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Renal Damage in Metabolic Syndrome

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Abstract: This article presents a modern view of the concept of MS and CKD, discusses its main diagnostic criteria, issues of etiology and pathogenesis. The study of the relationship between MS and CKD suggests that the high prevalence of kidney dysfunction in the general population is largely determined by nephropathies of a metabolic nature, including those associated with obesity. Identification of risk factors and markers of poor prognosis in patients of this category seems extremely important in relation to the possibility of increasing the early diagnosis of the disease, and their timely elimination seems to be one of the main approaches to the comprehensive prevention of CKD in these patients.

Keywords: metabolic syndrome, kidneys, obesity, arterial hypertension, pathogenesis.

Relevance. The relevance of the problem of metabolic syndrome (MS) is determined by both its high prevalence and the variety of clinical manifestations, negative impact on the cardiovascular system and kidney function. Often it is kidney damage that determines the prognosis of patients with metabolic syndrome. It has been shown that in MS, the risk of developing chronic kidney disease (CKD) and its severity increase by more than 2.5 times and are directly proportional to the number of MS symptoms (from 2.2 times with one symptom to 5.9 times with 5 symptoms) [2 -4]. Even with 3 symptoms, the risk of having CKD is 75% [5].

It is known that the combination of chronic kidney disease and metabolic syndrome is a factor of high cardiovascular risk, including fatal cardiovascular events. At the same time, metabolic syndrome is one of the conditions in which an “asymptomatic” version of chronic kidney disease can be observed.

Metabolic syndrome (MS) is a set of genetic, physiological, biochemical and clinical factors, the manifestation of which is the development of insulin resistance, dyslipidemia, visceral obesity, arterial hypertension, hypercoagulable state, endothelial dysfunction, hyperuricemia. The high relevance of the study of MS is due to its significant prevalence throughout the world. About one in four or five adults (depending on country and ethnic group) has metabolic syndrome. With age, there is an increase in incidence. The proportion of people with MS among the population over 30 years of age is 10–20%, and in the USA it is 25% [1–4]. The average global prevalence among men and women is 24%. If it was previously believed that MS was characteristic of older people, then studies conducted by the American Diabetes Association show an increase in the incidence among young people aged 20–29 years. It is expected that by 2025 the number of patients with this syndrome will be 300 million people. Therefore, the World Health Organization (WHO) considers MS a global epidemic.

The relationship between insulin resistance (IR) and CKD has been identified for a long time [6–8]. A similar relationship occurred between the presence of metabolic syndrome and an increased risk of CKD [9] and proteinuria [10]. It was later shown that plasma insulin, C peptide, glycated hemoglobin (HbA1c) and HOMA-IR levels progressively increase in individuals with CKD [11]. Subsequently, the connection between the deterioration of renal function and the progression of IR found even more confirmation [12–14].

According to Melnik A.A. (2017) risk factors for CKD in MS are: insulin resistance, obesity, dyslipidemia, high blood pressure, reactive oxygen species, inflammatory cytokines, increased activity of coagulation factors, inhibition of the fibrinolytic system. Insulin resistance and hyperinsulinemia associated with metabolic syndrome may be causes of renal inflammation and fibrosis. The effects of insulin are multifaceted. They occur through stimulation of mesangial and proximal tubular cells

producing TGF-β (transforming growth factor β) [16] and promote the formation of IGF-1 (insulin-like growth factor 1) in vascular smooth muscle cells and other cell types [17]. IGF-1, in turn, increases the activity of tissue growth factor and cytokines.

This is manifested by a profibrinogenic effect on renal tubular cells and interstitial fibroblasts [18]. In addition, IGF-1 reduces the activity of matrix metalloproteinase-2, an enzyme responsible for extracellular matrix degradation, thereby promoting extracellular matrix expansion and renal fibrosis. Pathological disorders in the kidneys in patients with MS are manifested by an increase in microvascular tubular atrophy, interstitial fibrosis and global or segmental sclerosis [12].

One of the main risk factors for metabolic syndrome is dyslipidemia, which may be associated with an altered lipoprotein spectrum and modified lipoproteins. Dyslipidemia caused by MS is a lipid triad: 1. Increased postprandial lipoproteins with a high TG content. 2. Decrease in HDL-C levels. 3. Increase in small dense LDL-C particles. Dyslipidemia in metabolic syndrome contributes to the risk of chronic kidney disease. Manttari et al [9] in the ARIC study, using a meta-analysis method, showed that elevated triglycerides and low plasma HDL-C are independent risk factors for the development of CKD. With dyslipidemia, which is observed in patients with MS, atherosclerotic changes in the renal arteries may occur, contributing to the development of renovascular arterial hypertension. Characteristic signs of dyslipidemia in MS, leading to kidney damage, are an increase in serum levels of TG, total cholesterol, LDL-C, as well as lipid deposition in the mesangium and tubulointerstitium, which contributes to the progression of CKD.

