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Clinical and Pathogenetic Aspects of the Appearance of Chronic Kidney Disease in Patients with Type II Diabetes Mellitus

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Summary: In modern medicine, one of the urgent problems is type 2 diabetes mellitus, which, according to the calculation of many scientists, will affect one in three in the world. This is connected both with a way of life, which includes physical inactivity, an unbalanced diet rich in carbohydrates, and stress. As a result, chronic kidney disease occurs, due to the colossal load on this organ. In routine practice, guided by the clinical guidelines "Chronic kidney disease in patients with diabetes mellitus", for the diagnosis and successful prevention of the development of CKD, the determination of CKF by creatinine and the level of albuminuria is used. Unfortunately, these methods, despite their informativeness, have a number of limitations. Thus, a transient increase in albumin excretion is possible with decompensation of carbohydrate metabolism, a high-protein diet, after heavy physical exertion, against a background of fever, with urinary infection, etc.).

Relevance.

Risk Factors for Diabetic Nephropathy. The need to predict the occurrence of DN, including the end-stage renal dysfunction in people with DM, is dictated, as mentioned above, by the fact that DN is the cause of dialysis-requiring CKD in 40–50% of cases. The mentioned study demonstrated that significant risk factors for the development of CKD in the population of people with diabetes are older age, retinopathy, albuminuria, glycohemoglobin (HbA1c) ≥ 7%, anemia and hyperuricemia [13,16].

Age. Old age is a non-modifiable factor in the development of CKD.One publication noted that among 550 patients with type 2 diabetes aged 35 years and older, the overall prevalence of albuminuria was 34.6%. G.T. Russo et al (2018) studied the association of clinical variables and quality of care measures with estimated glomerular filtration rate (GFR) + albuminuria in 157,595 patients with type 2 DM, stratified by age. The prevalence of reduced estimated GFR + albuminuria was shown to increase with age. In addition, this subgroup of patients had the worst risk factor profile compared with individuals without renal insufficiency, regardless of age. Apparently, in older age groups, a decrease in kidney function occurs against the background of morphological changes in the kidneys that occur with age, in particular, a decrease in their size, a decrease in effective renal blood flow in the cortical layer, glomerular hyalinosis, sclerotic changes in the interstitium and atrophic changes in the tubules. . As a rule, with age, the value of GFR gradually decreases (especially after 40 years) by about 1% per year, and GFR in women is usually 15% lower than in men with the same level of blood creatinine. At the same time, with an increase in age and a decrease in GFR, a number of biochemical changes are formed in the patient's body, which almost completely coincide with the so-called non-classical or non-traditional risk factors for cardiovascular diseases [2,14].

The role of hyperglycemia

The classic kidney damage in DM is the development of diabetic nephropathy, a microvascular complication of DM, which is characterized by the development of nodular or diffuse glomerulosclerosis [3,7]. requiring RRT. According to modern concepts, the development of DN,

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CKD is a multifactorial process; among the mechanisms of development, the role of metabolic, hemodynamic, and genetic factors is discussed [1,8]. Undoubtedly, chronic hyperglycemia is the leading cause of the development of all vascular complications of DM, including CKD, initiating reactions such as oxidative stress, non-enzymatic glycosylation of proteins, the polyol pathway of glucose oxidation, which further provokes the development of pathological changes in the kidneys [9,10]. Also, the pathological effect occurs indirectly through intrarenal hemodynamics: hyperglycemia contributes to the dilatation of the afferent arteriole, resulting in the development of kidney hyperperfusion [4,6]. The result of intraglomerular hypertension is the high permeability of basement membranes for various plasma components (proteins, lipids), which are deposited in the intercapillary space, provoking hyperproduction of pro-inflammatory cytokines, stimulates mesangial cells of the glomeruli of the kidneys, increases the production of type IV collagen, the result is the development of glomerusclerosis. Hyperglycemia as a risk factor for the development of damage to renal structures is not currently discussed, the critical importance of carbohydrate metabolism compensation has been repeatedly confirmed in many large-scale studies, such as UKPDS, DCCT, etc.

