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FEATURES OF KIDNEY DAMAGE IN CHILDREN WITH OBESITY
(Literature review)

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SUMMARY

The review provides information about the morphology and function of the kidneys in children with obesity. The influence and interrelationship of numerous pathogenetic factors affecting the functioning of the kidney is discussed. The use of early biomarkers of kidney pathology in obesity with an assessment of the level of lipid and carbohydrate metabolism, insulin resistance, serum leptin and adiponectin is promising for diagnosing renal lesions in obesity in children.

Keywords: obesity, kidneys, children.

INTRODUCTION

In the last decade, the prevalence of obesity has acquired the character of a pandemic, which is a medical and social health problem throughout the world [5,14]. According to the World Health Organization global estimate in 2016, more than 340 million children and adolescents aged 5-19 years and 41 million children under 5 years of age were overweight or obese (WHO, 2016) [60,61].

The relevance of this problem also lies in the fact that the high prevalence of obesity contributes to the development of chronic diseases, including chronic kidney disease [6,10,16,41].

Obesity is one of the main symptoms of the metabolic syndrome, however, characteristic changes in the kidney tissue in obesity are also detected in the absence of concomitant arterial hypertension and type 2 diabetes mellitus or when these conditions are compensated. Glomerulopathy associated with obesity (GPO) [obesity-related nephropathy] is a nosological unit recognized not only in therapeutic, but also in pediatric nephrology [16,33].

Currently, the term end-stage renal disease (ESRD) or "end-stage renal disease" (ESRD) is widely used in the literature, which is understood as the development of renal failure as an outcome of a number of different factors. The morphological manifestation of ESRD is glomerulosclerosis and tubulointerstitial fibrosis. The most common causes of ESRD are considered to be systemic arterial hypertension with the development of a primary wrinkled kidney and type 2 diabetes mellitus (DM2), which has been shown in a number of experimental and clinical studies[4,20,21]. On the other hand, it was found that an increase in the risk of developing cardiovascular diseases, in particular arterial hypertension, correlates with the level of pathological fat accumulation, and the development of DM2 is usually preceded by obesity [31,44]. Moreover, it has been shown that the presence of obesity significantly reduces life expectancy, and in two out of three cases, death occurs from a disease associated with lipid metabolism and overweight. [25].

Despite the fact that both of the most common causes of ESRD are directly related to excess body weight, only recently have obesity been considered as a possible cause of kidney failure [54], and its association with kidney pathology is discussed only in a few clinical studies. Thus, the importance of obesity as a predisposing factor in the development of focal segmental glomerulosclerosis has been shown[38,56]. In immunoglobulin A nephropathy, excess body weight is considered as an independent risk factor affecting overall and renal survival [24,42]. In kidney transplant patients, the role of obesity in the development of chronic graft rejection and worsening overall prognosis is discussed. [37,47,62]. The literature contains only a few works describing the structural and functional changes in the kidneys in obesity. They are expressed in focal glomerulosclerosis and other changes resembling the morphological picture in T2DM [39]. The mechanisms of the development of the pathological process in the kidneys under the influence of excess body weight are little studied and only a few, mostly experimental, research works in this area are known[29,35,43]. However, the data accumulated to date make it possible to form an idea of the contribution of obesity and its accompanying metabolic, hormonal, and hemodynamic disorders to the formation of pathological changes in the function and structure of the kidneys.

The Framingham Heart Study and 18-year follow-up showed a higher risk of developing stage III chronic kidney disease (CKD) in obese patients (body mass index (BMI) > 30 kg/m2) compared with overweight patients (BMI 25 –30 kg/m2) [32]. It has been proven that in patients with nephropathies against the background of visceral obesity, the lipid spectrum of blood serum is characterized by an increase in lipid atherogenicity with a decrease in high-density lipoprotein cholesterol [18], an increase in serum triacylglycerols, total cholesterol, very low-density lipoprotein cholesterol in combination with hyperleptinemia and impaired glucose tolerance [18]. It has been established that an increase in serum leptin and a violation of lipid metabolism in children with nephropathies against the background of visceral obesity is associated with changes in echographic indicators of the structural state of the kidneys, intrarenal hemodynamics, and a partial decrease in renal functions[2,3].

