

The Importance of Tubular Function in Chronic Kidney Disease

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Abstract: Glomerular filtration rate (GFR) and proteinuria-albuminuria are the renal functional parameters currently used to evaluate chronic kidney disease (CKD) severity. However, tubular secretion is another important renal functional parameter to be taken into account since proximal tubule (PT) secretion, in particular, is a crucial renal mechanism for endogenous organic cations, anions and drug elimination. The residual diuresis is a relevant survival predictor in patients on dialysis, since their urine is produced by the glomerular and tubular functions. It has been hypothesized that drugs which up-regulate some renal tubular transporters could contribute to uremic toxin excretion, and nephroprotection. However, if tubular transporters' down-regulation observed in CKD patients and experimental models is a PT adaptation to avoid intracellular accumulation and damage from uremic toxins, consequently the increase of toxin removal by inducing tubular transporters' up-regulation could be deleterious to the kidney. Therefore, a deeper understanding of this phenomenon is currently needed. In conclusion, tubular function has an important role for endogenous organic cations, anions and drug excretion in CKD patients, and a deeper understanding of its multiple mechanisms could provide new therapeutic alternatives in this population.

Keywords: tubular function, chronic kidney disease, drugs

Introduction

Glomerular filtration rate (GFR) and proteinuria-albuminuria are the renal functional parameters currently used to evaluate chronic kidney disease (CKD) severity. Besides, whereas knowing the patient's GFR value is useful for adjusting some medication doses, as well as predicting chronic nephropathy patient's cardiovascular risk, CKD progression, and death; the magnitude of urinary protein-albumin excretion also helps to predict patient's CKD progression and his/her cardiovascular risk.¹ However, despite GFR and urinary protein-albumin excretion parameters, tubular secretion is another important renal functional variable to be taken into account because of the following reasons:¹⁻³

First, proximal tubule (PT) secretion is the main mechanism for achieving urinary excretion of most of the medications, and endogenous organic anions. In addition, unlike GFR, PT secretion includes the ability to excrete protein-bound solutes since it is equipped with varied transporter machinery which participates in the basolateral uptake and luminal excretion of solutes, such as the organic cation/anion/zwitterion solute carrier family (SLC) (Figure 1).¹⁻⁴

Second, around 24 of the 153 compounds, which have been confirmed as characteristic uremic toxins, interact with organic anion transporters (OATs), and

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Organic cation transporter 2 (OCT2; SLC22A2)
Organic anion transporter 1 and 3 (OAT1/3; SLC22A6 and SLC22A8)
Organic anion transporting polypeptide 4C1 (OATP4C1; SLCO4C1)
Multidrug and toxin extrusion proteins (MATEs; SLC47A1/2)
Adenosine triphosphate (ATP)-binding cassette transporter family: P-glycoprotein (P-gp), also termed Multi Drug Resistance gene 1 (ABCB1)
Multidrug resistance associated protein 2 and 4 (MRP2/4; ABCC2/4)
Breast cancer resistance protein (BCRP; ABCG2)

Figure 1 Organic cation/anion/zwitterion solute carrier family (protein; gene).

7 of these substances: acid uric, indoxyl sulfate (IS), p-hydroxyhippuric acid, 3-carboxy-4-methyl-5-propyl-2-furanopropanoic acid (CMPF), xanthine, indoleacetic acid, hippuric acid, have been documented to present elevated serum levels in uremic patients.³

Third, the OATs handle drugs (antibiotics, antivirals, diuretics, nonsteroidal anti-inflammatory drugs), toxins (mercury, aristolochic acid), and nutrients (vitamins, flavonoids), and play a central role in the metabolism of gut microbiome metabolites. Since OATs are expressed in many organs, and they have a strong selectivity for particular signaling molecules (eg.: sex steroids, odorants, etc.), they may function in remote interorgan communication by regulating levels of signaling molecules and key metabolites in tissues and body fluids. This mechanism is known as the remote sensing and signaling hypothesis (RSSH).⁵

Fourth, OATs, specially OAT1, OAT2, OAT3 and OAT4, and URAT1, are crucial in the pathophysiologic mechanisms related with intracellular accumulation and toxicity of uremic toxins. Acute or chronic renal injury

can exert a profound reduction on OAT gene and protein expression level. This down-regulation of OAT expression in PT could represent an adaptation to high exposure to toxins.³

Fifth, solutes clearance studies suggest that GFR and PT secretion could be reduced at different rates among old and chronic nephropathy patients; thus, due to the participation of tubular secretion in drugs excretion, evaluation of tubular secretion activity could be crucial for deciding the medication dose in older, and CKD individuals.¹

