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UROMODULIN AS AN EARLY MARKER IN THE DIAGNOSIS OF CHRONIC KIDNEY DISEASE.

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Abstract. Uromodulin (Tamm-Horsfall protein; Umo; TCB) is a specific renal protein synthesized exclusively in the epithelial cells of the thick ascending loop of Henle and the initial section of the distal convoluted tubule. TCB is secreted predominantly into the lumen of the tubule and then enters the urine. A minor portion of uromodulin is secreted across the basolateral membrane into the renal interstitium and eventually enters the systemic circulation. This article discusses the importance of uromodulin in the early diagnosis of chronic kidney disease, changes in its amount in the blood and urine in cardiovascular diseases.
Keywords: Uromodulin, chronic kidney disease, glomerular filtration rate.

Uromodulin (UMO) is a glycoprotein with a molecular weight of 80–90 kDa [1, 2, 3, 4] expressed in the epithelial cells of the thick ascending loop of Henle (TALOH) [9, 10] and, possibly, the initial parts of the distal tubule [6 , 7, 11]. This protein is encoded by the UMOD gene. THP consists of several domains and is largely glycosylated (30% of molecular weight) [3, 4].

Uromodulin was first discovered by I. Tamm and F.L. Horsfall in 1950, when they isolated a protein from urine that inhibited hemagglutination of viruses [5, 6]. At first, after the name of the authors, the protein was named "Tamm-Horsfall protein" (THP). 1985 A.V. Muchmore and J.M. Decker isolated a protein from the urine of pregnant women, which was named uromodulin (UMO), because it showed immunosuppressive effects on T cells in vitro [1]. Soon D. Pennica et al. demonstrated that the amino acid sequences of UMO and THP are almost identical [2]. Since that time, UMO and THO have been used interchangeably for the same protein.

THP is a multifunctional protein. It is critical for modulating renal ion channel activity, fluid balance, renal and systemic inflammatory responses, intertubular interactions, urinary mineral crystallization, and bacterial adhesion. In addition, mutations in the UMO gene cause a group of congenital kidney diseases, and changes in THP expression are associated with an increased risk of urinary tract infections, stone formation, hypertension, hyperuricemia, and acute injury or chronic kidney disease [7].

Structure and secretion of uromodulin.

The urinary monomer UMO consists of 563 amino acids. Monomeric forms of this glycoprotein in urine have been reported after the addition of urea [8].

Independent studies have shown the presence of a smaller but significant basolateral UMO secretion, protein release into the blood [9, 10]. For example, when using immunoelectron microscopy of rat kidneys, S. Bachmann et al. showed that the ratio of apical/basal UMO secretion is 2:1 [9]. It is known that UMO is determined in the blood serum of healthy people at concentrations of 30–540 ng/mL [11–13].

Some researchers believe that basolateral UMO transport may even predominate (or, in any case, suffer less) over apical transport in the development of kidney damage. Hence, there is a reasonable desire to use the ratio of basal and apical THP secretion as an estimated indicator characterizing the state of the tubulointerstitial compartment of the renal parenchyma [14].

According to the results of a number of studies, the daily excretion of UMO in the urine in healthy people ranges from 9 to 66 mg [12, 13, 15–17], although some authors also cited higher values: 70–113 mg [11, 18]. ULV excretion positively correlates with eGFR, urine volume, salt and protein intake [13, 17, 19]. The half-life of UMO in the blood is about 16 h in humans [20].

Factors that can enhance the expression or excretion of UMO are: increased salt intake alone or in combination with furosemide [19, 21] and high protein in the diet [22]. Associations between sodium chloride intake and UMO excretion are believed to be most pronounced in salt-sensitive hypertension [21]. An increase in the salt content in the diet of male Sprague-Dawley rats leads to a relatively stable increase in mRNA and UMO levels in the urine. This indicates that in this situation, the increase in the content of THP in the urine reflects an increase in its intrarenal synthesis [19]. Angiotensin I-converting enzyme inhibitors [23], possibly colchicine [24, 25], and selective inhibitors of type 2 cyclooxygenase contribute to a decrease in the synthesis of THP and its excretion in the urine [26].

Relationship between THP and Chronic Kidney Disease (CKD**).**

The results of many studies, including those carried out in recent years, indicate that the excretion of UMO in the urine decreases as the functional state of the kidneys deteriorates [27, 28, 29].

A. Kottgen et al. obtained data suggesting an increase UMO concentrations in urine with a decrease in GFR [30]. However, their results were derived from the Framingham Heart Study (FHS) and Atherosclerosis Risk in Communities (ARIC) population studies. At the same time, lower levels of GFR and higher values of UMO concentration in urine were observed in homozygotes for the C-allele of carriers of polymorphism rs4293393 of the UMOD gene.

