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AIM AND SCOPE

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REVIEW

Extracellular vesicles as mediators of vascular inflammation in kidney disease

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Abstract

Vascular inflammation is a common cause of renal impairment and a major cause of morbidity and mortality of patients with kidney disease. Current studies consistently show an increase of extracellular vesicles (EVs) in acute vasculitis and in patients with atherosclerosis. Recent research has elucidated mechanisms that mediate vascular wall leukocyte accumulation and differentiation. This review addresses the role of EVs in this process. Part one of this review addresses functional roles of EVs in renal vasculitis. Most published data address anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis and indicate that the number of EVs, mostly of platelet origin, is increased in active disease. EVs generated from neutrophils by activation by ANCA can contribute to vessel damage. While EVs are also elevated in other types of autoimmune vasculitis with renal involvement such as systemic lupus erythematodes, functional consequences beyond intravascular thrombosis remain to be established. In typical hemolytic uremic syndrome secondary to infection with shiga toxin producing *Escherichia coli*, EV numbers are elevated and contribute to toxin distribution into the vascular wall. Part two addresses mechanisms how EVs modulate vascular inflammation in atherosclerosis, a process that is aggravated in uremia. Elevated numbers of circulating endothelial EVs were associated with atherosclerotic complications in a number of studies in patients with and without kidney disease. Uremic endothelial EVs are defective in induction of vascular relaxation. Neutrophil adhesion and transmigration and intravascular thrombus formation are critically modulated by EVs, a process that is amenable to therapeutic interventions. EVs can enhance monocyte adhesion to the endothelium and modulate macrophage differentiation and cytokine production with major influence on the local inflammatory milieu in the plaque. They significantly influence lipid phagocytosis and antigen presentation by mononuclear phagocytes. Finally, platelet, erythrocyte and monocyte EVs cooperate in shaping adaptive T cell immunity. Future research is needed to define changes in uremic EVs and their differential effects on inflammatory leukocytes in the vessel wall.

Key words: Extracellular vesicle; Atherosclerosis; Kidney disease; Glomerulonephritis; Macrophage

Core tip: This review addresses the role of extracellular vesicles (EVs) in vascular inflammation that can cause renal damage and is also shaped by uremic mediators. Vasculitides are common causes of renal damage. Functionally, neutrophil EVs induced by anti-neutrophil cytoplasmic antibody contribute to endothelial damage. EVs are main distributors of shiga toxin in the circulation and into tissues in typical hemolytic uremic syndrome. In atherosclerosis in patients with and without kidney disease, endothelial EVs are elevated. Uremic EVs are deficient in mediating vascular relaxation. EVs modulate mononuclear phagocyte differentiation, cytokine production, lipid phagocytosis and antigen presentation, atherosclerotic inflammatory processes significantly altered in uremia.

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INTRODUCTION

Subcellular membrane vesicles collectively termed extracellular vesicles (EVs) are a third pathway of intercellular communication between direct cell-to-cell contact and secretion of soluble signaling molecules[1]. EVs can be secreted by virtually all cell types and contain a variety of components[2,3]. They are already present under physiologic conditions in a variety of bodily fluids[4]. EVs critically modulate local and systemic inflammatory and immune processes[4-7]. How EVs affect leukocytes and their function in the arterial wall in patients with kidney disease will be discussed for both acute vasculitis and chronic vascular inflammation in atherosclerosis.

LEUKOCYTES IN THE VASCULAR WALL

Leukocytes are an integral part of the healthy vessel[8,9] and differentially increase in vascular inflammation[10]. The arterial wall is invaded by blood leukocytes in inflammation both directly across the main vascular endothelium and through vasa vasorum of larger vessels. This process is a tightly regulated cascade of leukocyte activation, rolling, adhesion and transmigration, to date studied mostly in neutrophilic granulocytes[11-13]. Vascular inflammation is mostly found in the arterial tree and microvessels including glomerular capillaries. Inflammation of the much thinner venous wall is rarely a clinical problem beyond reaction to intravascular thrombosis[10]. This is remarkable as most endothelial leukocyte adhesion and transendothelial migration is observed in venules[14]. Vascular inflammation is central in allo-immune processes such as transplant rejection. These have recently been reviewed (among others[15,16]). This review focuses on native arteries and glomerular capillaries.

Impaired renal function during both acute kidney injury and chronic kidney disease significantly influences the structure of the arterial wall, affecting arterial endothelial cells and smooth muscle cells[17,18]. Structural changes are most obvious in enhanced atherosclerosis development[19-21]. A prominent feature in humans and mouse models with end stage kidney disease is extraosseous calcification of the arterial media[19,22]. Chronic inflammation in atherosclerosis occurs in normal and reduced kidney function, however, both innate and adaptive leukocytes are specifically altered by renal impairment[23-25].

CHARACTERIZATION OF EVS

Since the first description of "platelet-dust" in 1967[26], EVs were found in diverse biological fluids[27]. Important factors of EV characterization are size and surface markers indicating their cellular origin[5,28-30]. EVs are a very heterogeneous population as both characteristics additionally vary with mode of EV generation[31]. In addition, most of the currently used flow cytometry instruments are not optimal for detection of particles of submicrometer size[32,33]. Organizations such as the Society for Extracellular Vesicles, formed in 2011, and databases such as EVpedia (http://evpedia.org) are instrumental in establishing reliable standards, including specification of preanalytical procedures and basic clinical information[4,27,34].

Currently, two main groups of EVs are distinguished by both size and mode of generation: Exosomes and microparticles[1,3,28,29] (Figure 1). Exosomes are small EVs, ranging from 30-100 nm. They originate from endosome-derived multivesicular bodies and are released to the extracellular space when the multivesicular bodies fuse with the plasma membrane[35,36]. Microparticles (also referred to as ectosomes, membrane vesicles, nanovesicles and shedding vesicles) measure 100-1000 nm[3,30,35,37]. They directly bud off from the plasma membrane[35,36]. Both types of vesicles are enclosed by a lipid bilayer, but due to the fact that microparticles directly bud from the plasma membrane, they have a more similar membrane composition to their parent cell than exosomes[28,35]. For example, leukocyte surface proteins such as CD14, CD36 and CD11c are found on leukocyte microparticles[38]. Phosphatidylserine was initially thought to be enriched on microparticles only, but was later also found on exosomes[3]. Exosomes display endosome-associated proteins like annexins, flotillins or CD63 on their surface[28]. However, the expression of these proteins on microparticles cannot be completely excluded[3]. In addition to a possible biological overlap, this also reflects the technical challenge of multicolor fluorescence analysis of small particles[32,33]. Principal intravesicular contents such as cytoplasmic proteins, metabolites, RNAs, microRNAs and lipids can be found in both, exosomes and microparticles, however, in different abundance[2,3,35]. In addition to exosomes and microparticles, apoptotic bodies have been described as a separate entity by some authors[35,36,39]. These have been defined as large (1-5 μm) vesicles

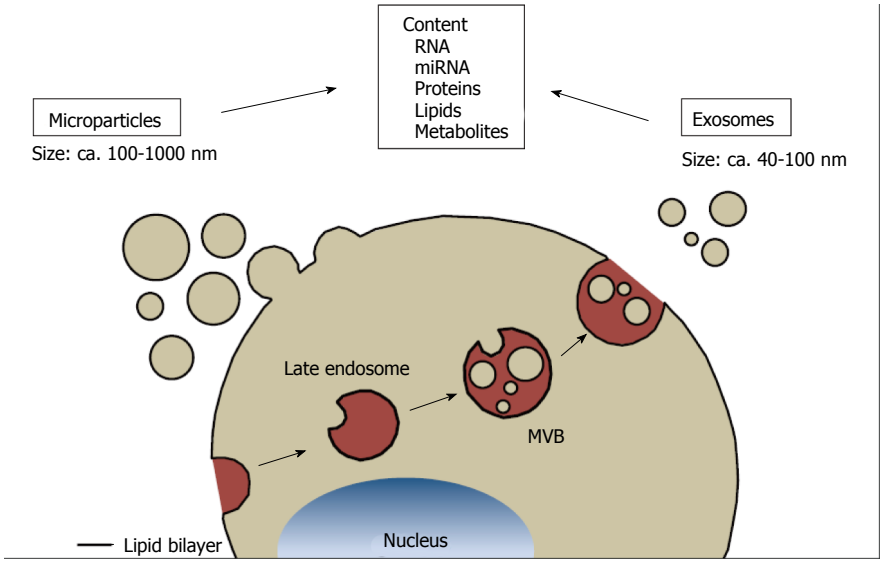

Figure 1 Classification of extracellular vesicles. Types of extracellular vesicles are distinguished by their mode of generation. Microparticles directly bud off the plasma membrane and measure approximately 100-1000 nm. Exosomes are released by fusion of multivesicular bodies with the plasma membrane and their sizes range between 40-100 nm. Both types of extracellular vesicles can contain RNA, microRNA, proteins, lipids and metabolites. MVBs: Multivesicular bodies.

generated during apoptosis. However, other EVs also express the inner membrane marker Annexin V on their surface.

Following current recommendations[29], the overarching term EV will be used for all secreted vesicles in this review and further characterization will be provided by naming specific surface markers.

EVS IN CHRONIC KIDNEY DISEASE

In end stage renal disease, both the uremic milieu and hemodynamic changes during the dialysis procedure can contribute to EV generation[40]. Uremic toxins such as p-cresol and enoxylsulfate induced EV shedding from HUVECs[41]. Hemoconcentration by dialysis increased blood viscosity, thereby decreasing shear stress and EV generation[42]. In addition, morphologically similar EVs may serve different functions is generated in an uremic milieu - for example, EVs from healthy controls, but not patients with end stage renal disease conferred endothelium mediated arterial relaxation *in vitro*[43].

Counts and provenience of circulating EVs have been characterized in patients with chronic renal impairment with and without renal replacement therapy. Some studies found elevated serum concentrations of total and $CD42^+$ platelet EV[44-46], total, endothelial ($CD31^+$, $CD114^+$)[43,46], platelet ($CD41^+$), and erythrocyte ($CD235^+$) EVs[43] in patients with end stage renal disease, while in others, total plasma EV concentrations were unaltered[47,48] or only endothelial EVs were increased[41]. Also, the effect of the hemodialysis procedure is controversial with an increase in some[47] but not other studies[44,45]. The currently available studies included relatively small patient numbers and discrepancies that are at least partly explained by pre-analytical variables such as different modes of blood draw, storage and anticoagulation, flow cytometry equipment and surface markers used. However, addressing a possible pathophysiologic cause, a recent study further stratified patients with moderate kidney disease (mean GFR 39 mL/min) according to the presence of cardiovascular disease defined by significant stenosis on coronary angiography[49]. EVs of both platelet ($CD42^+$) and endothelial ($CD31^+$) origin were significantly higher in patients with coronary artery disease, irrespective of renal impairment. Indeed, a large number of observational studies report increased concentrations of circulating EVs in atherosclerosis[50-53]. Especially endothelial EV concentrations appear to be predictive for cardiovascular prognosis[54]. This was confirmed in a recent observation in a large group of 844 individuals from the Framingham offspring cohort. Endothelial EV counts ($CD31^+$ or $CD114^+$) correlated with hypertension, elevated triglycerides the metabolic syndrome and an overall higher Framingham in patients inversely correlated with brachial artery flow-induced dilatation and positively correlated with indices of arterial stiffening[43]. Endothelial ($CD31^+$) EV concentration was associated with severe hypertension in a number of cohorts[55,56]. Concentrations significantly correlated with renal damage manifesting as micro- or macro-albuminuria in this condition[57].

The currently available data is also limited by a mostly cross-sectional study design that precludes detection of temporal changes in single patients[52]. Measurement of EV concentration is evaluated as a predictive factor in a number of ongoing prospective trials[58]. However, there are some longitudinal data for patients with end stage kidney disease. A follow up study of 81 hemodialysis patients for a mean of 50 mo revealed that endothelial ($CD31^+$) EV concentration in serum obtained after the long interval was a significant predictor of all cause and cardiovascular mortality, an association that was not observed for $CD41^+$ platelet, $CD11b^+$ leukocyte or $CD235^+$ erythrocyte EVs[59]. Another prospective study investigated endothelial EV counts ($CD31^+$) in a cohort of 227 patients with end stage renal disease who were scheduled for kidney transplantation[48]. Endothelial EVs significantly decreased during 60 d of longitudinal follow up after kidney transplantation. However, they did not differ from

healthy controls at start of the trial[48] which may reflect that these patients represent a subgroup with relatively few co-morbidities.

In summary, chronic elevation of endothelial EVs currently appears to be significantly associated with vascular dysfunction and atherosclerosis in renal disease.

THE ROLE OF EV IN RENAL VASCULITIS

Systemic inflammation is frequently associated with elevated EV concentrations. Pathophysiologically, monocytic and endothelial EVs can directly induce MCP1, interleukin (IL)-6 and VEGF production in human podocytes[60] thus enhancing glomerular injury. Investigations of EVs in systemic lupus erythematodes (SLE), ANCA vasculitis and typical hemolytic uremic syndrome (HUS) will be reviewed. It is also of note that our literature review revealed no information on EVs in either the pathogenesis or regarding the circulating EV counts in other common forms of renal vasculitis, including postinfectious glomerulonephritis, a historically common cause of renal vascular inflammation, and IgA nephropathy as the currently most common entity in the Western world.

RHEUMATIC DISEASE WITH RENAL INVOLVEMENT

EVs function has been studied in systemic rheumatic disease[61,62]. In SLE, a common rheumatic cause of glomerulonephritis, elevated levels of EVs, particularly of platelet origin, have consistently been detected in patients with active antiphospholipid syndrome[63-66], and also in Sjögrens syndrome[64] and closely been associated to intravascular thrombosis. Mechanisms of modification of inflammation of the vascular wall by EVs in SLE have not been reported to date. However, EVs in SLE display increased amounts of immunoglobulin and complement[67] and it is conceivable that they may contribute to deposition of these in the renal glomerulum. Furthermore, the proteome of these EVs in SLE appears to differ from healthy controls[68] and EVs constituents in SLE such as Galectin 3 binding protein have also been detected in glomerular deposits in individual patients with lupus-associated glomerulonephritis[69].

ANCA ASSOCIATED VASCULITIS

In anti-neutrophil-cytoplasmic antibody (ANCA) associated vasculitis, a number of studies have shown elevated serum EV concentrations during active disease[47,70-72]. Counts reverted normal during remission. In addition, counts were significantly higher than in patients with other glomerulonephritides such as IgA nephropathy, minimal change disease, diabetic nephropathy but also lupus nephropathy[47,71]. Most EVs in ANCA disease were of platelet origin, but leukocyte and endothelial derived EVs were also found[47,70-73]. Histologically, ANCA vasculitis presents as acute necrotizing vasculitis not only of the glomeruli, but arteries of all sizes with predilection of small vessels[74]. The most prominent infiltrating cell types are neutrophilic granulocytes and even more abundantly, monocytes[75]. However, most research on leukocyte function within the vascular wall has concentrated on neutrophils. ANCA can induce generation of EVs from pre-activated, *e.g.*, tumor necrosis factor (TNF)α primed neutrophils[72,76,77]. These particles increased CD54 surface expression and IL-6 and IL-8 production from human vein endothelial cells (HUVECs) *in vitro*, suggesting that they can promote inflammation of the vessel wall[72]. ANCA induced EVs also contained tissue factor and may thus promote hypercoagulability and the increased rates of thrombosis observed in patients with ANCA disease[76,77].

TYPICAL HUS

Typical HUS is a complication of enteral infection with shiga toxin producing strains of *Escherichia coli* (STEC). EVs are highly elevated in patients with active systemic disease and platelet EV attach to leukocytes, most abundantly monocytes in peripheral blood[78-80]. Recent research shows that EVs are also generated from erythrocytes in this condition[81], a type of EV that can activate monocytes to produce pro-inflammatory cytokines[82]. Platelet monocyte complexes and EV generation from both can be induced by shiga toxin. These EVs contain tissue factor and can thereby contribute to the microthromboses characteristic of the disease[80]. They also bore activated complement constituents, namely C3 and C9[78]. Neutrophils phagocytosed them, a process that may further contribute to their activation, adhesion and vascular inflammation[78]. Both leukocyte and platelet EVs contain shiga toxin and significantly contribute to its spreading into tissues including podocytes and tubular epithelium in the kidney[83] thus contributing to toxicity. Whether or not shiga toxin increases or diminishes leukocyte lifespan appears to depend on experimental conditions *in vitro*[84]. *In vivo*, increased rates of both monocyte and neutrophil cell death were observed during STEC-HUS[79]. It is conceivable that shiga toxin transferred into the vascular wall by EVs will also influence vascular resident leukocytes[83].

THE ROLE OF EVS IN VASCULAR INFLAMMATION IN ATHEROSCLEROSIS

EVs are abundant within the atherosclerotic wall which may enhance their biologic functions[6]. EVs from human endarterectomy specimens have been isolated by serial centrifugation and analyzed by flow cytometry in comparison to material from macroscopically unaffected arteries[85,86]. A detailed analysis determined that most plaque EVs are of leukocyte origin, including 29% macrophage ($CD14^+$), 15% lymphocyte ($CD4^+$), 8% granulocyte ($CD66b^+$) provenience[86]. No platelet, but erythrocyte and smooth muscle cell markers were detected in EVs from the plaque lysate, recent *in vitro* data providing first evidence of EV generation from smooth muscle cells in

contact with pro-atherogenic lipids[87]. The analysis of plaque EV provenience was confirmed by subsequent studies including proteome analysis[38,88].

Mechanistic roles of EV action in atherosclerotic inflammation have mostly been ascribed to their protein content[50,51] including large cytoplasmic protein structures such as proteasomes and inflammasomes[89,90]. In addition, other constituents such as nucleic acids, notably microRNA[91,92], glycosylation pattern[93] and lipids[94] critically contribute to EV function in atherosclerosis[6,90,91]. Elevated systemic lipid levels and local deposition in the plaque makes EV lipids likely candidates for modulation of plaque development[95]. High levels of free cholesterol induce generation of phosphatidylserine and tissue factor rich EVs from human monocyte-derived macrophages, partly induced by caspase-3 mediated apoptosis. Systemically, circulating EV concentrations, mostly of platelet origin ($CD41^+$) were significantly decreased after lipid apheresis in humans[96]. In renal impairment, lipoprotein function is markedly changed and protective functions are lost[97,98] making it a possible mediator of the observed functional shift in uremic EVs.

Patients with chronic kidney disease from any cause are at a markedly elevated risk of cardiovascular morbidity and mortality[97,99-101]. Medial calcification is characteristic of end-stage kidney disease[99,100]. Atherosclerotic plaques in moderate renal impairment are mostly found in the arterial intima and are histologically similar to lesions in normal renal function[102], a phenotype that has been replicated in animal models of atherosclerosis[103,104]. Given the high prevalence of cardiovascular disease already in the general population, the role of inflammatory leukocytes in atherosclerotic plaque development has been explored in human samples and atherosclerotic animal models with a variety of methods including histology, flow cytometry and live cell imaging[105-107]. Numbers of both adaptive and innate leukocytes in the vessel wall markedly increase during atherogenesis. With specific regards to renal impairment, current data on EV effects on innate and adaptive leukocyte populations prominent in atherosclerotic lesion formation will be reviewed.

THE ROLE OF EVS IN LEUKOCYTE INTERACTION WITH THE ENDOTHELIUM

When entering the vascular wall and again with growing intimal plaques, leukocytes come into close contact with endothelial cells. As a possible mechanism of proatherogenic EV effects on endothelial cells, CD40 ligand on human carotid plaque EVs is required for endothelial cell activation and neoangiogenesis by promotion of endothelial cell proliferation[88]. EVs isolated from human atherosclerotic plaques can transfer ICAM-1 to endothelial cells, thus facilitating leukocyte, mainly monocyte adhesion and transmigration[108]. They also expressed TNFα converting enzyme and plaque EVs that increase shedding of both TNFα and activated protein C from activated HUVECs[109]. The fact that monocyte and T cell EVs induced matrix metalloproteinase in synovial fibrocytes in rheumatoid arthritis suggests that this is a general EV property[110]. Neutrophil EVs increased endothelial cell IL-6 release *in vitro*[111]. T cell EVs generated both in *in vitro* and *in vivo* and EVs from patients with myocardial infarction decreased flow induced endothelial relaxation and downregulate eNOS expression[112,113]. As a potential positive feedback loop, NOS inhibition induces L-selectin and PSGL-1 expressing EVs from neutrophilic granulocytes seeded to HUVECs *in vitro*, that in turn increasing neutrophil transmigration[114]. Given NO inhibition by a range of uremic toxins[115], it is conceivable that these processes cooperate in renal impairment to impair vascular function.

Circulating EV counts are highly elevated during acute arterial thrombosis in a large number of studies. These have recently been reviewed and will therefore only been referred to in relation to vascular leukocytes in this manuscript[116-119]. However, it is of note that EV phosphatidylserine surface expression as a pro-thrombotic mediator was significantly increased in patients with the nephrotic syndrome of different etiologies[120] and the *in vitro* pro-coagulant effect of EVs from both hemodialysis and peritoneal dialysis patients was enhanced[46].

GRANULOCYTES

Neutrophilic granulocyte concentrations in peripheral blood and even more so, the neutrophil/lymphocyte ratio, are well-documented predictors of cardiovascular mortality[121,122]. This relationship is also highly significant in patients with end stage renal disease[123]. Recent animal data suggest that neutrophils mechanistically promote hypertension associated vascular damage and endothelial dysfunction[124]. Neutrophils are essential in early atherosclerotic plaque development, probably by NET formation[125]. They also generate a variety of EVs with pro- and anti-inflammatory functions[111,126-128]. Acting directly on the parental cell type, Annexin A1 present in neutrophil EVs inhibits neutrophil rolling, adhesion and migration in mice[126]. Neutrophil extravasation is promoted by close neutrophil contact with platelets and platelet EVs[12,13] (Figure 2). Both platelets and neutrophils generate long tethers during adhesion, some of which remain as free vesicles in the environment[129,130]. The essential role of platelet particles for directed neutrophil migration through the vessel wall is under active *in vivo* investigation by advancing imaging techniques[11-13,131,132]. Thrombus formation after plaque rupture directly activates neutrophils[133], a process that continues to be mechanistically explored in experimental arterial lesions[134]. Antagonizing either glycoprotein Ⅰb or ⅡbⅢA on platelet EV inhibited neutrophil activation[135,136]. This may be relevant beyond acute thrombosis, as enhanced platelet activation by junctional adhesion molecule A deficiency[137] increased while deletion of glycoprotein Ib decreased myeloid cell activation and atherosclerotic lesion size[138]. These data suggest that platelet and platelet EV interactions with granulocytes promote also chronic

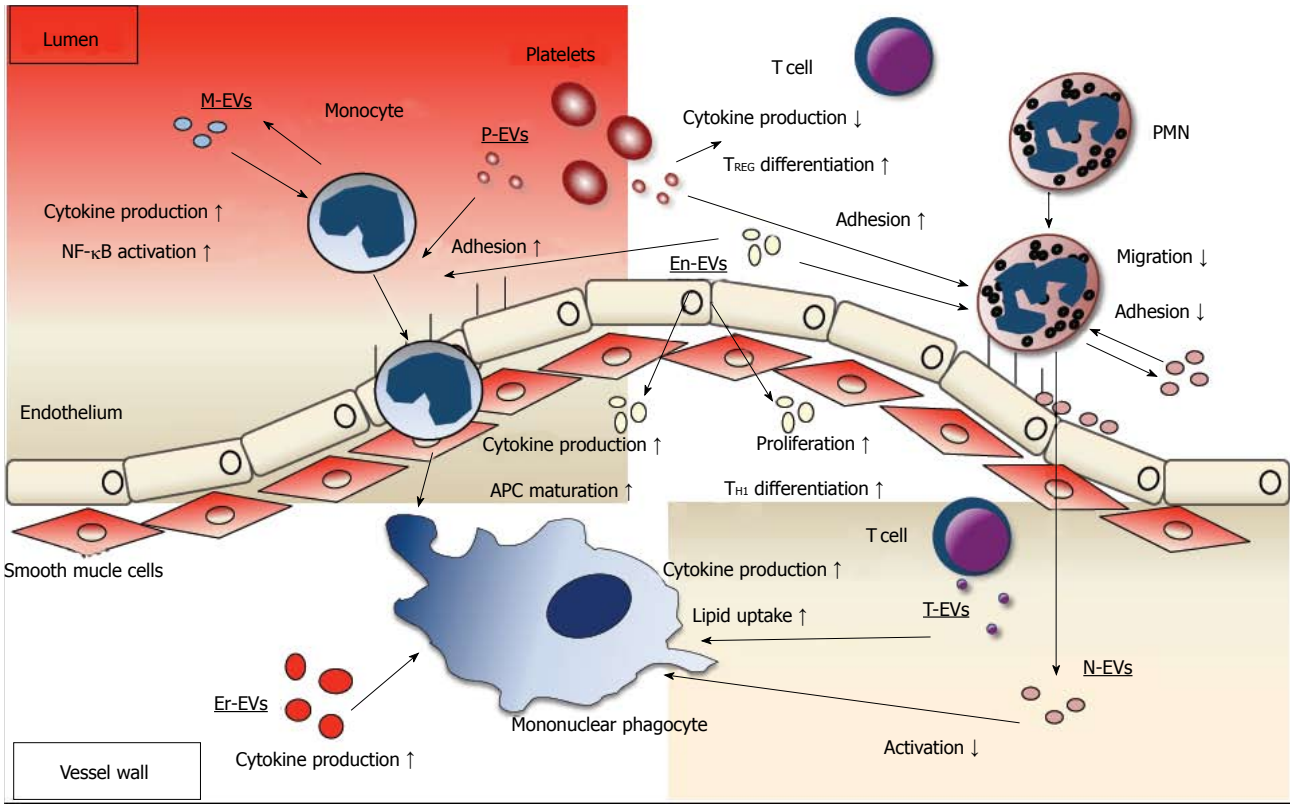

Figure 2 Roles of extracellular vesicles in leukocyte function in the atherosclerotic plaque. Data on interaction of EVs with neutrophilic granulocytes, monocytes and mononuclear phagocytes and T lymphocytes is summarized. Regarding neutrophilic granuloctes (PMN), platelet EVs (P-EV) promote neutrophil (PMN) adhesion to the endothelium, neutrophil EVs (N-EV) mostly decrease adhesion and migration through the endothelium. Regarding monocytic cells, endothelial (En-EV) and P-EVs promote adhesion to the endothelium. Inside the plaque, En-EVs promote antigen presenting cell (APC) maturation and cytokine production and erythrocyte EVs (Er-EVs), monocyte EVs (M-EVs) and T cell EVs (T-EVs) increase cytokine production. T-EVs also increase lipid uptake. N-EVs suppress activation. Regarding T cells, P-EVs decrease cytokine production, En-EVs promote T cell proliferation and TH1 differentiation. EVs: Extracellular vesicles.

atherosclerosis, in the absence of plaque rupture or thrombosis.

MONOCYTES AND MONONUCLEAR PHAGOCYTES

Myeloid phagocytes are central in atherosclerotic plaque development. They have a dual role with lipid uptake on the one hand, resulting in foam cell formation that can lead to cell death and thereby necrotic plaque cores and antigen presentation to cells of the adaptive system on the other hand[139-143]. In atherosclerosis enhanced by renal impairment, lesional macrophage content increased[104,144]. Angiotensin receptor I on myeloid cells[144-146] and IL-17[104] are instrumental in mediating this phenotype. Myeloid derived phagocytes in the atherosclerotic plaques differentiate from immigrating monocytes, but also proliferate locally, especially in mature plaques in which they are subject to the local milieu[147]. Both processes are influenced by EVs (Figure 2).

Monocyte adhesion to the endothelium *in vitro* was enhanced platelet EVs, induced by storage, thrombin or shear stress[148-150]. Platelet EVs also increased monocyte surface expression of adhesion molecules such as CD11a, CD11b integrins, platelet adhesion molecule 1 (CD31), CD33 lectin, and receptors such as CD14 and CD32 Fc receptor[148-150]. Endothelial EVs elicited by oxidized LDL or homocysteine from rat arterial endothelial cells contained high levels of heat shock protein 70 (HSP70) that increased monocyte adhesion *in vitro*[151]. *In vivo* in murine atherosclerosis, RANTES from platelet EVs coated the endothelium resulting in enhance monocyte adhesion[152].

Macrophage phenotype has a decisive role in plaque growth and stability of the lesion. In renal impairment, histologic analysis of the plaque showed that markers of M1 macrophage polarization were up-regulated with corresponding down-regulation of M2 markers[153]. Erythrocyte EVs that are found atherosclerotic plaques[86] induced TNFα production in monocytes in a CD40 ligand dependent fashion[82]. Platelet EVs induced secretion of cytokines that promote atherosclerotic plaque formation such as TNFα, IL-1β and IL-8 in a monocytic cell line *in vitro*[149]. IL-1β that is central atherogenesis[154] is itself contained in EVs released from platelets[155,156] and myeloid phagocytes[157-159]. However, cytokine induction by platelet EVs is not universal as small platelet EVs inhibited human monocyte-derived phagocyte TNFα and IL-10 secretion while TGFβ production was enhanced[160]. Human granulocyte EVs increased macrophage TGFβ1, but not IL-6 or IL-8 expression and blocked pro-inflammatory responses induced by zymosan or LPS. The authors

also noted large donor variations in response to EVs suggesting that genetic factors may have a significant influence[127]. Annexin 1 is a potential mediator of the anti-inflammatory effects of granulocyte EVs[126]. Autocrine effects of monocytic EVs on monocyte differentiation and cytokine production varied with cell culture conditions. phorbol-12-myristate 13-acetate (PMA) elicited EVs from THP1 cells induced cell cycle arrest and macrophage differentiation TGFβ1 dependently[161] while human monocyte EVs increased TNFα and IL-6, release reactive oxygen species production and induced nuclear factor (NF)-κb activation[162]. Interestingly, NO, a pathway that is significantly inhibited in uremia, markedly enhanced EV release from RAW264 macrophages *in vitro*[163]. T lymphocyte EVs induced in both peripheral blood T lymphocytes and a human T cell line by phytohemagglutinin (PHA) and PMA increased TNFα, IL-1β and soluble IL-1 receptor a production in monocytes in a dose-dependent manner. This was not observed for EVs from unstimulated T cells[164,165]. Both TNFα and IL-1β generation were inhibited by HDL, connecting these studies directly to regulation of inflammation in the atherosclerotic plaque.

Regarding lipid phagocytosis, lipid and cholesterol content in peritoneal macrophages from atherosclerotic mice with renal impairment was significantly higher than in control animals[166] and the ability to take up labeled exogenous oxidized LDL particles significantly impaired in aortic macrophages[104]. This was attributed to decreased cholesterol efflux, mediated by decreased expression of the transporter ABCA1[166]. Platelet EVs increased uptake of oxidized LDL if present during macrophage differentiation *in vitro*. This protocol also increased CD14, CD36 and CD68 surface receptor expression[150]. In contrast, small platelet EVs with less than 50 nm diameter decreased lipid uptake *via* reduction of CD36 surface expression by enhanced ubiquitination[167] T lymphocyte EVs from PHA-activated human T lymphocytes increased cholesterol uptake in THP-1 cell and human monocyte derived macrophages[168].

Regarding antigen presentation, expression of the antigen presenting cell marker CD11c significantly increased in atherosclerotic aortas of mice with renal impairment[104]. T cell proliferation was significantly higher in their then aortas of atherosclerotic control mice. In addition, life cell imaging demonstrated that aortic T cell interactions with $CD11c^+$ cells were significantly more frequent and longer in vessels from mice with renal impairment[104]. There is a large body of evidence for a role of EVs in antigen presenting cell function[6]. While many studies focused on tumor antigens, some may be directly relevant to atherosclerosis. Endothelial EVs from a human microvascular cell line induced by TNFα enhanced antigen presenting cell maturation, indicated by morphologic maturation, up-regulation of HLA-DR, CD83 and CCR7 and IL-6 secretion in a cell line and human plasmacytoid dendritic cell, but not in myeloid cells. While the stimulated cells were capable of inducing mixed lymphocyte reaction, interferon γ (IFNγ) was not induced by the co-incubation. Platelet and T cell EVs were used as controls and did not elicit this response[169]. Erythrocyte EVs enhanced T cell proliferation by modulation of monocyte maturation and induction of TNFα[82]. In a somewhat different setting, platelet EV recovered from thrombin-activated platelet supernatants induced HLA-DR expression in immature DCs during differentiation from human PBMC. This was mediated by CD40L[170], a protein that has been detected on human carotid plaque EVs[88]. Small EVs from resting platelets exerted a contrary effect and decreased HLA-DP, DQ, DR and CD80 expression during human PBMC differentiation[160]. While CD14 expression decreased similar to control cells, platelet EV also decreased endocytic capacity. Neutrophil EVs decreased immature dendritic cell phagocytic capacity and increased TGFβ release. Furthermore, LPS mediated maturation was severely impaired including surface marker expression, cytokine production and induction of T cell proliferation[171] extending the protective neutrophil effect from endothelium to monocyte derived phagocytes.

In summary, EVs of different cellular origins modulate mononuclear phagocyte functions that promote atherosclerosis in renal impairment.

LYMPHOCYTES

T cells are major modifiers of plaque formation among adaptive immune cells while the role for B cells is controversial[105-107]. B cell interaction with EVs can enhance or diminish B cell function[172,173], however, a link to atherosclerosis remains to be defined.

Among T helper cells, IFNγ-producing T_{H1} cells strongly promote atherosclerotic lesion formation. In the current experimental models, there appears to be no major role for T_{H2} cells in atherogenesis, while regulatory T cells and their marker cytokines such as IL-10 can attenuate lesion formation[105-107]. The impact of T_{H17} cells and their marker cytokine IL-17, which has a significant role in attraction of innate leukocytes such as neutrophilic granulocytes and monocytes[174], appears to be highly context-dependent[10,175]. Recent data show that proatherogenic lipoproteins can enhance T_{H17} polarization[176]. IL-17 production in T cells is markedly enhanced by environmental chemicals *via* the aryl hydrocarbon receptor[177-180]. Its ligands are well known uremic toxins[181,182]. Indeed, the IL-17 production was significantly increased in a cohort of patients with end stage renal disease[183]. Mechanistically, IL-17 was instrumental in increased myeloid cell accumulation and lesion burden in moderate renal impairment[104].

The effect of EVs on T cell function *in vitro* significantly varies depending on the cell of origin (Figure 2). Endothelial EVs enhanced $CD4^+$ T cell proliferation in mixed lymphocyte reaction *via* modulation of dendritic cell maturation, resulting in enhanced TNFα and IFNγ secretion[169]. Similarly, EVs from TNFα-stimulated HUVECs induced T_{H1} differentiation in human PBMCs[184]. Erythrocyte EVs induced T cell proliferation indirectly *via* monocyte derived antigen presenting cell polarization. This stimulated the production of the pro-atherogenic cytokines IL-1β, IL-2,

IL-7, IL-17 and IFNγ during co-culture of human PBMCs[82]. In contrast, small platelet EVs directly interacted with $CD4^+$ T cells. They decreased IFNγ, TNFα and IL-6 production during polarization[185]. This was at least in part due to an increase in regulatory T cells induced by EV TGFβ. EVs from antigen presenting cells promote T cell priming[186,187]. In atherosclerosis, plasma and plaque EVs contain MHC Ⅰ, MHCⅡ and CD40L as EV surface antigens and it is therefore conceivable that these processes are also active during atherosclerosis *in vivo*[38,88].

CONCLUSION

Data on mechanisms how EVs modulate leukocyte adhesion, differentiation and vascular function in inflammation have greatly enhanced our understanding of these pathophysiologic processes. Experimental results suggest a number of mechanisms that enhance EV generation and modulate their function in renal patients. While analytic tools continue to be optimized and therapeutic options are limited to inhibition of platelet EVs at this point, EV counts start to serve as activity and prognostic markers in different conditions.

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REVIEW

Major comorbid disease processes associated with increased incidence of acute kidney injury

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Abstract

Acute kidney injury (AKI) is commonly seen amongst critically ill and hospitalized patients. Individuals with certain co-morbid diseases have an increased risk of developing AKI. Thus, recognizing the co-morbidities that predispose patients to AKI is important in AKI prevention and treatment. Some of the most common co-morbid disease processes that increase the risk of AKI are diabetes, cancer, cardiac surgery and human immunodeficiency virus (HIV) acquired immune deficiency syndrome (AIDS). This review article identifies the increased risk of acquiring AKI with given co-morbid diseases. Furthermore, the pathophysiological mechanisms underlying AKI in relation to co-morbid diseases are discussed to understand how the risk of acquiring AKI is increased. This paper reviews the effects of various co-morbid diseases including: Diabetes, cancer, cardiovascular disease and HIV AIDS, which all exhibit a significant increased risk of developing AKI. Amongst these co-morbid diseases, inflammation, the use of nephrotoxic agents, and hypoperfusion to the kidneys have been shown to be major pathological processes that predisposes individuals to AKI. The pathogenesis of kidney injury is complex, however, effective treatment of the co-morbid disease processes may reduce its risk. Therefore, improved management of co-morbid diseases may prevent some of the underlying pathology that contributes to the increased risk of developing AKI.

Key words: Acute kidney injury; Kidney disease; Human immunodeficiency virus; Co-morbidities; Diabetes; Cancer; Cardiac surgery; Acquired immune deficiency syndrome; Risk factors; Immune response; Cardiovascular disease

Core tip: In order to prevent, diagnose, and prophylactically treat patients, healthcare providers must identify co-morbidities that significantly increase the likelihood of acute kidney injury (AKI). Any treatments that compromise cardiac output, renal perfusion pressure, and glomerular hemodynamics risk ischemic injury to the kidney. The innate and adaptive immune responses, which are activated by renal epithelial cell necrosis contribute to the

progression of AKI. These factors have been shown to be enhanced in diabetes, cancer, cardiac surgery and human immunodeficiency virus acquired immune deficiency syndrome patients.

