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DISORDER OF LIPID METABOLISM IN CHRONIC KIDNEY DISEASE

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Abstract: Chronic kidney disease is a proven risk factor for the development and progression of lipid metabolism disorders. These disorders are based on an increase in the blood plasma content of cholesterol, triglycerides, low—density lipoproteins and a decrease in the level of high-density lipoproteins, apoproteins of the A family (ApoA-I and ApoA-II). There is a decrease in the activity of enzymes: lipoprotein lipase, hepatic triglyceride lipase, lecithin-cholesterol-acetyltransferase.

Key words: Periodontitis, diabetes, hyperglycemia, inflammation, oral microflora, immune response, glycemic control, periodontal care, vascular changes.

QANDLI DIABET BILAN KASALLANGAN BEMORLARDA PERIODONTIT KECHISHINING O‘ZIGA XOSLIGI

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Annotatsiya. Surunkali buyrak kasalligi lipid almashinuvi buzilishining rivojlanishi va rivojlanishi uchun tasdiqlangan xavf omilidir. Ushbu buzilishlar qon plazmasi tarkibidagi xolesterin, triglitseridlar, past zichlikdagi lipoproteinlar miqdorining oshishi va yuqori zichlikdagi lipoproteinlar, A oilasining apoproteinlari (ApoA-I va ApoA-II) darajasining pasayishiga asoslangan. Fermentlarning faolligi pasayadi: lipoprotein lipaza, jigar triglitserid lipazasi, lesitin-xolesterin-asetiltransferaza.

Kalit so‘zlar: surunkali buyrak kasalligi, xolesterin, triglitseridlar, past zichlikdagi lipoproteinlar, yuqori zichlikdagi lipoproteinlar, lipoproteinlipaza.

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Chronic kidney disease (CKD) is a violation of homeostasis caused by an irreversible decrease in the mass of active kidney nephrons, which occurs in all progressive kidney diseases and is manifested by a multi—symptom complex reflecting the participation in this process of almost all organs and systems of the patient. CKD is defined as damage to the kidneys or a decrease in their function for 3 months or more, regardless of the diagnosis. Such a time limit (the criterion of "persistence") was chosen as a temporary parameter for determining CKD because in these terms, acute variants of the development of renal dysfunction, as a rule, end in

recovery. Chronic kidney disease is an important medical and social problem of our time, the prevalence of which reaches 5-11% in the general population [4, 14]. A number of factors have a significant impact on the development and progression of chronic kidney dysfunction in a particular population, which include: an increase in the age of the population, the incidence of certain infections, alcohol and smoking, environmental conditions, climate, dietary traditions, genetic characteristics of the population, etc. About 40% of adults have an increased risk of developing CKD, including a significant number of patients with hypertension, metabolic syndrome and diabetes mellitus, which leads to a sharp decrease in quality of life, high mortality, as well as the need to use expensive methods of end—stage replacement therapy - dialysis and kidney transplantation. The rapidly increasing number of patients with end-stage renal insufficiency (ESRD) requires a constant increase in the cost of dialysis and kidney transplantation. Despite the fact that only a small proportion of patients with CKD require renal replacement therapy (RRT), the costs of RRT are very significant and become burdensome even for countries with highly developed economies. CKD is a generalizing term and an independent diagnosis. In addition to the variety of etiological factors characteristic of CKD, most chronic kidney diseases have a single mechanism of progression, and morphological changes in the kidneys in renal insufficiency are of the same type. Ultimately, they are reduced to the predominance of fibroplastic processes with the replacement of functioning nephrons by connective tissue and renal wrinkling, which leads to the death of nephrons. Therefore, CKD is currently a global public concern.

Modern international recommendations suggest classifying CKD into five stages, taking into account the glomerular filtration rate (GFR) [12] (Table. 1), since GFR has an independent diagnostic and prognostic value. In addition, the new recommendations suggest the separation of stage 3 CKD into stages 3a and 3b due to the fact that the renal prognosis is not the same in groups of people with stage 3 CKD with GFR from 59 to 45 ml/min/1.73 m2 and from 44 to 30 ml/min/1.73 m2.

