НИРКИ KIDNEYS

UDC 616.61+616-072.5 DOI: https://doi.org/10.22141/2307-1257.11.2.2022.363

L.D. Denova
Shupyk National Healthcare University of Ukraine, Kyiv, Ukraine

The value of proteomic studies of the latest markers of kidney damage in the urine to assess the course, progression and complications in patients with CKD

For citation: Počki. 2022;11(2):68-80 doi: 10.22141/2307-1257.11.2.2022.363

Abstract. *Chronic kidney Disease (CKD) is the cause of both morbidity and mortality worldwide. In Ukraine, 12 % of the population is diagnosed with CKD. Significantly worsen the quality of life in patients with CKD progression of renal fibrosis and impaired mineral homeostasis. Early diagnosis and treatment are the main measures to prevent CKD progression and delay adverse effects. Deficiency of early, non-invasive biomarkers adversely affects the ability to rapidly detect and treat CKD. Proximal tubular lesions play an important role in the progression of CKD. There are new markers of kidney damage, such as uromodulin (UMOD), Klotho protein and post-translational modifications of fetuin A (FtA). Treatment of CKD in the early stages may improve renal function and/or slow the progression of CKD.*
Keywords: *chronic kidney disease; hyperphosphatemia; uromodulina; Klotho protein; fetuin A*

CKD has a significant impact on global health. CKD is the cause of both morbidity and mortality worldwide, in addition, CKD is a major economic burden for both patient and the country [1, 2].

CKD is a serious public health problem, which affects 13.4 % of adult population and causes 1.2 million deaths per year [1, 3]. CKD is available in 12 % of population of Ukraine [4]. In the United States, significant prevalence of CKD, approximately 1 in 7 people over the age of 30 suffers from CKD. More than 800 million people worldwide suffer from CKD [5]. The prevalence of CKD in the world is 10–16 % of the total population. In the elderly it reaches 30 % [4]. CKD was declared a hidden epidemic [1].

Since 2002, the term CKD combines a variety of nosological forms with a high probability of progression of chronic pathological process in the kidneys with the subsequent accession of chronic renal failure, which requires renal replacement therapy (peritoneal dialysis, hemodialysis or kidney transplantation) [4].

CKD is a decrease in renal function that correlates with glomerular filtration rate (GFR) of less than 60 ml/min/1.73 m^2 and/or markers of renal failure lasting at least 3 months, characterized by structural and/or functional renal changes according to clinical, laboratory, instrumental, morphological studies, which provide a basis for the exclusion of acute pathological process in the kidneys [1, 4, 6–9] (see table 1).

New terms have been proposed for CKD:

1. Diabetic kidney disease — diabetes + CKD (formerly diabetic nephropathy (KDOQI, 2007, 2012)).

2. Hypertensive disease of the kidneys, which is a consequence of hypertension.

3. Ischemic kidney disease resulting from the development of atherosclerosis [4].

Patients with CKD are prone to hypertension, cardiovascular disease, fibrosis and bone disorders. Currently, only dialysis or kidney transplantation is an effective treatment for CKD [5, 10, 11].

Fibrosis in CKD usually progresses. Excessive accumulation of matrix components of connective tissue is considered fibrosis. Fibrosis can affect the pancreas, kidneys, skin, lungs, eyes, heart and liver. This is the final pathological process of maladaptive repair, characterized by the formation and accumulation of extracellular matrix, mainly in local mesenchymal cells [11] (see table 2).

Mesenchymal cells, such as fibroblasts and myofibroblasts, play an important role in the onset and development of fibrosis. This process is closely related to inflammation and tissue regeneration, which usually occurs during and after the inflammatory response, and is initiated by various types of tissue damage. Pathological fibrous remodeling process is often the cause of organ dysfunction. Fibrosis is associated with high morbidity and mortality [11, 12].

For correspondence: Lidiia D. Denova, Shupyk National Healthcare University of Ukraine, Dorohozhytska st., 9, Kyiv, 04112, Ukraine; e-mail: marbua18@gmail.com
Full list of author information is available at the end of the article.

In CKD, almost always, there are violations of mineral homeostasis. In humans, calcium and phosphorus levels are maintained by a balance between deposition in bone tissue, reabsorption in the kidneys and absorption in the intestine [13]. Mineral imbalances, namely hypervitaminosis D_3, hypercalcemia and hyperphosphatemia, can affect the aging process, which is often observed in Klotho protein deficiency. Animal models have shown that maintaining mineral homeostasis by increasing Klotho protein levels inhibits aging [14, 15].

CKD can be complicated by a rare and life-threatening syndrome — calciphylaxis (calcific-uremic arteriolopathy), which is characterized by the appearance of small vascular calcifications that lead to occlusion of blood vessels and tissue necrosis. The term "calciphylaxis" was first used by Hans Cellier in 1961, a rare, pathological condition in which there is medial calcification of arteries and arterioles, as well as proliferation of intima and fibrosis [16–18].

Early diagnosis and treatment are the main measures to prevent CKD progression and delay adverse effects. Deficiency of early, non-invasive biomarkers adversely affects the ability to rapidly detect and treat CKD. Treatment of CKD in the early stages may improve renal function and/or slow the progression of CKD [1].

In clinical practice, renal impairment is still assessed by serum creatinine, cystatin C and albuminuria, as well as by the value of GFR, which is determined by various equations. There is a nonlinear correlation between creatinine, cystatin C and GFR: relatively small initial increases in these markers are defined as a significant decrease in GFR [1, 8].

For example, approximately 30 % of patients with diabetic kidney disease have normal urinary albumin levels. Or it may be absent in hypertensive or tubulointerstitial kidney disease. Albuminuria occurs before the GFR begins to decline. At the same time, the concentration of creatinine in the serum begins to increase when approximately 40–50 % of the renal parenchyma is damaged [1].

Therefore, the diagnosis of early stages of CKD is not effective enough. Several alternative markers have been studied, namely β_2-microglobulin, KIM-1 (kidney injury molecule-1), NGAL (lipocalin associated with neutrophil gelatinase) and L-FABP (liver fatty acid binding protein) [1, 9, 19–31].

Damage to the proximal tubules plays an important role in the progression of CKD [1]. Therefore, markers of damage to the proximal tubules of the kidneys are of greatest interest. In addition to KIM-1, NGAL, and L-FABP, there are less studied markers such as UMOD, Klotho protein, and posttranslational modifications of FtA (see table 3).

Table 1. Prognosis of CKD, based on the categories of GFR and albuminuria: KDIGO 2012

				Categories of persistent albuminuria		
				A1	A2	A3
				Normal or slightly elevated	Moderately elevated	sharply elevated
				< 30 mg/g; < 3 mg/mmol	30–300 mg/g; 3–30 mg/mmol	> 300 mg/g; > 30 mg/mmol
Categories of GFR (ml/min/1.73 m²)	C1	Normal or high	≥ 90	Low risk*	Moderate risk	High risk
	C2	Slightly reduced	60–89	Low risk	Moderate risk	High risk
	C3a	Moderately reduced	45–59	Moderate risk	High risk	Very high risk
	C3b	Significantly reduced	30–44	High risk	Very high risk	Very high risk
	C4	Sharply reduced	15–29	Very high risk	Very high risk	Very high risk
	C5	Renal failure	< 15	Very high risk	Very high risk	Very high risk

Note: * — in the absence of other markers of kidney damage or CKD.

Table 2. Klotho signaling pathways and effects in pathological conditions [86]

Genetic modification/ soluble protein	Exiperimental animals	*In vitro/in vivo*	Disease/ pathological condition	Signal pathways that are involved in the implementation of the effect	Obtained effects
1	2	3	4	5	6
Soluble protein	Mice	*In vivo*	Stress-induced apoptosis in cardiomyocytes	Inhibition of p38, JNK	Inhibition of stress and apoptosis of the endoplasmic reticulum
Soluble protein	Mice	*In vivo*	Cardiac hypertrophy, experimental hypertension with Klotho deficiency	Inhibition of calcium channel, TRPC6, FGFR1	Prevention of hypertrophy, normalization of blood pressure

The ending table 2

1	2	3	4	5	6
Soluble protein	Mice, H9c2 cells and neonatal cardiomyocytes	*In vivo, in vitro*	Damage to the heart muscle caused by hyperglycemia	Inhibition of fibrosis, oxidative stress, mitochondrial dysfunction and inhibition of inflammation induced by activation of NF-κB and ROS	Prevention of heart muscle damage
Soluble protein	Mice db/db (model of type 2 diabetes)	*In vivo*	High systolic pressure, fibrosis and renal hypertrophy, hyperglycemia	Enhanced Klotho and superoxide dismutase expression, inhibition of fibronectin, HIF, TGF-β1 and TNF-α expression, renal phosphorylation of mTOR and Akt	Prevention of renal fibrosis and normalization of blood pressure
Soluble protein	Mice db/db (model of type 2 diabetes)	*In vivo*	Hyperglycemia		Partial normalization of sugar levels, increased insulin secretion
Soluble protein	Mice	*In vivo*	Diabetes mellitus is induced by the introduction of streptozotocin		Prevention of apoptosis in β-cells of the pancreas
Soluble protein	Mice db/db	*In vivo*	Diabetes	Klotho deficiency is accompanied by activation of NF-κB	Klotho deficiency is accompanied by inflammatory processes in the kidneys
Soluble protein/ KL1 domain	Immunodeficient Mice nude	*In vivo, in vitro*	Human breast cancer	Inhibition of IGF-1 binding to its receptor	Inhibits the development of tumors *in vivo* and the growth of cancer cells in culture
Soluble protein/ KL1 domain	Mice	*In vivo, in vitro*	Pancreatic cancer	Modulation of bFGF and IGF-I signaling pathways	Inhibits the proliferation of cancer cells *in vitro*
Genetic modification ratsratsrats	Rats	*In vivo*	Diabetes mellitus is induced by the introduction of streptozotocin	Inhibition of Rho-associated coiled-coil kinase	Prevents kidney fibrosis, renal hypertrophy
Genetic modification	Mice	*In vivo*	Demyelination	Inhibition of Akt and ERK	Intensification of remyelination
Genetic modification	Mice	*In vivo*	Cognitive impairment, epileptic activity	Increases the expression of GluN2B subunits of NMDA receptors	Decrease in frequency of epileptic seizures, increase in spatial memory
Genetic modification/transfection	Human mesangial cells	*in vitro*	Hyperglycemia	Inhibition of Egr-1, TGFβ1/ SMAD3 signaling pathway	Inhibits fibrotic processes