Creatinine and Uric Acid Renal Tubular Transport

The creatinine clearance is extensively used for evaluating patient's GFR, but 10–40% of this clearance is the consequence of active tubular secretion in the PT, and this phenomenon is even increased in renal disease.⁶ Even though several studies have documented a link between the SLC22A2 gene and serum creatinine and estimated GFR values, the SLC22A2 genotype has also been documented to be associated with a net tubular creatinine secretion phenotype (OCT2), proving that using creatinemia to determine kidney function can be clearly biased.^{7,8} In animal models, the role of OAT in creatinine excretion has been documented since the administration of para-aminohippuric acid, an OAT inhibitor, significantly reduced the secretion of creatinine and increased its plasma level. In addition, studies which used OAT1- and OAT3-deficient mice confirmed the above-mentioned phenomenon, showing a more relevant role for OAT3.^{6,7} Regarding uric acid, its renal tubular handling is determined by a balance between its tubular secretion and reabsorption, two processes which take place in PT.^{9–12} Studies in humans have documented that uric acid reabsorption is mainly mediated by urate transporter 1 (URAT1; *slc22a12*), whose activity is inhibited by uricosuric agents (eg: probenecid). Additionally, since URAT1 is a member of the OATs, and four of them have been localized at the basolateral and luminal areas of the PT, studies have suggested that all of them may mediate urate transport in both the renal secretion and reabsorption. Besides, a renal-specific transporter RST, which is mainly localized at the apical surface of the PT may also contribute to PT urate reabsorption.^{13,14} Increased oxidative stress and hypovolemia stimulate urate tubular reabsorption, with angiotensin II, epinephrine and insulin hormones acting as potential mediators.¹⁵ Regarding

hippuric and kynurenic acids, these substances can contribute to CKD progression through further solute retention. In an animal model, which investigated the effect of high serum uric acid levels on uremic toxin levels, kynurenic acid was found as a substrate for MRP4 and BCRP tubular transporters. It was documented that high serum uric acid level was associated with the accumulation of the kynurenic acid (toxin), most likely due to a uric acid-induced carrier dysfunction. Thus, in order to maintain normal serum urate levels, an adequate function of several kidney carriers (BCRP and MRP4) is needed. Therefore, it has been hypothesized that high serum uric acid levels could indirectly induce CKD by leading to uremic toxin retention.^{3,10}

Drugs and Renal Tubular Transport

The kidneys in human beings mainly express OCT2 (SLC22A2), which is crucial for removing cationic substances from blood, such as metformin, cimetidine, cisplatin, antihistamines and some antibiotics.⁷ Besides, the multidrug and toxin extrusion protein 1 (MATE1) and its isoforms (MATE2 and MATE2-K), which are encoded by the SLC47A gene family, frequently work with OCTs. MATE1 is expressed mainly in the kidney and liver, while MATE2-K is located only in PT. These carriers can have a marked effect on drugs pharmacokinetics due to genetic MATE1 and MATE2-K polymorphisms have been related to variability in renal drug handling and toxicity.⁷ In the kidney, 4 multidrug carriers (P-gp, MRP2, MRP4, and BCRP) coordinately pump several compounds into the urine. The MRPs mediate the transport of several organic anionic substances and their metabolites, including glucuronide, glutathione, and sulfate conjugates. Besides, MRP4 additionally has been related to nucleotides and prostaglandins efflux.⁷

Substrate studies have revealed that OATs can transport many clinically relevant xenobiotics and endogenous chemicals, such as ochratoxin A, tetracycline, mercuric conjugates, and adefovir. This property makes OATs vulnerable since they interact with several toxins, making them primary targets for toxicity. Consequently, mutations in OATs sequences may result in these carriers dysfunction, and consequently an accumulation of toxins at the PT which result in further extrarenal toxicity because of substrate competition for extrarenal OATs transport, and delayed clearance of toxins.¹⁶ In this sense, the OATP4C1 reduction in the PT during uremia could be one of the mechanisms of altered urinary excretion of

many medications (eg, digoxin, etc.) and uremic toxins observed in kidney insufficiency. Studies have documented that overexpression of human SLCO4C1 in the kidney ameliorated not only hypertension but also kidney inflammation and insufficiency. Thus, drugs that up-regulate SLCO4C1 in the kidney could facilitate the excretion of uremic toxins, reducing kidney inflammation, renal damage progression and time of dialysis initiation.³ It is worth mentioning that in human PT cells, pravastatin and fluvastatin significantly increased SLCO4C1 mRNA expression, and in vitro studies have documented that thyroid hormone (T3) uptake, a SLCO4C1 substrate, was facilitated by pravastatin and fluvastatin, that suggesting SLCO4C1 function augment in PT. In vivo studies have also documented that tubular excretion was significantly increased in pravastatin-treated animals. Therefore, all these studies suggest that statins could up-regulate SLCO4C1 transcription to facilitate the uremic toxins excretion.⁷ Toyohara et al found that various statins upregulate SLCO4C1 transcription, and based on these findings, it has been suggested that drugs that upregulate SLCO4C1, as is the case of pravastatin, could have therapeutic effect in CKD patients.¹⁷

