e-ISSN 2544-1620

Medical Science Pulse 2020 (14) 3

Reviews

Published online: 17 Jul 2020

DOI: 10.5604/01.3001.0014.3089

UROMODULIN – BIOMARKER OF RENAL FUNCTION WITH PROMISING CLINICAL APPLICATION

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A – study design, **B** – data collection, **C** – statistical analysis, **D** – interpretation of data, **E** – manuscript preparation, **F** – literature review, **G** – sourcing of funding

ABSTRACT

Uromodulin (also known as Tamm-Horsfall protein) is a glycoprotein produced exclusively in the kidneys, mainly in the epithelial cells of the thick ascending limb of the loop of Henle. Under physiological conditions, it is the most abundant urinary protein. A small proportion is released into the renal interstitium and then into the blood, where it can be detected and used as a potential parameter of renal function. Uromodulin has numerous physiological roles and potential pathogenetic significance, including providing protection against urinary tract infections and the formation of urinary deposits, as well as being involved in the immunomodulatory functions and regulation of water and electrolyte balance by the kidneys. Unlike classic renal markers (such as creatinine), uromodulin levels decrease with progressive renal dysfunction. A significant advantage of this parameter is therefore the detectable changes in concentration at the early stages of development of chronic kidney disease. In addition, assessment in clinical materials, such as urine and blood, is relatively simple by immunoenzymatic methods. It is evident that the quantitative determination of uromodulin in blood serum is associated with a lower risk of laboratory error and has a better correlation with renal function. Based on previous studies, Tamm-Horsfall protein / uromodulin can be considered a valuable parameter for standard diagnostics of kidney function and renal diseases. It appears that no other marker is currently able to reflect the integrity and functional state of the renal tubules as sensitively as uromodulin. Due to the potential of this parameter, the article presents and overview of the current information available about uromodulin, as well as the available diagnostic tests and the frequency of their use in clinical practice.

Keywords: Tamm-Horsfall protein, chronic kidney disease, acute kidney failure, Umod

Background

In 1950, scientific researchers I. Tamm and F.L. Horsfall described the discovery of a mucoprotein in urine, which they proceeded to designate Tamm-Horsfall protein (THP) [1]. Three decades later, A.V. Muchmore and J.M. Decker isolated an 85 kDa glycoprotein from the urine of a pregnant woman and demonstrated its immunosuppressive properties on the activity of T lymphocytes and monocytes *in vitro*. They named this molecule uromodulin (Umod) [2]. It eventually became clear that THP and Umod referred to the same protein, and both designations are still used in the literature. However, during the 21st century there has been a dramatic increase in knowledge concerning the pathogenic and prognostic significance of Umod in various forms of kidney disease, and its function, genetics, synthetic and secretory pathways have been studied in detail. Nephrologists are interested in a parameter that would sensitively reflect changes in kidney function, shifting focus onto Umod, which is secreted both into the urine via the renal tubules and, in small amounts, into the blood via the renal interstitium.

Currently, Umod appears to be superior to other markers in terms of reflecting the functional state of the renal tubules. The aim of this review is to examine literature, predominantly Pubmed-sourced and originating over the last 5 years, to provide an analysis of Umod's clinical significance, including aspects of the protein's biology, physiology, characterization as a marker of renal function, and an overview of available diagnostic tests and their use in clinical practice.

