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DIABETIC NEPHROPATHY: SHORT REVIEW

Key words: *nephropathy, diabetes mellitus, kidney, diabetic complications.*

Abstract. *The article deals with the short review of main pathophysiological mechanisms of diabetic nephropathy development and methods for the early detection of renal injury in diabetic patients with a help of different biomarkers in body fluids and tissues.*

Introduction. The global epidemic of diabetes is a major health problem. Diabetic nephropathy (DN) can develop in about 1/3 of diabetic individuals and is characterized by specific glomerular and tubular lesions in the kidney. These lesions are associated with progression to end stage renal disease with subsequent requirement for renal dialysis and transplantation. Despite the significance of DN, there is still incomplete understanding of the pathogenic mechanisms, particularly those underlying the differential susceptibility to DN [9].

The diabetic complications including neuropathy, cardiovascular diseases, and nephropathy which is one of the most complications developed in late stage increase the morbidity and mortality. Diabetic nephropathy occurs in approximately 30% of diabetic patients and leads to renal failure in most countries. The first sign of nephropathy was detected by microalbuminuria (presence of albumin in urine) but doesn't cover all patients with renal impairment.

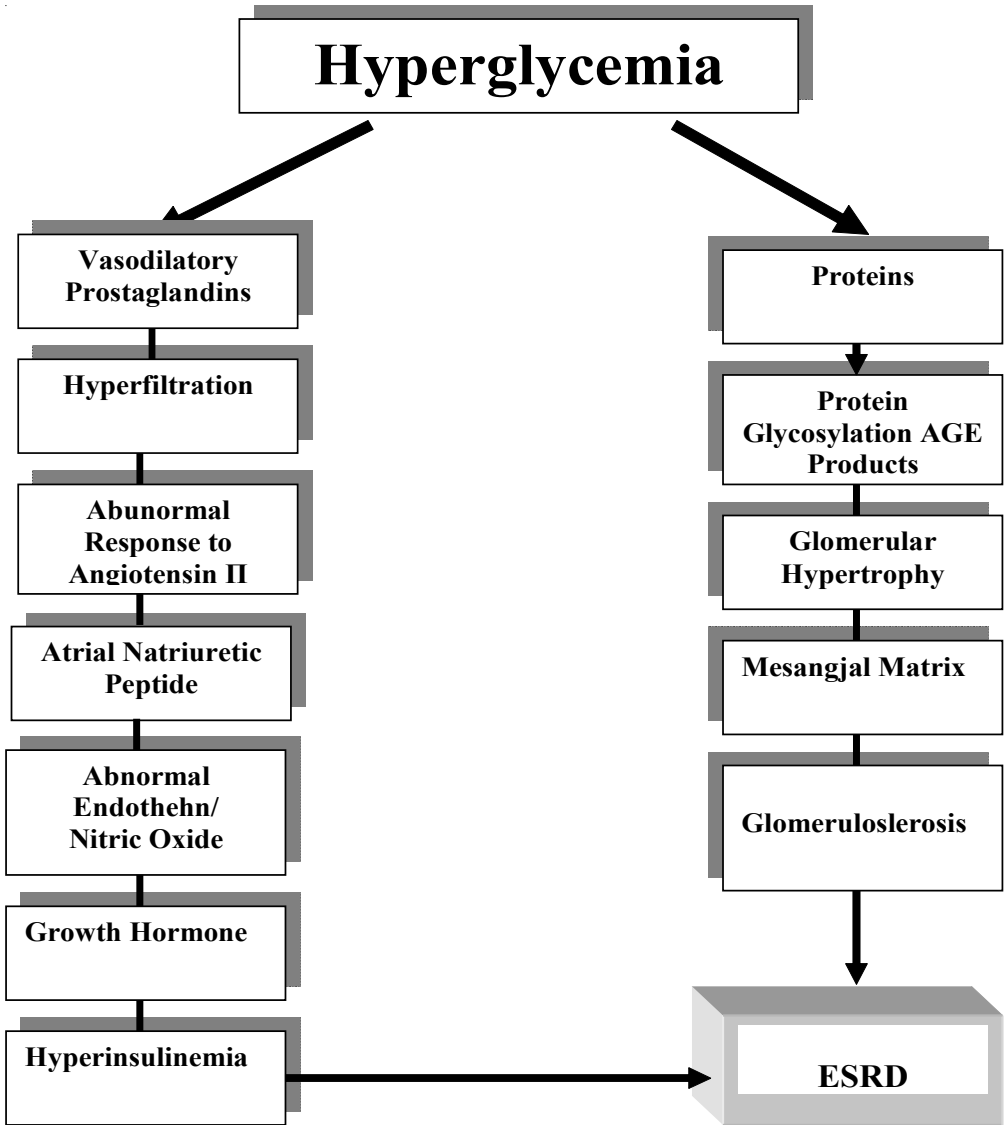

Fig.1. General scheme of the hyperglycemia influence.

Diabetic nephropathy, also known as Kimmelstiel-Wilson syndrome or nodular diabetic glomerulosclerosis or intercapillary glomerulonephritis, is a clinical syndrome characterized by albuminuria (>300 mg/day or >200 mcg/min) confirmed on at least two occasions 3-6 months apart, permanent and irreversible decrease in glomerular filtration rate (GFR) (table 1.), and arterial hypertension. The syndrome was first described by a British physician Clifford Wilson (1906-1997) and American physician Paul Kimmelstiel (1900-1970) in 1936 [3].

	Decline in glomerular filtration rate (ml/min/year)	
Diabetes	**Type 1**	**Type 2**
Normoalbuminuria	1,2 - 3,6	0,96
Microalbuminuria	1,2 - 3,6	2,4
Proteinuria	9,6 - 12	5,4 - 7,2

Table 1. Decline in glomerular filtration rate in various stages of type 1 and type 2 diabetes.

There are five stages in the development of diabetic nephropathy [14].

Stage I: Hypertrophic hyperfiltration. In this stage, GFR is either normal or increased. StageI lasts approximately five years from the onset of the disease. The size of the kidneys is increased by approximately 20% and renal plasma flow is increased by 10%-15%, while albuminuria and blood pressure remain within the normal range.

