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Current view on molecular pathways of kidney damage in diabetic nephropathy.

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Abstract

Due to the imperfection of early detection of diabetic nephropathy in children, there is a need to create panels of potential biomarkers of glomerular and tubular dysfunction or interstitial kidney damage. The lesion of the tubulo-interstitial department precedes the lesion of the glomerular aparniate of the kidneys, so the relevant markers require more detailed study and analysis. The latter can be detected before the onset of micro albuminuria, allow monitoring of the disease, show a close relationship with the progression of diabetic nephropathy, decreased glomerular filtration rate. The search for early markers of kidney damage in type I diabetes is important and undeniably promising in terms of early clinical diagnosis of this severe progressive complication.

Keywords: Kidney Damage, T1D, Markers.

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Introduction

Diabetic Nephropathy (DN) is one of the most common, severe and prognostic complications of diabetes mellitus. In many countries, DN is a major cause of chronic renal failure. According to the international diabetes federation, one of in three patients with type I diabetes and one of in four patients with type II diabetes die from end-stage chronic renal failure. It was previously thought that kidney damage develops more than 10 years after the onset of diabetes, but modern research confirms the development of diabetic nephropathy in the first years of diabetes. The latter can develop in patients with latent diabetes and at the beginning of the disease.

According to the center for medical statistics of the ministry of health of Ukraine, there is an increase in the total number of children aged 0-14 with diabetes first detected (increased by 22% from 1995 to 2015). Thus, there has recently been an increase in the incidence of young children, which increases the risk of early development of chronic complications of diabetes [1-3]. Diabetic nephropathy is a specific lesion of the renal vessels in diabetes mellitus, accompanied by the formation of nodular or diffuse glomerulosclerosis, the terminal stage of which is characterized by the development of chronic renal failure.

Terminology and classification

The main clinical manifestations of diabetic nephropathy:

- Kimmeltstiel-Wilson glomerulosclerosis;
- Ischemic nephropathy (atherosclerotic lesion of the renal artery) [4-6];
- Urinary tract infections (papillary necrosis);
- Glomerulonephritis;
- Functional acute renal failure ;
- Detrusor paresis and obstruction (Table 1).

Stage of diabetic nephropathy	Clinical and laboratory characteristics	Terms of development
I-Stage of renal hyperfunction	↑GFR	Develops in the onset of the disease
	↑Renal circulation	
	Renal hypertrophy	
	albuminuria<30 mg/day	
II-Stage of initial structural changes in the kidneys	Thickening of the basement membranes of the glomerular capillaries	2-5 years from the onset of diabetes
	Mesangium enlargement	
	↑GFR	
	Albuminuria<30 mg/day	

III-Onset diabetic nephropathy	Microalbuminuria (30-300 mg/day)	5-15 years from the onset of diabetes
	↑GFR	
	Arterial hypertension	
IV-Stage of severe diabetic nephropathy	Glomerulosclerosis	10-25 years from the onset of diabetes
	Proteinuria (↑500 mg/day)	
	↓GFR	
	Arterial hypertension	
V-Stage of uremia	Total diffuse or nodular glomerulosclerosis	More than 15-20 years from the onset of diabetes or 5-7 years from the onset of proteinuria
	↓GFR (<10 ml/min)	
	Arterial hypertension	
	Impaired nitrogenous excretory function of the kidneys (↑creatinine, urea)	
	Symptoms of intoxication	

Table 1. Characterized by the development of chronic renal failure.

Mandatory Research Methods

- Research of micro albuminuria;
- Research of proteinuria (in the general analysis of urine or in the urine collected for days) (Table 2);
- Examination of urine sediment (erythrocytes, leukocytes);
- Studies of creatinine and serum urea [7];
- GFR research.

	The concentration of albumin in the morning portion of urine*, mcg/min	**Concentration of albumin in the morning portion of urine**, mg/l**	**Urine albumin/creatinine ratio***, mg/mmol**
Normoalbuminuria	<20	<30	<2.5(male)
			<3.5(female)
Microalbuminuria	20-200	30-300	2.5-25.0(male)
			3.5-25.0(female)
Proteinuria	>200	>300	>25

Table 2. Examination of urine sediment (erythrocytes, leukocytes). *: If MALB is detected, repeat the test three times in 2-3 months. **: If proteuria is detected, repeat the test three times a month. ***: Alternative study.