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INTRODUCTION

According to the Acute Kidney Injury Network (AKIN), AKI is an abrupt loss in kidney function within 48 h, as defined by an increase in serum creatinine of 26.4 μmol/L (0.3 mg/dL) or more; a percentage increase in serum creatinine of more than 50% from baseline; or a reduction in urine output, oliguria (< 0.5 mL/kg hourly for > 6 h)[1,2]. AKI can be characterized by severe changes in kidney function. The severity of these changes are time sensitive, thus, early treatment may minimize the complications associated with AKI[3]. AKI is most often secondary to extrarenal events in critically ill patients, specifically those that are hospitalized an are suffering from progressive degenerative diseases[4]. AKI has been shown to occur in 1% of patients admitted to the hospital and it has been shown that up to 7% of patients develop AKI during hospital stays[1,5,6]. The incidence of AKI in intensive care units (ICU) has been shown to range from 20% to 50%[7]. On average 5% of patients in the ICU with severe AKI require renal replacement therapy (RRT)[8].

Patients are at an increased risk of death from postoperative AKI. According to Hobson *et al*[9] the risk-adjusted 90-d postoperative mortality was 6.5% for patients with AKI (ranging from mild to severe) in comparison to 4.4% in patients without AKI. Some of these surgical procedures include thoracoabdominal aortic surgery[10], bone marrow transplantation[11] and cardiac surgery[12]. AKI, as a result of ischemia, is also a frequent clinical event. In the hospital setting, ischemic-AKI occurs in 50% of patients with AKI[13]. Ischemic-AKI occurs for a variety of reasons such as the use of vasoconstrictive drugs or radiocontrast agents and/or hypotension associated with sepsis or blood loss after surgery or trauma[2]. Individuals who survive AKI have an increased risk of short and long-term complications. Some of these complications include a 10-fold greater risk of chronic kidney disease, a 3-fold greater risk of end stage renal disease and double the risk of death[14,15].

Biomarkers have become a novel concept for the early diagnosis of AKI. A combination of two urinary cell-cycle arrest biomarkers, insulin-like growth factor-binding protein 7 (IGFBP-7) and tissue inhibitor of metalloproteinases-2 (TIMP-2) have been used to predict the risk of moderate and severe AKI (defined by stages 2 and 3 respectively according to the KDIGO classification of AKI)[16]. These biomarkers have been said to perform better than existing markers such as NGAL, KIM-1, interleukin (IL)-18, L-FABP and Cystatin C[17,18]. In AKI, these biomarkers localize in the site of injury where they are involved in the process of the G1 cell-cycle arrest, which acts to prevent cells from continuous division when DNA is damaged[19]. Two independent multicenter cohort studies conducted by Kashani *et al*[17] and Bihorac *et al*[18] allowed for the development of the FDA approved NEPHROCHECK® Test system. The test system is comprised of assays for TIMP-2 and IGFBP-7, which is to be used in conjunction with clinical evaluations. This system is used as a clinical aid in the risk assessment for moderate to severe AKI within 12 h of patient assessment[17,18]. As such, these new advancements allow for the early detection of AKI.

Several epidemiological studies have proposed a wide array of risk factors for AKI. These include acute clinical conditions, diagnostic, or therapeutic procedures, and chronic disease states. However, they do not highlight the relationship of co-morbid diseases with the pathophysiology of AKI in a systematic manner. As such, this paper seeks to identify important co-morbidities and illustrate mechanisms by which these co-morbidities increase the incidence of AKI. Identifying co-morbidities that significantly increase the likelihood of AKI will allow healthcare providers to prevent, diagnose, and prophylactically treat patients, thereby reducing the long-term complications associated with AKI.

Pathogenesis and co-morbid disease processes in AKI

Renal blood flow is highly regulated to ensure oxygen delivery for normal renal function[20]. Cardiac output, renal perfusion pressure, and glomerular hemodynamic factors are major determinants of renal blood flow autoregulation. If these factors are compromised, ischemic and toxic injury to the kidney can occur[20,21]. The afferent arteriole plays an important role in autoregulation to maintain glomerular filtration rate (GFR). There are two mechanisms by which the afferent arteriole regulates GFR: (1) the myogenic reflex occurs when renal perfusion pressure rises causing the smooth muscle of the afferent arteriole to constrict; and (2) tubuloglomerular feedback (TGF) is sensitive to sodium delivery to the macula densa causing vasoconstriction of the afferent arteriole[22]. Further, cyclooxygenase inhibitors such as aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) that may be taken by patients with co-morbid diseases can cause severe intrarenal vasoconstriction, serious decline in GFR, and worsen AKI[23-25].

The core pathology of AKI can be broken down into degenerative processes that target the tubular epithelium, vasculature and activate the immune response leading to a decline in kidney function. AKI associated with ischemia reperfusion injury, sepsis or toxins causes a rapid loss of proximal tubular cell cytoskeletal integrity and cell polarity[26]. As a result, there is a shedding of the proximal tubule brush border and loss of polarity with the

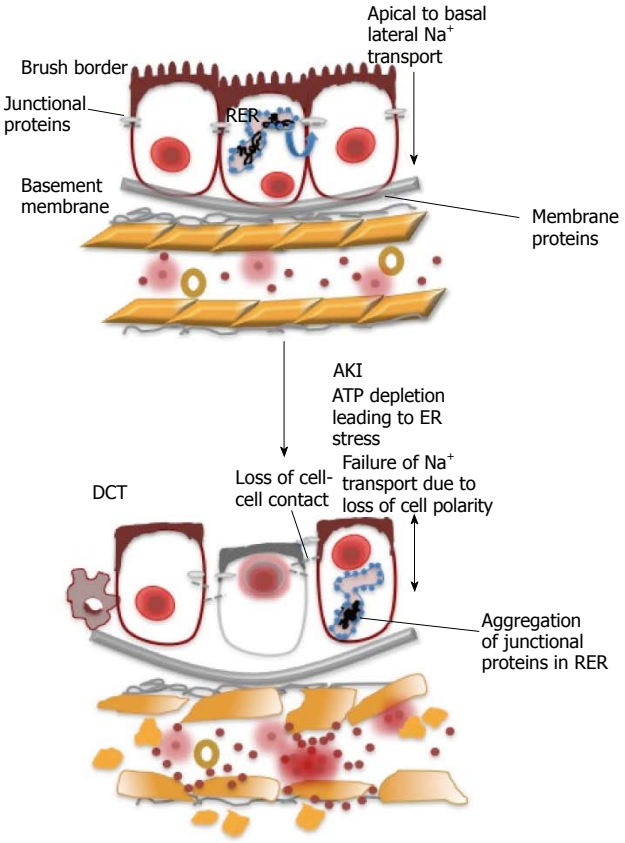

Figure 1 Epithelial cell damage. Ischemia reperfusion injury, sepsis or nephrotoxins are some the main causes of damage to epithelial cells resulting in AKI. The damage induces changes to the cytoskeleton, adhesion molecules and membrane proteins. ATP depletion results in the disruption of tight junctions causing back-leak of the filtrate as the actin cytoskeleton structure is altered. Endoplasmic reticulum stress caused by ATP depletion causes the aggregation of junctional proteins inducing an increase in the permeability of the endothelium. The loss of cell polarity due to AKI results in the failure of Na^+ reabsorption allowing high concentrations of Na^+ to reach the distal tubule stimulating an aberrant TGF response. AKI: Acute kidney injury; TGF: Tubuloglomerular feedback; ATP: Adenosine triphosphate; ER: Endoplasmic reticulum.

mislocalization of adhesion molecules and other membrane proteins such as Na^+/K^+-ATPase and β-integrins[26]. ATP depletion can cause ER stress, which causes protein misfolding, including epithelial junction proteins, leading to loss of cell polarity and failure of sodium readsorption. This results in an aberrant TGF response (Figure 1)[2,26] caused by loss of the ability of the proximal tubular cells to reabsorb filtered sodium, thus, increasing sodium delivery to the distal nephron. With an increase in the delivery of sodium to the macula densa, the TGF mechanism of autoregulation senses hyperfiltration, causing afferent arteriole constriction[20]. However, the perfusion of the kidney may already be compromised by prerenal causes leading to an exaggerated TGF response, resulting in a sudden and substantial drop in GFR[20].

AKI and inflammation

Both the innate and adaptive immune responses, activated by tubular epithelial cell necrosis, are key contributors to the progression of AKI[1,21]. Activation of the inflammatory process triggers the expression of cytokines and chemokines like tumor necrosis factor (TNF) and IL-6 through toll-like receptors that detect materials released in response to injury and interact with their ligand receptors to activate a proinflammatory response to the site of injury. Upregulation of chemokines and adhesion molecules in the endothelium results in the infiltration of inflammatory cells such as neutrophils, lymphocytes, and macrophages from blood vessels to the interstitium of the kidney[1,21,27].

AKI and endoplasmic reticulum stress

AKI caused by ischemia, nephrotoxic drugs, or contrast agents has been associated with endoplasmic reticulum (ER) stress[27]. The ER has a pivotal role in the maintenance of protein homeostasis where it controls the concentration, conformation, folding and transport of synthesized proteins[27]. Disruptions such as hypoxia, glucose depletion, and oxidative stress can prevent the correct functioning of the ER where an accumulation of misfolded proteins in the ER lumen initiates the unfolded protein response (UPR)[27,28]. The UPR serves as an adaptive response attempting to re-establish normal ER functioning through the activation of calcium-dependent molecular chaperones such as glucose-regulated protein-78[1,27]. The UPR pathway can also induce the transcription of pro-apoptotic genes that cause cell death. Oxidative stress and inflammation are compounded by ER stress *via* the UPR, which contribute to glomerular and tubular damage in patients with AKI[27].

AKI and endothelium and vasculature damage

When the endothelium is damaged, the arteriole responds to a local high concentration of vasoconstrictive agents with a greater magnitude, as the injured endothelial cells produce a decreased amount of vasodilatory substance. There is an increase in the permeability of the endothelium post-injury, consequently resulting in a loss of fluid into the interstitium, thereby compromising blood flow[27]. Chronic hypoxia alongside the downregulation of angiogenic factors can cause a decline in the number of blood vessels and consequently lead to increased fibrosis that works in a positive feedback mechanism to reinforce its progression and ultimately cause epithelial cell injury and apoptosis[27,28]. Smaller constrictive vessels respond more intensely to vasoconstrictive agents (*e.g.,* angiotensin Ⅱ, thromboxane A_2, prostaglandins *etc.*), but have a decreased response to vasodilators (acetylcholine, bradykinin, NO)[27]. These effects can be a consequence of alterations in the endothelium due to injury or enhanced leukocyte-endothelial adhesion. The latter effects can cause the obstruction of the small vessels and activate the inflammatory response, which becomes a vicious cycle of coagulation that prevents the delivery of vital nutrients and oxygen to the epithelial cells[27].

Co-morbidities and AKI

Damage to the kidneys, as a result of AKI, may be enhanced with the presence of co-morbidities and thereby complicate the treatment procedure. One study defined

the incidence, risk factors and outcomes of AKI in a patient population from the Scottish Hip Fracture Audit database[29]. These patients who sought treatment for femur fracture and developed AKI showed an increase in inpatient morbidity, mortality (within 30 and 120 d) and length of hospital stay with multiple co-morbidities[29]. This study highlights the co-morbidities associated with the development of AKI including, diabetes mellitus, vascular disease, hypertension and pre-morbid chronic renal disease. The data presented in this study suggests that most cases of AKI occur post-surgery and the causes of AKI are multi-factorial comprising of pre, intra- and post-operative factors[29].

Diabetes-associated AKI

Globally, in 2014, it is estimated by the World Health Organization (WHO) that 387 million people suffer from Diabetes mellitus (DM), where 90% of the cases are of Type Ⅱ diabetes[30]. The risk of AKI has been shown to be increased in patients with DM, with an adjusted odds ratio of 1.99, compared to non-DM controls with the same GFR[31]. It was determined that individuals who require dialysis, which is indicative of the severity of AKI, were an older patient group with DM and included individuals who had other complications such as hypertension and proteinuria[31]. A reason proposed for the higher risk of AKI in patients with DM is the frequent occurrence of complications associated with DM. Some of these complications include, cardiovascular disease; heart failure; exposure to medications such as diuretics and others that serve as nephrotoxic agents[32].

A greater susceptibility to ischemic insults of the diabetic kidney has been shown in experimental rodent models and in diabetic patients[33]. One study examined the influence of 30-min renal ischemia in rats with streptozotocin-induced DM. This study showed a complete recovery of the renal function in non-DM rats while DM animals showed a permanent loss of renal function[34]. DM rats, 8 wk after ischemia was induced, became completely anuric with tubular atrophy, and had extensive inflammation and tubulointerstitial fibrosis, which became evident within 4-wk post-surgery[34]. Another study led by the same investigators showed treatment of these rats with insulin prior to the ischemic event reduced ischemic injury[35].

The mechanism by which diabetes increases the severity of AKI has not yet been well established, but a great deal of research supports the connection between obesity, inflammation, and insulin resistance[36]. Inflammatory cytokines such as TNF-α and IL-6 are produced by adipocytes and have been shown to cause insulin resistance[36,37]. In rodent models of diabetes and diabetic humans, the increased upregulation of inflammatory cytokines in the kidney and urine have been shown[38]. These changes have been shown to result in long-term renal complications such as proteinuria and renal hypertrophy[38]. To experimentally determine the mechanistic role of TNF-α in facilitating the heightened risk of ischemic injury in Type Ⅱ diabetic mice, one study used a neutralizing TNF-α antibody or nonimmune globulin control[39]. The mice were pre-treated with TNF-α antibody or nonimmune globulin injections 20 min before bilateral renal ischemia[39]. This study showed that the treatment with the TNF-α antibody was renal-protective against ischemic injury. Thus, the study concluded that diabetes increases the susceptibility to ischemic AKI due to an elevated TNF-α-mediated inflammatory response[39].

Although a majority of the scientific community agrees that diabetes increases the severity of AKI, some controversy surrounding DM and susceptibility to AKI exists. A study conducted by Venot *et al*[40] has shown no role of DM in increasing the risk of AKI or RRT. Instead, DM has been shown to only worsen the renal prognosis at discharge, determined by patients need for RRT, levels of serum creatinine and the recovery of renal function[40]. Additionally, the data from another study has shown that the history of DM is based on unclear self-reports of patients or records, and thereby does not reflect the current glucose control. Thus, using diabetes as a marker for a heightened risk of AKI at baseline clinical assessment in patients undergoing cardiac surgery may not be a useful tool in predicting renal injury outcomes[41]. Moreover, patients without a formal diagnosis of DM can suffer from chronic hyperglycaemia (CHG) due to pathological glycemic control or early stages of DM[41,42]. This study highlights that hyperglycaemia is also associated with cardiac dysfunction, susceptibility to infections and endothelial dysfunction, which pose as risk factors of perioperative morbidity and mortality after coronary artery bypass grafting (CABG) surgery[41]. The results of this study suggest that the measurement of Hemoglobin A1c (HbA1c) of $\geqslant$ 6.0%, which is an established tool used in the evaluation of diabetic control and CHG in patients with DM, is associated with a higher incidence of AKI after CABG[41]. Thus, a patient's blood glucose levels should be evaluated for CHG, independent of DM, as it could be a strong determinant of AKI.

Cancer-associated AKI

AKI is an important complication of cancer and cancer-therapy where cancer patients are susceptible to a number of kidney lesions that can cause complications in the efficacy of treatment[43]. Factors such as the type and severity of malignancy (a solid tumour or hematologic process), associated complications such as co-morbidities and illnesses, and types of cancer management and therapy cause variability in when AKI is acquired[43]. One study conducted on Danish cancer patients reported the highest rates of AKI were in patients with kidney cancer at 44%, myeloma at 33% and liver cancer at 31.8%[44]. The rate of AKI in critically ill cancer patients was shown to be between 12% and 49%, with 9% to 32% of these patients requiring RRT[5,45,46], which is higher when compared to patient populations of an illness of similar severity[45,47,48]. Thus, AKI management in cancer patients is essential for patient survival and recovery.

AKI in cancer patients can be divided into prerenal, intrarenal or postrenal causes. Prerenal AKI is most

commonly seen in cancer patients due to hypotension as a result of intravascular volume depletion caused by sepsis, vomiting, or diarrhea[43]. Hypercalcemia due to parathyroid hormone release, which increases bone resorption and renal tubular resorption of calcium, is seen in 10% to 30% of malignancies[49,50]. This can lead to a prerenal state of AKI due to vasoconstriction as well as volume depletion from natriuresis and diuresis[49,50]. Additionally, prerenal causes can result from the use of medications such as diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers or nonsteroidal anti-inflammatory agents for tumours, and/or other medical conditions such as hypertension or congestive heart failure[43]. Intrarenal causes of AKI in cancer patients consist of primary glomerular disease, acute tubular necrosis attributable to toxins or ischemia, infiltrative processes due to immune system activation, and microangiopathic processes[43]. Postrenal AKI is a result of kidney obstruction that is common in malignancies in the bladder, prostate, uterus, and cervix[43].

Nephrotoxicity by means of cancer therapy is one of the leading causes of AKI in cancer patients[51]. In a multivariate model, the OR for developing AKI from chemotherapy was 1.61, 4.55 for intravenous contrast and 1.52 for antibiotics[51]. Renal injury can be induced in a variety of ways by nephrotoxic drugs. In general, intrarenal vasoconstriction, direct tubular toxicity and intratubular obstruction are damaging results of nephrotoxic agents[51]. High levels of toxins are delivered and reabsorbed by the kidneys, which lead to increased intracellular concentrations of nephrotoxins in the tubular cell and medullary interstitium[51]. Further, the kidney is a site for drug metabolism and clearance[52]. Thus, the kidney can breakdown compounds that may be relatively harmless into toxic metabolites, or impairment of renal function can cause chemotherapeutic agents to concentrate in the kidneys without being cleared[52,53]. Delayed drug metabolism and excretion, due to increased concentrations of nephrotoxins, can result in increased systemic toxicity requiring an adjustment of treatment dosage[53]. As such, the nephrotoxic potential of anti-cancer agents can be significantly increased if there is pre-existing kidney damage and or a presence of concomitant co-morbidities such as heart failure and sepsis[53].

Cardiac surgery-associated AKI

Cardiac surgery-associated (CSA) - AKI is an important clinical problem that stems from a complex multifactorial pathogenic process. The incidence of CSA-AKI is 25%[54]. Mortality associated with the development of AKI can be as high as 60%, with an average of 15%-30% depending on the measurement and defining criteria of AKI[55]. Factors that increase the risk of CSA-AKI can be divided into preoperative and intraoperative (associated with and followed by postoperative CSA-AKI) categories.

The preoperative period is a critical point wherein renal injury can occur due to fluctuations in hemodynamics, exposure to nephrotoxic agents and the activation of the inflammatory response[55]. Injury, as a result of the aforementioned, can be substantiated when a patient undergoes surgery that decreases renal perfusion and reduces renal functional reserve. Patients undergoing conventional coronary bypass (CCB) often present with renal injuries that can range from minor to severe[55]. The pre-existing renal injury condition can be further amplified with the use of drugs such as diuretics, NSAIDs or angiotensin receptor blockers that can impair the autoregulation of renal blood flow[56]. Additionally, incidents of preoperative hypotension may lead to endothelial injury that can impair the production of vasodilatory substances such as NO causing vasoconstriction as a result of catecholamines and angiotensin Ⅱ to further exacerbate injury[57,58].

The intraoperative period is when patients are exposed to anaesthesia and undergo CCB, these significantly impair hemodynamics and activate the innate and adaptive immune response[55]. Hemodynamic changes can be controlled and regulated given that a patient's medical history is thoroughly assessed and the kidney is perfused accordingly during surgery. However, if not controlled, hemodynamic changes can lead to regional renal ischemia and can induce or extend renal injury[55]. Additionally, the activation of inflammatory mediators can initiate in the preoperative period and extend into the intraoperative period. An elevation of TNF-α levels have been observed in patients with pre-existing congestive heart failure, which further amplifies the inflammatory response during CCB in intraoperative period[59,60]. Neutrophils and the vascular endothelium are activated, inducing the upregulation of adhesion molecules such as platelets[60]. These events activate the upregulation of cytotoxic free-radicals[61], proteases[62], cytokines[63] and chemokines (IL-6, IL-8 and TNF-α)[63,64].

Postoperative events that impair renal function are similar to causative factors of AKI that are frequently found in intensive care setting such as the use of vaso-active agents, hemodynamic instability, exposure to nephrotoxic medications, volume depletion, and sepsis. Postoperative cardiac performance may be compromised with ventricular dysfunction causing reduced blood flow to the kidney and subsequently resulting in AKI[55].

Human immunodeficiency virus-associated AKI

Human immunodeficiency virus (HIV) infection that may progress to acquired immune deficiency syndrome (AIDS) creates an immunosuppressed state allowing for life-threatening opportunistic infections and cancers to thrive[65]. In contrast to AKI as a result of pre-renal and post-renal causes, HIV-associated AKI is most often due to HIV-mediated viral or immunological disease and or nephrotoxicity from treatments[66]. Risk factors for AKI in HIV infection include low $CD4^+$ levels, AIDS, hepatitis C and liver disease[67]. Additionally, medications used to treat HIV such as anti-retroviral therapy (ART) or highly active

antiretroviral therapy (HAART) may also increase the risk of developing AKI due to their nephrotoxic properties[66]. The OR of HIV patients acquiring AKI in pre-HAART has shown to be 2.9 and substantially increased to 6.0 in post-HAART[66]. ART causes severe immunosuppression where the $CD4^+$ count becomes dangerously low at < 200 cells/mm^3; normal values ranging from 500 cells/mm^3 to 1200 cells/mm^3[68]. The decreased $CD4^+$ count is an independent predictor of experiencing AKI and is a vital predictor of HIV related morbidity and mortality[69]. Furthermore, co-viral-infections have been shown to increase the incidence of AKI. Hepatitis C virus co-infection occurs in 15%-30% of HIV-infected patients in the United States, where 30% of AKI events are a result of underlying liver damage[69].

Although no reliable data exists on the incidence and causes of AKI especially amongst HIV^+ patients, South Africa, where 5.6 million of the 34 million people infected with HIV reside[67], faces problems of herbal intoxication, sepsis due to opportunistic infections, or severe gastroenteritis with dehydration[68,70]. AKI has been shown to be a critical cause of mortality particularly amongst indigenous black communities where herbal remedies are prescribed by traditional healers as curative measures for problems such as AIDS-related abdominal pain, diarrhea or to eliminate HIV from the system[70-72]. One of the most common nephrotoxic plants is the Impila (Callilepis laureola), found in regions of South Africa, Democratic Republic of Congo, Zimbabwe, and Zambia[73,74]. Nephrotoxicity from herbal remedies can arise from direct causes such as renal injury due to acute tubular necrosis and acute interstitial nephritis or indirectly as a result of intravascular hemolysis and dehydration due to diarrhea[68]. Therefore, HIV plays a major role in AKI from direct infection processes and treatment regimens.

CONCLUSION

AKI is an important clinical event that manifests in critically ill patients. AKI is associated with a multitude of risk factors that disrupt the homeostatic processes of the kidneys. Its complexity stems from pre-existing co-morbidities of patients that vary in severity, thereby making an overarching systematic treatment and management protocol difficult to deliver to patients suffering from AKI. A great deal of light has been shed upon the mechanistic basis by which AKI develops and progresses with the assessment of risk factors, however research efforts and emphasis should be placed on developing treatment interventions that can reverse or attenuate renal injury. To do this, therapeutic strategies need to be devised on a case-by-case basis where the identification of important co-morbid diseases such as DM, cancer, cardiac surgery and HIV takes place.

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Health literacy in kidney disease: Review of the literature and implications for clinical practice

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Abstract

Health literacy is the capacity of an individual to understand information related to a disease in order to make an informed decision. In patients with kidney diseases, studies have reported increasing impact of limited health literacy on health outcomes. Our paper discusses current literature on health literacy in kidney diseases.

Key words: Health literacy; Kidney diseases; Rapid estimate of adult literacy in medicine; Hemodialysis; Peritoneal dialysis; Chronic kidney disease

Core tip: Health literacy is an increasing recognized cause of suboptimal care and management of chronic diseases in patients. Our paper reviews the current literature on its prevalence and impact in the population with kidney diseases. More studies are needed in patients with kidney diseases to better understand the effect of limited health literacy.

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BACKGROUND

According to the Institute of Medicine, health literacy is defined as "the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make informed health decisions"[1]. It is a complex phenomenon including diverse communication skills of individuals beyond simply being able to read. It also involves oral understanding (speaking and listening skills), numeracy, and cultural and conceptual knowledge. The prevalence of limited health literacy is higher amongst the elderly, minorities, and those with lower socioeconomic status including income and education[2].

Health literacy is particularly important in the large

and growing number of patients with chronic kidney disease (CKD) due to the complexity of the disease, which requires a high level of patient involvement and self-management skills. Patients with kidney disease must follow appropriate dietary restrictions, adhere to complex medication regimens, make decisions about dialysis, and keep up with multiple appointments in the health care system. Despite having data on methods to delay disease progression, kidney outcomes are suboptimal in part related to patient factors. Of these, there is increasing evidence that health literacy plays an important role in the care of patients with kidney disease[3,4]. We present currently available health literacy screening tools, studies of health literacy in patients with kidney disease, and strategies to address health literacy in clinical practice.

HEALTH LITERACY MEASURES

There are a variety of health literacy screening tools available, many of which have been studied in patients with kidney disease. One of the most commonly used tools is the Rapid Estimate of Adult Literacy in Medicine (REALM), which is a 66-item word recognition test. Scores are based on the total number of words a patient can correctly identify and pronounce, categorized by grade-equivalent reading level. Scores range from 0 to 66 with lower scores representing more limited health literacy (0 to 18 = less than 4th grade reading level; 19 to 44 = 4th to 6th-grade reading level; 45 to 60 = 7th to 8th-grade reading level; > 60 = 9th-grade reading level or above). Limited health literacy is defined as a REALM score < 60. The REALM takes about three minutes to administer[5]. It has been studied in patients with chronic kidney disease and kidney failure, including transplant, hemodialysis, and peritoneal dialysis patients[6,7]. A kidney transplant specific version is also available, the REALM-T[8].

Another commonly used health literacy screening tool is the Test of Functional Health Literacy in Adults (TOFHLA). This test uses the modified cloze procedure, where every fifth to seventh word is omitted from reading passages and subjects select the correct word from among a set of four options. The full version involves 50 reading comprehension items in 3 passages and 17 numeracy items, and takes about 22 min to complete[9]. The shortened version (S-TOFHLA) includes 36 reading comprehension items and takes about 7 min to complete[10]. Scores are categorized into inadequate, marginal, and adequate health literacy. Both versions are available in Spanish.

Routine use of the REALM and TOFHLA has been largely limited by administration time; therefore, shorter literacy screening instruments are increasingly being used. A 3-item brief health literacy screen (BHLS) is available[11], which uses the following self-report questions: (1) How confident are you filling out medical forms by yourself? (2) How often do you have someone help you read hospital materials? and (3) How often do you have problems learning about your medical condition because of difficult understanding written information? Answers are scored on a 5-point Likert scale. The BHLS takes approximately 1 min to complete and has been validated against the REALM and the S-TOFHLA in the hemodialysis population[12]. The areas under the receiver operator curves comparing BHLS were reported as 0.71 (95%CI: 0.61-0.80) for the REALM, and 0.73 (95%CI: 0.59-0.88) for the S-TOFHLA. The use of a single item version using just one of these questions (confidence with forms) has been validated against the REALM in patients on peritoneal dialysis[13].

The newest vital sign (NVS) is another instrument that can be used to assess health literacy. This test uses a nutrition label from a pint of ice cream and requires patients to answer six questions related to the information on the label[14]. A score of 4 or more indicates adequate literacy, a score of 2-3 indicates possible limited literacy and a score of 0-1 indicates high likelihood of limited literacy[15]. Devraj *et al*[16] have used this tool in the CKD population to examine the association between health literacy and kidney function. More recently, this tool has been used to assess literacy outcomes in the kidney transplant population[17,18].

HEALTH LITERACY IN CHRONIC KIDNEY DISEASE

Despite the increased awareness of the importance of health literacy in kidney care[19], there have been few studies examining health literacy in patients with chronic kidney disease not on dialysis. Wright *et al*[20] reported an 18% prevalence of limited health literacy in a single cohort of 401 patients with CKD stage 1-5 in an outpatient study. In this study, limited health literacy based on the REALM was associated with poorer CKD knowledge. Another study of 2340 patients with mild-moderate CKD reported a prevalence of limited health literacy of 28% in non-Hispanic Blacks and 5% in non-Hispanic Whites. This study used the S-TOFHLA as a tool to measure health literacy[21]. The investigators reported that participants with limited health literacy had lower estimated glomerular filtration rate (eGFR) (34 mL/min *vs* 42 mL/min per 1.73 m^2); higher urine protein/24 h (0.31 g *vs* 0.15 g); a higher self-reported cardiovascular disease (61% *vs* 37%); and were less likely to have blood pressure < 130/80 mmHg (51% *vs* 58%). Finally, Devraj *et al*[16] also found an association of limited health literacy with kidney function. In a small study of 150 patients with CKD stages 1-4, every unit increase in the Newest Vital Sign score was associated with a 1.9% increase in eGFR. Further studies are needed of health literacy in patients with earlier stages of kidney disease, since their care and needs are different than those with more advanced disease.

HEALTH LITERACY IN DIALYSIS

There has been more research on the impact of health

literacy in the dialysis population compared to those with earlier stages of kidney disease. In peritoneal dialysis, three studies have reported the prevalence of limited health literacy ranging from 6% to 50%[6,7,13,22]. In previous studies by us, the prevalence of limited health literacy was similar in peritoneal dialysis[13] and hemodialysis[23] study populations. In addition, limited health literacy was not associated with an increased risk of infectious complications or hospitalizations. This suggests that the presence of limited health literacy should not preclude consideration of peritoneal dialysis for renal replacement therapy, provided patients receive appropriate hands-on training that is tailored to their individual literacy needs[7].

In the hemodialysis population, the largest study by Cavanaugh *et al*[24] examined health literacy in 480 incident hemodialysis patients using the REALM. They reported a prevalence of 32% of limited health literacy in their cohort, which is similar to what was reported by Grubbs et al in their study of 62 hemodialysis patients using the S-TOFHLA[25]. On the other hand, Green et al reported a prevalence of limited health literacy of 16% in their analysis of 260 patients on maintenance hemodialysis using the REALM[23]. Variations in prevalence of limited health literacy may be due to differences in patient populations or the use of alternative health literacy assessment tools. In all these studies, limited health literacy was seen more often in non-white people and those with lower educational status and lower income levels[23,24,26].

In terms of outcomes, Green *et al*[26] reported that limited health literacy was independently associated with an increased incidence of missed dialysis treatments, emergency department visits, and dialysis related hospitalizations. Another study of 72 patients on hemodialysis reported that people with limited health literacy had worse blood pressure control than those with adequate health literacy[27]. Moreover, limited health literacy has been associated with an increased risk of death in hemodialysis patients[24].

HEALTH LITERACY IN KIDNEY TRANSPLANT

Limited health literacy may be a barrier to kidney transplantation. Grubbs et al reported that the access to kidney transplantation is reduced in patients with inadequate health literacy. They reported, in a cohort of 62 dialysis patients, that participants with inadequate health literacy had 78% lower hazard of referral for transplant work up than those with adequate health literacy (AR = 0.22; 95%CI: 0.08-0.60; P = 0.003)[25].

In another study by Dageforde *et al*[28], living kidney donors and recipients were compared with the deceased donor recipients. They reported that the deceased donor kidney transplant recipients were more likely to have moderate or low health literacy than living donor kidney transplant recipients (OR = 1.911; P = 0.022). They also found that the living donors had a higher level of health literacy.

More recently, Kazley *et al*[17] examined health literacy and its impact on kidney transplant outcomes. They used the REALM-T (REALM modified for the transplant population), NVS and Decision Making Capacity Assessment Tool (DMCAT). They reported that each of these tools significantly predicted whether or not a patient was listed for transplant. However, the NVS and DMCAT tool significantly predicted whether a patient actually received a transplant.

Table 1 Clinical "red flags" for limited health literacy

Patient registration forms that are incomplete or inaccurately completed
Non-adherence with medications or treatments
Frequently missed appointments
Lack of follow-through with labs, imaging tests, or referrals
Unable to name medications, explain what medications are for, or explain timing of medication administration
May offer excuses to deflect reading tasks
"I forgot my glasses"
"Let me bring this home so I can discuss it with my children"
Seldom have questions
Seek help only when illness is advanced
Have difficulty explaining medical concerns

IMPLICATIONS FOR CLINICAL PRACTICE

There is now convincing evidence that limited health literacy is common in patients with kidney disease and associated with a variety of adverse outcomes. In clinical practice, providers can consider routinely screening for health literacy in order to identify at-risk patients who may need more tailored care. In fact most studies till date have looked at the impact in chronic kidney disease and dialysis population. The data in population with acute kidney injury is sparse and it will be interesting to see future studies looking at prevalence and influence of health literacy in this subset of patients with renal failure. However, consideration must be given to time constraints and the potential to induce shame[29]. Clinical "red flags" can also be used to predict which patients may have limited health literacy (Table 1)[30], but it is important to note that many patients who struggle with understanding may not exhibit any of these signs. A better approach recommended by most experts is to implement the use of health literacy "universal precautions", which encourages the systematic use of clear health communication principles to promote better understanding for all patients[31,32]. Key clear health communication principles are shown in Table 2. Communications skills training have been shown to be effective at increasing the use of a variety of these skills[33]. A health literacy universal precautions toolkit is available online at http://nchealthliteracy.org/toolkit. Additional resources include an online plain language medical dictionary (www.lib.umich.edu/plain-

Table 2 Clear health communication techniques

Explain things clearly in plain language
Avoid medical jargon (for example, state "long-term" rather than "chronic")
Avoid vague terms such as "negative" test result
Slow down
Focus on 1-3 key points or messages - and repeat
Confirm understanding using teach-back
"I want to be sure that I explained your medication correctly. Can you tell me how you are going to take this medication?"
Effectively encourage patients to ask questions
"What questions do you have?" rather than "Do you have any questions"
Use analogies and pictures
Use patient friendly educational materials
4^{th}-6^{th} grade reading level
Picture-based
Write down important instructions

language-dictionary) and readability formulas (www.readabilityformulas.com) to target written materials at the appropriate reading level (4^{th}-6^{th} grade). Several recently published reviews of the readability of patient education materials in chronic kidney disease are also available[34,35].

CONCLUSION

In summary, health literacy is an important consideration in kidney disease care. Tools are available to help providers address health literacy in clinical practice. Collective efforts are critically needed to reduce the impact of limited health literacy and improve the quality of care and outcomes of this high-risk population[36].

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MINIREVIEWS

Proton-pump inhibitor-induced hypomagnesemia: Current research and proposed mechanisms

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Abstract

Since the early reports nearly a decade ago, proton-pump inhibitor-induced hypomagnesemia (PPIH) has become a well-recognized phenomenon. While many observational studies in the inpatient and outpatient populations have confirmed the association of PPI exposure and serum magnesium concentrations, there are no prospective, controlled studies to support causation. Molecular mechanisms of magnesium transporters, including the pH-dependent regulation of transient receptor potential melastatin-6 transporters in the colonic enterocyte, have been proposed to explain the effect of PPIs on magnesium reabsorption, but may be a small part of a more complicated interplay of molecular biology, pharmacology, and genetic predisposition. This review explores the current state of research in the field of PPIH and the proposed mechanisms of this effect.

Key words: Hypomagnesemia; Proton-pump inhibitor; Magnesium; Nephrology; Renal

Core tip: Proton-pump inhibitor (PPI)-induced hypomagnesemia has become a well-recognized phenomenon over the past decade, through the publications of case reports and larger observational studies in the inpatient and outpatient populations. However, there are no prospective, controlled studies to support causation. Molecular mechanisms of magnesium transporters, including the pH-dependent regulation of transient receptor potential melastatin-6 transporters in the colonic enterocyte, have been proposed to explain the effect of PPIs on magnesium reabsorption, but may only comprise a small part of a more complicated interplay of molecular biology, pharmacology, and genetic predisposition.

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MAGNESIUM HOMEOSTASIS

Magnesium is the fourth most abundant intracellular

ion, and despite its relatively low extracellular concentration, it has numerous essential functions in intracellular metabolism and ion transport. The majority of total body magnesium is housed within bone cells, while the remaining 1% circulates in the blood. As with most electrolytes, the balance of intake, absorption, and excretion in the gastrointestinal and renal systems, as well as the constant flux between the circulating and storage compartments within the serum and bone, respectively, are the determinants of magnesium homeostasis.

The small and large bowels are responsible for magnesium absorption *via* passive and active transport. Paracellular movement between intestinal epithelial cells, or enterocytes, occurs across a concentration gradient. Though the magnesium permeability of the small intestine is poorly understood, its relatively ion-permeable nature is presumed to be due to the relatively low expression of tight junction proteins[1]. Active transport of magnesium occurs more distally in the small intestine (*i.e.*, cecum) and large bowel. The enterocyte apical cell membrane proteins transport magnesium from the intestinal lumen into the circulating blood *via* dedicated ion channels. Located on the luminal surface, these proteins have been identified as transient receptor potential melastatin (TRPM) 6 and 7. Their high affinity for magnesium actively helps the body maintain adequate magnesium levels through upregulation of magnesium absorption, especially in times of decreased magnesium intake[2-5]. The cyclin M4 exchanger (CNNM4 Na^+-Mg^+) is located on the basolateral surface and may be responsible for ultimate magnesium reabsorption into the serum after luminal absorption into the cytosol of the enterocyte[6]. During periods of decreased dietary magnesium, the active transport pathways can increase magnesium absorption significantly[7].