Table 1

Classification of CKD stages by GFR level

Stage	Characteristics of renal function	GFR level (ml/min/1.73 m2)
C1	High or optimal	> 90
C2	Slightly reduced	60–89
C3a	Moderately reduced	45–59
C3b	Significantly reduced	30–44
C4	Sharply reduced	15–29
C5	Terminal renal failure	<15

The GFR index at the level of 90 ml/min is accepted as the lower limit of the norm. The GFR value < 60 ml/min was chosen due to the corresponding death of more than 50% of nephrons.

Disorder lipid metabolism in CKD

In patients diagnosed with CKD, one of the risk factors for this disease is the development and progression of lipid metabolism disorders [5, 10, 17]. According to numerous clinical studies, hyperlipidemia ranks first among metabolic disorders in CKD [18,19].

The assumption of the relationship between lipid accumulation and kidney disease was first made back in 1860 by Rudolf Virchow [22], who in his lectures at the Institute of Pathology in Berlin noted "fatty degeneration of the renal epithelium as a stage of Bright's disease" (the historical designation of glomerulonephritis, described in the XIX century by the British scientist Richard Bright, one of the fathers-the founders of nephrology) [8,9].

In 1982, an article by J. Moorhead et al. was first published in the Lancet journal [15], in which the authors proposed the hypothesis of lipid nephrotoxicity, which served as an incentive for further research of lipids in kidney disease. This was the first publication to introduce the notion that compensatory synthesis of liver lipoproteins in response to urinary albumin excretion can lead to progressive kidney disease and that the pathogenesis of atherosclerosis and glomerulosclerosis in kidney damage may have a common pathway. In this process, persistent albuminuria stimulates excess lipoprotein synthesis in the liver, thereby disrupting the lipid synthesis cycle. It has been suggested that many of the diseases of the glomerular and tubulointerstitial apparatus are associated with atherosclerosis (the term "glomerular atherosclerosis" is proposed), including dyslipidemia. Since then, numerous clinical and laboratory studies have confirmed the hypothesis that hyperlipidemia is the result of compensatory synthesis of liver lipoproteins in response to urinary albumin excretion and contributes to the progression of atherosclerosis and glomerulosclerosis [6].

Hyperlipidemia can have its effect on the progression of renal damage in several ways. 1. By developing intrarenal atherosclerosis. 2. Through the toxic effect of lipids on the structures of the nephron.

The main mechanisms of CKD progression associated with lipid metabolism differ depending on the stage of the process. At the same time, there are some common developmental features, which are based on elevated levels of cholesterol (HC), triglycerides (TG), low-density lipoproteins (LDL) and low levels of high-density lipoproteins (HDL) in blood plasma [1,21]. It has been shown that in nephrological patients dyslipidemia leads to damage to the endothelium of glomerular capillaries and deposition of lipids in mesangial cells, which bind and oxidize LDL, stimulating the proliferation of mesangium and the development of glomerulosclerosis [20]. Hyperlipidemia increases the activation of mesangial cells with LDL receptors, which leads to stimulation of cell proliferation and increased synthesis of macrophages, chemotaxis factors, extracellular matrix components, plasminogen activator-1, reactive oxygen species, etc.[11,13,16].

At the same time, LP deposited in the basement membrane of cells bind glycosaminoglycans and thereby increase the permeability of the membrane to proteins. As a result of this process, lipoproteins (LP) filtered in the glomeruli settle in the tubules of the kidneys, which initiates tubulointerstitial processes and sclerosis. In the future, an increased content of lipids leads to their capture by the epithelium of the tubules and deposit inside the

cells. The deposition of lipids in mesangiocytes and tubular epithelium gives the cells a characteristic foamy appearance. This leads to their dystrophy and atrophy with the accumulation of lipid material in the intercellular space [2] (Fig. 1).

