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УРОМОДУЛИН — БИОЛОГИЧЕСКАЯ ЗНАЧИМОСТЬ И ПЕРСПЕКТИВА КЛИНИЧЕСКОГО ПРИМЕНЕНИЯ

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Uromodulin — Biological Significance and Prospects for Clinical Use

Резюме

Уромодулин является уникальным белком, вырабатываемым в почках клетками эпителия восходящей толстой части петли Генле. Он реализует физиологические механизмы не только на канальцевом уровне, но и участвует в координации общеорганизменных процессов. Основными функциями уромодулина являются: препятствие камнеобразованию за счет нарушения агрегации солей кальция и реабсорбции воды, координация электролитного баланса, препятствие воспалительным процессам локально и системно. Экспрессия уромодулина и его качественные характеристики находятся под генетическим контролем. В связи с этим патология канальцевого аппарата или мутации генов, кодирующих уромодулин, приводят к развитию первичных или вторичных тубулопатий с дисфункцией других органов и систем. Вместе с тем известно, что уромодулин является не полностью изученным белком как по структуре, так и по особенностям выполняемых им функций. Проведен анализ научно-исследовательских сведений, в том числе экспериментальных работ по изучению уромодулина в отечественных и международных источниках литературы, с изложением полученного материла в данной рукописи.

Ключевые слова: *уромодулин, белок Тамма-Хорсфалла, структура, функции, тубулопатии, артериальная гипертензия, обмен ионов, камнеобразование, генетические мутации*

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Abstract

Uromodulin is a unique protein produced in the kidneys by epithelial cells of the ascending thick portion of the loop of Henle. It implements physiological mechanisms not only at the tubular level, but also participates in the coordination of general body processes. The main functions of uromodulin are an obstacle to prevent stone formation due to a violation of the aggregation of calcium salts and water reabsorption, coordination of electrolyte balance, and an obstacle to inflammatory processes locally and systemically. Moreover, the expression of uromodulin and its qualitative characteristics are under genetic control. In this regard, the pathology of the tubular apparatus or mutations in the genes encoding uromodulin lead to the development of primary or secondary tubulopathies with dysfunction of other organs and systems. At the same time, it is known that uromodulin is an incompletely studied protein both in terms of structure and features of the functions it performs. A thorough analysis of research data, including experimental work on the study of uromodulin in domestic and international literature sources, was carried out, with a presentation of the material in this manuscript.

Key words: *uromodulin, Tamm-Horsfall protein, structure, functions, tubulopathies, arterial hypertension, ion exchange, stone formation, genetic mutations*

Conflict of interests

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ADTKD — autosomal dominant tubulointerstitial kidney diseases, AKI — acute kidney injury, CKD — chronic kidney disease COX-2 — cyclooxygenase-2, ESRD — end-stage renal disease, GCKD — glomerulocystic kidney disease, GPI — glycosylphosphatidylinositol, HNF1β — hepatocyte nuclear factor 1β, IL-17, IL-23 — interleukin 17, interleukin 23, NKCC2 — Na + -K + -2Cl- cotransporter, ROMK — renal outer medullary K^+ channel, TAL — thick ascending limb of the loop of Henle, TLR-4 — toll-like receptor 4, TNF-α — tumor necrosis factor α, TRPM2 — transient receptor potential cation channel subfamily M 2, TRPV5/TRPV6 — transient receptor potential cation channel subfamily V member 5/6, UMOD — uromodulin gene, UTI — urinary tract infection, ZP — zona pellucida

Introduction

The history of uromodulin discovery goes back to 1873 when an Italian researcher Carlo Ravina isolated the protein cylindrin in urine and suggested that it was produced by urinary casts [1]. In 1950, Igor Tamm and Frank Horsfall established that human and animal urine contains a glycoprotein that could prevent viral hemagglutination [2, 3]. In 1985, A. V. Muchmore and J. M. Decker analyzing the urine of pregnant women revealed a protein that could suppress the expression of T-cells and monocytes [4]. Due to its local expression in renal tubules and the ability to regulate local immune response, the researchers named it uromodulin. In 1987, D. Pennica et al. discovered that uromodulin and the Tamm — Horsfall protein have the same amino acid sequence and, consequently, represent identical protein structures [2]. Later, Muchmore and Decker established that uromodulin had a high affinity with interleukin-1 and could be a soluble form of interleukin-1 receptors [5]. The interest in the properties of uromodulin and the specific features of its metabolism was the reason for its further detailed study as a potential marker of tubular dysfunction. The prognostic value of uromodulin is now considered not only in primary kidney diseases, but also in the early diagnosis of secondary nephropathies.