T.M. El-Achkar and X.R. Wu, trying to somehow connect the contradictory and ambiguous information about the role of UMO in kidney damage (in particular, in the regulation of the immune response), came to the conclusion that THP can have a pro-inflammatory effect on myeloid cells and an anti-inflammatory effect on epithelial cells [31]. At the same time, according to the first scenario, the effect of UMO is mainly aimed at stimulating dendritic cells, which should clear the kidney

tissue from cellular detritus formed during the induction of kidney damage. Activation of THP in this case by a negative feedback mechanism suppresses the signaling pathways of inflammation in epithelial cells. According to the second scenario, urine UMO and the glycoprotein entering the interstitium due to basolateral secretion have different immunogenic properties. Such differences are determined by the features of glycosylation of these two types of protein. UMO, which occurred as a result of basolateral secretion, interacts with certain receptors on the membranes of tubular cells, which leads to inhibition of inflammatory signaling pathways in them [31]. In this context, it is significant that recently there have been reports that parts of the THP molecule can be used (at least in the future) for anti-TNF-α therapy in inflammatory diseases, antibody-depleting therapy in autoimmune disorders and immune activation in immunocompromised states [32].

The results of another already cited clinical study showed that a low level of UMO excretion is associated not only with a greater severity of tubulointerstitial damage, but also with a greater risk of an accelerated decrease in eGFR in patients with IgA nephropathy [33]. These data seem to indicate a nephroprotective effect of THP. However, population-based studies have found that increased urinary UMO concentration, associated with the most common UMOD polymorphism, precedes the onset of CKD [34].

Uromodulin and cardiovascular diseases.

When examining a group of elderly people P.S. Garimella et al. showed that patients from the group with higher urinary UMO levels were less likely to have diabetes mellitus, coronary artery disease, stroke, heart failure, they had lower values of systolic blood pressure, body mass index, C-reactive protein, as well as higher levels of GFR [28]. A study found that higher urinary UMO excretion was associated with a lower risk of CKD progression and mortality in a multivariate analysis that adjusted for eGFR [28]. The authors consider several potential reasons for this dependence. First, a higher UMO may reflect more functioning tubules and/or tubular reserve, which in turn may slow the progression of kidney disease. If so, then THP may reflect tubular health and provide prognostic information in addition to glomerular markers of kidney health (eGFR). Second, a higher urinary UMO may be indicative of greater preservation of tubular function, such as erythropoietin production, maintenance of acid-base and mineral homeostasis. Preservation of these tubular functions, in turn, can reduce mortality. Third, it is possible that higher urinary UMO levels are protective due to anti-inflammatory properties, bacterial binding, and prevention of crystal formation [35, 36]. The authors suggest that urinary UMO may be a marker of tubular health, providing prognostic information independent of estimated GFR and urinary albumin/creatinine ratio.

Uromodulin in blood serum

It should be borne in mind that most of the studies that attempted to assess the relationship of UMO with the characteristics of the functional state of the kidneys,

clinical manifestations of nephropathies or morphological changes in the renal tissue in humans were based mainly on the study of the parameters of renal excretion of THP. However, in recent years, there has been a serious interest in the values of the concentration of this protein in the blood serum (plasma), including in terms of diagnostics. At the same time, as already mentioned, the value of serum UMO concentration closely positively correlates with the level of eGFR in patients with CKD [37, 38–42], and its changes make it possible to detect the presence of chronic kidney damage earlier than some other markers of renal dysfunction (for example, even cystatin C) [41]. In addition, it has recently been shown that patients with low serum UMO levels are significantly more likely to develop CKD than those with high concentrations of this glycoprotein [42].

The results of the already cited work [37] indicate that in patients with glomerulopathies, the concentration of uromodulin in the blood serum, apparently, is more closely associated with eGFR, the severity of glomerular and tubulointerstitial changes in the renal parenchyma and, most likely, can serve as a better integral characteristic. the state of this organ than the concentration of this protein in the urine or the value of its urinary excretion. However, as an integral assessment of the state of the kidneys, the serum concentration of THP still does not exceed the GFR, but, perhaps, allows earlier detection of damage to the tubulointerstitial compartment of the kidney than the glomerular filtration rate [37].

Conclusion.

The current knowledge regarding the significance of changes in metabolism and excretion of UMO in patients with CKD due to various nephropathies (including glomerulopathies) only indicate that the excretion (and possibly production) of this glycoprotein decreases as the severity of renal dysfunction increases. There is some evidence of the potential involvement of THP in the progression of nephropathies, modulation of renal ion transport, and the development of arterial hypertension in CKD.

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