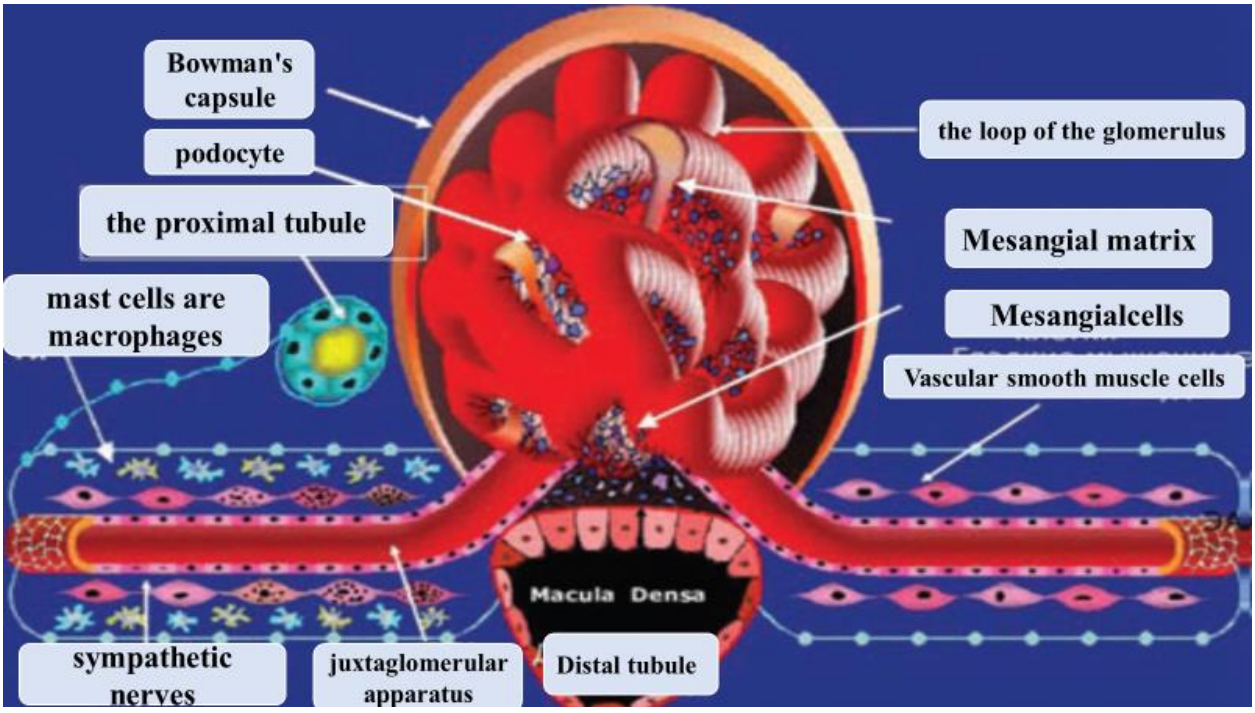

Figure 1. A — normal nephron;