After absorption through the gastrointestinal tract, about 20% of magnesium in the blood is protein-bound (mostly to albumin), while 15% is complexed to anions. The remaining majority (65%) of extracellular magnesium is unbound in its ionized form. As opposed to other cations, like calcium, acid-base disturbances have little effect on this distribution[8]. Intracellularly, predominantly as the complexed, non-ionized form, magnesium has essential roles in the mechanisms behind the maintenance of DNA stability and repair as well as the regulation of the enzymatic activity of hundreds of enzymes[9]. Over the past two decades, numerous magnesium transporters have been identified, facilitating magnesium flux across cell membranes into the intracellular environment to accomplish these roles. The rate of transport varies among tissue types and higher concentrations of magnesium measured within rapidly growing cells suggests that the rate of intracellular magnesium transport is likely associated with the relative metabolic activity of the cell and its capacity to proliferate through its activating effect on DNA, RNA, and protein synthesis[10,11].

Approximately 80% of circulating magnesium is filtered into the urinary space. While most other ions are predominantly absorbed *via* the proximal tubule, the majority of filtered magnesium is reclaimed in the thick ascending Loop of Henle (TAL). In the TAL, the passive reabsorptive pathway is dependent on "claudins", or tight junction proteins. Claudins 16 and 19, which are not expressed within the tight junctions of small intestine enterocytes, have been implicated as modulators of magnesium balance, and can lead to renal magnesium wasting when absent[12]. Additional studies show that claudins demonstrate "interdependence", as they require each other for appropriate placement into the tight junctions within the distal convoluted tubule (DCT)[13]. Active, high affinity transcellular magnesium reclamation occurs through these TRPM6 transporters. As such, the DCT determines the ultimate magnesium concentration in the urine, and along with appropriate gastrointestinal absorption, ensures magnesium homeostasis.

In contrast to other predominantly intracellular cations such as potassium and calcium, and despite its crucial roles in cell proliferation and intracellular enzymatic activity, there is no hormonal axis solely dedicated to magnesium homeostasis. In addition, alterations in circulating serum magnesium concentrations are offset by a much larger intracellular magnesium depot, so that a negative daily magnesium balance may not manifest with lower magnesium concentrations. Intracellular magnesium depletion and normal serum magnesium concentrations may coexist, and total magnesium deficiency might not manifest until cellular stores are exhausted[9]. Therefore, using serum magnesium levels to diagnose magnesium deficiency is inherently challenging. The "intravenous magnesium loading test" is a method used to better approximate a magnesium deficit[14]. The concentrations of intravenously infused magnesium and the magnesium excreted in the urine are carefully measured to estimate total body magnesium balance. In individuals with sufficient total body magnesium, only 10% of the intravenously infused magnesium should be retained, while the remaining 90% is excreted through the urine. Individuals with intracellular magnesium depletion are expected to increase the absorption rate to > 50%-60%[15]. This test allows for a more accurate representation of the magnesium absorption required to achieve homeostasis. However, it is not performed in the context of patient care as a laboratory standard for accurate result interpretation does not yet exist. In the current state of the evaluation of magnesium disorders, despite the concerns noted above, clinicians and clinical researchers readily use serum magnesium concentrations to estimate total body magnesium.

EARLY REPORTS OF PROTON PUMP INHIBITOR INDUCED HYPOMAGNESEMIA

The link between proton pump inhibitor (PPI) use to hypomagnesemia was first recognized by the scientific community through a published case report in 2006[16].

Since then, numerous case reports have demonstrated this relationship, independent of other electrolyte abnormalities. These reports typically describe patients with chronic PPI exposure, presenting with symptoms characteristic of hypomagnesemia, including arrhythmias and symptoms of neuroexcitability such as seizures and tetany[17]. Numerous different formulations of PPIs have been implicated, indicating that the association is likely a drug class effect. Hypomagnesemia is typically improved after the PPI is discontinued, and PPI re-challenge results in hypomagnesemia recurrence[18]. Conversely, in patients prescribed histamine-2 receptor antagonists, an older class of medications for gastric acid suppression, hypomagnesemia does not recur. Notably, a majority of these case reports could not account for additional etiologies of magnesium deficiency, including malabsorptive conditions, poor dietary intake (*i.e.*, malnutrition of alcohol use), or diuretic-related renal magnesium excretion, prompting the more recently published observational studies.

Estimating the exact usage of PPIs is difficult given its availability both over-the-counter and with a doctor's prescription. It has been suggested that prescriptions for PPIs are in excess of 100 million per year. Increased reporting of the proton-pump inhibitor-induced hypomagnesemia (PPIH) phenomenon to the United States Food and Drug Administration's Adverse Events Reporting System in combination with the early published case reports, resulted in the release of a "drug safety communication" in 2013[19]. The announcement alerted health care professionals to the risk of hypomagnesemia among chronic PPI users, particularly among those on a diuretic or other medications known to affect magnesium levels, with the consideration of obtaining baseline and regular follow-up serum magnesium concentrations over time. While large studies have confirmed this increased risk with concomitant diuretic use[20], others have encountered the PPIH phenomenon among both "casual" (intermittent) PPI users, and chronic users alike[21].

LIMITATIONS OF PUBLISHED OBSERVATIONAL STUDIES

Subsequent larger observational studies further support this association in both inpatient and outpatient populations[22-24], but all have significant limitations, and to date, no well-designed study to accurately describe the potential hypomagnesemic effect of PPIs has been done. While the FDA communication states that these effects occur in longer-term PPI use, duration of exposure to PPI therapy has been difficult to quantify in retrospective studies. PPIs are widely available without a prescription and this may lead to under-reporting to medical providers. Additionally, it is likely that some patients may be taking them on an "as-needed" basis rather than daily or twice a day, making any subsequent measurements of hypomagnesemia uninterpretable. Among the limitations of the observational data, residual confounding due to indication is perhaps the most challenging. Since PPIs are primarily used to treat disorders of the gastro-intestinal tract, and likely are also associated with alterations in dietary behavior, the PPI-associated hypomagnesemia could simply reflect less dietary intake. Furthermore, despite the widespread use of PPIs, the overall reported incidence of PPIH remains low. Although studies that examine the effect of PPI on either ionized magnesium concentrations, intracellular magnesium stores, or magnesium balance, have yet to be performed, a large observational study suggests the PPI exposure is not associated with an increased risk of arrhythmias, as one might expect in the setting of intracellular magnesium deficiency[25]. Uncertainty about the causal relationship of PPI use and magnesium will remain without carefully designed, prospective studies that clearly address PPI therapy duration and magnesium balance through the measurement of magnesium intake and magnesium excretion before and after PPI exposure.

THE PPIH PHENOMENON: POTENTIAL MECHANISMS

Early reports suggested that PPIH was not due to renal magnesium wasting, but rather decreased gastrointestinal absorption[26], and additional studies further support renal magnesium conservation in the setting of PPIH[27]. A recent study examining 24-h urine magnesium excretion in PPI-exposed patients showed that PPI users had lower urinary magnesium. The statistical models controlled for other measures of dietary intake, implicating decreased intestinal magnesium uptake[28]. These clinical observations highlighting decreased intestinal magnesium uptake are supported by more recent mechanistic studies, which have focused on the potential effect of PPI use on the TRMP6 transporter, the major pathway of intestinal magnesium absorption.

Intracellular magnesium regulates TRPM6 activity along with pH[29,30] whereby a more acidic milieu increases TRPM6 activity. Since PPI therapy decreases gastric hydrogen proton secretion, thereby increasing lumen pH, PPI use could potentially decrease TRPM6 activity, resulting in decreased magnesium absorption[31-33]. Figure 1 demonstrates this hypothesis. Adding complexity to this hypothesis, longer term PPI use actually increases the amount of intestinal protons in the distal small bowel[34] and significantly decreases basic pancreatic secretions[35]. However, since the majority of active magnesium reabsorption occurs in the cecum and colon, this effect may dissipate before reaching these locations further along the gastrointestinal tract.

PPI exposure may also lead to upregulation of the distal colon's H^+-K^+ ATPase (cHK-α), a homolog of the gastric H^+-K^+ ATPase targeted by PPIs, increasing its activity by 30%[36]. However, when studied, increased cHK-α expression did not lead to any changes in serum magnesium levels, urinary magnesium excretion, or fecal magnesium excretion. Given this finding, it is plausible

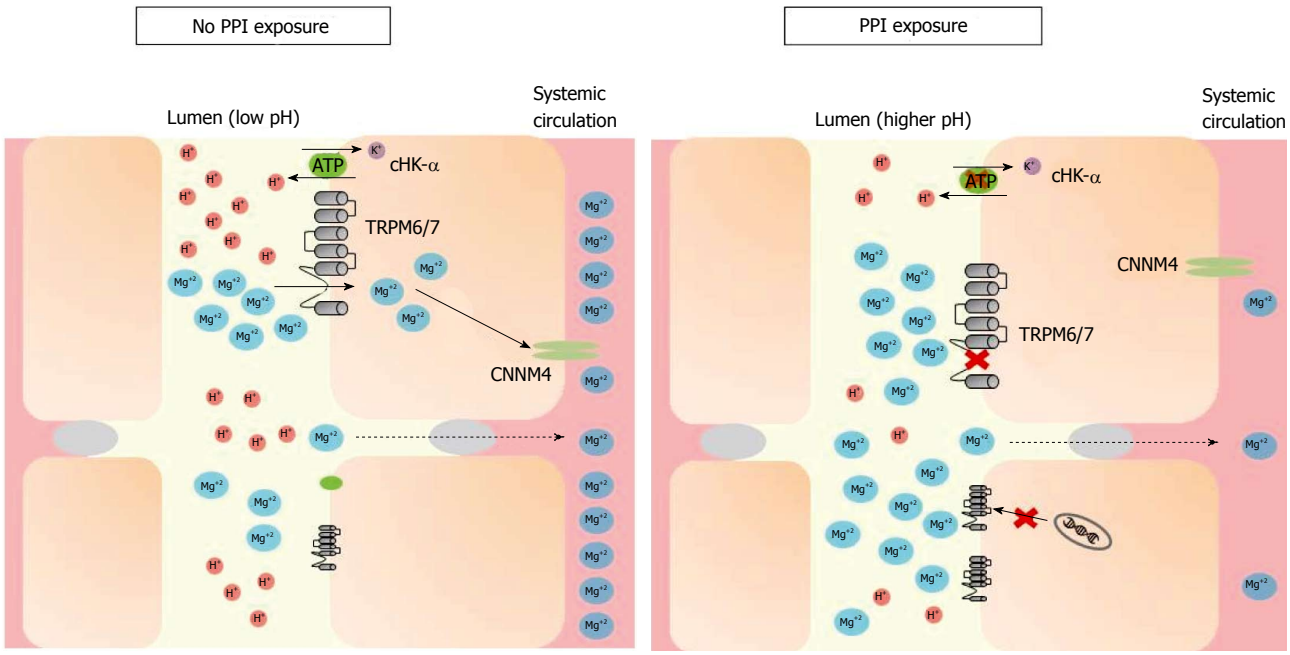

Figure 1 Under conditions of magnesium deficiency, proton-pump inhibitors may inhibit magnesium absorption by increasing the pH of the intestinal lumen, through both gastric and non-gastric antagonism of the H^+-K^+ ATPase pump ("proton pump"). TRPM6/7 affinity for magnesium decreases in a higher pH environment. While this may trigger mRNA transcription of TRPM6 channels in most individuals, hypomagnesemia may develop when this compensation is incomplete or the individual has additional risk factors. TRPM: Transient receptor potential melastatin; cHK-α: Colonic hydrogen-potassium ATPase; CNNM4: Cyclin M4; PPI: Proton-pump inhibitor.

that this increased mRNA expression level of colonic TRPM6 may compensate for the reduced TRPM6 currents caused by the pH-dependent downregulation described above[31]. While this appropriate overexpression of TRPM6 in times of magnesium deficiency may help ameliorate intestinal magnesium malabsorption and maintain total body magnesium balance, individual epigenetic variations in this response could explain why PPI-induced hypomagnesemia is not uniformly seen among PPI users[37,38].

While never evaluated in the setting of PPI use, early studies have employed a radiolabeled magnesium challenge and suggest that the magnesium secretion from the intestine is a small component of magnesium homeostasis[39]. It is currently unclear whether the lack of a "sensing mechanism" within enterocytes that could prompt upregulation of magnesium absorption in times of dietary magnesium restriction could contribute to the clinically significant hypomagnesemia seen in some with PPIH.

Although most have focused on a potential effect of PPI therapy on the TRPM6, and potentially, the Cyclin M4 (CNNM4), transporters in the intestine, there are a number of other ubiquitously expressed transporters previously identified as contributory to magnesium homeostasis including TRPM7[4], magnesium transporter 1 (MagT1)[40], Cyclin M3 (CNNM3)[41], solute carrier family 41 member 1 (SLC41A1)[42], nonimprinted in Prader-Willi/Angelman Syndrome family (NIPA)[43], and membrane magnesium transporters 1 and 2 (MMgT1/2)[44]. While these transporters may play important roles in overall magnesium homeostasis, their role in magnesium transport and specific locations within the colon is unclear. Therefore, they remain potential targets for investigation of how PPIs may interact with them and ultimately lead to hypomagnesemia.

Genome-wide association studies (GWAS) have also identified potential loci that may influence serum magnesium levels[45]. Follow-up studies in individuals of African-American ancestry specifically focused on two loci, *MUC1* and the aforementioned *TRPM6*, and analyzed gene-environment interactions, finding significant effect modification of insulin levels with *TRPM6* and progestin levels with *MUC1*[46]. While the mechanism of TRPM6-associated hypomagnesemia is better characterized, the influence of transcriptional variations of *MUC1*, which normally encodes a transmembrane mucin forming part of the mucosal barrier of the intestine[47], remains unexplored.

FUTURE RESEARCH DIRECTIONS

Nearly a decade after the initial reporting of PPIH, there is increasing awareness of the phenomenon. Case reports and observational studies have contributed to our understanding of the prevalence of PPIH among a variety of patient populations with unique risk factors for its development. In conjunction with the clinical findings of preserved renal magnesium reabsorption in periods of magnesium deficiency, molecular physiology studies have proposed a viable pH-dependent mechanism for the role of TRPM6 within colonic enterocytes. However, much uncertainty regarding the relatively rare occurrence of PPIH remains, with individual genetic variation at specific

loci and under-characterized magnesium transporters among the highest-yield unexplored research directions. Additionally, prospective studies that carefully control for nutritional intake among PPI users and accurately measure total body magnesium are needed to help determine causality of the association of PPI use and hypomagnesemia.

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Upper tract urothelial carcinoma: Paradigm shift towards nephron sparing management

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Abstract

Upper tract urothelial carcinoma (UTUC) is relatively rare compared to urothelial carcinoma of the lower tract, comprising only 5%-10% of all urothelial cancers. Although both entities share histologic properties, UTUC tends to be more invasive at diagnosis and portend a worse prognosis, with a 5 year overall mortality of 23%. To date, the gold standard management of UTUC has been radical nephroureterectomy (RNU), with nephron sparing techniques reserved for solitary kidneys or cases where the patient could not tolerate radical surgery. Limited data from these series, as well as select series where nephron-sparing endoscopic management has been offered to a broader patient base, suggest that minimally invasive, nephron sparing techniques can offer comparable oncologic and survival outcomes to RNU in appropriately selected patients. We review the current literature on the topic and discuss long term outcomes and sequelae of the gold standard treatment, RNU. We also discuss the oncologic outcomes of minimally invasive, endoscopic management of UTUC. Our goal is to provide the reader a comprehensive overview of the current state of the field in order to inform and guide their treatment decisions.

Key words: Urothelial carcinoma; Ureteroscopy; Upper tract; Endoscopy; Minimally invasive

Core tip: In the appropriate patient population, minimally invasive endoscopic treatment of upper tract urothelial carcinoma provides comparable oncologic and survival outcomes to the gold standard radical nephroureterectomy.

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INTRODUCTION

Urothelial cell carcinoma (UCC), a common malignancy encountered by urologists, is the 4th most common

overall neoplasm and the 8th most common cause of cancer death in men. Upper tract urothelial carcinoma (UTUC), however, is a relatively rare neoplasm, comprising only 5%-10% of all UCCs and 5%-7% of all renal neoplasms[1-3]. Despite their histologic similarities, UTUC and lower tract UCC may represent two distinct oncologic entities. The natural history of both disease states differs, in that 60% of UTUCs are invasive at diagnosis compared to 15%-25% of lower tract UCCs. UTUC portends a worse prognosis, with an overall 28% 5-year extra vesicle recurrence rate and a 23% 5-year mortality[4]. The prognosis for muscle invasive UTUC is particularly grim, with a 5 year cancer specific survival (CSS) less than 50% for pT2 /T3 lesions and less than 10% for pT4 lesions[5,6].

Given the wide body of lower tract UCC literature and the well documented bladder tumor recurrence rate following UTUC, management and surveillance of lower tract disease is standardized and well adhered to. In contrast, most of the recommendations for management of UTUC and subsequent surveillance have been extrapolated from current guidelines for lower tract UCC. Only one specific guideline from the European Association of Urology (EUA) currently exists for the surgical management of UTUC, as well as no randomized controlled trials (RCT) compared to 238 RCTs for bladder cancer[7,8]. UTUC is, at best, included as a subset in guidelines for bladder cancer amongst other professional societies such as the American Urological Association (AUA) and International Consultation on Urological Diseases (IDUC)[9-11].

The gold standard treatment for UTUC is radical nephroureterectomy (RNU) with ipsilateral bladder cuff excision[4]. As our instrumentation technology improves, endoscopic management of UTUC has become feasible. Early experience with endoscopic management of UTUC has been limited to patients with solitary kidneys, bilateral disease, or those who are not surgical candidates to undergo RNU. Data from these cases, though limited to retrospective, unmatched comparative studies, demonstrates no short and mid-term difference in overall survival and CSS between endoscopic management and RNU[12].

The lack of concrete management guidelines for UTUC, as well as the feasibility of nephron sparing treatment techniques, raises questions of the appropriateness of our current management strategies. In this article we review existing treatment options for UTUC, their effectiveness from an oncologic standpoint, as well as the morbidity incurred long term due to impaired renal function. Though we encourage the reader to come to their own conclusion, we propose that in appropriately selected patients, endoscopic treatment of UTUC is as effective as RNU with lower long term renal complications.

We performed a review of the literature from January 1980 to January 2015, including all English language articles using the search terms "endoscopic management", "ureteroscopic management", "percutaneous management" and "UTUC". A total of 236 articles were reviewed, yielding 66 articles pertinent to the topic. Outcome measures of upper tract recurrence, overall survival, and CSS were extracted from retrospective and prospective studies.

EPIDEMIOLOGY

As previously discussed, UTUC represents a relatively rare subset of urothelial carcinoma. Bladder tumors represent 90%-95% of all UCs, while UTUCs account for only 5%-10% of all UCs, with an annual incidence in western countries of 2 new cases per 100000 people[3]. Among UTUCs, pyelocaliceal tumors are twice as common as ureteral tumors. Concurrent bladder tumors are diagnosed with UTUC in 17% of UCC patients. Bladder recurrence after UTUC is common, occurring in 22%-47% of patients, while contralateral upper tract recurrence occurs in only 2%-6%[13]. Upper tract recurrence after a primary bladder tumor is reported as rare, with an incidence of 1.7%-3.1%[14,15]. UTUCs have a peak incidence in the elderly population, between age 70 and 80, and are three times more prevalent in men than in women[16]. Hereditary UTUC exists as a component of hereditary nonpolyposis colorectal carcinoma (HNPCC) or Lynch syndrome[17].

DIAGNOSIS AND STAGING

The most common presenting symptom of UTUC, occurring in 70%-80% of cases, is either gross or microscopic hematuria[18]. Flank pain is less common, occurring in 20%-40% of cases, while presentation with a lumbar mass is even more rare, occurring 10%-20% of the time. Both of these entities likely represent advanced disease with worsened prognosis[19,20].

CT imaging with and without IV contrast has replaced IV excretory urography and ultrasound as the gold standard imaging modality with the highest accuracy for diagnosing UTUC. Its sensitivity ranges from 67%-100% and specificity from 93%-99%, depending on the technique used[18]. CT imaging cannot accurately stage UTUC, as staging relies on depth of invasion, which is difficult to determine on imaging alone. However, the presence of hydronephrosis in conjunction with known or suspected UTUC portends a worse prognosis, as it is associated with advanced stage disease[21,22]. Other imaging modalities, such as contrast enhanced MRI, are still in their infancy for diagnosis of UTUC, with a limited sensitivity of 75% for tumors < 2 cm[23].

Cytology alone is of limited utility as it is less sensitive for UTUC than for bladder tumors. If utilized, it should be performed in situ, with samples being taken directly from the collecting system or ureter *via* the ureteroscope[24]. Flexible ureteroscopy is a highly effective means of diagnosis, either through direct visualization of tumor in the ureter, renal pelvis and collecting system, or *via* ureteroscopic biopsies, which approach 90% accuracy regardless of the total volume of tissue sample

obtained[25]. As with CT imaging, accurate staging is difficult with ureteroscopy and biopsies, as the nature of the biopsy forceps makes obtaining muscle in the specimen difficult. Tumor grade is often used as a proxy for stage given that most high grade tumors are also high stage[5]. Though there are some who advocate for use of imaging findings alone for diagnosis of UTUC, this makes determining the prognosis difficult, as one is not able to determine tumor grade (and thus, by proxy, estimate stage) without tissue specimens. Our recommendation is thus to perform ureteroscopic biopsies on all patients with suspected UTUC.

TREATMENT OPTIONS

RNU

The gold standard treatment for UTUC is RNU with concomitant management of the ipsilateral intramural ureter[4]. Traditionally this was performed as an open procedure, adherent to standard oncologic principles, namely avoiding entry into the urinary tract to prevent gross spillage of tumor. With the evolution of laparoscopic and robotic surgery, minimally invasive variants of RNU have been developed. Thus far, short to mid term oncologic outcomes seem to be equivalent between laparoscopic and open techniques; however, we currently lack the follow up to prove long term oncologic equivalence between these modalities[26]. Management of the ipsilateral intramural ureter is critical for adequate recurrence free survival (RFS), as this is the area of highest recurrence. Various methods exist for excising the intramural ureter - extravesical, transvesical, and endoscopic (the "pluck" technique). All three have shown no difference in CSS and OS; endoscopic management techniques have, however, shown higher local bladder recurrence rates[27]. It is not currently standard practice to perform a retroperitoneal lymph node dissection (LND) along with RNU; a growing body of data suggest it increases median time until recurrence and improves CSS[28].

LONG TERM IMPACT OF RNU

Aside from the immediate perioperative complications of RNU, which do not differ greatly from any large oncologic resection, patients undergoing this procedure must contend with the long term impact of losing an entire renal unit. Initial studies on creatinine clearance and GFR, performed on the donor nephrectomy population, did not show a long term decrease in renal function[29-31]. However, one could argue that these donor nephrectomy patients represent a carefully selected cohort of patients that lack the risk factors for renal deterioration after major surgery. A study of patients undergoing nephrectomy for renal cell carcinoma, arguably a patient cohort more closely matched to that of the UTUC population, showed that 10% of patients had significant deterioration of their creatinine post nephrectomy[32]. A study of 131 patients undergoing nephroureterectomy showed an 18% decrease in GFR at a median of 5 year follow up[33]. Another retrospective study of 374 patients undergoing RNU showed an even higher decrease in GFR, at 32%, with no significant trend towards GFR recovery over time[34]. It would seem apparent from the data that nephroureterectomy does indeed lead to significant impairment of renal function.

Renal impairment, end stage renal disease (ESRD) in particular, accounts for a large percentage of health care spending in the elderly[35]. Cost analysis data from UTUC patients undergoing either RNU or renal sparing treatment for UTUC demonstrates a 3-fold to 10-fold cost savings of nephron sparing treatment over RNU over a 10 year period with similar oncologic outcomes[36]. Perhaps more importantly, overall survival and quality of life of patients whose renal insufficiency necessitates dialysis has been proven to be greatly diminished compared to the non dialysis dependent population[37]. Urologists have globally accepted the aforementioned arguments as strong reasons for renal preservation in the management of small renal masses - could these principles be selectively applied to UTUC?

NEPHRON SPARING TREATMENTS FOR UTUC

The rationale for conservative surgery for UTUC stems from the fact that most UTUC is superficial and low grade[38]. Thus, coupled with the aforementioned drawbacks of renal loss and decreased GFR, as well as improvements in endoscopic technology, allow for pursuit of renal sparing techniques. Currently available nephron-sparing treatments for UTUC include ureteroscopic retrograde tumor ablation, percutaneous antegrade tumor ablation, or segmental ureterectomy. As the focus of this review is endoscopic management of UTUC, segmental will not be discussed further here.

Patient selection is critical, as currently endoscopic management techniques are only advisable for low grade, small volume tumors or for patients who would otherwise not be fit to undergo RNU[7] (Figure 1). The decision between retrograde ureteroscopic tumor management and antegrade percutaneous ablation depends primarily on tumor size and location. Large tumors in the renal pelvis are best approached in a percutaneous fashion, while ureteral tumors lend themselves to a ureteroscopic approach. Small tumors in the collecting system may be approached by either fashion[12,38].

Currently no randomized controlled trials exist comparing endoscopic management techniques to the gold standard radical nephroureterectomy. Most of the published data come from small, retrospective and unmatched comparative studies. A 2014 meta-analysis of eight retrospective series, totaling 1002 patients, demonstrated no statistically significant difference in overall survival and CSS between the two modalities. The authors hesitated to conclude oncologic equivalence given the low level of the evidence[12] Additionally, patients tended to be selected for favorable tumor characteristics, such as low grade features and small tumor size. Analysis

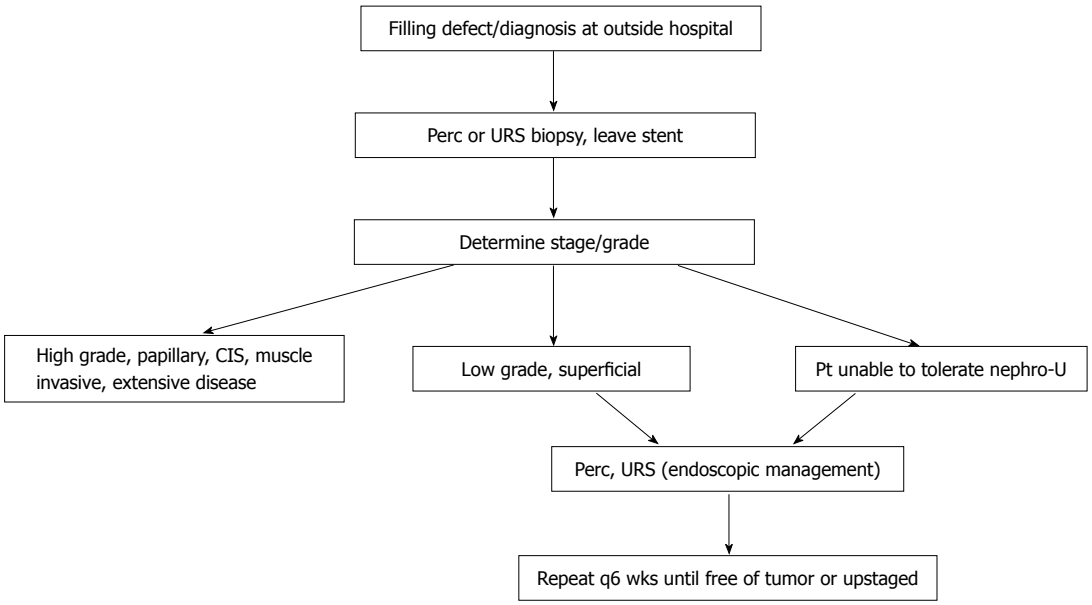

Figure 1 Sample treatment algorithm for patients with upper tract urothelial carcinoma.

of all the existing literature reveals that ureteroscopic ablation of the tumor is associated with high rates of upper urinary tract recurrence (15%-90%) and intravesical recurrence (12%-70%). Tumor grade, size and multi-focality predict upper tract recurrence while previous history of bladder cancer predicts intravesical recurrence (Table 1)[39-57]. The large variations in population size, initial tumor characteristics and length of follow up likely explain the broad range of observed outcomes.

Similarly, the only data on outcomes of percutaneous management of UTUC come from retrospective series (Table 2)[58-66]. Overall, patients managed percutaneously had similar clinical features to those managed ureterscopically - namely low grade, small focal tumors. Those undergoing percutaneous ablation had lower rates of upper tract recurrence (10%-65%) and intravesical recurrence (10%-42%) than those treated with the ureteroscopic approach. Given the high rate of comorbidities, much like in the uretoscopic population, the overall survival was poor (68%-96%) while the CSS was high (75%-100%).

DISCUSSION - BROADENED INDICATIONS FOR NEPHRON SPARING TREATMENTS?

Currently, the only "imperative" indications for systematically offering nephron sparing treatment of UTUC include anatomically or functionally solitary kidneys, substantial renal insufficiency with the impending threat of hemodyalisis or bilateral UTUC[7]. We believe that, though limited in its retrospective nature, the exisiting data indicate that the patient population to whom nephron sparing treatment is routinely offered as a first line option should be expanded.

UTUC continues to challenge urologists as a potentially devastating disease that tends to affect older, sicker patients. As this review of the literature demonstrates, patients treated with ureteroscopic or percutaneous means have a much higher CSS than OS, meaning that they eventually succumb to their comorbidities, and not their cancer. Thus, we believe that patients with significant comorbidities make excellent candidates for first line nephron sparing options. Ureteroscopic and percutaneous approaches offer similar CSS, at least according to medium term data, while avoiding the morbidity and potential of a RNU for an already unhealthy patient population.

Amongst otherwise healthy UTUC patients, we believe nephron sparing treatments should still be offered to those patients with low grade, low stage disease. Although UTUC is more often invasive at diagnosis, truly low grad and low stage disease seems to follow a similarly indolent course, with frequent recurrence but rare progression, as low grade bladder cancer[2,3,7]. Thus, as endoscopic technology and techniques improve, allowing for better ureteroscopic evaluation and biopsy, we should be better able to separate low grade from high grade disease. Patients with low grade disease have shown excellent CSS in the existing endoscopic management literature; using these treatments would allow us to spare them the morbidity of losing a renal unit.

Post-treatment surveillance is critical for achieving excellent CSS outcomes. Thus, patients considered for endoscopic management of their UTUC must be compliant. At our institution we repeat ureteroscopic or percutaneous surveillance ever 3-6 mo for 2 years and then annually; similar variations on this surveillance protocol exist throughout the literature. Additionally, CT imaging allows for detection of progression to metastatic disease and should be performed at regular time intervals.

Table 1 Outcomes of ureteroscopic management of upper tract urothelial carcinoma

Ref.	*n*	Grade on biopsy (G1/G2/G3 *vs* LG/HG)	F/U (mo)	Outcomes (%)
Schmeller *et al*[39] (1989)	16	6/10/0	14	19 UTR, 100 OS, 100 CSS
Andersen *et al*[40] (1989)	10	NA	35	NA
Gaboardi *et al*[41] (1994)	18	12/6/0	15	50 UTR, 100 OS, 100 CSS
Engelmeyer *et al*[42] (1996)	10	9/1/0	10	70 UTR, 90 OS, 100 CSS
Chen *et al*[57] (2000)	23	22LG/21HG	23	64 UTR, 12 IVR
Daneshmand *et al*[43] (2003)	30	7/6/14	31	90 UTR, 23 IVR, 77 OS, 97 CSS
Matsuoka *et al*[44] (2003)	27	10/2/0	33	26 UTR, 15 IVR
Iborra *et al*[45] (2003)	23	NA	NA	35 UTR, 96 CSS
Johnson *et al*[46] (2005)	35	35/0/0	32	68 UTR, 100 CSS
Rouprêt *et al*[47] (2006)	27	19LG/8HG	52	15 UTR, 22 IVR, 77 OS, 81 CSS
Reisinger *et al*[48] (2007)	10	10/0/0	73	50 UTR, 70 IVR, 100 OS, 100 CSS
Krambeck *et al*[49] (2007)	37	2/13/7	32	62 UTR, 37 IVR, 35 OS, 70 CSS
Painter *et al*[50] (2008)	45	NA	NA	89 CSS
Lucas *et al*[51] (2008)	39	27LG/12HG	33	46 UTR, 62 OS, 82 CSS
Pak *et al*[36] (2009)	57	NA	53	90 UTR, 93 OS, 95 CSS
Cornu *et al*[52] (2010)	35	16LG/6HG	24	60 UTR, 40 IVR, 100 OS, 100 CSS
Gadzinski *et al*[53] (2010)	34	NA	58	84 UTR, 75 OS, 100 CSS
Cutress *et al*[54] (2012)	73	34/19/6	54	69 UTR, 43 IVR, 60 OS, 90 CSS
Grasso *et al*[55] (2012)	80	66LG/14HG	38	81 UTR, 59 IVR, 74 OS, 87 CSS
Fajkovic *et al*[56] (2013)	20	14LG/3HG	20	25 UTR, 15 IVR, 45 OS, 95 CSS

G1: Grade 1; G2: Grade 2; G3: Grade 3; LG: Low grade; HG: High grade; F/U: Follow up; UTR: Upper tract recurrence; IVR: Intra-vesical recurrence; OS: Overall survival; CSS: Cancer specific survival; NA: Not available.

Table 2 Outcomes of percutaneous management of upper tract urothelial carcinoma

Ref.	*n*	Grade on biopsy (G1/G2/G3 *vs* LG/HG)	F/U (mo)	Outcomes (%)
Tasca *et al*[58] (1992)	10	1/5/0	19	50 UTR, 90 OS, 100 CSS
Fuglsig *et al*[59] (1995)	26	NA	21	31 UTR, 96 OS, 100 CSS
Plancke *et al*[60] (1995)	10	6/3/11	28	10 UTR, 10 IVR, 90 OS, 100 CSS
Patel *et al*[61] (1996)	26	11/11/1	45	35 UTR, 42 IVR, 75 OS, 91 CSS
Clark *et al*[62] (1999)	17	6/7/4	24	33 UTR, 75 OS, 82 CSS
Goel *et al*[63] (2003)	20	15LG/5HG	64	65 UTR, 15 IVR, 75 CSS
Palou *et al*[66] (2004)	34	7/21/5	51	44 UTR, 74 OS, 94 CSS
Rouprêt *et al*[64] (2007)	24	17LG/7HG	62	13 UTR, 17 IVR, 79 OS, 83 CSS
Rastinehead *et al*[65] (2009)	89	50LG/39HG	61	33 UTR, 68 OS
Fiuk (current study)	65	34LG/33HG	28	55 OS, 87 CSS

G1: Grade 1; G2: Grade 2; G3: Grade 3; LG: Low grade; HG: High grade; F/U: Follow up; UTR: Upper tract recurrence; IVR: Intra-vesical recurrence; OS: Overall survival; CSS: Cancer specific survival; NA: Not available.

Urinary cytology is not as useful in UTUC and thus is left to the surgeon's discretion.

We thus propose that nephron sparing treatment of UTUC, either ureteroscopic or percutaneous, be offered as a first line therapy to the following patient populations: (1) any patient with an anatomically or functionally solitary kidney; (2) any patient with renal insufficiency great enough to impose the threat of hemodyalisis with any further renal insult; (3) any patient with multiple bilateral UTUC tumors; (4) any patient with comorbidities great enough to be life limiting or to incur additional risk with nephroureterectomy; and (5) any patient with low grade, low stage disease who can be trusted to commit to 3-6 mo surveillance.

By using a risk-adapted strategy for expanding current indications for first line endoscopic treatment of UTUC, we hope to minimize renal unit loss without compromising oncologic safety. Development of improved biopsy techniques, urothelial cancer biomarkers, and improved prediction nomograms may help further delineate these indications in the future.

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Cooling dialysate during in-center hemodialysis: Beneficial and deleterious effects

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Abstract

The use of cooled dialysate temperatures first came about in the early 1980s as a way to curb the incidence of intradialytic hypotension (IDH). IDH was then, and it remains today, the most common complication affecting chronic hemodialysis patients. It decreases quality of life on dialysis and is an independent risk factor for mortality. Cooling dialysate was first employed as a technique to incite peripheral vasoconstriction on dialysis and in turn reduce the incidence of intradialytic hypotension. Although it has become a common practice amongst in-center hemodialysis units, cooled dialysate results in up to 70% of patients feeling cold while on dialysis and some even experience shivering. Over the years, various studies have been performed to evaluate the safety and efficacy of cooled dialysate in comparison to a standard, more thermoneutral dialysate temperature of 37 ℃. Although these studies are limited by small sample size, they are promising in many aspects. They demonstrated that cooled dialysis is safe and equally efficacious as thermoneutral dialysis. Although patients report feeling cold on dialysis, they also report increased energy and an improvement in their overall health following cooled dialysis. They established that cooling dialysate temperatures improves hemodynamic tolerability during and after hemodialysis, even in patients prone to IDH, and does so without adversely affecting dialysis adequacy. Cooled dialysis also reduces the incidence of IDH and has a protective effect over major organs including the heart and brain. Finally, it is an inexpensive measure that decreases economic burden by reducing necessary nursing intervention for issues that arise on hemodialysis such as IDH. Before cooled dialysate becomes standard of care for patients on chronic hemodialysis, larger studies with longer follow-up periods will need to take place to confirm the encouraging outcomes mentioned here.