Biology, physiology, functions and pathogenetic significance of uromodulin

Uromodulin (Umod) is synthesized exclusively in the kidneys by epithelial cells of the thick ascending limb (TAL) of the loop of Henle, as well as to a lesser extent (about 1/10 the amount produced in TAL) in the early part of distal convoluted tubule (DCT) [3–5]. Umod production occurs in the rough endoplasmic reticulum (RER), and after appropriate modifications in the Golgi apparatus it is exported via transport vesicles through the apical membrane to the extracellular space [6]. The protein molecules are anchored in the cell membrane by glycosylphosphatidylinositol (GPI) and are released into the lumen of the renal tubules upon proteolysis of intermolecular bonds by the serine protease hepsin [7,8]. Remaining in close proximity to epithelial cells after proteolytic cleavage, Umod forms part of a protective hydrophobic gel covering the above-mentioned cells [3,6], which may, in some cases, form hyaline castings [3]. Umod glycoprotein molecules released into the urine behave as monomers and polymerize [7,9]. Most of the glycoprotein produced in the cells goes to the renal tubules and into the urine, where it makes the largest fraction of urinary proteins [3,9,10]. Daily excretion of Umod via the urine of healthy people has been estimated to be about 50 mg (ranging 20–75 mg) [9–11]. A small amount of Umod enters the interstitial tissue through the basolateral membrane of epithelial cells and, from there, enters the bloodstream [9,10]. The mechanism by which a small fraction of secreted Umod, normally released into the urine, proceeds to the interstitium is likely via retrograde leakage through intercellular spaces, which may occur as a result of kidney damage [10]. It has been estimated that protein levels are approximately 1000 times higher in urine (urinary uromodulin or uUmod) than in blood serum (serum uromodulin or sUmod) [3,9]. In the bloodstream, the glycoprotein molecules remain in the form of monomers and do not polymerize [9]. One of the regulating factors of Umod secretion from renal tubular epithelial cells is the activation status of the calcium-sensing receptor (CaSR). Activation of this receptor reduces the secretion of Umod by TAL cells and, in converse, its inactivation increases this secretion [4,12,13].

Investigating the molecular mechanisms underlying protein production, it was determined that the gene encoding uromodulin (*UMOD*) is located at the 16p12.3-p13.11 loci [14]. Hereditary mutations in this gene underlie the development of a group of diseases known as "autosomal dominant tubulointerstitial kidney disease; UMOD-related" (ADTKD-UMOD). The most common mutations found in genetic tests are missense mutations and small deletions in exons 3 and 4 [15,16]. The spectrum of symptoms of this rare monogenic pathology includes hyperuricemia, gout, interstitial renal fibrosis and progressive Ren Fail. They stem from disruptions in the maturation processes of the protein and its accumulation in the RER, resulting in excessive signaling of intracellular stress and disorders of Umod release and function [15,17].

Genome-wide association study (GWAS) showed that some types of single nucleotide polymorphisms (SNP) within the *UMOD* gene promoter deregulate the genetically determined production and release of Umod and thus impact all functions of this protein in the body, potentially predisposing an individual to the development of hypertension, nephrolithiasis or chronic kidney disease (CKD) [4,18,19]. Both protein synthesis and activity may be disturbed in either direction. Hypoactivity and/or deficiency in Umod, as well as hyperactivity and/or excess of Umod, can be potentially pathological and contribute to the development of diseases.

Umod is associated with many physiological functions, both local (within the kidneys) and systemic [13,20]. The hydrophobic gel covering the epithelial cells of TAL and DCT has protective functions attributed to Umod proteolytically cleaved from GPI. It protects against the development of urinary tract infections such as acute pyelonephritis by preventing the adhesion and colonization of bacteria on the cell surface [3,21]. Umod probably contributes to maintenance of water and electrolyte homeostasis by reducing water permeability [6,10]. A detailed summary of the physiological roles of Umod, along with the potential pathological effects of disorders in the synthesis and/or activity of this protein in the body, is presented in Tab. 1.

Uromodulin as a marker of renal function

The usefulness of Umod as an indicator for monitoring renal function, by determining the protein's concentration in people with impaired kidney function and Ren Fail as well as in healthy people, has been extensively scientifically characterized. Currently, diagnostic tests based on serological methods to monitor sUmod and uUmod are available on the medical market which can deliver results in a relatively short time. These include enzyme-linked immunoassay (ELISA) tests, in which the reaction plate is coated with monoclonal antibodies against Umod and specific reactivity is determined by measuring absorbance and converting this into a parameter concentration [22].

The appropriate conditions for the pre-analytical processing and storage of urine samples is essential in order to obtain reliable and reproducible results [22,23]. As previously mentioned, in the urine uUmod occurs in the form of polymers, while in the blood sUmod remains a monomeric form [7,9]. This is important for the determination of protein levels by ELISA. In addition, Umod polymerization in urine probably alters the availability and modality of protein antigens detected by antibodies in ELISA assay [9]. Steubl et al. have demonstrated in a study involving 933 participants that the concentra-

Table 1. Physiological functions and pathological significance of uromodulin [summary based on 2–6, 9, 13, 15, 19, 21,24–38].