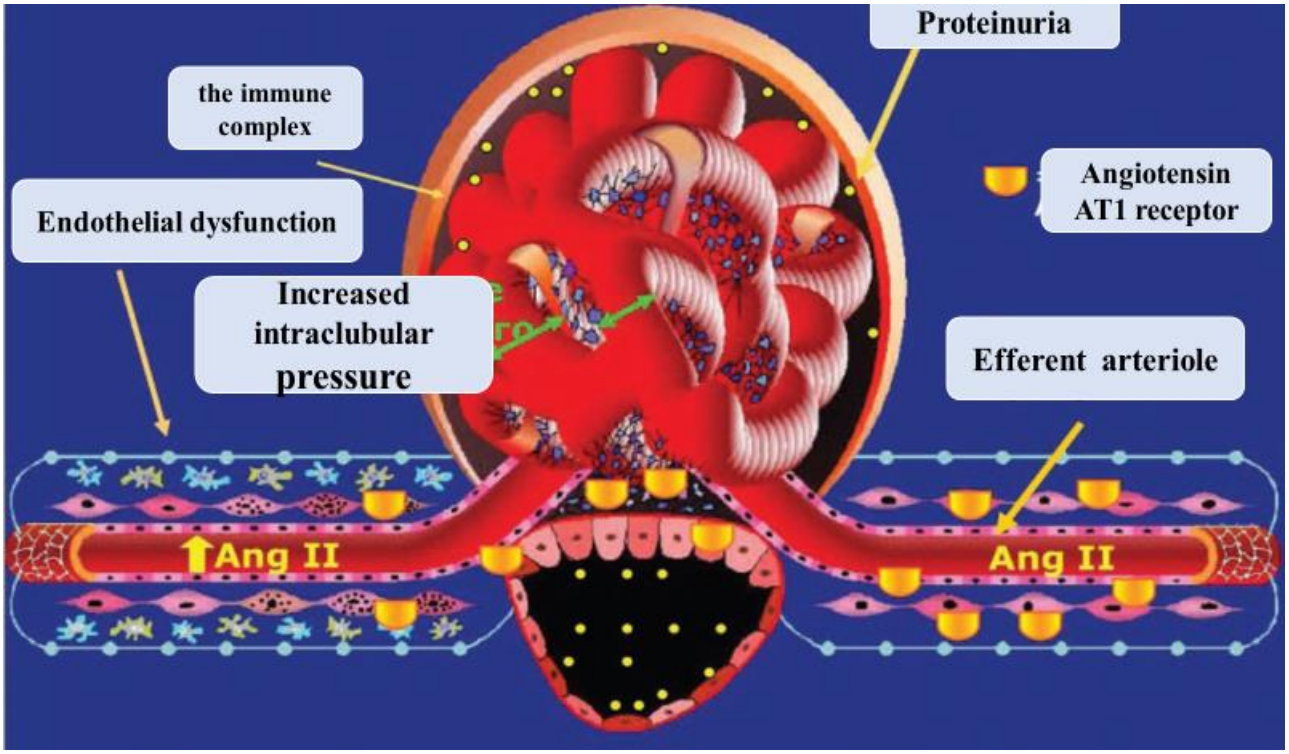

Figure 1. B — activation of mesangial cells in hyperlipidemia. Occlusion of glomerular capillaries by lipid deposits and foam cells reduces glomerular filtration. This leads to an increase in systemic blood pressure, intraclubular pressure in intact nephrons and contributes to glomerulosclerosis

The morphological substrate of CKD is glomerulosclerosis, characterized independently of the primary pathology of the kidneys by mesangium sclerosis, expansion of the extracellular matrix, which includes laminin, fibronectin, heparan sulfate proteoglycan, type IV collagen and interstitial collagen (normally absent in the glomeruli). An increase in the extracellular matrix replacing functionally active tissue is a complex process involving various growth factors, cytokines and heat shock proteins. It was found that in most patients with GFR of about 25 ml/min and below, terminal chronic renal failure occurs regardless of the nature of the disease. There is an adaptive response of intrarenal hemodynamics to the loss of mass of active nephrons. This is manifested in a decrease in resistance in the afferent and efferent arterioles of functioning nephrons, leading to an increase in the rate of intraclubular plasma flow, that is, to hyperperfusion of the glomeruli and an increase in hydraulic pressure in their capillaries. As a result, hyperfiltration occurs, and subsequently glomerulosclerosis. Tubular epithelial dysfunction is closely related to the development of tubulo-interstitial fibrosis (Fig. 2).