Stage II: The quiet stage. This stage starts approximately two years after the onset of the disease and is characterized by kidney damage with basement membrane thickening and mesangial proliferation. There are still no clinical signs of the disease. GFR returns to normal values. Many patients remain in this stage until the end of their life.

Stage III: The microalbuminuria stage (albumin 30-300 mg/dU) or initial nephropathy. This is the first clinically detectable sign of glomerular damage. It usually occurs five to ten years after the onset of the disease. Blood pressure may be increased or normal. Approximately 40% of patients reach this stage.

Stage IV: Chronic kidney failure (CKF) is the irreversible stage. Proteinuria develops (albumin > 300 mg/dU), GFR decreases below 60 mL/min/1.73 m2, and blood pressure increases above normal values.

Stage V: Terminal kidney failure (TKF) (GFR < 15 mL/min/1.73 m2). Approximately 50% of the patients with TKF require kidney replacement therapy (peritoneal dialysis, hemodialysis, kidney transplantation) [19].

Objectives of the research. Nowadays, the scientists use a lot of methods for the early detection of renal injury in diabetic patients. Still they look for the generalbiomarker, which will give an opportunity to prevent ESRD (End Stage Renal Disease). In this short review we try to consider some of them.

Discussion. Pathogenesis of diabetic nephropathy is very complicated and results from the interaction of hemodynamic, metabolic andgenetic factors.

Glomerular hyperfiltration is the basic pathogenic way in DN. This leads to intraglomerular hypertension [3, 6]. Progression from glomerular hyperfilteration leads to the stage of basement membrane thickening. This is the earliest detectable change in the course of diabetic nephropathy. This is followed by expansion of mesangium and finally by nodular sclerosis. At this stage, the kidney may leak more serum albumin (plasma protein) than normal in the urine (albuminuria), and this can be detected by sensitive medical tests for albumin. This stage is called "microalbuminuria". As diabetic nephropathy progresses, increasing numbers of glomeruli are destroyed by progressive nodular glomerulosclerosis. Consequently, urine albumin increases to the point that it may be detected by ordinary urinalysis techniques. At this stage, a kidney biopsy generally clearly shows diabetic nephropathy [9, 21]. The Armanni-Ebstein change or Armanni-Ebstein cells consists of deposits of glycogen in the tubular epithelial cells (pars straight of proximal convoluted tubule and loop of Henle). Because most diabetics are treated before this stage, it is very rare to see it at the present time. It appears in decompensated diabetics with glycemia higher than 500 mg/dL and in the presence of severe glycosuria; it is a reversible alteration without functional manifestations. The interstitium shows non specific chronic changes [2, 19].