Criteria for diabetic nephropathy

The earliest method of diagnosing diabetic nephropathy is Micro Albuminuria (MALB). An early marker of kidney damage is intraglomerular hypertension, which is considered the main cause of the development and progression of diabetic nephropathy [8-10]. It is diagnosed by increasing the glomerular filtration rate of more than 140 ml/min. Typically, glomerular damage leads to proteinuria, which is due to increased penetration of plasma proteins such as albumin and transfers (normally not filtered through the glomerulus), and increased extracellular matrix protein synthesis [2,11].

Pathogenesis (known and new data)

The pathogenesis of diabetic nephropathy is complex and includes the following components

- Hereditary;
- Metabolic (hyperglycemia, hyperlipidemia, hyperuricemia);
- Hemodynamic (intraglomerular hypertension, hypertension);
- Hormonal (hyperinsulinemia, activation of the renin-angiotensin-aldosterone system);
- Immune (imbalance of production of pro-inflammatory and anti-inflammatory cytokines, growth factors, etc.) disorders.

In diabetic nephropathy, all cellular elements of the kidney are affected:

- Glomerular endothelium;
- Mesangium cells;
- Podocytes;
- Epithelium of tubules.

Typically, damage to the glomeruli leads to proteinuria, which is caused by increased penetration of plasma proteins such as albumin and transferrin (normally not filtered through the glomerulus), and increasing the synthesis of extracellular

matrix proteins. The main changes in the morphology of the kidney in the glomerular region: expansion of the mazang, thickening of the basement membrane, the formation of nodules Kimmelsteil-Wilson, which eventually progress to glomerulosclerosis [1]. According to modern research, damage to the tubular-interstitial department plays an important role in the pathogenesis of DN. The latter are caused by chronic hyperglycemia, hypoxia, toxins, hypertension, and increased protein load. Given the interaction between the tubular-interstitial and glomerular divisions, glomerular lesions cause further microcirculation disorders that lead to hyper filtration in unaffected glomeruli with a natural increase in intraglomerular pressure (Figure 1). Hyper filtration with intraglomerular hypertension damages the rest of the glomeruli and tubules, causing further glomerulosclerosis and tubular interstitial fibrosis, later a decrease in glomerular filtration [5].

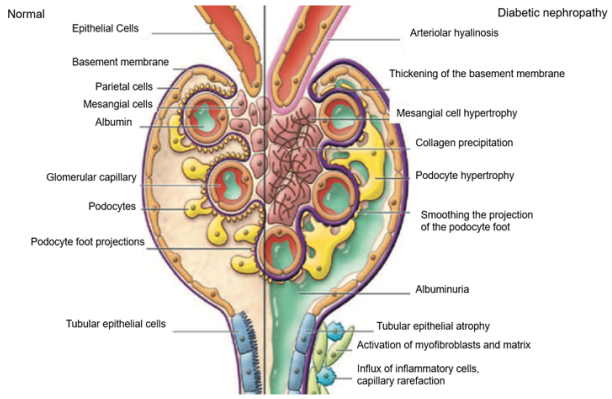

Figure 1. Structural lesions in diabetic nephropathy.

Traditional and additional markers of diabetic nephropathy

Biomarkers of renal dysfunction in diabetic nephropathy include creatinine, creatinine clearance, urea, Mg2+, urinary angiotensin. Markers of functional disorders of the tubular apparatus of the kidney also play an important role in early diagnosis, analysis of the progression of the pathological process.

They include: kidney injury molecule-1 (KIM-1) trans membrane glycoprotein, which is expressed on the apical membrane of cells of the proximal tubules of the kidneys. In physiological processes in the kidneys KIM-1 is not identified. The appearance of this marker in the urine indicates in the early stages of the development of the inflammatory process, fibrosis and is associated with the tubule interstitial inflammatory component of the development of DN (Figure 2). In the group of patients with diabetes, the determination of KIM-1 preceded the development of MALB, which confirms the primary lesion of the tubular department in the case of DN [10].