Key words: Hemodialysis; Dialysate temperature; Cool dialysate; Intradialytic hypotension; Hypotensive episodes;

Hemodynamic stability; Cool temperature dialysis

Core tip: Cooled dialysate is commonly employed to reduce the incidence of intradialytic hypotension (IDH) in patients on chronic dialysis. The studies to date that have evaluated cooled dialysate are limited by small sample size and it has not become the standard of care for managing IDH. However, the small studies that exist are promising and suggest that cooling dialysate improves hemodynamic tolerability of dialysis, minimizes IDH, and exerts a protective effect over major organs including the heart and brain. More studies are needed to assess the long-term effects of cooling dialysate in this population.

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INTRODUCTION

According to the KDOQI Clinical Practice Guidelines, intradialytic hypotension (IDH) is defined as a symptomatic decrease in systolic blood pressure of ⩾ 20 mmgHg or a decrease in mean arterial pressure (MAP) by 10 mmHg with symptoms being characterized by abdominal discomfort, nausea, vomiting, muscle cramps, dizziness, restlessness, and anxiety, amongst others[1]. It occurs in approximately 20%-30% of dialysis sessions[2] and is the most frequent complication of renal replacement therapy[3]. IDH is multifactorial in etiology but is largely attributed to the rapid reduction of blood volume that occurs with ultrafiltration and the inadequate cardiovascular response to the reduction in blood volume[2,4]. Populations predisposed to IDH include the elderly and those with diabetes and cardiovascular diseases[3].

IDH is an independent risk factor for mortality in patients on hemodialysis[5,6] and may negatively affect their quality of life[7]. It is also associated with increased morbidity including frontal lobe atrophy[8], myocardial injury[9], and mesenteric ischemia[10]. Nephrologists employ various methods on dialysis to minimize IDH including sodium modeling, ultrafiltration profiling, addition of calcium or bicarbonate to the dialysate bath, and dialysate cooling. While each method has its positive and negative attributes, the focus of this review will be on dialysate cooling.

Extracorporeal cooling of blood on dialysis first came about over three decades ago when it was noted to curb the incidence of IDH. Since then, it has been employed as a measure to mitigate IDH although it has not become standard of practice in chronic hemodialysis units.

DISCUSSION

Core body temperature and the effect of cooled dialysate

Humans keep their core body temperature (CBT) within a narrow range. When CBT rises, the body increases peripheral blood flow or initiates sweating in an attempt to remove heat from the body by convection or radiation, respectively. Shivering is usually an involuntarily thermoregulatory mechanism employed by the body to generate heat when CBT falls. While on dialysis, the dialysate temperature is set to an arbitrary standard of 37 ℃ (98.6 °F) in an effort to achieve a "normal" CBT and maintain isothermia. However, a significant amount of variability exists amongst individuals when it comes to CBT. First, CBT follows a circadian pattern that peaks between 4 and 9 pm and nadirs between 2 and 8 am[11,12]. CBT tends to be lower in elderly individuals[12], higher in women than in men, and is highest in black women[13]. In hemodialysis-dependent individuals, CBT is usually lower than in the non-dialysis population[11,14], with nearly 40% having a CBT less than 36.5 ℃[15] compared to the mean CBT of 37 ℃ (range, 36.2 ℃ to 37.5 ℃) in non-dialysis dependent individuals[12]. The importance of this becomes evident when one considers that even a slight change in CBT on dialysis initiates thermoregulatory mechanisms which may be detrimental on dialysis. For example, a supraphysiologic dialysate temperature, such as 37 ℃, could raise the CBT in any given individual resulting in vasodilation and consequent cardiovascular instability. The vasodilation may be in direct competition with the expected vasoconstriction which occurs in the setting of ultrafiltration and could further lead to hemodynamic compromise.

Since supraphysiologic dialysate temperature was viewed as suboptimal and potentially detrimental, the idea that subphysiologic dialysate temperature might be beneficial arose, specifically in those individuals that suffered from IDH. Cooled dialysate temperature was postulated to be beneficial for the following reasons: First, it avoided heat accumulation and hence counterproductive thermoregulatory vasodilation; second, it likely led to a catecholamine surge which induced both peripheral vasoconstriction and cardiac inotropy[16]. However, at the time various potential consequences surrounding cooled dialysate remained unclear. Would dialysis adequacy be inferior? Would it cause prolonged vasoconstriction potentially placing vulnerable vascular beds at risk for ischemia? Would patients be tolerant of the cooled CBT on dialysis? Finally, would it be effective at minimizing IDH?

Various studies have since been performed to address the above issues. Kaufman *et al*[17] aimed to evaluate the efficacy of cooled dialysate during short-time, high Kt/V dialysis treatments. He postulated that cooled dialysate might increase urea compartmentalization during dialysis

treatment leading to increased urea rebound post-dialysis and hence decrease dialysis efficacy. The study was performed in 15 patients who underwent a total of 56 dialysis sessions. Each participant served as their own control. Dialysate temperatures were adjusted to either lower CBT (cooled dialysis) or keep CBT at a thermoneutral temperature. Dialysate cooling resulted in -266 ± 15 kJ heat-energy exchange per treatment whereas thermoneutral dialysis averaged 5 ± 31 kJ per treatment; dialysate temperature averaged 35.7 ℃ ± 0.02 ℃ and 37.1 ℃ ± 0.02 ℃, respectively. Cooled dialysis resulted in statistically greater increases in the peripheral vascular resistance index and MAP. It also reduced the maximum intradialytic fall in MAP and necessary interventions by staff to address hypotensive symptoms. There were no statistical changes in blood volume, cardiac index, urea rebound, or effective Kt/V. The authors concluded that cooling dialysate stabilized hemodynamics during dialysis, reduced the number of staff interventions required to address IDH symptoms, and did so without affecting the efficacy of high-efficiency dialysis. A systematic review that evaluated 22 studies comprising of 408 patients has since concluded that using cooling dialysate temperature does not reduce dialysis adequacy[18].

Ayoub *et al*[19] aimed to gauge patient perception of cooled dialysate. Five patients known to have IDH were dialyzed for three sessions using cooled dialysate (35 ℃) followed by another three sessions with dialysate temperature set at 36.5 ℃. The same was done in a second group of five patients known to have stable blood pressures during and after their dialysis sessions. Their results demonstrated that cooling dialysate resulted in a statistically significant increase in ultrafiltration in the group known to have IDH. This group also experienced significantly higher intra- and post-dialysis MAPs with cooled dialysate. While the IDH-prone group had no episodes of hypotension with cooled dialysate, they had a total of seven episodes of hypotension with neutral temperature dialysate, all requiring nursing intervention ($P < 0.001$). There was no statistical difference in intra-dialytic pulse rates between the two groups nor did cooling dialysis have an effect on urea removal between the two groups. Patients' perception about cooled dialysis was assessed by a questionnaire designed specifically for this study. It comprised of the following questions: "How did you feel while being dialysed on cool temperature? Compared with normal temperature dialysis of 36.5 ℃, did you feel any differences while being dialysed on cool temperature? If yes, what were the differences? Would you like to continue cool temperature dialysis?" The results of the questions were as follows: 80% of patients felt more energetic after being dialyzed with cooled dialysate; 80% felt a dramatic improvement in their general health with cooled dialysate; 80% requested to always be dialyzed with cooled dialysate; 20% reported feeling cold during dialysis. The authors concluded that for patients prone to IDH, cooled dialysate improved hemodynamic stability during and after dialysis, improved tolerance of dialysis, reduced the number of nursing interventions required to address IDH, and had an overall positive impact on patients' energy and activities of daily living. This is the only study to date that has specifically assessed patient perception of cooled dialysate temperature. However, a systematic review by Selby *et al*[18] pooled the results of five studies in which symptoms were reported during cooled dialysis. Their analysis demonstrated that patients undergoing cooled dialysis were 1.98 (95%CI: 0.38-3.57) times more likely to become symptomatic than patients dialyzed with standard dialysate temperatures. When the analysis omitted the study by Ayoub and Finalyson[19] due to milder symptoms being reported compared to the other four studies, the results were non-significant with symptoms occurring 1.5 (95%CI: -0.2-3.2) times more often with cooled dialysis than during standard dialysis.

A similar study by Jost *et al*[20] compared cooled dialysate to thermoneutral dialysate to specifically evaluate its efficacy on "problem" patients. The design used a double-blinded, cross-over protocol to evaluate 12 patients, six of whom were prone to IDH and six known to have large interdialytic weight gains defined as consistently gaining > 4 kg in the interdialytic period. Each patient served has their own control and was randomly assigned to one session of dialysis at 35 ℃ and one at 37 ℃. Results demonstrated significantly lower blood pressures at 1, 2, and 3 h of dialysis at a thermoneutral dialysate temperature when compared to the cooled dialysate temperature. A total of 18 episodes of symptomatic hypotension occurred during the study period, 16 of which occurred in the IDH-prone group. Furthermore, no episodes of symptomatic hypotension occurred during cooled dialysis ($P < 0.01$). The authors concluded that cooling dialysate significantly improved hemodynamic tolerance during dialysis and also significantly reduced the incidence of IDH during dialysis in patients prone to IDH. These studies added to the literature supporting cooled dialysate as an effective way of reducing IDH.

Cooled dialysate compared to other modalities used to minimize IDH

Dheenan and Henrich[21] were the first to compare cooled dialysate to other methods that are commonly employed to mitigate IDH. They used a single-blinded, cross-over protocol to evaluate 10 patients on chronic hemodialysis with a history of IDH. Patients were randomized to one week periods (three dialysis sessions) of five varying dialysis protocols performed in a random and blinded fashion. Each patient underwent four protocols commonly employed to minimize IDH in addition to a standard dialysis protocol which served as a control. The protocols were as follows: A standard dialysis group with dialysate sodium of 138 mEq/L (served as the control group), high sodium dialysate (patient dialyzed using a steady dialysate sodium of 144 mEq/L), sodium modeling using a step function design (dialysate sodium declined from 152 to 140 mEq/L in the last 30 min of

dialysis), ultrafiltration (one hour of isolated ultrafiltration in which 50% of the target weight loss was removed followed by three hours of isovolemic dialysis), and cool temperature dialysis in which dialysate was cooled to 35 ℃ (sodium concentration was 140 mEq/L in this group). The results revealed indistinguishable weight losses with each protocol suggesting that the volume of ultrafiltration was consistent across each protocol. However, the results demonstrated superiority of sodium modeling and cooled dialysate groups over the other groups, and multiple similarities between these two methods. Both had significantly fewer hypotensive signs and symptoms per treatment and fewer hypotensive episodes per treatment when compared with standard treatment. Both also had significantly fewer nursing interventions for IDH per treatment when compared to the ultrafiltration and control group. The nadir MAP was significantly lower in the control and ultrafiltration groups whereas the upright post-dialysis blood pressure was best preserved in the sodium modeling and cooled dialysate groups. Sodium modeling was tolerated by all but one patient who developed hypertension, headache, and nausea; 6 out of the 10 reported increased thirst sensation however this did not translate into increased interdialytic weight gain during the one week follow-up period. Cooled dialysate, however, was not well tolerated. Seven of 10 patients reported a "cold" sensation and two patients were noted to be shivering on dialysis.

A similar study by Rezki *et al*[22] evaluated 16 patients in a two-phase protocol. The first phase consisted of three standard HD sessions with a sodium concentration of 140 mEq/L with dialysate temperature at 37 ℃ and served as the control for each patient. During the second phase, patients were dialyzed successively under the following conditions: Fixed sodium dialysate concentration at 144 mEq/L, sodium modeling from 152 to 138 mEq/L, one hour of ultrafiltration alone followed by three hours of standard dialysis, dialysis with cooled dialysate (T < 37 ℃), and a combination of sodium modeling with cooled dialysate. When compared to the control protocol, there was a statistically significant decrease in the signs and symptoms of hypotension and in the incidence of IDH when patients were dialyzed with sodium modeling, cooled dialysate, or the combination protocol. When compared to the control protocol, fewer medical staff interventions were required when patients were dialyzed with the combination protocol or cooled dialysate. There was no increase in subjective thirst or in interdialytic weight gain when a protocol employing sodium modeling was performed. In this study, four of the 16 patients noted shivering when dialyzed with cooled dialysate.

Both of these studies suggest that cooling dialysate temperature is as effective a method as sodium modeling when it comes to mitigating IDH. They also suggest that cooling dialysate may be poorly tolerated and associated with patient discomfort on HD. However, sodium modeling has been associated with a number of side effects including worse hypertension and increased interdialytic weight gain due to increased thirst[23]. Whether one method is superior at reducing IDH or is better tolerated than the other remains to be seen in a larger trial with longer follow-up periods.

Effect of cooled dialysate on vulnerable vascular beds

One of the questions that arose when cooled dialysate was first introduced was whether vasoconstriction would also occur at an arteriolar level and potentially place vulnerable vascular beds at risk for end-organ injury. Since that time, it has become apparent that dialysis itself is a hemodynamic stressor[24] which triggers circulatory stress and consequently damages vasculature in the heart, mesentery, and brain[25-27] amongst other organs. Two recent trials demonstrated that cooled dialysate imparts a protective effect in these organs.

Eldehni *et al*[25] hypothesized that ultrastructural injury to the white matter in the brain might be mitigated by cooling dialysate hence reducing dialysis-induced circulatory stress. This was evaluated by randomizing 38 incident dialysis patients to dialyze for 12 mo at either 37 ℃ or 0.5 ℃ below their core body temperature; the latter was determined by averaging each patient's temperature by tympanic thermometer during six sessions prior to commencing the trial. An individualized temperature was chosen as it is thought to be better tolerated than an arbitrary temperature of 35 ℃[28]. A form of magnetic resonance imaging (MRI) called diffusion tensor imaging (DTI) was used to evaluate the structural integrity of the brain white matter at baseline and after 12 mo of thrice-weekly dialysis. DTI was chosen as an imaging modality as it has previously been used to detect clinically significant changes in cerebral small vessel disease[29]. Additionally, MAP extrema points were measured over the course of 12 mo. MAP extrema points measure the frequency and amplitude required to maintain optimal organ perfusion; higher extrema points correlate with high variation in organ perfusion and translates to detrimental perfusion of vulnerable vascular beds[25,30]. After 12 mo, patients dialyzed at 37 ℃ exhibited patterns of ischemic brain injury on MRI that were not noted in the cooled dialysate group. Additionally, patients dialyzed at 37 ℃ had a notable worsening of their MAP extrema points that was not seen in the cooled dialysate group. Both of these results were statistically significant. The authors concluded that cooling dialysate minimized injurious perfusion of cerebral vascular beds and consequently decreased the degree of brain injury noted on DTI. An advantage to this study is the long-term follow-up over the course of one year. However, despite having a larger sample size than in earlier studies evaluating the effects of cooled dialysate, it was still limited by a small sample size. Additionally, the study suffered from a high dropout rate of 47.9%, although this was primarily due to difficulty in recruiting patients on incident HD; there were no dropouts reported as a result of the intervention.

Odudu *et al*[24] used the same patient population and study design as Eldehni *et al*[25] to evaluate whether cooled dialysate would have cardioprotective effects

over the course of a 12 mo follow-up. Fifty-four incident dialysis patients were randomized to a dialysate temperature of either 37 ℃ or 0.5 ℃ below their core body temperature and followed for 12 mo. Tagged cardiac magnetic resonance imaging was performed at baseline and at 12 mo; the imaging modality was chosen for its high reproducibility and use as a reference standard technique to evaluate regional left ventricular (LV) strain. While there was no statistically significant change in the study's primary outcome, change in resting ejection fraction, there were multiple significant secondary outcomes of note. The cooled dialysate group experienced a significant reduction in both LV mass as well as LV end-diastolic volumes. The control group had a significant reduction in peak systolic strain, diastolic function, and segmental LV strain whereas these functions were preserved in the cooled dialysate group. As markers of subclinical cardiomyopathy, these findings suggest that cooled dialysate had a protective cardiac effect over the one year study period. Lastly, aortic distensibility, an independent marker for future cardiovascular events, was also preserved in the cooled dialysate group and significantly decreased in the control group. Whether these findings suggest that cooled dialysate may one day be linked to a decreased risk of cardiovascular events in the dialysis population remains to be seen.

CONCLUSION

Cooling dialysate first came into practice three decades ago after it was noted to curb the symptoms of patients suffering from IHD on dialysis. Since then, many benefits of cooled dialysate temperatures have come to light. Multiple studies have demonstrated improved hemodynamic tolerance on dialysis specifically in patients prone to IDH without any adverse effect on dialysis adequacy. It is an inexpensive intervention that also reduces the frequency of nursing involvement to address IDH in patients on chronic hemodialysis. More recently, studies suggest that one year of cooling dialysate temperature in incident dialysis patients mitigates features of subclinical cardiomyopathy and ischemic brain injury when compared to patients dialyzed at the standard 37 ℃.

While the cooler temperatures may cause discomfort in some patients, recent studies suggest that a temperature of 0.5 ℃ below an individual's CBT is better tolerated than an arbitrary temperature of 35 ℃. Additionally, Ayoub and Finlayson[19] demonstrated that cooled dialysate may actually improve a patient's energy following dialysis, and in their cohort of patients, individuals requested to be dialyzed with cooled dialysate temperatures following the study. Finding a "sweet spot" for cooled dialysate may allow for increased patient satisfaction and in turn, improve patient compliance with dialysis. The advantages and disadvantages of cooling dialysate are summarized in Table 1.

Unfortunately, all of the studies performed to date on cooled dialysate have been limited by small sample sizes. Larger studies are needed in order to be generalizable to a greater portion of the chronic hemodialysis population. From a patient perspective, it will be important to study perception and comfort with dialysis at cooler temperatures since there appears to be a trend toward a higher incidence of symptoms with cooled dialysis when compared to standard dialysis. Studies with longer follow-up times would be useful to evaluate the effects of sodium modeling and cooled dialysate on incidence of IDH as well as its effects on interdialytic weight gain and hypertension. Longer follow-up would also allow for assessment of the effects of cooled dialysate on vulnerable vascular beds and their clinical correlates, for example cardiovascular events, dementia, memory, executive function, *etc*. Encouraging results in such studies would have the potential to change the standard of care in patients on chronic hemodialysis.

Table 1 Advantages and disadvantages of cooling dialysate temperatures

Advantages	Disadvantages
Improved hemodynamic tolerance during and after dialysis	Patient discomfort
Improved patient energy	Shivering
Preservation of vulnerable vascular beds (subclinical cardiomyopathy and ischemic brain injury)	
Fewer nursing interventions needed	

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Use of percutaneous nephrostomy and ureteral stenting in management of ureteral obstruction

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Abstract

The management options for ureteral obstruction are diverse, including retrograde ureteral stent insertion or antegrade nephrostomy placement, with or without eventual antegrade stent insertion. There is currently no consensus on the ideal treatment or treatment pathway for ureteral obstruction owing, in part, to the varied etiologies of obstruction and diversity of institutional practices. Additionally, different clinicians such as internists, urologists, oncologists and radiologists are often involved in the care of patients with ureteral obstruction and may have differing opinions concerning the best management strategy. The purpose of this manuscript was to review available literature that compares percutaneous nephrostomy placement *vs* ureteral stenting in the management of ureteral obstruction from both benign and malignant etiologies.

Key words: Percutaneous nephrostomy; Urinary diversion; Ureteral obstruction; Quality of life; Ureteral stents; Pelvic malignancy; Urinary drainage

Core tip: Ureteral obstruction as a consequence of malignant or benign etiologies is a common urologic entity that is often challenging for clinicians to determine the optimal method of urinary decompression. There is no consensus on the use of stents *vs* percutaneous nephrostomy in the management of ureteral obstruction as well as a lack of clear superiority of stenting over percutaneous approach in terms of complications and quality of life considerations. Therefore, treatment decisions must be individualized using a multidisciplinary approach involving the patients, their family and members of the treatment team.

Hsu L, Li H, Pucheril D, Hansen M, Littleton R, Peabody J,

Sammon J. Use of percutaneous nephrostomy and ureteral stenting in management of ureteral obstruction. *World J Nephrol* 2016; 5(2): 172-181 Available from: URL: http://www.wjgnet.com/2220-6124/full/v5/i2/172.htm DOI: http://dx.doi.org/10.5527/wjn.v5.i2.172

INTRODUCTION

Ureteral obstruction is a heterogeneous clinical entity, and it is often challenging for the clinician to determine the optimal method of decompression. Malignant ureteral obstruction can arise from intrinsic urologic malignancy such as prostate or bladder cancer, or extrinsic involvement from another primary malignancy, most commonly of gynecologic or colorectal origin[1-3]. The therapeutic goal of urinary drainage in malignant disease is to adequately drain the upper urinary tracts for symptomatic relief with maintenance of renal function, allowing the initiation of systemic therapy while minimizing further urologic intervention, hospitalization and negative impact on the quality of life[2-4]. On the other hand, the etiology of benign ureteral obstruction is generally a consequence of intraluminal pathology, such as ureteropelvic junction obstruction, ureteral stones or ureteral stenosis. Extraluminal benign obstruction can arise from localized mass effect of benign tumors such as uterine leiomyomas or retroperitoneal fibrosis[5-7]. Benign ureteral obstruction caused by ureteropelvic junction obstruction is primarily managed with definitive treatment of the underlying condition[8].

There are no clear guidelines regarding optimal methods of urinary decompression in the management of ureteral obstruction. The purpose of this article is to review recent literature assessing outcomes of retrograde ureteral stenting and percutaneous nephrostomy (PCN) insertion in the treatment of ureteral obstruction resulting from malignant and benign etiologies to elucidate the associated morbidity, effects on quality of life and variability in technical success.

DATA ACQUISITION

PubMed was used to search for articles addressing the management of malignant and benign ureteral obstruction using key phrases "ureteral stent" and "nephrostomy". This yielded 850 articles that were screened by title and abstract. Screened articles were then independently evaluated by two authors (HL and LH) for inclusion in the review. Manuscripts were included if they reported original research comparing PCN and ureteral stenting. Exclusion criteria included a study focus on pediatric populations, no differentiation between antegrade *vs* retrograde stenting, or study population totaling < 10. A total of 16 articles were included in the final review.

PCN *VS* URETERAL STENTING IN THE SETTING OF MALIGNANCY

Malignant ureteral obstruction may occur secondary to contiguous tumor invasion, extrinsic ureteral compression by pelvic malignancies, or by pelvic metastases of tumors that originate from outside the pelvis such as breast, gastric or pancreatic cancers. Obstruction can also occur in the setting of retroperitoneal or pelvic lymphadenopathy due to metastatic disease, or as a consequence of treatment resulting in retroperitoneal fibrosis or ureteral stricture[9,10].

Obstruction may be evident during staging of the disease or workup for impaired renal function as evidenced by hydronephrosis with renal cortical atrophy on abdominal imaging. Additionally, patients may experience acute flank pain, renal failure, uremia or sepsis secondary to urinary tract infections. The rationale for decompression aims to offer relief of the above symptoms, to alleviate complications from renal insufficiency and to facilitate systemic therapy.

Determining the etiology of obstruction may be helpful in planning treatment approaches as tumors involving the bladder, uterine cervix and prostate cancer are known to have lower retrograde stenting success rates[11]. The etiology of obstruction is also important for estimating patient prognosis. Non-urologic malignancies such as gastric and pancreatic cancers have a worse prognosis with shorter overall survival than urologic malignancies[12,13].

Prognostication and quality of life: To decompress or not to decompress?

Although the intention of diversion is to prolong patient survival, this goal is often not achieved with diversion. Malignant ureteral obstruction can be a sign of advanced disease[14,15] and patients with ureteral obstruction secondary to advanced malignancies traditionally have poor life expectancy measured in months even if relief of ureteral obstruction is achieved. In a prospective study of 205 patients with obstructive uropathy secondary to advanced cervical cancer, urinary diversion with PCN drainage or ureteral stenting was found to be associated with modest survival advantage in the months immediately after diversion[16]. However, there was no significant difference in quality of life when compared to patients who elected not to undergo diversion[16]. In contemporary studies, the median survival of patients with ureteral obstruction secondary to pelvic malignancies after urinary diversion ranges from 96 to 144 d[17,18], with 88% mortality within one year of decompression[18].

Objective criteria have been studied to prognosticate survival after urinary diversion in patients with ureteral obstruction secondary to advanced malignancy. Ishioka *et al*[18] studied survival in 140 patients with urinary obstruction secondary to advanced incurable malignancies

and identified predictors of poor prognosis associated with shorter survival time after palliative urinary diversion by PCN: Serum albumin before diversion (≤ 3 g/dL), degree of hydronephrosis (grade 1 or 2) and three or more events related to disseminated malignancy[18]. Patients with 2 or 3 of these predictors had a 2% survival rate at 6 mo while patients with none of these characteristics had a 69% survival rate[18]. Cordeiro *et al*[17], in a prospective study of 208 patients who underwent ureteral stenting or PCN for malignant ureteral obstruction, identified the number of events related to malignancy ≥ 4 and Eastern Cooperative Oncology Group (ECOG) index ≥ 2 to be significantly associated with poor prognosis after urinary diversion with a median survival rate of 7.1% at 12 mo in the unfavorable risk group[17]. On the basis of these findings, ureteral stenting and nephrostomy tubes may not be indicated in poor risk patients.

Following ureteral stenting or PCN placement, quality of life may be impaired secondary to irritative urinary symptoms, pain, need for tube changes on a regular basis and often worse performance status[19,20]. In a prospective direct comparison of the quality of life after nephrostomy or stent placement in 46 patients with malignant urinary tract obstruction, Monsky *et al*[19] found no significant difference in the quality of life between treatment groups based on standardized validated surveys. In this study, patients managed with stenting reported more irritative voiding symptoms and pain while patients undergoing nephrostomy placement required more frequent tube changes secondary to complications.

In summary, there is no clear evidence that urinary diversion in the setting of malignant urinary obstruction improves the quality of life. Additionally, no significant difference has been reported between the two diverting modalities. Urinary decompression may be justified if improvement in renal function will facilitate systemic therapy and alleviate symptoms of ureteral obstruction. However, with an understanding that this specific condition entails poor prognosis, all treatment decisions must be decided on an individual basis with a multidisciplinary approach involving the patients, their family, and members of the treatment teams.

Complications of PCN and retrograde ureteral stenting

The complications profile differs for ureteral stents and nephrostomy tubes and warrants consideration when managing malignant ureteral obstruction. Patients with ureteral stents commonly experience irritative lower urinary tract symptoms and somatic pain, requiring some form of analgesia in up to 70% of patients within seven days of the procedure[21]. Other complications such as stent failure from encrustation and obstruction, ureteral perforation, stent migration, stent fracture and the forgotten stent have been well documented[22-24]. Mild hematuria is common after ureteral stenting as a result of urothelial irritation. Significant hematuria after ureteral stenting can be caused by arterio-ureteral fistula between the ureter and the common or internal iliac arteries. This rare phenomenon has been reported in the setting of pelvic malignancies treated with surgery and radiation[22]. On the other hand, external tubes and drainage bags as a part of daily PCN care have associated complications involving tube blockage, leakage and dislodgement requiring additional tube changes in up to 83% of patients compared to 16% with ureteral stents[19]. Inadvertent bowel transgression is a rare complication of PCN when the colon lies in a retrorenal position. Pleural complications including pneumothorax, hemothorax, empyema, and hydrothorax may occur in less than 0.1%-0.2% of patients[25]. Bleeding and gross hematuria may occur from puncture of intercostal vascular structures or parenchymal vessels, which are usually self-limited, requiring transfusion in 2%-4% of standard nephrostomy insertions[22]. Late arterial bleeding occurs from pseudoaneurysms, arterio-venous and arterial calyceal fistulas secondary to injury of renal arterial branches[22]. In a study by Song *et al*[26] of 70 patients managed with PCN *vs* ureteral stenting for gynecologic malignancies, 14% of patients who underwent stenting were noted to have gross hematuria one week after insertion and 8% of patients had severe hematuria after PCN insertion secondary to cancer-related poor coagulation states. These complications were managed conservatively without need for acute intervention. In addition, there was no statistically significant difference in the overall complication rates between the two groups of patients[26].

Inflammatory systemic complications such as sepsis, febrile urinary tract infections and pyelonephritis may develop as a consequence of drainage and manipulation of potentially infected, obstructed urinary systems, which are further compounded by the immunosuppressive state of advanced malignancy and subsequent systemic treatments. In studies of ureteral obstruction in advanced malignancies, Cordeiro *et al*[17] reported a higher proportion of pyelonephritis in patients treated with PCN *vs* ureteral stenting (P = 0.002). Conversely, Ku *et al*[27] reported acute pyelonephritis affecting 5.9% of patients managed with ureteral stents and 3.8% of patients with percutaneous nephrostomies, and febrile episodes in 10% and 15%, respectively. There was no statistically significant difference in the overall stent-related or nephrostomy-related complications as well as the accumulated incidence of inflammatory systemic complications between the two groups[27]. Similarly, no significant difference was observed in the incidence of urinary tract infections between the two treatment modalities[19].

While complications of PCN and ureteral stenting are well documented in the literature with variable incidences, data from comparative analyses of the two modalities are limited (Table 1), PCN and ureteral stent placement have comparable overall complication rates based on available evidence. Neither cystoscopic stent placement nor PCN insertion is exempt from major complications such as bleeding and sepsis or minor complications associated

Table 1 Percutaneous nephrostomy *vs* retrograde stent in malignant ureteral obstruction

Ref.	Study design	Cohort	Diagnosis	Stent	Complications	Nephrostomy	Complications	Mortality	Conclusions
Feng *et al*[1], 1999	Retrospective, 1984-1996	*n* = 37 (20 female) patients with ureteral obstruction due to pelvic malignancy	Diuretic renogram or abdominal CT scan	22/31 underwent successful stent placement, 13/31 (42%) remained successfully diverted with stents	Migration (1), encrustation requiring cystolitholapaxy (1), intractable pain requiring repositioning (2)	6 had primary PCN placement, 9/31 had PCN placed due to unsuccessful placement of stent, 6/22 had PCN placed due to failed internal stent, 3 failed stent but did not have PCN placement	Dislodgement requiring reinsertion (3)	NR	33% of patients with disease confined to primary organ or locally advanced disease were managed successfully by stents *vs* 36% of patients with distant metastases, 92% of cervical cancer patients required PCN (89% failed initial internal stents), 50% of prostate cancer patients required PCN but 100% of patients who initially had successful stent placement did not require PCN at average follow-up of 15 mo, 100% colon cancer patients required PCN due to failure of internal stents
Hyppolite *et al*[32], 1995	Retrospective, 1989-1994	*n* = 34 females with gynecologic malignancy	US and serum cr > 1.5 mg/dL	8 (3 had PCN as well)	6/7 (86%) developed urosepsis	17 (unilateral/ bilateral)	7/17 (41%) (1 urosepsis, 3 bleeding, 3 urine leak)	2/34 died within 2 wk and declined intervention, 3/7 who underwent stent placement died from urosepsis from procedure	Stenting predisposes to urosepsis and should be avoided. Bilateral nephrostomy allows significant improvement of renal function
Kanou *et al*[48], 2007	Retrospective, 1990-2003	*n* = 75 (45 female) patients with pelvic malignancy, patients with normal excretion from 1 kidney excluded	NR, need for primary PCN reported to be based on CT, MRI, or cystoscopic evaluation	37/51 underwent successful stent placement, 29/37 (78%) remained successful	Earlier replacement (5), discomfort requiring no intervention (2)	24 had primary PCN placement, 14/51 had PCN due to inability to place stent, 8/37 had PCN placed after failed stent	Dislodgement (9), obstruction requiring exchange (4), difficulty in exchange (2), pain/ dermatitis (3), minor hemorrhage (2)	66/75 with mean survival of 5.9 (PCN) and 5.6 mo (stent)	Higher percentage (78%) of success may be related to utilizing stents without shaft side holes
Ku *et al*[27], 2004	Retrospective, 2000-2002	*n* = 148 (80 female) patients with advanced malignancy causing ureteral obstruction	US, CT, or MRI with high grade obstruction, impaired renal function, clinical symptoms, or febrile UTI	68 (5 had antegrade stent placement), 60/68 (89%) remained successful	8 (11.8%)	80 (5 secondary PCN after failed stent placement), 1/80 failed PCN	7 (8.8%)	NR	Stenting and PCN placement have similar outcomes in terms of decreases in serum creatinine, complications, and incidence of pyelonephritis but significant differences in failure (11% stent *vs* 1.3% PCN) suggesting that patients with retrograde stenting may have ongoing obstruction requiring eventual PCN placement
Monsky *et al*[19], 2013	Prospective survey	*n* = 30 (16 female) patients with malignancy-related ureteral obstruction	Initially evaluated by symptoms of urinary obstruction such as pain, deterioration of renal function, or infection and confirmed by CT	15 patients (22 stents)	Dislodgement (1), Pain (1), Infection (1), Fistula (1)	15 patients (24 PCN)	Dislodgement (7), Pain (4), Infection (3) Obstruction (4), Leak (1)	2/30	Patients with PCN or stents have similar QOL. Patient with stents have more irritative symptoms while PCN may experience more minor complications requiring more frequent changes
Song *et al*[26], 2012	Retrospective, 2006-2010	*n* = 75 females with gynecologic malignancy	US, CT, or MRI with hydronephrosis, elevated cystanin(sic) c, or clinical symptoms	61/75 underwent stent placement, 50/61 (82%) were managed with stents successfully	16/25	14/75 underwent PCN after unsuccessful stenting, 11/61 required PCN after failure with stent management	24/50	61/75 with mean survival of 9 mo for stent and PCN cohort	Progression to PCN was noted in patients with bladder invasion and severe hydronephrosis. Multivariate analysis revealed that obstruction > 3 cm and elevated cystatin(sic) > 2.5 mg/L predicted stent failure. Stenting was less expensive and required less procedural time as compared to PCN

CT: Computed tomography; PCN: Percutaneous nephrostomy; MRI: Magnetic resonance imaging; NR: Not reported/studied; US: Ultrasonography.

with impaired quality of life.

Efficacy of PCN and ureteral stenting in malignant ureteral obstruction

In the setting of malignant obstruction, ureteral stent placement has well described technical limitations. Cystoscopic placement of ureteral stents may be technically difficult in the setting of advanced malignancy and is associated with high failure rate when extrinsic obstruction is secondary to pelvic or retroperitoneal tumors[28,29]. However, PCN requires an external collection device that often results in quality of life impairment for which some patients may initially refuse the procedure. As such, the most efficacious management of malignant ureteral obstruction has not been well established and remains controversial. In many instances, the type of urinary diversion may depend on clinician bias and expertise, procedure availability, and urgency of the diversion[30,31].

It is well reported that a percutaneous approach to malignant urinary decompression has high technical success rates[1,27,32]. When urgent relief of ureteral obstruction is the only factor in determining the modality of drainage, PCN appears to be the more reliable approach in the setting of advanced malignancy. Ku *et al*[27] reported a greater chance of progressive loss of patency after ureteral stenting compared to PCN in which the incidence of failed diversion secondary to obstruction was 11% and 1.3%, respectively. Feng *et al*[1] demonstrated initial success of stent placement in 71% of patients with pelvic malignancies with late stent failure in 41%, necessitating PCN placement with 100% success rate. In this study, 89% of cervical cancer patients failed initial stent placement and 92% ultimately required percutaneous drainage[1]. In a similar setting, Ganatra *et al*[11] reported late stent failure in more than one third of patients within 6 mo of initial stent placement. Gross tumor invasion evident at cystoscopy was a significant risk factor for stent failure with progression to PCN[11]. Song *et al*[26] reported successful management of ureteral obstruction secondary to gynecological malignancies by ureteral stenting in 67% of patients with greater trend toward PCN progression noted in patients with tumor invasion of the bladder. Other studies by Docimo *et al*[29], Cheung *et al*[33] and Yosspeowitch *et al*[34] demonstrated post-procedural stent failure rates in extrinsic malignant ureteral obstruction ranging from 42%-45%. Despite the high rate of ureteral stent failure, a difference in median survival between the two treatment modalities has not been demonstrated[26].

In general, variables such as the type and level of obstruction, renal insufficiency, degree of hydronephrosis, systemic treatment post-stenting, cystoscopic evidence of bladder invasion and length of obstruction greater than 3 cm have been found to be predictors of stent failure in the setting of malignant ureteral obstruction[11,26,33,34]. Furthermore, prostate, cervical and bladder cancers causing ureteral obstruction due to tumor invasion of the trigone have a higher primary stent failure rate compared to non-pelvic malignancies[1,20]. Therefore, primary PCN placement should be advocated in these patients. Patients with prostate cancer who underwent successful internal stent placement, however, were found to have long duration of stent function and low late failure rate[20].

In summary, PCN is an effective method of diversion in patients with ureteral obstruction secondary to advanced malignancies. This should be the primary method of decompression in patients whose tumors are visualized to involve the urinary bladder. When adequate urinary decompression has been achieved, conversion of a PCN to an antegrade stent is possible, thus eliminating the need for nephrostomy collection devices to minimize complications and improve patient independence. For patients with other pelvic or non-pelvic malignancies, retrograde ureteral stenting may be attempted. If successful, long-term drainage may be expected, however close monitoring is required for late stent failures. If stent placement is unsuccessful, percutaneous drainage remains an option and is nearly always technically successful.