Hormones. The role of hormones was experimentally demonstrated in the study by Serri et al, who showed that the infusion of somatostatin analogues (octreotide) partly led to the decrease in hyperfiltration and kidney size. In their study, glycemic regulation, plasma glucagon, and growth hormone levels remained unchanged, but the concentration of insulin-like growthfactor-1 (IGF-1) decreased [16]. Pathogenetic role of IGF-1 has not been completely elucidated, but it is known that exogenous administration of his hormone in non-DM patients leads to afferent arteriolar dilation and GFR increase, which are the changes also observed in initial diabetic nephropathy. The identical

hemodynamic changes, along with the increase in kidney size, occur in experimental animal models after the infusion of IGF-1. Sex hormones may also influence hyperfiltration. Cherney et al. observed a decrease in kidney blood flow and vascular resistance in response to hyperglycemia in women, but not in men. The same study showed that the addition of angiotensin-converting enzyme inhibitor (ACEI) resulted in a decrease in blood pressure in both men and women, but GFR decreased only in women [10, 20].

Microalbuminuria was detected in patients of severe kidney impairment as hypertension and glomerular basement impairment. Prediabetic hypertensive patients may develop nephropathy in noninsulin-dependent diabetic subjects. Glycemic control is the most important for glucose level in diabetes and the most important is glycated hemoglobin (HA1C) as a good index of glucose level. Once diabetic nephropathy was well detected according to the therapeutic protocols, including glycemic and blood pressure, controls were followed up. Diabetic nephropathy can be prevented to a significant degree by early detection using novel biomarkers in body fluids and tissues [4, 5].

Albuminuria is a sign of kidney disease, including diabetic nephropathy. The glomerular capillary wall acts as a glomerular filtration barrier (GFB) and includes 3 components: fenestrated glomerular endothelium, glomerular basement membrane (GBM), and podocytes with processes bridged by slit diaphragms. The effects of the GBM and podocytes on the selective properties of the GFB have attracted much interest in recent years. Because the fenestrae of glomerular endothelial cells are approximately 60nm diameter without the diaphragm and albumin has a diameter of only 3.6 nm, the endothelium is thought to contribute little to the protein barrier function of the glomerular capillary wall [9, 11]. Recently, several lines of evidence have suggested that there is a 200- to 400-nm-thick membrane-like layer covering the luminal surface of the glomerular endothelium; this is called the endothelial cell surface layer (ESL). The ESL is a hydrated, gel-like structure that includes 2 components: the glycocalyx, which is connected to the endothelium with several "backbone" molecules, mainly proteoglycans and glycoproteins, and the endothelial cell coat, which is attached to the glycocalyx and is composed of secreted proteoglycans, glycosaminoglycans, glycoproteins, and plasma proteins [7]. Many studies have shown that the ESL also plays an important role in the permeability barrier (including the GFB). Patients with preeclampsia or hemolytic uremic syndrome have albuminuria, and their glomerular endothelia are injured. Additionally, Jeansson and Haraldsson showed that infusion enzymes, which digest glycosaminoglycans, decrease the thickness of the ESL and promote increased flux of albumin across the glomerular capillary barrier. Singh et al. demonstrated that treatment with heparanase on the human glomerular endothelial cell glycocalyx in vitro removed the majority of the glycocalyx and increased the passage of albumin across the cell monolayer [22]. These studies suggested that injuries to the glomerular ESL increased the flux of albumin across the GFB and caused proteinuria, indicating the importance of the ESL in glomerular permselectivity. Additionally, reduced systemic glycocalyx volume is inversely correlated with the albumin-to-creatinine ratio in type 1 diabetes. High glucose reduces the biosynthesis of glycosaminoglycan in the glomerular endothelial cell glycocalyx and increases the passage of albumin across endothelial cell monolayers [7]. Studies have shown that hyperglycemia leads to reduced charge-selectivity and proteinuria, altering the composition of the glomerular barrier. However, to fully elucidate the mechanisms involved in these processes, we must first determine whether ESL plays a role in the protein barrier function of the GFB in vivo [3, 6].