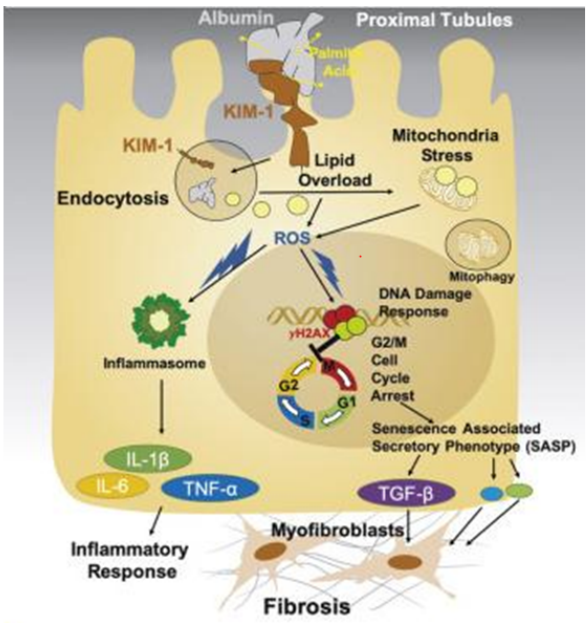

Figure 2. KIM-1 mediates fatty acid uptake by renal tubular cells to promote progressive diabetic kidney disease. (Mori Y).

Liver-type fatty acid binding protein it is considered an endogenous antioxidant that plays a protective role in tubular and interstitial disorders. An early increase in this marker was observed in patients with type 1 diabetes and norm albuminuria (before the development of micro and macro albuminuria) [6]. In Japan, it is officially approved as a biomarker of the tubular kidney. Neutrophil Gelatinase Associated Lipocalin (NGAL) acts as a stimulator of proliferation of affected cells. NGAL acts as a stimulator of proliferation of affected cells and counteracts bacterial infections. Urine NGAL is higher in diabetic patients compared to the healthy group, even with normoalbuminuria [8]. Its positive correlation with serum cystatin C, serum creatinine, albuminuria, albumin-creatinine ratio, duration of diabetes, glycosylated hemoglobin, urinary IL-18, angiotensinogen and negative correlation with glomerular filter rate. Cystatin C is a protein with a molecular weight that belongs to the inhibitors of cysteine proteases and is produced by all nuclear cells of the human body. Serum cystatin C is considered a sensitive marker of glomerular lesions, while urinary cystatin C is an indicator of disruption of physiological processes in the proximal tubules of the kidneys [10].

Determination of cystatin C in the blood can be an indicator of hyper filtration in hypertension, DN and allows assessing renal function in pediatric and elderly patients. N-acetyl-β-D glucosaminidase (NAG) lysosomal enzyme of many tissues of the body with the greatest activity in the cells of the proximal tubules of the kidneys, secreted by the epithelium of the proximal tubules and involved in the degradation of mucopolysaccharides and glycoproteins [9]. The appearance of the enzyme in the urine indicates signs of pathological changes in the tubule interstitial structures of the kidney. Increased NAG is observed in patients with diabetes mellitus and normal albuminuria, preceded by MALB. The reason for the increase in NAG in the urine is hemodynamic changes in the tubules

due to renal hypoxia. β2-microglobulin (B2M) is synthesized by immunocompetent cells and its level in serum is determined only by the state of the glomerular basement membrane, part of the peptide is absorbed and catabolized in the proximal tubules of the kidneys, which ensures its stable level in urine. An increase in the concentration of serum B2M occurs under conditions of subclinical renal dysfunction of glomerular localization, and an increase in the content of peptide in the urine indicates tubular lesions. It's a low molecular weight protein, an indicator of tubular dysfunction and a prognostic marker for diabetic nephropathy [6,8-10].