Specific Aspects of the Structure and Function of Uromodulin

Urinary protein spectrum is represented mainly by uromodulin. It is expressed only in kidneys, by epithelial cells of the thick ascending limb of the loop of Henle (TAL), and is secreted at an average rate of 50–100 mg/day [6, 7]. This explains the high prognostic value of uromodulin in the early diagnosis of tubular dysfunction of any etiology. A small part of uromodulin is also expressed in other tubular loci, however, this information is not generally acknowledged [8].

It should be mentioned that uromodulin is secreted in TAL in the endoplasmic reticulum as a precursor (84 kDa) that is subject to N-glycosylation, attachment to the apical surface of epithelial cells through its C-terminal propeptide, and connection with glycosylphosphatidylinositol (GPI). It should be emphasized that most part of uromodulin is expressed apically into the tubule lumen, and its small part has a basolateral secretion, i.e., in the interstitium. Then, when exposed to hepcidin, through a series of transformations, uromodulin is released from the GPI-precursor-uromodulin complex into the lumen of tubules in the form of homopolymer filaments about 2.5 μm long [9]. Uromodulin is defined in urine as a high molecular weight protein assembled

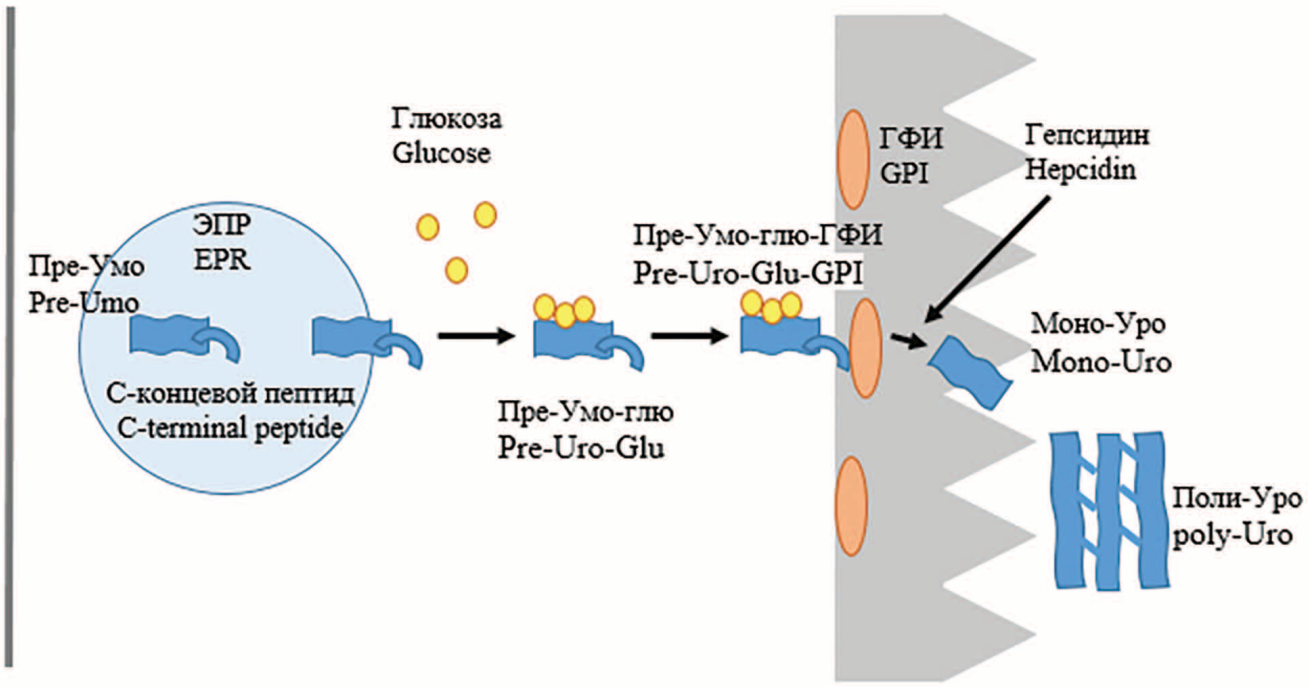

Figure 1. *Mechanism of uromodulin formation*
Note: EPR — endoplasmic reticulum, Pre-Umo — uromodulin precursor, Pre-Uro-Glu — glycosylated uromodulin precursor, GPI — glycoside phosphatidylinositol, mono-Uro — uromodulin monomer, poly-Uro — uromodulin polymer

into a polymer (Figure 1). Uromodulin development in the endoplasmic reticulum takes a long time; it is probably due to the complexity of the formation of tertiary structure [6].

Uromodulin includes three domains that are similar in structure to the epidermal growth factor and function as protein-protein interaction: central domain of 8 cysteines with still unclear function; zona pellucida (ZP) domain; complex for attachment to GPI [6]. The function of ZP domain is to perform protein polymerization processes, i.e., the formation of long filaments from homopolymers in urine. Uromodulin structure is characterized by a large amount of cysteine that, presumably, forms a complex three-dimensional protein structure due to disulfide bridges. Total amount of cysteine is 48 units with 616 amino acid bases [10].

Under normal conditions, hepcidin functions in tubular cell membrane. Hepcidin transforms the hydrophobic uromodulin molecule into a hydrophilic one by cleaving uromodulin and releasing ZP [11]. Thus, the outer hydrophobic area is blocked and the inner hydrophilic one is exposed [12]. Structural damage to tubular epithelial cells allows the development of functionally defective uromodulin molecule; it remains attached to the cell surface resulting in emerging low concentrations of uromodulin in urine.