Notes: p38 — mitogen-activated protein kinase; JNK — N-terminal kinase c-Jun; GluN2B — ionotropic glutamate receptor (NMDA 2B); NMDA — N-methyl-D-aspartate; Akt — protein kinase B; ERK — extracellular signal-regulated kinase; IGF-1 — insulin-like growth factor 1; bFGF — basic fibroblast growth factor; Egr-1 — early transcription transcription factor growth-1; SMAD3 — mother against decapentaplegic homologue 3; NF-κB — nuclear kappa factor B; HIF — hypoxia-induced factor 1; TGF-β1 — transforming growth factor beta 1; TNF-α — tumor necrosis factor alpha; mTOR — mechanical target of rapamycin; ROS — reactive oxygen species; TRPC6 — canonical transient receptor potential 6; FGFR1 — fibroblast growth factor receptors 1; KL — extracellular domain of α-Klotho protein.

Table 3. Diagnosis of CKD depending on the presence of markers of damage and functional status of the kidneys (E.M. Shilov, 2012)

GFR, ml/min/1.73 m²	Markers of damage of the kidneys	
	Yes	No
≥ 90	CKD	Norm
60–89	CKD	Risk group
< 60	CKD	CKD

What do we know about these markers?

UMOD. There is evidence that this protein was first described by Carlo Rovida in 1873. [32] But scientifically, the Tamma-Horsvall protein was discovered by Horsvall and Tamma in 1950, when a study of viral hemagglutination in the urine revealed a protein that inhibits viral hemegglutination. In 1985 it was rediscovered by Decker and Muchmore as an immunomodulatory glycoprotein, and in 1987 Pennica et al. identified the primary structure of UMOD, which showed that UMOD is similar to the Tamm-Horsfall protein [33–36].

It is the most common protein in the urine of a healthy person. UMOD is an acidic protein with a mass of 90 kDa, which has a low isoelectric point (pI 5.00). It is synthesized exclusively by the uroepithelium, which lines the thick ascending limb of Henle's loop (Tal) and the distal tubules [33, 35–41]. UMOD is involved in the regulation of apical transport systems, in Tal and in the initial segment of the distal convoluted tubule, affecting salt reabsorption [33, 35, 38, 42–44].

The predominant amount of UMOD is excreted in the urine, in the interstitium of the kidneys, the expression of UMOD is negligible [36, 45, 46]. In the lumen of the urinary tract, UMOD monomers form homopolymer filaments that encapsulate and aggregate uropathogens (type 1 fibrous *Escherichia coli*) and are excreted in the urine [33]. UMOD is an important regulatory protein of innate immunity that can bind complement fragments [47–50].

UMOD is a structurally homopolymeric glycoprotein that prevents the adhesion of a bacterial pathogen. The C-terminal module of the UMOD transparent zone mediates its polymerization. There is no detailed information about the N-terminal region of the UMOD branch. It is assumed that it has a domain with eight cysteines [51, 52].

In addition to the classical apical release, UMOD is sorted to a lesser extent into the basolateral domain of tubular epithelial cells, where it is released into the interstitium, and from there enters the bloodstream [36, 38, 53, 54]. The circulating form of UMOD is predominantly monomeric, as presented by Micanovic et al. (see figure 1).

The concentration of UMOD in the serum compared to urine is much lower (20–50 ng/ml vs. 20–50 mcg/ml, respectively) [36]. Serum UMOD (sUmod) can reflect the functional mass of the nephron [38, 55, 56]. In circulating UMOD, there is a linear correlation with the GFR of patients with CKD, which may help in the diagnosis of early stages of renal damage when creatinine levels are still within normal limits [38, 57–61]. According to scientific studies, the half-life of UMOD with urine is approximately 16 hours, but the range of fluctuations is large, from 3 hours to 7 days [38]. Hepsin plays an important role in the polymerization and processing of UMOD [44].

UMOD is a multifunctional protein that plays an important role not only in urinary but also in systemic homeostasis. It has been suggested that UMOD is another hormone-like peptide that forms systemic immunity and inflammatory signal balance, and also acts as a regulator of oxidative stress [36, 38, 62, 63]. Recent in vitro studies have shown that UMOD inhibits monocyte function, viral hemagglutination, and antigen-mediated T cell proliferation [64]. It is involved in the regulation of chemotaxis, phagocytosis and apoptosis, has a positive effect on transepithelial migration of neutrophils (through specific receptors on the cell surface) [64, 65].

Studies suggest that UMOD is involved in the protection of the urinary tract from infections and stone formation [66–68], in the regulation of salt transport, in kidney damage and innate immunity [41, 69–71]. Rare missense mutations in the UMOD gene are the most common cause of autosomal dominant tubulointerstitial kidney disease, which is characterized by tubular damage and the development of interstitial fibrosis and no glomerular damage, with the addition of renal failure. The mechanism of damage and development of fibrosis is associated with the accumulation of intracellular aggregates of mutant UMOD in Tal [33, 36, 40, 72–76].

In the lumen of the tubules UMOD forms high molecular weight threads, which are part of the hyaline cylinders. UMOD is prone to increased glycation (up to 30–40 % of its molecular weight). Structural and functional changes in protein can cause kidney and urinary tract disease. Changing the glycosylation profile of UMOD makes it a potential biomarker of renal health [36, 77–80]. UMOD levels in urine and serum reflect the number of intact nephrons [38].

Klotho protein. Professor Makoto Kuro-O and a group of scientists in 1997 discovered the Klotho gene, which inhibits aging. It was named after the goddess of ancient Greek mythology, who spun the thread of life. A year later, Y. Matsumura et al. on chromosome 13q12, in humans, the α-Klotho gene was identified [15, 81, 82].

Studies have shown that simulated overexpression of the Klotho gene inhibits the phenotypic manifestations of aging and increases life expectancy. The Klotho gene is one of the "anti-aging" genes [82, 83].

Klotho protein was later found to have three isoforms α, β and γ [84, 85]. Chromosome 4 contains an incomplete copy of the Klotho gene with a similar nucleotide sequence called β-Klotho [82].

The β-Klotho gene encodes a single-pass transmembrane protein, which is predominantly expressed in the pancreas, white adipose tissue, and liver, and is involved in the regulation of bile acid synthesis by fibroblast growth factor (FGF) [82]. γ-Klotho (clotho/lactase-florizine) is a lactose-like protein found in the kidneys, brown adipose tissue and eye structures. The function of the γ-Klotho protein is still unclear [85, 86].

The Klotho gene is expressed mainly in the distal convoluted tubules of the kidneys and the epithelial cells of the vascular plexus in the brain. This gene is determined in other organs, but in low concentrations [15].

Cells that express the Klotho gene: uroepithelium of the distal tubules of the kidneys, epithelial cells of the vascular plexus, as well as cells of the pituitary gland, pancreas, parathyroid glands, prostate, placenta, heart, aorta, bladder, skeletal muscles, colon and small intestine, ovaries and testicles [15, 82].

The Klotho gene has 5 exons, 4 introns and encodes the Klotho protein, which has two forms, secretory and trans-

membrane [82, 87]. Two transcripts are formed by alternative RNA splicing, which encode the secretory and membrane forms of the Klotho protein [15].

The membrane form of the Klotho protein has transmembrane, intracellular and extracellular domains. Matrix metalloproteinases of the ADAM family (A Disintegrin And Metalloproteinase) cleave 10 and 17 extracellular domains that enter the extracellular space. This is a soluble form of Klotho protein [15].

The Klotho gene encodes the Klotho transmembrane peptide, which is a required co-receptor for FGF-23, a hormone required for the regulation of parathyroid hormone, phosphorus, and vitamin D [83, 88]. By stimulating renal phosphate excretion and reducing serum dihydroxyvitamin D_3, it induces a negative phosphate balance [84, 89, 90].

There are 3 members of the Klotho family: transmembrane proteins of different lengths. Soluble forms of Klotho can be obtained by proteolytic cleavage of the transmembrane form by β-secretases [91].

In humans, the transmembrane form of the Klotho protein is located in the cell membrane and Golgi apparatus, consists of 1012 amino acids, has a molecular weight of ~ 130 kDa, and includes 3 domains: extracellular domain and transmembrane domain with a short cytoplasmic domain at the C-terminus, and has a signal sequence at the N-end [82, 91].

The extracellular domain has two regions of internal repeats (KL1 and KL2) of homologous β-glucosidase sequences with sequence coincidence from 20 to 40 %, the short intracellular domain has a length of 10 amino acids [82, 91].