PCN *VS* STENTING IN THE SETTING OF NON-MALIGNANT URETERAL OBSTRUCTION

Non-malignant causes of ureteral obstruction can be intrinsic such as stone disease, ureteral stricture or congenital ureteropelvic junction obstruction, or extrinsic such as idiopathic retroperitoneal fibrosis.

Nearly all clinicians agree that obstructing stones, with a concern for sepsis require immediate decompression of the urinary system[31]. Though large epidemiologic studies of the management of obstructed infected nephrolithiasis demonstrate higher rates of sepsis and mortality associated with PCN placement relative to ureteral stenting, the observational nature of the analysis highlights the need for prospective analyses of PCN *vs* stenting for obstructive nephrolithiasis[35]. Despite this obvious need, there are few studies comparing the efficacy of ureteral stenting *vs* PCN in the setting of obstructive urolithiasis (Table 2). The choice between PCN and stenting is often made by the urologist at initial presentation and can be influenced by factors including disease severity, stone size, location of stone, eventual modality of definitive stone management, or even availability of in-house interventional radiology services[31]. Retrospective studies reveal that both procedures have high success rates[23,36]. In the setting of unsuccessful stenting, PCN is often successful, but the contrary is not always true. Furthermore, patients are often selected for PCN over ureteral stenting in the setting of larger stones and if they are more severely ill[36,37]. Goldsmith *et al*[36] studied 130 patients who underwent decompression for obstructing ureteral stone with PCN or stent placement. Although patients who underwent PCN placement had longer hospital stay, other outcomes such as time to definitive stone management, rates of spontaneous stone passage, and initiation of stone metabolic workup were not statistically different. The authors noted that the

Table 2 Percutaneous nephrostomy *vs* retrograde stent utilization in ureteral stone disease obstruction

Ref.	Study design	Cohort	Diagnosis	Stent	Complication	Nephrostomy	Complications	Conclusions
Ahmad *et al*[23], 2013	Retrospective, 2010-2011	*n* = 300 (20/100 (stent) and 36/200 (PCN) had malignant obstruction)	NR	97/100 had successful placement, 3 proceeded to have PCN	37/97 (38%) complication rate (7 fever/sepsis, 10 bleeding/hematuria, 12 pain/irritation, 1 ureteral perforation, 2 stent migration, 5 stone encrustation	195/200 had successful PCN placement	25/195 (12.8%) complication rate (7 fever/sepsis, 9 bleeding/ hematuria, 9 dislodgement)	PCN had lower incidence of complications as compared to stenting
Goldsmith *et al*[36], 2013	Retrospective, 1995-2011	*n* = 130 patients with infected urolithiasis who underwent procedural decompression	CT and 2/4 SIRS criteria	69/71 successful stent placement, 2 proceeded to PCN	NR	58/59 successful PCN placement, 1 proceeded to retrograde stent	NR	Patients selected for PCN had larger stones and were more severely ill. Patients who underwent PCN had longer hospital stay on multivariable analysis. Time from septic event to definitive treatment, rates of spontaneous stone passage, and initiation of metabolic stone workup were the same between the two groups
Joshi *et al*[41], 2001	Prospective, non-randomized	*n* = 34 patients (22 male) with obstructing ureteral stones	X-ray, US, *IV* urography	21	NR	13	NR	Stent patients were more likely to report hematuria, dysuria, urgency as compared to PCN patients. Stent patients required analgesics more frequently than the PCN group. Patients in the PCN required more daily care as compared to stent patients. EuroQOL questionnaire revealed differences in mobility, self care, and problems with usual activity and pain between the two cohorts but no significant differences in overall QOL
Mokhmalji *et al*[38], 2001	Prospective randomized, 1996-1998	*n* = 40 patients with ureteral stone and evidence of infection	Imaging modality NR and 1 major (renal colic, fever, ston e > 15 mm, sepsis and elevated Cr > 1.7 mg/dL) or 2 minor criteria (lower UTI, wbc change, diminished patient compliance)	16/20 successfully underwent stent placement	Fluoroscopy exposure > 2 min (40%), IV analgesics (35%)	20/20 underwent initial PCN, 4/20 underwent subsequent PCN due to failed attempted stent	Fluoroscopy > 2 min (10%), IV analgesics (10%)	Time to definitive therapy was longer in stent group as compared to PCN group due to persistent signs of urinary tract infection. Unsuccessful stent placement occurred in older patients and with stones located in proximal ureter. No statistical differences in QOL but a trend to lower QOL was seen in stent patients who were male or < 40 yr
Pearle *et al*[40], 1998	Prospective randomized, 1995-1997	*n* = 42 patients with ureteral stone and evidence of infection	*IV* pyelography, US, X-ray, CT, or retrograde pyelography with WBC > 17000 mm or temperature > 38 ℃	21 underwent successful stent placement		20/21 underwent successful PCN, 1 proceeded to undergo retrograde stent placement		Fluoroscopy and procedural times shorter in stent vs PCN cohort. Higher number of positive urine cultures post-PCN was noted as compared to post-stent placement. Length of stay, blood culture positivity, and time to WBC and temperature normalization were not statistically different. Costs associated with stent placement more than twice of that of PCN. Increased back pain noted in PCN group
Yoshimura *et al*[37], 2004	Retrospective, 1994-2003	*n* = 53 (59 events) patients underwent emergency drainage with ureteral stones and SIRS criteria	NR	35 stent events	NR	24 PCN events	NR	Patients who underwent stent had smaller stones but similar rates of ICU management as compared to PCN

SIRS: Systemic inflammatory response syndrome; QOL: Quality of life; US: Ultrasound; *IV*: Intravenous; WBC: White blood cell count; NR: Not reported/studied; ESWL: Extracorporeal shock-wave lithotripsy.

method of initial decompression correlated with eventual approach selected for definitive stone management. Patients treated with PCN were more likely to undergo percutaneous definitive management, while patients managed with ureteral stenting were more likely to be treated with a ureteroscopic approach[36].

Two prospective studies comparing PCN *vs* stent management of obstructing ureteral stones have conflicting outcomes. Mokhmalji *et al*[38] in 2001 prospectively randomized 40 patients to receive either PCN or stent. Sixteen out of twenty stents were successfully placed while all twenty PCNs were successfully placed initially. All unsuccessful stents were successfully managed by PCN. Their results demonstrated that stent utilization was less successful as compared to PCN and there was a trend for longer antibiotic therapy due to persistent signs of urinary tract infection in patients who underwent stent placement. Consistent with Mokhmalji *et al*[38], a large epidemiologic survey reveals that stent failure as evidenced by the need for nephrostomy placement has been noted to be related to male gender, renal stone location, and acute kidney injury[39]. In contrast, Pearle *et al*[40] randomized 42 patients to receive PCN *vs* stents. This study failed to demonstrate one procedure to be more successful than the other[40]. All 21stents and 20 out of 21 PCNs were successfully placed. One failed PCN successfully underwent stent placement. Their results demonstrated an increased incidence of bacterial urinary colonization post-procedure in the PCN group as compared to the stent group, but overall no differences in time to clinical improvement or length of stay were noted.

In stone disease, the decision for PCN *vs* stent appears to be dictated by stone size and clinical presentation. The prospective studies looking at both procedures revealed no definitive best practice and nearly all of the studies reported on different outcomes making direct comparison impractical.

Quality of life with short-term PCN vs stent

Unlike malignant ureteral obstruction, decompression with PCN or stenting in stone disease is often short-term with eventual removal. In light of this, quality of life considerations for these patients are not necessarily the same as for those requiring long-term decompression, and should be studied in this population as well. Joshi *et al*[41] prospectively surveyed 21 stent and 13 PCN patients using the EuroQol, a validated general quality of life questionnaire, as well as procedure specific questions focusing on symptoms in three categories - dysuria, pain, and daily care. Patients were surveyed by a single interviewer on the day of definitive therapy. Patients who had stents were more likely to require analgesic medications and reported urinary symptoms such as dysuria, hematuria, and urgency. PCN patients required more daily care of nephrostomy, but overall there were no statistically significant differences in utility scores calculated from the five EuroQol domains encompassing mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Mokhmolji *et al*[38] confirmed that there were no statistically significant differences between the two procedures in terms of general well-being and state of mind when assessing patients who underwent stent *vs* nephrostomy immediately post-operatively and 2-4 wk subsequently[38]. These studies suggest that both stents and PCN decrease the quality of life and although patients did not prefer one procedure over the other, they should be made aware of potential discomforts associated with each procedure given the options.

PCN vs ureteral stent for idiopathic retroperitoneal fibrosis

Idiopathic retroperitoneal fibrosis is a rare disease of unknown etiology and is characterized by chronic inflammation within the retroperitoneum resulting in ureteral obstruction in up to 50% of cases[42-45]. Mertens *et al*[46] conducted a retrospective study of 30 patients with idiopathic retroperitoneal fibrosis involving 44 renal units from January 2002 to April 2010 with a median nephrostomy or stent dwelling time of 9.3 mo. PCN was placed as the first intervention in 27% of the entire cohort (12/44), and ultimately the majority of these patients (9/12) received subsequent ureteral stent placement[46]. In contrast, the majority of renal units (32/44) initially underwent attempted stent placement, which was successfully initiated in 79% (25/32) and successfully maintained in 80% (20/25). The authors found that the overall rate of complication (obstruction, dislodgment, bleeding requiring transfusion, acute pyelonephritis, and urosepsis) was similar for both cohorts (PCN 21% *vs* stent 17.9%; $P = 0.79$). Ultimately, the investigators concluded that both stents and PCN were safe methods of urinary tract drainage with similar complication profiles. Complementary advantages were noted and the authors concluded that both methods of drainage may be utilized given the relapsing/remitting course of disease[46].

CLINICIAN PREFERENCES FOR PCN *VS* URETERAL STENTING

Patient choice is heavily influenced by physician recommendations[47], and as there are no clinical guidelines and little published evidence directing the use of PCN *vs* ureteral stenting, physicians often rely on their personal experience and preference in advising their patients. Further, patients may receive conflicting advice from various providers, as the clinician advising intervention is often not the clinician who also performs the intervention (medical oncologist *vs* urologist *vs* interventional radiologist).

In 2006, Lynch *et al*[31] conducted a postal survey amongst 153 radiologists and 132 urologists residing in the United Kingdom to determine current opinion regarding utilization of PCN *vs* ureteral stent for acute renal obstruction. Despite a meager response rate of 19.3% (18.3% of radiologists and 19.3% of urologists), the authors demonstrated 90%-100% consensus for urinary

tract decompression for the clinical scenarios of "clinical sepsis" and "elevated creatinine and potassium", while only 50% of clinicians felt unobstruction was indicated in the scenario of "ureteral obstruction with hydronephrosis with advanced malignancy for palliation[31]. Additionally, clinicians disagreed on the method of decompression with urologists favoring PCN over ureteral stent placement more often than radiologists for all clinical scenarios (74% *vs* 49%; median preference rate urologist *vs* radiologist) other than patients with "uncomplicated benign disease" and in those patients with "coagulopathy". The authors speculated that the results were driven by logistical (availability of operating rooms and anesthesia) and patient factors (evidence of pelvic malignancy, radiotherapy, chronic upper tract stricture) rather than financial motives, given the absence of monetary incentives to providing care in the United Kingdom health system[31].

Similarly, Hyams *et al*[30] sought to compare intervention preferences for malignant external ureteral obstruction utilizing a web-based survey sent to 3000 American clinicians (1500 urologists and 1500 medical oncologists). While only 15% of urologists and 12.4% of medical oncologists responded, there was significant disagreement between urologists and medical oncologists in regards to management of hypothetical clinical scenarios. For example, oncologists were more likely to recommend PCN as the next option after stent failure in unilateral obstruction (79% *vs* 62%, $P < 0.0001$), where as urologists were more likely to suggest stent manipulation including upsizing, stent exchange, internalizing, *etc.,* (37% *vs* 17%). Further, perception of complication varied between both groups. Urologists reported the greatest risk of dislodged PCN (48% *vs* 18%, $P < 0.0001$), while medical oncologists primarily feared infection (40% *vs* 8%). In regards to indwelling ureteral stents, urologists were most concerned about the negative impact on quality of life (65% *vs* 13%, $P < 0.0001$) while oncologists were again primarily concerned with risk of infection (43% *vs* 3%). Of note, both urologists and oncologists agreed that indwelling ureteral stents afford greater comfort (87% *vs* 93%, $P = 0.07$) and quality of life (95% *vs* 93%, $P = 0.46$)[30]. Taken together, both studies indicate consensus amongst clinicians for urinary tract unobstruction in certain clinical scenarios (sepsis and AKI), yet significant divergence of opinion in other scenarios (malignant external ureteral obstruction). Additionally, the preference of PCN *vs* ureteral stenting varies both by clinician specialty and nationality[30,31]. Both groups of investigators advocate for additional prospective studies, clinical guidelines, and ultimately increased communication between specialists[30,31].

CONCLUSION

This review sought to find consensus on the use of PCN *vs* stents in the treatment of ureteral obstruction. There were no prospective studies that compared PCN *vs* stent utilization in the management of malignant ureteral obstruction. Of the retrospective studies reviewed, the majority could not find a difference in complication rates or quality of life between the two procedures. Due to the retrospective nature of the studies, success rates could not be effectively compared between the two methods as patient selection for either procedure was based often on clinician and/or patient preference. In summary, most authors recommended stent utilization as a first step if possible and nephrostomy drainage if there is concern for difficulty in retrograde access of the ureters, or in the setting requiring immediate relief of kidney dysfunction. This area would certainly benefit from additional prospective studies as often the reasoning behind initial ureteral stent placement is driven by clinician preference arising from the belief that ureteral stents provide a decreased risk of infection and increased quality of life despite studies citing no statistical differences in these areas[19,27].

Both retrospective and prospective studies were reviewed for management of obstruction due to stone disease. The retrospective studies were of heterogeneous quality demonstrating significant differences in stone size between patients who underwent PCN and stent placement. The prospective studies revealed that overall quality of life was similar although with different bothersome aspects in each of the two groups. Overall, stent utilization tended to require more analgesia as compared to PCN. The available studies revealed conflicting results on rates of infection between the two procedures, as well as time to definitive therapy, and length of hospital stay.

Although PCN and stent utilization appear to be mostly clinician-driven, certain patterns of practice are notable. Most clinicians prefer stent utilization due to presumed benefits associated with decreased rates of infection and improved patient comfort, while PCN utilization is noted for more definitive efficacy of urinary drainage. This review has revealed multiple studies showing either no difference or conflicting evidence regarding infection rates and we urge clinicians to be aware of this lack of clear superiority of ureteral stenting over PCN. Finally, given that quality of life studies have not demonstrated a clear superiority of ureteral stenting over PCN, when long term PCN and stent management is being considered, the patient should be centrally involved in the discussion, and the decision for either procedure will need to be agreed upon mutually.

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Sentinel lymph node biopsy in renal malignancy: The past, present and future

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Abstract

Sentinel lymph node biopsy (SLNB) is now an established technique in penile and pelvic cancers, resulting in a lower mortality and morbidity when compared with the traditional lymph node dissection. In renal cancer however, despite some early successes for the SLNB technique, paucity of data remains a problem, thus lymph node dissection and extended lymph node dissection remain the management of choice in clinically node positive patients, with surveillance of lymph nodes in those who are clinically node negative. SLNB is a rapidly evolving technique and the introduction of new techniques such as near infra-red fluorescence optical imaging agents and positron emission tomography/computed tomography scans, may improve sensitivity. Evidence in support of this has already been recorded in bladder and prostate cancer. Although the lack of large multi-centre studies and issues around false negativity currently prevent its widespread use, with evolving techniques improving accuracy and the support of large-scale studies, SLNB does have the potential to become an integral part of staging in renal malignancy.

Key words: Sentinel lymph node biopsy; Dynamic sentinel node; Renal malignancy; Lymphoscintigraphy; Near infra-red fluorescence; Penile cancer; Lymphatic drainage

Core tip: A number of studies have examined the use of sentinel lymph node biopsy in urogenital malignancies. In penile and prostate cancer it has been found to be a valuable tool to aid staging and accurately predict prognosis. Its use in renal cancer is poorly explored and would benefit from a better understanding of the lymphatic drainage of the kidney. It is also proposed that modifications of the technique such as use of positron emission tomography/computed tomography scanning and near infra-red fluorescence optical imaging agents may further improve the technique making it a feasible option for use in renal malignancy.

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INTRODUCTION

Renal cancer is now the 8th most common cancer in the United Kingdom and its incidence is rising[1]. Advancements in imaging modalities and easy access to ultrasounds mean that tumours are often detected earlier and consequently with a smaller size than previously. Whilst size of tumour and haematogenous spread are acknowledged to be proportionately linked, small tumours do have the potential for early lymphatic spread and distant metastases[2]. Unlike other urogenital malignancies such as penile cancer, lymphatic spread in renal cancer is often unpredictable making it unsuitable for en-block lymph node dissection[3-5].

Sentinel lymph node biopsy (SLNB) offers a well-recognised alternative to lymph node dissection and is already widely used in melanoma and breast cancer[6,7]. It is also already an accepted part of management in certain urological malignancies such as penile and pelvic malignancy[8-12]. Associated with a lower mortality and morbidity cost than the traditional alternative, it still offers clinicians the opportunity to stage disease and equally importantly, to identify patients in whom tumour resection alone may not be curative[10,13,14].

In renal cancer however, lymph node dissection and extended lymph node dissection still remain the management of choice in clinically node positive patients with renal malignancy, with surveillance of lymph nodes in those who are clinically node negative[15]. Here, we examine the potential of SLNB in renal malignancy and some of the techniques that may be implemented in the future.

LYMPH DRAINAGE AND THE KIDNEY

The use and success of SLNB is reliant on the ability to reliably predict the lymphatic drainage of the organ and the dissemination of disease in a stepwise fashion. Of all urogenital malignancies, penile cancer exhibits the most reliable lymphatic drainage, allowing us to predict with some accuracy areas where the sentinel nodes will reside[16]. Conversely, renal cancer, with the potential for both haematogenous and lymphatogenous spread is the least reliable, and it is only by using a mixture of cadaveric and sentinel lymph node mapping that basic patterns have been observed[17]. Lymph node involvement in the absence of other metastases is common in pelvic and penile cancers, but uncommon in renal cancer.

Lymphatic drainage of the kidney can be grouped into three categories relative to their position to the renal vein: Anterior, posterior and intravascular. From the right kidney, the anterior bundles drain to the paracaval, precaval, retrocaval and interaortacaval nodes. Importantly the retrocaval nodes provide a route of entry to the thoracic duct, facilitating more distant lymphatic spread. Posterior bundles drain to paracaval, retrocaval and interaortocaval nodes. Drainage from the intravascular bundles remains poorly understood[18-20].

Different from the right kidney, anterior bundles in the left kidney drain to the para-aortic and pre-aortic nodes, while posterior bundles drain to the para-aortic and retro-aortic nodes. In the case of the left kidney, it is direct from the posterior bundle, rather than *via* nodes from the anterior bundle that connection to the thoracic duct is made[17,21,22]. Lymphatic drainage from both kidneys may also run to the retroperitoneal lymph nodes, and from these spread to the thoracic duct. Overall, lymph node involvement is reported at rates of 4%-5% and considered to be a poor prognostic indicator[23,24].

Despite not offering therapeutic benefit in renal malignancy, SLNB does offer the opportunity to histologically confirm the presence of positive nodes without full lymphadenectomy. In the absence of such clarity, the current European recommendation is to wait for nodes to become clinically palpable before excision, this can have significant implications on mortality. In penile cancer, since the introduction of SLNB and immediate lymphadenectomy for node positive patient, 3 year cancer survival increased to 84%, compared to just 35% for those who had lymph nodes excised only after they became clinically palpable[25]. A further study reported a 5 year cancer survival of 91% for patients with penile squamous cell carcinoma after introduction of SLNB, compared to 82% before its introduction[13].

THE SENTINEL NODE CONCEPT IN UROGENITAL CANCER: HOW DID WE GET HERE?

The concept of a sentinel node was introduced by Halstead who proposed that tumour cells spread from the primary lesion sequentially along the lymph chain, only spreading beyond the first node once it has been overwhelmed by tumour[26]. It was Gould however, in a paper on parotid malignancy, who initially described these first nodes as sentinel nodes[27].

When SLNB was first introduced, sentinel nodes were identified solely using either intraoperative or preoperative lymphangiograms. This was first trialled for urogenital malignancy by Cabanas[28] in 1977. In a study of 100 patients he successfully proved the existence of a sentinel node in disseminated penile malignancy. In 46 of those patients he was able to perform lymphangiogram guided SLNB and from this concluded that a positive SLNB was a good indicator for further surgical intervention in the form of a full regional lymph node dissection[28]. However, this technique was associated with a high failure rate and poor reducibility as nodes were often difficult to identify and locate and the technique did not allow for anatomical variation between patients[29].

This concern was addressed with the introduction of blue dye allowing for cutaneous lymph node mapping. Once injected at the primary tumour site, the blue dye travels along the lymphatic chain to the sentinel node, making it easier for the surgeon to identify. Introduced in 1989 for melanoma, cutaneous lymph node mapping now has since been explored for use in breast, penile and cervical cancer[30-34].

The concept of cutaneous mapping was rapidly followed by the introduction of radiolabelled racer using a gamma probe. Proposed by the team at Vermont medical centre, their study, on 16 feline models, found that the use of radiolabelled tracer detected with a gamma probe was comparable to blue dye tracer but additionally allowed the surgeon to confirm excision of the correct node and determine possible presence of residual lymph nodes[34].

In 2000, Horenblas *et al*[32] examined the feasibility of dynamic SLNB (DSNB) in penile cancer. Using a combination of lymphoscintigraphy, patent blue dye and a gamma probe they concluded that DSNB held potential as a promising staging technique[35]. Their conclusion, supported by Tanis *et al*[8] who cited an 80% sensitivity for this procedure, cemented the role of DSNB in penile cancer. It was in this form that the Augsberg group introduced DSNB to prostate cancer[36]. They successfully demonstrated the validity of DSNB for use in prostate cancer and in a further study of 117 patients, the same group demonstrated a sensitivity of 96% for the procedure, a validation replicated in bladder cancer in Sherif *et al*[37]'s study of 13 patients[38]. They concluded that not only can DSNB be used to identify sentinel nodes in patients with known bladder cancer but that it has the additional advantage over traditional lymphadenectomy of identifying nodes outside the standard lymphadenectomy areas.

TAILORING THE SENTINEL NODE CONCEPT FOR RENAL CANCER

It was Bernie *et al*[39] in 2003 who introduced DSNB to renal cancer. Combining the use of blue dye and intraoperative gamma probes they successfully demonstrated that in 40 porcine models, excised sentinel nodes exhibited an increased radioactive count when compared to controls[39].

In 2010 Bex *et al*[40] continued the work of Bernie, confirming the use of sentinel node mapping in renal malignancy in human models. They successfully demonstrated that the use of pre-operative lymphoscintigraphy combined with the injection of technetium 99m under either ultrasonography (US) or computed tomography (CT) guidance can be used to identify sentinel nodes in renal malignancy.

Single-photon emission computed tomography (SPECT) CT combines single proton emission computed tomography with CT in order to provide more precise information about the presence and location of sentinel nodes. The concept of such anatomical fusion imaging, as an alternative to planar lymphoscintography was first introduced for use in prostate cancer in 2005. That study successfully demonstrated that images from CT scan and SPECT scanning could be superimposed in all 12 of the patients studied and successfully identified 87% of lymph nodes[41]. A Swedish study in 2006, expanded this work to bladder cancer when they successfully demonstrated that SPECT CT scanning detected 21 sentinel nodes in five patients, compared to just two with planar lymphoscintography[42].

In 2011, Sherif *et al*[37] trialled SPECT CT for use in lymph node mapping for renal cancer. Their study of 13 patients introduced pre-operative SPECT scanning to lymph node mapping in renal malignancy. They combined lymphoscintigraphy and SPECT CT imaging, with both radiolabelled tracer and patent blue dye in order to identify sentinel nodes. This study successfully detected 32 sentinel nodes in 10 of 11 patients, 28 of which were detected by the use of radiolabelled tracer. The patent blue dye was used in 8 patients but only identified sentinel nodes in one patient[43].

SLNB IN RENAL CANCER: WHERE NEXT?

SLNB in renal cancer, still lags well behind its penile and pelvic counterpart and has some way to go before a widespread implementation can be considered. In addition to concerns about small studies, concerns about sensitivity-in particular false negatives, and patient selection remain.

Renal cancer is not alone in these concerns, with many papers initially raising similar concerns around false negative rates in penile and pelvic cancers. A study of 2020 patients undergoing SLNB for prostate cancer cited a false a negative rate of 6.2%, whilst a study in 2011 of SLNB in penile malignancy cited an even higher rate of 15%[44,45]. In both cases, figures are controversial and highly variable, and measures such as pre SLNB CT to exclude macrometastases, a potential cause of false negatives, have been implemented[8,44,46,47]. More importantly, SLNB has overcome these problems to become part of the accepted management for both penile and pelvic cancers.

Below, we discuss alternative or additional techniques that are currently being explored in other urogenital malignancies. These may hold the solution for the redemption of SLNB for use in renal malignancy.

IMPROVING SENSITIVITY

Near infra-red fluorescence optical imaging agents (NIRF) is a non-radioactive, more penetrative alternative to radiolabelled tracers and patent blue, which may provide the solution to concerns around sensitivity. First introduced in 2003 in mice models, it was initially studied in breast cancer, with Melancon *et al*[47] successfully demonstrating that NIRF provided a superior alternative

to T1 weighted MR, identifying all six cervical nodes, compared to just four[48]. The first use of NIRF in urogenital malignancy was in 2011, when lymphatic pathways in prostate cancer were mapped with indocyanine[49]. NIRF has since been used bladder cancer and in robot assisted SLNB in both bladder and prostate cancer[50,51].

The introduction and acknowledgement of NIRF as a tracer, has led to the potential for a hybrid tracer, combining the fluorescence of NIRF with the well-established pharmacokinetics and bio-distribution of radiocolloids such as technetium 99m. The use of a multimodal tracer was first studied in mice in 2011[52]. Since then its use has been studied in prostate and melanoma with the finding that it is equally effective tracer with faster distribution than blue dye[53,54]. Similarly in penile cancer, a study of 65 patients, cited an increased sensitivity (96.8%) compared to patent blue dye alone (55.7%)[55].

The use of positron emission tomography/CT (PET/CT) as part of the SLNB procedure has also been explored as a means of improving false negative rates. Here fluorodeoxyglucose PET/CT scan was performed routinely preoperatively in patients undergoing SLNB for penile squamous cell carcinoma. In a study of 129 patients, involving 254 basins, use of both techniques, reduced false negative rates to 5.6%, proving that it may have potential to improve the SLNB technique[56]. PET/CT has been more vigorously explored in breast cancer, where a study of 191 patients concluded that it had the highest specificity of Ultrasound and MRI, but that it required all 3 in combination to reach the highest sensitivity[57]. There is no current available work on its role in SLNB for renal cancer and its impact here remains to be seen.

IMPROVING PATIENT SELECTION

Patient selection remains one of the challenges of lymph node disease. At present all patients who are clinically node positive in all urological malignancy undergo full regional lymphadenectomy. Historically, those with node negative disease in penile and bladder cancer were undergoing SLNB despite concerns that a high false negative rate means that disease may go unidentified. To address this, colleagues in the Netherlands introduced an ultrasound scan for patients with clinically node negative disease. Any suspicious nodes visualised underwent fine needle aspiration and cytology. Those with a negative FNAC or absence of suspicious nodes proceeded to SLNB procedure, consisting of lymphoscintigraphy and injection of patient blue, whilst those with a positive FNAC proceeded straight to inguinal lymph node dissection. The introduction of the pre-operative ultrasound, combined with a decision to explore all groins after lymphoscintigraphy, rather than those with suspicious nodes, reduced their false negative rate from 19.2% to 4.8%[58]. Similarly, a study of 500 inguinal basins, cited a 91% sensitivity rate with blue dye and radiolabelled tracer, which rose to a 94% with the introduction of the pre-operative ultrasound[59].

An alternative solution would be the introduction of mathematical algorithms such as the Partin table and Briganti nomograms used in prostate malignancy. These algorithms calculate the likelihood of lymph node involvement, and only those with a high calculated risk proceed to lymphadenectomy[60,61]. The concept of identifying risk factors for positive lymph nodes in renal malignancy was first introduced in 2004 but it was Hutterer who created the first nomogram in 2007[62,63]. In 2015 local symptoms, clinical node stage and lactate dehydrogenase were identified as independent predictors of lymph node disease, using all of these as determining factors in their nomogram which they cited as having a concordance index of 0.89[64]. Further work and external validation has yet to be published and there is no current evidence to suggest that it could be extrapolated for an incorporation into use for SLNB.

IMPROVING MORBIDITY

One of the acknowledged benefits of SLNB when compared to the traditional alternative of lymphadenectomy is a reduced morbidity[65]. This could be reduced further with the introduction of laparoscopic sentinel nodes, a theory explored by Kamprath *et al*[66] in 2000, when they proved that laparoscopic sentinel nodes in cervical cancer would result in lower morbidity and also reduce post-operative pain, with shorter duration of stay when compared to an open procedure. Such a procedure has already been trialled in prostate cancer with good effect[67].

Similarly, the SLNB has the potential to be performed robotically. This concept was explored by Rossi *et al*[68], who concluded that a robotic lymph mapping procedure for use in endometrial and cervical cancer was not only feasible, but an efficient and reliable technique. A further study successfully used NIRF to identify sentinel drainage in pelvic cancers in robot assisted procedures[50,51]. Whilst no direct comparisons have been made between traditional SLNB techniques and the robotic technique, a study comparing robotic and open surgical staging for endometrial cancer, demonstrated a lower incidence of post op ileus, duration of say, infection and cardiopulmonary complications in patients who underwent a robot procedure whilst still achieving similar lymph node yields[69]. If such findings can be extrapolated to SLNB and in particular to renal cancer, this may have a positive impact on morbidity.

CONCLUSION

SLNB offers the potential for accurate staging in renal cancer, the accuracy of which may have huge implications for prognosis. In its current form however, SLNB lacks not only the support of large, multi-centre studies but, like its predecessors in penile and pelvic malignancy, continues to be plagued by concerns around high false negative rates. With the investigation

and implementation of enhanced techniques, and support from large cohort size studies, SLNB does have the potential to become an integral part of staging in renal malignancy.

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Experimental models of renal calcium stones in rodents

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Abstract

In human nephrolithiasis, most stones are containing calcium and are located within urinary cavities; they may contain monohydrate calcium oxalate, dihydrate calcium oxalate and/or calcium phosphates in various proportion. Nephrolithiasis may also be associated with nephrocalcinosis, *i.e.*, crystal depositions in tubular lumen and/or interstitium, an entity which suggests specific pathological processes. Several rodents models have been developed in order to study the pathophysiology of intrarenal crystal formation. We review here calcium rodent models classified upon the presence of nephrolithiasis and/or nephrocalcinosis. As rodents are not prone to nephrolithiasis, models require the induction of a long standing hypercalciuria or hyperoxaluria (thus explaining the very few studies reported), conversely to nephrocalcinosis which may occur within hours or days. Whereas a nephrotoxicity leading to tubular injury and regeneration appears as a critical event for crystal retention in nephrocalcinosis models, surprisingly very little is known about the physiopathology of crystal attachment to urothelium in nephrolithiasis. Creating new models of nephrolithiasis especially in different genetic mice strains appears an important challenge in order to unravel the early mechanisms of urinary stone formation in papilla and fornices.

Key words: Nephrolithiasis; Nephrocalcinosis; Oxalate; Crystal; Urothelium

Core tip: We review here calcium rodent models classified upon the presence of nephrolithiasis or nephrocalcinosis which appear as two different entities. Nephrocalcinosis appears related to tubular cell injuries in the setting of urinary supersaturation whereas the pathophysiology of nephrolithiasis is mostly unraveled. Though few models are available, attachment of crystals in the fornix or in the

papilla appear as a striking feature. Creating mice models of nephrolithiasis are thus required to understand the interaction between crystals and urothelium.

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INTRODUCTION

Renal stone is a common disease, occurring in 8% of the population. This disease is multifactorial and mainly considered related to environmental factors, especially western diet[1]. Calcium stones are encountered in 80% of cases and contain calcium oxalate (72%), phosphate oxalate (14.7%) and often a mixture of the two[1,2]. Among calcium oxalate crystals, calcium oxalate monohydrate crystalline form is oxalate dependent, whereas calcium oxalate dihydrate crystalline form is calcium dependent. Calcium deposits can be located within urinary cavities, in papilla and also in medullar collecting ducts as described in Cacchi-Ricci disease[3]. Thus, though urine supersaturation is a prerequisite and accounts for crystal composition, it does not explain the diversity of calcium stone localization[4]. Several animal models have been developed to investigate the pathophysiology of calcium oxalate nephrolithiasis, in rodent but also in larger animals such as porcine model[5]. However, a majority of studies were performed in rodents due to an ease of access though most models lead to nephrocalcinosis instead of nephrolithiasis. Surprisingly, very few studies were performed in mice despite the possibility to create transgenic animals in order to study the early mechanisms of urinary stone formation in papilla and fornices.

We review here rodent models of calcium renal stone according to the presence of nephrocalcinosis, nephrolithiasis or the presence of the two features.

MODELS OF NEPHROCALCINOSIS

Oxalate minipumps

Administration of potassium oxalate (1.5 mol/L) by subcutaneous osmotic minipumps induces nephrocalcinosis in male Harlan-Sprague Dawley rats[6,7]. Hyperoxaluria is detected as soon as day 1 and intrarenal deposits of COM crystals (birefringent crystals) are present mostly in tubules by day 14 with no reported renal failure. Interestingly, renal morphology of kidneys is normal although localized regions of inflammation are present. In some focal sites, tubular debris with cytoplasm vacuolization and also some regenerating tubules are present. At the time of crystal retention osteopontin (OPN), tumor necrosis factor (TNF) and kidney injury molecules (KIM) synthesis are significantly increased as assessed by northern blot[6] further assessing tubular injuries. No crystal retention within urinary cavities is reported (Table 1).

Intraperitoneal administration of oxalate

A single injection of sodium oxalate solution (7 mg/100 g body weight) in male Sprague Dawley rats is responsible for hyperoxaluria and CaOx crystals within tubules[8]. Some small crystal aggregates are indeed present by 1 h in the loop of Henle, by 3 h in collecting ducts and by 6 h on papillary tips. Interestingly, crystals are initially intraluminal and later are located in tubular cells and also in the interstitium. CaOx crystals aggregate into tubular lumen leading to obstruction and lumen dilatation, with tubular cells necrosis, luminal cellular debris and exposure of basal lamina[8]. The authors suggest that calcium oxalate crystals would appear in the lumen within proximal tubular segment and would coat cellular debris and urinary macromolecules, thus enhancing self aggregation and finally leading to tubular obstruction. Simultaneously, at the papillary tip, urothelial cells are injured with crystal deposits forming lesions suggestive of Randall Plaques[8].

Ethylene glycol administration

Ethylene glycol (EG) administration is a well-known model of nephrocalcinosis: EG metabolizes into glycolate, glyoxylate, and oxalate leading to COM crystals in both urine and kidneys[9]. Rats receiving EG-supplemented drinking water (0.75% vol/vol) develop hyperoxaluria and hypercalciuria one day after initiation[10]. Moreover, intra tubular crystal deposits are detected as soon as day 1 both in medulla and cortex altogether with tubular injury, dilatation, regeneration and interstitial inflammation. Several macromolecule such as OPN, bikunin or Tamm-Horsfall (TH) protein that could either inhibit or promote calcification are also induced[11]. Of notice, glycolate and glyoxylate metabolites seem to modify normal tubular epithelium into a crystal-binding epithelium[10]. This EG model is currently used to study crystal binding molecules, crystal clearance and the relevance of several macromolecular inhibitors such as OPN in crystal retention[10,12,13].

Hydroxyproline administration

The amino acid hydroxyproline (HyP) is a precursor of oxalate. In physiological conditions, HyP is first metabolized in mitochondria into glyoxylate and further metabolized to glycine by alanine glyoxylate aminotransferase (AGT) or to glycolate by glycolate reductase. Finally, glycolate is oxidized to oxalate by lactate dehydrogenase (LDH)[14,15].

Diet supplements: After 7 d of exposure, Sprague-Dawley rats supplemented with HyP 5% in diet, develop a hyperoxaluria and many urinary crystals (a mixture of COD, COM, struvite and CaP crystals)[16]. Noteworthy, after 28 d of supplements, all rats develop CaOx deposits in both medulla and cortex tubules, with some plaques

Table 1 Rodent models of nephrocalcinosis

Ref.	Species	Crystal main compounds	Crystals location	Animal Model	Read out	Urinary phenotype	Renal injury
Tawashi *et al*[17], 1980	Rats	CaOx	Tubules	HyP injection *i.p.* (10 mL/kg),	1 d	Hyperoxaluria	Kidney dilatation, oedema
Khan *et al*[8], 1982	Rats	CaOx	Tubules, interstitium, papillary tips	Sodium oxalate Injection (7 mg/100 g body weight)	1 h	Hyperoxaluria	Tubular obstruction and dilatation
Marengo *et al*[6], 2004	Rats	COM crystals	Tubules (cortex, medulla)	potassium oxalate SC (Minipump)	14 d	Hyperoxaluria	Tubular injury, dilatation, regeneration, interstitial inflammation
Vervaet *et al*[10], 2009	Rats	COM crystals	Tubules	Ethylene glycol (0.75%)	1-6 d	Hyperoxaluria	Tubular injury, dilatation and regeneration, interstitial inflammation
Khan *et al*[16], 2006	Rats	CaOx	Tubules (cortex, medulla), Papillary tips (plaques § stones)	5% Hyp supplement	28 d	Hyperoxaluria	Inflammation, tubular injury
Mo *et al*[20], 2004	Mice	CaOx	Collecting ducts (medulla, papilla)	Tamm-Horsfall KO mice	2-4 mo		ND
Chau *et al*[23], 2003	Mice	-CaP	Tubules (cortex, medulla), Papilla	Npt2 KO mice + HyP supplement (4 wk)	From birth	Hypercalciuria, Hyperphosphaturia	ND
Knight *et al*[24], 2012	Mice	CaOx (COM + COD)	Tubules (Cortex, medulla) interstitium	GRHPR KO mice	After 4 wk (HyP supplements)	Hyperoxaluria	ND

CaP: Calcium phosphate; CaOx: Calcium oxalate; COM: Calcium oxalate monohydrate; COD: Calcium oxalate dihydrate.

and stones in papillary tips[16]. In this model, crystal deposits are also associated with inflammation and damaged tubules; OPN is also up-regulated in tubules surrounding crystals; and hypercalciuria does not seem mandatory for renal CaOx deposits.