The gel-like structure of uromodulin partially determines its important functionality, in particular, impaired aggregation of calcium salts and water reabsorption, management of electrolyte balance, and the relationship with pathogenic microflora.

Correlation between uromodulin and stone formation. The correlation between uromodulin secretion and stone formation is still the subject of scientific discussions. However, the large number of studies include data on a negative correlation between this protein and the risk of kidney stones. It has been established that uromodulin prevents the aggregation of calcium salts and promotes its absorption. However, most of the studies have been conducted in vivo in laboratory animals, and only several of them were performed in patients or in ionic solution in vitro, so, this is of research interest.

In the study by G. Pourmand et al. (2006), two groups of patients were compared that were ranked based on the presence of at least two episodes of oxalate stone formation and no history of nephrolithiasis [13]. There was no statistically significant difference in the average daily level of uromodulin in urine between two groups ($p = 0.53$). Meanwhile, a correlation was established between low levels of uromodulin and

the presence of bacteriuria in the group of patients with nephrolithiasis (p = 0.0001). The authors concluded that uromodulin can lead to aggregation of calcium salts in the presence of inflammation.

On the contrary, P. Tosukhowong et al. in their recent study (2018) confirmed elevated uromodulin levels in urine in patients with a history of oxalate stones who were previously prescribed limestone powder that neutralized oxalate precipitation [14]. In a review article by K. P. Aggarwal et al. (2013) on the effects of uromodulin, it is concluded that uromodulin inhibits the binding of calcium salts in human urine by attachment to the surface of calcium crystals, thus disrupting their aggregation [15]. In another in vivo experimental study on laboratory animals with knockout of the gene encoding uromodulin secretion, high calcium level in urine was determined that was associated with a high risk of stone formation compared with the control group; along with this, calcium precipitates were found in interstitium, renal medulla, tubules, and bladder [16–18].

The mechanism of stone formation, mainly of calcium oxalates, urates and phosphates associated with decreased secretion of uromodulin by tubular epithelial cells, has not been studied yet. Several factors were identified that associate the Tamm — Horsfall protein with nephrolithiasis.