It has been proven that kidney disease progresses in patients with hypertension with the formation of nephrosclerosis and the development of a primary wrinkled kidney. In type 2 diabetes, tubulointerstitial fibrosis, glomerulosclerosis, and diabetic nephropathy develop[9].

Obesity-associated kidney disease with diabetes develops when several metabolic and hemodynamic factors interact, activating common intracellular signals, which, in turn, cause the production of cytokines and growth factors that form kidney failure. The mechanisms underlying glomerular hyperfiltration in obesity are widely discussed in the literature[7]. The recognized mechanism is data on an increase in sodium reabsorption in the immediate vicinity of the tubules or the loop of Henle, leading to the development of tubuloglomerular feedback - an indirect decrease in afferent arteriole resistance, an increase in intracapsular pressure and glomerular filtration rate [48].

Among the main factors in the progression of kidney damage in obesity are: insulin resistance (IR), hyperinsulinemia, dyslipidemia, impaired systemic and renal hemodynamics, ischemia of kidney tissues, auto- and paracrine effects of adipose tissue hormones [7, 13,17]. Currently, when evaluating the pathophysiological mechanisms of kidney damage, special attention is paid to studying the role of the metabolic syndrome (MS). Many authors believe that the key

pathogenetic link in kidney damage is the production of biologically active substances, adipocytokines, by adipose tissue, which makes it possible to consider adipose tissue as an active endocrine organ. Among adipokines, special attention is paid to leptin and adiponectin. [28].

It has been established that the initial increase in the glomerular filtration rate associated with obesity is an early compensatory response that contributes to the restoration of salt balance, despite the ongoing activation of reabsorption. Long-lasting glomerular hyperfiltration is the cause of the development of damage to the kidney tissue, especially in patients with a combination of hypertension. There are studies that show a reduction in glomerular hyperfiltration and damage to kidney tissue with weight loss[27].

Determination of markers of endothelial dysfunction is currently relevant in many diseases, including kidney diseases [12]. Endothelial dysfunction in CKD patients is considered as an imbalance between vasoconstrictors and relaxing factors, between anti- and procoagulant mediators, growth factors and their inhibitors[46].

The relationship of endothelial dysfunction (ED) with kidney damage seems to be natural, but insufficiently studied. The pathological role of endothelial dysfunction is described in chronic pyelonephritis, chronic glomerulonephritis [1].

Currently, endothelial dysfunction is understood as an imbalance between the production of vasodilating, athrombogenic, antiproliferative factors, on the one hand, and vasoconstrictor, prothrombotic, and proliferative substances produced by the endothelium, on the other [1]. Decreased endothelial synthesis of nitric oxide (NO), increased levels of endothelin-1, circulating von Willebrand factor, plasminogen activator inhibitor, homocysteine, thrombomodulin, soluble molecule of vascular intercellular adhesion B1, C-reactive protein, microalbuminuria and others are considered to be markers of endothelial dysfunction. [8].

Microalbuminuria is a proven highly sensitive marker of prognostically unfavorable kidney damage, and also reflects the presence of endothelial dysfunction. The detection of non-selective proteinuria indicates a gross damage to the renal structures and, in addition, becomes a direct damaging factor contributing to the progression of nephrosclerosis. The damaging effect of systemic arterial hypertension on the kidneys is realized through a violation of renal hemodynamics under the influence of a cascade of changes in the renin-angiotensin-aldosterone system (RAAS). The appearance of these clinical symptoms indicates a pronounced, often irreversible damage to the renal tissue. In this regard, active research continues on early biological indicators of kidney damage, among which markers of endothelial dysfunction are being actively studied[1].

