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КАНАЛЬЦЕВЫЙ АППАРАТ ПОЧЕК — НАУЧНОЕ И ПРИКЛАДНОЕ ЗНАЧЕНИЕ

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Kidney Tubules — Scientific and Applied Value

Резюме

В настоящее время существует высокий научный интерес к изучению особенностей структуры и функций канальцев почек. Актуальность темы обусловлена потенциальной возможностью выявления разнообразных маркеров нарушения функции канальцев и использования их для ранней диагностики не только тубулопатий, но и гломерулярных нарушений. В клинической практике маркеры канальцевой дисфункции используются недостаточно. В статье представлены сведения об анатомо-функциональных особенностях проксимального и дистального отделов канальцевого аппарата, изложены высокоорганизованные механизмы межмолекулярного взаимодействия, представлены основные биологически активные вещества, изменение концентрации которых является следствием повреждения канальцев. Представленная рукопись является продуктом глубокого анализа и систематизации имеющихся данных в российских и зарубежных информационно-аналитических порталах.

Ключевые слова: *структура и функция канальцев почек, маркеры канальцевой дисфункции*

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Abstract

Currently, there is a high scientific interest in studying the features of the structure and functions of the tubules of the kidneys. The relevance of the topic is due to the potential possibility of identifying various markers of tubular dysfunction and using them for early diagnosis of not only tubulopathies, but also glomerular disorders. In clinical practice, markers of tubular dysfunction are used insufficiently. The article presents information about the anatomical and functional features of the proximal and distal parts of the tubular apparatus, outlines highly organized mechanisms of intermolecular interaction, presents the main biologically active substances, the change in the concentration of which is a consequence of damage to the tubules. The presented manuscript is the product of a deep analysis and systematization of the available data in Russian and foreign information and analytical portals.

Key words: *structure and function of renal tubules, markers of tubular dysfunction*

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AKI — acute kidney injury, BAS — biologically active substance, CKD — chronic kidney disease, FABP (L-FABP) — liver fatty acid-binding protein, GFR — glomerular filtration rate, HNF1β — hepatocyte nuclear factor-1β, IL-18, IL-6 — interleukin-18, interleukin-6, IGFBP7 — insulin-like growth factor-binding protein 7, KIM-1 — kidney injury molecule-1, MMP2, MMP9 — matrix metalloproteinases 2 and 9, MRP2/ABCC2 — multidrug resistance protein 2, NAG — N-acetyl-β-D-glucosaminidase, NGAL –neutrophil gelatinase-associated lipocalin, NHE1 — sodium-hydrogen exchanger isoform 1, OAT — organic anion transporter, OCT — organic cation transporter, TIMP-2 — tissue inhibitor of metalloproteinase-2, α-GST — α-glutathione-S-transferase, β_2-MG — β_2 microglobulin, π-GST — π-glutathione-S-transferase

Introduction

The study of renal pathology is of great interest not only for nephrology practice, but also for medicine in general. The high relevance of this issue is conditioned, first of all, by the functions performed by kidneys, as well as by the interaction with heart, blood vessels, brain, gastrointestinal tract, and endocrine system. High morphological organization of kidneys determines their streamlined normal functioning, while the pathological effect of exogenous and/or endogenous factors leads to impaired structure and function of kidneys with the development of the so-called "vicious circle" of kidneys and a co-dependent organ. One of the main functions of kidneys is to maintain the balance of intra- and extracellular fluid in response to changes in external and internal stimuli. Kidneys regulate the activity of organs and systems with the functions of excretion, metabolism and incretion [1]. It is for this reason that renal pathologies initiate the development of continuums with co-dependent organs associated with the increased risk of comorbidities. Functional or organic renal injury most often results in glomerular and tubular functional impairment.

Markers of filtration disorders are well-known and are used to a greater extent to verify chronic processes of primary or secondary renal pathology. The decreased glomerular filtration rate (GFR) indicates glomerular damage due to functional (reversible) or structural (irreversible) remodeling. It is important to emphasize that tubular epithelium has high capacity to regenerate and restore its structure [2, 3]. Thus, it is known that about 70 thousand tubular epithelial cells are excreted in urine per 1 hour, and about 1.5 million cells — per one day [4]. Despite the high regenerative ability, renal tubular cells are highly vulnerable to damaging factors — proteinuria, toxins, metabolic disorders [5]. Long-term, persistent exposure to a trigger factor, i.e. in decreased regeneration processes, or congenital inferiority of tubular apparatus, leads to irreversible structural reorganization of tubules. It is assumed that the damage to the tubular and glomerular apparatus is a single mechanism — the continuum of disease process [6]. Glomerulopathies or tubulopathies primarily affect glomeruli or tubules, and with the disease progression, other parts of nephron become involved in the pathological process [7]. This statement can be illustrated with the increased risk of

developing chronic kidney disease in patients with acute kidney injury (AKI) [8, 9].

The markers of tubular dysfunction are widely used in clinical practice. It is conventionally accepted that tubular dysfunction is a process that characterizes the course of AKI of any etiology or of congenital tubulopathy. In the recent years, there has been an increase in tubulopathies [10, 11] and mortality associated with AKI [12, 13]. Diagnostic significance of the markers of tubular dysfunction in tubulopathies is pathogenetically substantiated. It is supposed that pathological changes in tubules with underlying CKD precede glomerular changes [14] and are key factor in the prognosis of clinical course [15]. This assumption is confirmed by numerous examples — the tubular hypertrophy in CKD [16], especially in the presence of diabetic nephropathy [17, 18], congenital glomerulopathies [19], and involutive nephron loss [20]. It forms a basis for conducting new studies aimed at the review of pathophysiological mechanisms of tubular damage as the early signs of nephron damage.

Specific features of the structure and functioning mechanisms of tubular apparatus

The main function of renal tubules is to maintain homeostasis, i.e. the balance of water-salt status in the body, which is necessary for the functioning of the cells of organs and systems, acid-base balance [21]. Such functioning is possible due to the structure of the tubular apparatus of nephron. Structural features of the epithelial cells of renal tubules provide their main function, that is, transportation (tubular metabolism — reabsorption, secretion, excretion). Most of the proximal tubular epithelium is the simple cuboidal epithelium [22]. The difference between the epithelium of proximal tubules and that of distal ones is the presence of microvilli (brush border) that increase the surface for contact with glomerular ultrafiltrate, thin and long mitochondria at the basal pole and numerous vesicles involved in the transport of 60–80 % of ultrafiltrate [22, 23]. This structure of proximal tubule provides the following functions: reabsorption of trace elements, electrolytes and minerals, reabsorption 60–80 % of sodium and water [24]. Moreover, it is known that renal tubules consist of at least 16 types of epithelial cells, each performing its own functions [25]. In 1988, Renal Commission of the International Union of Physiologic Sciences suggested not to distinguish between the types of epithelial cells, but to determine the segments of renal tubules and their corresponding functions. Dividing proximal renal tubule into segments was based on topographic and anatomical characteristics. This classification allowed studying the mechanisms of the sequential functioning of renal tubules in normal and pathological conditions and using it in the morphological description of renal biopsy samples. Proximal tubule is conventionally divided into three segments: S1, S2, S3. Segments S1 and S2 are considered to be the convoluted proximal tubule, and S3 is the late proximal tubule. The main shortcoming of this classification is the lack of definite boundaries for the transition from one segment to another. S2 is located in cortex, S3 — in medulla, and S1 is the remaining part of proximal tubule. Moreover, it was found that, alongside with the general functions of proximal tubule, S2, in contrast to S1 and S3, secretes organic anions and cations [24].