First, uromodulin controls calcium reabsorption through epithelial channel TRPV5 (transient receptor potential cation channel subfamily V member 5), that is, it develops their receptor interaction. TRPV5 is a calcium-selective channel that allows transcellular transport from the apical to the basolateral surface of epithelial cell using a receptor mechanism. Evidence was obtained that the TRPV6 (transient receptor potential cation channel subfamily V member 5) channel that is a homologue of the TRPV5 channel and is heterogeneously associated with it, is also under the mediated control of uromodulin. Since calcium and sodium reabsorption are closely related, hypercalciuria and hypernatriuria are often found at the same time. This mechanism of electrolyte reabsorption is associated with a single Na-Ca exchanger that facilitates electrolyte transport through the cell. However, calcium transport in distal tubules is not associated with sodium reabsorption [19]. In this regard, uromodulin seems to play a key role in calcium transport through the cell. In a number of studies, it was found that hypercalciuria was detected in rats with a mutant type of uromodulin in the presence of normal sodium excretion in urine [20, 21].

Secondly, the uromodulin molecule in urine has a negative charge; it is directly related to the inhibition of calcium ion aggregation [1].

Thirdly, there is evidence that the component composition of urine affects kidney stone development, namely, qualitative and quantitative full value of present macromolecules. That is, the aggregation of calcium phosphate and oxalate takes place at a low concentration of uromodulin in urine, however, in the presence of other molecules that can inhibit or, on contrary, potentiate the aggregation process [22]. These molecules include, for example, osteopontin, bikunin, prothromin fragment 1, inter-alpha-trypsin [22]. This may explain the opposite results of the studies of the uromodulin effect on the possibility of stone formation.

The role of uromodulin in infectious, inflammatory and immune responses. The Tamm — Horsfall protein plays an important role in reducing the risk of urinary tract infections (UTIs) by its function as an antimicrobial protein. Uromodulin can capture bacteria using the polymeric structure of the protein, thereby inactivating the pathogenic properties of microorganisms. It is assumed that the high-mannose polypeptide chains of uromodulin are similar to the receptors on urothelium, and, using a competitive mechanism, they bind to the pili lectin of uropathogenic microflora (for example, *E. coli*), thereby impairing adhesion and colonization of urinary tract [10]. The studies conducted demonstrate a low probability of UTI development with underlying high level of uromodulin in urine regardless of the presence of conventional risk factors [23]. In laboratory animals with a defect in the gene encoding uromodulin expression, high titers of bacteria excreted in urine and severe pyelonephritis were found [24].

Moreover, the regulation of local immunity by uromodulin contributes to reducing the risk of developing infectious and inflammatory response of genitourinary system. The results of several studies demonstrate the role of uromodulin in the development of not only local, but also of systemic immune response. It is assumed that uromodulin functions upon activation of the macrophage system by increasing macrophage transcript and stimulating chemotaxis and phagocytosis [25, 26]. Data on the correlation between uromodulin secretion and neutrophilic infiltration of cells, monocytes and dendritic cells are presented. Uromodulin promotes the maturation of the latter via TLR-4 (toll-like receptor 4) signaling pathway, and thus additionally potentiates the activity of innate and acquired immunity [26]. Decreased concentration of uromodulin in urine is associated with higher levels of immunocompetent factors such as IgG28 (Immunoglobulin G 28), C3a (complement component 3a), C1q (complement component 1q), factor H and TNF-α (tumor necrosis factor-α) [27]. The relationship with proximal tubular

cells of S3 segment contributes to the suppression of the synthesis of renal cytokines in the presence of high uromodulin level in urine. It is also assumed that there is a relationship with systemic oxidative stress through the inhibition of TRPM2 (transient receptor potential cation channel subfamily M2) channels controlled by uromodulin [28]. Thus, uromodulin produces its nephroprotective effect in the cases of glomerulonephritis and tubulointerstitial nephritis. It is important to emphasize that not only urinary, but also serum uromodulin appears to be a promising biomarker for the progression of tubulointerstitial injury [28].