Intraperitoneal administration: In Sprague-Dawley rats i.p. administration of high dose of HyP (2, 5 g/kg), is followed by a massive deposition of calcium oxalate in renal parenchyma within 24 h with presumably an acute renal failure: Increased kidney volume and weight kidney, inflammation and oedema[17].

Genetically modified animals

TH KO mice: Tamm Horsfall protein is synthesized by renal tubules and abundant in mammalian urine[18,19]. TH is considered as a critical nephrolithiasis inhibitor, acting against crystal growth and aggregation[1]. Indeed, TH KO mice between 2 and 4 mo old have crystal deposits located in medullar collecting ducts[20]. Additional treatment with vitamin D and EG (1% in drinking water) for one month is responsible for a significant increase of crystal deposits especially in ascending limb of Henle loop (outer medulla), where TH is normally expressed. This model demonstrates the physiological relevance of TH protein in nephrocalcinosis prevention. Some studies suggest that the presence of Ca^{2+}-binding domains and negatively charged sialylated residues would explain TH crystal inhibiting property[21].

Npt2 KO mice: Co-transporters sodium/inorganic phosphate (Na/Pi) located in proximal tubules mediate 60%-70% of filtered phopshate reabsorption[22]. In this nephron segment, Na/Pi Type Ⅱa (Npt2) represents 80% of Na/Pi cotransporter mRNA and plays a major role in the maintenance of Pi homeostasis[23]. $Npt2^{-/-}$ mice are hypophosphatemic due to a renal Pi leak which in turn increases calcitriol synthesis resulting in the occurrence of hypercalciuria. Renal sections of $Npt2^{-/-}$ pups mice display crystal deposits within tubules both in cortex, medulla and papilla. Interestingly, renal calcifications are increased in newborns and weaning pups and decrease thereafter in adult mice suggesting that the magnitude of urinary calcium and phosphate would be critical factors in this model. Accordingly, crystal deposits are mainly composed of hydroxyapatite (a calcium phosphate species) which is consistent with both a renal phosphate wasting and hypercalciuria. In this model, OPN is also up-regulated and expressed in tubules in the vicinity of apatite crystals. The reversal of crystal deposits appears also here as a remarkable feature.

GRHPR KO mice: Primary hyperoxaluria is a monogenic disease resulting from a liver enzyme deficiency. In type 1 primary hyperoxaluria, alanine glyoxylate aminotransferase, which catalyze transamination of glyoxylate to glycine in physiological conditions is deficient. In type 2, two enzymes are dysfunctional (glyoxylate reductase and hydroxypyruvate reductase), which normally catalyse the reduction of glyoxylate to glycolate and hydroxypyruvate to D-glycerate[14]. Hence, increased glyoxylate which is finally oxidized to oxalate[24] is responsible for a massive hyperoxaluria leading to nephrocalcinosis in human. Mice deficient in glyoxylate reductase (GR)/hydroxypyruvate reductase (GRHPR) or in alanine glyoxylate amino-transferase (AGT KO) develop as expected an inadequate

Table 2 Rodent models of nephrolithiasis

Ref.	Species	Crystals main compound	Crystals location	Animal model	Read out	Urinary phenotype	Renal injury
Bushinsky *et al*[25], 2006	Rats	CaP[2] CaOx[1]	Renal cavity (fornices) Papilla	Hypercalciuric rats (Genetic selection) under supplements [3]calcium 1.2% [4]calcium 1.2% + HyP 5%	18 wk after birth	Hypercalciuria Hyperoxaluria	None
Unpublished personal data	Mice	CaOx	Renal cavity (fornices)	Water supplement: HyP 4% + vitamin D (1000 UI) + ammonium chloride (0.28 mol/L) + calcium (0.25%)	15 d	Hypercalciuria Hyperoxaluria Hypocitraturia	None

[1]Indicatethe CaP or Paox nature of crystal obtained either with [3]calcium 1.2% or [4]calcium 1.2% + HyP 5% as indicated column 5 above; [2]Have been erased. CaP: Calcium phosphate; CaOx: Calcium oxalate; HyP: Hydroxyproline.

removal of glyoxylate[24], with nephrocalcinosis occurring only in 25% of untreated GRHPR mice (crystal deposits are mostly intraluminal and few are located in the interstitium). However, after Hyp administration (1% in the diet) for one month, all GRHPR KO mice develop severe nephrocalcinosis, but only 20% for AGT KO mice. These data further strengthen the remarkable resistance of mice to renal crystal retention.

MODELS OF NEPHROLITHIASIS

Genetic hypercalciuric stone forming rats

Hypercalciuria is present in many patients with kidney stones (40%) and is often considered idiopathic. Hypercalciuria leads to urine supersaturation and thus increases calcium renal stone risk factors[1,25]. Genetic hypercalciuric stone forming rats (GHS) (selected for 70 generations) have urine calcium excretion 8 to 10 fold above normal values. The authors demonstrated that hypercalciuria stems from 3 mechanisms: (1) an increased calcium intestinal absorption; (2) an decreased (Calcium sensor dependent) calcium tubular reabsorption; and (3) an increased bone resorption[25]. As a matter of fact, after 18 wk of age, all GHS rats develop kidney stones. Noteworthy, stone composition is mostly apatite ($CaHPO_4$) when animals are fed with a standard 1.2% calcium diet, probably explained by urine $CaHPO_4$ supersaturation which increases faster than CaOx supersaturation[26]. Conversely, an additional diet supplement of HyP 5% induces CaOx stones formation[27] with crystal deposits mainly in contact with urothelial cells lining the papilla and in the fornix areas. Interestingly, similarly to tubular cells surrounding crystals, some urothelial cells in contact with crystals are indeed proliferating and also expressing high levels of OPN[28]. This model thus appears very close to human renal stone disease as no nephrocalcinosis is observed though very rare and scattered crystal deposits may be detected within renal parenchyma (Table 2).

Hydroxyproline supplement in drinking water

Whereas Hyp administration in the diet induces nephrocalcinosis, Khan *et al*[16] reported crystal deposits in renal pelvis and fornices after rat exposure to Hyp in drinking water for 28 d. A very few crystals are also seen in the tubules and in the papillary base. This model, thus also looks very similar to human nephrolithiasis disease since most crystals are located within urinary cavities. Conversely to rats, mice develop mainly nephrocalcinosis after Hyp administration in drinking water (see below).

MODELS OF NEPHROCALCINOSIS ASSOCIATED WITH NEPHROLITHIASIS

Glycolic acid administration

Administration in male Wistar-strain rats of a glycolic acid diet during 4 wk leads to hyperoxaluria and CaOx tubular crystals both within cortex and medulla but also in pelvic cavities[29] (Table 3).

Vitamin B-6 deficient diet

The liver enzyme alanine/glyoxilate amino-transferase which plays a key role in the conversion of glyoxylate (oxalate precursor) to glycine is vitamin B6 dependent; thus, vitamin B6 deficiency causes its dysfunction[30]. Indeed, vitamin B6 deficient diet induces hyperoxaluria and hypocitraturia. Urinary oxalate excretion increases within 2 h after an intravenous hydroxypyruvate load in vitamin B6 deficients rats. These rats develop both calcium oxalate deposits in tubules, plaques on papillary tips and stones in renal fornices, pelvis and bladder[31]. Another study slightly differs and shows only nephrocalcinosis with CaOX and CaP crystals in the papillary and parenchyma, tubular atrophy, interstitial fibrosis and chronic inflammatory infiltration[32].

Small bowel resection

Ileal resection (IR) or bypass in humans may lead to massive hyperoxaluria and nephrolithiasis due to increased intestinal oxalate absorption[33,34]. Indeed, CaOx nephrolithiasis has been estimated to occur in 15%-30% of patients after intestinal bypass surgery[35]. The surgery decreases bile and pancreatic actions which trigger a poor fat absorption resulting into decreased calcium oxalate complexes and increased free oxalate (and oxalate salts which are efficiently absorbed in the colon segment) in intestinal lumen. Thus, dietary oxalates absorption increases leading to increased oxalate urine excretion[35]. Moreover, these patients share a tendency to chronic volume contraction due to loss of water and

Table 3 Rodent models of nephrocalcinosis/nephrolithiasis

Ref.	Species	Crystals main compound	Crystals location	Animal model	Read out	Urinary phenotype	Renal injury
O'Connor *et al*[35], 2003	Rats	CaOx CaP	Collecting ducts in cortex, medulla and papillary tips Urinary pelvis	Intestinal resection (40-45 cm)	4 mo after surgery	Hyperoxaluria, Hypocitraturia	Interstitial inflammation
Ogawa *et al*[29], 1990	Rats	CaOx	Cortex and medulla tubules	Glycolic acid supplements	4 wk	Hyperoxaluria	
Di Tommaso *et al*[32], 2002	Rats	CaOx CaP	Tubules, plaques on papillary tips, renal fornices, pelvis and bladder	Vitamine B6 deficient diet	12 wk	Hyperoxaluria, hypocitraturia	Tubules, inflammation

CaP: Calcium phosphate; CaOx: Calcium oxalate.

salt in diarrheal stool, which leads to decreased urine volumes. They also have decreased absorption, and therefore diminished urinary excretion, of citrate and magnesium, which normally act as inhibitors of CaOx crystallization[34].

Intestinal resection (distal ilium) performed on male Sprague-Dawley rats fed individually with a low calcium and hight oxalate diet (0.02% calcium, 18% lipid, 1% sodium oxalate) reproduces hyperoxaluria, hypocitraturia and nephrocalcinosis (by 4 mo). Calcium deposits are located in the cortex, medulla and papillary tip and contain CaOx, apatite and calcium carbonate[35]. Of notice, crystal deposits are present in several collecting ducts associated with interstitial inflammation; crystal aggregates are detected near the fornix and 87% of kidneys display some calculi within pelvic lumen, measuring 0.5-2 mm[35]. This model thus appears very similar to human enteric hyperoxaluria with both nephrocalcinosis and nephrolithiasis.

CONCLUSION

Concerning renal calcium stones, the most striking difference between rodents and humans lies in a special resistance of rodents to crystal retention noteworthy in female mice[36]. Among all models, a hydroxyproline enriched diet responsible for both nephrocalcinosis and nephrolithiasis appears close to conditions encountered in a clinical setting when patient intakes of proteins are high. Nephrocalcinosis appears in several models due to the severity of oxalate burden but focusing data also epithelial phenotypical changes following injuries and/or crystal exposure would be a requirement for the onset of crystal adhesion and intratubular nephrocalcinosis, a mechanism called "fixed particle theory". *In situ* macromolecular inhibitors would in supersaturating condition unexpectedly promote crystal aggregation. The models associating nephrolithiasis and mild nephrocalcinosis suggest that such processes may be, at various degrees, more frequent in humans than expected. To date, no reliable models for Randall plaques are available with only two nephrolithiasis models but all in rats. Despite the differences between humans and rodents mentioned above, creating a nephrolithiasis model in mice appears indeed an important challenge in order to better understand the early of urinary stone formation in papilla and fornices, the weight of calcium intake or absorption, enhanced bone resorption, and relevant macromolecules at play. It should also allow to test whether the "fixed particle theory" also applies to urothelium. Studying a nephrolithiasis model in specific genetically modified mice could also provide a deep insight into the very efficient rodent crystal clearance processes with potential translational applications.

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How botulinum toxin in neurogenic detrusor overactivity can reduce upper urinary tract damage?

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Author contributions: Baron M did the literature search and drafted the manuscript; Grise P did the literature search and added critical revision and comments to the manuscript; Cornu JN did the literature search, finalized the manuscript, provided critical revision of intellectual content, and supervised the work.

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Abstract

Intradetrusor injections of botulinum toxin are the cornerstone of medical treatment of neurogenic detrusor overactivity. The primary aim of this treatment is to ensure a low pressure regimen in the urinary bladder, but the mechanisms leading to long-term protection of the urinary tract remain poorly understood. In this paper, we highlight the potential benefits of intradetrusor injections of botulinum toxin regarding local effects on the bladder structures, urinary tract infections, stone disease, vesico ureteral reflux, hydronephrosis, renal function based on a comprehensive literature review.

Key words: Botulinum toxin; Urinary tract infection; Kidney function; Neurogenic detrusor overactivity; Hydronephrosis; Urolithiasis

Core tip: Intradetrusor injection of botulinum toxin prevent damage of the upper urinary tract *via* several potential mechanisms including reduction of bladder pressure, urothelium and suburothelium modifications, sensory receptors expression, and hypoxia reduction. These data could explain the favourable effects of intradetrusor injection of botulinum toxin on urinary tract infections, stone disease, vesico ureteral reflux, hydronephrosis, renal function.

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INTRODUCTION

Neurogenic lower urinary tract dysfunction is a highly prevalent disease, impairing significantly patient's quality of life, and results in a huge medico-economic burden[1]. In particular, neurogenic detrusor overactivity (NDO)

is a common feature in the context of neurological diseases, resulting most of the time in urgency, increased frequency and urge urinary incontinence (UUI)[2]. NDO (which can be associated with sphincter dyssynergia) is also at high risk of upper urinary tract deterioration in the long term, because of high bladder pressure, low BC and low bladder capacity. A bladder pressure > 40 cmH_2O has indeed been stated as the major urodynamic warning for upper urinary tract deterioration[3]. This increase in bladder pressure can be due to NDO but also to detrusor sphincter dyssynergie in itself, that may need a specific treatment. The current review will only deal with the effect of botulinum toxin injection in the detrusor to treat NDO.

The management of NDO has two aims. While patients often focus on symptom relief (especially UUI), another objective is the long term protection of the upper urinary tract, in order to preserve renal function. To achieve these goals, NDO management must restore a continent, low pressure reservoir without vesico ureteral reflux (VUR), along with an adequate capacity and a good compliance. The first line treatment of NDO is antimuscarinics but many patients do not respond to antimuscarinics therapy, and require further treatment[4].

Intradetrusor injections of botulinum toxin are one of the options available in patients who do not respond to medical therapy. This approach has now been approved and is extensively used for NDO management[5]. Two types of botulinum toxin are available on the market: Abobotulinum toxin-A (Dysport) and onabotulinum toxin-A (Botox). Whilst the clinical efficacy of the treatment has been assessed in well-designed prospective studies and meta-analyses, the long term effect on prevention of upper urinary tract disease such as urinary tract infections (UTIs), VUR, hydronephrosis, stones, and chronic kidney disease is not fully understood yet.

The aim of this review was to summarize available evidence about how botulinum toxin can prevent upper urinary tract disease in a context of NDO.

EVIDENCE SYNTHESIS

Bladder effect

Urodynamic data: In addition to relief of lower urinary tract symptoms, intradetrusor injections of botulinum toxin have been shown to substantially modify the results of urodynamic studies in patients with NDO. Schurch *et al*[6] in 2000, for the first time, injected 300 UI of botulinum-A toxin (Botox) in the detrusor of 21 patients with spinal cord injury (SCI) who had UUI by DO refractory to antimuscarinics. At 6 wk, 17 out of 19 patients (89.4%) had complete continence. The overall mean reflex volume (RV) significantly increased from 215 ± 90.4 mL before the injections to 415.76 ± 211.1 (P = 0.016) after the injections. The mean maximum cystometric bladder capacity (MCC) significantly increased from 296 ± 145.2 to 480 ± 134.1 (P = 0.016), respectively. There was also a significant decrease after treatment in mean maximum detrusor voiding pressure (MDP) from 65.6 ± 29.2 cm water to 35 ± 32.1 (P = 0.016). Mean post-void residual urine volume (PVR) catheterized at the end of the urodynamic examination increased significantly from a mean of 261.8 ± 241.3 mL to 490 ± 204.8 (P = 0.016).

Following this first proof of concept, a number of other trials have investigated the changes in UDS after Intradetrusor injections of botulinum toxin. Through another prospective randomized, placebo controlled, double-blind, multi-center in 2005, Schurch *et al*[7] have found no significant difference between 200UI and 300UI of onabotulinum toxin A injections. However this comparative study was focused on incontinence episodes as a primary endpoint and do not allow conclusion about the comparison of urodynamic features. Reitz *et al*[8] in a prospective, open labeled study, used 300 U of Botox in the detrusor of 231 neurologic patients [167 SCI, 11 MS, 22 myelomeningocele (MMC)]. The evaluation was made at 12 and 36 wk. At 12 wk, the mean MCC increased significantly from 272 to 420 mL (P < 0.0001) while the mean MDP decreased from 61 cmH_2O to 30 cmH_2O (P < 0.0001). The mean bladder compliance (BC) also increased significantly from 32 mL/cmH_2O to 72 mL/cmH_2O and the mean PVR increased from 236 to 387 mL (P < 0.0001). At 36 wk, the results were quite similar although the mean BC was not significantly different from baseline (32 mL/cmH_2O to 51 mL/cmH_2O). These urodynamic data were correlated with a rate of 132 (73.3%) patients fully continent at 12 wk.

In a long term follow-up of 17 SCI patients at 6 years after 300 UI botulinum-toxin A injections, Giannantoni *et al*[9] in 2009 showed persistent urodynamics modifications. The unhibited detrusor contraction (UDC) first volume increased significantly from 213 ± 40.8 at baseline to 344 ± 32.6 at 4 mo, 365.4 ± 49.7 at 1 year, 410.8 ± 60.2 at 3 year, 413.7 ± 58.9 at 6 years (P < 0.001 between baseline and 6 years follow-up). Correspondingly the UDC maximum pressure decreased from 97.6 ± 32.4 to 23.8 ± 10.8 at 6 years (P < 0.01) whereas maximum cystometric capacity increased from 243 ± 64.7 to 420.8 ± 55.7 (P < 0.001).

The results are quite similar with Abobotulinum toxin A (Dysport). Del Popolo *et al*[10] in 2008 have retrospectively evaluated three Dysport doses (500 U, 750 U and 1000 U) in 199 patients with SCI and NDO refractory to antimuscarinics. The evaluation was made at 3, 6 and 12 mo. The mean MCC increased significantly from 226 to 407 mL after the first injection and was still at 380 after seven injections while the mean BC significantly increased from 27 mL/cmH_2O to 41 mL/cmH_2O after one and seven injections. There was no significant difference between all doses. In 2010, our team has reported the comparison of two Dysport doses (500 U and 750 U) in a prospective, double-blind, randomized, comparative trial[11]. Seventy-seven patients were included, 49 had SCI, 18 had MS and 11 had other neurological causes. At four weeks, the mean MCC increased from 242 to 434 mL with Dysport 500 U and from 180 to 423 mL with Dysport

750 U. The BC also increased from 32 to 37 mL/cmH_2O and from 23 to 59 mL/cmH_2O for Dysport 500 U and 750 U respectively. There were no significant differences between two groups.

These studies highlight the important urodynamic modifications induced by intradetrusor botulinum toxin injections.

Pathophysiology: Botulinum toxin act at the neuromuscular junction level by temporarily blocking acetylcholine (Ach) presynaptic release from parasympathetic nerves. It induces a paralysis of the detrusor smooth muscle that induce urodynamic changes and symptoms relief.

Serotype type A cleaves the SNAP-25 protein complex which plays an important role in the fusion of neurotransmitter-filled transmitter vesicles with the plasma membrane and their release during exocytosis. This induces an highly specific blockage of acetylcholine release at the neuromuscular junction of somatic and autonomic presynaptic nerve terminals[12].

Those fragments of SANP-25 protein complex are detectable in the bladder for longer periods that would be expected in striated muscle[13]. However, this motor effect does not entirely explain all the bladder changes. In fact, at the bladder level, BoNT/A seems to have a role in modulating both efferent and afferent neurologic activity, *i.e.*, both motor and sensitive fibers[14].

Apostolidis *et al*[15] showed that BoNT/A injections for human DO decrease sensory receptors P2X3 and TRPV1 levels in suburothelial nerve fibers. Those sensory receptors are overexpressed in neurological bladder suburothelium and are believed to play a role in sensory signal transduction in normal animal bladder[16]. At 4 and 16 wk after BoNT/A intradetrusor injections in 38 patients (22 with neurologic DO and 16 with idiopathic DO, there was a significant decrease in P2X3-immunoreactive and TRPV1-immunoreactive (-IR) ($P < 0.0004$ and $P < 0.0008$, respectively), when significant improvements were observed in clinical and urodynamic parameters. P2X3-IR and TRPV1-IR fibers decrease were significantly correlated with reduction of urgency episodes at 4 and 16 wk ($P < 0.0013$ at 4 wk and $P < 0.02$ at 16 wk), but not maximum cystometric capacity or detrusor pressures.

Conte *et al*[17] also showed that, after BoNT/A injections for detrusor overactivity, patients with Parkinson disease or SCI, significantly reduced at MCC, the expected soleus Hoffman reflex (H reflex) inhibition, whereas in those with SCI, it turned the H reflex facilitation into a slight inhibition. This reflex (basically defined as a reflectory contraction of muscle after stimulation of the related sensory fibers) tests the afferent information from the bladder (C and Aδ fibers) that modulates the spinal motoneuron excitability. Those results highlight the fact that BoNT/A might influences H reflex modulation at MCC by reducing bladder afferent signalling.

However, motor effect seems to play a major role in increasing MCC and BC and decreasing MDP significantly. It creates a low pressure bladder during filling and storage phases. The ureteral outlet may be affected by a bladder pressure over 40 cmH_2O or by a BC under 10 mL/cmH_2O leading to upper urinary tract functional obstruction[3]. Prolonged periods of elevated detrusor pressure during bladder filling or voiding have been found to put the upper urinary tract at risk[18]. Primary aim of therapy in patients with such problems is conversion to a low pressure bladder during filling even if this leads to incomplete emptying and the need to supplement emptying with catheterization.

Effect on UTIs

Clinical results: The impact of intra-detrusor botulinum toxin injections on UTIs has been investigated in various clinical trials. Gamé *et al*[19] in 2008 has evaluated the impact of BoNTA 300 U on symptomatic UTIs (sUTIs). sUTIs were defined by the association of bacteriological criteria and symptoms such as fever, intensification of spasticity, intensification of autonomic hyperreflexia, pain and worsening of the neurological status. Of the thirty patients, 15 had SCI, 14 had MS and 1 had myelitis. All had at least one episode of sUTIs during the 6 mo prior to the injection (mean number 1.79 ± 0.39 per patient). At 6 mo, the number of sUTIs decreased significantly (0.2 ± 0.41) ($P = 0.003$) with only three patients having sUTIs (one pyelonephritis, one prostatitis, one orchitis). Of those three patients, two had SCI and one suffered from MS and they were those in whom BoNTA injections had the least effect on urodynamic changes. The overall incidence of bacteriuria was 43%.

In 2009, GIannantoni *et al*[9], at 6 years follow-up of 300 U botulinum toxinA injections, in 17 SCI patients, reported a decreased in UTIs episodes from 6.7 ± 2.1 per year at baseline to 1.6 ± 1.3 at 4 mo, 3.3 ± 2.1 at one year, 1.7 ± 2.0 at 3 years and 1.8 ± 0.5 at 6 years ($P = 0.001$ between baseline and 6 years). However the definition of symptomatic UTI used in the trial is not specified.

Cruz *et al*[20], evaluated in 2011 the safety of onabotulinumtoxinA, in a randomized, double-blind, controlled study *vs* placebo. 275 patients (121 SCI, 154 MS) were randomized in three groups (92 to placebo, 92 to onabotulinumtoxinA 200 U, and 91 to onabotulinumtoxinA 300 U). The mean rate of UTI was similar between all treatment groups, including placebo, in the SCI population (50%, 52%, 56.4% for placebo, 200 U and 300 U groups) whereas in the MS population, it was higher in the onabotulinumtoxinA groups compared with placebo (32%, 58%, 70% for placebo, 200 U and 300 U groups). Twelve percent, 30%, and 42% of patients in the placebo, onabotulinumtoxinA 200-U, and 300-U groups respectively, initiated CIC after the first injection. However, this level 1 study presented a major pitfall, that is the absence of clear definition of UTIs. Indeed the authors confused symptomatic UTIs (with clinical signs, including fever, and a positive urine culture) and asymptomatic bacteriuria (colonization), that is obviously increased by the high rate of self catheterization. In another level 1

study, Ginsberg *et al*[21] evaluated the safety of BoNTA in a randomized, double blind, controlled placebo trial in 416 patients (227 MS, 189 SCI). Two doses of Botox were used (200 U and 300 U). At 12 wk evaluation, the most frequent adverse effects reported were UTI and urinary retention. In MS population, the rate of UTI was higher after BoNTA than placebo (51% and 50% in 300 U and 200 U groups *vs* 28% for placebo) while it was similar in all groups in patients with SCI (42%, 48%, 50% in placebo, 200 U, 300 U groups respectively). But again, the authors disclosed that there was no clear definition between symptomatic and asymptomatic UTIs, so these studies cannot results in valuable hypotheses.

In a more focused study, Kuo *et al*[22] reported in 2011, among 132 onabotulinumA 200 U injections in 33 SCI patients, nine episodes of febrile UTIs (6.8%) and 37 (28%) episodes of asymptomatic UTI. Herschorn *et al*[23] in 38 patients with SCI and 19 with MS found a similar rate of UTI between placebo and 300 UI of onabotulinum A: 55 and 57% respectively. However, he didn't separate MS and SCI patients. Jia *et al*[24] in 2013 found similar results in men with SCI receiving 300 U of botox. The mean number of sUTIs prior to surgery was 1.49 ± 1.43 per patient over 6 mo and decreased to 0.78 ± 0.96 (P = 0.023) at 6 mo post-operatively. However, the overall sUTIs frequency had the tendency to decrease in patients who developed two or more UTIs before injection and to increased in patients who presented one or zero UTI before injection. The sUTIs included two acute epidymitis episodes. The others were acute pyelonephritis.

Physiopathology: UTIs are a major cause of morbidity and one of the main reason for hospitalization in neurologic patients[25]. It must be distinguished from asymptomatic bacteriuria, which is not threatening for the patient. One important confounder in clinical studies about intradetrusor injections of botulinum toxin is that treated patients often practice self catheterization, that increases the risk of *asymptomatic bacteriuria*. But the overall rate of *symptomatic* UTIs is thought to be decreased.

In the neurogenic patient, there are some structural and physiological factors that can be related to an increased risk of UTIs including: Over-distention of the bladder, vesicoureteral reflux, high pressure voiding, large post-void residuals, presence of stones in the urinary tract, and outlet obstruction (detrusor- sphincter dyssynergia, urethral stricture, enlarged prostate)[26]. The method of bladder drainage has also a strong influence on UTI. The use of clean intermittent catheterization (CIC) has permitted to significantly overall decrease the mean rate of UTI in patients with neurological disorders[26], despite the fact that CIC are associated with asymptomatic bacteriuria[27].

Botulinum toxin injections and CIC (when needed) result in both a low pressure bladder regimen and minimal post-void residual, that are two conditions lowering the risk of symptomatic UTIs. Indeed, the major factor of UTI is DO (eventually combined with outflow obstruction) which induce maximum detrusor pressure[28], resulting in reduced blood flow as shown by animal models[29]. Focal bladder hypoxia is associated with further deterioration of the detrusor function and fibrosis[30,31], and has been postulated to favor adherence of bacteria to the urothelium[32].

Many other mechanisms have been proposed as key factors influencing occurrence of UTIs (Figure 1). Wöllner *et al*[33] have shown that BoNT/A had a no direct antibacterial effect. Thirunavukkarasusx *et al*[34] demonstrated a high modulation of genes and pathway involved in neuroinflammatory, focal adhesion, cell adhesion molecules and gap junctions genes in intestinal epithelial cells lines treated with botulinumtoxinA. Although it has not been studied, there might be the same effects in the urothelium that could decrease bacterial adhesion.

Moreover, the symptoms of UTI presented by neurological patients may be induced by a local inflammation arising from the local release of inflammatory mediators such as substance P (SP), neurokinin A, glutamate and calcitonin gene-related peptide (CGRP) from afferent nerves. Bacteria could cause a direct stimulation of afferent A-delta and C-fibres with an increased release of those neurotransmitters inducing dysuria, urgency, frequency and general symptoms such as malaise, fever and increased spasticity. *In vitro*[35] and *in vivo*[36] analysis have shown an effect of botulinum toxin in reducing glutamate release and decreasing pain. This might alleviate bladder symptoms and the awareness of sUTI by the patients. Furthermore, CGRP is a potent vasodilator, and SP enhances vascular permeability. These substances are involved in the physiological control of blood flow. The potential effect of botulinum toxin on modulation of inflammation and sensory pathways and its potential influence on UTIs occurrence remains to be elucidated.

EFFECT ON UPPER URINARY TRACT

Effect on VUR and hydronephrosis

VUR causes UTI, hydronephrosis and alters the upper urinary tract by mechanically delivering infected urine to the renal pelvis. BoNTA injections have been postulated as having a positive influence on VUR through various ways.

Clinical data: Very few studies have evaluated the impact of BoNTA on VUR and renal pelvis dilatation. To our knowledge, no studies have ever reported on VUR nor renal pelvis dilation induced by botulinum toxin as a primary outcome. Classically, trigonal injections are avoided owing to the potential risk of precipitating VUR from inhibition of the active trigonal antireflux mechanism. Nevertheless, according to the literature review by Davis *et al*[37] in 2015, no study have shown new onset of RVU nor worsening of preexisting RVU, induced by trigonal injections.

In the opposite, RVU treated by BoNTA injections

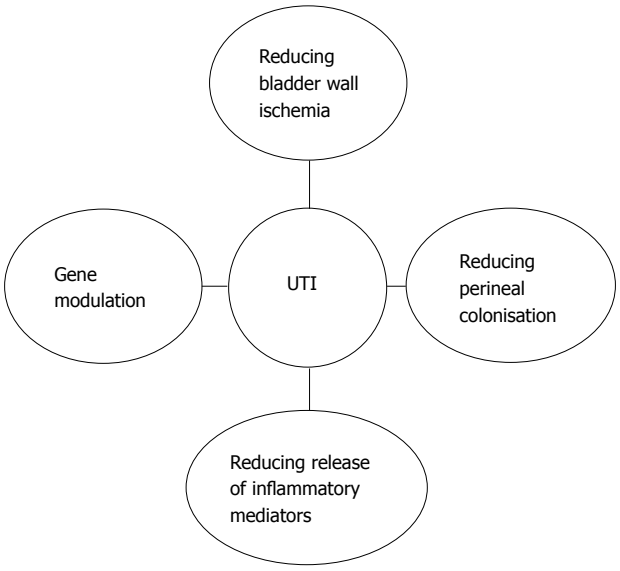

Figure 1 Pathophysiological explanation of how botulinum toxin A might decrease urinary tract infection occurrence. UTI: Urinary tract infection.

has been described. In a randomized, single-blinded study, Abedl-Meduig[38] compared initial detrusor *vs* combined detrusor-trigone 300 IU BTX-A injections in 38 adults with SCI and refractory neurogenic urinary incontinence due to NDO. At baseline 2 patients in the detrusor arm had unilateral grade 2 and 3 VUR while 2 in the combined arm had unilateral grade 1 and 3 VUR, respectively. At week 8 no patient had new onset VUR or upgrading of preexisting VUR. Mascarenhas *et al*[39] in 2008, performed trigonal injections in 21 neurological patients (12 SCI, 8 viral myelitis, 1 MS), 20 had no VUR previous to the injection and 1 had VUR grade Ⅱ unilateral. At 8 wk evaluation, no cases of *de novo* VUR were detected and the patient with preinjection VUR had complete resolution of the reflux. For Gamé *et al*[19] who used 300 U of BOTOX in 30 neurologic patients, 6 patients had VRR previously to the injections, and only 2 had one reflux remaining after the injections. But the difference was not significant. None of them had infections after treatment. Giannantoni *et al*[9] in 2009 studied 17 SCI patients with DO. Three had VUR of grade Ⅲ prior to treatment. At one year post injection, no one had persistent VUR.

Arrabal-Polo *et al*[40] in 2012 have presented the case of a children non neurologic who presented a primary reflux and was successfully treated with botulinum toxin after failure of endoscopic treatment (Deflux and Macroplastique).

Giannantoni *et al*[9], detected on kidney and bladder ultrasound, bilateral and monolateral renal pelvis dilatation in six and five patients, respectively, before the injection. At for weeks after the 300 U Botox injection, the dilatation disappear in all patients. Those results were maintened at 3 and 6 years follow up. In Mascarenhas study[39], of 21 neurological patients, four (19.0%) had mild hydronephrosis and one (4.8%) had moderate hydronephrosis at baseline. Postoperative ultrasound after 8 wk of BoNTA injections, showed no hydronephrosis in 20 (95.2%) patients and mild hydronephrosis in 1 (4.8%, $P = 0.125$).

Pathophysiology: The occurrence of VUR result from different mechanisms which defines whether reflux is considered as primary or as secondary. In general, VUR is considered primary if there is a deficiency of the uretero-vesical junction (UVJ). Secondary reflux is caused by overwhelming of the normal function of the UVJ. Bladder neurological dysfunction is often the root cause of secondary reflux[41]. Chronic increases in intravesical pressure resulting from bladder outlet obstruction or detrusor overactivity can distort bladder architecture and UVJ. It can cause herniation of the bladder mucosa through the weakest point of the hiatus above the ureter and produce a "Hutch diverticulum" and secondary reflux[42].

Uretero-hydronephrosis is also induced by high bladder pressure. Thus, reducing bladder pressure by botulinum toxin may improve VUR and hydronephrosis. Although low bladder pressure is achieved, a major deterioration of the UVJ might lead to persistent VUR. Indeed, increase wall tension in the ureter might lead to a significant decrease in smooth muscle perfusion and cause ischaemic lesion in the ureter[43].

This emphasizes the importance to control the bladder pressure at the initial stage of an overactive neurogenic bladder in order to avoid secondary damages on bladder and upper urinary tract. These data also point out the potential interest, notably in children, of an urodynamic evaluation as primary VUR can be due to an anatomical defect but also a severe voiding dysfunction, especially if bilateral.

Effect on bladder and renal stone

Clinical data: No study has evaluated the relationship between botulinum toxin and renal stones. Only Wefer *et al*[44] in 2010 reported less than 6 patients out of 214 (2.8%) presenting bladder stones. However he was not able to determine wether these disorders was BoNTA treatment related. Ginsberg *et al*[21] reported in 2012, out of 416 patients, only one case of bladder stone formation after 300 U botox injection.

Pathogenesis: Renal and bladder calculi are an important source of morbidity for patients with neurogenic bladder. The incidence of renal stones in neurogenic patient is about 6.8%[45] higher than in the common population. Old series have reported that most of the calculi were of struvite, induced by UTI[46]. However, more recent trials have established that stones may also be of metabolic origin. For instance, Matlaga *et al*[47] in 2005 has evaluated 32 renal calculi in a population of MMC and SCI, and found only 37.5% of struvite calculi and 62.5% of metabolic calculi. This modification of the origin of the stones might be due to a decrease in UTI in neurological population over the years, due to improvement of the urinary conditions in those patients.

By decreasing the mean rate of UTI and UUT

Table 1 Urinary tract infections after botulinum toxin injections in contemporary series

Ref.	Type of toxin	Patients	sUTI before injections	sUTI after injection	*P*	Bacteriuria % (*n*)	Symptomatic and asymptomatic UTI after injections	*P*
Gamé *et al*[19], 2008	Botox 300 UI	30 15 MS 14 SCI 1 Myelitis	1.79/pp/6 mo	0.2/pp/6 mo	0.003	43		
Giannantoni *et al*[9], 2009	Botox 300 UI	17 SCI	6.7/pp/yr	1.8/pp/yr	0.001			
Cruz *et al*[20], 2011	Placebo Botox 200 UI 300 UI	154 MS					Placeb: 32% 200 UI: 58% 300 UI: 70%	$P < 0.05$ (*vs* placebo)
Cruz *et al*[20], 2011	Placebo Botox 200 UI 300 UI	121 SCI					Placebo: 50% 200 UI: 52.6% 300 UI: 56.4%	
Kuo *et al*[22], 2011	Botox 200 UI	33 SCI		6.80%		28 (37)		
Herschorn *et al*[23], 2011	Placebo Botox 300 UI	57 38 SCI 19 MS					Placebo: 55% 300 UI: 57%	
Ginsberg *et al*[21], 2012	Placebo Botox 200 UI 300 UI	227 MS					Placebo: 28% 200 UI: 51% 300 UI: 50%	
Ginsberg *et al*[21], 2012	Placebo Botox 200 UI 300 UI	189 SCI					Placebo: 42% 200 UI: 48% 300 UI: 50%	
Jia *et al*[24], 2013	Botox 300 UI	SCI 41	1.49/pp/6 mo	0.78/pp/6 mo				

sUTIs: Symptomatic urinary tract infections; SCI: Spinal cord injury.

dilatation, BoNTA injections may lead to decrease the incidence of struvite calculi but further studies are warranted.