In the paper by Carney E.F. (2019), it is reported that the ultrastructure of different segments of the proximal tubules has different endolysosomal potential [26]. In her work on an experimental model of kidneys, the author in real time demonstrated the degree and the possibility of absorption of fluorescent ligands in different parts of proximal tubule. It was demonstrated that in the S1 segment, lysozyme, albumin, and dextran were absorbed in the process of receptor-mediated endocytosis, while in the S2 segment, only dextran was absorbed. The author points out the high significance of this study as a further perspective in determining the "target" in differentiated diagnosis and treatment, as well as the need to continue research in order to establish the functioning mechanisms of different epithelial cells of proximal tubules.

The distal tubule of kidney starts from macula densa to the collecting system of nephron and includes 2 main parts: distal convoluted and connecting tubules. Distal tubule can be also divided into early and late parts, according to their function [27].

Distal tubules have a well-ordered structure of epithelial cells, however, near the connecting tubules, epithelium becomes heterogeneous and interspersed with intercalated cells which are responsible for regulating acid-base balance. Epithelial cells in cytosol have a large number of mitochondria, and cell nuclei are located to a greater extent on the apical surface in basolateral membrane which has deep folds [27]. Large number of mitochondria in the cells of distal tubules (the highest density among renal cells) indicates the energy-intense function of distal tubules — transport of electrolytes, such as sodium reabsorption, potassium secretion, maintaining the balance of magnesium and calcium. There are channels and co-transporters for the active transfer of electrolytes throughout distal tubules, as well as receptors that are sensitive to mineralocorticoids. A schematic drawing of proximal and distal tubules is shown in Figure 1.

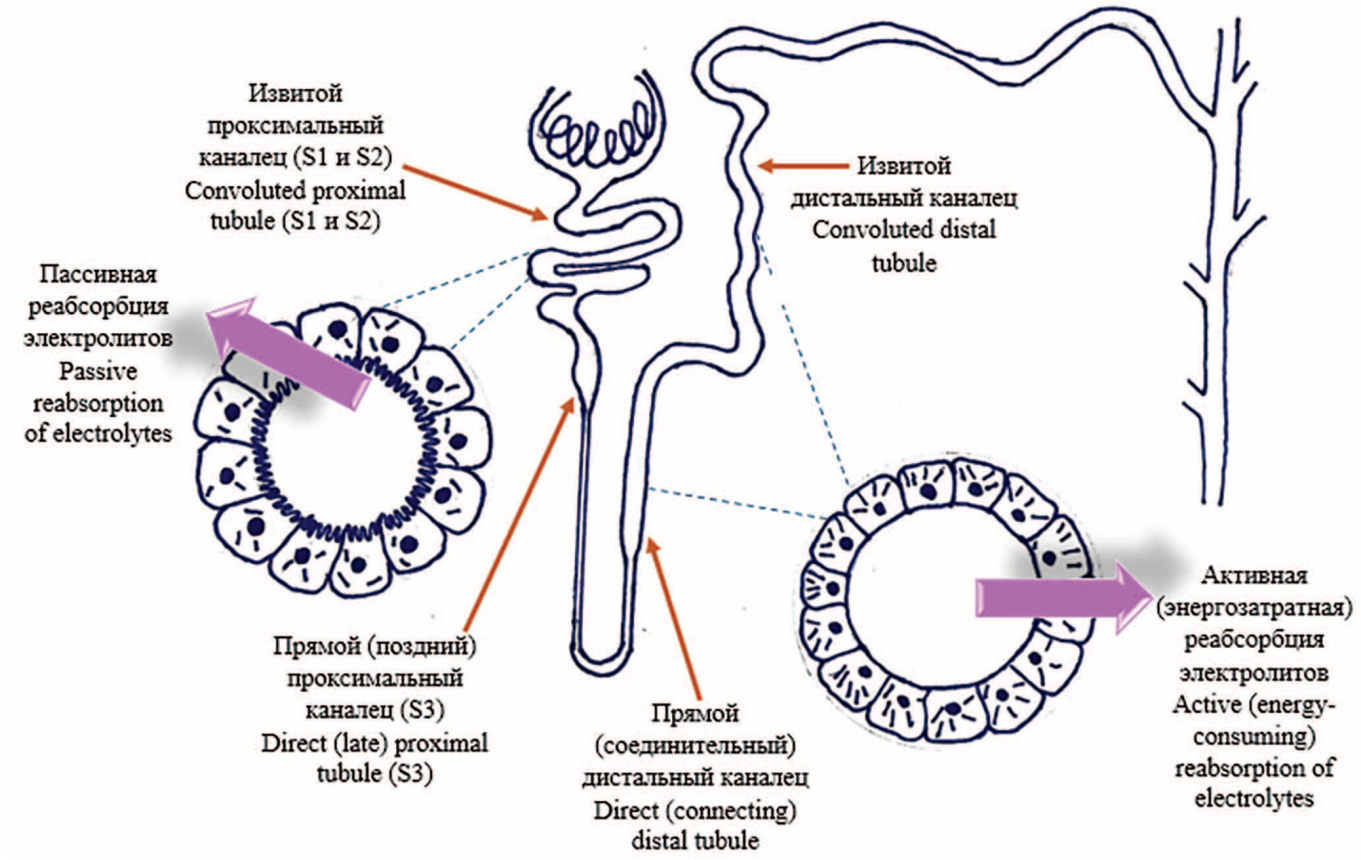

Figure 1. *Schematic representation of the system of proximal and distal tubules of the nephron*

It is important to notice that tubular epithelial cells have polarity and communicate with each other by intercellular junction complexes. Due to cell polarity, the division of plasma membrane into two parts is developed that differ qualitatively in their composition of proteins, lipids and the presence of a sensory organelle on the apical surface, i.e. a primary (non-motile) cilium. The contribution of cilia to the normal functioning of tubular epithelium is high, since this organelle controls, first of all, the signaling pathways required for indirect communication with partner proteins, trace substances, and minerals for the physiological transport of substances in the intercellular space [28]. Signaling pathway molecules and receptors are located within the cilium and separated from cytoplasmic membrane. Moreover, the cilia of tubular epithelium are involved in the regulation of proliferation, regeneration, and cell apoptosis that is of great importance for tubular apparatus [28, 29]. Review of literature sources helped to establish that the pathology of primary cilia is most often associated with the development of cysts in kidneys (single or associated with other diseases), as a rule, of a congenital nature, that is, Bardet–Biedl syndrome, Meckel–Gruber syndrome, Joubert syndrome, Senior–Loken syndrome, autosomal dominant and autosomal recessive polycystic kidney disease [30].