The mechanism of immune response regulation with uromodulin is not fully understood. An indirect interaction with immunocompetent cells or with their receptor apparatus is assumed.

There are also data on the regulation of systemic immune response by uromodulin. In the experimental study by R. Micanovic et al. (2015), the authors demonstrated that systemic neutrophilia developed with uromodulin deficiency [26]. The authors attributed the obtained data to the increased cytokine effect (IL-23, IL-17) in the absence of the sufficient control of uromodulin level emphasizing the role of kidneys in the regulation of not only granulopoiesis, but also of neutrophil homeostasis. The anti-inflammatory effect of uromodulin is also known; it is associated with the suppression of the activity of renal cytokines and lymphokines — interleukin-1, TNF-α [29].

It has been confirmed that ischemic damage to the tubules shifts the uromodulin expression from the apical surface of cell to the basolateral one; it indicates protein secretion into interstitial tissue in order to reduce the severity of its damage [29]. In a study conducted in a cohort of patients with sepsis but with no severe acute kidney injury (AKI), the data were obtained indicating that patients were more stable at higher blood concentrations of uromodulin [25]. Moreover, in a subgroup of patients with acute distress syndrome, uromodulin was isolated in the bronchoalveolar lavage of damaged lungs. It is important to note that AKI development was associated with a systemic decrease in uromodulin level and, as a result, with decreased immune response in general. The authors conducted a similar study on experimental animals with deficiency and normal expression of uromodulin in different variants of sepsis development. Attempts were made to treat them with the monomeric form of uromodulin; positive results in the form of improving the survival of animals were achieved. The authors convincingly show and present pathogenetically substantiated facts on the protective role of the uromodulin molecule excreted by kidneys during generalized inflammation [25].

Thus, uromodulin is, in particular, a promising biomarker for AKI, as well as chronic nephropathy of any origin. Development of drug products analogous to uromodulin will most likely help to solve the discussed clinical problems.

The role of uromodulin in homeostatic regulation. An important function of uromodulin is to control homeostasis by controlling the reabsorption of electrolytes such as sodium, potassium, and magnesium.

About 25 % of the filtered NaCl is reabsorbed in the thick ascending limb of the loop of Henle. Na + -K + -2Cl- cotransporter (NKCC2) is required to reabsorb NaCl in TAL; it also helps to reabsorb most part of sodium that is also expressed in TAL [30]. Uromodulin controls the function of NKCC2 and thus has an effect on reabsorption mechanisms. In an experimental study on laboratory rats with knockout for the gene expressing uromodulin, a subapical atypical accumulation of NKCC2 protein and its normal distribution on the apical part of epithelial cells [31]. Moreover, diuresis volume after intraperitoneal administration of furosemide was lower in the population of mice without uromodulin compared with the control group of healthy animals. The role of uromodulin in the functional coordination and other aquaporin and electrolyte channels was established. Thus, on the basis of experimental data, it was found that uromodulin promotes the expression of COX-2 (cyclooxygenase 2), thereby improving the function of aquaporin-2 and sodium-hydrogen exchanger [32]. In 2014, one of the journals of the American Heart Association (AHA) presented the information on the autocrine effect of TNF-α on the NKCC2 cotransporter that suppressed its activity [30]. Therefore, uromodulin binding to TNF-α allows additional control of sodium reabsorption.

The ability of uromodulin to directly or indirectly regulate the electrolyte exchange of potassium, chlorine, magnesium, and calcium ions in nephron tubules was established [32].

Uromodulin participation in the regulation of sodium reabsorption explains its role in the development of hypertension. It is known that in experiments on the potentiation of uromodulin expression and secretion, natriuresis and a tendency to hypotension developed [33, 34], and its deficiency resulted in hypertension [35–37].

Uromodulin ability to have an effect on the balance of reabsorption/excretion and other electrolytes was determined. To regulate the function of NKCC2, ROMK (renal outer medullary K^+ channel) and TRPM6 channels for the purpose of transcellular transport of magnesium, potassium, and calcium from the apical surface of distal tubular cells to the basolateral one, uromodulin expression is required [38–40].