Glycation end-products. Part of the excess glucose in chronic hyperglycemia binds to free amino acids of circulating or tissue proteins. This non-enzymatic process produces reversible early glycation products, and later, irreversible advanced glycation end products (AGEs), which accumulate in the tissues and contribute to the development of microvascular complications of DM. AGEs modulate the cell activation, signal transduction, and cytokine and growth factor expression through the activation of R-dependent and R-independent signal pathways. Bonding to their podocyte receptors, AGEs may induce expression of some factors considered to play the key role in the pathogenesis of diabetic nephropathy, such as transforming growth factor-beta (TGF-beta) and connective tissue growth factor (CTGF) [8, 17]. In non-diabetic mice, the infusion of early products of glycation up to the concentration seen in diabetic mice increases the kidneys blood flow, GFR, and intraglomerular pressure, which are characteristic of untreated DM [15, 16].

Podocytes are cells present outside the basement membrane of nephron. In pathological cases, podocytes are expected to be easily found in urine of diabetic patients with micro and macroalbuminuria. Human podocytes have been found to be damaged in diabetic nephropathy patients. An elevation in foot-process pores has been detected in diabetic patients and correlated directly with microalbuminuria. A

decreased number of podocytes (podocytopenia) in diabetic patients were detected in many cases [17, 20].

Reactive Oxygen Species. Increasing evidence shows the importance of reactive oxygen species (ROS) in the pathogenesis of diabetic nephropathy. Although the ROS production may be influenced by numerous mechanisms, the most important role in their production is played by superoxide produced by glycolysis and oxidative phosphorylation in the mitochondria. ROS activate all importantpathogenetic mechanisms, such as increased production of AGEs, increased glucose entry into the polyol pathway, and PKC activation. In addition, ROS directly damage endothelial glycocalyx, which leads to albuminuria without the concurrent damage to the GBM itself [13, 18].

Urinary excretion of **immunoglobulin M** (IgM) was found to be a better index of impaired kidney function than albuminuria in diabetic patients. However, it has not been regarded as an early biomarker of end stage renal disease, while plasma cystatin C levels could be a useful marker for renal dysfunction in diabetic patients with normoalbuminuria [4, 10].

Prorenin. Increased serum prorenin plays a role in the development of diabetic nephropathy in children and adolescents. Prorenin binds to a specific tissue receptor, leading to the activation of the signal pathway of mitogen-activating protein kinases (MAPK), which potentiate the development of kidney damage. Using an experimental model of diabetic nephropathy, Ichihara et al. indicated a possible role of prorenin in the development of diabetic nephropathy. In their study, a prolonged prorenin receptor blockade cancelled the activation of MAPK, which prevented the development of diabetic nephropathy despite the increased activity of angiotensine II [18].

Osteopontin (OPN) is a calcium binding protein which is expressed in bone, endothelial cells, and glomerular basement membrane. It is involved in bone turnover and inflammation. In diabetic patients, plasma osteopontin level was significantly correlated with the degree of diabetic nephropathy. In urine, increased OPN excretion level was detected in animal model of acute renal disease. This study was designed for evaluation of urinary podocyte in combination with osteopontin and plasma cystatin C to explore the early, more specific, and sensitive biomarkers for nephropathy in diabetic patients. It can help the physicians in controlling the occurrence of renal failure [1, 23].

Lipids may play a role in DN, but to date, the research focus has been on neutral lipids such as triacylglycerols and cholesterol. Phospho- and glycolipids are two major classes of lipid molecules that carry out many biological functions ranging from regulation of physical properties of cellular membranes to cell signaling. In diabetes, changes in the levels of these lipids in blood and tissues cause dysregulation of different cellular processes associated with pathogenesis. Thus, phospho- and glycolipids may have a role in DN [11].