Functions	Detailed description	Pathological significance of abnormalities in synthesis/activity	
		↓ down	↑ up
Prevention of urinary tract infections (UTI)	– Inhibition of the adhesion of uropathogenic bacteria to the epithelium of the urinary tract. Higher levels of uUmod have been associated with a lower risk of developing UTI in the elderly [3,21, 24,25].	– More frequent and recurrent UTI [3,15]	-
Prevention of nephrolithiasis	– Inhibition of the formation of calcium-containing kidney stones. – Prevention of hypercalciuria by regulating calcium homeostasis [4,26,27].	– Nephrolithiasis – Hypercalciuria	-
Maintenance of water and electrolyte homeostasis	– Promoting NKCC2 activity (Na^+-K^+-$2Cl^-$ reabsorption), including transport to the apical cell membrane and phosphorylation [4,5,19,28]. – Promoting NCC activity (NaCl reabsorption) [4,5]. – Promoting ROMK ion channel) activity (excretion of K^+), including transport to the apical cell membrane [4,28]. – Homeostasis of magnesium metabolism, including promoting the activity of the TRPM6 ion channel (reabsorption of Mg^{2+}) by inhibiting endocytosis [29]. – Homeostasis of calcium metabolism, including promoting the activity of the TRPV5 ion channel (reabsorption of Ca^{2+}) by inhibiting endocytosis [4,27].	– Initially NKCC2 dysfunction, followed by excessive compensatory responses, such as prolonged RAA system activation and hypertension – Water-electrolyte imbalance [28,30]	– Salt sensitive hypertension – Water-electrolyte imbalance [19]
Immunomodulatory properties (pro- and anti-inflammatory)	Umod remains immunologically neutral in the lumen of renal tubules and has immunogenic properties in the renal interstitium and in the blood [31]: – Activation of the NLRP3 inflammasome and of the process of pyroptosis (a pro-inflammatory form of programmed cell death) to modulate the number of pro-inflammatory macrophages and to regulate the antibacterial response [31,32]. – Stimulation of monocytes/macrophages for the secretion of pro-inflammatory cytokines (IL-1β) and for phagocytic activity, promoting the development of interstitial nephritis [31,33]. – Stimulation of dendritic cells activity via Toll-like receptor 4 (TLR4), influencing mechanisms of innate immunity [34]. – Stimulation of neutrophils activity and migration through renal tubular epithelium [9,35,36]. – Inhibition of T lymphocytes activity [2,9].	An imbalance in the quantity and/or activity of Umod may promote dysregulation of immune responses in the kidneys, resulting in increased risk of extensive damage, prolonged healing time in acute inflammation and interstitial kidney fibrosis [13,33]	
Excretion of uric acid and prevention of hyperuricemia	– Support of renal excretion of uric acid. Lower uUmod levels have been associated with higher serum uric acid levels [6,37]	– Hyperuricaemia – Gout [6,30]	-
Oxidative stress	– Inhibition of the activity of TRPM2 non-selective calcium channel. – Inhibition of the formation of reactive oxygen species (ROS) locally and systemically. A decrease in sUmod level has been observed after the acute kidney injury (AKI) incident [38]	– Increased ROS production and increased risk of damage caused by oxidative stress [13]	-

NKCC2: sodium potassium chloride (Na-K-Cl) cotransporter 2; NCC: sodium chloride (NaCl) co-transporter; ROMK: renal outer medullary potassium channel; TRPM6: transient receptor potential melastatin 6; TRPV5: transient receptor potential cation channel subfamily V member 5; RAA: renin-angiotensin-aldosterone; NLRP3: NOD-, LRR- and pyrin domain containing protein 3; TRPM2: transient receptor potential cation channel, subfamily M, member 2; IL-1β: interluekin 1β.