Patients with neurogenic bladder are at increased risk of bladder stone formation. According to Chen *et al*[45], within 10 years after SCI, 15% to 30% of patients will have formed at least one stone. The risk of forming a subsequent stone quadruples when a patient has already formed one stone[48]. Furthermore, the manner in which the bladder is managed in SCI appears to have a significant impact on the risk of stone formation. One large study of over 450 patients noted that the use of CIC was associated with a significant reduction in the risk of bladder stone formation, with an annual risk of 0.2%, compared with 4% in those patients managed by a chronic indwelling catheter[48].

CIC in patients treated by BoNTA might be beneficial for decreasing bladder stones formation. In the opposite, in patients who were not using CIC previously to the injections, there might be and increase risk of developing bladder calculi. However, this remains hypothetical and needs to be further established by dedicated, well performed clinical trials.

Effect on chronic kidney disease

Clinical data: In a long term follow-up of 17 patients during 6 years after 300 U of botulinum injections, Giannantoni *et al*[9] didn't show any impairment of renal function. Kuo *et al*[21] evaluated the impact of botulinum toxin 200 U on renal function in 33 patients with supra sacral SCI. Videourodynamic and 99mTc-DTPA renal scanning for glomerular filtration rate (GFR) were performed at screening and every 3 mo during 24 mo of assessment. Onabotulinum toxin injections were repeated every 6 mo. GFR significantly decreased throughout the treatment course (96.27 ± 22.50 at baseline *vs* 83.51 ± 23.96 at 24 mo, $P = 0.028$). There was no significant change in mean serum Cr levels during the same period (0.623 ± 0.183 *vs* 0.675 ± 0.175, $P = 0.802$).

In 2014, the same team[49] evaluated the effect of 300 U *vs* 200 U of onabotulinum toxinA on renal function in 72 SCI patients. During the follow-up period, the changes in GFR from baseline to all time points did not differ significantly within each group or between the two groups. At baseline, the GFR was 94.2 ± 22.1 mL/min and 84.2 ± 19.6 mL/min in 200-U and 300-U groups, respectively. At the end-point, the GFR was 90.5 ± 24.2 mL/min and 88.0 ± 28.2 mL/min in the 200-U and 300-U groups, respectively.

There were no significant difference between 300 U group and 200 U group ($P = 0.197$) neither between group with compliance > 30 and group with low compliance (< 30).

Four patients had improved their renal function (2 in 200 U and 2 in 300 U group) at the end of the study. Inhibited detrusor contracture decreased significantly after the second detrusor injection of 300-U of onabotulinumtoxinA compared to that in the 200-U group.

Pathophysiology: The ultimate consequence of all upper urinary tract complications in neurological patients is the impairment of renal function. Although bladder management methods have evolved in recent decades, chronic renal insufficiency remains a significant cause of morbidity and it is one of the major concern to have in mind when treating those patients[50].

In urodynamics studies, a bladder pressure > 40 cmH_2O mostly due to detrusor hyperreflexia and low BC are the major risk factors for renal damage in SCI patients[3]. However, CIC, antimuscarinic therapy, and regular urodynamic monitoring have been reported to reduce the risk of renal failure[51].

These studies show that renal function remains stable when patient have urodynamics modifications after botulinum toxin injections but without significant improvement (Table 1). However, the median term in follow-up of these series may be a limit for renal function study. The neurological disorder in also an important point to consider and SCI patients are more at risk of renal deterioration than multiple sclerosis patients. It highlights the fact that patients must be followed carefully on long term after botulinum injections.

Early and repeated detrusor onabotulinumtoxinA injections could therefore be beneficial to SCI patients before upper urinary tract deterioration.

An explanation why detrusor botulinum injection may not improve renal function is that anatomical renal damages may be irreversible, and also that renal deterioration may be caused by other factors. In particular, SCI patients are at higher risk to develop cardiovascular disease than others[52]. Many other confounding factors in neurological patients can induce renal impairment such as, diabetes, obesity, lipid disorders, metabolic syndrome, and disturbances of the autonomous nervous system, which may result in blood pressure abnormalities, arrhythmias and cardiac disease[51,53].

All these factors have to be taken into account when evaluating the long-term impact of on kidney function in the neurological patients. For the moment, this has not been correctly assessed and BoNTA are postulated as protective for the urinary tract in the long term, mainly through indirect benefits.

CONCLUSION

Botulinum toxin injections regulate urodynamic parameters in a context of neurogenic OAB. It furthermore may have a positive effect on UTIs, but this has to be put in perspective with the increased use of CIC. There is also an anticipated positive effect of BoNTA injections on hydronephrosis, VUR and stone disease, but with a weaker level of evidence. Long term effects on renal function are also probably positive, but this parameter remains multifactorial.

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ORIGINAL ARTICLE

Observational Study

Matrix metalloproteinase-2 as a superior biomarker for peritoneal deterioration in peritoneal dialysis

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Author contributions: All authors contributed to the drafting and approval of the manuscript; Kusano E and Nagata D managed this multicenter clinical study; Morishita Y, Inoue M, Akimoto T, Saito O and Muto S collected the patients' clinical data and samples; Hirahara I analyzed the biomarker levels and data and wrote this paper.

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Abstract

AIM: To investigate the efficacy of effluent biomarkers for peritoneal deterioration with functional decline in peritoneal dialysis (PD).

METHODS: From January 2005 to March 2013, the subjects included 218 PD patients with end-stage renal disease at 18 centers. Matrix metalloproteinase-2 (MMP-2), interleukin-6 (IL-6), hyaluronan, and cancer antigen 125 (CA125) in peritoneal effluent were quantified with enzyme-linked immunosorbent assay. Peritoneal solute transport rate was assessed by peritoneal equilibration test (PET) to estimate peritoneal deterioration.

RESULTS: The ratio of the effluent level of creatinine (Cr) obtained 4 h after injection (D) to that of plasma was correlated with the effluent levels of MMP-2 ($\rho = 0.74$, $P < 0.001$), IL-6 ($\rho = 0.46$, $P < 0.001$), and hyaluronan ($\rho = 0.27$, $P < 0.001$), but not CA125 ($\rho = 0.13$, $P = 0.051$). The area under receiver operating characteristic curve for the effluent levels of MMP-2, IL-6, and hyaluronan against high PET category were 0.90, 0.78, 0.62, and 0.51, respectively. No patient developed new-onset encapsulating peritoneal sclerosis for at least 1.5 years after peritoneal effluent sampling.

CONCLUSION: The effluent MMP-2 level most closely reflected peritoneal solute transport rate. MMP-2 can be a reliable indicator of peritoneal deterioration with functional decline.

Key words: Encapsulating peritoneal sclerosis; Matrix

metalloproteinase-2; Peritoneal dialysis; Peritoneal solute transport; Peritoneal deterioration

Core tip: Peritoneal effluent samples were obtained from 218 peritoneal dialysis (PD) patients with end-stage renal disease at 18 centers. The effluent levels of biomarkers matrix metalloproteinase-2 (MMP-2), interleukin-6, hyaluronan, and cancer antigen 125 were measured. Peritoneal solute transport rate was assessed by peritoneal equilibration test (PET) to estimate peritoneal deterioration. Among the biomarkers in the effluent, MMP-2 level correlated most significantly with peritoneal solute transport rate. The area under the receiver operating characteristic curve analysis for effluent MMP-2 level against high PET category was 0.90. MMP-2 may be a superior biomarker for peritoneal deterioration during PD.

Hirahara I, Kusano E, Morishita Y, Inoue M, Akimoto T, Saito O, Muto S, Nagata D. Matrix metalloproteinase-2 as a superior biomarker for peritoneal deterioration in peritoneal dialysis. *World J Nephrol* 2016; 5(2): 204-212 Available from: URL: http://www.wjgnet.com/2220-6124/full/v5/i2/204.htm DOI: http://dx.doi.org/10.5527/wjn.v5.i2.204

INTRODUCTION

Long-term peritoneal dialysis (PD) causes peritoneal deterioration with structural changes and functional decline such as ultrafiltration loss and increased solute transport rate, resulting in the cessation of PD treatment; thus, these are the major problems related to PD. At worst, peritoneal deterioration may even cause encapsulating peritoneal sclerosis (EPS), a serious but rare complication of PD with extremely high mortality rate[1-4]. To undergo PD safely and adequately, preventing the progression of peritoneal deterioration is important.

The mechanism of peritoneal injury is not well-known, but it may develop through multiple factors such as infectious peritonitis and continuous exposure to non-physiological PD fluid with low pH, high osmolarity, and high glucose and glucose degradation product levels[2-5].

Solute transport rate through the peritoneal membrane is often measured by peritoneal equilibration test (PET) to estimate PD efficiency and peritoneal deterioration[3,4,6,7]. Transport rate increases with peritoneal deterioration and a state of higher transporter membrane is a factor contributing to the development of EPS in patients on PD. However, the D/P creatinine (Cr) value from a single test of the PET is not sufficiently predictive of EPS, and monitoring the time-course changes are necessary[4]. In addition, PET is invasive because it requires blood sampling and patients need to spend half a day in hospital or clinic because the test takes a long time. Therefore, the PET is not performed routinely in many medical centers. It is thus necessary to evaluate peritoneal deterioration using an easy and non-invasive method.

Some biomarkers such as matrix metalloproteinase-2 (MMP-2), interleukin-6 (IL-6), hyaluronan, and cancer antigen 125 (CA125) in the peritoneal effluent are often measured non-invasively to estimate peritoneal deterioration[2,4,8-20].

MMP-2 degrades extracellular matrix components such as fibronectin and type Ⅳ collagen, which comprise the basement membrane. MMP-2 is produced by mesenchymal cells, macrophages, and endothelial cells in the peritoneum and plays important roles in angiogenesis, epithelial-to-mesenchymal transition (EMT) of mesothelial cells, inversion of transdifferentiated mesothelial cells, and migration of cells that promote inflammation or fibrosis[2,5,8,10,21-23]. Effluent MMP-2 level correlates with peritoneal solute transport rate and has a possibility to predict EPS[8-10]. On the other hand, Lopes Barreto *et al*[20] recently reported that the time course of MMP-2 appearance rates, studied by mean values from a model of repeated linear measures 4 years prior to EPS diagnosis, showed no difference between long-term controls and patients with EPS. IL-6 is a cytokine involved in acute phase inflammation and its effluent level is associated with high peritoneal solute transport rate[2,4,13,14]. Goodlad *et al*[19] reported that effluent levels of IL-6, monocyte chemotactic protein-1, and CCL15 (eukotactin) did not improve prediction of future EPS compared with a model that used known clinical risk factors although these cytokines were found at higher levels in the effluent of patients who subsequently developed EPS. Hyaluronan, a large glycosaminoglycan that is constitutively synthesized by mesothelial cells, plays important roles in the maintenance of mesothelial cell morphology, re-mesothelialization, and wound repair[15]. Intraperitoneal hyaluronan production increases with membrane permeability and length of time on PD[16]. Effluent hyaluronan level may be a useful biomarker to assess functional and morphological changes of peritoneum[4,16]. CA125 is a high molecular weight glycoprotein that is secreted from mesothelial cells; its concentration in effluent and appearance rate can indicate a change of the peritoneal mesothelial cell mass[4,16-18]. According to the guidelines for peritoneal dialysis of Japanese Society for Dialysis Therapy[4], it is very hard to evaluate peritoneal deterioration by a single biomarker, and, at present, no examination can be an absolutely reliable diagnostic method alone. For this reason, comprehensive judgment based on the results of multiple examinations is needed. Presently, the establishment of a simple and highly reproducible method with high sensitivity and specificity is extremely important.

The aim of this study was to compare many biomarkers and understand their individual properties and to confirm the efficacy of effluent biomarkers for peritoneal deterioration in peritoneal membranes with high solute transport rate.

MATERIALS AND METHODS

Design

The trial was conducted as a prospective, observational study at 18 centers in Japan. All patients were followed for at least 1.5 years after the measurement of effluent levels of the biomarkers.

Patients

PD patients with end-stage renal disease were analyzed based on peritoneal effluent biomarkers during the period of January 2005 through March 2013. Patients with bacterial peritonitis at the time of the analysis or in the preceding 4 wk were excluded from this analysis. After analysis of biomarkers, all patients were followed-up for more than 1.5 consecutive years to confirm for development of EPS.

Analysis of biomarker levels in the peritoneal effluents

The peritoneal solute transport rate was assessed by PET[3,4,6]. Intraabdominal fluid was drained and 2 L of PD fluid containing 2.27%-2.5% glucose was injected intraperitoneally. The Cr level of peritoneal effluents obtained 4 h after the injection (D) was divided by that of plasma (P) to obtain the D/P Cr ratio. The glucose level of peritoneal effluents obtained 4 h after injection (D) was divided by that obtained immediately after injection (D0) to obtain the D/D0 glucose ratio. The effluent levels of MMP-2, IL-6, hyaluronan, and CA125 obtained at PET were measured by enzyme-linked immunosorbent assay (MMP-2: GE Healthcare, NJ, United States; IL-6: RD System, Inc., Minneapolis, MN, United States; hyaluronan: Seikagaku Biobusiness, Tokyo, Japan; CA125: Immunospec Co., CA, United States).

Statistical analysis

Statistical analyses were performed using R statistical software version 2.15.1 (R Foundation for Statistical Computing). Receiver operating characteristic (ROC) curve analyses were performed to evaluate the diagnostic accuracy of MMP-2, IL-6, hyaluronan, and CA125. Comparisons between two groups were performed by Wilcoxon's test. Relationships between clinical variables and effluent biomarker levels were analyzed by Spearman's correlation test. A P value of < 0.05 was considered to be significant.

Clinical trial registration

This study was registered as the MAJOR IN PD study (Multicenter Analysis in Japan, ORiginal INdicator of Peritoneal Deterioration) in the University Hospital Medical Information Network-Clinical Trials Registry (UMIN-CTR), which was approved by the International Committee of Medical Journal Editors (No. UMIN000010572).

RESULTS

A total of 218 PD patients, including one patient with EPS, were analyzed and their characteristics are summarized in Table 1. Biomarker levels in the peritoneal effluent of all patients are shown in Table 2. The relationship between the effluent levels of the biomarkers and the characteristics of the patients is shown in Table 3. Effluent CA125 level was affected by sex and etiology of end-stage renal disease. Effluent IL-6 and hyaluronan levels correlated significantly with PD duration ($P < 0.05$, $P < 0.01$, respectively). Effluent MMP-2 and IL-6 levels significantly reflected the number of peritonitis episodes. The peritoneal solute transport rate determined by PET was correlated with MMP-2, IL-6, and hyaluronan levels in the effluent and the correlation coefficient between D/P Cr and MMP-2 level was significantly the highest (Figures 1 and 2, Table 4). The effluent level of each biomarker was correlated with that of the remaining biomarker (Table 4). In the patient with EPS, MMP-2, IL-6, hyaluronan,

Table 1 Characteristics of peritoneal dialysis patients

Characteristics of patients	
Sex (male/female)	122/96 (56% male)
Etiology (non-DM/DM)	179/36 (17% diabetes)
Age (yr)	56 (20, 46, 64, 84)
PD duration (mo)	40 (1, 15, 63, 206)
Peritonitis episode (times)	0 (0, 0, 1, 9)
D/P Cr	0.65 (0.38, 0.59, 0.71, 0.88)
D/D 0 glucose	0.40 (0.21, 0.34, 0.44, 0.59)

Data except sex and etiology of renal failure are expressed as median with minimum value, interquartile range, and maximum value. PD: Peritoneal dialysis; Cr: Creatinine; DM: Diabetes mellitus; non-DM: Non-diabetes mellitus.

Table 2 Biomarker levels in the peritoneal effluent

Biomarker	Level in the peritoneal effluent
Matrix metalloproteinase-2 (ng/mL)	159 (14, 107, 220, 681)
Interleukin-6 (pg/mL)	14.6 (1.5, 7.6, 29.6, 253.5)
Hyaluronan (ng/mL)	109 (5.1, 53, 204, 889)
Cancer antigen 125 (U/mL)	6.7 (0.7, 4.0, 12.1, 91.8)

Data are expressed as median with minimum value, interquartile range, and maximum value.

Table 3 Correlation between patient characteristics and effluent biomarker levels

	Biomarker levels in the peritoneal effluents			
	MMP-2	IL-6	Hyaluronan	CA125
Sex (male/female)	$P = 0.92$	$P = 0.54$	$P = 0.48$	$P < 0.05$
Etiology (non-DM/DM)	$P = 0.18$	$P = 1.00$	$P = 0.56$	$P < 0.05$
Age (yr)	$\rho = 0.076$	$\rho = 0.12$	$\rho = 0.046$	$\rho = -0.096$
	$P = 0.27$	$P = 0.092$	$P = 0.50$	$P = 0.16$
PD duration (mo)	$\rho = 0.050$	$\rho = 0.15$	$\rho = 0.25$	$\rho = -0.062$
	$P = 0.47$	$P < 0.05$	$P < 0.01$	$P = 0.93$
Peritonitis episode (times)	$\rho = 0.17$	$\rho = 0.25$	$\rho = 0.092$	$\rho = -0.012$
	$P < 0.05$	$P < 0.001$	$P = 0.20$	$P = 0.86$

ρ values were derived from Spearman's correlation coefficient. PD: Peritoneal dialysis; MMP-2: Matrix metalloproteinase-2; IL-6: Interleukin-6; CA125: Cancer antigen 125; DM: Diabetes mellitus; non-DM: Non-diabetes mellitus.

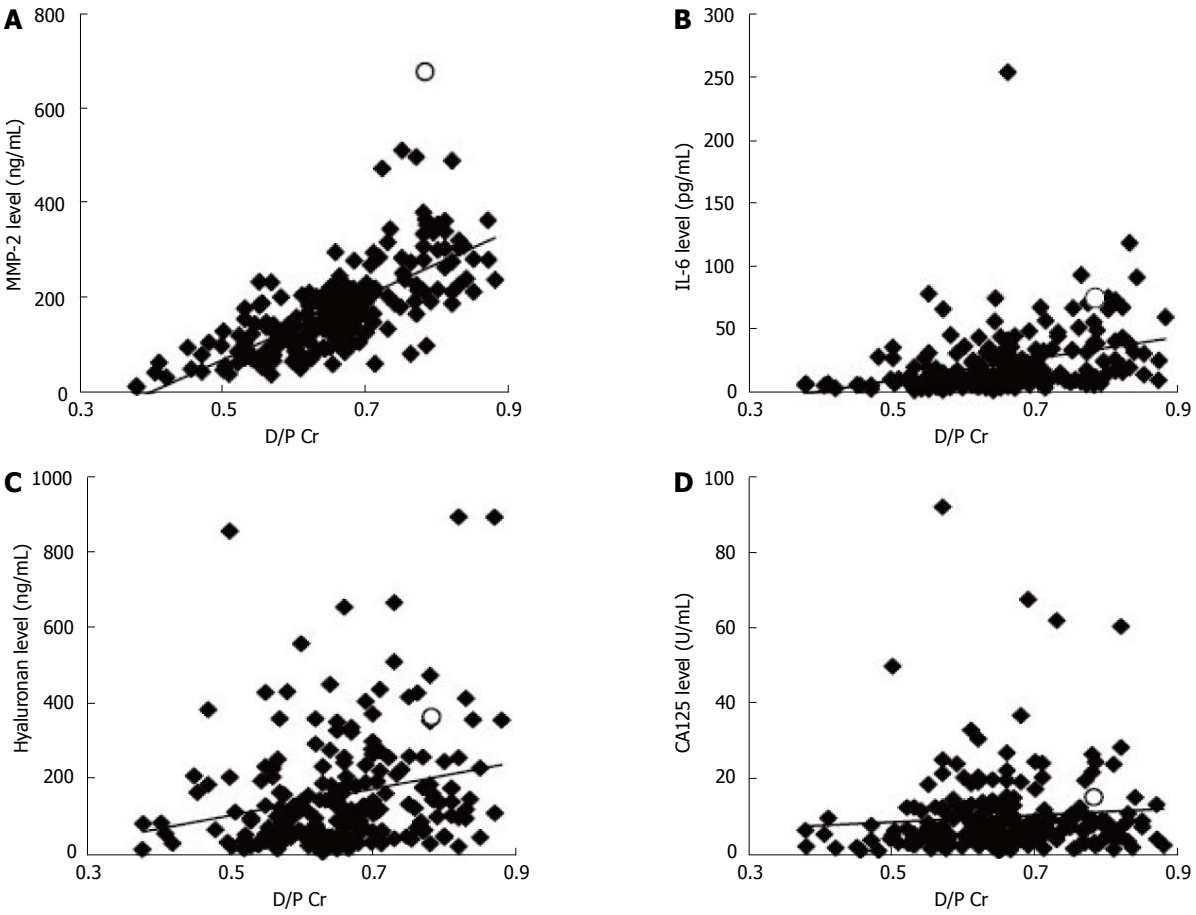

Figure 1 The relationships between peritoneal solute transport rate and effluent biomarker levels. Peritoneal transport rate was represented by D/P Cr ratio and was compared with effluent MMP-2 level (A), effluent IL-6 level (B), effluent hyaluronan level (C) and effluent CA125 level (D). The biomarker levels of the one patient with EPS are shown by open circles. MMP-2: Matrix metalloproteinase-2; IL-6: Interleukin-6; CA125: Cancer antigen 125; Cr: Creatinine; EPS: Encapsulating peritoneal sclerosis.

Table 4 Correlation between effluent biomarker levels and the results of peritoneal equilibration test

	D/P Cr	D/D0 glucose	MMP-2	IL-6	Hyaluronan	CA125
D/P Cr	ρ = 1	ρ = -0.86 *P* < 0.001	ρ = 0.74 *P* < 0.001	ρ = 0.46 *P* < 0.001	ρ = 0.27 *P* < 0.001	ρ = 0.13 *P* = 0.051
D/D0 Glucose		ρ = 1	ρ = -0.65 *P* < 0.001	ρ = -0.28 *P* < 0.001	ρ = -0.22 *P* < 0.005	ρ = -0.094 *P* = 0.19
MMP-2			ρ = 1	ρ = 0.54 *P* < 0.001	ρ = 0.40 *P* < 0.001	ρ = 0.1 *P* < 0.05
IL-6				ρ = 1	ρ = 0.45 *P* < 0.001	ρ = 0.26 *P* < 0.001
Hyaluronan					ρ = 1	ρ = 0.18 *P* < 0.01
CA125						ρ = 1

ρ values were calculated by Spearman's correlation coefficient. Cr: Creatinine; MMP-2: Matrix metalloproteinase-2; IL-6: Interleukin-6; CA125: Cancer antigen 125.

and CA125 levels were 681 ng/mL, 74.7 pg/mL, 362 ng/mL, and 15.1 U/mL, respectively; his effluent MMP-2 level was the highest among all PD patients. The highest MMP-2 level was 514 ng/mL among patients without EPS onset. In the patient with the highest IL-6 level (253.5 pg/mL), there was accumulation of ascitic fluid with C-reactive protein level of 1.3 mg/dL; his effluent MMP-2, hyaluronan, and CA125 levels were 236 ng/mL, 651 ng/mL, and 4.0 U/mL, respectively.

In the present study, the proportion of PD patients with high PET category was 9.6%. ROC curves were constructed to assess the ability of the biomarkers in distinguishing high category of PET (Figure 3). MMP-2 and IL-6 levels in the peritoneal effluents from high PET

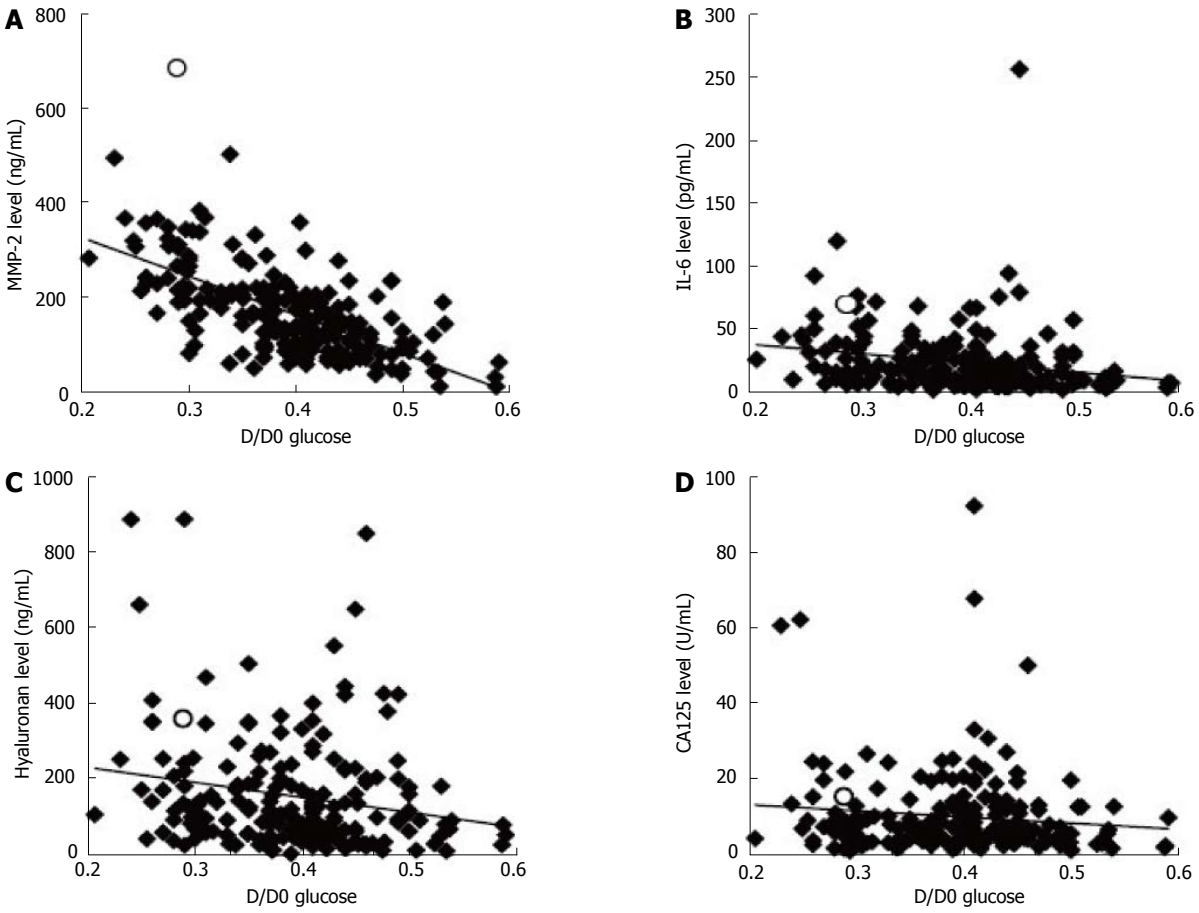

Figure 2 The relationships between D/D0 glucose and effluent biomarker levels. The glucose absorption rate was represented by D/D0 glucose and was compared with effluent MMP-2 level (A), effluent IL-6 level (B), effluent hyaluronan level (C) and effluent CA125 level (D). The biomarker levels of the one patient with EPS are shown by open circles. MMP-2: Matrix metalloproteinase-2; IL-6: Interleukin-6; CA125: Cancer antigen 125; EPS: Encapsulating peritoneal sclerosis.

Table 5 Test performance of effluent biomarkers cut-off levels to distinguish the high category of peritoneal equilibration test

Biomarkers	Cut-off level	Sensitivity (95%CI)	Specificity (95%CI)	AUC
MMP-2-	214 ng/mL	0.95 (0.86 to 1.00)	0.79 (0.74 to 0.85)	0.90
	219 ng/mL	0.86 (0.71 to 1.00)	0.81 (0.76 to 0.86)	
	228 ng/mL	0.81 (0.62 to 0.95)	0.84 (0.79 to 0.89)	
	238 ng/mL	0.76 (0.57 to 0.95)	0.87 (0.82 to 0.91)	
IL-6	16.8 pg/mL	0.81 (0.62 to 0.95)	0.60 (0.53 to 0.67)	0.78
	19.3 pg/mL	0.76 (0.57 to 0.90)	0.65 (0.58 to 0.73)	
	20.0 pg/mL	0.71 (0.52 to 0.90)	0.66 (0.60 to 0.73)	
	24.8 pg/mL	0.67 (0.48 to 0.86)	0.75 (0.66 to 0.79)	
Hyaluronan	94.5 ng/mL	0.81 (0.62 to 0.95)	0.47 (0.41 to 0.54)	0.62
	101.5 ng/mL	0.71 (0.52 to 0.90)	0.51 (0.44 to 0.58)	
	108.0 ng/mL	0.67 (0.48 to 0.86)	0.52 (0.45 to 0.58)	
	115.0 ng/mL	0.62 (0.43 to 0.81)	0.53 (0.46 to 0.53)	
CA125	3.85 U/mL	0.81 (0.62 to 0.95)	0.23 (0.17 to 0.29)	0.51
	4.45 U/mL	0.71 (0.52 to 0.90)	0.30 (0.23 to 0.37)	
	6.55 U/mL	0.62 (0.43 to 0.81)	0.50 (0.43 to 0.57)	
	7.05 U/mL	0.52 (0.33 to 0.71)	0.53 (0.46 to 0.59)	

AUC: Area under curve; MMP-2: Matrix metalloproteinase-2; IL-6: Interleukin-6; CA125: Cancer antigen 125.

category patients were significantly higher than these levels from non-high PET category patients (MMP-2: $P < 0.001$, IL-6: $P < 0.001$, hyaluronan: $P = 0.068$, CA125: $P = 0.876$). The results from the ROC curve analysis and cut-off points for the high PET category are also shown in Table 5.

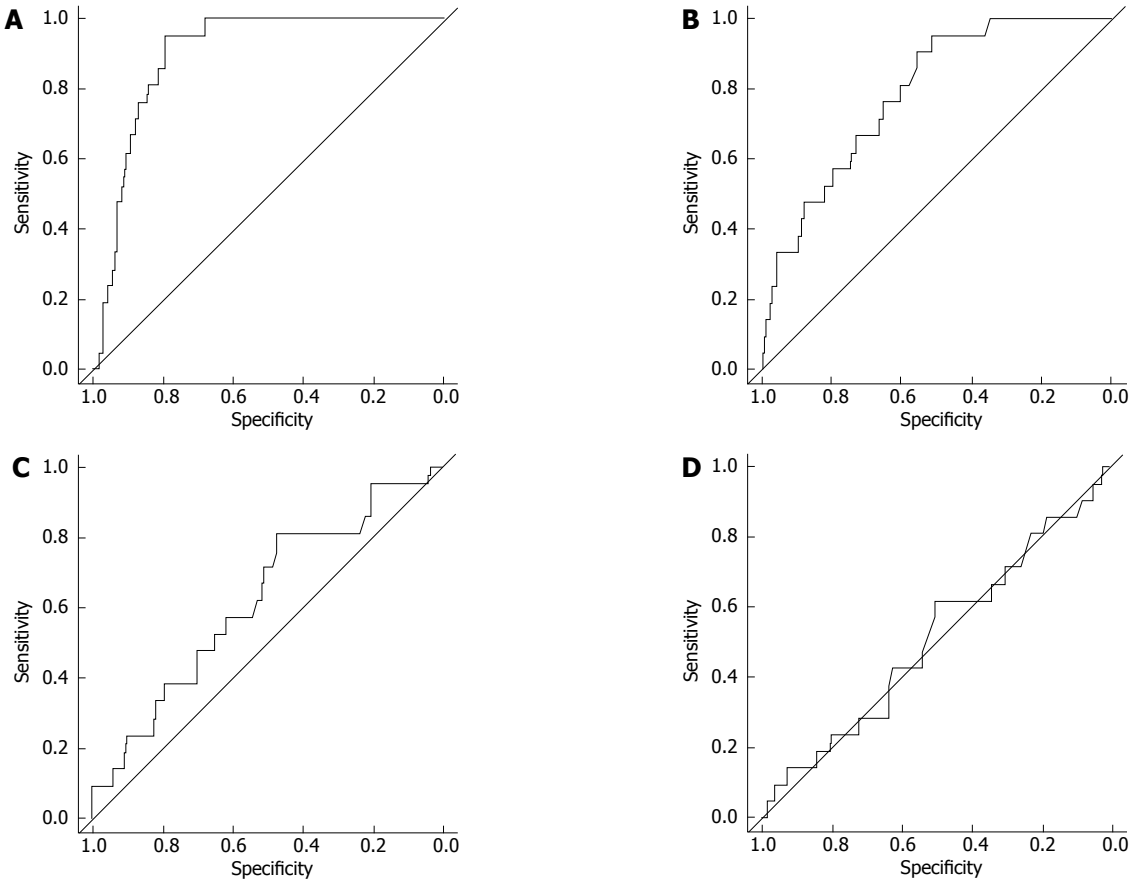

Figure 3 Receiver operating characteristic curve analysis of effluent biomarkers for the diagnosis of patients in the high category of D/P creatinine. A: Matrix metalloproteinase-2; B: Interleukin-6; C: Hyaluronan; D: Cancer antigen 125.

No patients developed new-onset EPS for at least 1.5 years after measurement of the effluent biomarkers.

DISCUSSION

For a safe and adequate PD, monitoring PD efficiency or peritoneal deterioration by increases in peritoneal solute transport rate is important. In addition to PET, some effluent biomarkers such as MMP-2, IL-6, hyaluronan, and CA125 are often measured to estimate peritoneal injury or progression to EPS during PD[2,4,8-20]. But there are no absolutely reliable diagnostic method[4]. Then, we analyzed the properties and efficacies of these biomarkers.

In the present multicenter clinical study, the results of PET most strongly correlated with effluent MMP-2 level among the biomarkers that we analyzed. High category of PET that is classified by high peritoneal solute transport rate was distinguished with high sensitivity and specificity by effluent MMP-2 level. In addition, effluent MMP-2 level of the patient with EPS was the highest among all PD patients that we analyzed. In our previous multicenter clinical studies, effluent MMP-2 level was high in patients with peritoneal injury[8,9]. Cho *et al*[11] have reported that high effluent MMP-2 level is associated with peritoneal solute transport rate. Barreto *et al*[12] also observed significant correlations between peritoneal transport parameters and effluent MMP-2 levels. Yamamoto *et al*[24] reported that high peritoneal membrane transport state may be a risk factor for EPS. Kawaguchi *et al*[3] summarized that an increase in D/P Cr ratio may constitute an independent and early marker of EPS. The Japanese Society for Dialysis Therapy Guidelines for Peritoneal Dialysis[4] has recommended that PET should be routinely performed to evaluate peritoneal deterioration. In patients showing serial increase and persistently high D/P Cr for over 12 mo, progression of peritoneal deterioration could be suspected and discontinuation of PD should be considered. We previously reported that among 13 patients with MMP-2 level > 600 ng/mL except the patients, who had been diagnosed as EPS when MMP-2 levels were analyzed, 7 patients (54%) developed EPS and 3 patients (23%) died in a prospective study[8]. In that study, only one patient with an MMP-2 level < 600 ng/mL developed EPS. In the present study, the effluent MMP-2 level of all patients without EPS onset was < 600 ng/mL and no patient developed EPS for at least 1.5 years after measurement of MMP-2 level. From these reports and results, MMP-2 may be expected to become a predictive marker for EPS. Recently, a retrospective clinical study by Lopes Barreto *et al*[20] was reported that the area under the ROC curve of MMP-2 appearance rate improved to 0.70 (95%CI: 0.51-0.899; P = 0.06) at one year prior

Table 6 Test performance of effluent matrix metalloproteinase-2 cut-off levels to predict the encapsulating peritoneal sclerosis in peritoneal dialysis patients

Cut-off level	Sensitivity (95%CI)	Specificity (95%CI)	AUC
458.5	1.00 (1.00 to 1.00)	0.96 (0.94 to 0.98)	0.99
609.5	0.88 (0.63 to 1.00)	0.99 (0.98 to 1.00)	
863.5	0.63 (0.25 to 0.88)	1.00 (0.99 to 1.00)	

AUC: Area under curve.

to the diagnosis of EPS. They compared 11 PD patients who developed EPS with 33 control PD patients using a 1:3 case control design. The absence of statistically significant findings may be explained by insufficient sample size. In this time, we additionally conducted ROC curve analysis to predict EPS by using eight PD patients with EPS *vs* 452 control PD patients who have been registered in our database[8,9]. A summary of the results are shown in Table 6. In addition, as a result from ROC curve analysis using a 1:3 case control design as same as the analysis by Lopes Barreto *et al*[20], the area under the ROC curve for prediction of EPS in our study was 0.97 (95%CI: 0.92-1.00; $P < 0.01$) at 1 year prior to EPS diagnosis. The estimated sensitivity and specificity for prediction EPS development were 0.96 (95%CI: 0.88-1.00) and 1.00 (95%CI: 1.00-1.00), respectively, for a threshold effluent MMP-2 level of 414 ng/mL. Our data show higher sensitivity and specificity compared with the results by Lopes Barreto *et al*[20]; this discrepancy may be because of differences in the study designs (prospective and retrospective) or in methods of analysis. Our samples were prepared in the same manner at the 4-h PET and MMP-2 level was obtained as an absolute concentration. On the other hand, Lopes Barreto *et al*[20] analyzed effluent MMP-2 level as appearance rate. In the present study, effluent MMP-2 level significantly reflected the number of occurrence of peritonitis. Peritonitis, which induces peritoneal tissue injury, occurs 3.3 times more frequently in those who develop EPS than in those who do not[3]. This suggests a close relationship of peritonitis with peritoneal injury and developing EPS. Thus, effluent MMP-2 may be a superior indicator of peritoneal injury or a predictive marker for EPS.

