone: +81-3-38155411 Fax: +81-3-58008806
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Abstract

Renal tubules regulate blood pressure and humoral homeostasis. Mediators that play a significant role in regulating the transport of solutes and water include angiotensin Ⅱ (AngⅡ) and nitric oxide (NO). AngⅡ can significantly raise blood pressure via effects on the heart, vasculature, and renal tubules. AngⅡ generally stimulates sodium reabsorption by triggering sodium and fluid retention in almost all segments of renal tubules. Stimulation of renal proximal tubule (PT) transport is thought to be essential for AngⅡ-mediated hypertension. However, AngⅡ has a biphasic effect on in vitro PT transport in mice, rats, and rabbits: stimulation at low concentrations and inhibition at high concentrations. On the other hand, NO is generally thought to inhibit renal tubular transport. In PTs, NO seems to be involved in the inhibitory effect of AngⅡ. A recent study reports a surprising finding: AngⅡ has a monophasic stimulatory effect on human PT transport. Detailed analysis of signalling mechanisms indicates that in contrast to other species, the human NO/guanosine 3′,5′-cyclic monophosphate/extracellular signal-regulated kinase pathway seems to mediate this effect of AngⅡ on PT transport. In this review we will discuss recent progress in understanding the effects of AngⅡ and NO on renal tubular transport.

Key words: Angiotensin Ⅱ; Nitric oxide; Proximal tubules; Thick ascending limb; Distal tubules; Na^+ transport

Core tip: Angiotensin Ⅱ (AngⅡ) and nitric oxide (NO) play important roles in the regulation of renal tubular transport. AngⅡ has a biphasic effect on renal proximal tubule (PTs) transport, and NO seems to inhibit the effect of AngⅡ. In human PTs, however, AngⅡ seems to have an NO-dependent monophasic stimulatory effect. We will discuss the recent findings in this field.

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INTRODUCTION

Angiotensin Ⅱ (AngⅡ) is a strong pressor, acting on various organs and systems, including the kidney. It binds to angiotensin receptors, of which the main subtypes are angiotensin receptor type 1 (AT1R) and type 2 (AT2R)[1]. Although other classes of angiotensin and their receptors, such as AT7R[2], occur, the receptor with the dominant effect in the kidney seems to be AT1R. Recently, Coffman *et al*[3] demonstrated that renal AT1R is the essential target of AngⅡ-induced hypertension[3]. By showing the importance of renal AT1R in the emergence of hypertension, their study suggests that renal AT1R will be the target for therapy and the prevention

of hypertension.

Nitric oxide (NO) is a gaseous vasoactive substance produced by nitric oxide synthase (NOS). NO has been shown to play important roles in the regulation of renal tubular transport. However, its role seems to be pleiotropic and varies according to circumstances.

NOS has three isoforms, NOS1, NOS2 and NOS3, previously referred to as neuronal NOS (nNOS), inducible NOS (iNOS), and epithelial NOS (eNOS), respectively. Renal tubules have each of these NOS isoforms[4,5]; however, the details of their actions in the tubules are still unclear.

NO seems to inhibit NaCl reabsorption in the renal tubules and induces natriuresis. Inhibiting NOS decreased urine volume and NaCl excretion, without changing renal blood flow and the glomerular filtration rate[6-10]. Overall, NO is thought to inhibit the reabsorption of NaCl and fluid by tubules.

ANG Ⅱ AND TUBULES

Ang Ⅱ in proximal tubules

Ang Ⅱ has been widely known as a strong pressor and regulator of cardiovascular and renal function[11]. In the classical pathway, AT1R mediates the effects of Ang Ⅱ[1]. Proximal tubules (PTs) reabsorb approximately 60% to 70% of the sodium filtered in the glomeruli. Therefore, the regulation of sodium reabsorption in this segment is important for the maintenance of blood pressure and humoral homeostasis[12,13]. In the PTs, Ang Ⅱ is known to stimulate sodium and water transport. Although Ang Ⅱ affects transport processes in several nephron segments, as discussed below, its effect on PT transport may be its most important effect. In particular, the stimulatory effect of Ang Ⅱ in the PTs has significant importance for the emergence and progression of hypertension[14].

Ang Ⅱ acts mainly *via* type 1 and type 2 angiotensin receptors. The type 1 receptor has 1A and 1B subtypes and is thought to raise blood pressure[1]. AT2R is also thought to be located in the PTs[15-17]. Some investigators argue that AT2R may mediate the inhibitory effect of Ang Ⅱ[18]. However, most data, including our own obtained from AT1R knockout mice[13,19-21], indicate that AT1R is the dominant receptor mediating the biphasic effects of Ang Ⅱ in the PTs.

In PTs, the basolateral electrogenic sodium-bicarbonate cotransporter type 1 (NBCe1) and the apical sodium-proton exchanger type 3 (NHE3) mainly regulate sodium reabsorption[22]. In addition, sodium is reabsorbed and coupled with amino acids[23], glucose[24], phosphate[25], and other solutes from the apical side[14]. Sodium is also reabsorbed *via* Na^+-K^+-ATPase (NKA) from the basolateral side[26], which offers the driving forces for NBCe1 and NHE3.

Ang Ⅱ is known to have biphasic effect on the PTs of rats, mice and rabbits. Low concentrations (picomolar to nanomolar) of Ang Ⅱ stimulate PT transport, while high concentrations (nanomolar to micromolar) inhibit PT transport[27,28]. In PTs, Ang Ⅱ regulates major sodium transporters, such as NHE3, NBCe1, and NKA, in a biphasic manner[19,29-32]. The activation of protein kinase C and/or a decrease in cAMP concentration, followed by the activation of the extracellular signal-regulated kinase (ERK) pathway, may be responsible for the stimulatory effect of Ang Ⅱ[33-35]. On the other hand, the activation of the phospholipase A2/arachidonic acid/5,6-epoxyeicosatrienoic acid (EET) and/or the NO/guanosine 3',5'-cyclic monophosphate (cGMP) pathways[29,36,37] may be responsible for the inhibitory effect of Ang Ⅱ. The concentration of Ang Ⅱ is known to be much higher in kidney than plasma[38,39], suggesting that the inhibitory effect of Ang Ⅱ may also have some physiological significance in the regulation of renal tubular function and blood pressure.

Ang Ⅱ in the thick ascending limb

There are some reports that Ang Ⅱ stimulates net NaCl absorption in the thick ascending limb (TAL). Wang and colleagues showed that Ang Ⅱ stimulates basolateral Cl^- channels by activating the protein kinase C-dependent NADPH oxidase pathway, inducing net NaCl absorption[40]. Garvin *et al*[41] investigated the regulation of NKA activity in Ang Ⅱ-induced hypertension[41]. They showed that Ang Ⅱ-induced hypertension is accompanied by increased NKA activity in rat TAL, which may be at least partially due to Ang Ⅱ-stimulated superoxide production[42] *via* NADPH oxidase[43]. Moreover, Ang Ⅱ binding to AT1R was shown to inhibit ADH-stimulated transport in the rat TAL suspension cells[44]. Overall, Ang Ⅱ seems to stimulate Na^+ reabsorption in the TAL *via* AT1R.

Ang Ⅱ in the distal tubules

In the distal tubules, approximately 10% to 20% of the filtered Na^+ is reabsorbed. Na^+ enters the tubule cells *via* the sodium-chloride cotransporter (NCC) and exits from the basolateral side *via* NKA, while Cl^- exits *via* chloride channels (ClC-Kb)[14].

Recent studies indicate that With-No-Lysine Kinase (WNK), Oxidative stress-responsive kinase (OSR) 1, and STE20/SPS1-related proline alanine-rich kinase (SPAK) importantly regulate transport in distal tubules.

WNKs are atypical protein kinases, as their name "With No Lysine (K)" implies[45]. They are expressed in various organs and tissues, including renal distal tubules, and modulate several biological processes, such as solute transport, cell growth, and neurotransmission[46]. WNKs have subtypes, such as WNK1, WNK2, WNK3, WNK4 and kidney-specific (ks-) WNK1. The kidney expresses WNK1, WNK3, WNK4 and ks-WNK1, where they modulate the function of NCC in the distal tubules.

In distal tubules, Ang Ⅱ seems to activate NCC *via* phosphorylation. Hoorn *et al*[47] showed that Ang Ⅱ induces the phosphorylation of NCC, enhancing sodium retention in rat kidneys, independent of aldosterone[47]. On the other hand, Uchida and colleagues showed that,

although Ang Ⅱ increases NCC phosphorylation *via* the WNK-OSR1/SPAK pathway, the effect of aldosterone in this pathway is predominant[48]. Using WNK4 knockout mice, Gamba *et al*[49] showed that Ang Ⅱ stimulates NCC *via* a WNK4-SPAK dependent pathway and that WNK4 is involved in Ang Ⅱ-stimulated aldosterone secretion[49]. The detailed mechanisms by which Ang Ⅱ, WNK-SPAK/OSR1 and aldosterone regulate transport in the distal tubules transport remain to be clarified.

Ang Ⅱ in the connecting tubules and collecting tubules

In the last portion of the tubules, the connecting tubules (CNT) and the collecting tubules (CD), Na^+ is mainly reabsorbed *via* an epithelial Na^+ channel (ENaC) on the luminal side and NKA on the basolateral side. The amount of Na^+ reabsorbed from these segments represents only a small fraction of the total Na^+ absorption by the kidney, but its regulation contributes to the fine-tuning of sodium and fluid homeostasis.

ENaC is a heteromultimeric channel, with three homologous subunits (α, β, γ)[50,51]. Loss-of-function mutations of ENaC cause pseudohypoaldosteronism type I (PHA-I), while gain-of-function mutations cause Liddle's syndrome[52,53]. PHA-I features renal salt wasting associated with hyperkalaemia, while Liddle's syndrome shows arterial hypertension with hypokalaemia. Pharmacologically, amiloride directly and reversely blocks the ENaC.

In the CNT and CD segments, aldosterone has been thought to play a principal role in regulating basal and long-term ENaC activity[54]. Recently, however, Korbmacher *et al*[55] demonstrated that, in the distal convoluted tubules (DCT2) and CNT, ENaC function is largely independent of aldosterone[55]. They suggested that glucocorticoids and/or Ang Ⅱ may be responsible for the aldosterone-independent ENaC activity. Ang Ⅱ itself may directly stimulate amiloride-sensitive Na^+ reabsorption in CNT and CD, independent of aldosterone[56,57]. Indeed, several studies have reported that the Ang Ⅱ/AT1R pathway can regulate ENaC expression[58-61]. This effect of Ang Ⅱ is thought to be mediated *via* AT1R[62,63]. In obese Zucker rats, moreover, enhanced AT1R activity may result in the ENaC activation, suggesting a role for Ang Ⅱ in Na retention in diabetes and obesity[60].

THE EFFECT OF NO IN THE TUBULES

NO in the PTs

As described above, NO has been thought to inhibit net NaCl and fluid absorption through renal tubules. However, Wang and colleagues argued that NO has a biphasic effect on the PTs. Low concentrations of an NO donor, sodium nitroprusside (SNP; 10^{-6} mol), stimulated PT fluid (J_V) and bicarbonate absorption (J_{HCO3}) by 30%-50%, while high concentration of SNP (10^{-3} mol) inhibited Jv and J_{HCO3} by 50%-70%[64]. However, most other studies report that NO inhibits PT transport[65-67]. In particular, NO has been shown to decrease NHE3 and NKA activities[67,68]. Overall, NO is generally thought to inhibit NaCl, HCO_3^-, and volume reabsorption in the PTs.