Specific Aspects of the Genetic Control of Uromodulin Expression

Currently, there are more than 200 registered mutations of the gene encoding uromodulin expression and secretion (*UMOD*); they are localized in the 3rd, 4th, 5th, and 8th exons [32, 41, 42]. *UMOD* is located on chromosome 16p12.3 [41]. Mutation in *UMOD* leads to the impaired amino acid sequence of cysteine that is accompanied by changes in the protein folding sequence. Thus, immature uromodulin is developed that accumulates intracellularly in endoplasmic reticulum and is unable to be transported to the apical membrane of cells. Considering that the uromodulin molecule includes 48 cysteine residues linked by 24 disulfide bridges, modifications of genetic mutations are quite variable.

The high interest in uromodulin is also due to the development of rare kidney diseases that are usually associated with heterozygous mutations in *UMOD*. Monozygotic mutations are much less common [42]. Since the clinical course and pathophysiological mechanisms of these diseases are similar, a group of autosomal dominant tubulointerstitial kidney diseases (ADTKD) was identified that includes familial juvenile hyperuricemic nephropathy, type 2 medullary cystic kidney disease, and glomerulocystic kidney disease (GCKD) [41]. These rare diseases are considered to be uromodulin-associated. ADTKD are characterized by: hyperuricemia (including symptomatic one), interstitial fibrosis, tubular atrophy, and low urinary uromodulin level [43]. However, a wide variability in the clinical signs of ADTKD is described, even of its familial forms. The mechanism of tubular damage in ADTKD is centered around the accumulation of defective uromodulin in endoplasmic reticulum, as well as cell damage with further development of tubular and interstitial fibrosis, as well as cysts. All these processes lead to the development of chronic kidney disease (CKD) with different rates of progression.

In addition to the development of rare ADTKD, changes in the controlling *UMOD* are known that contribute to its uneven binding with its promoter, not to the impaired amino acid sequence of the protein. In this case, there is increased uromodulin expression and the development of salt-sensitive hypertension due to the activation of sodium chloride cotransporter (NKCC2) [42]. Hypertension is often accompanied by hyperuricemia that can be explained by increased reabsorption of urates together with sodium.

Obviously, the polymorphism of UMOD mutations is quite large and poorly known. There are questions regarding the implementation of the effects performed by defective uromodulin on the development of concomitant pathological processes and, most importantly, why one type of genetic mutations leads to the accumulation of defective uromodulin in endoplasmic reticulum with its decreased level in urine, while another variant, on the contrary, results in its increased expression?

Regulation of Uromodulin Expression and Secretion

Factors that regulate the expression and secretion of uromodulin are not well understood. In addition to genetic control, there are data on several factors of endogenous and exogenous stimulation of protein synthesis.

Thus, hepatic nuclear factor (HNF1β) binds to uromodulin DNA target regions and potentiates its expression [29]. Factors that increase uromodulin level in urine include excessive intake of NaCl and high-protein diets [29]. There is evidence of increased urinary calcium associated with increased concentration of uromodulin [44]. Considering the discussed functions of uromodulin, it can be assumed that increased potassium and chlorine levels may also have a positive correlation with this protein.

In the experimental study on laboratory rats, it was found that uromodulin level in urine decreased along with a decrease in COX-2 concentration. Moreover, the authors mentioned that low levels of uromodulin could result not from a direct effect of COX-2 deficiency, but from an indirect effect associated with TAL damage [45]. At the same time, factors leading to a decrease in uromodulin expression include the following: use of angiotensin converting enzyme inhibitors, colchicine, antidiuretic hormone, urinary tract obstruction, hypothyroidism [10, 29].

Prognostic Significance of Uromodulin and Its Possible Use

Compared to the biomarkers of glomerular damage, tubular biomarkers are not widely used in clinical practice. In this regard, uromodulin is a promising indicator of impaired renal function or damage due to the exclusive location of its secretion in nephron tubules.

Uromodulin appears to be a promising biomarker of tubular damage of any origin and of the progression of glomerular diseases with the development of the glomerular-tubular continuum. Decreased uromodulin level in the group of patients with CKD demonstrates an increased risk of developing end-stage renal disease (ESRD) [46, 47]. Moreover, there is evidence that uromodulin can be used as a biomarker in Fabry disease and active lupus nephritis [10].