IL-6 that plays a critical role in inflammatory processes is secreted in large quantities by peritoneal mesothelial cells in response to inflammatory stimuli and is modulated by exposure to PD solutions[13]. In the present study, effluent IL-6 level correlated with the results of PET and PD duration. On the other hand, although effluent IL-6 level in the EPS patient was high, the highest effluent IL-6 level was observed in another patient with accumulation of ascitic fluid and C-reacted protein-positive. This suggests that effluent IL-6 level reflected strong inflammation rather than EPS development. Cho *et al*[13] reported that effluent IL-6 level predicted increasing peritoneal solute transport rate and significantly increased with longer PD duration. Pecoits-Filho *et al*[14] also reported that effluent IL-6 level was correlated with high peritoneal solute transport rate. PD duration, in addition to high peritoneal solute transport rate, is a risk factor for EPS[25,26]. Abovementioned studies and our results suggest the efficacy of IL-6 as a biomarker of peritoneal deterioration. On the other hand, Goodlad *et al*[19] reported that although IL-6 was at higher levels in the effluent of patients who subsequently developed EPS, it did not improve prediction of future EPS compared with a model that used known clinical risk factors. Also in our study, a patient with the highest IL-6 level did not developed to EPS. As mentioned above, effluent IL-6 level may reflect deterioration of peritoneal membrane but it has to be kept in mind that effluent IL-6 level strongly reflects inflammation with or without EPS development.

Hyaluronan is constitutively synthesized by mesothelial cells and plays a crucial role in the maintenance of mesothelial cell morphology and re-mesothelialization. In particular, low molecular weight hyaluronan promotes angiogenesis, matrix protein synthesis, and transcription of MMPs[15]. In the present study, effluent hyaluronan level also significantly reflected PET results and PD duration. Yamagata *et al*[16] reported that intraperitoneal hyaluronan production increased with both higher membrane permeability and longer time on PD. Monitoring of hyaluronan in the peritoneal effluent may be useful as a marker to assess functional and morphological changes in the peritoneum in long-term PD patients. Effluent hyaluronan level may reflect deterioration of peritoneal membrane.

The concentration or appearance rate of CA125 in PD effluent has been used as a biomarker for mesothelial cell mass in patients on PD. In the present study, although there was no association between effluent CA125 level and peritoneal solute transport, effluent CA125 level correlated weakly with all other biomarkers. Effluent CA125 level of male patients was significantly lower than that of female patients; in addition, the level of diabetic patients was significantly lower than that of non-diabetic patients. In several previous studies, the concentration and appearance rate of CA125 in peritoneal effluent had significant negative correlation with the duration of dialysis[17]. In contrast, three cross-sectional studies found that duration of PD did not affect the CA125 level in the peritoneal effluent. Peritoneal transport parameters and a history of peritonitis in PD patients were not related to effluent CA125[16,17]. A few previous studies did not observe a relationship between patient sex and effluent CA125[17]. However, in a prospective study, effluent CA125 level was significantly lower in male patients than in female patients at 6 and 12 mo after PD initiation[17]. Ditsawanon *et al*[17] reported that effluent CA125 level and appearance rate can also be used to follow-up individual patients who are not infected to evaluate peritoneal fibrosis, which is characterized by loss of mesothelial cells. Krediet[18] described that effluent CA125 in stable PD patients without acute peritonitis is a marker of mesothelial cell mass, but has large inter-individual variability. Serial measurements over time can

be used for assessment of peritoneal mesothelial mass in individual patients, but effluent CA125 level may depend on individual characteristics of patients.

In conclusion, the peritoneal solute transport rate was most strongly correlated with the effluent level of MMP-2 among the biomarkers that were measured in the present study. MMP-2 may be useful as an indicator of peritoneal deterioration and can also potentially become a predictive marker with high sensitivity and specificity for EPS. Future studies should examine the serial changes of effluent MMP-2 level in relation to the progression of peritoneal injury. More patients should be tested to confirm the efficacy of MMP-2 as a biomarker and to eliminate selection bias of patients.

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COMMENTS

Background

Peritoneal dialysis (PD) is a blood purifying method for patients with end-stage renal disease. Long-term PD causes peritoneal deterioration with structural changes and functional decline, resulting in the cessation of PD treatment; these are the major problems associated with PD. At worst, peritoneal deterioration causes encapsulating peritoneal sclerosis (EPS), a serious complication of PD with extremely high mortality rate. To undergo PD safely and adequately, diagnosis of peritoneal deterioration is important.

Research frontiers

Solute transport rate through the peritoneal membrane is often measured by peritoneal equilibration test (PET) to estimate PD efficiency and peritoneal deterioration. However, the results from PET are not sufficient predictors of EPS onset, and monitoring the time-course changes are necessary. In addition, PET is invasive and takes a long time. It is thus necessary to evaluate peritoneal deterioration using an easy and reliable non-invasive method.

Innovations and breakthroughs

In this study, the peritoneal solute transport rate most strongly correlated with the effluent level of matrix metalloproteinase-2 (MMP-2) among some biomarkers. MMP-2 could also predict EPS with high sensitivity and specificity at 1 year prior to EPS onset.

Applications

The data in this study suggested that effluent MMP-2 may be useful as a reliable indicator of peritoneal deterioration and a predictive biomarker with high sensitivity and specificity for EPS.

Terminology

MMP-2 degrades Type IV collagen and fibronectin, which are components of extracellular matrix, and plays a critical role in cell migration, angiogenesis, and epithelial to mesenchymal transition of mesothelial cells.

Peer-review

This is a good article.

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ORIGINAL ARTICLE

Observational Study

Chronic kidney disease in children and adolescents in Brunei Darussalam

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Abstract

AIM: To determine epidemiology of Bruneian paediatric chronic kidney disease (CKD) patients and factors that affect growth and progression of disease.

METHODS: A cross-sectional study conducted on all children below 18 years old who were diagnosed with CKD over a ten year period (2004 to 2013). The reference population was all children (< 18 years old) suffering from CKD and attending the tertiary paediatric nephrology clinic in Brunei Darussalam. Demographic (current age, age of diagnosis, gender, ethnicity), anthropometric (weight and height), diagnosis, laboratory data (serum creatinine and haemoglobin, urinalysis) and blood pressure were extracted from the patients' clinical case notes and recorded using a data collection form.

RESULTS: The study revealed a high national prevalence [736 per million child population (pmcp)] and incidence (91 pcmp) of CKD. If CKD was defined at Stage 1, 2, 3, 4 or 5, the associated prevalence figures were 736, 132, 83, 50 and 33 pmcp. Glomerulonephritis accounted for 69% of all prevalent cases, followed by congenital abnormalities of kidney and urinary tract (20%) and tubulointerstitial diseases (8%). Minimal change disease being the most common histological diagnosis. The median age of diagnosis was 4.5 years, with congenital disease patients experiencing an earlier onset of diagnosis. A large

proportion of patients were below the 5% percentile for height and weight. Non-glomerular diseases, adolescent and female patients were significantly associated with poor growth, but not glomerular filtration rate, age of diagnosis or steroid usage.

CONCLUSION: Brunei has a high prevalence of chronic kidney disease in the paediatric population with glomerulonephritis being the most common disease.

Key words: Brunei; Children; Adolsecent; Chronic kidney disease; Epidemiology

Core tip: This study provides demographic data for chronic kidney disease (CKD) in children and adolescents in Brunei Darussalam. Due to the small population, referral pattern and healthcare infrastructure of the country, the authors believe that the research has enabled a closer estimate of national prevalence and incidence of all stages of CKD than most countries. To our knowledge, this study is the first of its kind to report on epidemiology of CKD from the earliest stages.

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INTRODUCTION

Chronic kidney disease (CKD) affects almost 500 in 1 million people per year, among which 1%-2% are in the paediatric age range (0-17 years old)[1]. Childhood and adolescent CKD, particularly in later stages, are associated with serious cardiovascular, neurologic, metabolic and other clinical complications. Further understanding in the epidemiology of CKD plays a fundamental role in identifying populations at risk as well to evaluate the interventions undertaken. Existing paediatric epidemiological data on incidence and prevalence are flawed by methodological differences between the various data sources in characterising age groups, degree of renal insufficiency and disease classifications[2]. Most of the robust and available CKD data are extrapolated from national registries with adult ESRD cohorts in developed countries. To date, there are scarce epidemiological data on paediatric patients with earlier stages of CKD, especially in developing Asian countries where there are limited procedures and activities to collect and publish valid epidemiological data.

In Brunei Darussalam, there has been no published or collated information for this group of patients. Therefore, this study serves to determine the epidemiological characteristics and clinical factors [gender, diagnosis, glomerular filtration rate (GFR), steroid usage] affecting growth and progression of kidney disease in the Bruneian paediatric CKD population. Additionally, comparisons were also made with data from pub-med listed literature on demographics and characteristics of international paediatric CKD patients.

MATERIALS AND METHODS

This was a cross-sectional study conducted on all children below 18 years old who were diagnosed with CKD over a ten year period (2004 to 2013). The reference population was all children (< 18 years old) suffering from CKD and attending the tertiary paediatric nephrology clinic in Brunei Darussalam. All available cases were included without sampling. Demographic (current age, age of diagnosis, gender, ethnicity), anthropometric (weight and height), diagnosis, laboratory data (serum creatinine and haemoglobin, urinalysis) and blood pressure were extracted from the patients' clinical case notes and recorded using a data collection form.

Weight and height retardation were defined as less than fifth percentile on the Disease Control and Prevention (CDC) growth charts[3]. CKD was defined as GFR < 60 mL/min per 1.73 m^2 or the presence of kidney damage (structural or functional abnormalities other than decreased GFR) for more than three months[4]. GFR was estimated by Schwartz's formula when height was recorded[5]. The value of *k* varied with age and gender, being 0.33 in preterm infants (< 1 year old), 0.45 in full-term infants (< 1 year old), 0.55 in children (< 13 years old) and adolescent girls (≥ 13 years old), and 0.70 in adolescent boys (≥ 13 years old)[5]. For children without height records (n = 3), eGFR-Pottel's formula was used[6,7]. Anaemia was defined by the Clinical Practice Guidelines of the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI guidelines) as haemoglobin level less than a specific threshold which varied with children's age and gender[3]. Blood pressure readings were compared with blood pressure tables for children and adolescents, which were dependent on age and height. The diagnosis and classification of hypertension were accorded with National Heart, Lung, and Blood Institute (NHLBI)'s guidelines[8].

RESULTS

The male to female gender ratio was 1.3:1. Socio-demographic characteristics and aetiological diseases of the study sample are shown in Table 1. The most common aetiology was glomerular diseases (n = 61) followed by congenital abnormalities of kidney and urinary tract (CAKUT) and tubulointerstitial diseases. Nine out of 61 cases were biopsied with minimal change disease (n = 4) being the most common histological diagnosis. The median age of diagnosis (data skewed to the right) was 4.5 (IQR = 6.0) years, with congenital disease patients

Table 1 Socio-demographic characteristics of study sample (89 patients)

Variable	*n* (%)	Mean (SD)
Current age (yr)		11.3 (4.12)
1-4	1 (1.1)	
5-9	30 (33.7)	
10-14	36 (40.4)	
15-18	22 (24.7)	
Gender		
Male	51 (57.3)	
Female	38 (42.7)	
Race		
Malay	76 (85.4)	
Chinese	9 (10.1)	
Others	4 (4.5)	
Aetiology		
Glomerular	61 (68.5)	
CAKUT	20 (22.5)	
Tubulointerstitial	8 (9.0)	

CAKUT: Congenital abnormalities of kidney and urinary tract.

Table 2 Anthropometric, clinical and laboratory characteristics of the study sample

Variable	*n*	*n* (%)	Mean (SD)	Median (IQR)
Weight in kilogram	87		-	29.90 (23.60)[1]
< 5th percentile		22 (25.3)		
⩾ 5th percentile		65 (74.7)		
Height in cm	74		-	123.70 (27.60)[2]
< 5th percentile		23 (31.1)		
⩾ 5th percentile		51 (68.9)		
Systolic blood pressure (mmHg)	79		111.8 (13.86)	-
Diastolic blood pressure (mmHg)	79		70.9 (10.40)	-
Normal		40 (50.6)		
Pre-hypertensive		12 (15.2)		
Stage 1 hypertension		21 (26.6)		
Stage 2 hypertension		6 (7.6)		
Haemoglobin level (g/dL)	82		12.7 (1.65)	-
Normal		63 (76.8)		
Anaemia		19 (23.2)		
eGFR (mL/min per 1.73 m^2)	86		124.6 (52.99)	-
Stage 1 (> 90)		70 (81.4)		
Stage 2 (60-89)		6 (7.0)		
Stage 3 (30-59)		4 (4.7)		
Stage 4 (15-29)		2 (2.3)		
Stage 5 (< 15)		4 (4.7)		
Proteinuria	82		-	-
Yes		42 (51.2)		
No		40 (48.8)		
Haematuria	82		-	-
Yes		21 (25.6)		
No		61 (74.4)		

[1]The distribution is skewed to the right; [2]The distribution is skewed to the left. eGFR: Estimated glomerular filtration rate; IQR: Interquartile range.

experiencing an earlier onset of diagnosis.

Twenty-five point three percent and thirty-one point one percent of patients were under the 5% percentile for weight and height respectively. Patients with non-glomerular disease were found to be statistically most likely to have growth hindrance (P = 0.001 and P = 0.003 for weight and height respectively). A significant proportion of patients were hypertensive (34.2%) and anaemic (23.2%). Proteinuria and haematuria were present in 51.2% and 25.6% of patients respectively. The majority of patients were in Stage 1 CKD (81.4%) but 4 patients (4.7%) had end stage renal disease (on peritoneal dialysis). The anthropometric, clinical and laboratory characteristics of the study sample are shown in Table 2. The study found that there was no significant correlation between GFR and age of diagnosis with weight and height (Table 3). Steroid usage was not associated with growth attenuation (P = 0.111 and P = 0.579 for weight and height respectively) in patients with glomerular disease. However female, adolescent and non-glomerular patients were statistically more likely to experience growth attenuation. Details are shown in Tables 3 and 4.

Table 3 Correlation between glomerular filtration rate, current age and age of diagnosis with weight and height

		Weight	Height
GFR	Correlation coefficient	0.168[1]	0.176[1]
	P value	0.125	0.140
	n	85	72
Current age	Correlation coefficient	0.609[1]	0.541[2]
	P value	0.001	0.001
	n	87	74
Age at diagnosis	Correlation coefficient	0.450[1]	0.368[2]
	P value	< 0.001	0.002
	n	84	71

[1]Spearman's rank correlation; [2]Pearson's correlation. GFR: Glomerular filtration rate.

Based on population statistics for children of Brunei Darussalam, the age adjusted annual incidence of CKD over the 10 year range (2004-2013) is shown in Figure 1. The cumulative incidence and prevalence of all stages of CKD in 2013 were 91 and 736 per million child population (pmcp) respectively.

DISCUSSION

There is limited literature on the epidemiology of CKD in the paediatric population. Most paediatric patients with mild CKD are not represented in national registries, due to the asymptomatic nature of the condition. From our local experience, diseases with a more "dramatic" presentation like glomerulonephritis were more likely to be picked up and followed up by nephrologists. "Silent disease" may be missed especially in developing countries where screening, diagnosis and awareness of diseases may not be as extensive and comprehensive. The major difficulty in comparing studies is the inconsistent criteria used to define CKD. Our interpretation of the literature revealed that it is commonplace to disregard CKD stage

Table 4 Relationship between gender and aetiology with weight and height

	Weight		χ^2 statistic (*df*)	*P* value[1]	Height		χ^2 statistic (*df*)	*P* value[1]
	< 5th percentile *n* (%)	⩾ 5th percentile *n* (%)			< 5th percentile *n* (%)	⩾ 5th percentile *n* (%)		
Gender								
Male	9 (17.6)	42 (82.4)	3.81	0.051	10 (21.7)	36 (78.3)	4.95	0.026
Female	13 (36.1)	23 (63.9)	(1)		13 (46.4)	15 (53.6)	(1)	
Aetiology								
Glomerular	9 (15.0)	51 (85.0)	10.83	0.001	10 (20.0)	40 (80.0)	8.84	0.003
Non-glomerular	13 (48.1)	14 (51.9)	(1)		13 (54.2)	11 (45.8)	(1)	

[1]χ^2 test for independence.

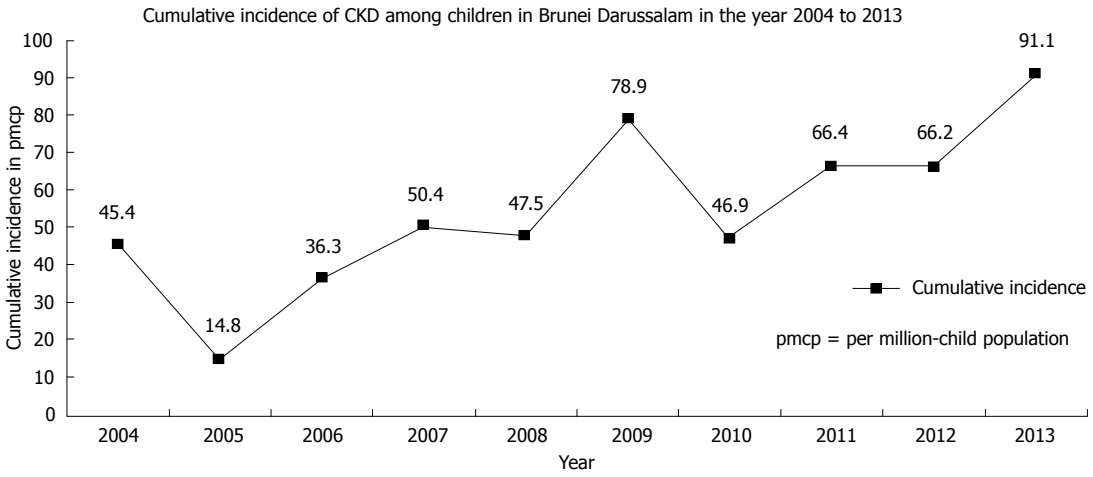

Figure 1 Cumulative incidence of chronic kidney disease among children in Brunei Darussalam in the year.

1 due to the lack of tangible physical and serological evidence of kidney impairment. However one can argue that such paediatric patients (*e.g.*, nephrotic syndrome in remission) are debatably at higher risk of future kidney damage than their GFR-matched adult counterparts (with age related deterioration) due to the inherent reduced threshold for renal injuries and longer lifelong exposure to renal insults. For this research, we have made a conscious effort to include patients with all stages of CKD in an attempt to elucidate the true estimate for CKD prevalence and incidence in our population.

Our research revealed an estimated incidence and prevalence that is higher than most countries. However, if CKD definitions were set at Stage 1, 2, 3, 4 and 5, then the calculated prevalence would be 736, 132, 83, 50 and 33 pmcp respectively. The incidence of CKD in Brunei has shown progressive increments in the ten year period from 2004 to 2013, consistent with trends in the adult population[9]. Local data from the Brunei Dialysis and Transplant Registry revealed a prevalence of 75 pmp in the young adult ESRD (CKD stage 5D) population (age 19-30), with a similar trend of increment over the last ten years[10]. If only CKD stage III or lower patients are to be considered, our prevalence of 83 pmcp is on par with data from European studies with similar CKD profiles like Italy (74.7 pmcp)[11], Belgium (56 pmcp)[12] and Spain (71.1 pmcp)[13]. The prevalence of paediatric ESRD (33 pmcp) was also consistent with trends from developed Western and affluent Asian countries[14]. Data from other developing Asian countries were available but direct comparisons on incidence and prevalence were difficult because of the difference in patients' population. Table 5 compares Bruneian data with PubMed listed literature (from the past 15 years) on prevalence, incidence and other demographic data from other countries.

There were some important differences between the aetiology of kidney diseases in our cohort with the local adult population and the international paediatric literature. The spectrum of disease differed markedly from our adult population, where diabetes mellitus and hypertension were the main aetiological diseases[9]. There appeared to be a progression of importance for diabetes mellitus as an aetiological cause with increasing age. Glomerulonephritis (52%), diabetes mellitus (23%) and CAKUT (15%) were the three main causes of ESRD in our young adult population (age 19-30)[10]. Globally, congenital causes (CAKUT) accounted for the most common aetiology among paediatric CKD[2]; this was reported in developed countries including United States[15], United Kingdom[23] and Italy[11]. However, only twenty patients (22.5%) were diagnosed with congenital anomaly in this study. On the contrary,

Table 5 Comparisons of paediatric epidemiological data from different countries from 1990-2015

	Period	No. of patients	Main aetiology	Male/female ratio	Mean age at diagnosis	GFR/CKD stage	Incidence	Prevalence
Brunei	2004-2013	89	GN (69%)	1.3	4.5	Mainly CKD 1 (81%)	91	736 (CKD1) 132 (CKD2 and above) 83 (CKD3 and above) 50 (CKD4 and above) 33 (CKD5)
Italy[10]	1990-2000	1197	CAKUT (58%)	2.0	6.9	GFR 42 (mean)	12.1	75
Belgium[11]	2001-2005	143	CAKUT (59%)	1.3	3.0	Mainly CKD 3 (67%)	11.9	56
Spain[12]	2007-2008	605		1.9	3.9	GFR 52 (mean)	8.7	71
United States[15]	1994-2007	7037	CAKUT (48%)					
Kuwait[16]	1996-2003	171	CAKUT 62%	2.7	33 mo	30% of patient reached ESRD within 18 mo of diagnosis	38-55	
Vietnam[17]	2001-2005	152		1.7	11.3	65% received RRT		5.1
Sudan[18]	2001-2006	205	GN 25%	1.7	9.8	63% of cohort reached ESRD during the follow up period		
Turkey[19]	2005	282	"Urological problem" 44.3%	1.3	8.0	CKD2-5	11.9	
Thailand[20]	1982-2005	101	GN 35%	1.6			Not rare	Double in last 6 yr of research
Jordan[21]	1988-2001	202	CAKUT 42%	1.3	7.5	59/202 patients require RRT	10.7	51
China[22]	1990-2002	1658	GN 52%	1.5	8.18	Mean serum creatinine 594.7 mmol/L		

CKD: Chronic kidney disease; GFR: Glomerular filtration rate; CAKUT: Congenital abnormalities of kidney and urinary tract; GN: Glomerulonephritis; ESRD: End stage renal disease.

there was a high prevalence of glomerular diseases (68.5%), comparable to published data from developing countries like Vietnam[17], Sudan[18], Thailand[20] and Malaysia[24]. It has been postulated that high proportions of glomerulonephritis may be related to high prevalence of bacterial, viral and parasitic infections that commonly affect the kidneys in developing countries[14]. Furthermore, many paediatric CKD patients with CAKUT may have been referred directly to surgeons, with no subsequent follow up by nephrologists. As many of these patients do not have overt clinical symptoms, there may have been a delay in presentation of renal disease. This may have led to the patients being missed by this research leading to an underestimate of the prevalence of this disease.

Our study reports a male preponderance of 1.3. This is universally consistent with all the published studies in the literature which reported a range between 1.3 and 2.7. This gender disproportionality can be explained by the higher incidence of congenital disorders (obstructive uropathy, renal dysplasia and prune belly syndrome) in boys[9]. Even after excluding these congenital defects, boys were still more likely to be affected by CKD[11]. The median age of diagnosis (4.5 years) was similar to developed European countries (range of 3.3-6.9 years) but lower than developing Asian countries (range of 7.5 to 13 years). We suspect that this is related to healthcare infrastructure and health seeking behaviours of the population rather than the intrinsic characteristics of the disease in the population.

Poor growth in children with CKD is associated with increased morbidity and mortality[25]. A significant proportion of our patients were below the 5th percentile for weight (25.3%) and height (31.1%). This is not unusual for children with CKD due to congenital predisposition, electrolyte imbalances, malnutrition, bone disease and medications[26]. Hamasaki *et al*[27] revealed that Asian CKD patients with congenital anomalies, lower GFR, being small for date and asphyxia at birth are more likely to have growth impairment. Our research showed that female and adolescent patients are more likely to experience growth attenuation. Adolescent patients usually experience growth spurts in their teenage years and it is not surprising to find that growth attenuation is maximal during this period. We observed other studies[28,29] also derived similar results with females being more antropometrically challenged than males, likely from a difference in age when they experience their growth spurts. Consistent with some literature reports[30,31], this study did not find an association with steroid usage and growth attenuation in patients with glomerular disease. This suggests that GN diseases were predominantly steroid responsive and steroid regime was consistently kept to a minimum. This study also showed that there was no correlation between GFR and growth (weight and height), which corresponded with some reports from the literatures[32,33]. We were not able to find an association between clinical and epidemiological factors linked with progression of renal disease.

We acknowledge that the sample size of this study is small and this may have affected the statistical evaluation of clinical and demographic factors, particularly in

association with growth. Since this is a retrospective study, there were some incomplete datasets from patients that were lost on follow up. We would also have like to scour paediatric, urological and general practitioner clinics for unreferred CKD patients but this would have gone beyond the realms of the ethical agreement set for the study.

This study is the first to describe the epidemiology of CKD among children and adolescents in Brunei Darussalam. The spectrum of disease is dissimilar to that in our adult population. We reported a higher incidence and prevalence than most countries because we were able to capture patients at earlier stages of their diseases. Our clinic is a one-stop referral centre for all cases of paediatric CKD in the country and we believe that it enables us to capture most of the symptomatic CKD patients in the country, regardless of stages of disease. We believe that this is unique as it allows us to predict the true scale of paediatric CKD and provide a closer estimate of national prevalence and incidence of CKD than most other countries. Furthermore, this study has heightened our awareness of growth attenuation and highlighted the need for early involvement of dieticians, nutritionists and social workers to improve the nutrition, education and social welfare of future paediatric CKD patients in our clinics.

COMMENTS

Background

Demographic data on paediatric patients with chronic kidney disease (CKD) are limited. This is especially true for patients with earlier stages of CKD and from developing countries. This study provided epidemiological characteristics of Bruneian patients from all five stages of CKD. In addition, analysis was done to elucidate factors that may have affected growth of patients and progression of renal disease. The study revealed a high national prevalence [736 per million child population (pcmp)] and incidence (91 pcmp) of CKD. If CKD was defined at Stage 1, 2, 3, 4 or 5, the associated prevalence figures were 736, 132, 83, 50 and 33 pcmp. Glomerulonephritis accounted for 69% of all prevalent cases. A large proportion of patients were below the 5% percentile for height and weight. Non-glomerular diseases, adolescent and female patients were significantly associated with poor growth, but not glomerular filtration rate, age of diagnosis or steroid usage.

Research frontiers

In comparison with other studies, the authors believe that we have a closer national estimate of CKD in the paediatric population due to our ability to capture CKD patients through our one-stop tertiary clinic and the relative small population in the country. Additionally, the authors identified that a significant proportion of the patients have attenuated growth, prompting us to advocate early interventions by nutritionists, dieticians and social workers to supplement treatment options by physicians to augment and intensify growth and physical development.

Innovations and breakthroughs

The authors believe that the authors are one of very few studies to predict the prevalence and incidence of CKD in the paediatric population, particularly for the earlier stages of diseases where patients may remain asymptomatic. More studies will be needed to evaluate this further.

Applications

Knowledge of national prevalence and incidence of CKD in the paediatric population can help service providers plan future population needs for renal replacement therapy and can help public health promotion exercises to identify early disease and to delay progression to irreversible end stage renal disease.

Terminology

CKD: Chronic kidney disease; GFR: Glomerular filtration rate; KDOQI: National Kidney Foundation's Kidney Disease Outcomes Quality Initiative; CAKUT: Congenital abnormalities of kidney and urinary tract; GN: Glomerulonephritis; ESRD: End stage renal disease; Pmcp: Per million child population.

Peer-review

A reasonable first analysis of congenital pediatric renal disease in a previously unstudied population with findings in the range of what might has been predicted.

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CASE REPORT

Comamonas testosteroni-associated peritonitis in a pediatric peritoneal dialysis patient

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Abstract

Comamonas testosteroni (*C. testosteroni*) has been rarely observed as an infectious agent in clinical practice. Few reports described its potential pathogenicity in bloodstream and abdominal infections. Here, we report our experience in the treatment of a *C. testosteroni*-associated peritonitis in a four-year-old girl receiving chronic peritoneal dialysis (PD). The organism was shown to be highly susceptible to appropriate antibiotic therapy. Infection responded promptly and the patient was managed conservatively without withdrawal from PD.

Key words: *Comamonas*; Peritonitis; Peritoneal dialysis; Comorbidity; Children

Core tip: *Comamonas testosteroni* (*C. testosteroni*) has been largely overlooked as a potential pathogen in humans. This case reports not only the first description of a *C. testosteroni*-associated peritonitis in a pediatric patient, but also emphasizes the risk of uncommon causes of bacterial peritonitis especially in peritoneal dialysis children with severe comorbidities.

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INTRODUCTION

Comamonas testosteroni (*C. testosteroni*) is an aerobic Gram-negative organism with a widespread

environmental distribution. Infection by *C. testosteroni* is infrequent, however there are some reports describing its potential causative role in bacteremia, meningitis, urinary tract infections, endocarditis, cellulitis, and pneumonia[1,2]. Isolation of *C. testosteroni* has also emerged in localized peritonitis as a complication of perforated appendicitis[3,4].

Here, we present our experience in the treatment of a *C. testosteroni*-associated peritonitis in a four-year-old girl receiving chronic peritoneal dialysis (PD).

CASE REPORT

The girl was previously diagnosed with end-stage renal disease due to atypical haemolytic-uraemic syndrome, and she had been treated with automated PD for 10 mo. The girl was also affected by severe motor-cognitive impairment and idiopathic epilepsy.

She was admitted to our Department with a 24-h history of high-grade fever and complaining of abdominal pain. Physical examination revealed abdominal tenderness, along with cloudy peritoneal effluent. The patient's white blood cell count was normal (6130/mm^3), whereas the C-reactive protein was significantly increased (290 mg/L). The leukocyte in peritoneal effluent showed a count of 6600/mm^3 (90% polymorphonucleated). One month before this event, the patient had experienced a *S. aureus* peritonitis, for which she had completed a 3-wk course of intraperitoneal therapy with glycopeptide.

After admission, empiric antibiotic therapy was started with both intravenous ceftazidime and teicoplanin. The fever subsided within 48 h and the leukocyte count in effluent resulted normal (< 100/mm^3) within 72 h from the start of antibiotic treatment. Signs and symptoms of peritonitis regressed within 48 h. On hospital day 3, cultures from peritoneal effluent resulted positive for *C. testosteroni*. Antibiotic treatment was then simplified, with single-agent intraperitoneal ciprofloxacin in order to complete a 3-wk course of therapy. The patient was discharged and a follow-up after 14 and 30 d showed persistent normalization of leukocyte in peritoneal effluent, negative control cultures, and regular PD course. To date, after 12 mo from the *C. testosteroni* peritonitis, the patient did not experience any other significant infectious episode. She is still on chronic PD and in the waiting list for renal transplantation.

DISCUSSION

Case reports provide important and detailed information for educational purposes related to clinical practice, which is often lost in larger studies[5]. This concept is especially true if the disease described is rare. Clinical experience is the starting point of evidence-based medicine and the sharing of treatment outcomes represents a preliminary guideline for the future management of similar cases.

Peritonitis remains a frequent complication of PD in children and is the most common reason of technique failure. The microbiology is characterized by a predominance of Gram-positive organisms, with fungi responsible for less than 5% of episodes[6]. The vast majority of patients are treated successfully with antibiotics administered intraperitoneally and continue PD. The poorest outcomes are observed in patients with Gram-negative organisms or fungi peritonitis and in those with a relapsing infection. In this cases, early PD catheter removal with transient switch to haemodialysis is sometimes required[7]. Despite the lower prevalence, fungal infections are associated with the highest mortality rate.

C. testosteroni is a gram-negative aerobic bacillus that is found in various environments, including soil, water, plants, and animals. In spite of its wide environmental distribution, there are few reports on its involvement in human infections[1]. Most of the reported infections by this organism are community-acquired, however some authors suggested that it can also survive for a long time in the hospital setting. Indeed, it can colonize several devices, such as intravenous lines, respiratory equipment, and humidifiers[8,9]. This seems mostly due to an extraordinary capability of this organism in both environmental adaptation and biofilm formation[10]. Nevertheless, few molecular biological investigations were taken on the pathogenicity and virulence of *C. testosteroni*. Very recently, Liu *et al*[11] conducted a comprehensive genomic analysis among 10 *C. testosteroni* strains. They identified 24 types of virulence factors that were involved in several functions such as adherence, anti-phagocytosis, invasion, and secretion system. Moreover, the authors found that most of the virulence factors were owned by all of the strains and were highly conserved. These results supported the molecular biological basis of the potential pathogenicity of this bacterium.

Along with its own virulence factors, pathogenicity of *C. testosteroni* seems to be emphasized in patients with some degree of immunosuppression such as malignancy, prematurity, primary or secondary immunodeficiency induced by chronic liver disease and end-stage renal disease[1,12]. Moreover, bacterial translocation from the gastrointestinal tract seems to play an important role in the pathogenesis of infections[13].

Very recently, Altun *et al*[14] published the first continuous ambulatory PD patient treated for a *C. testosteroni*-associated peritonitis. The authors described a 29-year-old woman with end-stage renal failure secondary to hypertensive nephrosclerosis who had been treated with CAPD for 10 mo. In this case, along with the chronic dialysis status, the predisposing factor for peritonitis with this pathogen was probably a previous laparoscopic intervention because of incidental dislocation of an intrauterine device to the space between the peritoneum and the anterior abdominal wall. Signs and symptoms of peritonitis regressed rapidly during a 14-d period of oral ciprofloxacin.

C. testosteroni is usually sensitive to a broad range of antibiotics, including aminoglycosides, cephalosporins, fluoroquinolones, carbapenems, piperacillin-tazobactam, cephalosporins, and trimethoprim-sulfamethoxazole[15]. According to the survey by Farshad *et al*[1], 32 out of 35 reported cases of human infection by this bacterium were

promptly responsive to antibiotic treatment. Outcome was fatal in three cases, including a 64-year-old woman on hemodialysis with a central venous catheter-related bacteremia[12].

To our knowledge, the present case is the second report of a *C. testosteroni*-associated peritonitis in a PD patient, but is the first description in pediatric age. Information regarding immune function in children with chronic kidney disease or receiving dialysis are sparse. The incidence of infectious episodes in children on dialysis is higher than that found in adults; moreover, immaturity of the immune system may also contribute to its dysfunction especially in children with chronic diseases and several co-morbidities. In our patient, both dialysis status and severe motor-cognitive impairment may have increased the pathogenicity of *C. testoteroni*, similarly to previous adult case reports. Moreover, the previous and recent episode of *S. aureus* peritonitis might have represented a further predisposing factor to *C. testosteroni* infection. In fact, in PD patients, bacterial peritonitis induces a subsequent breakdown of intestinal barrier function and a transient impairment of host mucosal immune defense[16]. This may have allowed further enteric low-virulence organisms to enter the peritoneal cavity by transmural migration and to cause peritonitis[17].

C. testosteroni should be kept in mind as a rare cause of bacterial peritonitis in children receiving chronic PD. With the improvement in care of end-stage renal disease patients and given the potential for favorable outcomes, a higher number of children with severe co-morbidities is now started to PD. Clinical management of these children is demanding; in a report of the International Pediatric Peritoneal Dialysis Network, Neu *et al*[18] showed that children on PD with comorbidity had a higher hospitalization rate than did patients without a comorbidity. Infections from both common and unusual pathogens were the most frequent reasons for hospitalization and mortality. Our experience confirms that *C. testosteroni* peritonitis responds promptly to adequate antibiotic therapy. A conservative management can be adopted without loss of the PD catheter and withdrawal from the PD.

COMMENTS

Case characteristics

A 4-year-old girl with severe motor-cognitive impairment, idiopathic epilepsy, and receiving chronic peritoneal dialysis (PD) was admitted with a 24-h history of high-grade fever and complaining of abdominal pain.

Clinical diagnosis

Physical examination revealed abdominal tenderness, along with cloudy peritoneal effluent.

Differential diagnosis

Bacterial (Gram-positive or Gram-negative) peritonitis, fungal peritonitis, culture negative peritonitis, encapsulating peritoneal sclerosis.

Laboratory diagnosis

WBC count was within normal limits, C-reactive protein was significantly increased (290 mg/L), and laboratory investigations in peritoneal effluent showed a leukocyte count of 6600/mm^3 (90% polymorphonucleated cells) with a positive culture for *Comamonas testosteroni* (*C. testosteroni*).

Treatment

Intraperitoneal ciprofloxacin in order to complete a 3-wk course of therapy.

Related reports

Infection by *C. testosteroni* is infrequent, however there are some reports describing its potential causative role in bacteremia, meningitis, urinary tract infections, endocarditis, cellulitis, and pneumonia. Isolation of *C. testosteroni* has also emerged in localized peritonitis as a complication of perforated appendicitis.

Term explanation

C. testosteroni-associated peritonitis represents a rare complication of chronic PD. The pathogenicity of this bacteria might be increased in immunodeficient patients, in children with severe chronic diseases, and affected by co-morbidities.

Experience and lessons

C. testosteroni should be kept in mind as a rare cause of bacterial peritonitis in children receiving chronic PD. *C. testosteroni* peritonitis responds promptly to adequate antibiotic therapy, therefore a conservative management can be adopted without loss of the PD catheter and withdrawal from the PD.

Peer-review

C. testosteroni-associated peritonitis in PD patients is a rare condition. This case-report can add some new information to clinical practitioners.

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