Adipose tissue secretes adipocytokines, which influence glucose and lipid metabolism, inflammatory processes, and other bioactivities. It is thought that adipocytokines contribute to the increased risk of vascular complications in patients with type 2 diabetes by modulating vascular function and affecting inflammatory processes. Adiponectin, the most abundant adipocytokine, was found to be decreased in conditions such as obesity, insulin resistance, type 2 diabetes, macrovascular complications and coronary artery disease (CAD). In addition, adiponectin, by improving insulin sensitivity and hyperglycemia, might affect the development or progression of diabetic microvascular complications [11, 14]. However, the relationship between microvascular complications and serum adiponectin level is controversial. Leptin has been suggested as a sensitive marker for the diagnosis of obesity-related diseases. Also, leptin exerts atherogenic and angiogenetic effects, and is associated with the development of type 2 diabetes and cardiovascular disease (CVD). However, only a few studies have addressed the relationship between plasma leptin levels and diabetic microvascular complications, and showed contradictory results.

Bilirubin, an endogenous product of heme catabolism, is a potent anti-oxidant that effectively scavenges peroxyl radicals, and suppresses the oxidation of lipids and lipoproteins. Several nonclinical studies have shown a protective effect of bilirubin in preventing kidney damage in diabetic patients with Gilbert syndrome, a common hereditary disorder (incidence of 5-10% of the population) characterized by high levels of unconjugated bilirubin, vascular complications were reported to be infrequent. Furthermore, serum bilirubin concentrations were shown to be negatively correlated with urinary albumin levels, and positively correlated with glomerular filtration rate (GFR) in cross-sectional studies in patients with type 2 diabetes mellitus. In contrast, there were no associations between serum bilirubin levels with estimated GFR (eGFR) or albuminuria in the USA diabetic population [9, 12].

Tumor necrosis factor-α (TNF-α) is a proinflammatory cytokine with a wide range of biological effects including immuno-inflammatory activation and stimulating expression of vascular adhesion

molecules, which promotes the atherogenic process. Diabetes includes an inflammatory component thought to be related to diabetic complications, and studies support the hypothesis that dysregulation of the TNF superfamily might be involved in the development of diabetic vascular complications. Hyperglycemia also increases the glomerular expression of TGF-beta; matrix proteins are specifically stimulated by this growth factor. Furthermore, the expression of bone morphogenic protein 7 (BMP-7) in DM is decreased, and the expression of profibrinogenic TGF-beta is increased [15, 19].

Nephrine Expression. Nephrine is a transmembrane protein, the main structural element in slit diaphragm and as such, it is important for the maintenance of filtration membrane integrity. More recent studies have shown the association between the decreased expression of nephrine and albuminuria progression in the model of human diabetic nephropathy [6, 9].

MicroRNAs (miRNAs) are small, endogenous noncoding RNAs, 21-25 nucleotides in length. Alteration in serum/ plasma levels of miRNAs is closely associated with many diseases, including differentiation, inflammation, allergic reactions, diabetes, and several types of cancer. In addition to their presence in cells/tissues and in plasma, miRNAs are also present in other body fluids, including saliva, urine, tears, amniotic fluid, and breast milk. The type and concentration of these miRNAs in body fluids have also been correlated with disease types and pathological processes and can potentially be used as disease biomarkers to monitor physiological and/or pathological states. Urinary miR-126 may appear to be upregulated or downregulated in the progression of diabetic kidney disease. The early detection of its presence in urine may assist the prediction of the disease course [13, 22].

The general scheme of the pathogenesis of diabetic nephropathy given below was proposed by Eric Wong.