It has been suggested that a site involved in transmembrane cleavage is located between sites KL1 and KL2. In humans, the secretory form of the protein, which consists of 549 amino acids, predominates. The secretory form is a circulating humoral factor [82] (see figure 2).

Studies have shown that in adults aged 20 years and older, the concentration of Klotho protein in the serum ranged from 239 to 1266 pg/ml [15].

It has been suggested that the Klotho protein inhibits aging by inhibiting intracellular insulin/insulin-like growth factor 1 signaling pathway. Reduction of oxidative stress with increasing levels of Klotho protein, due to inhibition of the p53/p21 pathway is a mechanism that slows aging and oncogenesis [15, 92, 93].

There are several potential mechanisms that contribute to the antifibrotic effect of Klotho in CKD, such as its inhibition of intracellular signaling Wnt, FGF23 and transforming growth factor (TGF-β) [5, 11, 94–97].

Its greatest expression is observed in the distal tubules of the kidneys [88]. Circulating levels of Klotho (soluble α-Klotho) are due to the extracellular domain of the Klotho protein and are thought to be a surrogate marker of Klotho expression in the kidney and the functional number of nephrons [83, 88].

Soluble Klotho affects endothelial function, oxidative stress, aging, and cell apoptosis [88]. Decreased Klotho gene expression and Klotho protein secretion have been reported in patients with CKD, coronary heart disease, and diabetes mellitus [82]. Klotho whey protein levels decrease with age [15].

FtA. Pedersen first described FtA in 1944 and gave it its name from the Latin word fetus because of its high amount in fetal calf serum. Later, a multifunctional phosphorylated glycoprotein (also known as Alpha-2-Geremans-Schmid) was discovered by Schmidt, Heremans, and Burgess in 1961 [99–102]. It is a protein consisting of a long chain A (282 amino acids) and a short chain B (27 amino acids) connected by a short chain of 40 amino acids and weighing 52 to 60 kDa [99, 101–103].

During fetal development, FtA expression is detected in all major organs and the vascular plexus [98,99]. In serum, the concentration of FtA ranges from 0.4 to 1.0 g/l [98, 100]. FtA is synthesized mainly (> 95%) in the liver (named hepatokin), can be synthesized in the kidneys, accumulates in large quantities in calcified bone, blood and cerebrospinal fluid [98, 99, 103].

FtA has an effect on energy homeostasis, cell growth, adipocytes and inflammation (can be both positive and negative acute phase protein), interacts with the insulin