tion of sUmod correlated more strongly with the estimated glomerular filtration rate (eGFR) than the level of uUmod [39]. Therefore, the determination in serum appears to be a more reliable test reflecting the clinical condition of patients. However, study results should be interpreted based on patients' personal data, including gender and age. It has been observed that adult women exhibit a slightly higher concentration of sUmod than either adult men or children. Among a group of 190 healthy blood donors aged 18–60 years, the average sUmod levels in women were found to be 230 ng/ml and in men were 188 ng/ml [9]. In a group of 443 children, the average concentration was 193 ng/ml [9]. It was initially assumed that values below 100 ng/ml in women and below 80 ng/ml in men and children should raise suspicion of renal dysfunction [9], however, these cutoffs may also be age dependent. Statistically significant differences in the concentration of sUmod between sexes were also observed in an older age group by the "KORA F4 Study", involving 1079 participants aged 62–81, which reported average sUmod values of 170 ng/ml in women and 138 ng/ml in men [40]. As this and other studies demonstrated, a significant decrease in the level of sUmod is evident in people over 60–65 years of age with respect to younger people [9,41]. This is likely a result of the physiological aging process of the kidneys and the body in general. Aging-related changes in the kidney typically affect the volume of the renal cortical layer and are associated with a decline in eGFR [42]. It is possible, however, that the production and release of Umod may remain undisturbed for a long time despite a decrease in eGFR.

Uromodulin and traditional parameters of renal function

Numerous studies have shown a positive correlation between both sUmod and uUmod concentrations and the eGFR value [11,39,43–48], although this correlation appears stronger with respect to sUmod than for uUmod [39]. In addition, an inverse relationship has been demonstrated between Umod levels and conventional renal markers, such as serum creatinine, urea or cystatin C [44–48]. Concentrations of these commonly referenced parameters increase due to their retention in the body as kidney function decreases. This suggests that higher levels of sUmod and uUmod are indicators of high renal functionality and are associated with a lower risk of developing end-stage renal disease (ESRD) in patients with chronic kidney disease (CKD), as well as with a lower risk of rapid loss of kidney function and eGFR decline [49–51].

Prajczer et al. reported findings which appear to contradict the above-mentioned conclusions [52]. They showed that the eGFR value positively correlates with uUmod and negatively with sUmod. The explanation for this apparent inconsistency may be the fact that the kidneys of patients with CKD may be predisposed to increased retrograde leakage of Umod into the renal interstitium and then the blood, thereby inducing increased inflammatory responses [10,32]. This damages the failing kidneys even more and, by virtue of the this repeated cycle, impairs kidney function, reduces eGFR and, thereby, urinary excretion of Umod. The pathomechanism described above can also be an explanation for the findings of Köttgen et al., who proposed that high concentrations of Umod in urine may forebode the development of CKD for many years [53]. It is possible that in kidneys exhibiting some sort of dysfunction, the inflammatory component and the etiology of primary disorders may influence the serum Umod level and its correlation with eGFR. Nevertheless, there are not many scientific reports on large study groups that would lead to conclusions similar to those presented by Prajczer et al.

Changes in the concentration of Umod can be observed already in the early stages of loss of kidney function, which is a significant advantage over traditional markers that do not show clear deviations from the norm until a much more advanced disease stage. It has been observed that blood creatinine concentrations may remain at the same level until 50% of renal function is lost [54]. Using statistical analyses such as the receiver operating characteristics (ROC) and area under the curve (AUC), sUmod level most effectively differentiated healthy people without kidney disease (non-CKD) from patients with stage 1 CKD (CKD-1) when compared with eGFR, cystatin C and creatinine. As the CKD stages progressed, the concentration of sUmod decreased. The differences between sUmod levels for all adjacent pairs of CKD stages were statistically significant, except for stages 1 and 2 [9,44]. Furthermore, sUmod has been shown to be a valuable parameter for monitoring kidney transplant function in that lower and slower recovering levels may be associated with a higher risk of failure or delayed activity, while rapid post-surgical increase in sUmod levels suggests immediate start of function and proper organ acceptance [45,55,56].

One of the greatest advantages of Umod over conventional renal markers is related to the fact that its concentration is independent of the glomerular filtration process [57], with production and release occurring only within the kidneys via TAL and DCT1 cells. The serum concentration of Umod, more than any other renal parameter, reflects the structural and functional status of renal tubules and renal interstitium [9,44,46]. Therefore, Umod can be considered as an important complementary marker for use in routine diagnostics, although at present it is not commonly used in clinical diagnostic practice.