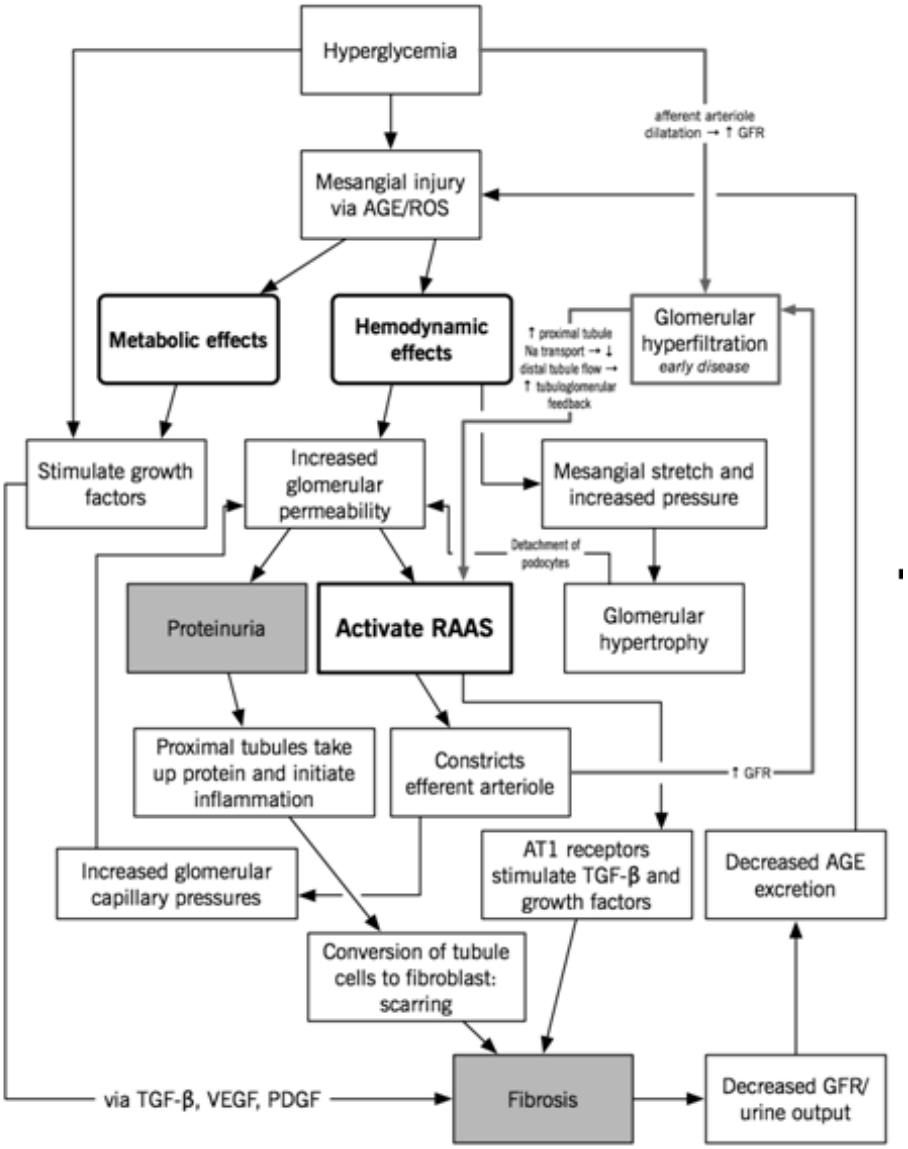

Fig.2.Pathophysiology of diabetic nephropathy

Conclusion. In the last several years an enormous progress made not only in understanding of the risk factors and mechanism of the development of diabetic nephropathy, but also in the treatment possibilities aimed at preventing the progression of diabetic nephropathy. Early detection of this chronic DM complication along with the treatment of main risk factors (hyperglycemia, hypertension, and dyslipidemia) and use of renoprotective drugs may decrease the progression of this kidney disease.

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ДІАБЕТИЧНА НЕФРОПАТІЯ: КОРОТКИЙ ОГЛЯД

Т.М. Бойчук, М.І. Грицюк

Резюме. Стаття надає інформацію щодо з короткого огляду літератури з основних патофізіологічних механізмів розвитку діабетичної нефропатії та методів раннього виявлення ураження нирок у хворих на цукровий діабет за допомогою різноманітних біомаркерів в рідинах і тканинах організму.

Ключові слова: нефропатія, цукровий діабет, нирки, ускладнення діабету.

ДИАБЕТИЧЕСКАЯ НЕФРОПАТИЯ: КРАТКИЙ ОБЗОР

Т.М. Бойчук, М.И. Грыцюк

Резюме. В статье представлена информация по короткому обзору, касающемуся основных патофизиологических механизмов развития диабетической нефропатии и методов раннего выявления поражения почек у больных сахарным диабетом при помощи разнообразных биомаркеров в жидкостях и тканях организма.

Ключевые слова: нефропатия, сахарный диабет, почки, осложнения сахарного диабета.

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