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 worsens 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; uromodulin; 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 m² 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:
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].
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 hyperparathyroidism D₃, 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 β₂-microglobulin, KIM-1 (kidney injury molecule-1), NGAL (lipocalin associated with neutrophil gelatinase) and L-FABP (liver fatty acid binding protein) [1, 9, 19–21] .

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**

<table>
<thead>
<tr>
<th>Categories of GFR (ml/min/1.73 m²)</th>
<th>Categories of persistent albuminuria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A1</td>
</tr>
<tr>
<td></td>
<td>Normal or slightly elevated</td>
</tr>
<tr>
<td>&lt; 30 mg/g; &lt; 3 mg/mmol</td>
<td>30–300 mg/g; 3–30 mg/mmol</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Genetic modification/soluble protein</th>
<th>Experimental animals</th>
<th>In vitro/in vivo</th>
<th>Disease/pathological condition</th>
<th>Signal pathways that are involved in the implementation of the effect</th>
<th>Obtained effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soluble protein</td>
<td>Mice</td>
<td>In vivo</td>
<td>Stress-induced apoptosis in cardiomyocytes</td>
<td>Inhibition of p38, JNK</td>
<td>Inhibition of stress and apoptosis of the endoplasmic reticulum</td>
</tr>
<tr>
<td>Soluble protein</td>
<td>Mice</td>
<td>In vivo</td>
<td>Cardiac hypertrophy, experimental hypertension with Klotho deficiency</td>
<td>Inhibition of calcium channel, TRPC6, FGFR1</td>
<td>Prevention of hypertrophy, normalization of blood pressure</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soluble protein</td>
<td>Mice, H9c2 cells and neonatal cardiomyocytes</td>
<td><em>In vivo, in vitro</em></td>
<td>Damage to the heart muscle caused by hyperglycemia</td>
<td>Inhibition of fibrosis, oxidative stress, mitochondrial dysfunction and inhibition of inflammation induced by activation of NF-κB and ROS</td>
<td>Prevention of heart muscle damage</td>
</tr>
<tr>
<td>Soluble protein</td>
<td>Mice db/db (model of type 2 diabetes)</td>
<td><em>In vivo</em></td>
<td>High systolic pressure, fibrosis and renal hypertrophy, hyperglycemia</td>
<td>Enhanced Klotho and superoxide dismutase expression, inhibition of fibronectin, HIF, TGF-β1 and TNF-α expression, renal phosphorylation of mTOR and Akt</td>
<td>Prevention of renal fibrosis and normalization of blood pressure</td>
</tr>
<tr>
<td>Soluble protein</td>
<td>Mice db/db (model of type 2 diabetes)</td>
<td><em>In vivo</em></td>
<td>Hyperglycemia</td>
<td>Prevention of heart muscle damage</td>
<td></td>
</tr>
<tr>
<td>Soluble protein</td>
<td>Mice</td>
<td><em>In vivo</em></td>
<td>Diabetes mellitus is induced by the introduction of streptozotocin</td>
<td>Enhanced Klotho and superoxide dismutase expression, inhibition of fibronectin, HIF, TGF-β1 and TNF-α expression, renal phosphorylation of mTOR and Akt</td>
<td>Prevention of renal fibrosis and normalization of blood pressure</td>
</tr>
<tr>
<td>Soluble protein</td>
<td>Mice db/db (model of type 2 diabetes)</td>
<td><em>In vivo</em></td>
<td>Intestinal permeability, hyperglycemia</td>
<td>Severe hyperglycemia and development of diabetic complications</td>
<td>Prevention of diabetic complications</td>
</tr>
</tbody>
</table>

**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)

<table>
<thead>
<tr>
<th>GFR, ml/min/1.73 m²</th>
<th>Markers of damage of the kidneys</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Yes</strong></td>
<td><strong>No</strong></td>
</tr>
<tr>
<td>CKD</td>
<td>No</td>
</tr>
<tr>
<td>CKD</td>
<td>Risk group</td>
</tr>
<tr>
<td>CKD</td>
<td>CKD</td>
</tr>
</tbody>
</table>

**Table 3. Diagnosis of CKD depending on the presence of markers of damage and functional status of the kidneys (E.M. Shilov, 2012)**
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 Tamm–Horsfall protein was discovered by Horsfall and Tamm in 1950, when a study of viral hemagglutination in the urine revealed a protein that inhibits viral hemagglutination. 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 (pl 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 I 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 D₃, 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 ranges 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 heparin), 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](image-url)
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 cannot maintain the basal activity of the liver promoter compared with long isoforms of C/EBP, which predominates 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 calcioprotein particles (consisting of calcioprotein monomers) [98, 104, 105, 129—133].

The mineral binding site, in FTA, is located in the N-terminal cystatin-like domain of CYI [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 anionization 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-xB [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 cysteinepeptidase 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 is 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


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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 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 ран них, 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 фетуїн А. Лікування ХХН на ранніх стадіях може покращити функцію нирок і/або сповільнити прогресування ХХН.

Ключові слова: хронічна хвороба нирок; гіперфосфатемія; уромодулін; Klotho; фетуїн А
### Biomarkers of CKD

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Synthesis Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uromodulin</strong></td>
<td>Synthesized by uroepithelium lining the thick ascending limb of Henle's loop.</td>
</tr>
<tr>
<td><strong>Klotho protein</strong></td>
<td>Synthesized mainly in the distal convoluted tubules of the kidneys and epithelial cells of the vascular plexus in the brain.</td>
</tr>
<tr>
<td><strong>Fetuin A</strong></td>
<td>Synthesized mainly (more 95%) in the liver and kidneys.</td>
</tr>
</tbody>
</table>

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

### Біомаркери ХХН

<table>
<thead>
<tr>
<th>Біомаркер</th>
<th>Синтезування дуже переважно в дистальних звивистих канальцях нирок та епітеліальних клітинах судинного сплетення в головному мозку.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Уромодулін</strong></td>
<td>Синтезується виключно епітелієм товстого висхідного відділу петлі Генле.</td>
</tr>
<tr>
<td><strong>Білок Клото</strong></td>
<td>Синтезується переважно в дистальних звивистих канальцях нирок та епітеліальних клітинах судинного сплетення в головному мозку.</td>
</tr>
<tr>
<td><strong>Фетуїн А</strong></td>
<td>Синтезується переважно (понад 95%) у печінці й нирках.</td>
</tr>
</tbody>
</table>

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