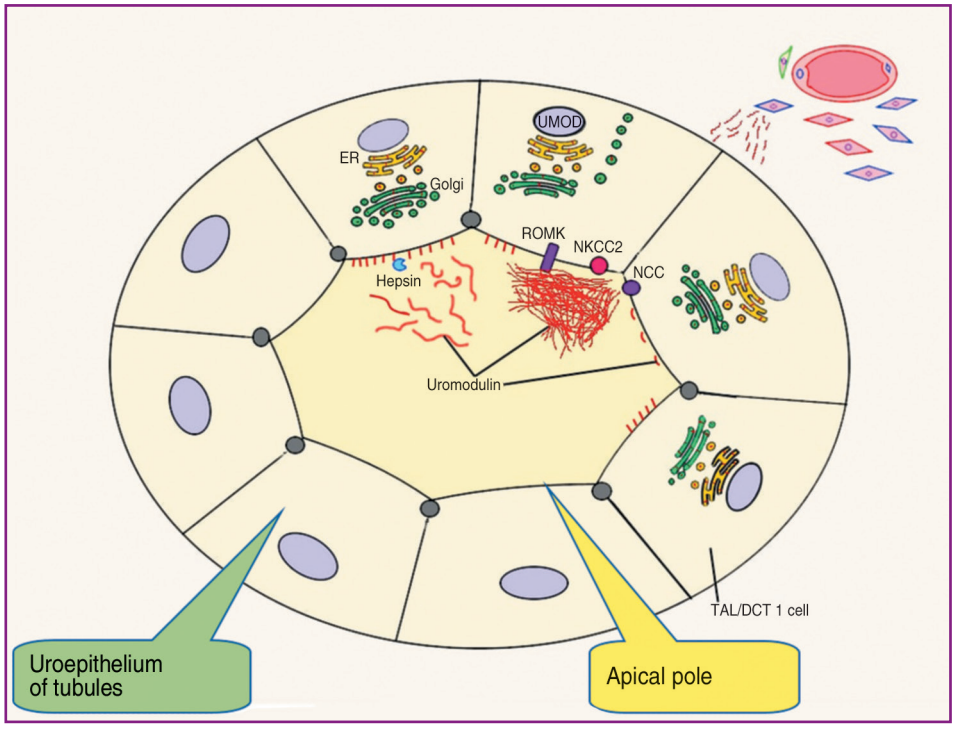

Figure 1

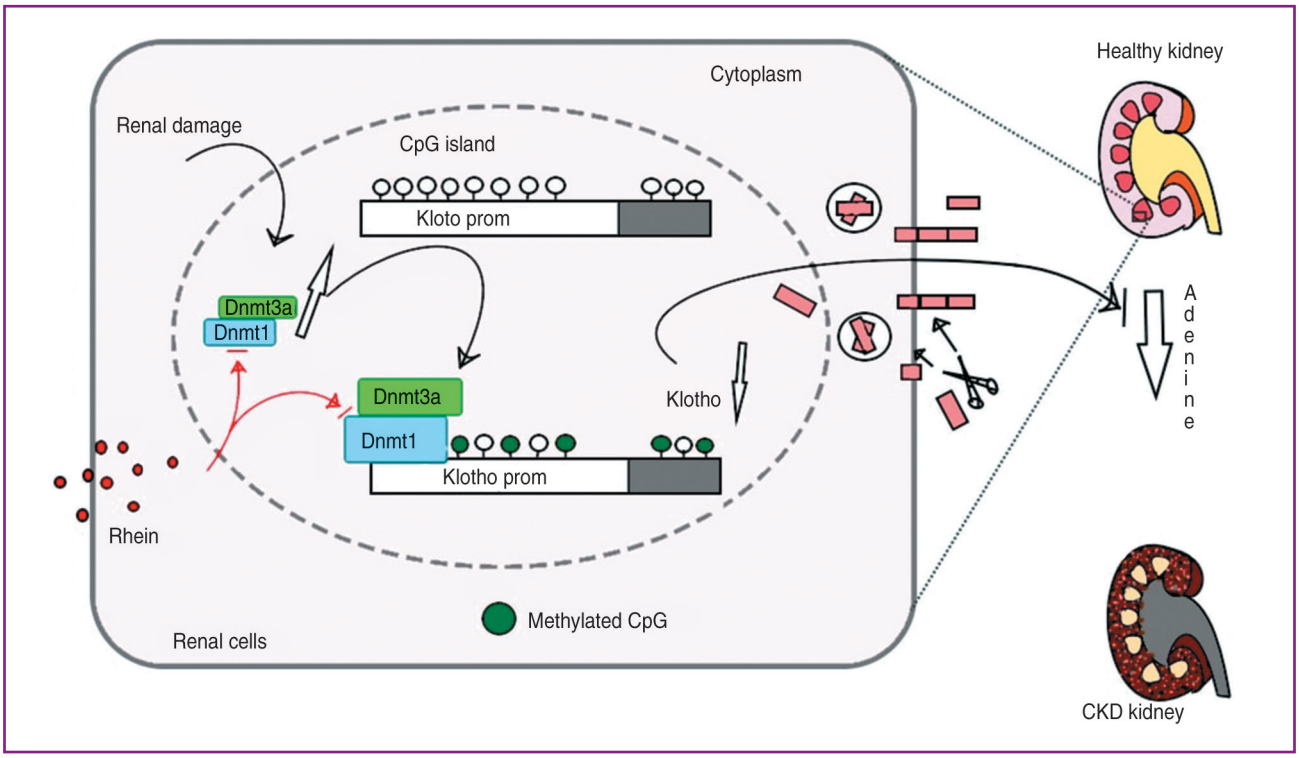

Figure 2

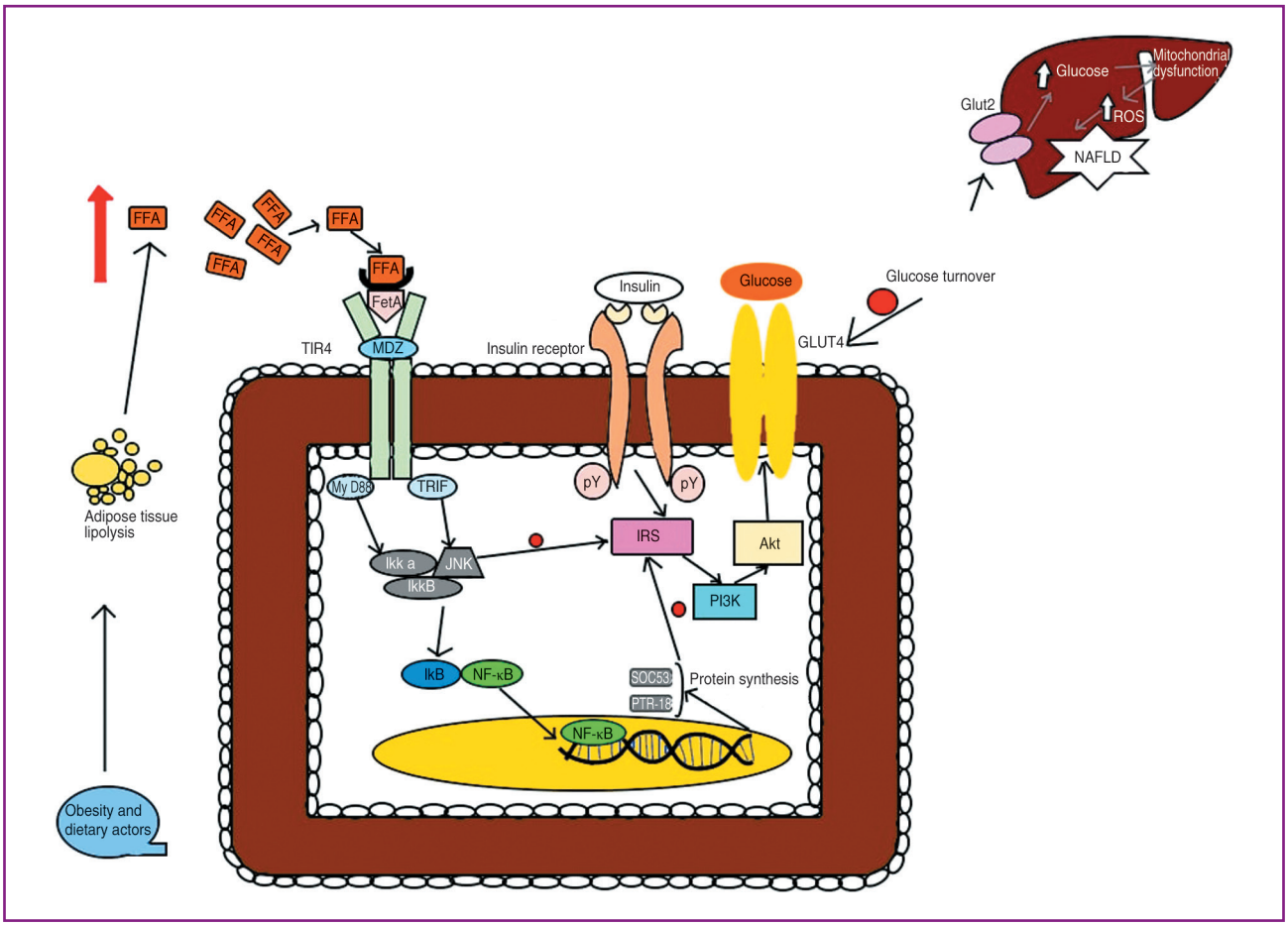

Figure 3

receptor by inhibiting its tyrosine kinase [99, 100, 104–113]. It is an indirect regulator of inflammation, calcification, polarization of macrophages and fibrosis in tissues [98, 108, 114–119].

In the late 1970s, LeBreton and colleagues discovered that FtA is one of the major negative proteins in the acute phase. The emergence of short isoforms of C/EBP transcription factor, which can not maintain the basal activity of the liver promoter compared with long isoforms of C/EBP, which predominate in hepatocytes at rest [98].

Occupies an important place in the prevention of renal lithogenesis and coronary heart disease by inhibiting excessive mineralization [99, 120–124]. FtA due to its ability to inhibit apoptosis and enhance phagocytosis of apoptotic residues reduces mineralization stress [98, 125–128].

Also, FtA is a transport protein for phosphate and calcium, which plays an important role in bone mineralization, through the binding of small clusters of phosphate and calcium, thereby preventing their growth, aggregation and loss of minerals, preventing cells from absorbing these soluble protein-mineral colloids. known as calciprotein particles (consisting of calciprotein monomers) [98, 104, 105, 129–133].

The mineral binding site, in FtA, is located in the N-terminal cystatin-like domain of CY1 [98]. Small calcium phosphate complexes (Posner clusters) are a better FtA ligand than ionic calcium [98]. *In vivo* and *in vitro* studies have shown a direct effect of elevated phosphate levels on endothelial function [134].

For saturated fatty acids, FtA is an adapter protein (endogenous ligand) by which they activate Toll-like receptor 4 [105, 108]. FtA plays an important role in the binding of minerals, lectins (including galectin-3) [108, 135–137] or lipids, is involved in inhibiting the signal transmission to beta-growth factor or anthonization of insulin receptors [98, 108, 138]. FtA is a necessary cofactor in inhibiting the expression of proinflammatory cytokine, tumor necrosis factor, together with spermidine, activating the accumulation of triacylglycerol and NF-κB [98, 108] (see figure 3).

FtA, like Fetuin-B, which is rich in histidine, kininogen, and glycoprotein, belongs to the type 3 cystatins family, which is a cysteinpeptidase inhibitor [98]. To date, no specific target peptidase for FtA has been identified [98].

FtA undergoes significant posttranslational modifications, which include proteolytic processing from single-chain precursor to circulating double-chain protein complex, N- and O-glycosylation, sulfation and phosphorylation of threonine and serine, which affect its activity and stability [98, 101, 102, 139].

Conclusions

Early diagnosis of CKD, identification of patients in whom it may progress to end-stage renal disease, are relevant and very important. Indicators, including creatinine levels, estimated GFR and proteinuria, do not fully meet clinical needs. Therefore, new biomarkers are needed to assess CKD progression. And not one biomarker, but a combination of different biomarkers. Thus, as we see, markers of kidney damage such as UMOD, Klotho protein, FtA are relevant today, and not only for early diagnosis, they can be the basis for the development of new drugs in nephrology for the treatment of patients with CKD, including , and diabetic nephropathy. These biomarkers are characterized by the detection of early damage, localization of damage. They give an estimate concerning further progression of the disease, severity and death [140].

References

1. *Benjamin O, Lappin SL. End-Stage Renal Disease. 2021 Sep 16. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–.*
2. *Mizdrak M, Kumrić M, Kurir TT, Božić J. Emerging Biomarkers for Early Detection of Chronic Kidney Disease. J Pers Med. 2022 Mar 31;12(4):548. doi: 10.3390/jpm12040548.*
3. *Catanese L, Siwy J, Mavrogeorgis E, et al. A Novel Urinary Proteomics Classifier for Non-Invasive Evaluation of Interstitial Fibrosis and Tubular Atrophy in Chronic Kidney Disease. Proteomes. 2021 Jul 13;9(3):32. doi: 10.3390/proteomes9030032.*
4. *Kovalenko VM, editor. Internal Medicine. Textbook for students of institutions of higher medical education of III-IV level of accreditation and doctors of postgraduate education based on the recommendations of evidence-based medicine. Kyiv: Morion; 2019. 960 p.*
5. *Yuan Q, Ren Q, Li L, et al. A Klotho-derived peptide protects against kidney fibrosis by targeting TGF-β signaling. Nat Commun. 2022 Jan 21;13(1):438. doi: 10.1038/s41467-022-28096-z.*
6. *Yin T, Chen Y, Tang L, Yuan H, Zeng X, Fu P. Relationship between modifiable lifestyle factors and chronic kidney disease: a bibliometric analysis of top-cited publications from 2011 to 2020. BMC Nephrol. 2022 Mar 25;23(1):120. doi: 10.1186/s12882-022-02745-3.*
7. *Petra E, Siwy J, Vlahou A, Jankowski J. Urine peptidome in combination with transcriptomics analysis highlights MMP7, MMP14 and PCSK5 for further investigation in chronic kidney disease. PLoS One. 2022 Jan 19;17(1):e0262667. doi: 10.1371/journal.pone.0262667.*
8. *Šalamon Š, Bevc S, Ekart R, Hojs R, Potočnik U. Polymorphism in the GATM Locus Associated with Dialysis-Independent Chronic Kidney Disease but Not Dialysis-Dependent Kidney Failure. Genes (Basel). 2021 May 28;12(6):834. doi: 10.3390/genes12060834.*
9. *Będzichowska A, Jobs K, Kloc M, Bujnowska A, Kalicki B. The Assessment of the Usefulness of Selected Markers in the Diagnosis of Chronic Kidney Disease in Children. Biomark Insights. 2021 Apr 20;16:11772719211011173. doi: 10.1177/11772719211011173.*
10. *Gan Y, Zhao M, Feng J. Association of fetuin-A levels and left ventricular diastolic dysfunction in patients on haemodialysis. Int Urol Nephrol. 2021 Aug;53(8):1689-1694. doi: 10.1007/s11255-021-02796-9.*
11. *Panizo S, Martínez-Arias L, Alonso-Montes C, et al. Fibrosis in Chronic Kidney Disease: Pathogenesis and Consequences. Int J Mol Sci. 2021 Jan 2;22(1):408. doi: 10.3390/ijms22010408.*
12. *Ludes PO, de Roquetaillade C, Chousterman BG, Pottecher J, Mebazaa A. Role of Damage-Associated Molecular Patterns in Septic Acute Kidney Injury, From Injury to Recovery. Front Immunol. 2021 Mar 1;12:606622. doi: 10.3389/fimmu.2021.606622.*

13. Lavainne F, Guillot P, Figueres L. Chronic kidney disease - Mineral bone disorders: Physiopathology and guidelines. Rev Med Interne. 2022 Apr;43(4):225-232. French. doi: 10.1016/j.revmed.2022.01.009.

14. Goyal R, Jialal I. Hyperphosphatemia. 2021 Sep 28. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–.

15. Tomo S, Birdi A, Yadav D, Chaturvedi M, Sharma P. Klotho: A Possible Role in the Pathophysiology of Nephrotic Syndrome. EJIFCC. 2022 Apr 11;33(1):3-10.

