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# THE IMPORTANCE OF HEMODYNAMIC FACTORS IN THE DEVELOPMENT OF DIABETIC NEPHROPATHY

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✓ ***Resume***

***This article presents current data on the basic mechanisms of development and progression of diabetic nephropathy (DN), which are the same for both types of diabetes mellitus (DM). Diabetic nephropathy results from the interaction of various factors (metabolic, hemodynamic, neurogenic, and toxic ones) in a genetically predisposed diabetic patient. This manuscript reviews the role of hemodynamic factors in the development of diabetic nephropathy. First, the role of glomerular blood pressure changes is described, together with different factors that may influence it in different mechanisms.***

***Key words: diabetes, diabetic nephropathy, microalbuminuria, hyperglycemia, dyslipidemia***

# ЗНАЧЕНИЕ ГЕМОДИНАМИЧЕСКИХ ФАКТОРОВ В РАЗВИТИИ ДИАБЕТИЧЕСКОЙ НЕФРОПАТИИ

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***В этой статье представлены современные данные о базовых механизмах развития и прогрессирования диабетической нефропатии (ДН), которые одинаковы при обоих типах сахарного диабета (СД). Диабетическая нефропатия обусловлена взаимодействием различных факторов (метаболических, гемодинамических, нейрогенных и токсических) у генетического предрасположенного диабетического пациента. В этой рукописи рассматривается роль гемодинамические факторы в развитии диабетической нефропатии.***

***Ключовая слова: Сахарный диабет, диабетическая нефропатия, микроалбуминурия, гипергликемия, дислипидемия***

# ДИАБЕТИК НЕФРОПАТИЯ РИВОЖЛАНИШИДА ГЕМОДИНАМИК ОМИЛЛАРНИНГ АХАМИЯТИ

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***Қандли диабет билан касалланган генетик мойиллик бўлган беморларда диабетик нефропатия турли хил омилларнинг (метаболик, гемодинамик, нейроген ва токсик) ўзаро таъсири натижасида келиб чиқади. Ушбу мақолада диабетик нефропатия ривожланишида гемодинамик омилларнинг аҳамияти баён этилган. Асосан гломеруляр қон босими ўзгариш механизмлари ва унга таъсир қилувчи турли хил омиллар тавсифланган.***

***Калит сўзлар: қандли диабет, диабетик нефропатия, микроалбуминурия, гипергликемия, дислипдемия***

**Relevance**

The World Health Organization has officially recognized diabetes as an incurable disease at the modern level of medical science and clinical practice, charging the patient himself a fee for a responsible attitude to his health. It can be assumed that the global transition of mankind to a way of life dramatically divorced from nature, naturally giving rise to diabetes, is paid for by such a powerful biological shake-up of the entire planetary population [1-3]. Diabetic nephropathy (DN) is one of the most serious complications of diabetes mellitus (DM), leading to early disability and death of patients from end-stage renal failure [3, 4]. The prevalence of DN is constantly increasing, which occurs as a result of the interaction of genetic and environmental factors in patients with both type 1 and type 2 diabetes [1,5].

DN as a form of pathology in diabetes is characterized by a complex of lesions of the arteries, arterioles, glomeruli and tubules of the kidneys, resulting from disturbances in the metabolism of carbohydrates and lipids [4–7]. Today, the term "diabetic nephropathy" is more often used, since the term "diabetic glomerulosclerosis" reflects already advanced morphological changes [8–10].

It is customary to distinguish three stages of DN: the stage of microalbuminuria (MAU); the stage of proteinuria with preserved renal function and the stage of chronic renal failure (CRF) [2, 9]. It was found that only at the stage of MAU (the so-called silent stage) is it possible to prevent the progression of kidney pathology and prevent the development of chronic renal failure [3, 6-9].

The frequency of detection of DN is closely related to the duration of diabetes, this dependence is more studied in type 1 diabetes (insulin-dependent), due to a more accurate determination of the debut [12]. The frequency of development of DN in patients with a duration of type 1 diabetes up to 10 years is 5-6%, before 20 years - 20-25%, before 30 years - 35-40%, before 40 years - 45%, the maximum peak of development of DN falls on periods from 15 to 20 years of the existence of SD [5, 6, 9, 13]. In type 2 diabetes, the same dependence of the DN frequency on the duration of the DM has been established [14].

The formation of kidney damae in diabetes and the development of DN is a continuously progressive multifactorial process, among the pathogenetic theories of which metabolic, hemodynamic and genetic are recognized as significant [15]. Diabetic nephropathy, the most common cause of end-stage renal disease in developed countries, is believed to be the result of interactions between metabolic and hemodynamic factors. Hemodynamic factors are also implicated in the pathogenesis of DN and include heights of intraglomerular pressure and activation of various vasoactive hormone pathways, including the aldosterone system (RAAS) of renin-angiotensin, endothelin, and urotensin. These altered hemodynamics act independently and in conjunction with metabolic pathways to activate intracellular second messengers such as protein kinase C and cartakinases, nuclear transcription factors such as nuclear factor kappab and various growth factors such as prosclerotic cytokines, transforming growth factor beta1, connective tissue growth factor and angiogenic growth factor, growth factor that enhances vascular permeability, endothelial growth factor. Ultimately, these molecular mechanisms lead to increased renal albumin permeability, and extracellular matrix accumulation, which, as a result of increased proteinuria, leads to glomerulosclerosis and tubulointertiary fibrosis. In the past, treatment for diabetic nephropathy has focused on controlling hyperglycemia and interrupting the RAAS with certain antihypertensive agents. New targets, some of which involve glucose-dependent pathways, appear to be a major focus of new therapies against the development and progression of kidney damage from diabetes. It is likely that the resolution of diabetic nephropathy will require synergistic therapies.