There are microtubules inside the epithelial cells which are important in maintaining the cytoskeleton, the shape and mobility of cells [31]. Microtubules are comprised of heterodimers of α- and β-tubulins. It is worth noting that in some renal pathologies, microtubules act as a mediator leading to acetylation and modification of epithelial cells. It is assumed that the pathology of microtubules can be the cause of the development of a cascade of mechanisms that lead to the damage to tubular apparatus, and subsequently to glomeruli [32]. A schematic drawing of the structure of the proximal and distal tubules of epithelial cell is shown in Figure 2.

It is important to note that renal pathology is not limited to one type of cells, but can be caused by damage both to epithelial and endothelial, mesenchymal, or immune cells [33].

Thus, the high organization of the structure of renal tubules allows performing a consistent series of mechanisms that are responsible for steady intra- and extracellular balance and are required for the effective functioning of organs and systems.

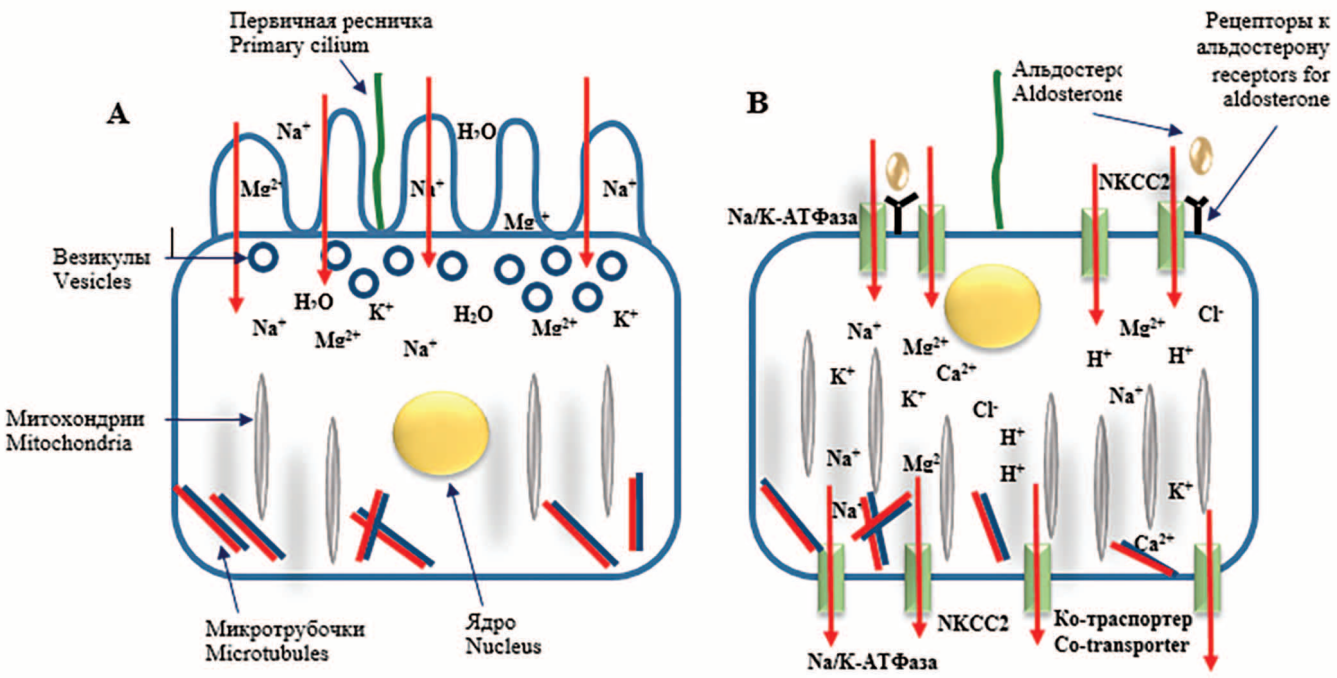

Figure 2. *Schematic representation of the structure of the epithelial cell of the proximal (A) and distal (B) tubules*

Specific features of molecular interactions during the functioning of renal tubules

Well-coordinated functioning of renal tubules is important for maintaining stable blood plasma composition. Many factors are involved in the maintenance of the homeostasis in body fluids depending on endogenous and/or exogenous changes in stimuli. The question arises: what mechanisms in tubular epithelium are involved in developing stimuli that adjust plasma homeostasis? These mechanisms are not fully understood, however, the basic processes and phenomena that contribute to the regulation of homeostasis are known: specific features of the structure of epithelial cells, state of receptor apparatus, molecular pool of interactions that form signaling pathways, and other renal and extrarenal stimuli.

Transporter molecules in proximal tubule help to develop the clearance of toxic substances, mainly uremic toxins, protein/substance complexes that move through glomerular filter, drug metabolites. Thus, it is understood that the process starting in the proximal tubule is a specific "sorting" of reabsorbed and excreted substances that entered tubules after glomerular filtration. The integrity of tubular structure and normal sequential mechanism of transport substances allow performing the effective clearance of glomerular filtrate and maintaining the balance of blood homeostasis.

Intermolecular complexes of transmembrane proteins between epithelial cells develop tight or "loose" contacts complementing cell cytoskeleton, as well as contact with protein compounds of neighboring cells and with cytoplasmic proteins [29]. It is also important to notice that the epithelium of proximal tubules is able to reabsorb substances paracellularly and transcellularly, while the distal tubule transports substances most particularly transcellularly due to the density of epithelial cell contacts. The presence of transmembrane complexes develops the apical polarity of cells and the intercellular flow of substances with urine. Proteins involved in intermolecular interactions are cadherins [29, 33], catenins, nectin, afadin, occludins, junctional adhesion molecules, and claudins [32]. These proteins determine the epithelial phenotype of cells. There are different subtypes of cadherins in kidneys. In particular, membranous or cytoplasmic expression of E-cadherin and β-catenin is observed in distal tubules, while N-cadherin is expressed in the proximal ones [34]. Cadherin/catenin and nectin/afadin complexes are attached to the actin cytoskeleton and microtubules of cells [33]. Complexes develop with the help of Ca^{2+}-mediated mechanism.