Finally, it is worth mentioning that these transporters may also play a role in the RSSH as part of a molecule communication network operative throughout the body in normal and diseased states, such as acute or chronic kidney injury.^{18,19}

Uremic Toxins in Chronic Kidney Disease

Uremic syndrome is characterized by uremic toxins retention not only due to GFR reduction but also to PT functional loss, since PT is responsible for active metabolite secretion.³ In this sense, it has been documented that IS excretion by residual kidney function is about 54% of the concomitant urea excretion, which demonstrates the important role of tubular secretion in IS renal excretion.⁶ Moreover, uremia seems to inhibit efflux carriers at clinically significant levels, contributing to additional uremic toxin accumulation and several chronic nephropathy complications.³

It is known that many uremic toxins can generate apoptosis in smooth muscles, neutrophils, and PT cells, as well as a direct deleterious effect on cell metabolism, particularly in the mitochondria.³ Retained uremic solutes contribute to competitive inhibition of drug carriers and

consequently to renal drug handling alteration.⁴ Moreover, the retained uremic metabolites can contribute to CKD progression, and increased cardiovascular morbidity. Polyamines, which are derived from lysine, arginine or ornithine catabolism, are identified as cationic metabolites retained in uremia, which are related to cell toxicity through proteins and DNA damage.⁴ Therefore, reducing uremic toxins accumulation can protect against hypertension and renal damage progression in CKD patients. In this sense, it has been reported that OAT transporter SLCO4C1 overexpression in rat kidney reduced serum uremic toxins, hypertension, cardiomegaly, and inflammation in the setting of renal failure.

In uremic syndrome, multiple biological pathways are affected, including those controlled by solute carrier (SLC) and ATP-binding cassette (ABC) transporters and drug-metabolizing enzymes, many of which are also involved in pharmacokinetics. The RSSH identifies SLC and ABC transporter-mediated communication between organs and/or between the host and gut microbiota as key to the homeostasis of metabolites, antioxidants, signalling molecules, microbiota-derived products and dietary components in the organism.²⁰

Wu et al demonstrate a central role for OAT1 and/or OAT3 in the handling of over 35 uremic toxins, including those derived from the gut microbiome (eg, CMPF, phenylsulfate, indole-3-acetic acid). As described in the RSSH, many of these molecules are involved in interorgan and interorganismal communication, suggesting that uremia is, at least in part, a disorder of this remote communication system.²¹

Wanchai et al documented a significant increase in serum lipopolysaccharide, serum lipids, and insulin resistance, as well as a decrease in renal Oat 3 function along with kidney dysfunction in high-fat diet-fed rats. These alterations were improved by *Lactobacillus paracasei* HII01 treatment. Therefore, it seems that probiotic supplementation alleviated renal inflammation, leading to improved renal Oat3 function in this animal model. This study suggests the RSSH between intestines and kidneys by which probiotics could facilitate renal handling of gut microbiota products through the improvement of Oat3 function.^{22,23}

Kidney Disease and Renal Tubular Transporters

It is currently known that preserved residual diuresis is related to better clinical outcomes than anuria in dialysis patients,

since the former retains active PT transport processes.³ These transport processes are effective in removing highly protein-bound toxins, which are not adequately removed by conventional dialysis (eg, IS, p-cresyl sulfate, and CMPF). Thus, current data suggest that renal excretion mechanism of uremic toxins is predominantly not by GFR but rather by active PT secretion.^{1,3} However, if OAT down-regulation observed in kidney insufficiency patients and animal models indicates a PT cells adaptation to reduce the intracellular retention of, and cellular damage from, uremic toxins, thus the increased toxin clearance by artificial OAT up-regulation could be followed by increased PT cell death from toxic exposure and residual renal function diminution.¹⁻⁴ In acute and chronic kidney injury animal models, the uptake transporter is down-regulated since polyamine uremic toxins, such as putrescine, spermine, cadaverine, spermidine, and polyamine breakdown product (acrolein), and the guanidino compounds (guanidine and methylguanidine), caused inhibition of OCT2-mediated transport.³ However, it is worth pointing out that not all tubular transporters suffer same changes in renal failure patients, since basolateral OATP4C1 expression is decreased, multidrug resistance-associated protein 2 (MRP2) is increased, and P-glycoprotein (P-gp) suffers no change.^{3,4}