NO in the TAL

In the TAL, approximately 30% of filtered Na^+ is reabsorbed[14]. The major Na^+ transporters here are the $Na^+/K^+/2Cl^-$ cotransporter (NKCC2) and NHE3 on the apical side as well as NKA on the basolateral side.

Garvin and colleagues found that NO donors inhibit Cl^- and HCO_3^- reabsorption[69,70]. They found that NO inhibits NKCC2 and NHE3 activity, but not NKA activity[71,72]. Using $NOS3^{-/-}$ mice, they also showed that NOS3 is responsible for NO production in the TAL[73,74]. HCO_3^- reabsorption in the TAL is accomplished by H^+ secretion *via* apical NHE3[75]. In the rat TAL, NO increases cGMP levels[76,77], and cGMP analogues inhibit J_{HCO3}[70] and J_{Cl}[78,79]. The inhibition of cGMP-dependent kinase (cGK) blocked the inhibitory effect of NO on J_{HCO3}, but not on J_{Cl}[70,80]. On the other hand, the inhibition of cGMP-stimulated phosphodiesterase (PDEII) blocked the inhibitory effect of NO on J_{Cl}[80]. Thus, the NO/cGK pathway seems to mediate the inhibitory effect on J_{HCO3}, while the NO/PDEII pathway seems to mediate the inhibitory effect on J_{Cl}[80].

NO in the CNT and CD

Recently, Wall and colleagues have showed that NO reduces Cl^- absorption through ENaC in mouse CD[81]. In the cultured *Xenopus laevis* distal nephron cell line 2F3, Bao and colleagues showed that the activity of ENaC was reduced by a cyclic GMP analogue or by an atrial natriuretic peptide[82]. Moreover, in cGKII knockout mice, ENaC inhibition induced a much greater increase in UNa^+V (2.6-fold) than in wild-type mice (1.9-fold), suggesting that ENaC activity is upregulated in the knockouts[83]. Integrating these results, NO and its signal transduction system appear to inhibit ENaC in CD and to induce natriuresis, therefore preventing sodium retention and hypertension.

The interaction between Ang Ⅱ and NO in PT

As previously described, the Ang Ⅱ effect on Na^+ reabsorption in the proximal tubule is biphasic in rodents and rabbits[27,28]. The inhibitory effect of Ang Ⅱ is mediated by the PLA2/arachidonic acid/EET and/or NOS/NO/cGMP pathways. In rat PTs, for example, the regulation of NKA by Ang Ⅱ seems to be dependent on the NO/cGMP pathway[35,36].

On the other hand, the effects of Ang Ⅱ on PT sodium transport in humans have not yet been clarified. To this end, we analysed the effects of Ang Ⅱ on human PTs isolated from the cortex of kidneys removed for renal carcinoma. Surprisingly, Ang Ⅱ, in contrast to other species, was found to induce a monophasic stimulation of human PT transport[84]. Specifically, Ang Ⅱ induced a dose-dependent stimulation of NBCe1, NHE3, and J_{HCO3} that was apparently mediated by both luminal and basolateral AT1Rs.

Table 1 Summary of angiotensin II effects on tubular transport

Nephron segment	Potential targets	Effects	Ref.
PT	NHE3, NBCe1	biphasic in rats, mice, rabbits	[19,27-32]
	J_{HCO3}	monophasic stimulation in humans	[84]
TAL	NKA, NKCC2, Cl channel	stimulation	[40-43]
	NADPH oxidase		
DCT	NCC	stimulation	[47,49]
	WNK4?		
CNT/CD	ENaC	stimulation	[55,59-61]

PT: Proximal tubule; TAL: Thick ascending limb; DCT: Distal convoluted tubules; CNT: Connecting tubules; CD: Collecting tubules; NHE3: Apical sodium-proton exchanger type 3; NBCe1: Basolateral electrogenic sodium-bicarbonate cotransporter type 1; NKA: Na^+-K^+-ATPase; NKCC2: $Na^+/K^+/2Cl^-$ cotransporter; NCC: Sodium-chloride cotransporter; ENaC: Epithelial Na+ channel.

Table 2 Summary of nitric oxide effects on tubular transport

Nephron segment	Potential targets	Effects	Ref.
PT	NHE3, NBCe1	inhibition in rats, mice, rabbits	[65-68,84]
	J_{HCO3}	biphasic in rats?	[64]
		monophasic stimulation in humans	[84]
TAL	NKA, NKCC2	inhibition	[69-72]
	J_{Cl}, J_{HCO3}		
CNT/CD	ENaC	inhibition	[81,83]

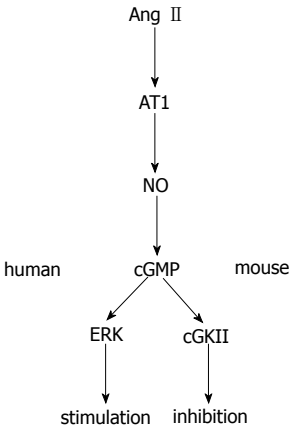

Figure 1 Species difference in angiotensin II/nitric oxide signalling in proximal tubules. In humans, NO/cGMP stimulates PT transport via ERK. In mouse, by contrast, NO/cGMP inhibits PT transport via cGKII. Ang II: Angiotensin II; NO: Nitric oxide; cGMP: Guanosine 3',5'-cyclic monophosphate; ERK: Extracellular signal-regulated kinase.

In contrast to other animals, both arachidonic acid and 5,6-EET failed to inhibit NBCe1 stimulation, which may partly account for the lack of an inhibitory effect of Ang Ⅱ in human PTs. Notably, however, we found that the contrasting responses to the NO/cGMP pathway could largely explain the different actions of Ang Ⅱ on PT transport in humans and other species. Thus, inhibition of the NOS/cGMP/cGKII pathway converted the inhibitory effect of 10^{-6} mol Ang Ⅱ on mouse PT transport into a stimulatory effect. SNP dose-dependently inhibited PT transport in wild-type but not in cGKII mice. By contrast, the inhibition of NOS/cGMP/ERK pathway completely suppressed the stimulatory effect of Ang Ⅱ on human PT transport. While the inhibition of cGKII did not affect the Ang Ⅱ effects, SNP dose-dependently stimulated transport in human PT. Western blotting with phosphor-specific antibodies revealed that Ang Ⅱ induced a dose-dependent cGKII activation in mouse but not in human kidney cortex samples. On the other hand, SNP induced a dose-dependent ERK activation in human but not in mouse samples. Collectively, these results indicate that while the NO/cGMP/cGKII pathway mediates the inhibitory effect of Ang Ⅱ in mouse PTs, the NO/cGMP/ERK pathway mediates the stimulatory effect in human PTs as shown in Figure 1.

We confirmed that human PTs do express cGKII. On the other hand, NO/cGMP failed to activate ERK in PTs from cGKII KO mice, indicating that the simple removal of cGKII from mouse PTs cannot reproduce the dose-dependent stimulatory effect of Ang Ⅱ in human PTs. Therefore, the reason why the NO/cGMP pathway, acting as the down-stream mediator of Ang Ⅱ, has contrasting effects on PT transport in humans and in other species is currently unknown. However, it is interesting to note that while the role of intrarenal NO in the adaptive natriuretic response to sodium loading has been well established in rodents, a similar role for NO has not been established in humans[85-90]. In any case, the human-specific stimulatory effect of the NO/cGMP pathway on PT transport may offer a novel therapeutic target for human hypertension.

CONCLUSION

The absorption of Na^+ in renal tubules is regulated by various factors, among which Ang Ⅱ and NO play

significant roles. In general, Ang Ⅱ stimulates sodium reabsorption and triggers fluid retention, leading to hypertension, while NO seems to induce natriuresis. However, our in vitro data suggest that NO may have distinct effects on PT transport in human and other species. Tables 1 and 2 summarize the effects of Ang Ⅱ and NO on renal tubular transport.

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MINIREVIEWS

Roles of the (pro)renin receptor in the kidney

Yoichi Oshima, Satoshi Morimoto, Atsuhiro Ichihara

Yoichi Oshima, Satoshi Morimoto, Atsuhiro Ichihara, Department of Medicine II, Endocrinology and Hypertension, Tokyo Women's Medical University, Shinjuku-ku, Tokyo 162-8666, Japan
Author contributions: Oshima Y collected the literature, wrote the paper and created the figures; Morimoto S corrected and revised the paper; Ichihara A also checked the manuscript and provided financial support.
Correspondence to: Satoshi Morimoto, MD, PhD, Associate Professor, Department of Medicine II, Endocrinology and Hypertension, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan. smorimoto@endm.twmu.ac.jp
Telephone: +81-3-33538111 Fax: +81-3-52697327
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Abstract

Prorenin receptor (PRR) is a multi-functioning protein possessing at least four different roles: (1) working as a receptor for renin and prorenin producing angiotensin I from angiotensinogen thus enhancing the tissue renin-angiotensin system; (2) inducing intracellular signals when a ligand binds to PRR; (3) participating in the functions of vacuolar proton ATPase; and (4) constituting the Wnt signaling receptor complex. Here, the roles of PRR in kidney physiology and diabetic conditions as well as recent findings regarding a soluble form of PRR are discussed. We also propose the possible mechanism concerning diabetic nephropathy as "trade-off hypothesis" from a PRR point of view. In brief, under hyperglycemic conditions, injured podocytes degrade degenerated proteins and intracellular organelles which require V-ATPase and PRR for vesicle internal acidification. Sustained hyperglycemia overproduces PRR molecules, which are transported to the transmembrane and bind to increased serum prorenin in the diabetic condition. This enhances tissue renin-angiotensin system and PRR-mediated mitogen-activated protein kinase signals, resulting in increased injurious molecules such as transforming growth factor-β, cyclooxygenase2, interleukin-1β, and tumor necrosis factor-α ending in diabetic nephropathy progression. Although many findings led us to better PRR understanding, future works should elucidate which PRR functions, of the four discussed here, are dominant in each cell and kidney disease context.

Key words: Prorenin receptor; Atp6ap2; Soluble prorenin receptor; Kidney; Diabetic nephropathy; Podocyte

Core tip: Prorenin receptor (PRR) has shown its multi-functionality in at least four different aspects. In this review, the roles of PRR in kidney physiology and diabetic conditions as well as recent findings regarding a soluble form of PRR are discussed. Additionally, we propose the possible mechanism concerning diabetic nephropathy as "trade-off hypothesis" from a PRR point of view.