The role of dyslipidaemia and obesity

Together with hyperglycemia, changes in the lipid spectrum have a significant impact on the development of diabetic microangiopathies. Dyslipidemia in DM is characterized by: an increase in the rate of formation and concentration of very low-density lipoproteins (VLDL), a decrease in high density lipoproteins (HDL), hypertriglyceridemia, an increased content of free (non-esterified) fatty acids (NEFA) [12]. In addition to the diabetic causes of dyslipidemia, the world has faced non-communicable epidemics of obesity and overweight and the kidneys are considered a separate target organ for obesity, the defeat of which is considered as an independent risk factor for the development of renal failure [5]. Thus, between 1978 and 2013, the proportion of overweight and obese adults (BMI ≥25 kg/m2) worldwide increased from 28.8% to 36.9% among men and from 29.8% to 38.0 % among women [11].

Kidney damage in obesity is a complex multifactorial process. It includes direct factors directly related to obesity that determine the development of specific obesity-associated glomerulopathy (O-GP), as well as a number of obesity-related conditions (insulin resistance, metabolic syndrome, diabetes mellitus, dyslipidemia, hyperuricemia, arterial hypertension), which predispose to the development of CKD. Obesity-associated glomerulopathy (O-GP) is one of the variants of kidney damage, which is characterized by glomerular hypertrophy and the formation of adaptive focal segmental glomerulosclerosis, which develop against the background of podocyte maladjustment in insulin resistance. The glomerulus enlarges in response to obesity-induced increases in GFR, renal plasma flow, filtration fraction, and tubular sodium reabsorption. Violation of intrarenal hemodynamics - the development of a "hyperfiltration" kidney is accompanied by a damaging effect of adipose tissue hormones (hyperleptinemia, activation of the RAAS, a decrease in the production of adiponectin); with ectopic lipid deposits in the kidney. The morphological picture of O-GP is characterized by a low density of glomeruli in the kidney (oligonephronia), leading to hypertrophy of the renal glomeruli and tubules; the development of perihilar focal segmental glomerulosclerosis (FSGS), severe podocyte damage and the development of a "fatty" kidney. The clinical picture of O-GP is characterized by a slow and gradual development of albuminuria, not exceeding stage A3 (300-1999 mg/day). Approximately 1/3 of patients develop an incomplete nephrotic syndrome with massive proteinuria, but without edema and hypoproteinemia. Complete nephrotic syndrome is observed in no more than 6% of patients with O-GP. Thus, altered fatty acid and cholesterol metabolism are increasingly recognized as key mediators of renal lipid accumulation, inflammation, oxidative stress, and fibrosis [11].

The role of endothelial dysfunction

The endothelium plays an important role in the control of vascular tone. It provides regulation of the lumen of the vessel, depending on the speed of blood flow and systemic pressure. The importance of the endothelium was stated as early as 1980 in Nature. The authors found the ability of an isolated artery to independently change muscle tone in response to acetylcholine without participation of

central (neurohumoral) mechanisms. Endothelial cells were then compared to the cardiovascular endocrine organ, linking blood and tissues. Endothelial cells release mediators of relaxation of smooth muscle cells of the vascular wall, the main of which is nitric oxide (NO), which is of decisive importance in maintaining vascular tone [5]. With prolonged damaging effects of hyperglycemia, hemodynamic overload, endothelial dysfunction occurs. The main manifestation of which is a decrease in the expression of endothelial NO-synthetase, a violation of the bioavailability of NO, the activity of angiotensin-converting enzyme (ACE) increases on the surface of the endothelial cell, the synthesis of vasoconstriction factors: angiotensin II, endothelin, etc., increases. together with proliferation become its main responses to external stimuli. In DM, a combination of protein kinase C activity factors, processes of non-enzymatic protein glycation, hyperproduction of free radicals causes deep damage to the endothelium, contributing to the initiation and progression of diabetic microangiopathies.The role of arterial hypertension in the development of CKD