Claudins are the basic part of the tight junctions of tubular epithelial cells. They are located along the lateral

membrane of one cell connecting with a similar molecule in another cell. Their main role is making "pores" (barriers) for the passage of the ions of small diameter [35], as well as participation in the signaling pathways of molecular interactions [33]. There are several isoforms of claudins. It is considered that the location of expression of a particular claudin determines cell function and specific features of its permeability. Claudins are expressed in different parts of nephron: tubules, glomeruli, podocytes. Claudin isoforms include 2–4, 7, 8, 10a, 10b, 14 isoforms [35].

Attention should also be paid to integrins, i.e. the substances that are required for the development of cell/extracellular matrix bonds. Integrins account for the most part of the structure of transmembrane receptors located on cell surface. Integrins are primarily considered as adhesive molecules, however, they also act as signaling centers in the transmission of cell metabolism processes, since they determine the sensitivity of a cell to specific microenvironment [33].

The role of microtubules in the pathogenesis of the development of tubular pathology has been stated earlier. It should be noted that CAMSAP3 (Calmodulin-regulated spectrin-associated protein 3) is involved in the correct orientation of microtubules inside a tubular epithelial cell [36]. CAMSAP3 belongs to a family of proteins regulated by calmodulin and spectrin; their main function is to bind the negatively charged poles of tubular epithelial cell.

An important element of intermolecular interactions for tubular functioning is the analysis of the functioning of receptor apparatus in relation to transporting filtrate molecules. The physiology of receptor apparatus which directly or indirectly affects the functions of tubules remains the object of investigation to the present day. Receptors are divided into 3 types — mechanical, chemical and physical, i.e. according to their activation on exposure to a specific stimulus. Mechanical receptors of tubules are the most well-characterized and represent the expression of receptor apparatus on cell surface with a change in filtrate density and rate, i.e. implementation of the "shift" theory. Receptor apparatus activated by chemical factors (filtrate composition — glucosuria, impaired acid-base balance), physical factors (changes in filtrate temperature and environment).

Receptors of renal tubules with normal structure are responsible for paracellular and intracellular diffusion of substances, and their impaired function may be associated with the development of diseases or fatal conditions. Thus, it has been experimentally shown in laboratory animals that genetic deletion of TRPM6 (Transient Receptor Potential Cation Channel Subfamily Member 6) channel is associated with embryonic death in laboratory rats due to the impaired transport of magnesium ions [37]. Or, for example, a genetic defect of TRPM6 in human leads to severe hypomagnesemia and secondary hypercalcemia. TRP (transient receptor potential) channels are a transport route through the hardly permeable plasma membrane of epithelial cell; they are activated in response to the changes of environment. TRP superfamily can be divided into 7 subfamilies which, in turn, are further classified into a number of classes according to their protein structure and function. TRPs are present not only in tubules, but also in glomeruli and podocytes. It should be noted that the control of TRPM6 expression located in tubular epithelium is carried out by several endocrine factors, primarily — insulin, estrogen, and epidermal growth factor. Anticancer treatment with cetuximab often results in hypomagnesemia; this fact can be explained by inhibition of basolateral epidermal growth factor receptors that are required for the functioning of TRPM6 [37]. In addition to endocrine factors, other systems can have an impact on the expression of receptor channel. An example of the physiological control of TRPM6 function is magnesium balance during dieting — low intake of magnesium with food results in channel activation and increasing magnesium reabsorption, and diet with magnesium overdose leads to decreased expression [37]. This example highlights the high importance of tubular function at organ and system levels.

The receptors themselves are important from clinical and scientific points of view in regard to the global performance of tubular function. It is known that blood proteins in small quantities reach the ultrafiltrate due to glomerular filtration. Protein molecules that are transported through glomeruli are reabsorbed by receptor interaction (ligand-associated bonds). In proximal tubular epithelium, there are endocytic receptors represented by cubilin and megalin, i.e. protein structures that bind molecules for their further transportation. Megalin (or autoantigen with underlying Heymann nephritis) is attributed to the class of lipoproteins and is located on the apical surfaces of the epithelial cells of proximal tubules. Cubilin is a receptor (glycosylated extracellular protein) for intrinsic vitamin B12 factor that is originally recognized as a teratogenic factor in the experimental studies in rats. Genetically reduced expression of cubilin leads to hereditary megaloblastic anemia (Imerslund–Grasbeck syndrome, selective vitamin B12 malabsorption with proteinuria). Cubilin is also located in proximal tubules, on their apical surface. Megalin and cubilin can produce complexes with each other bringing into action the receptor mechanism.

There are also other forms of receptors that are involved in the intracellular regulation of ion diffusion.