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INTRODUCTION

Prorenin receptor (PRR), also known as ATP 6-associated protein 2 (Atp6ap2), was cloned in 2002 as a single transmembrane protein whose ligand is renin and its precursor prorenin[1]. Initially, the roles of PRR were thought to enhance the tissue renin-angiotensin system (RAS) by binding PRR to its ligand, while also inducing intracellular signal transductions such as mitogen-activated protein kinase (MAPK) pathways independent of the RAS. However, recent findings have revealed additional aspects of PRR, including it functioning as an accessory protein of vacuolar proton ATPase (V-ATPase) and constituting the Wnt receptor complex. This review discusses PRR in kidney physiology and diabetic nephropathy, and in addition to recent findings regarding the kidney

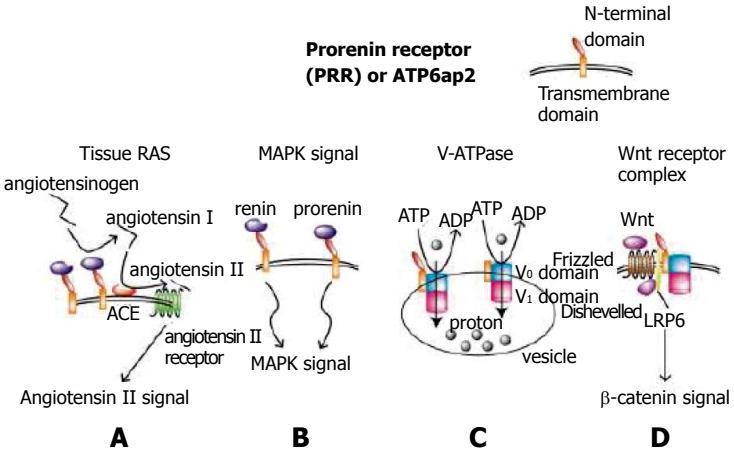

Figure 1 Four roles of prorenin receptor. A: When renin or prorenin binds to prorenin receptor (PRR), renin or prorenin enzymatic activity is enhanced through non-proteolytic conformational change, catalyzing angiotensinogen to angiotensin I. Produced angiotensin I is catalyzed by angiotensin-converting enzyme, yielding angiotensin II that induces angiotensin II receptor-mediated signal transduction, ending in enhanced tissue renin-angiotensin system (RAS)[45]; B: When PRR is bound to a ligand, renin, or prorenin, a mitogen-activated protein kinase (MAPK) signal is induced[1]; C: PRR, with or without the N-terminal domain, is required as a subunit of V-ATPase, which actively transports protons into vesicles such as endosomes, lysosomes, and autophagosomes using energy obtained by degrading ATP to ADP[9]. The V0 and V1 domains build up V-ATPase; D: PRR is required as an adaptor protein between V-ATPase and LRP6, which are members of the Wnt receptor complex[5,46].

and a soluble form of PRR.

PRORENIN RECEPTOR IN KIDNEY PHYSIOLOGY

After its discovery by cloning a single transmembrane protein PRR a dozen years ago, PRR has shown its multi-functionality in at least four different aspects (Figure 1). One of these is to enhance angiotensin I production from angiotensinogen by non-proteolytically increasing catalyzing activity of renin or prorenin when bound to PRR, resulting in enhanced RAS (Figure 1A). Another is to induce MAPK signal transduction pathway when PRR is bound to its ligand renin or prorenin[1] (Figure 1B). PRR is located on the X chromosome and is distributed widely in the kidney, heart, brain, liver, placenta and pancreas, although its' physiological role has not been elucidated until recently because of embryonic lethality of complete knockout of PRR in mice.

We previously generated floxed PRR mice and mated them with mice expressing Cre recombinase under the control of a podocyte-specific podocin promoter to create conditional PRR knockout mice in podocytes. Unexpectedly, these mice died of nephrotic syndrome and renal failure resulting from disturbed V-ATPase function. This provided evidence that, under physiological condition PRR is needed for maintaining vacuoles-such as endosomes, lysosomes, and autophagosomes- through normal V-ATPase function in mouse podocytes[2] (Figure 1C). Similar results in regard to podocytes[3] and cardiomyocytes[4] were obtained from another group and ours, respectively.

In *Xenopus*, PRR binds to V-ATPase and LRP6 to form a Wnt signaling receptor complex as an adaptor protein, showing that PRR is indispensable for normal Wnt signal transduction[5] (Figure 1D). The embryonic lethality of PRR full knockout in mice may be related to abrogated Wnt signals because Wnt signal is required for the formation of a primitive streak in early mouse embryogenesis[6]. PRR is also required for early embryogenesis in zebrafish[7]. PRR has been shown to be involved in nephrogenesis; mice with conditional PRR knockout in the ureteric bud developed renal hypodysplasia[8]. These mice were not embryonically lethal, presumably because the uretic bud is derived from the intermediate mesoderm, which develops long after the formation of the primitive streak.

Recently, the N-terminal of the PRR extracellular domain, which interacts with prorenin/renin, has been proven indispensable for V-ATPase biogenesis[9]. Although prorenin/renin does not influence overall V-ATPase activity[5,9], in vitro experiments using MCDK cells revealed prorenin and a handle region peptide that corresponds to the part of the prorenin responsible for binding to PRR and increases the initial linear phase of V-ATPase activity through binding to PRR[10]. Further investigations are expected to elucidate the roles of PRR in association with prorenin/renin, V-ATPase, and Wnt signals in physiological and developmental conditions in the kidney.

PRORENIN RECEPTOR IN DIABETIC NEPHROPATHY

In diabetes mellitus (DM), a sustained hyperglycemic state leads to diabetic nephropathy, causing end-stage renal disease. It has been reported that an elevated plasma prorenin concentration is associated with microalbuminuria[11] and diabetic nephropathy[12] in patients with DM. Tissue angiotensin Ⅱ levels are also increased in the kidneys of DM rats[13-15], suggesting activated tissue RAS. This is consistent with the multiple clinical trials showing that angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) have reno-protective effects against diabetic nephropathy[16-19], although these effects were limited. Adversely, plasma renin activity is suppressed in patients with diabetic nephropathy[20,21], reflecting a suppressed systemic RAS possibly resulting from activated tissue RAS in the kidneys. Recently, podocytes have been thought to play an important role in diabetic nephropathy and albuminuria[22,23]. Identifying PRR has led to a better understanding of diabetic nephropathy.

Albuminuria is caused by the breakdown of the

filtration barrier composed of endothelial cells, glomerular basement membranes, and podocytes. PRR has been heavily detected in mouse podocytes through immunoelectron microscopy[24]. Because transgenic rats overexpressing human PRR[25] developed slowly progressive proteinuria and enhanced MAPK signals mainly in the glomeruli podocytes[26], it is likely that podocytes are vulnerable to PRR-dependent signal transduction. The MAPK signals could be aggravated in the diabetic condition, in which both PRR and prorenin are upregulated, as discussed later in this article. This effect is believed to be independent of angiotensin Ⅱ because rat prorenin bound to human PRR did not show renin activity.

In rats with streptozotocin-induced diabetic nephropathy, PRR protein up-regulation were observed in their kidneys[27]. High glucose increased mRNA and protein PRR levels in cultured podocytes[28]. This experimental evidence shows that PRR is up-regulated in the podocytes of DM; thus, in DM, both the ligand prorenin and its receptor PRR increase.

Electron microscopic analysis in DM mice revealed that podocytes go through a hypertrophic state before the atrophic state. This hypertrophy reflects the occurrence of many vesicles (presumably lysosomes and autophagosomes) resulting from injured intracellular organelles[29]. Also, Golgi apparatus, rough endoplasmic reticulum, and free ribosome develop because of increased protein production demand resulting from cell injury[29] (Figure 2B). It is possible that these increased intracellular organelles might call for PRR up-regulation because PRR is required for V-ATPase activity, which acidifies intracellular vesicles (Figure 2C). V-ATPase is required for both maturation of synthesized proteins and degradation by lysosomes and autophagosomes that affects proteins and organelles.

As discussed previously, the serum prorenin level is increased in DM patients. Inhibition of prorenin binding to PRR by subcutaneous administration of a handle region peptide prevents diabetic nephropathy development, characterized by the inhibition of albuminuria and glomerulosclerosis in DM rats[15]. Moreover, nephropathy regression was observed in the peptide-treated handle region, but not inhibitor-treated ACE, in DM rats[30]. Handle region peptide treatment inhibited diabetic nephropathy in angiotensin Ⅱ type 1a receptor-deficient mice, suggesting the effectiveness of PRR signal transduction blockade in inhibiting diabetic nephropathy apart from angiotensin Ⅱ effects. This is consistent with the results of clinical trials showing a partial effect of ACE inhibitors or ARB in diabetic nephropathy in humans[16-19]. Other in vivo data showed that PRR increases transforming growth factor-β1[31], cyclooxygenase2[32], and cytokines such as interleukin-Iβ and tumor necrosis factor-α[33] in diabetic nephropathy. Our hypothesis here is that overproduced PRR counteracting cell injury could exhibit adverse effects through PRR-distinctive signal transductions, angiotensin Ⅱ-mediated effects, and other injurious molecules contributing to the progression of diabetic nephropathy. We term this the "trade-off hypothesis" (Figure 2E). According to our preliminary data using human PRR over-expression in transgenic rats, albuminuria was not seen in the early stages of diabetic nephropathy, whereas albuminuria was seen in wild-type rats. This experimentally supports our hypothesis.

V-ATPase is indispensable for the normal function of endosomes, lysosomes, and autophagosomes, whereas diabetic nephropathy is associated with endoplasmic reticulum stress[34] and autophagy[35]. Future experiments are needed to investigate the pathophysiological functions of PRR both in V-ATPase and signal aspects in diabetic nephropathy.

SOLUBLE PRORENIN RECEPTOR AND KIDNEY DISEASE

PRR is a single transmembrane protein with a proteinase cleavage site at the N-terminal domain near the transmembrane domain[36,37]. Cleavage of PRR by either furin[36] or ADAM19[38] results in the dissociation of the N-terminal fragment as soluble PRR (sPRR).

In healthy subjects, plasma sPRR did not exhibit circadian or posture variation or correlate with renin, prorenin or aldosterone levels[39], although serum sPRR negatively correlated with an estimated glomerular filtration rate independent of age, blood pressure, and glucose metabolism in essential hypertension and normotensive subjects[40]. sPRR correlated positively with urinary angiotensinogen[40], which is a biomarker of intrarenal RAS[41]. Moreover, in patients with chronic kidney disease, serum sPRR negatively correlated with estimated glomerular filtration rate and chronic kidney disease stage[42]. In human kidneys with end-stage renal disease, intrarenal PRR was immunostained mainly in tubules, suggesting a possible contribution of increased renal PRR expression to elevated sPRR in end-stage renal disease[43]. These findings suggest that sPRR might reflect the intrarenal RAS status.

However, in addition to the changes in sPRR levels being modest and not offering a set cut-off line for clinical use, these levels are affected by many other factors including, RAS inhibitor administration[39], lipid metabolites such as high-density lipoprotein cholesterol and triglycerides[40], age[40], and obstructive sleep apnea syndrome[44]. Moreover, the correlation between sPRR level and the activity of furin or ADAM19 has not yet been investigated under these conditions. Further investigations are expected to determine the relationships, if any, between kidney disease and sPRR, PRR, tissue RAS, V-ATPase and Wnt.