The hemodynamic theory takes into account that metabolic and structural changes in the vascular bed in DN determine the severity of circulatory disorders in the kidneys, leading to an increase in glomerular filtration. The increase in glomerular filtration directly depends on the degree of hyperperfusion due to dilatation of arterioles, which determine the nature of the increase in the rate of intraglomerular blood flow. Found: the higher the hyperglycemia, the higher the hyperfiltration. Hyperfiltration is closely correlated with an increase in HbA1c levels. An increase in glucose concentrations up to 12.5 mmol / L in patients with hyperfiltration was accompanied by an additional increase in GFR by 12% [23].

Prolonged exposure to a powerful hydraulic press initiates mechanical stimulation of the adjacent glomerular structures, which promotes collagen overproduction and accumulation in the mesangium, initial sclerotic processes, disruption of the architectonics and permeability of the glomerular basement membrane [24].

An imbalance in the regulation of the tone of the efferent and efferent glomerular arterioles in diabetes also causes the development of intraglomerular hypertension and an increase in the permeability of the basement membranes of the glomerular capillaries. The reason for this imbalance is the ultra-high activity of the local renin-angiotensin-aldosterone system (RAAS) and its key component, angiotensin II (AT-II), the concentration of which in the kidney is 1000 times higher than its content in plasma [9, 11, 23]. Activation of renal AT-II and its combination with AT-I receptors of efferent arterioles leads to spasm of these vessels, and with prolonged exposure - to their hardening. The connection of AT-II with AT-I receptors in the tubules of the interstitium of the kidneys activates the synthesis of pro-inflammatory mediators, cytokines, chemokines, growth factors, which together provoke the development of glomerulosclerosis, tubulointerstitial fibrosis and the formation of chronic renal failure. Consequently, the hemodynamic effects of AT-II make a significant contribution to the formation of DN. In this case, the effect of AT-II on the metabolism of the mesangial matrix, which is mediated by prosclerotic cytokines, is of great importance [9].

Progressive glomerular fibrosis and tubulointerstitial renal hypertension is the leading pathological process that determines the development of chronic renal failure in DN. The formation of renal fibrosis under conditions of continuous action of hyperglycemia and other hemodynamic factors is associated with an imbalance of fibrogenic and antifibrogenic growth factors that regulate the processes of proliferation, differentiation, apoptosis and synthetic function of glomerular and tubular cells.

Under conditions of hyperglycemia in hyperfiltering kidneys, activation of the synthesis of fibrogenic factors is observed, such as transforming growth factor β-1 (TGFβ1), tumor necrosis factor α (TNFα), fibroblast growth factor, vascular endothelial growth factor, while suppressing the production of antifibrogenic factors (bone morphogenetic protein 7, hepatocyte growth factor) [9, 11, 21].

Microalbuminuria is the earliest recorded clinical manifestation of diabetic glomerulopathy. Metabolic mechanisms activated by hyperglycemia, glycated proteins, hemodynamic factors such as intraglomerular hypertension and oxidative stress are the main pathways for the formation of DN at the molecular level [25].

Moreover, AT-II also stimulates the uptake of ultrafiltered proteins in tubular cells and the production of pro-inflammatory and pro-fibrotic cytokines in the kidneys. Migration of macrophages and other inflammatory cells into the tubulointerstitial space occurs.

Increased synthesis and decreased metabolism of extracellular matrix proteins in tubular cells and interstitial fibroblasts enhance interstitial fibrosis. Moreover, under conditions of high local concentration of AT-II and TGFβ1, tubular cells can change their phenotype and become fibroblasts — a process called the transition of the epithelium to the mesenchyme, which leads to interstitial fibrosis and tubular atrophy due to the loss of epithelial cells [22].

Another explanation for the development of albuminuria in DN was proposed, which primarily includes disturbances in the tubular circulation (reabsorption) of ultrafiltered proteins, but these changes are not strictly necessary in changing the capabilities of the glomerular ultrafiltration barrier [26].

## Conclusion

Thus, hemodynamic factors, both independently and through the activation of the common pathway, contribute to the characteristic dysfunction observed in diabetic nephropathy.

DN occurs as a result of the interaction of hemodynamic factors in the renal microcirculation. There is no doubt that there is a positive association between hyperglycemia, which is necessary but not sufficient, and microvascular complications. It is obvious that molecular biological studies of the pathogenetic mechanisms of the development of DN will lead to the development of new promising directions in the prevention of this pathology.

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