16. Turek M, Stępniewska J, Różański J. The Multifactorial Pathogenesis of Calciphylaxis: A Case Report. Am J Case Rep. 2021 Jun 7;22:e930026. doi: 10.12659/AJCR.930026.

17. Nseir V, Bradauskaite G, Pedroza M, Minimo C, Zaki R, Chewaproug D. A Rare Case of Calciphylaxis in an Orthotopic Liver Transplant Recipient with Acute Kidney Injury. Exp Clin Transplant. 2021 Apr;19(4):382-385. doi: 10.6002/ect.2017.0123.

18. Whitehead M, Shanahan CM. Circulating uromodulin: a cytokine trap for osteoinductive inflammatory mediators in chronic kidney disease? Cardiovasc Res. 2021 Feb 22;117(3):651-652. doi: 10.1093/cvr/cvaa348.

19. Correll VL, Otto JJ, Risi CM, et al. Optimization of small extracellular vesicle isolation from expressed prostatic secretions in urine for in-depth proteomic analysis. J Extracell Vesicles. 2022 Feb;11(2):e12184. doi: 10.1002/jev2.12184.

20. Tran AC, Melchinger H, Weinstein J, et al. Urine testing to differentiate glomerular from tubulointerstitial diseases on kidney biopsy. Pract Lab Med. 2022 Apr 6;30:e00271. doi: 10.1016/j.plabm.2022.e00271.

21. Wen Y, Parikh CR. Current concepts and advances in biomarkers of acute kidney injury. Crit Rev Clin Lab Sci. 2021 Aug;58(5):354-368. doi: 10.1080/10408363.2021.1879000.

22. Ix JH, Shlipak MG. The Promise of Tubule Biomarkers in Kidney Disease: A Review. Am J Kidney Dis. 2021 Nov;78(5):719-727. doi: 10.1053/j.ajkd.2021.03.026.

23. Puthumana J, Thiessen-Philbrook H, Xu L, et al. Biomarkers of inflammation and repair in kidney disease progression. J Clin Invest. 2021 Feb 1;131(3):e139927. doi: 10.1172/JCI139927.

24. You R, Zheng H, Xu L, et al. Decreased urinary uromodulin is potentially associated with acute kidney injury: a systematic review and meta-analysis. J Intensive Care. 2021 Nov 15;9(1):70. doi: 10.1186/s40560-021-00584-2.

25. Chang C, Obeid W, Thiessen-Philbrook H, Parikh CR. Sample Processing and Stability for Urine Biomarker Studies. J Appl Lab Med. 2021 Nov 1;6(6):1628-1634. doi: 10.1093/jalm/jfab082.

26. Obert LA, Elmore SA, Ennulat D, Frazier KS. A Review of Specific Biomarkers of Chronic Renal Injury and Their Potential Application in Nonclinical Safety Assessment Studies. Toxicol Pathol. 2021 Jul;49(5):996-1023. doi: 10.1177/0192623320985045.

27. Rudnicki M, Siwy J, Wendt R, et al; PERSTIGAN working group. Urine proteomics for prediction of disease progression in patients with IgA nephropathy. Nephrol Dial Transplant. 2021 Dec 31;37(1):42-52. doi: 10.1093/ndt/gfaa307.

28. Mukhin N, Konoplev G, Oseev A, et al. Label-Free Protein Detection by Micro-Acoustic Biosensor Coupled with Electrical Field Sorting. Theoretical Study in Urine Models. Sensors (Basel). 2021 Apr 6;21(7):2555. doi: 10.3390/s21072555.

29. Ascher SB, Scherzer R, Estrella MM, et al; SPRINT research group. Kidney tubule health, mineral metabolism, and adverse events in persons with CKD in SPRINT. Nephrol Dial Transplant. 2021 Sep 2:gfab255. doi: 10.1093/ndt/gfab255.

30. Bullen AL, Katz R, Jotwani V, et al. Biomarkers of Kidney Tubule Health, CKD Progression, and Acute Kidney Injury in SPRINT (Systolic Blood Pressure Intervention Trial) Participants. Am J Kidney Dis. 2021 Sep;78(3):361-368.e1. doi: 10.1053/j.ajkd.2021.01.021.

31. van Duijl TT, Ruhaak LR, Smit NPM, et al. Development and Provisional Validation of a Multiplex LC-MRM-MS Test for Timely Kidney Injury Detection in Urine. J Proteome Res. 2021 Dec 3;20(12):5304-5314. doi: 10.1021/acs.jproteome.1c00532.

32. You R, Chen L, Xu L, et al. High Level of Uromodulin Increases the Risk of Hypertension: A Mendelian Randomization Study. Front Cardiovasc Med. 2021 Sep 1;8:736001. doi: 10.3389/fcvm.2021.736001.

33. Joseph CB, Mariniello M, Yoshifuji A, et al. Meta-GWAS Reveals Novel Genetic Variants Associated with Urinary Excretion of Uromodulin. J Am Soc Nephrol. 2022 Mar;33(3):511-529. doi: 10.1681/ASN.2021040491.

34. Holzmann-Littig C, Renders L, Steubl D. Uromodulin - a new marker of kidney function? Clin Nephrol. 2021 Jun;95(6):347-349. doi: 10.5414/CN110303.

35. Wang J, Liu L, He K, Gao B, Wang F, Zhao M, Zhang L, On Behalf Of The Chinese Cohort Study Of Chronic Kidney Disease C-Stride. UMOD Polymorphisms Associated with Kidney Function, Serum Uromodulin and Risk of Mortality among Patients with Chronic Kidney Disease, Results from the C-STRIDE Study. Genes (Basel). 2021 Oct 23;12(11):1687. doi: 10.3390/genes12111687.

36. Denova LD. Uromodulin as a potential candidate marker for predicting the course of chronic kidney disease. Pocki. 2021;10(4):237-243.doi: 10.22141/2307-1257.10.4.2021.247898.

37. Franceschini N, Le TH. Urine Uromodulin and Genetics of its Variation. J Am Soc Nephrol. 2022 Mar;33(3):461-462. doi: 10.1681/ASN.2022010027.

38. Chan J, Svensson M, Tannæs TM, Waldum-Grevbo B, Jenssen T, Eide IA. Associations of Serum Uromodulin and Urinary Epidermal Growth Factor with Measured Glomerular Filtration Rate and Interstitial Fibrosis in Kidney Transplantation. Am J Nephrol. 2022;53(2-3):108-117. doi: 10.1159/000521757.

39. Then C, Herder C, Then H, et al. Serum uromodulin is inversely associated with biomarkers of subclinical inflammation in the population-based KORA F4 study. Clin Kidney J. 2020 Sep 6;14(6):1618-1625. doi: 10.1093/ckj/sfaa165.

40. Then C, Then HL, Lechner A, et al. Serum uromodulin and decline of kidney function in older participants of the population-based KORA F4/FF4 study. Clin Kidney J. 2020 May 1;14(1):205-211. doi: 10.1093/ckj/sfaa032.

41. Mary S, Boder P, Rossitto G, et al. Salt loading decreases urinary excretion and increases intracellular accumulation of uromodulin in stroke-prone spontaneously hypertensive rats. Clin Sci (Lond). 2021 Dec 22;135(24):2749-2761. doi: 10.1042/CS20211017.

42. Alesutan I, Luong TTD, Schelski N, et al. Circulating uromodulin inhibits vascular calcification by interfering with pro-inflammatory cytokine signalling. Cardiovasc Res. 2021 Feb 22;117(3):930-941. doi: 10.1093/cvr/cvaa081.

43. Ponte B, Pruijm M, Ackermann D, et al. Uromodulin, Salt, and 24-Hour Blood Pressure in the General Population. Clin J Am Soc Nephrol. 2021 May 8;16(5):787-789. doi: 10.2215/CJN.11230720.

44. Li S, Wang L, Sun S, Wu Q. Hepsin: a multifunctional transmembrane serine protease in pathobiology. FEBS J. 2021 Sep;288(18):5252-5264. doi: 10.1111/febs.15663.

45. Nanamatsu A, Mori T, Ando F, et al. Vasopressin Induces Urinary Uromodulin Secretion By Activating PKA (Protein Kinase A). Hypertension. 2021 Jun;77(6):1953-1963. doi: 10.1161/HYPERTENSIONAHA.121.17127.

46. Turner M, Staplin N. UMOD-ulating CKD risk: untangling the relationship between urinary uromodulin, blood pressure, and kidney disease. Kidney Int. 2021 Dec;100(6):1168-1170. doi: 10.1016/j.kint.2021.09.019.

47. Singh G, Gohh R, Clark D, et al. Vignette-Based Reflections to Inform Genetic Testing Policies in Living Kidney Donors. Genes (Basel). 2022 Mar 26;13(4):592. doi: 10.3390/genes13040592.

48. Shen F, Liu M, Pei F, Yu L, Yang X. Role of uromodulin and complement activation in the progression of kidney disease. Oncol Lett. 2021 Dec;22(6):829. doi: 10.3892/ol.2021.13090.

49. Yu L, Pei F, Sun Q, et al. Uromodulin aggravates renal tubulointerstitial injury through activation of the complement pathway in rats. J Cell Physiol. 2021 Jul;236(7):5012-5021. doi: 10.1002/jcp.30208.

50. Bai L, Xie Q, Xia M, et al. The importance of sialic acid, pH and ion concentration on the interaction of uromodulin and complement factor H. J Cell Mol Med. 2021 May;25(9):4316-4325. doi: 10.1111/jcmm.16492.