SUMMARY

In physiological and developmental conditions, it has been suggested from the experiments discussed previously that PRR primarily exhibits as V-ATPase or Wnt

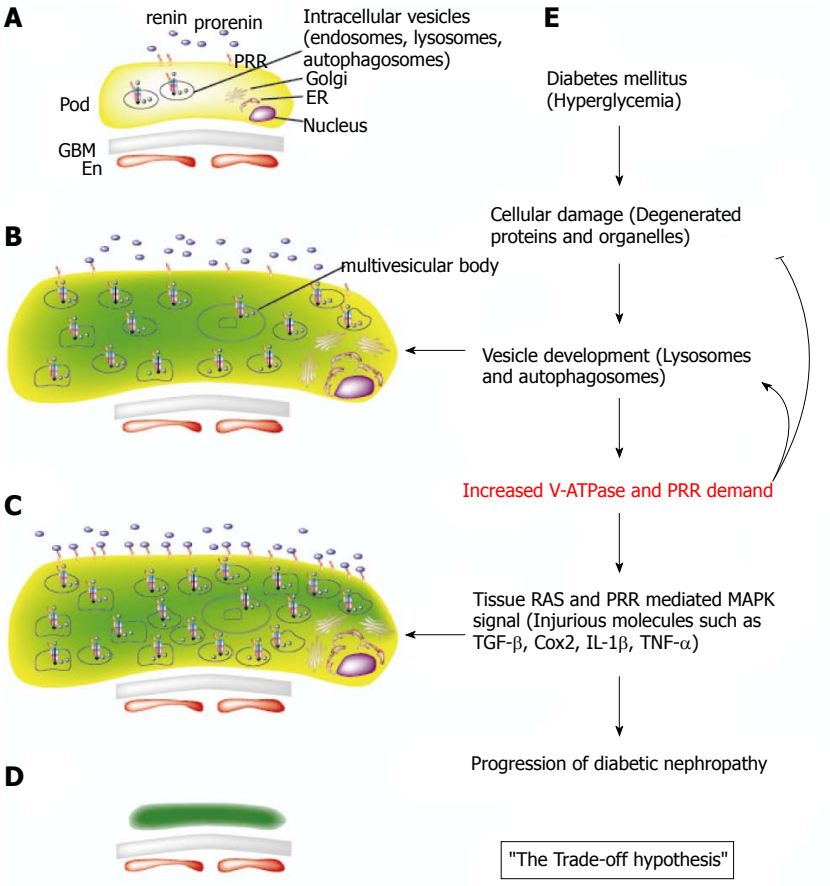

Figure 2 The trade-off hypothesis in diabetic nephropathy from the prorenin receptor perspective. A: Normal podocyte intracellular structure; B: Under hyperglycemic conditions, injured podocytes degrade degenerated proteins and intracellular organelles, forming vesicles such as lysosomes and autophagosomes, which require V-ATPase and prorenin receptor (PRR) for internal acidification; C: Sustained hyperglycemia overproduces PRR molecules, which are transported to the transmembrane and bind to increased serum prorenin in the diabetic condition. This enhances tissue renin-angiotensin system (RAS) and PRR-mediated mitogen-activated protein kinase (MAPK) signals; D: Atrophic or apoptotic podocytes after long-term hyperglycemic conditions. The changes in the glomerular basement membrane and endothelial cells are not shown; E: The schematic view of the trade-off hypothesis. In diabetes mellitus, podocyte injury occurs by producing degenerated proteins and organelles, which in turn are degraded in lysosomes and autophagosomes. This process requires V-ATPase and PRR production for internal acidification of the vesicles. PRR overproduction enhances tissue RAS and PRR-mediated MAPK signals, resulting in increased injurious molecules such as transforming growth factor-β, cyclooxygenase2, interleukin-1β, and tumor necrosis factor-α. Progression and deterioration of diabetic nephropathy occurs at the end. En: Endothelial cell; ER: Endoplasmic reticulum; GBM: Glomerular basement membrane; Pod: Podocyte.

signaling instead of RAS enhancement or PRR-distinct MAPK signal transduction. These former functions are related to fundamental cellular survival and embryo development. On the other hand, in DM, inhibition of prorenin binding to PRR has the beneficial effect of inhibiting diabetic nephropathy, which is not achieved in Ang II blockade. In DM, PRR primarily works as an RAS enhancement or MAPK signal on top of V-ATPase. Involvement of Wnt signals in diabetic nephropathy has not been investigated throughly.

The shift of PRR's function from a physiological condition to a DM condition could be attributed to altered PRR demand. As in the trade-off hypothesis, a hyperglycemic state leads to increased PRR demand caused by increased V-ATPase activity to recycle or degrade intracellular organelles and proteins. The overproduced PRR is transported to the cell membrane, which triggers RAS enhancement and PRR-dependent MAPK signals *via* prorenin binding. As a result, diabetic nephropathy progression occurs.

The significance of sPRR in kidney disease is not clearly defined because sPRR changes in kidney disease are too modest to set a cut-off line for clinical use. Yet, it is possible that sPRR reflects intrarenal RAS status.

CONCLUSION

Rigorous work has uncovered PRR physiology and pathophysiology in the kidneys. The multi-functioning protein PRR can shift its role from the physiological condition to the DM condition depending on underlying cellular conditions. V-ATPase is believed to help cells maintain a clean environment; however, in DM, it may have adverse effects in terms of overproduced PRR. This functional shift may occur because, unlike other molecules, PRR not only is important in fundamental cellular survival but also in disease progression. According to the trade-off hypothesis, over-expression of PRR may have beneficial effects in the very early stages of diabetic nephropathy, although PRR may have harmful effects in the late stages. Future works should elucidate which PRR functions, of the four discussed here, are dominant in each cell and kidney disease context.

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RETROSPECTIVE STUDY

Quality of life in end stage renal disease patients

Veena D Joshi

Veena D Joshi, K.G. Patel Children's Hospital, Jalaram Marg, Karelibaug, Vadodara 390018, Gujarat, India
Author contributions: Joshi VD contributed to this work.
Correspondence to: Dr. Veena D Joshi, Consultant (Biostatistics and Medical writing), K.G. Patel Children's Hospital, Jalaram Temple Road, Karelibaug, Vadodara 390018, Gujarat, India. joshiveena0@gmail.com
Telephone: +91-265-2463906
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Abstract

AIM: To understand factors associated with quality of life (QOL), examine types of QOL instruments, and determine need for further improvements in QOL assessment.

METHODS: The method used databases (Pubmed, Google scholar) and a bibliographic search using key words QOL, end stage renal disease, Hemodialysis, Peritoneal dialysis, instruments to measure QOL, patients and qualitative/quantitative analysis published during 1990 to June 2014. Each article was assessed for sample size, demographics of participants, study design and type of QOL instruments used. We used WHO definition of QOL.

RESULTS: For this review, 109 articles were screened, out of which 65 articles were selected. Out of 65 articles, there were 19 reports/reviews and 12 questionnaire manuals. Of the 34 studies, 82% were quantitative while only 18% were qualitative. QOL instruments measured several phenomenon such as physical/psychological health, effects and burdens of kidney disease, social support etc. those are associated with QOL. Few studies looked at spiritual beliefs, cultural beliefs, personal concerns, as per the WHO definition. Telemedicine and Palliative care have now been successfully used however QOL instruments seldom addressed those in the articles reviewed. Also noticed was that longitudinal studies were rarely conducted. Existing QOL instruments only partially measure QOL. This may limit validity of predictive power of QOL.

CONCLUSION: Culture and disease specific QOL instruments that assess patients' objective and subjective experiences covering most aspects of QOL are urgently needed.

Key words: Quality of Life; Hemodialysis; Peritoneal dialysis; Patient; End stage renal disease; Quality of life instruments

Core tip: Quality of life (QOL) in end stage renal disease patients is an important outcome measure. This study tried to understand the dimensions of various QOL instruments and association of various risk factors with QOL. Since each instrument measures specific aspect of QOL, use of any one of these instruments allows studies to measure QOL only partially compromising on the validity of the predictive power of QOL. Furthermore, less attention has been given on conduct of qualitative and longitudinal studies. There is an urgent need to develop disease and culture specific instrument that covers most aspects of QOL.

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INTRODUCTION

In medicine most assessments are conducted by laboratory tests or examinations from healthcare workers. Quality of Life (QOL), though equally important to assess the quality and outcomes of medical care, is not routinely measured. QOL instruments measure individ-

ual's own views of his wellbeing. The core components of QOL are physical, functional, psychological/emotional, and work/occupational[1]. This review will discuss QOL of adult end stage renal disease (ESRD) patients. For this review, we used the World Health Organization's (WHO) definition of QOL which is "individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns". It is a broad ranging concept affected by the person's complex physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of their environment[2]. QOL can be used to gauge health system performance, mortality indicators, and compare health of groups[3].

This review focused on adult ESRD patients since renal disease is a serious illness and treatment is challenging and prolonged. Globally, the estimated prevalence of chronic kidney disease (CKD) (the first four stages out of five) is 7.2% in adults over the age of 30 years[4]. CKD is a major determinant of poor health outcome of noncommunicable diseases affecting 5% to 8% of world's population[5]. Despite the substantial resources committed to the treatment of ESRD and significant improvements in the quality of dialysis therapy, patients continue to experience significant mortality and morbidity and a reduced quality of life[6]. With improved medication, medical treatment, medical care and health technology, patients may be living longer but are they living a better life? The effect of the treatment is not only measured in terms of survival, but also in terms of well-being. There is an ever expanding body of literature related to various factors that affect QOL, like genetic, environmental, psychosocial, stress, emotional, and co-morbidities. Findings have shown that lower scores on QOL were strongly associated with higher risk of death and hospitalization[7,8] than clinical parameters such as serum albumin levels[8] in cases of ESRD patients. It is also noticed that QOL in ESRD is most affected in the physical domains, and nutritional biomarkers are most closely associated with these domains compared to Kt/V (marker of dialysis adequacy), mineral metabolism indices, and inflammatory markers which are poor health related quality of life (HRQOL) correlates[9]. These findings demand more attention towards patients' essential QOL measures and indicators.

While assessing QOL, both subjective and objective information is necessary since they derive distinct types of information. Objective measures may be more suitable in detecting treatment effects, such as the number of days on dialysis. Subjective information (such as happiness, satisfaction, spiritual and religious beliefs) is also necessary to complete the QOL picture and enhance the interpretation of objective data. Both the illness and the treatment of ESRD influence subjective QOL factors.

Recently (2014), Boudreau JE has talked about the functional definition of concept of QOL by discussing three attributes: (1) the ability to engage in vigorous activities; (2) the ability to engage in social and occupational roles; and (3) the ability to perform activities of daily living (ADL)[10]. Reviews were conducted that included the type of measures, the instrument development process, study sample characteristics, particular quality of life domains, and reliability and validity testing. Some reviews provided an overview of the instruments used and judged the instruments in terms of their comprehensiveness, reliability, and validity[11]. Few studies sought to establish which domains of QOL are most affected by ESRD[9]. Review by Gentile[12] did provide a variety of generic and disease targeted health related QOL instruments for patients suffering from ESRD. Yet, reviews have rarely discussed whether existing QOL instruments have covered both objective and subjective patient experiences as per the WHO definition of QOL.

Based on this background, the aim of this review was to understand the factors associated with QOL of adult ESRD patients, examine the various dimensions that QOL instruments measure, and identify if there is a need to expand the measurements of QOL.

MATERIALS AND METHODS

The search strategy detailed in Figure 1 was used to identify published literature in the English language during the years 1990 to June 2014. The search was conducted during March - June 2014 using the search criteria (key words, year and language) as mentioned in Figure 1. The search was conducted with MEDLINE, PubMed and was further expanded with Google Scholar using the same search criteria mentioned above. Title and abstracts of the studies were checked with the key words to screen the articles. This process generated 109 studies including research papers, reviews, reports and manuals relevant to our scope of interest.