Markers of vascular lesions in diabetic nephropathy

High plasma prorenin levels are a predictor of micro vascular complications such as albuminuria/proteinuria in patients with diabetic nephropathy. It is an established fact that insulin resistance and endothelial dysfunction are closely associated conditions [6]. At the same time there is a decrease in insulin-mediated and endothelium-dependent vasodilation. Therefore, it can be assumed that endothelial dysfunction is an integral aspect of insulin resistance syndrome and contributes to its increase, increased vascular reactivity, which leads to even greater vascular disorders. Prorenin is a preprohormone, the first active component of RAAS, which is synthesized by the juxtaglomerular apparatus of the kidneys (myoepithelial cells surrounding the afferent arterioles) and excreted from the cells by a signal peptide [7].

Until recently, prorenin was thought to be only an inactive precursor to renin. However, when it was found that its concentration in the circulating blood is ten times higher than the concentration of renin (and in pregnancy and diabetes 100 times), it was thought that prorenin may play its own biological role in the body. To date, two types of receptors have been identified, found in mesangial cells and cells of the distal and collecting tubules of the kidneys, to which both prorenin and renin can bind, causing completely different biological effects. When they bind, prorenin and renin are deposited inside the cells. Binding of prorenin to the prorenin receptor triggers 2 main mechanisms: angiotensin 2-dependent due to the conversion of prorenin to the active form due to conformational changes, angiotensin 2-independent mechanism prorenin receptor-dependent intracellular mitogen activated proteinase kinase mechanism. Animal (rat) studies have shown that prorenin and the prorenin receptor plays a key role in the pathophysiology of DN [7-9].

Oxidative stress is the process of damaging Reactive Oxygen Species (ROS) of organs and tissues at the cellular level as a result of an imbalance in the functional activity of pro-oxidant systems, *i.e.,* systems that support and prevent oxidation. This process may be the result of a lack of antioxidant protection due to disruption of the synthesis of endogenous antioxidants, and excessive production of free radicals. The most characteristic feature of metabolic changes in DN is the imbalance between the processes of catabolism and anabolism, its deepening - through the development of hypoxic processes. Therefore, special attention is paid to the study of enzymes involved in key processes of degradation of biomolecules, in particular the final link of purine metabolism [1]. Xanthine oxidase (XO) is a pro-oxidant enzyme. XO is an enzyme that catalyzes the reaction of hypoxanthine through xanthine to uric acid (Figure 3). Dependence of increase in plasma activity of xanthine oxidase of pathological process in renal vessels *in vivo* is revealed [8].

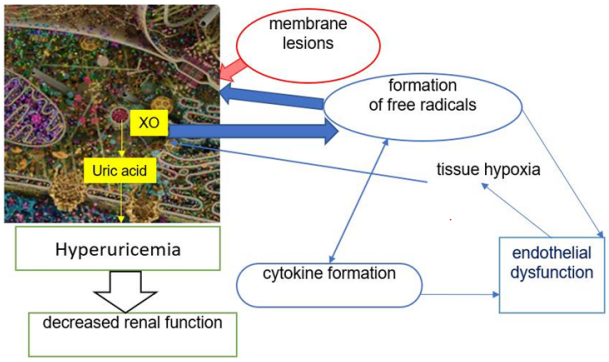

Figure 3. Xanthine oxidase as a marker of metabolic disorders, endothelial dysfunction, oxidative stress.

Hyperglycemia is an activator of oxidative processes in diabetes mellitus and diabetic nephropathy. Against the background of hyperglycemia activates a number of metabolic pathways of glucose conversion, resulting in excessive formation of reactive forms of oxygen and nitrogen, which, interacting with other compounds, is converted into * OH, hydrogen peroxide (H_2O_2) and peroxynitrite (ONOO-), which leads to the development of stress (Figure 4) [10].

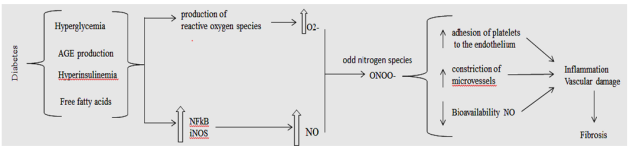

Figure 4. General scheme of vascular damage under the conditions of DN. iNOS - inducible nitric oxide synthase. NO - (mono) nitric oxide. NFkB is the nuclear factor Kappa Bi. ONOO – peroxynitrite.

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