During the research of Zhalilov Sh.Kh. et al. (2024) studied the relationship between indicators of subclinical kidney damage and impaired endothelial function and established the following conclusions: In patients with metabolic syndrome, in addition to the known manifestations, there may also be disturbances in the functional state of the kidneys and endothelium, which in the early stages are manifested by changes in glomerular filtration rate, increased the level of urinary excretion of albumin and an increase in the concentration of endothelin-1 in the blood. The direct correlation of the level of albumin excretion in the urine and the level of endothelin-1, as well as the coincidence of the correlation relationships of these indicators with a number of clinical and laboratory indicators of metabolic syndrome, allows us to consider an increase in the level of albumin excretion in the urine as one of the markers of endothelial dysfunction.

According to S.V. Nedogoda et al. (2018) presented the pathogenetic mechanisms of kidney damage in metabolic syndrome (factors and mechanisms): Adiponectin - reduction of tubular inflammation; Arterial hypertension - Increased intraglomerular pressure with deterioration of glomerular filtration and increased protein filtration (microalbuminuria and proteinuria); Visfatin - Pro-inflammatory effect: increased formation of tumor necrosis factor alpha (TNF-α), interleukins IL-6, IL-1β); Dyslipidemia - Atherosclerosis of the renal arteries; Excessive formation of adipose tissue - Deterioration of hemodynamics (increased kidney mass, increased glomerular planar surface and effective plasma flow, decreased glomerular filtration rate, mesangial expansion, podocyte damage, development of focal segmental glomerulosclerosis); Plasminogen activator inhibitor type 1 (PAI-1) - Prothrombotic status; Insulin resistance (IR) and hyperglycemia - Activation of the renin-angiotensin-aldosterone system; decreased production of nitric oxide and oxidative stress [11]. Inflammation (overproduction of transforming growth factor beta (TGF-β) and increased production of insulin-like growth factor 1 (IGF-1) in vascular smooth muscle cells. Fibrosis (IGF-1 reduces the activity of matrix metalloproteinase-2 and promotes expansion of the extracellular matrix and the development of renal fibrosis) ; Leptin - Sodium retention, hyperactivation of the sympathoadrenal system, increased formation of collagen and TGF-β1, leading to thickening of the basement membrane and glomerulosclerosis; Resistin - Proinflammatory effect (increased formation of TNF-α, IL-6, lipoprotein-associated phospholipase A2), increased formation of endothelin 1; , monocyte chemotactic factor 1 (MCP-1), vascular endothelial adhesion molecule (VCAM) and increased infiltration of smooth muscle cells; Tumor necrosis factor α (TNF-α) - Increased insulin resistance and production of reactive oxygen species, leading to worsening renal endothelial dysfunction, microalbuminuria. , mesangial expansion and fibrosis.

The literature presents many studies indicating the negative impact of MS not only on the heart and blood vessels, but also on kidney function, which leads to the development of chronic kidney disease (CKD). The results of the studies ACCOMPLISH, ALTITUDE, SHARP, ADVANCE, ROADMAP, CARRESS-HF [11] and some others made it possible to recognize CKD as an independent risk factor for the development of cardiovascular diseases and equivalent to coronary artery disease in terms of the risk of complications. The increase in the incidence of CKD is largely due to the high prevalence of hypertension, obesity, the increase in the incidence of type 2 diabetes mellitus, as well as the prevalence of MS, the presence of which increases the likelihood of developing CKD, and this probability increases as the number of MS components increases. In patients with 2, 3, 4 and 5 MS criteria, compared with patients without them or with 1 MS criterion, the likelihood of developing CKD increases by 2.25, 3.38, 4.23 and 5.85 times, respectively [12].

In addition, MS is a risk factor for the development of CKD for patients under 60 years of age, and this relationship is linear [13]. Among the risk factors that determine the development and progression of cardiorenal syndrome, which is understood as maladaptive remodeling of the cardiovascular system, combined with CKD, a special place is occupied by the initial component of MS - abdominal obesity [14], which is an independent risk factor for irreversible deterioration of kidney function: an increase in the index body weight by 10% causes an increase in the probability of a persistent decrease in glomerular filtration rate (GFR) by 1.27 times, which is associated with the development of relative oligonephronia (relative deficiency of nephron mass, i.e., a decrease in the mass of functioning renal tissue compared to the total body weight) in obesity [15]. Currently, CKD is diagnosed by detecting anatomical or structural kidney damage and/or a decrease in GFR.

A significant role in the development of hypertension, obesity and MS belongs to increased activity of the sympathetic part of the autonomic nervous system (S-ANS) [17]. In turn, hypersympathicotonia associated with insulin resistance leads to a number of complications, including remodeling of the heart and blood vessels, disorders of lipid and carbohydrate metabolism, and hyperinsulinemia [18]. Already with the appearance of the first signs of kidney damage in the form of increased filtration load (hyperfiltration), hypersympathicotonia is also observed, which contributes to the progression of damage to target organs, including the kidneys [19]. A number of studies describe various hormonal disorders: activation of the hypothalamic-pituitary-adrenal axis, increased levels of testosterone and androstenedione and decreased production of progesterone in women, decreased production of testosterone, dihydrotestosterone and growth hormone in men, increased production of norepinephrine, promoting activation of the C-ANS and development abdominal obesity [10].

Thus, MS is pathogenetically associated with CKD and is an independent prognostic factor for its development; it is the involvement of the kidneys that often determines the prognosis and quality of life of such patients [11].

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