Inclusion and exclusion criteria (as mentioned in Figure 1) were applied to the selected abstracts for relevance. If the author was not satisfied with the content of the abstract, the full paper was accessed and the same inclusion/exclusion criteria were applied. A total of 62 research papers met the criteria. The bibliography of the research papers was then reviewed to identify additional literature published in English that met the inclusion criteria. Three more research studies were identified by this process. In total, 65 research papers, reports, reviews and quality of life questionnaire manuals were included in this review

These 65 research papers were then arranged into four principal categories as follows: (1) Reports, reviews, published series, discussion articles; (2) Quantitative studies; (3) Qualitative studies; and (4) Quality of life questionnaire manuals (Table 1).

RESULTS

For this review 109 articles were screened, out of which 65 articles were selected. Out of 65 articles, there were

Table 1 First Author, year of publication, study design and questionnaire used

Ref.	Study design	
Reviews, Published series, Reports, Discussion articles		
Donald[1], 2009	Published Series article	
POFS ABUSE[2], 1997	WHOQOL Instruments Report	
Romero *et al*[3], 2013	Discussion article	
EpiCast[4], 2014	Report	
Couser *et al*[5], 2012	Policy Forum	
Obrador *et al*[6], 2014	Review	
Schatell *et al*[7], 2012	Report	
Berman *et al*[9], 2008	Systematic Review	
Edgell *et al*[11], 1996	Review	
Gentile *et al*[12], 2003	Review	
Kimmel *et al*[21], 2006	Review	
Johansen[30], 2007	Report	
Kutner[31], 2010	Rehabilitation Report	
Valderrábano *et al*[46], 2001	In-depth Review	
Fleck *et al*[53], 2007	Discussion	
Carver *et al*[57], 1995	Review	
Blinkhorn[61], 2012	Review	
O'Connor *et al*[64], 2012	Review	
Catania *et al*[65], 2013	Report	
Quantitative	Study design	Questionnaire used
Mapes *et al*[8]	Longitudinal	KDQOLSF-36
Kao *et al*[13], 2009	Cross sectional	SF-36
Abraham *et al*[14], 2008	Case control, follow up	WHOQOL-BREF
Kimmel *et al*[15], 2008	Prospective	Satisfaction with Life Scale (SLS), McGill QOL, Single item
Patel *et al*[16], 2002	Prospective	McGill QOL, Beck Depression
Griva *et al*[17], 2009	Cross sectional	SF-36
Elder *et al*[19], 2008	Cross sectional, case mix	KDQOLSF-36
Sanner *et al*[20], 2002	Cross sectional	SF-36, Nottingham Health Profile
Tondra[22], 2014	Conceptual Framework, CS	Quality of Life Index Dialysis,
Mingardi *et al*[23], 1999	Prospective	SF-36
Seica *et al*[24], 2009	Cross sectional	SF-36, KDQOLSF-36
Bakewell *et al*[25], 2002	Longitudinal /intervention	KDQOLSF-36
Theofilou[26], 2012	Cross sectional/ Observational	WHOQOL-BREF, GHQ-28
Kim *et al*[28], 2013	Cross sectional	KDQOLSF-36
White *et al*[29], 2002	Retrospective cohort	SF-36
Painter *et al*[32], 2000	Experimental/Intervention	SF-36
Ouzouni *et al*[33], 2009	RCT	SF-36, Quality of Life Index
Agakhani *et al*[34], 2012	Case control/comparative	SF-36
Hegazy *et al*[35], 2013	Intervention/Pre-post	Karnofsky performance scale
Abraham *et al*[36], 2009	Prospective, intervention	Karnofsky performance scale
Moattari *et al*[37], 2012	RCT	SF-12
Brennan *et al*[38], 2007	Intervention, report	SF-36
Cukor *et al*[39], 2013	RCT	KDQOLSF-36, Beck Depression Inventory
Lii *et al*[40], 2007	Intervention/Experimental	SF-36
Sathvik *et al*[52], 2008	Cross sectional	WHOQOL-BREF
Pagels *et al*[50], 2012	Cross sectional	SF-36
WHOQOL-SRPB[54], 2005	Cross cultural/sectional study	WHOQOL-SRPB
Yong *et al*[63], 2009	Prospective cross sectional	SF-36, Charlson Comorbidity Index
Qualitative		
Baudeau *et al*[10], 2014	Concept analysis	
Fennegan-John *et al*[18], 2013	Interviews, FGD	
Arabi[41], 2006	Interview	
Rygh *et al*[59], 2012	Interviews with patients	
Stroetmann *et al*[60], 2000	Observational	
Jablonski[62], 2007	Observational	
QOL instruments		
Choices for Healthy Outcomes In Caring for End Stage Renal Disease[27]		
Sickness Impact profile[42]		
SF-36[43]		
SF-12[44]		
Nottingham Health Profile[45]		
EQ-5D[47]		
McGill Quality of Life Questionnaire[48]		
GHQ-28[49]		
WHO-BREF[51]		
Dialysis Symptom Index[55]		

KDQOL-SF36[56]	
CKD Questionnaire[58]	

QOL: Quality of life; CKD: Chronic kidney disease.

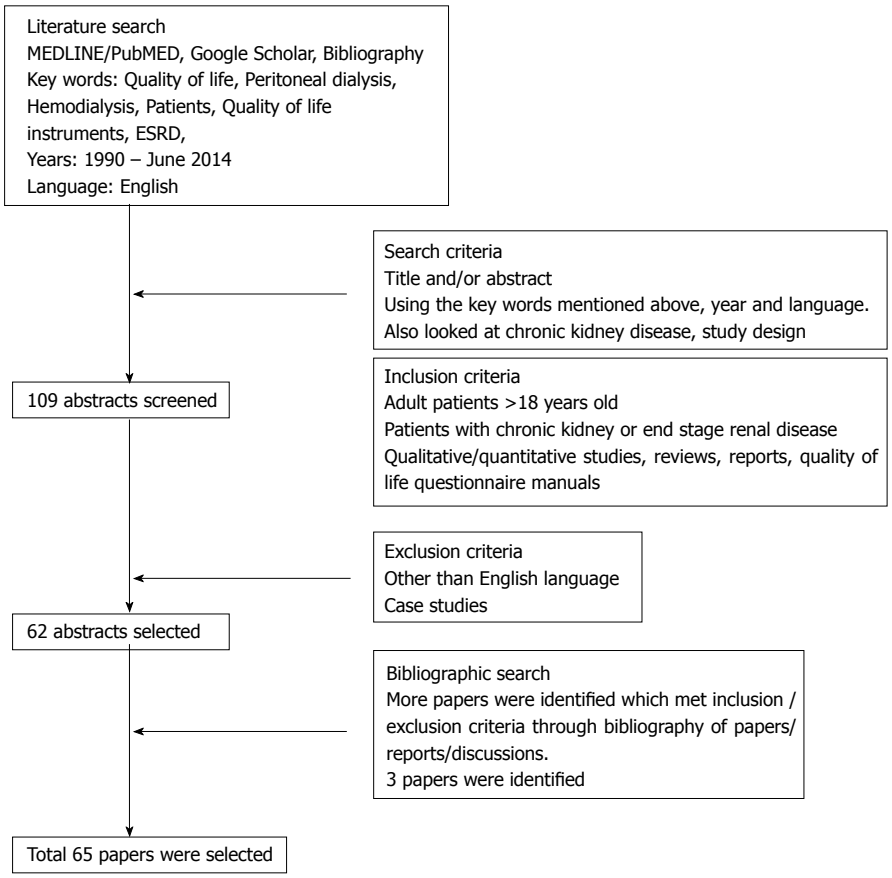

Figure 1 Literature search strategy. Flow chart below shows how the studies were selected for this article.

19 reports/reviews and 12 questionnaire manuals. Of these 34 studies, 82% were quantitative while only 18% were qualitative. Most quantitative studies were cross sectional. Only two studies used longitudinal design.

Association of various factors with QOL and outcome

The treatment for ESRD patients imposes heavy restrictions that affect QOL. QOL usually includes both objective and subjective evaluations of both the positive and negative aspects of life. Researchers have reported demographic, clinical, social, psychological, and treatment related associations with QOL[1].

It has been proven that the patient's perception is more important than the clinical assessment in determining QOL[15]. Figure 2 illustrates several factors having linear, inverse or no association with QOL. Studies have commented that QOL can be enhanced by intervention techniques as mentioned in Figure 2. The same figure further shows that lower scores on all three summary scores of QOL (physical component summary, mental component summary and kidney disease component summary) were strongly associated with death and hospitalization as revealed by Mapes in DOPPS study[8] (predictive power of QOL).

Qualitative research

Qualitative research produces rich information that is not possible to get by quantitative research. Qualitative research conducted on ESRD patients has reported some of the themes (subjective measures) for QOL. These themes were physiological impact, impact of treatment, impact on daily life, psychological impact, impact on relationships, social impact and coping responses[20]. Another study came up with three themes and sub themes as: (1) "life restricted" with sub-themes "being tied down", "feeling left out", and "doing without"; (2) "staying alive" with sub-themes "love from others", "accept illness as part of life", and "trust in God"; and (3) "feeling good" with sub-themes "personal satisfaction" and "being happy"[41].

QOL instruments

Some QOL instruments provide a standard assessment of health. These instruments include questionnaires designed to be applicable for general population such as the Sickness Impact Profile (SIP)[42], the SF-36[43], SF-12[44], the Nottingham Health Profile[45,46] (used for primary care), the European Quality of Life Instrument - EQ-5D[47], the McGill QOL (MQOL)[48] scale