Since renal function has a key role in body detoxification of several xenobiotics and endogenous by-products, and SLC22A organic carriers mediate the urinary excretion of these substances, the structural and physiological variations of these carriers during acute renal injury have a direct impact on systemic clearance of their substrate drugs, resulting in drug accumulation and adverse events. The SLC22A carriers dysregulation induced by ischemia or toxic agents (eg, cisplatin, etc.) during acute renal failure causes uremic syndrome and/or adverse drug effects. Moreover, a uremic toxin, and OAT1/3 substrate (eg, IS) might mediate the acute renal damage progression induced by renal ischemia or toxicity.^{24,25}

Uremic Toxins and Renal Tubular Transporters

Several organic anionic uremic toxins (eg, IS, CMPF, indoleacetate, hippurate), which bind to serum albumin, are excreted from the kidneys by tubular secretion, and OATs play a central role in this process.^{26,27} However, hippuric acid, IS, and kynurenic acid inhibited MRP4 or BCRP uptake, while phenylacetic acid and indoleacetic acid only reduce MRP4 uptake. Conversely, quinolinic

acid, oxalate, and putrescine did not alter transport mediated by MRP4 or BCRP.⁷ Besides, OCT2-mediated uptake is the first step in the kidney secretion of many cationic endogenous metabolites or xenobiotics, and its transport failure leads to cationic metabolites accumulation, phenomenon which has been associated with cardiovascular implications. In addition, it has been documented that OCT2-mediated uptake was inhibited by polyamine and guanidino cationic uremic toxins.⁴ Wikoff et al found that several substances, as is the case of IS, which derive from hepatic Phase II metabolism of enteric gut precursors and interact with the renal Oat1 transporter (Slc22A6), accumulate in chronic nephropathy. This finding supports the existence of a complex and remote communication between the gut microbiome, liver metabolism, and elimination via renal Oats, as well as the importance of Oat1 in the endogenous toxins handling in uremia.²⁸ Takada et al demonstrated that ATP-binding cassette transporter subfamily G member 2 (ABCG2) is a major transporter of the uremic toxin IS and identify ABCG2 as an important factor influencing CKD progression.²⁹

OAT could play a central role in tubular secretion of the toxin p-cresyl sulfate (PCS), which is an OAT1 and OAT3 substrate. Most low-molecular-weight uremic toxins are excreted into urine, and in this process, protein-bound uremic toxins are minor contributors to tubular secretion. Protein-bound uremic toxins (eg, IS, CMPF, indoleacetate and hippurate) are excreted from the kidneys via OATs, especially rat OAT1/OAT3 and human OAT1/OAT3. Since OATs are expressed by the kidneys, blood vessels and osteoblasts, it has been suggested that those uremic toxins could be transported via OATs and retained into many tissues.^{26,27} The main uremic compounds of gut origin which are mainly removed by PT secretion are PCS, IS, cinnamoylglycine (CMG), and hippurate. On one hand, higher excretion of CMG correlated to a lower fractional excretion of potassium and phosphate, while greater net PCS and IS clearances correlated to lower fractional excretion of sodium, calcium, and uric acid, and higher bicarbonatemia. On the other hand, the lowest hippurate excretion was correlated to a higher mortality after adjustment for race, sex, and age, and GFR, while a low CMG excretion was associated with a higher risk of dialysis. Studies have reported that serum PCS levels become 20 times elevated as kidney disease progresses, and its association together with higher IS serum levels with mortality, cardiopathy, and CKD progression.^{1,26,30}

Renal Tubular Structural Evaluation

Tamm-Horsfall protein (uromodulin), the most abundant urinary protein, is exclusively produced in the thick ascending limb of the Henle's loop (TAHL) and early distal tubule. Most of the uromodulin is released into the lumen, forming a layer on the tubule surface, being probably its role to protect tubular cells from ascending urinary tract infection and urolithiasis. Uromodulin concentration gradually decreases with progressive renal function impairment, thus its correlation with GFR is positive. Therefore, serum uromodulin helps to distinguish between patients with and without chronic nephropathy. Uromodulin is not an indirect GFR marker but a reliable marker of the intact number of TAHL cells, and consequently of their functionality. Besides, since uromodulin showed a significant association with proteinuria, uromodulin might also serve as CKD progression predictor.³¹ In addition, OATs themselves can be used as renal tubular injury biomarkers, since the abundance of OAT1, OAT3, and OAT4 protein from membrane fraction samples (exosomes) has been documented in the urine of acute kidney injury patients. This study documented that patients with early PT damage showed high urine OAT1 and OAT3 levels and low OAT4 levels, while patients suffering from acute renal failure showed a high amount of all these carriers.³

Conclusion

Tubular function has an important role for endogenous organic cations, anions and drugs excretion in chronic kidney disease patients, and a deeper understanding of its multiple mechanisms could provide new therapeutic alternatives in this population.

Disclosure

The authors report no conflicts of interest in this work.

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