Morphological changes in the nephron in obesity are similar to those in oligomeganephronia. In accordance with the concept of "three strikes" [19], a small number of nephrons at birth can be the "first strike", while the "third strike" is the development of obesity and insulin resistance. In the context of kidney disease in children, decreased nephron mass and risk of developing end-stage renal disease are associated with low birth weight for gestational age or premature birth with a body weight appropriate for gestational age [58]. Many studies provide support for the hypothesis that birth weight is associated with disease in later life (the Barker hypothesis). In particular, a relationship has been established between reduced birth weight and an

increased risk of coronary heart disease, type 2 diabetes mellitus, hypertension, hyperlipidemia, stroke and heart attack[36].

In advanced cases, secondary focal segmental glomerulosclerosis (FSGS) may develop [26]. This form differs in that it is not characterized by massive proteinuria, corresponding to the nephrotic syndrome, and there is practically no edema. In severely obese individuals with preserved kidney function, biopsy specimens show morphological changes, including glomerulomegaly, podocyte hypertrophy and fusion, mesangial matrix expansion, and mesangial cell proliferation[53]. Glomerulomegaly is the primary histopathological feature that distinguishes GPO from primary FSGS [52]. Glomerular basement membrane (GBM) thickening, previously thought to be an early manifestation of hyperglycemia and diabetic nephropathy, may be an additional pathological finding in obesity. Thickening of the GBM is found on biopsy in patients with nephrosclerosis associated with essential hypertension and in patients with HPO with normal glycemia. GBM thickness directly correlates with cholesterol and triglyceride levels [40]. According to American pathologists who studied 6818 kidney biopsies over a period of 15 years, the frequency of GNO increased 10 times: from 0.2% of all biopsies studied in 1986 to 2% in 2000 [50].

Adipose tissue produces a number of peptides of the blood pressure regulation system: angiotensinogen, angiotensin I and II, renin. These peptides directly affect renal blood flow and nephron function. The pathogenetic relationship between arterial hypertension (AH) and obesity is not completely clear. Obesity-associated hypertension is obviously the result of a combination of many factors. Obesity increases the risk of developing hypertension by 65–75% [49]. It has been hypothesized that elevated levels of insulin and leptin may activate obesity-associated hypertension by stimulating centers of the sympathetic nervous system (hypothalamus or nucleus tractus solitarius in the midbrain). The link between leptin and midbrain sympathetic centers involves two transmitters known as neuropeptide Y and melanocortin. Melanocortin receptor mutation found in families with early onset obesity [30].

The key link linking obesity and hypertension is an increase in tubular sodium reabsorption. An important determinant of tubular reabsorption is glomerular hyperfiltration.

Obviously, patients with obesity are not homogeneous in the nature of changes in intrarenal hemodynamics. Thus, when examining adult men with obesity (BMI > 36), Israeli nephrologists (Rabin Medical Center) identified two groups of patients that differed in the level of sodium filtration fraction (FFNa). In both groups, GFR significantly exceeded that in the group of people with normal body weight. In the group of patients with a high FFNa index, postglomerular oncotic pressure was 13% higher, and the fractional excretion of lithium (a marker of proximal sodium reabsorption) was 33% lower than in the control group. In the second group with normal FFNa levels, postglomerular oncotic pressure and fractional lithium excretion remained normal. The authors believe that the mechanism of hyperfiltration in severe obesity is heterogeneous [27]. Previous observations of these authors in patients with severe obesity showed that the renal plasma flow (RPF) changes to a lesser extent compared to GFR.