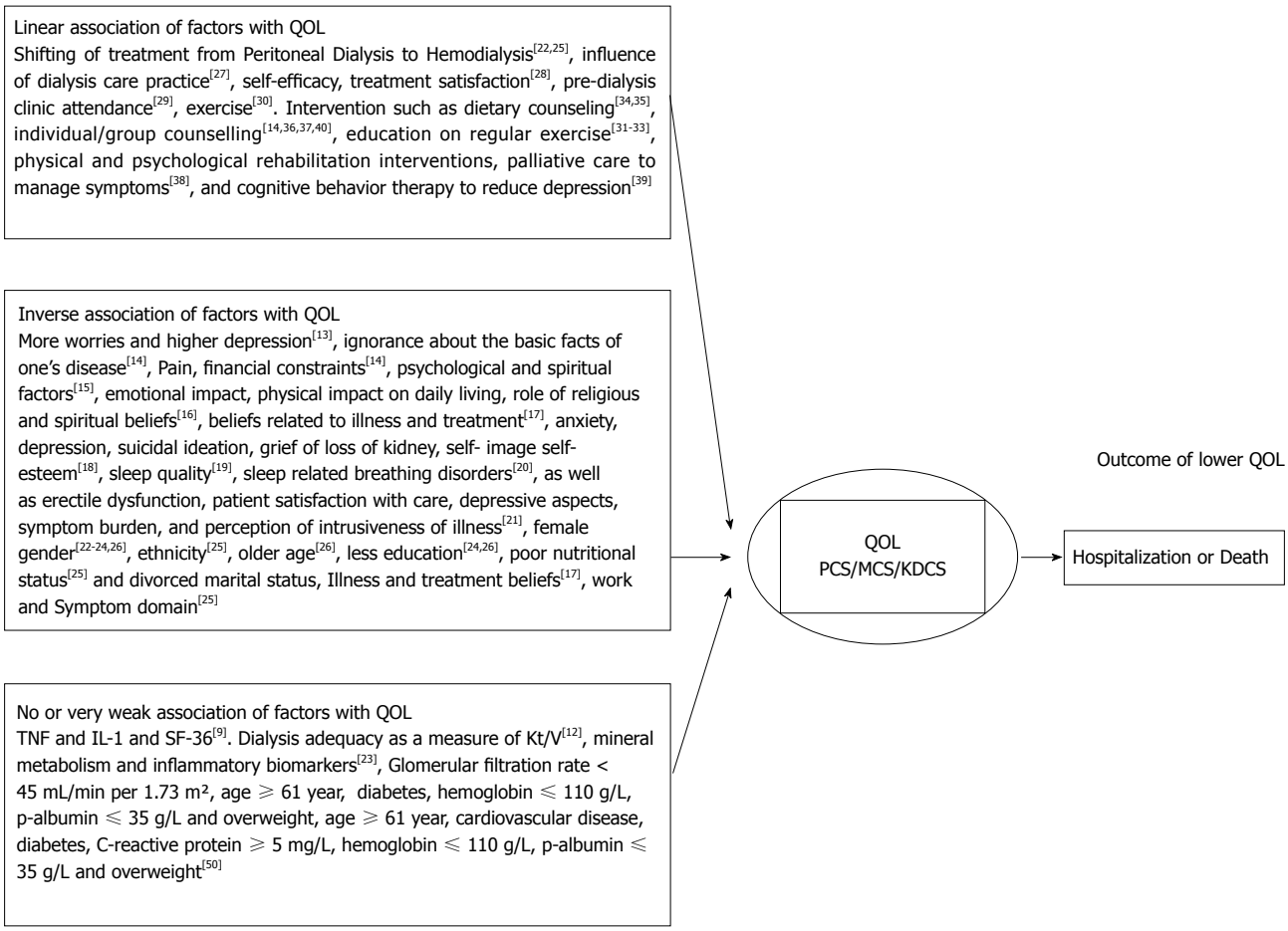

Figure 2 Factors associated with quality of life and predictive power of quality of life. Quality of life (QOL) is assessed based on several factors that show linear / inverse/no relationship with QOL. Based on these relationships QOL predicts Hospitalization or death. QOL: Quality of life; PCS: Physical component summary; MCS: Mental component summary; KDCS: Kidney disease component summary.

and GHQ- 28[49]. Instruments designed by WHO such as WHOQOL[50] WHOQOL-BREF[51,52] are used by researchers. WHOQOL-SRPB[53,54] is also used to assess spiritual, religious and personal beliefs (SRPB) within quality of life. In the CHOICE study, the research team is conducting several research projects for the development of patient-centered instruments for assessment of health-related quality of life[27].

There are three disease-targeted questionnaires developed for ESRD patients undergoing dialysis. Dialysis Symptom Index (DSI)[55], the Kidney Disease Quality of Life instrument Short Form- KDQOL-SF36[56]. The Choices for Healthy Outcomes in Caring for End-Stage Renal Disease ([ESRD] CHOICE)[27]. Additionally, few researchers use The Kidney Disease Questionnaire - KDQ[58], Renal Quality of Life Health Profile (RQLP), and Quality of Life Index-D. Each QOL tool covers a number of domains (measurements of different characteristics) and they measure quantitative outcomes[13]. Culture specific validation has been reported for these instruments in many countries. Every instrument is scored on different domains. There is no one instrument that measures all the domains or most of the patients' perceptions towards their disease or life. The most common instruments used were SF-36 and KDQOL. Data collected by administering these questionnaires was analyzed using quantitative methods. Most studies use descriptive cross sectional design[57]. In this review, out of 65 articles, 48% had used SF-36, 20% had used KDQOL, 16% had used WHOQOL and the remaining 16% had used GHQ-12, GHQ-28, McGill, DSI, QOLI (Table 1).

DISCUSSION

Researchers have reported a linear or inverse relationship between factors that improve or lower QOL. Researchers have defined attributes[10] or used frameworks[22] or models[3] that encompasses certain aspects of QOL, such as demographic data, information on diet, treatments and their impact, anthropometric biomarkers[50], and data related to mental health such as depression or anxiety. Most of the existing QOL instruments derived mainly quantitative information. Since QOL is subjective, more qualitative evidence needs to be gathered, assessed and understood. Although it is expensive and time consuming, incorporating qualitative methods will generate rich information.

Considering the WHO definition of QOL and its multidimensional aspects, the instruments and models reviewed only partly assess QOL. Some of the domains were omitted, such as patients' thinking, learning, memory concentration, self-esteem, patient's perception about his body image, patient's feelings about his health and the surrounding environment, patient's age, patient's dependence on medication or treatments, financial burden of treatment, and spiritual/religious beliefs[57]. While studies that have used WHO QOL have covered some of the above-mentioned characteristics, they have not specifically covered these in relation to kidney disease. Although Paul Kimmel has commented that there is a need for proper measurements for judging QOL for chronic kidney disease patients[21], not much attention has been given. There remains a need for an instrument that will capture the greatest number of QOL characteristics to get a broader understanding.

The results also reveal the need to conduct more longitudinal studies where researchers are able to detect changes in the characteristics of the population at a group level. Few longitudinal studies were conducted to report the usefulness of these instruments to find improvement in QOL over time. With longitudinal studies it would be possible to detect Minimal Clinically Important Difference (MCID) *i.e.*, a smallest change in treatment outcome that a patient himself would identify as important.

Culture plays a vital role in shaping individual QOL. An individual's values affects perception of QOL and this can differ between cultures as shown in DOPP study[8].

Furthermore, the current instruments were developed some time ago. [KDQOL-SF36 (1995), KDQOL-36, SF-36 (2002), SF-12, EQ-5D (2004)] Since then (1995), medical technologies (e-health) and medical services have improved. Although telemedicine[59], electronic/digital processes in health, healthcare practice using the Internet, video conferencing with patients, and electronic medical records have been implemented, these services are not evaluated for QOL. For example, there is little published research on telehealth in renal units[61]. Patients generally prefer to stay at home and telecare can extend homecare to peritoneal dialysis patients[60], but use of telehealth is under researched[61]. QOL instruments may be incorporated into telehealth assisted technologies for wider understanding and application.

For those who are not able to receive dialysis treatment, non dialytic management of ESRD seems to be a viable option. Patients managed conservatively had reported high symptom burden underscoring the need for concurrent palliative care[64]. Hence, physicians are now considering palliative care services that specialize in symptom management for ESRD patients[62,63]. This is especially important in frail, illiterate, elderly multimorbid patients with limited physical activity, where prognosis may not be altered by dialytic therapy. In such scenarios, palliative care will help improve quality of life. Though Catania G. has come up with a frame work to assess QOL with palliative care intervention[65], he has explained the complexity involved in measuring palliative care as an intervention. The existing QOL instruments have rarely looked at palliative care aspects for improvement of patient well-being. Inclusion of newer technologies and therapies measured over time may also help to establish the minimally important differences that would constitute a real change in scores as well as clinically meaningful differences.

Studies have shown that QOL has improved with hemodialysis treatment as compared to peritoneal dialysis[22,25]. Another study has shown that QOL is better for patients treated at home[60]. In most cases peritoneal dialysis treatment is given at home. These two results may look contradictory but they are reported by two different studies. Is it the type of treatment or the place of treatment that affects QOL? It will be interesting to know what will be the result when both aspects are looked at by the same study. When several other factors are studied and included in the model, with the help of statistical analysis it will be possible to identify which factor affects QOL the most. Most instruments do not cover health literacy, which also has an impact on QOL. In the case of illiterate patients, sufficient data may not be available, so pictorial forms of the instruments may help.

Since patient-reported baseline QOL levels provide additional predictive information[7], it is important to consider a patient's evaluation of their own QOL along with other aspects. A possible limitation of the study is that we were only able to review a portion of the research studies.

In summary, QOL is multidimensional where many indicators are intertwined and that affect person's overall QOL. Indicators based solely on certain characteristics of the patients pose serious restrictions to the measure of QOL. Ultimately, this may limit the predictive power of QOL. In examining QOL of ESRD patients, much work remains. The challenge for the next decade will be to continue to design a QOL instrument that takes both disease specific and culture specific subjective and objective factors into account so that it would be possible to get the complete assessment of QOL of ESRD patients.

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COMMENTS

Background

Quality of life (QOL) is considered as an important outcome measure. Researchers have claimed that it is even better than clinical parameters. Understanding QOL of end stage renal disease patients is necessary because renal disease is a serious illness and treatment is challenging and prolonged. Though there are various instruments to measure QOL, it is necessary to understand the dimensions used for assessment by these instruments and if there is a

need to improve the existing QOL instruments.

Research frontiers

There are several instruments to measure QOL. Each instrument measures certain dimensions of human characteristics. Most of the instruments record objective information and measure QOL quantitatively. Most of the studies use cross sectional design that gives only snap shot information. An instrument designed by WHO measure subjective information but do not assess information related to kidney disease. These instruments rarely record the modern technologies such as telemedicine, e-health, conservative care *etc.*

Innovations and breakthroughs

There is an urgent need to develop QOL instrument that will try to look at the majority of (objective and subjective) characteristics of patients as well as the effect of new technologies like e-health and therapies like palliative care. QOL instruments, those are currently in use, have been developed some time ago. [KDQOL-SF36 (1995), KDQOL-36, SF-36 (2002), SF-12, EQ-5D (2004)] Since then (1995), medical technologies (e-health) and medical services have improved.

Applications

The newly designed QOL instrument that takes both diseases specific and culture specific, objective and subjective factors into account will help physicians to plan targeted intervention strategies based on strongest and weakest factors that affect QOL. With availability of complete QOL assessment, it will be possible to predict disease outcome effectively.

Terminology

Studies have reported that QOL can be used as an outcome measure in terms of hospitalization and mortality. The strength of this prediction would depend on how rigorously and comprehensively QOL was assessed. This is indicated as validity of the predictive power of QOL.

Peer review

This is an interesting topic.

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OBSERVATIONAL STUDY

Residual urinary output in high body mass index individuals on chronic hemodialysis: A disregarded life vest?

Hernán Trimarchi, María S Raña, Alejandra Karl, José Andrews, Mariana Dicugno, Vanesa Pomeranz, Pablo Young, Mariano Forrester, Mirta Alonso, Fernando Lombi, Alexis Muryan

Hernán Trimarchi, María S Raña, Alejandra Karl, José Andrews, Vanesa Pomeranz, Mariano Forrester, Fernando Lombi, Nephrology, Hospital Británico de Buenos Aires, C1280AEB Buenos Aires, Argentina
Mariana Dicugno, Mirta Alonso, Alexis Muryan, Biochemistry, Hospital Británico de Buenos Aires, C1280AEB Buenos Aires, Argentina
Pablo Young, Internal Medicine Services, Hospital Británico de Buenos Aires, C1280AEB Buenos Aires, Argentina
Author contributions: All the authors solely contributed to this paper.
Correspondence to: Hernán Trimarchi, MD, Nephrology, Hospital Británico de Buenos Aires, Perdriel 74, C1280AEB Buenos Aires, Argentina. htrimarchi@hotmail.com
Telephone: +54-11-43096400 Fax: +54-11-43043393
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Abstract

AIM: To assess residual diuresis and diverse variables according to body mass index (BMI).