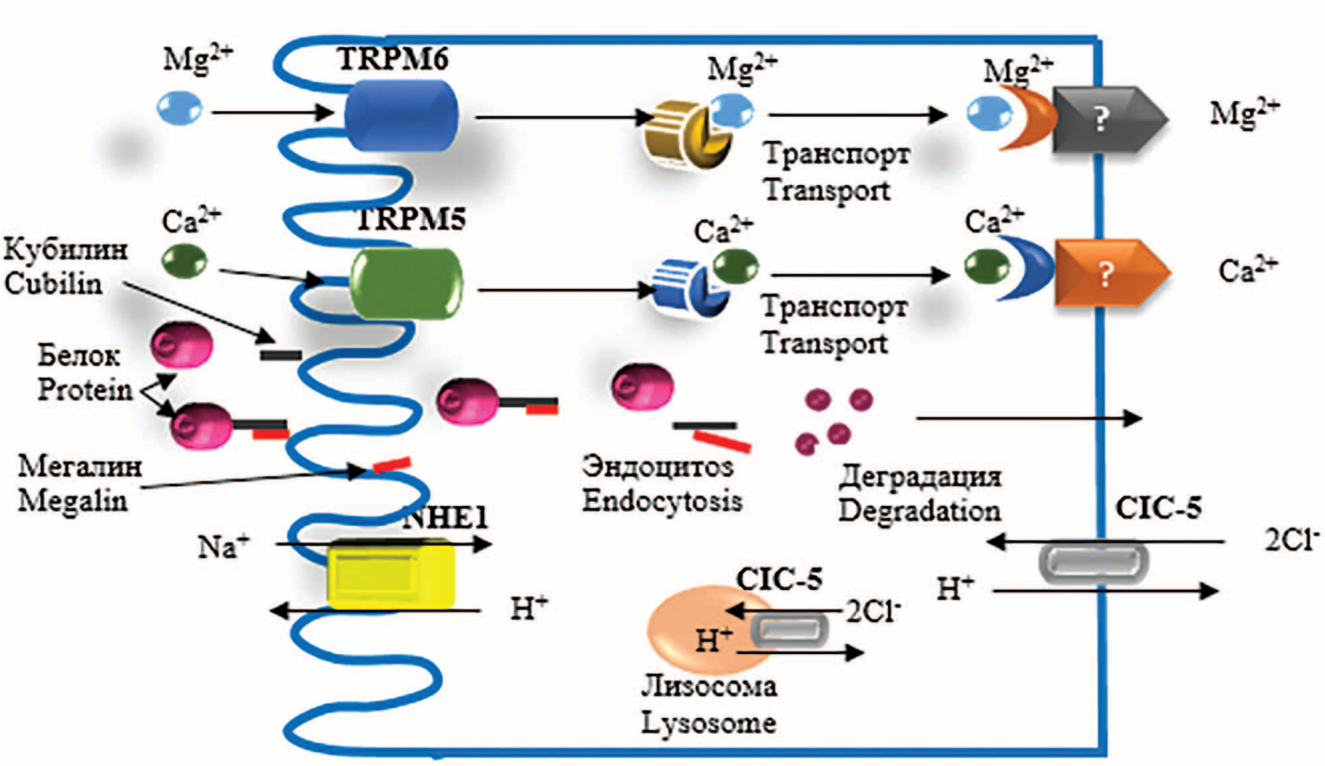

Figure 3. *Scheme of action of the main intracellular transporters in the epithelial cell of the proximal tubule*
Note: TRPM6 — Transient Receptor Potential Cation Channel Subfamily Member, NHE1 — Na-H exchanger 1, CIC-5 — chloride ion channel

Sodium-hydrogen exchanger isoform 1 (NHE1) is a protein expressed by the plasma membrane of tubular epithelial cell. NHE1 plays a key role in maintaining intracellular homeostasis — the balance of sodium and hydrogen ions [38]. In addition, NHE1 cytosolic tail is involved in the development of the cytoskeleton of a tubular endothelial cell, adapts the cell to changing conditions using signaling NHE1-dependent proteins, optimizes cell apoptosis by changing cell pH, and is also a part of signaling pathways that are responsible for the function of tubular epithelial cells [38].

CIC-5 (chloride ion channel) is a protein localized in the apical surface of the epithelial cells of proximal tubules and in the collecting ducts intercalated cells. The main function of CIC-5 is intracellular chlorine-hydrogen exchange; it is also involved in endosome acidification. A genetic mutation of CIC-5 leads to a congenital anomaly — Dent's disease (X-linked pathology of renal tubules) [38].

There are several other proteins that produce complexes with megalin to perform the function of receptor apparatus. This section describes the main components and mechanisms required to the functioning of tubules.

A schematic drawing of the intermolecular interaction in tubular epithelium is shown in Figure 3.

It is also important to note the specific features of molecular transport in the different areas of tubular apparatus. The transport of cations and anions takes place in the basolateral and apical parts of proximal tubular epithelium by the means of transporter molecules — organic anion transporters (OAT) and organic cation transporters (OCT). Transporters have similar structure; they include 12 α-helical transmembrane domains, at least one intracellular domain, and a large extracellular glycosylated loop. OAT and OCT are divides in subclasses depending on the specific features of their structure and function. Basolateral transport does not require ATP hydrolysis; it is carried out using K-Na-ATPase. The exchange messenger for an anion in the OAT complex is intracellular α-ketoglutorate of dicarboxylic acid which binds to OAT releasing the anion. The process of anion transport on the apical surface of cells is energy-intense and is performed through the capture of ATP by transport molecules (multidrug resistance protein 2 (MRP2/ABCC2) producing a complex with an anion [39]. Transport of cations is carried out by means of other transport associations — MATE transporters (multidrug and toxin extrusion) that belong to the SLC transporters family (solute carriers). Currently, several types of MATE transporters

are known (MATE1, MATE2 and MATE2-K. MATE1); among these, MATE2-K has the highest affinity for tubular epithelium, and MATE2 — to a lesser extent. The main function of MATE proteins is cation transport using the antiport mechanism on the apical side of epithelial cells, as well as the metabolites of drug products. It is important to note that MATE forms a complex with OCT localized in basolateral part; it allows performing the transport of a broader spectrum of cations [40].

Energy sources for tubular metabolism. To perform the complex processes of homeostasis in the body, kidneys require energy. It was established that energy processes in tubules are mainly possible due to ATP which is synthesized mainly in the mitochondria of proximal tubular cells. The substrate for ATP is fatty acid oxidation and, to a lesser extent, glucose [41, 42]. Fatty acids enter tubular cells via receptor transport (CD36 is expressed on cytoplasmic membranes), as well as in a complex of fatty acid binding proteins and other transport proteins [41, 42]. Complex fatty acids require binding to carnitine in the form of carnitine palmitoyltransferase 1 with its conversion into isoforms [42]. One of the known mechanisms is peroxisomal oxidation of fatty acids with the production of acetyl-CoA and subsequent transformation in ATP [43].

Markers of tubular dysfunction

Tubular epithelium is not a passive target for injury factors. Epithelial cells perform various functions; the most significant among these are the ability to produce pro-inflammatory factors, i.e. cytokines, chemokines, to develop receptor and signal pathways for signal transmission and, as a result, to coordinate different biological and pathological processes. Reversible or irreversible tubular dysfunction leads to the secretion of biologically active substances and/or decreased tubular reabsorption. In this case, molecules that are normally absent in urine and/or the increased level of nitrogen-containing bases in blood are the markers of acute or chronic tubular dysfunction; this fact is used in clinical practice.

Analysis of literature sources helped to identify a number of molecules that were secreted in increased amount when tubular epithelium was damaged. There are biologically active substances (BAS) produced only (or predominantly) by tubular epithelium. Differentiation of these substances according to the principle of dominant secretion has high applied and scientific significance.

BAS that are secreted and expressed only (predominantly) in tubular epithelium include uromodulin (Tamm–Horsfall protein), kidney injury molecule-1 (KIM-1), T-cell immunoglobulin and mucin domain 1 (TIM-1)). This group can also include glutathione-S-transferase enzymes (α-GST, π-GST), since they are part of the cytoplasm of tubular cells.