51. Stsiapanava A, Xu C, Nishio S, et al. Structure of the decoy module of human glycoprotein 2 and uromodulin and its interaction with bacterial adhesin FimH. Nat Struct Mol Biol. 2022 Mar;29(3):190-193. doi: 10.1038/s41594-022-00729-3.

52. Micanovic R, LaFavers KA, Patidar KR, et al. The kidney releases a nonpolymerizing form of uromodulin in the urine and circulation that retains the external hydrophobic patch domain. Am J Physiol Renal Physiol. 2022 Apr 1;322(4):F403-F418. doi: 10.1152/ajprenal.00322.2021.

53. Abdelsalam M, Motawea M, Kyrillos F, Abdel-Razik A, Zaki MES, Abdel-Wahab A. Study of Uromodulin Gene Polymorphism in Egyptian Patients with End-Stage Renal Disease. Saudi J Kidney Dis Transpl. 2021 Jan-Feb;32(1):157-162. doi: 10.4103/1319-2442.318517.

54. Mansour SG, Liu C, Jia Y, et al. Uromodulin to Osteopontin Ratio in Deceased Donor Urine Is Associated With Kidney Graft Outcomes. Transplantation. 2021 Apr 1;105(4):876-885. doi: 10.1097/TP.0000000000003299.

55. Usui R, Ogawa T, Takahashi H, et al. Serum uromodulin is a novel renal function marker in the Japanese population. Clin Exp Nephrol. 2021 Jan;25(1):28-36. doi: 10.1007/s10157-020-01964-y.

56. Ponte B, Sadler MC, Olinger E, et al. Mendelian randomization to assess causality between uromodulin, blood pressure and chronic kidney disease. Kidney Int. 2021 Dec;100(6):1282-1291. doi: 10.1016/j.kint.2021.08.032.

57. Enko D, Meinitzer A, Scherberich JE, et al. Individual uromodulin serum concentration is independent of glomerular filtration rate in healthy kidney donors. Clin Chem Lab Med. 2020 Oct 13;59(3):563-570. doi: 10.1515/cclm-2020-0894.

58. Cansever HN, Sari F, Cevikol C, Cetinkaya R, Süleymanlar G, Ersoy F. Serum uromodulin levels, MR imaging findings, and their relationship with eGFR-based CKD staging in ADPKD patients. Int Urol Nephrol. 2021 Jul;53(7):1383-1389. doi: 10.1007/s11255-020-02730-5.

59. Jie C, Yi-Ying Y, Miao C. Correlation of serum uromodulin levels with renal fibrosis and renal function progression in patients with CKD. Pak J Pharm Sci. 2021 Nov;34(6(Special)):2417-2422.

60. Yazdani B, Delgado GE, Scharnagl H, et al. Combined Use of Serum Uromodulin and eGFR to Estimate Mortality Risk. Front Med (Lausanne). 2021 Sep 8;8:723546. doi: 10.3389/fmed.2021.723546.

61. Then C, Herder C, Thorand B, et al; KORA-Study Group. Association of serum uromodulin with adipokines in dependence of type 2 diabetes. Cytokine. 2022 Feb;150:155786. doi: 10.1016/j.cyto.2021.155786.

62. LaFavers K. Disruption of Kidney-Immune System Crosstalk in Sepsis with Acute Kidney Injury: Lessons Learned from Animal Models and Their Application to Human Health. Int J Mol Sci. 2022 Feb 1;23(3):1702. doi: 10.3390/ijms23031702.

63. Jain RB, Ducatman A. Associations between the concentrations of α-klotho and selected perfluoroalkyl substances in the presence of eGFR based kidney function and albuminuria: Data for US adults aged 40-79 years. Sci Total Environ. 2022 May 17:155994. doi: 10.1016/j.scitotenv.2022.155994.

64. Močnik M, Marčun Varda N. Current Knowledge of Selected Cardiovascular Biomarkers in Pediatrics: Kidney Injury Molecule-1, Salusin-α and -β, Uromodulin, and Adropin. Children (Basel). 2022 Jan 13;9(1):102. doi: 10.3390/children9010102.

65. Ray SK, Masarkar N, Mukherjee S. Implications of Klotho Protein for Managing Kidney Disease - an Emerging Role in Therapeutics and Molecular Medicine. Curr Mol Med. 2021;21(6):484-494. doi: 10.2174/1566524020666201120143313.

66. Noonin C, Peerapen P, Yoodee S, Kapincharanon C, Kanlaya R, Thongboonkerd V. Systematic analysis of modulating activities of native human urinary Tamm-Horsfall protein on calcium oxalate crystallization, growth, aggregation, crystal-cell adhesion and invasion through extracellular matrix. Chem Biol Interact. 2022 Apr 25;357:109879. doi: 10.1016/j.cbi.2022.109879.

67. Hasan FT, Mohey MA. Association of genetic polymorphism and expression of UMOD gene and chronic kidney disease. Wiad Lek. 2021;74(9 cz 2):2297-2300.

68. Yang Y, Hong S, Li C, et al S. Proteomic analysis reveals some common proteins in the kidney stone matrix. PeerJ. 2021 Jul 27;9:e11872. doi: 10.7717/peerj.11872.

69. Wang Y, Du MF, Yao Set, al. Associations of Serum Uromodulin and Its Genetic Variants With Blood Pressure and Hypertension in Chinese Adults. Front Cardiovasc Med. 2021 Nov 17;8:710023. doi: 10.3389/fcvm.2021.710023.

70. Du MF, Yao S, Zou T, et al. Associations of plasma uromodulin and genetic variants with blood pressure responses to dietary salt interventions. J Clin Hypertens (Greenwich). 2021 Oct;23(10):1897-1906. doi: 10.1111/jch.14347.

71. Boder P, Mary S, Mark PB, et al. Mechanistic interactions of uromodulin with the thick ascending limb: perspectives in

physiology and hypertension. J Hypertens. 2021 Aug 1;39(8):1490-1504. doi: 10.1097/HJH.0000000000002861.

72. Utami SB, Endo R, Hamada T, et al. Hsp70 promotes maturation of uromodulin mutants that cause familial juvenile hyperuricemic nephropathy and suppresses cellular damage. Clin Exp Nephrol. 2022 Jun;26(6):522-529. doi: 10.1007/s10157-022-02196-y.

73. Shamam YM, Hashmi MF. Autosomal Dominant Tubulointerstitial Kidney Disease. 2022 Apr 16. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–.

74. Bleyer AJ, Wolf MT, Kidd KO, Zivna M, Kmoch S. Autosomal dominant tubulointerstitial kidney disease: more than just HNF1β. Pediatr Nephrol. 2022 May;37(5):933-946. doi: 10.1007/s00467-021-05118-4.

75. Wang D, Qiu Y, Fan J, et al. Upregulation of C/EBP Homologous Protein induced by ER Stress Mediates Epithelial to Myofibroblast Transformation in ADTKD-UMOD. Int J Med Sci. 2022 Jan 24;19(2):364-376. doi: 10.7150/ijms.65036.

76. Schaeffer C, Devuyst O, Rampoldi L. Uromodulin: Roles in Health and Disease. Annu Rev Physiol. 2021 Feb 10;83:477-501. doi: 10.1146/annurev-physiol-031620-092817.

77. Li Y, Cheng Y, Consolato F, et al. Genome-wide studies reveal factors associated with circulating uromodulin and its relations with complex diseases. JCI Insight. 2022 Apr 21:e157035. doi: 10.1172/jci.insight.157035.

78. Beenken A, Al-Awqati Q. Uromodulin fights UTI with sugars. Kidney Int. 2021 May;99(5):1057-1059. doi: 10.1016/j.kint.2020.12.035.

79. Li H, Kostel SA, DiMartino SE, Hashemi Gheinani A, Froehlich JW, Lee RS. Uromodulin Isolation and Its N-Glycosylation Analysis by NanoLC-MS/MS. J Proteome Res. 2021 May 7;20(5):2662-2672. doi: 10.1021/acs.jproteome.0c01053.

80. Patabandige MW, Go EP, Desaire H. Clinically Viable Assay for Monitoring Uromodulin Glycosylation. J Am Soc Mass Spectrom. 2021 Feb 3;32(2):436-443. doi: 10.1021/jasms.0c00317.

81. Liu Q, Li S, Yu L, Yin X, Liu X, Ye J, Lu G. CCL5 Suppresses Klotho Expression via p-STAT3/DNA Methyltransferase1-Mediated Promoter Hypermethylation. Front Physiol. 2022 Mar 1;13:856088. doi: 10.3389/fphys.2022.856088.

82. Gupta M, Orozco G, Rao M, Gedaly R, Malluche HH, Neyra JA. The Role of Alterations in Alpha-Klotho and FGF-23 in Kidney Transplantation and Kidney Donation. Front Med (Lausanne). 2022 May 6;9:803016. doi: 10.3389/fmed.2022.803016.

83. Wu SE, Chen WL. Soluble klotho as an effective biomarker to characterize inflammatory states. Ann Med. 2022 Dec;54(1):1520-1529. doi: 10.1080/07853890.2022.2077428..

84. Jin D, Jia M, Xie Y, Lin L, Qiu H, Lu G. Impact of klotho on the expression of SRGAP2a in podocytes in diabetic nephropathy. BMC Nephrol. 2022 Apr 18;23(1):151. doi: 10.1186/s12882-022-02765-z.