METHODS: Cross-sectional study (n = 57), with 3 groups. Group A: BMI < 25, n = 22; Group B: BMI 25-30, n = 15; Group C: BMI > 30, n = 20. Diuresis, hematocrit, albumin, C-reactive protein, Malnutrition inflammatory score, Pro-BNP, Troponin T, leptin and insulin levels are expressed as median and ranges (r).

RESULTS: Albumin (g/dL): GA *vs* GC, 3.70 (r2.20-4.90) *vs* 3.85 (r3.40-4.90), P = 0.02. Diuresis (mL/d): GA 690 (r0-1780); GB 660 (r60-1800); GC 840 (r40-2840). Diuresis GA *vs* GC, P = 0.01. Leptin (ng/mL): GA *vs* GC, 3.81 (r0.78-69.60) *vs* GC, 32.80 (r0.78-124.50), P < 0.001. Insulin (μU/mL): GA *vs* GB, 7 (r2-44) *vs* 11.50 (r4-38), P = 0.02; GA *vs* GC, 7 (r2-44) *vs* 19.5 (r5-155), P = 0.0001. Troponin T and Pro-BNP levels were not different. Significant correlations: GC, Insulin-UF: ρ = 0.53; P = 0.03; TroponinT-diuresis: ρ = -0.48, P < 0.05; Pro-BNP-diuresis: ρ = -0.39, P < 0.01; Troponin T-ProBNP: ρ = 0.77, P < 0.0001; albumin-Troponin T: ρ = -0.66, P < 0.0001; albumin-ProBNP: ρ = -0.44, P < 0.05.

CONCLUSION: High BMI associated positively with higher diuresis and albuminemia, and negatively with TropT and Pro-BNP. High BMI-associated better survival may be explained by better urinary output, lowering cardiovascular stress.

Key words: Hemodialysis; Residual diuresis; Body mass index; Troponin T; Pro-BNP; Insulin

Core tip: Cardiovascular disease is the major cause of death in hemodialysis, while residual diuresis and increased body mass index (BMI) are associated with better survival. We found that an elevated BMI > 30 associated positively with higher diuresis, insulin levels and albuminemia. This higher urinary output dialysis individuals with BMI > 30%, may reflect water retention, in part due to hyperinsulinemia, hyperleptinemia and secondary higher ultrafiltration rates. The ability to excrete water correlates negatively and significantly with Troponin T and Pro-BNP levels, reflecting lower myocardial and vascular overload. High BMI-associated better survival may be explained by better diuresis, and lower cardiovascular stress.

Trimarchi H, Raña MS, Karl A, Andrews J, Dicugno M, Pomeranz V, Young P, Forrester M, Alonso M, Lombi F, Muryan A. Residual urinary output in high body mass index individuals on chronic hemodialysis: A disregarded life vest? *World J Nephrol* 2014; 3(4): 317-323 Available from: URL: http://www.wjgnet.com/2220-6124/full/v3/i4/317.htm DOI: http://dx.doi.org/10.5527/wjn.v3.i4.317

INTRODUCTION

The International Task Force has established that worldwide 1.5 billion adults are overweight or obese, with nearly 500 million being obese[1]. Only in the United States, a third of the adult population is overweight and another third is obese[2]. In the general population, obesity is associated with higher rates of hypertension, diabetes, metabolic syndrome, cardiovascular disease, and death[3,4]. Morbidly obese adults present a 6-fold higher risk of diabetes compared with their lean peers[5]. Moreover, approximately 70% of hypertension can be attributed to excess weight[6,7]. Because a large proportion of chronic kidney disease is attributed to both diabetes and hypertension, conditions associated with high body mass index (BMI), it seems logical to suppose that obesity should be associated with bad prognosis in hemodialysis (HD) individuals. However, in HD patients obesity is independently associated with reduced all-cause mortality[8-11]. In this regard, there is a negative correlation between BMI and death, generally referred to as the obesity paradox[12]. In hemodialysis individuals, obesity seems to act as a protective factor[13,14] and in general, obese subjects display a better nutritional status, regardless of portraying a more severe cardiac condition[15]. While diabetes and obesity are two usually associated conditions, in HD diabetics tend to present increased morbidity and mortality rates but obesity has been reported to display better survival. Many variables have been ascribed as potential factors that could explain this apparent paradox about obesity in HD: A better nutritional status, higher albumin levels, and a lower inflammatory milieu as assessed by C-reactive protein (CRP), among other factors[8-11].

In end stage kidney disease, residual renal function or remnant diuresis is considered an important variable associated with better survival[16-18]. Besides a better volume management, residual diuresis has been associated with better preserved renal functions, such as calcium, phosphorus and vitamin D homeostasis, erythropoietin levels, and removal of middle molecules[19-24]. In this regard, residual renal function has been shown to present a greater influence on dietary protein intake and nutritional status[25-27]. However, with respect to urinary output, in obese hemodialyzed people the reported results are scant or controversial. In this regard, some studies have found an inverse association between obesity and diuresis, while this association has also been reported to be inconclusive[28,29].

In addition, insulin and particularly hyperinsulinemia itself due to peripheral tissue resistance and deeply involved in the pathogenesis of metabolic syndrome and obesity, has been reported to be elevated in high BMI individuals on HD[15,30]. Insulin causes myocardial hypertrophy and water and salt retention and is associated with diabetes and hypertension, conditions that contribute to high morbidity and mortality rates, particularly in end stage kidney disease[31]. Finally, leptin and insulin not only present similar metabolic and hemodynamic actions, but also display the same patterns of distribution with respect to BMI in HD[30,32].

We investigated cardiac and metabolic biomarkers in HD subjects with respect to urinary output, and propose another potential protective cardiovascular mechanism high BMI individuals display in HD. Finally, a consideration is addressed with respect to the importance of defining elevated body weight in hemodialysis, as obesity may not always be the case when other factors intervene, as fluid overload or muscle wasting.

MATERIALS AND METHODS

Design

Cross-sectional, prospective, observational study undertaken in 57 chronic clinically stable HD individuals.

Patients

The Teaching and Research Committee of the Hospital Británico de Buenos Aires approved this observational study. Each patient signed the respective informed consent. Fifty-seven patients with more than 3 mo of HD were enrolled. Exclusion criteria: Patients younger than 18 years old, or with an active cancer, acute infections, hepatopathy, non-treated hypothyroidism, anuria or BMI > 40 kg/m^2. Anuria was defined as a urinary output < 140 mL/d and proteinuria was considered positive when the daily excretion was > 0.15 g/d. One included patient was HIV positive and another one was HbsAg positive. Failed transplant patients were excluded. The population was divided into three groups as to BMI tertiles as described above. Group A, BMI < 25 (n = 22); Group B, BMI 25-30 (n = 15) and Group C, BMI > 30 (n = 20). Median age (range): Group A: 65 (36-83) years; Group B: 71 (26-88) years; Group C: 63 (33-79) years, P = 0.61. Moreover, the three groups were not different with regard to gender, time on chronic HD, estimated glomerular filtration rate at the beginning of HD, etiology of kidney disease, hypertension, diabetes mellitus, CRP levels, nutritional status evaluated by the malnutrition inflammatory score (MIS), daily diuresis, ultrafiltration rates and no difference in mean estimated GFR in the three groups when dialysis was initiated (Table 1). The rates of decline of diuresis were 13%, 17% and 6 %, respectively. Determinations: Mean automatic intradialytic ultrafiltration rates, mean average blood pressure per session, Troponin T (TropT), Pro-BNP, albumin, insulin levels and HOMA. Serum concentrations of albumin and CRP were measured by routine procedures. TropT levels were determined by electrochemoluminiscence, Cobas e411, Roche Diagnostics, Indianapolis, IN, United States, (normal value: < 1 ng/mL); Pro-BNP levels were measured by chemiluminescence, VITROS 5600®, Johnson and Johnson, New Jersey, United States: (reference values: < 125 pg/mL for subjects < 75 years and < 450 pg/mL for those > 75 years). Insulinemia was measured by electrochemoluminiscence, Cobas e411, Roche Diagnostics®, Indianapolis, Indiana United States, (normal value: 2-15

Table 1 Patient characteristics *n* (%)

Variable	Group A	Group B	Group C
N	22	15	20
Male gender	10 (45)	9 (60)	14 (70)
Diabetics	4 (18)	3 (20)	10 (50)
Hypertensives	15 (68)	12 (80)	17 (85)
Median age (yr)	65	71	63
Range	36-83	26-88	33-79
Median time on HD (mo)	12	26	15.5
Range	4-101	9-92	4-55
BMI (Mean ± SD) (kg/m2)	21.3 ± 2.4[b]	27.6 ± 1.4[b]	33.9 ± 4.2[b]
Median MIS	5.5	4	3
Range	1-21	2-8	0-13
Causes of ESRD			
Glomerulonephritis	8	7	11
Diabetes	2	2	3
Nephroangiosclerosis	7	3	4
Obstructive uropathy	1	0	1
Interstitial nephritis	1	1	1
Polycystic kidney disease	3	2	0
Median C-Reactive protein (mg/dL)	1.2	1.1	1.1
Range	0.50-12	0.20-8	0-4.5
Median urinary output (mL/d)	690	660	840
Range	140-1780	160-1800	140-2840
Median initial urinary output (mL/d)	790	800	890
Range	170-1860	180-1970	940-2900
Median albumin (g/dL)	3.70[a]	3.8	3.85[a]
Range	2.2-4.9	3.2-4.4	3.4-4.9

[b]$P = 0.001$, [a]$P = 0.02$. MIS: Malnutrition Inflammatory Score; ESRD: End-stage renal disease; HD: Hemodialysis.

μUI/mL). HOMA was calculated as follows: (Insulin x glycemia)/405. Leptin levels were determined by ELISA, Millipore®, Missouri United States.

Blood samples were obtained in fasting condition prior to the dialysis session. Depending on the dialysis schedule, 24-h urine samples were collected on Sundays or Mondays. All the determinations were performed at the Hospital Británico.

Hemodialysis aspects

High-flux biocompatible membranes were employed in the hemodialysis sessions (Polyflux 21 R®, Gambro, Sweden and Sureflux 190®, Nipro, Japan). Dialysis was performed using bicarbonate bath with a mean blood flow: 450 ± 50 mL/min, and a dialysate flow: 500 mL/min; mean time of the sessions lasted 4.0 ± 0.5 h. The ultrafiltration rate recorded was the one obtained by the automatic dialysis machines (Surdial 190, Nipro® Japan or Diamax, Nipro® Japan) in coincidence with the session when the blood samples were obtained.

Medications

The majority of the patients were receiving aspirin, beta-blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, and other commonly used drugs in HD: Subcutaneous erythropoietin, iv iron, calcium salts, potassium chelators, folic acid, vitamins, iv L-carnitine, statins, proton-pump inhibitors and benzodiazepines.

Statistical analysis

The results are expressed as the median (range), unless explained otherwise. Fisher exact test or Student test were used to determine categoric variables; for continuous variables, Mann-Whitney test was employed; for intervariable correlations Spearman Rank and ρ coefficient were calculated. *P* values $\leqslant 0.05$ were accepted as statistically significant. To compare the different variables with respect to BMI, χ^2 coefficients were calculated and the Kruskal-Wallis test was used.