BAS, with secretion and expression arising or increasing with the damage of tubular epithelium, however, that can be also expressed in other cells in the body, include neutrophil gelatinase-associated lipocalin (NGAL, lipocalin-2, siderocalin, 24p3), N-acetyl-β-D-glucosaminidase (NAG), hepatocyte nuclear factor-1β (HNF1β, vHNF1, TCF2 and LF-B3), tissue inhibitor of metalloproteinase-2 (TIMP-2), insulin-like growth factor binding protein 7 [IGFBP7, mac25, prostacyclin-stimulating factor (PSF), tumor adhesion factor (TAF), and angiomodulin (AGM)], liver fatty acid-binding protein (FABP, L-FABP, FABP1), gelatinases (matrix metalloproteinases — MMP2, MMP9), interleukin-18 (IL-18).

There are several biologically active substances which are only reabsorbed in renal tubules; if there is a pathology of tubular apparatus, they accumulate in urine. These biologically active substances include β_2-microglobulin (β_2-MG), cystatin C, and interleukin-6 (IL-6).

It is apparent that the tubular function markers are more often associated with the acute pathology of tubular apparatus; in particular, they are used in the diagnosis of AKI. However, with the expansion of the knowledge base about the specific features of tubular damage, many studies are currently being carried out aimed at studying the markers of tubular damage in case of primary or secondary chronic renal pathology.

NGAL was first isolated from neutrophils as a variant of its normal production in neutrophils. This biomarker remains until the destruction of mature neutrophil granules during infectious and inflammatory processes [44]. Further, NGAL expression from other cell types was found, and its main functions were identified, that is, its involvement in migration, proliferation, apoptosis, and differentiation of cells [44, 45]. Further analysis of the specific metabolic features and mechanisms of NGAL secretion allowed establishing that NGAL was secreted and expressed by renal tubular cells, to a greater extent in the area of the ascending part of the loop of Henle and in the collecting ducts in case of their damage [44].

NAG is a lysosome enzyme that is produced by cells of many types. NAG in kidneys is secreted and expressed in the lysosomes of proximal tubule and may be normally present in small amounts in urine [46]. Increased concentration of NAG in urine makes indicates tubular pathology. NAG, being a marker of tubular injury, is used for diagnosis of AKI, chronic renal diseases; there are data on its predictive role in cardiovascular diseases (arterial hypertension, chronic heart failure) and diabetes mellitus [47, 48].

KIM-1 is a glycoprotein receptor with the most significant expression in proximal tubule compared to other molecules. In addition, KIM-1 binds to phosphatidylserine to execute apoptosis. [49, 50]. According to the literature, this compound has the so-called "eat me" function; it means "labelling" of cells to initiate apoptosis. In the context of tubular pathology, not only apoptosis is performed this way, but also the removal of necrotic cell material, oxidized lipids [51].

Uromodulin is one of the most attractive molecules in studying tubular dysfunction and using it in clinical practice. Uromodulin is secreted in the ascending part of the loop of Henle and in distal tubule. The biological role of uromodulin is the binding of calcium oxalate (reducing the risk of kidney stones), with E. coli fimbriae (reducing the risk of urinary tract infections), homeostasis regulation by binding to the co-transporters of sodium (there is a correlation with the development of salt-sensitive arterial hypertension) [52, 53], potassium, chlorine, control the function of magnesium and calcium channels in distal tubules [54]. It was established that uromodulin level in urine corresponds to the mass and function of tubules and has a positive correlation with GFR [54]. There are known mutations of genes encoding the release and quality of uromodulin; the result is the development of renal fibrosis. In the KDIGO consensus report, an autosomal dominant kidney disease due to a mutation in the uromodulin gene was proposed to be called uromodulin-associated kidney disease (UAKD). A number of diseases associated with similar changes in tubulointerstitium, but of different etiology, are conventionally attributed to the group of autosomal dominant tubulointerstitial kidney diseases (ADTKD) [55].

Hepatocyte nuclear factor-1β (HNF1β) is a member of transcription factors family. HNF1β was first isolated in liver, however, it is of greater importance and has predominating secretion localization in kidneys, in particular, in all parts of tubular apparatus. HNF1β is important during embryogenesis for the normal development of kidneys, liver, pancreas, intestine, and genitourinary tract [56]. When tubular apparatus function is normal and there are no HNF1β gene mutations, hepatocyte nuclear factor-1β controls normal metabolism in tubules and transport of solutes by tubular epithelium [57]. Mutation of HNF1β genes is inherited in an autosomal dominant manner resulting in tubulointerstitial fibrosis, renal agenesis or hypoplasia, multicystic dysplastic kidneys, and glomerulocystic disease [57].

β_2-MG is a small protein that is located in all nucleated cells. A specific feature of β_2-MG is its almost complete metabolism via kidneys, with reabsorption through tubules [58]. In this regard, increased β_2-MG level in serum due to non-renal causes also leads to its increased concentration in urine. Clinical use of β_2-MG is reasonable in the cases of the development of renal amyloidosis along with hemodialysis, multiple myeloma, kidney cancer, tumors of extrarenal origin, secondary nephropathies, cardiovascular diseases (coronary heart disease, carotid atherosclerosis, intermittent claudication, etc.) [59–61]. β_2-microglobulinuria also develops with underlying autoimmune diseases, infectious and inflammatory processes [60].

Cystatin C is a low molecular weight protein that is located in all cells of the body, is completely filtered through glomeruli, and is reabsorbed in proximal tubules. Cystatin C is associated with many biological processes in the body, since it is involved in the activation of precursor proteins, protein metabolism, and apoptosis [62, 63]. Since the metabolism of cystatin C takes place in kidneys, its high prognostic value in nephrological practice is established: cystatin C is an indicator of glomerular function and tubular dysfunction in AKI [62]. Moreover, in 2012, KDIGO proposed to use serum cystatin C, both as a single indicator of renal function and, when combined with serum creatinine, in the formulas for calculating GFR in CKD [64]. Formulae that are recommended for use in clinical practice are CKD-EPI formula based on creatinine levels and CKD-EPI formula based on cystatin C and serum creatinine levels.

Tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7) are expressed in renal tubules when tubular epithelium is damaged [65]. IGFBP7 is secreted and expressed in the cells of proximal and distal tubules, while TIMP-2 — in distal tubules only. The functions of these biologically active substances include participation in various biological processes in the body, including apoptosis, cell aging, cell cycle, inflammation, and tubular regeneration [66]. Both biologically active substances are protein structures and established markers of early AKI. TIMP-2 is an inhibitor of metalloproteinases. Matrix metalloproteinases are one of the factors that cause damage to renal structure (glomeruli, tubules, vessels) through matrix degradation [67]. TIMP-2 interferes with this process, since it inhibits metalloproteinases and is involved in G1 phase of cell cycle arrest that is considered to be a key component in AKI progression [67]. IGFBP7 is also involved in cell cycle arrest. IGFBP7 is a member of the IGFBP superfamily and is involved in normal cell growth, differentiation, proliferation, and apoptosis; it is also a link in signaling pathways transferring information to receptors, proteins, and proteases [68].