Due to the establishment of a direct association with the parameters of glomerular filtration rate (GFR), it is obvious that low uromodulin concentration in urine can

Table 1. *Practical and scientific possibilities of using uromodulin*

№	Characteristic	Pathological conditions
I.	**Congenital pathologies associated with a defect in the uromodulin gene (*UMOD*)**	
1.	Gene mutations caused by a violation of the amino acid sequence of cysteine	Familial juvenile hyperuricemic nephropathy
		Medullary cystic kidney disease type 2
		Glomerulo-cystic kidney disease
2.	Decoupling of *UMOD* with the promoter	Salt sensitive hypertension
II.	**Acquired pathologies associated with impaired expression and secretion of uromodulin**	
1.	Violation of electrolyte homeostasis with a decrease in the concentration of uromodulin	Hypoelectrolytemia (sodium, potassium, magnesium, chlorine, calcium)
2.	Processes associated with infectious, inflammatory and immune responses	Increased risk of UTI with a decrease in the concentration of uromodulin
		Progression of GN, TIN
		Progression of inflammatory reactions in systemic inflammatory diseases (sepsis, ARDS)
		Development and progression of AKI
III.	**Stone formation (oxalates, urates, phosphates) with a decrease in the concentration of uromodulin**	Nephrolithiasis
		МКБ/ Urolithiasis disease
IV.	**Tubular damage and progression of glomerular lesions, including primary glomerular pathologies, with a decrease in the concentration of uromodulin**	Progression of primary and secondary nephropathy to terminal renal failure
		Marker of tubular injury, risk of terminal renal failure in Fabry disease
		Marker of tubular damage, risk of terminal renal in active lupus nephritis

Note: UTI — urinary tract infections, GN — glomerulonephritis, TIN — tubulointerstitial nephritis, ARDS — acute respiratory distress syndrome, AKI — acute kidney injury

be considered as an unfavorable predictor of decreased kidney function, in particular, of filtration function in secondary nephropathies. In some research papers, increased rate of CKD progression and increased overall cardiovascular risk is mentioned along with a decrease in uromodulin concentration in patients with cardiovascular diseases [48, 49].

In connection with the functions of uromodulin, low level of this protein in urine can be a biomarker for rare genetic anomalies (familial juvenile hyperuricemic nephropathy, type 2 medullary cystic kidney disease, glomerulocystic kidney disease). In those cases of hyperuricemic nephropathy in patients with gout, decreased urinary uromodulin/creatinine ratio was associated with the progression of CKD [50].

Uromodulin is mostly found in the apical surface of tubular cells, and to a lesser extent, in the basolateral one [51]. Excessive uromodulin in the basolateral part of cells is found during the development and progression, first of all, of the inflammatory process, as well as of the oxidative stress. Accumulating in the basolateral surface, uromodulin enters the interstitium and also elevates in systemic circulation. At the same time, the level of Tamm — Horsfall protein increases due to metabolic disorders and can lead to the development of "aggregates" potentiating stone formation and urinary tract obstruction. In this regard, the determination of uromodulin concentration in urine and in blood in patients with AKI or ischemic nephropathy seems to be prognostically significant.

It is established that uromodulin is also found in tubules between week 8 and 16 of gestation, and from week 20 — in the gestational waters of a pregnant woman [10]. In this case, uromodulin may also have prognostic potential as a marker for timely diagnosis of the developmental disorders of fetal tubular apparatus.

The information presented is shown in a table with the basic characteristics of uromodulin in practical and scientific context highlighted. It should be mentioned that considering the ongoing research on pathological and physiological responses associated with uromodulin, the data in the table have potential for scientific and clinical use.

Conclusion

A wide range of uromodulin functions, its mechanism of action, as well as the specific aspects of genetic control determine the wide potential of using this protein in clinical practice as a universal biomarker of kidney injury of various etiology. Further study of uromodulin and its role in metabolism will discover new potential predictive capabilities of the Tamm — Horsfall protein.

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