An increase in blood pressure is recognized as an important factor in the progression of kidney pathology, the development of CKD, like hyperglycemia. This is due to disturbances in intrarenal hemodynamics, leading to intraglomerular hypertension that develops in patients with diabetes in the early stages of the disease. These changes with unsatisfactory compensation of carbohydrate metabolism can lead to the development of both kidney damage and the progression of hypertension. In DM1, it was noted that an increase in blood pressure from an early age was detected in patients with CKD, while it is kidney damage that subsequently becomes the leading cause of AH in DM1 [6]. In DM2, AH often precedes the diagnosis of DM and was a predictor of the development of kidney damage, while at the onset of DM2, the level of BP correlates with the presence of MAU, thereby reflecting the degree and severity of endothelial dysfunction [7]. The level of blood pressure is mainly regulated by two physiological parameters: systemic vascular resistance and cardiac output. Based on this, we can conclude that the formation of AH requires a consistently high cardiac output together with vascular hypertonicity. These two factors exist in diabetic kidney disease. The first factor leading to an increase in cardiac output in the mechanism of action of aldosterone, when sodium reabsorption by the renal tubules increases and, as a result, hypervolemia develops. The second factor is endothelial dysfunction, which occurs due to hyperactivation of local RAS, hyperglycemia, oxidative stress, and increased vasoconstriction, which leads to an increase in both total peripheral vascular resistance and intraglomerular pressure [8].

Glycemic and BP control, combined with early initiation of nephroprotective drugs from the groups of angiotensin converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers (ARBs), may delay the progression of diabetic kidney disease. The WHO MSVDD multicentre study, 2001 [9] was devoted to the study of risk factors for the progression of CKD. The study included 3.5 thousand patients with type 1 and type 2 diabetes, the follow-up period was 8.4 years. The results showed that in T1DM, elevated BP is a predictor of the progression of DN and increased the risk by 50%. In DM2, an additional factor in the development of CKD was lipid metabolism disorders, namely, an increase in the level of triglycerides.

In the RENAAL study, which included more than 1.5 thousand patients with type 2 diabetes with CKD, it was shown that effective antihypertensive therapy (AT1 receptor blockers were used) reduced the risk of developing CKD by 20%, the risk of creatinine doubling by 25%, the need for hemodialysis or kidney transplantation by 28% [15]. Thus, hypertension is a powerful factor in the development and progression of kidney damage.

The pathogenesis of the role of the renin-angiotensin system

RAS is classically accepted as one of the main regulatory mechanisms for maintaining blood pressure and circulating blood volume [6]. In the juxtaglomerular apparatus of the kidneys, renin is secreted, under its action, angiotensin I is first converted from liver angiotensinogen, then, under the action of ACE, it passes into angiotensin II, which is the most powerful vasoconstrictor factor. The main goal of RAS activation is to maintain systemic blood pressure, this is achieved through the effects of angiotensin II, which also regulates the synthesis and secretion of aldosterone, fluid balance by influencing sodium reabsorption in the distal renal tubules. In this case, the thirst center is stimulated

and the release of antidiuretic hormone from the pituitary gland increases, which increases the volume of circulating blood and changes the tone of the glomerular arterioles. In DM, RAS in the systemic circulation is reduced, but local RAS in the kidneys, vascular endothelium, brain, and heart are hyperactive. At the same time, the level of renin and angiotensin II in the kidneys is a thousand times higher than the concentration of these hormones in the blood plasma. Thus, angiotensin II causes vasoconstriction of the efferent arteriole of the glomerulus and mediates the development of intraglomerular hypertension, as well as systemic hypertension. Both of these factors: impaired intrarenal hemodynamics and increased systemic blood pressure are the most important links in the pathogenesis of CKD in DM.