85. Kale A, Sankrityayan H, Anders HJ, Gaikwad AB. Klotho in kidney diseases: A crosstalk between the renin-angiotensin system and endoplasmic reticulum stress. Nephrol Dial Transplant. 2021 Nov 26:gfab340. doi: 10.1093/ndt/gfab340..

86. Nesterova AA, Glinka EYu, Tyurenkov IN, Perfilova VN. Protein Klotho – universal regulator of physiological processes in the organism. Successes of physiological sciences. 2020;51;(2):88-104. doi: 10.31857/S0301179820020083.

87. Li S, Kong J, Yu L, Liu Q. Abnormally decreased renal Klotho is linked to endoplasmic reticulum-associated degradation in mice. Int J Med Sci. 2022 Jan 9;19(2):321-330. doi: 10.7150/ijms.68137.

88. Ciardullo S, Perseghin G. Soluble α-Klotho levels, glycemic control and renal function in US adults with type 2 diabetes. Acta Diabetol. 2022 Jun;59(6):803-809. doi: 10.1007/s00592-022-01865-4.

89. Hu MC, Moe OW. Phosphate and Cellular Senescence. Adv Exp Med Biol. 2022;1362:55-72. doi: 10.1007/978-3-030-91623-7_7.

90. Du C, Wang X, Wu Y, et al. Renal Klotho and inorganic phosphate are extrinsic factors that antagonistically regulate hematopoietic stem cell maintenance. Cell Rep. 2022 Feb 15;38(7):110392. doi: 10.1016/j.celrep.2022.110392.

91. Buchanan S, Combet E, Stenvinkel P, Shiels PG. Klotho, Aging, and the Failing Kidney. Front Endocrinol (Lausanne). 2020 Aug 27;11:560. doi: 10.3389/fendo.2020.00560.

92. Zhao M, Murakami S, Matsumaru D, Kawauchi T, Nabeshima YI, Motohashi H. NRF2 pathway activation attenuates ageing-related renal phenotypes due to α-klotho deficiency. J Biochem. 2022 May 11;171(5):579-589. doi: 10.1093/jb/mvac014.

93. Lehtihet M, Stephanou C, Börjesson A, Bhuiyan H, Pohanka A, Ekström L. Studies of IGF-I and Klotho Protein in Relation to Anabolic-Androgenic Steroid and Growth Hormone Administrations. Front Sports Act Living. 2022 Mar 31;4:829940. doi: 10.3389/fspor.2022.829940.

94. Desbiens LC, Sidib A, Ung RV, Mac-Way F. FGF23-Klotho Axis and Fractures in Patients Without and With Early CKD: A Case-Cohort Analysis of CARTaGENE. J Clin Endocrinol Metab. 2022 May 17;107(6):e2502-e2512. doi: 10.1210/clinem/dgac071.

95. Wu Q, Fan W, Zhong X, Zhang L, Niu J, Gu Y. Klotho/FGF23 and Wnt in SHPT associated with CKD via regulating miR-29a. Am J Transl Res. 2022 Feb 15;14(2):876-887.

96. Isakova T, Yanucil C, Faul C. A Klotho-Derived Peptide as a Possible Novel Drug to Prevent Kidney Fibrosis. Am J Kidney Dis. 2022 Apr 22:S0272-6386(22)00620-5. doi: 10.1053/j.ajkd.2022.03.006.

97. Valiño-Rivas L, Cuarental L, Ceballos MI, et al. Growth differentiation factor-15 preserves Klotho expression in acute kidney injury and kidney fibrosis. Kidney Int. 2022 Jun;101(6):1200-1215. doi: 10.1016/j.kint.2022.02.028.

98. Rudloff S, Jahnen-Dechent W, Huynh-Do U. Tissue chaperoning-the expanded functions of fetuin-A beyond inhibition of systemic calcification. Pflugers Arch. 2022 Apr 11:1–14. doi: 10.1007/s00424-022-02688-6.

99. Icer MA, Yıldıran H. Effects of fetuin-A with diverse functions and multiple mechanisms on human health. Clin Biochem. 2021 Feb;88:1-10. doi: 10.1016/j.clinbiochem.2020.11.004.

100. Bassey PE, Numthavaj P, Rattanasiri S, et al. Causal association pathways between fetuin-A and kidney function: a mediation analysis. J Int Med Res. 2022 Apr;50(4):3000605221082874. doi: 10.1177/03000605221082874.

101. Magalhães P, Zürbig P, Mischak H, Schleicher E. Urinary fetuin-A peptides as a new marker for impaired kidney function in patients with type 2 diabetes. Clin Kidney J. 2020 Oct 23;14(1):269-276. doi: 10.1093/ckj/sfaa176.

102. Kovářová M, Kalbacher H, Peter A, et al. Detection and Characterization of Phosphorylation, Glycosylation, and Fatty Acid Bound to Fetuin A in Human Blood. J Clin Med. 2021 Jan 22;10(3):411. doi: 10.3390/jcm10030411.

103. Umapathy D, Subramanyam PV, Krishnamoorthy E, Viswanathan V, Ramkumar KM. Association of Fetuin-A with Thr256Ser exon polymorphism of α2-Heremans Schmid Glycoprotein (AHSG) gene in type 2 diabetic patients with overt nephropathy. J Diabetes Complications. 2022 Jan;36(1):108074. doi: 10.1016/j.jdiacomp.2021.108074.

104. Jirak P, Stechemesser L, Moré E, et al. Clinical implications of fetuin-A. Adv Clin Chem. 2019;89:79-130. doi: 10.1016/bs.acc.2018.12.003.

105. Birukov A, Polemiti E, Jäger S, Stefan N, Schulze MB. Fetuin-A and risk of diabetes-related vascular complications: a prospective study. Cardiovasc Diabetol. 2022 Jan 8;21(1):6. doi: 10.1186/s12933-021-01439-8.

106. Zhou Z, Chen H, Sun M, Jin H, Ju H. Fetuin-A to adiponectin ratio is an independent indicator of subclinical atherosclerosis in patients with newly diagnosed type 2 diabetes mellitus. J Diabetes Complications. 2022 Jan;36(1):108102. doi: 10.1016/j.jdiacomp.2021.108102.

107. Kothari V, Babu JR, Mathews ST. AMP activated kinase negatively regulates hepatic Fetuin-A via p38 MAPK-C/EBPβ/E3 Ubiquitin Ligase Signaling pathway. PLoS One. 2022 May 6;17(5):e0266472. doi: 10.1371/journal.pone.0266472.

108. Luís C, Soares R, Baylina P, Fernandes R. Underestimated Prediabetic Biomarkers: Are We Blind to Their Strategy? Front Endocrinol (Lausanne). 2022 Mar 7;13:805837. doi: 10.3389/fendo.2022.805837.

109. Ahn MB, Kim SK, Kim SH,. Clinical Significance of the Fetuin-A-to-Adiponectin Ratio in Obese Children and Adolescents with Diabetes Mellitus. Children (Basel). 2021 Dec 8;8(12):1155. doi: 10.3390/children8121155.

110. Harbuwono DS, Sazli BI, Kurniawan F, Darmowidjojo B, Koesnoe S, Tahapary DL. The impact of Ramadan fasting on Fetuin-A level in type 2 diabetes mellitus. Heliyon. 2021 May 15;7(5):e06773. doi: 10.1016/j.heliyon.2021.e06773.

111. Lőrincz H, Csige I, Harangi M, et al. Low Levels of Serum Fetuin-A and Retinol-Binding Protein 4 Correlate with Lipoprotein Subfractions in Morbid Obese and Lean Non-Diabetic Subjects. Life (Basel). 2021 Aug 27;11(9):881. doi: 10.3390/life11090881.

112. Susairaj P, Snehalatha C, Nanditha A, et al. Analysis of an Indian diabetes prevention programme on association of adipokines and a hepatokine with incident diabetes. Sci Rep. 2021 Oct 13;11(1):20327. doi: 10.1038/s41598-021-99784-x.

113. Högstedt A, Farnebo S, Tesselaar E, Ghafouri B. Investigation of proteins important for microcirculation using in vivo microdialysis after glucose provocation: a proteomic study. Sci Rep. 2021 Sep 27;11(1):19093. doi: 10.1038/s41598-021-98672-8.

114. Khan SR, Canales BK, Dominguez-Gutierrez PR. Randall's plaque and calcium oxalate stone formation: role for immunity and inflammation. Nat Rev Nephrol. 2021 Jun;17(6):417-433. doi: 10.1038/s41581-020-00392-1.

115. Chattopadhyay D, Das S, Guria S, Basu S, Mukherjee S. Fetuin-A regulates adipose tissue macrophage content and activation in insulin resistant mice through MCP-1 and iNOS: involvement of IFNγ-JAK2-STAT1 pathway. Biochem J. 2021 Nov 26;478(22):4027-4043. doi: 10.1042/BCJ20210442.

116. Ghadimi M, Foroughi F, Hashemipour S, et al. Decreased insulin resistance in diabetic patients by influencing Sirtuin1 and Fetuin-A following supplementation with ellagic acid: a randomized controlled trial. Diabetol Metab Syndr. 2021 Feb 5;13(1):16. doi: 10.1186/s13098-021-00633-8.

117. Werida RH, Abou-Madawy S, Abdelsalam M, Helmy MW. Omega 3 fatty acids effect on the vascular calcification biomarkers fetuin A and osteoprotegerin in hemodialysis patients. Clin Exp Med. 2022 May;22(2):301-310. doi: 10.1007/s10238-021-00740-w.