It is assumed that in diabetes mellitus [57] and obesity [27] in the kidneys, proximal sodium reabsorption increases under the influence of an unknown factor that activates tubuloglomerular feedback, and thus causes glomerular hyperfiltration. The authors believe that a vicious circle is being created: an increase in sodium reabsorption increases GFR, which,

in turn, leads to an increase in FF, an increase in postglomerular oncotic pressure, stimulation of proximal sodium reabsorption, and again to an increase in GFR. This action of hyperfiltration on sodium reabsorption reduces sodium excretion associated with high GFR and supports both salt retention and hyperfiltration. There are other mechanisms that increase proximal sodium reabsorption in obese individuals. Obesity is associated with RAAS activation caused by numerous factors, including the secretion of angiotensin II by adipocytes. An increase in the concentration of angiotensin II increases proximal sodium reabsorption without the effect of this hormone on the level of FF [57]. Another determinant of sodium excretion is pressure in the interstitial tissue of the kidneys. It is assumed that the increase in pressure in the interstitium may be caused by subcapsular fatty infiltration and abdominal fat deposits. This compresses the tubules, slows down the flow of urine and increases sodium reabsorption in the loop of Henle [34] and the proximal nephron [57].

It must be admitted that high GFR values cannot be considered a universal sign of obesity. Indian pediatricians, comparing this indicator in school-age children (mean age -9 years, i.e. before puberty) with overweight with a control group of children who did not differ in age and sex, but with normal body weight, did not find significant differences neither in GFR, nor in blood pressure, nor in albumin excretion [59].

In some adult patients with clinically significant obesity, there is a decrease in GFR, an increase in renal vascular resistance, and a decrease in effective renal blood flow [23]. Increased intra-abdominal pressure is a common occurrence in individuals with high waist-hip index values. It can cause compression of the renal vein and thus raise venous pressure and reduce renal perfusion. In addition, a rise in intra-abdominal pressure can increase pressure in the inferior vena cava, further impairing renal venous outflow. In support of this hypothesis, when measuring ileofemoral venous pressure, its high values were revealed with pronounced degrees of obesity, and a positive correlation of this indicator with intra-abdominal pressure was found [59]. Elevated intra-abdominal pressure may have other hemodynamic consequences: increased intrathoracic pressure, increased right heart workload, pulmonary hypertension, and reduced cardiac output. All of these conditions can also reduce renal perfusion[22].

Diagnosis of kidney damage in obese patients is generally straightforward. Changes in their urine, as a rule, are not very informative: leukocyturia, erythrocyturia are not characteristic (it must, however, be borne in mind that this category of patients is at greater risk of nephrolithiasis, primarily urate), proteinuria does not exceed the level of "trace" . A much more accurate method for diagnosing an early stage of kidney damage is the quantitative determination of albumin in the urine, which allows timely detection of microalbuminuria[45]. At the screening stage, it is possible to use test strips (micral test). Determination of serum creatinine concentration and calculation of glomerular filtration rate using the Cockroft-Gault or MDRD formulas are also mandatory, although it is believed that the diagnostic accuracy of these tests decreases in obese patients. It is necessary to evaluate indicators characterizing the metabolism of lipoproteins (serum concentration of total cholesterol, low, very low and high density lipoproteins, triglycerides), fasting glycemia and uricemia, as well as conducting diagnostic tests used to diagnose insulin resistance [3,15].

CONCLUSION

Obesity is the earliest and most noticeable sign of a metabolic disorder in a child. It appears much earlier than arterial hypertension, insulin resistance and diabetes mellitus. The prerequisites for all these states are laid in the prenatal period. Already in the early stages of excessive accumulation of adipose tissue in the body, significant changes occur in target organs. The kidneys are one of the first organs that take on a compensatory function with increasing body weight and at the same time undergo pathological changes.

The main links in the pathogenesis of obesity nephropathy are hemodynamic disorders, endothelial dysfunction, exposure to biologically active substances secreted by adipocytes, lipotoxicity, and latent inflammation. Pathological factors affecting the kidney are closely related, complement and activate each other, forming a complex interweaving. In pediatrics, it is practically important to single out the risk group for the formation of obesity nephropathy, metabolic syndrome, and cardiorenal syndrome. The risk group should include children born with low body weight for gestational age, children with signs of early obesity, children from families with obesity, impaired carbohydrate metabolism and arterial hypertension. Further research will make it possible to individualize the approach to each child with overweight, to diagnose and correct the leading link in impaired metabolism.

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