Liver fatty acid binding protein (FABP), also known as L-FABP or FABP1, is a fatty acid protein. FABP is

predominantly expressed in hepatocytes, as well as in many cells, such as enterocytes, proximal tubule cells, and alveolocytes [69]. L-FABP is filtered in glomeruli and reabsorbed in tubules. Damage to tubular epithelium is the result of the excessive reabsorption of L-FABP containing fatty acids [70]. Other damage factors (arterial hypertension, tubular ischemia, infections, toxic effects) are also possible with the increased expression of the gene that controls L-FABP that rapidly accumulates in urine and is used as a marker of tubular epithelium damage [71]. L-FABP, like other members of the FABP family, is currently being actively studied in order to determine their significance in nephrological practice, as well as to clarify the specific features of their metabolism and localization of expression in renal tubules. Fatty acid binding protein 2 (FABP2, I-FABP) is expressed in enterocytes, however, increased FABP expression has currently been found to correlate with the progression of chronic kidney disease in diabetic nephropathy [71].

Gelatinases (matrix metalloproteinases, MMP2, MMP9) are neutral proteinases that can destroy and change the structure of extracellular matrix due to protein degradation [72]. This function is positive because it reduces the process of fibrogenesis and prevents the development and progression of tubulointerstitial fibrosis. However, MMP2 and MMP9 also have other properties that have a damaging effect on renal tubulointerstitium. It was established that MMPs are involved in cell migration, cell–extracellular matrix adhesion, activation of epithelial–mesenchymal transition; they also mediate the activity of growth factors and the release of cytokines, including TGFβ — a primary factor in fibrosis and tissue remodeling [71]. It should be noted that one of the mechanisms for the development of tubular damage in glomerulopathies is MMP9 activation with excessive reabsorption of albumin in proximal tubules. Matrix metalloproteinases can be the markers of both acute and chronic tubular injury [72].

α-GST and π-GST are isoforms of glutathione-S-transferase found in the human body, namely, in proximal and distal tubules, respectively [73]. Based on their localization, it is obvious that these isoforms appear in urine when the integrity of tubular epithelial cells is impaired. Due to this, α-GST and π-GST are early markers of AKI; their significance has been confirmed by many studies [74]. At the same time, persistent low-intensity damage to tubular epithelium is also accompanied by the release of α-GST, π-GST into urine. The predictive value of these enzymes in diabetic nephropathy, glomerulonephritis, obesity-associated nephropathy, and glomerulopathies has been established [73].

IL-18 is a cytokine that plays an important role in the T-helper type 1 and 2 response. Moreover, IL-18 expression leads to the activation of other cytokines that are responsible for the initiation and maintenance of inflammation, i.e., TNF-α and IL-1β. IL-18 is in most cases expressed by tubular epithelial cells, as well as by dendritic cells, macrophages, neutrophils, basophils, keratinocytes, chondrocytes, synovial fibroblasts, cells of adrenal cortex, and osteoblasts [75].

Table 1. *Characterization of renal tubular function markers*

Marker	Place of production	Mechanism in the tubules	Values of normal indicators	Types of pathological conditions
KIM-1	Epithelium of the proximal tubule	Secretion, expression, excretion, reabsorption in small amounts	Urine — 0-2200 pg/ml [79] Blood — not normal	AKI, CHF There is evidence for the predictive role of KIM-1 in CKD
α-GST	The enzyme is localized mainly in the proximal tubule	Expression, excretion	Urine — 2.7-7.6 ng/mg/urine creatinine [80] Blood — not normal	AKI, diabetic nephropathy, other metabolic nephropathy, glomerulonephritis
π-GST	The enzyme is localized mainly in the distal tubule		Urine — 4.1-13 ng/mg/urine creatinine [80] Blood — not normal	
NGAL	NGAL is secreted in neutrophils; in case of kidney damage, it is secreted and expressed by cells of the renal tubules, to a greater extent in the area of the ascending loop of Henle and collecting ducts	When damaged, secretion, expression, excretion, reabsorption. In the absence of damage to the tubules — reabsorption	Daily urine — 17.1-29.7 ng / ml and 21.5 — 32.9 ng / g / creatinine (men) 52.2-75.7 ng/ml, 80.3-99.4 ng/g/ creatinine (women) [81] Blood — 43.0-86.3 mcg / l (men), 38.2-88.9 μg/l (women) [82]	AKI, CKD of any origin

Table 1. *(The end)*

NAG	Secreted in many cells. In the kidneys — in the lysosomes of the proximal tubule.	Secretion, expression, excretion, reabsorption	Urine — 1.6-5.8 U/g creatinine [83], 19.8-22.2 U/l (men), 16.5-20.5 U/l (women) [84] Blood — 270-495 U/l [85]	AKI, CKD, secondary tubulopathies — AH, CHF, DM
HNF1β	Secretion in all parts of the tubular apparatus, liver, bile ducts, thymus, pancreas, tracts, lungs and intestines	Secretion, expression, excretion, reabsorption	No data	Tubulointerstitial fibrosis, renal agenesis or hypoplasia, multicystic renal dysplasia, glomerulo-cystic disease, hyperuricemia, gout, diabetes mellitus, genital tract malformations, hyperparathyroidism
TIMP-2	Secretion in the distal tubules in renal injury. Found in all tissue cells	Secretion, expression, excretion, reabsorption	Urine — 188-244 pmol/l [86] Blood — 109-253 ng/ml [87]	AKI, there is evidence to predict the risk of CKD progression
IGFBP7	Secretion in the proximal and distal tubules in case of kidney damage. Found in all tissue cells	Secretion, expression, excretion, reabsorption	Urine — 2.60-4.09 ng/ml [88] Blood — no data	AKI, there is evidence to predict the risk of CKD progression
L-FABP	Secretion in the cells of the proximal tubules, hepatocytes, as well as in many other cells — enterocytes, alveolocytes	Secretion, expression, excretion, reabsorption	Urine — 0.3-8.4 μg/g creatinine [89] Blood — no data	AKI of any etiology, including ischemic genesis, tubular necrosis. There is evidence to predict the risk of CKD progression
MMP2 MMP9	Secretion of mesangial and epithelial cells of the tubules at an ultra-low level. Increases with damage to the tubules	Secretion, expression, excretion, reabsorption in a small amount is normal	Urine — not normal Blood — 475 to 798 ng/mL [90] Urine and blood — not normal [90]	AKI, CKD of any etiology, including kidney cancer (carcinoma). Any kidney disease characterized by the formation of fibrosis
IL-18	Secretion by epithelial cells in the proximal tubules, distal convoluted tubule, connecting tubules and collecting tubules in case of damage, monocytes, macrophages	Секреция, экспрессия, выведение, реабсорбция	Urine — not normally detected (may be detected in ultra-low concentrations) [91] Blood — less than 70 pg/ml [92]	AKI, ischemic kidney disease, glomerulonephritis, incl. lupus, diabetic and obstructive nephropathy
β_2-МГ	In all nucleated cells, except for erythrocytes	Reabsorbed in proximal tubules	Urine — in trace amounts (no more than 0.1 % of the total content in the body) Blood — up to 0.32 mg/l [93]	Infectious-inflammatory, autoimmune diseases of any etiology, amyloidosis in hemodialysis, kidney cancer, secondary nephropathies, multiple myeloma
Cystatin C	Synthesized by all nucleated cells, 100 % filtered by glomeruli	Reabsorbed in proximal tubules	Urine — not normal Blood — 0.50–0.96 mg/l (in men), 0.57–0.96 mg/l (in women) [94]	AKI, the prospect of use — the risk of progression of tubulopathies of any genesis
IL-6	It is synthesized in many immunocompetent cells. In the kidney tissue, IL-6 is expressed by podocytes, mesengial, and endothelial cells.	Reabsorbed in the tubules	Urine — not normal Blood — 1-2 pg/ml [95]	AKI of any origin, primary and secondary glomerulopathies, secondary nephropathies
Uro-modulin	Secretion and expression in thick ascending loop of Henle	Secretion, expression, excretion, reabsorption in small amounts	Urine — 0.2 to 49.9 μg/mL [96] Blood — not normal	AKI, autosomal dominant tubulointerstitial kidney disease (uromodulo-associated kidney disease), tubulopathies of any genesis