118. Anzai F, Karasawa T, Komada T, et al. Calciprotein Particles Induce IL-1β/α-Mediated Inflammation through NLRP3 Inflammasome-Dependent and -Independent Mechanisms. Immunohorizons. 2021 Jul 29;5(7):602-614. doi: 10.4049/immunohorizons.2100066.

119. Chen W, Fitzpatrick J, Monroy-Trujillo JM, et al. Associations of Serum Calciprotein Particle Size and Transformation Time With Arterial Calcification, Arterial Stiffness, and Mortality in Incident Hemodialysis Patients. Am J Kidney Dis. 2021 Mar;77(3):346-354. doi: 10.1053/j.ajkd.2020.05.031.

120. Janus SE, Hajjari J, Chami T, et al. Multi-Variable Biomarker Approach in Identifying Incident Heart Failure in Chronic Kidney Disease Results from the Chronic Renal Insufficiency Cohort (CRIC) Study. Eur J Heart Fail. 2022 May 19. doi: 10.1002/ejhf.2543.

121. Tiong MK, Smith ER, Pascoe EM, et al. Effect of lanthanum carbonate on serum calciprotein particles in patients with stage 3-4 CKD - results from a placebo-controlled randomised trial. Nephrol Dial Transplant. 2022 Feb 25:gfac043. doi: 10.1093/ndt/gfac043.

122. Sevinc C, Yilmaz G, Ustundag S. The relationship between calcification inhibitor levels in chronic kidney disease and the development of atherosclerosis. Ren Fail. 2021 Dec;43(1):1349-1358. doi: 10.1080/0886022X.2021.1969248.

123. Kuro-O M. Klotho and calciprotein particles as therapeutic targets against accelerated ageing. Clin Sci (Lond). 2021 Aug 13;135(15):1915-1927. doi: 10.1042/CS20201453.

124. Cui Z, Li Y, Liu G, Jiang Y. miR-103a-3p Silencing Ameliorates Calcium Oxalate Deposition in Rat Kidney by Activating the UMOD/TRPV5 Axis. Dis Markers. 2022 Feb 23;2022:2602717. doi: 10.1155/2022/2602717.

125. Poloczek J, Kazura W, Kwaśnicka E, Gumprecht J, Jochem J, Stygar D. Effects of Bariatric Surgeries on Fetuin-A, Selenoprotein P, Angiopoietin-Like Protein 6, and Fibroblast Growth Factor 21 Concentration. J Diabetes Res. 2021 Aug 6;2021:5527107. doi: 10.1155/2021/5527107.

126. Koeppert S, Ghallab A, Peglow S, et al. Live Imaging of Calciprotein Particle Clearance and Receptor Mediated Uptake: Role of Calciprotein Monomers. Front Cell Dev Biol. 2021 Apr 29;9:633925. doi: 10.3389/fcell.2021.633925.

127. Alshahawey M, El Borolossy R, El Wakeel L, Elsaid T, Sabri NA. The impact of cholecalciferol on markers of vascular calcification in hemodialysis patients: A randomized placebo controlled study. Nutr Metab Cardiovasc Dis. 2021 Feb 8;31(2):626-633. doi: 10.1016/j.numecd.2020.09.014.

128. Tiong MK, Krishnasamy R, Smith ER, et al. Effect of a medium cut-off dialyzer on protein-bound uremic toxins and min-

eral metabolism markers in patients on hemodialysis. Hemodial Int. 2021 Mar 28. doi: 10.1111/hdi.12924.

129. Werida RH, Abou-Madawy S, Abdelsalam M, Helmy MW. Omega 3 fatty acids effect on the vascular calcification biomarkers fetuin A and osteoprotegerin in hemodialysis patients. Clin Exp Med. 2022 May;22(2):301-310. doi: 10.1007/s10238-021-00740-w.

130. Roca-Tey R, Ramírez de Arellano M, González-Oliva JC, et al. Is fetuin-A a biomarker of dialysis access dysfunction? J Vasc Access. 2021 Jul 29:11297298211035846. doi: 10.1177/11297298211035846.

131. Kuro-O M. Phosphate as a Pathogen of Arteriosclerosis and Aging. J Atheroscler Thromb. 2021 Mar 1;28(3):203-213. doi: 10.5551/jat.RV17045.

132. Fernández P, Douthat W, Castellano M, et al. Biomarkers of bone and mineral disorders (FGF-23, fetuin-A) and vascular calcification scores as predictive tools for cardiovascular death in dialysis patients, at 10 years of follow-up. Medicina (B Aires). 2021;81(2):191-197. English.

133. Lin X, Zhu T, Xu F, et al. Plasma Exosomes Derived From Patients With End-Stage Renal Disease and Renal Transplant Recipients Have Different Effects on Vascular Calcification. Front Cell Dev Biol. 2021 Jan 28;8:618228. doi: 10.3389/fcell.2020.618228.

134. Düsing P, Zietzer A, Goody PR, et al. Vascular pathologies in chronic kidney disease: pathophysiological mechanisms and novel therapeutic approaches. J Mol Med (Berl). 2021 Mar;99(3):335-348. doi: 10.1007/s00109-021-02037-7.

135. Chou PR, Wu PY, Wu PH, et al. Investigation of the Relationship between Cardiovascular Biomarkers and Brachial-Ankle Pulse Wave Velocity in Hemodialysis Patients. J Pers Med. 2022 Apr 15;12(4):636. doi: 10.3390/jpm12040636.

136. Tiong MK, Cai MMX, Toussaint ND, Tan SJ, Pasch A, Smith ER. Effect of nutritional calcium and phosphate loading on calciprotein particle kinetics in adults with normal and impaired kidney function. Sci Rep. 2022 May 5;12(1):7358. doi: 10.1038/s41598-022-11065-3.

137. Wu PY, Lee SY, Chang KV, Chao CT, Huang JW. Gender-Related Differences in Chronic Kidney Disease-Associated Vascular Calcification Risk and Potential Risk Mediators: A Scoping Review. Healthcare (Basel). 2021 Aug 1;9(8):979. doi: 10.3390/healthcare9080979.

138. Mohammed SK, Taha EM, Muhi SA. A case-control study to determination FBXW7 and Fetuin-A levels in patients with type 2 diabetes in Iraq. J Diabetes Metab Disord. 2021 Jan 21;20(1):237-243. doi: 10.1007/s40200-021-00738-x.

139. Uedono H, Mori K, Ochi A, et al. Effects of fetuin-A-containing calciprotein particles on posttranslational modifications of fetuin-A in HepG2 cells. Sci Rep. 2021 Apr 5;11(1):7486. doi: 10.1038/s41598-021-86881-0.

140. Piwkowska A, Zdrojewski Ł, Heleniak Z, Dębska-Ślizień A. Novel Markers in Diabetic Kidney Disease-Current State and Perspectives. Diagnostics (Basel). 2022 May 11;12(5):1205. doi: 10.3390/diagnostics12051205.

Received 11.05.2022
Revised 23.05.2022
Accepted 03.06.2022

Information about author
Lidiia D. Denova, graduate student, Shupyk National Healthcare University of Ukraine, Kyiv, Ukraine; e-mail: marbua18@gmail.com; https://orcid.org/0000-0002-5678-5885

Conflicts of interests. Author declares the absence of any conflicts of interests and their own financial interest that might be construed to influence the results or interpretation of their manuscript.

Денова Л.Д.
Національний університет охорони здоров'я імені П.Л. Шупика, м. Київ, Україна

Значення протеомних досліджень новітніх маркерів ураження нирок у сечі для оцінки перебігу, прогресування й ускладнень у пацієнтів із ХХН

Резюме. Хронічна хвороба нирок (ХХН) є причиною як захворюваності, так і смертності в усьому світі. В Україні ХХН виявляють у 12 % населення. Суттєво погіршують якість життя у пацієнтів із ХХН прогресування фіброзу нирок і порушення мінерального гомеостазу. Основними заходами запобігання прогресуванню ХХН і відстрочення несприятливих наслідків є рання діагностика й лікування. Дефіцит ранніх, неінвазивних біомаркерів негативно впливає на здатність швидко виявляти й лікувати ХХН. У прогресуванні ХХН важливу роль відіграє ураження проксимальних канальців. Є новітні маркери ураження нирок, такі як уромодулін, білок Klotho і посттрансляційні модифікації фетуїну А. Лікування ХХН на ранніх стадіях може покращити функцію нирок і/або сповільнити прогресування ХХН.

Ключові слова: хронічна хвороба нирок; гіперфосфатемія; уромодулін; протеїн Klotho; фетуїн А

Graphic abstract/Графічний реферат

Biomarkers of CKD

Uromodulin	Klotho protein	Fetuin A
Synthesized by uroepithelium lining the thick ascending limb of Henle's loop.	Synthesized mainly in the distal convoluted tubules of the kidneys and epithelial cells of the vascular plexus in the brain.	Synthesized mainly (more 95 %) in the liver and kidneys.

They give an estimate concerning further progression of the disease, servility and death.

Біомаркери ХХН

Уромодулін	Білок Клото	Фетуїн А
Синтезується виключно епітелієм товстого висхідного відділу петлі Генле.	Синтезується переважно в дистальних звивистих канальцях нирок та епітеліальних клітинах судинного сплетення в головному мозку.	Синтезується переважно (понад 95 %) у печінці й нирках.

Для цих біомаркерів характерне виявлення ранніх пошкоджень, локалізації пошкодження. Дають оцінку щодо подальшого прогресування захворювання, тяжкості й смерті.