Uromodulin in other disease entities

The clinical value of Umod may probably extend further than just as a marker of kidney function. In recent years, evidence of a potential diagnostic and prognostic role of this protein in disease entities such as cardiovascular diseases, diabetes and metabolic syndrome has been brought to the fore, as well as to determine the risk of developing acute kidney injury (AKI) in patients undergoing cardiac surgery.

Higher sUmod levels are associated with a lower incidence of diabetes and hypertension and a lower risk of overall mortality, based on findings from a group of patients subjected to coronarography, which suggests Umod may have potential for predicting the risk of cardiovascular events [38,41]. A study involving 933 older patients by Steubl et al. leads to similar conclusions [43], however, Then et al. reported that the potential of sUmod as a biomarker of cardiovascular mortality in people aged 62 and older applied only the men [40].

In addition to its advantages as a biomarker of kidney and cardiac dysfunction, Umod is probably associated with glucose metabolism disorder. Leiherer et al. found a statistically significant inverse correlation between sUmod level and fasting glucose, based on 75 g oral glucose load and glycated hemoglobin tests. Patients with type 2 diabetes or prediabetes have been shown to exhibit lower sUmod concentrations compared with those without these disorders, which may indicate subclinical and early renal impairment [58]. Levels of glycated Umod (as the final glycation product) in urine were significantly higher in patients with diabetic kidney disease (DKD) compared with patients suffering from CKD without diabetes, which may be associated with impaired Umod function in diabetic patients, although the relationship underlying this association remains unclear [59]. In a study monitoring 527 patients with type 1 dia-

betes, a 12-year follow-up found that higher baseline sUmod concentrations were associated with a lower risk of developing coronary artery calcification (CAC) and diabetic kidney disease (DKD) [60]. In adolescents with type 1 diabetes, lower sUmod levels correlated with a higher degree of albuminuria, which may indicate the beginning of the development of kidney dysfunction [61].

Furthermore, Umod may serve as a marker for metabolic syndrome. The concentration of Umod in blood serum is inversely correlated with parameters which are indicative of persistent metabolic syndrome (including elevated triglycerides and elevated blood pressure), but does not necessarily allow the prediction of newly developing disorders [62].

Preliminary data also suggest that the risk of acute kidney injury (AKI) in patients undergoing cardiac surgery can be assessed based on Umod concentrations. A lower preoperative Umod-to-creatinine ratio in the urine has been associated with a higher risk of developing AKI as a complication after undergoing cardiac surgery in adults [63]. Reduced concentrations of uUmod in the preoperative period may also indicate a higher probability of AKI occurring in children after undergoing cardiopulmonary bypass (CPB) surgery [64]. However, no correlation between the sUmod concentration and the risk of developing AKI after acute pancreatitis could be demonstrated [65].

Conclusions

Seventy years after the discovery of Tamm-Horsfall protein, the factor now known as uromodulin is undergoing a revival as the subject of clinical research into its potential as a diagnostic parameter. Although its physiological role is still not fully defined, advanced research techniques such as meta-analyses of laboratory and clinical data are shedding further light on the potential of Tamm-Horsfall protein / uromodulin as a biomarker of renal function, alongside conventional parameters. Uromodulin is a more sensitive indicator than creatinine for the detection of early CKD. In addition, uromodulin concentration reflects the function of the renal tubules, which is currently not possible using other parameters. Higher concentrations of sUmod and uUmod have become associated with a lower risk of CKD progression, with a lower risk of CKD incidents, lower mortality in elderly patients and lower risk of AKI in the postoperative period. All these correlations demonstrate the close relationship between uromodulin and renal function, making it a specific and sensitive indicator of kidney health. Clinical application as a renal marker and the association of Umod with various disease entities requires further research in order to be able to introduce uromodulin monitoring into routine clinical practice as a diagnostic and prognostic tool with respect to kidney and other organ diseases.

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Word count: 2713 • Tables: 1 • Figures: – • References: 65

Sources of funding:
The research was funded by the authors.

Conflicts of interests:
The authors report that there were no conflicts of interest.

Cite this article as:
Chojęta D, Kozioł MM, Smarz-Widelska I.
Uromodulin – biomarker of renal function with promising clinical application.
Med Sci Pulse 2020; 14, 3: 84–90. Published online: 17 Jul 2020.

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Received: 1.06.2020
Reviewed: 27.06.2020
Accepted: 29.06.2020