Note: AH — arterial hypertension, IL — interleukin, AKI — acute kidney injury, DM — diabetes mellitus, CKD — chronic kidney disease, CHF — chronic heart failure

Table 2. *Classification of the pathology of the tubular apparatus*

№	Classification sign
I	**According to the etiological factor:** 1. Congenital 2. Acquired
II	**According to the topic of the pathological process:** 1. Pathology of the proximal tubule 2. Pathology of the distal tubule 3. Pathology of the loop of Genle 4. Pathology of the collecting duct 5. Combined forms
III	**According to the damage reaction:** 1. Acute – With complications: ✓ Within the nephron ✓ System ✓ With process timing – Without complications 2. Chronic
IV	**According to the reversibility of the pathological process:** 1. Reversible tubular pathology 2. Irreversible tubular pathology: А. No transformation; Б. With transformation: – autophagy – necrosis – epithelial-mesenchymal transition – atrophy – calcification
V	**According to the pathology of cytoplasmic and intracellular membranes of tubular epithelial cells:** 1. Pathology of tubules of toxic genesis 2. Pathology of tubules of metabolic origin 3. Pathology of tubules of medicinal genesis 4. Pathology of hypertensive origin 5. Pathology of ischemic genesis 6. Pathology of inflammatory genesis: – cytokine reactions – direct influence of infectious (bacterial, viral) facts of pathogenicity (enzymes, exotoxins, etc.) – autoimmune reactions (autoantigens, circulating immune complexes)
VI	**According to the characteristics of the affected structures of the epithelial cells of the tubules:** 1. Membranopathy 2. Co-transport damage 3. Receptor damage – cubilin – megaline – sodium-hydrogen exchanger (NHE1) – Chloride ion channel (CIC-5) 4. Mitochondrial damage 5. Lysosomopathies 6. Primary eyelash pathology; 7. Pathology of the cytoskeleton (microtubules)
VII	**According to the pathology of proteins that form intercellular contacts:** 1. Claudins 2. Integrins 3. CAVSAP3 (Calmodulin-regulated spectrin-associated protein 3)

IL-18 is involved in signaling pathways that take part mainly in the pro-inflammatory response [76]. It should be noted that many acute and chronic diseases are based on the inflammatory process, and IL-18 plays a key role in it. To perform its action, IL-18 requires a specific receptor and a protein that binds IL-18 [76]. IL-18 is used as a marker of tubular damage in cases of renal inflammatory diseases of any etiology, including AKI, autoimmune pathologies (primary and secondary glomerulonephritis), metabolic disorders (diabetic nephropathy), and obstructive kidney diseases [75].

IL-6 is reabsorbed by renal tubules and is found in many immunocompetent cells. In kidneys, IL-6 is expressed by podocytes, mesenchymal, and endothelial cells. IL-6 is a cytokine that provides pro-inflammatory, immune mechanism, as well as immediate response [77]. IL-6 is involved as the key component in several signaling pathways and has specific receptors for interactions with target organ cells, primarily, tubular and blood cells. An important pathological function of IL-6 is increasing the activity of epithelial sodium channel resulting in increasing sodium reabsorption in blood flow; this, in turn, leads to the growing risk of developing arterial hypertension, as well as to the stimulation of renin-angiotensin-aldosterone system [78]. IL-6 may have a prognostic value in the cases of AKI of any origin, primary and secondary glomerulopathies, secondary nephropathies.

Given the variety of markers of renal tubular functioning, it seems to be reasonable to summarize the presented material according to their main characteristics (Table 1.)

This table was drawn up based on the reference values of tubular function markers obtained from the studies conducted with the monitoring of parameters in a cohort of healthy volunteers.

Issues of classification of the pathology of tubular apparatus

Currently, there is no single classification of the pathology of tubular apparatus. The most obvious reason for the lack of systematization and structure of tubulopathies is the complex, highly organized structure of tubules and the variety of processes and mechanisms that are involved in their sequential function. The collaboration of the specialists of different profiles is required to develop a unified classification of tubulopathies that will be used in clinical practice and scientific research.

A deep and detailed review of literature sources allowed us to identify the key aspects that determine possible classification of the pathology of tubular apparatus (Table 2).

Conclusion

This literature review demonstrates the high relevance of further intensive study of the specific features of the highly organized tubular apparatus and of the mechanisms of intermolecular interaction therein. Available clinical data and pathomorphological results of studies gave us an idea on the potential use of the biomarkers of tubular dysfunction in the diagnosis of not only acute kidney injury or acute kidney disease, but also of chronic kidney disease.

It should be noted that a unified classification of tubular apparatus diseases is required for the consistency of terminology, understanding the pathogenetic processes, as well as for diagnostic and therapeutic measures. To address this problem, a working group of the experts in various fields, mainly nephrologists, morphologists, and geneticists should be created. Alongside with structurization, the implementation of such tubular diseases classification in clinical practice will allow to determine the process severity, risk category, possible complications, and to make many other significant assessments.

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