RESULTS

Groups were not different as to age, gender, time on HD, hematocrit, ultrafiltration rates (UF), inflammation status evaluated by CRP levels and MIS (Table 1). Median glomerular filtration rates (mL/min) were: GA: 10 (r: 7-15), GB: 9 mL/min (r: 8-17), GC: 10 (r: 8-14), mL/min. Although the nutritional status, assessed by MIS, was not different among groups, albumin levels were statistically different between subjects with low BMI compared to those with BMI > 30: GA *vs* GC, 3.70 g/dL (r 2.20-4.90) *vs* 3.85 g/dL (r 3.40-4.90), $P = 0.02$ (Table 1). Urinary outputs measured in ml/day were also different between both groups: GA 690 (r 0-1780) *vs* GC 840 (40-2840), $P = 0.01$ (Table 1). Leptin levels increased significantly from GA to GC and correlated significantly with insulin (Tables 2 and 3). Insulin levels increased positively and significantly with BMI determi-

Table 2 Blood measurements and ultrafiltration rates in all groups

Group	TropT (ng/mL)	UF rates (L)	Pro-BNP (pg/mL)	Insulin (μU/mL)	HOMA	Leptin (ng/mL)
GA	40	2	4970	7.00[a,b]	1.30[c,b]	3.81[b,d]
	(9-1081)	(0.8-4)	(216-234000)	(2-44)	(0.3-22.4)	(0.8-69.6)
GB	48	2.5	2180	11.50[a]	2.50[c]	18.60[d]
	(5-179)	(0.8-4)	(226-102000)	(4-38)	(1.10-9.30)	(4.7-47.40)
GC	41	3	2040	19.50[b]	3.75[b]	32.80[b]
	(4-186)	(0.5-4.0)	(139-166000)	(5.0-155.0)	(1.0-59.3)	(0.78-124.80)

[a]$P = 0.02$; [b]$P = 0.0001$; [c]$P = 0.03$; [d]$P = 0.01$. UF: Ultrafiltration; Pro-BNP: Pro-brain natriuretic peptide.

Table 3 Different correlations in Groups A and C

	GA BMI < 25	GC BMI > 30
VARIABLE	ρ; *P*	ρ; *P*
Insulin-ultrafiltration rate	0.21; 0.44	0.53; 0.03
TroponinT-diuresis	-0.46; 0.07	-0.48; < 0.05
Pro-BNP-diuresis	-0.43; 0.09	-0.39; < 0.01
TroponinT-proBNP	0.44; 0.09	0.77; < 0.0001
Albumin-TropT	-0.04; 0.87	-0.66; < 0.0001
Albumin-proBNP	-0.1; 0.72	-0.44; < 0.05
Leptin-insulin	0.34; 0.26	0.52; < 0.03

Pro-BNP: Pro-brain natriuretic peptide.

nations (μU/mL): GA *vs* GB, 7 (r 2-44) *vs* 11.50 (4-38), $P = 0.02$; GA *vs* GC, 7 (r 2-44) *vs* 19.5 (r 5-155), $P = 0.0001$ (Table 2). With respect to cardiac and hemodynamic biomarkers, TropT and Pro-BNP levels were not different amongst groups (Table 2). However, the following significant correlations were observed, all in high BMI patients: In GC, TropT-diuresis: $\rho = -0.48$, $P < 0.05$; Pro-BNP-diuresis: $\rho = -0.39$, $P < 0.01$; TropT-ProBNP: $\rho = 0.77$, $P < 0.0001$; insulin-UF rate: $\rho = 0.53$, $P = 0.03$; albumin-TropT: $\rho = -0.66$, $P < 0.0001$; albumin-ProBNP: $\rho = -0.44$, $P < 0.05$ (Table 3).

DISCUSSION

In the present study, we observed that subjects with high BMI displayed higher diuresis, albumin, leptin and insulin levels. In this group, higher urinary outputs correlated significantly with lower TropT and Pro-BNP levels. Albumin inversely and significantly correlated with TropT and Pro-BNP. As expected, insulin levels raised accordingly with BMI, but correlated significantly with UF rates only in individuals with high BMI. Besides, all groups were not different according to the time on HD, and initial urinary outputs were similar in the whole cohort (Table 1). Noteworthy, the rates of decline in diuresis were lower in patients with high BMI (6%) in comparison with those from either Groups A (13%) or B (17%).

In the literature, many manuscripts refer to obesity as a variable associated with a better survival in HD subjects[8-11,33]. Many causes have been attributed to explain this phenomenon. It is possible that one variable associated with good prognosis could be remnant dieresis. In the present work, this association occurred independently of the time on HD (Table 1). However, many studies have reported that obese subjects on HD present with low renal residual function[28,29]. In addition, in our study patients with BMI > 30 presented significantly higher albumin levels that correlated with better residual kidney function. This clinical picture of a better oncotic pressure coupled with a preserved diuretic function could lead to a lower vascular stress. Consequently, a smoother hemodynamic scenario would originate. According to our findings, higher albumin levels could not be ascribed to a better nutritional status, as MIS was not different among groups, or to a better inflammatory milieu, as CRP levels were similar in all subjects (Table 1). Noteworthy, residual renal function has been associated with higher albumin levels[25-27]. However, notwithstanding the cause, these higher albumin levels in GC could be exerting a more efficient intravascular oncotic pressure, removing more interstitial water. As a consequence, vessels could be better replenished, being more volume delivered to the kidneys. The result would be a higher urinary output. This hemodynamic situation is also illustrated by the fact that albumin is negatively correlated with TropT and Pro-BNP, two cardiovascular biomarkers that are increased in overfilling states and myocardial stretching[34-39] (Table 3). Although we reported significantly low ProBNP levels in high BMI individuals, we could not demonstrate this phenomenon in the present work[15] (Table 2). It is possible that this smoother hemodynamic setting could explain in part one of the causes of a higher survival rate in high BMI subjects. Finally, it could also contribute to the absence of hypertension in GC, which in the general population is associated with elevated BMI[40,41]. Interestingly, Trop T can increase not only due to vascular causes as myocardial infarction, vascular shear stress, endothelial damage, cardiomyocyte hypertrophy, but also due to muscular wasting in obese subjects on HD[35,36,42,43]. In this regard, TropT is a non-specific marker of cardiovascular origin. Taken together, we propose that in obese subjects on HD, the higher urinary output that patients with high BMI present is correlated with lower TropT and Pro-BNP levels. A better residual renal function could also contribute to lower TropT levels, as this molecule is cleared by the kidneys[35,36,42].

Moreover, an interesting additional factor that could play a role in preserved remnant diuresis in obesity is in-

sulin. As it occurred in one of our previous publications, in subjects with BMI > 30, insulin is again associated with higher UF rates in high BMI patients, albeit UF rates were not different amongst groups[30]. As expected, insulin increased in parallel with BMI, but did not correlate significantly with any other variable except fluid removal and only in high BMI individuals (Table 3). This phenomenon could be related to the ability of insulin to retain salt and water[44]. In turn, this fluid retention would be the trigger for a pressure-diuresis phenomenon and a maintained urinary output, probably potentiated by higher albumin levels. This increase in insulin could also reflect an insulin-resistant state in high BMI patients, which is inherent to obese individuals[44,45]. In addition, in our study high BMI was associated with lower Pro-BNP levels, which is in agreement with other publications that report the association between hyperinsulinemia and low Pro-BNP patients in obesity[15,45-47].

In our study, leptin is significantly high in GC, where its correlation with insulin is positive and significant. Recently, insulin has been reported to upregulate leptin gene expression. With respect to leptin sodium and water handling, the results are controversial. While some studies have shown leptin presents natriuretic effects, many others have reported its association with water and salt retention, sympathetic nervous system activation and hypertension, which could add to insulin hemodynamic effects[32,48]. With respect to the cardiovascular system, leptin (as insulin) is involved in the pathogenesis of myocyte hypertrophy[32,48].

Finally, the obesity paradox in hemodialysis has always been related to an elevated weight and assumed to be due to fat. However, BMI correlates with body fatness or density[49], but in these studies and in our present manuscript, the increase in body weight has not been discriminated in tissue compartments. An elevated BMI could be due to an increase in fat, water, bone density and/or muscle mass[50]. Therefore, increased body weight, particularly in end-stage kidney disease patients, is not a synonymous of obesity. Moreover, assuming overweight dialysis patients as obese, may be a misleading statement. We assume our GC subjects as obese due to high leptin and insulin levels and an elevated HOMA index, a characteristic profile encountered in obesity (Table 2).

Our manuscript contains several pitfalls. It is a cross-sectional study including a limited number of patients. Our findings must be interpreted with caution, as it joins previous studies with respect to the evaluation of body tissue and fluid composition and distribution. We call the attention of future authors to make the appropriate distinction when overweight patients are studied in the dialysis setting. Obesity is not a synonymous of high BMI in renal failure. Water retention and muscle wasting are to be addressed. Finally, these variables can operate simultaneously in these individuals. In this regard, bioimpedancy studies are mandatory. It is possible that whether this issue is taken into account, the obesity paradox in hemodialysis may not be such. In this regard, residual renal function would be more related to fluid overload and a pressure-diuresis forced situation.

In conclusion, our study shows that high BMI HD patients display higher diuresis rates, albumin and insulin levels. This higher urinary output dialysis individuals with BMI > 30 present, may reflect water retention, in part due to hyperinsulinemia, hyperleptinemia and secondary higher UF rates. The ability to excrete water correlates negatively and significantly with TropT and Pro-BNP levels, which would reflect a lower myocardial and vascular stress and a better hemodynamic status. Whether these events are associated with a better survival rate in HD should be appropriately assessed.

COMMENTS

Background

Cardiovascular disease is the most important cause of mortality in dialysis, while residual diuresis and increased body mass index (BMI) are associated with better survival. The authors studied residual diuresis and diverse variables according to BMI.

Research frontiers

To be able to discern between BMI and fluid retention in dialysis patients. Residual diuresis may be an important in outcome in these subjects, and high BMI subjects may display higher dieresis rates, lowering cardiovascular stress.

Innovations and breakthroughs

High BMI hemodialysis patients display higher diuresis rates, albumin and insulin levels. This higher urinary output dialysis individuals with BMI > 30 present, may reflect water retention, in part due to hyperinsulinemia, hyperleptinemia and secondary higher ultrafiltration rates rates. The ability to excrete water correlates negatively and significantly with TropT and Pro-BNP levels, which would reflect a lower myocardial and vascular stress and a better hemodynamic status.

Applications

In the every-day assessment of dialysis subjects, this paper suggests that obesity may not always be the reflection of a fat tissue, but the fluid overload must be taken into account. This water retention may explain the residual renal function this group may display, in relation with the pressure-diuresis phenomenon.

Terminology

The obesity paradox in dialysis states that this cohort of patients do better than other groups with lower BMIs. This is in contradiction with what occurs in the general population. The authors state that an elevated BMI may not always be a mere reflection of a higher fat tissue mass, but to an accumulation of water. The residual renal function displayed by these subjects may be due to a pressure-diuresis phenomenon.

Peer review

The present study aimed to investigate the associations between several cardiac and metabolic biomarkers as well as residual diuresis with BMI in chronic dialysis patients. The study is interesting and it could be published provided that the discussion should be re-written taking into account that some differences between groups.

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