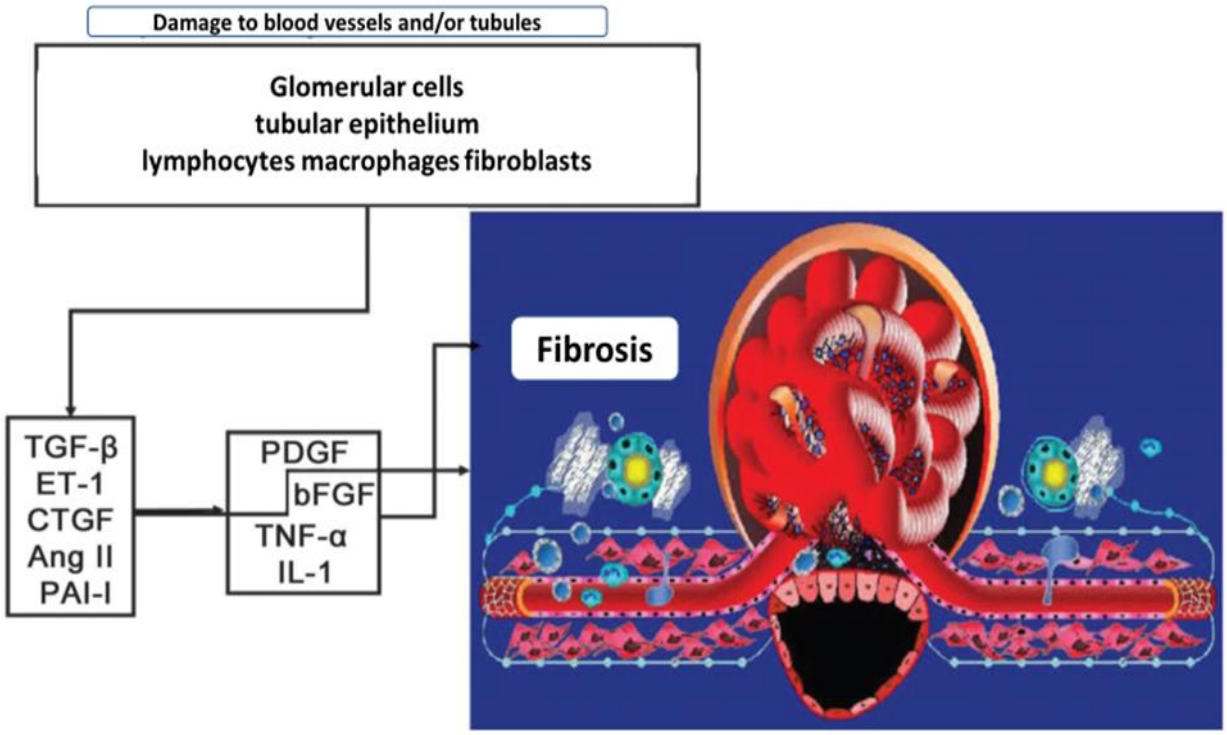

Figure 2. Damage to renal tissue and the development of fibrosis

The tubular epithelium is capable of synthesizing a wide range of cytokines and growth factors. In response to damage or overload, it enhances the expression of adhesion molecules, the synthesis of endothelin and other cytokines that contribute to tubulointerstitial inflammation and sclerosis. Any damage to the vessel wall stimulates platelet aggregation with the release of thromboxane, a powerful vasoconstrictor that plays an integral role in the development of hypertension. Hyperlipidemia stimulates increased platelet reactivity and aggregation, the combination of which with arterial hypertension is accompanied by even more pronounced glomerular changes.

Activation of lipid peroxidation in the membranes of endothelial cell structures leads to a loss of their functional activity and is one of the mechanisms for the development of kidney diseases, which determines the degree of intoxication in CKD [3]. At the stage of severe CKD, lipoproteins undergo modification and become oxidized LDL (ok-LDL). LDL-C contributes to

the adhesion of monocytes to the endothelium of glomerular capillaries and affects the cells of the tubular epithelium [7]. They bind to receptors in the mesangium and, through a number of cellular and molecular mechanisms, enhance inflammatory and fibrogenic processes in it. The cytotoxic effect of LDL-C is manifested in the induction of podocyte apoptosis with loss of nephrin and damage to the glomerular barrier.

Thus, dyslipidemia is closely related to the progression of CKD. Its effect is due to both atherosclerotic damage to the renal vessels and the direct nephrotoxic effect of lipids. Lipid—lowering therapy in patients with CKD has the main goal of preventing the development and progression of CKD itself.

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