Albuminuria/proteinuria. The appearance of albuminuria in DM indicates a violation of the integrity of the glomerular basement membrane and is the first laboratory marker of disease progression. In individuals with type 2 diabetes, risk factors for albuminuria are age, gender, arterial hypertension, hyperglycemia, lipid profile changes, smoking, insulin resistance, and metabolic syndrome. Persistent proteinuria is accompanied by inflammatory changes, both glomeruli and tubules. Studies conducted in recent years have shown that a slowdown in the filtration function of the kidneys precedes proteinuria. Proteinuria as a marker of kidney damage progression in type 2 DM was detected in 43.5% of cases.

Earlier, in a review study by M.V. Shestakova noted that since the onset of proteinuria, GFR begins to decrease by 1 ml/min per month (or about 10 ml/min per year), which leads to the development of end-stage renal failure already 7–10 years after the detection of persistent proteinuria. There is evidence that 1 in 4 women (26%) with type 2 diabetes have a GFR below 60 ml/min. Whereas 1 in 5 men (21%) with type 2 diabetes have a GFR below 60 ml/min. According to some data, the prevalence of albuminuria in type 2 diabetes is 43.5%. Previous epidemiological studies have shown that the prevalence of albuminuria in type 2 diabetes is 49%. In the above review study, it was noted that persistent albuminuria leads to pronounced structural changes in the glomeruli.As a rule, at this stage, proteinuria and a decrease in GFR are often recorded as an indicator of the formation of glomerulosclerosis. It should be noted here that adequate control of the glycemic profile and hypertension at an early stage of DN contributes to the reduction of albuminuria. Meanwhile, the albuminuric mechanism of CKD development is not mandatory in type 2 DM, in which a decrease in GFR by 40% or more is possible with normo- or microalbuminuria. It is important to remember that deterioration in renal nitrogen excretion in the absence of albuminuria may reflect the predominance of vascular and tubulointerstitial changes in the kidneys. In 22–24% of people with DM, screening provides a reduced GFR calculated using a formula available on the Internet. At the same time, almost every second patient with type 2 diabetes has signs of kidney damage. There is evidence that in type 2 DM, the presence of nephrotic proteinuria does not make it possible to unequivocally state the presence of DN. In about half of the cases, DN may be absent or combined with non-diabetic kidney pathology. According to the researchers, the development of renal failure against the background of nephrotic syndrome, especially in the presence of changes in the fundus of the eye and the absence of active urinary sediment, can be considered a characteristic manifestation of DN [7]. The most regular detection of interstitium fibrosis in patients with diabetes with proteinuria and renal failure. From the standpoint of the clinic, it should be emphasized that the clinical and morphological manifestations of kidney damage in type 2 diabetes are heterogeneous.So, in type 2 diabetes, at the onset of the disease, AH is found in 40–50%, albuminuria in 15–40%, and proteinuria in 7–10%. As shown in the clinical guidelines of the Russian Association of Endocrinologists (2016), in a series of kidney biopsies in patients with type 2 diabetes, even with proteinuria, atypical structural changes are detected in almost 30% of cases. Interestingly, only 30-40% of patients with type 2 DM have typical manifestations of DN.

According to H.H. Otu et al. (2007), microalbuminuria is not the earliest marker of damage to the glomerular basement membrane, and a decrease in CKF occurs in the late stages of nephropathy [8]. In addition, clinicians often have a situation where a decrease in GFR is detected with normoalbuminuria. So, according to I.I. Trofimenko et al. (2008), with a decrease in GFR<60 ml/min, 8.3% of patients with type 1 DM (DM1) and more than 40% of patients with DM2 do not have other manifestations of kidney damage (albuminuria, proteinuria, increased blood creatinine). In this case, the endocrinologist

cannot diagnose diabetic nephropathy (DN) and prescribe treatment. However, such patients need to be carefully monitored and controlled not only for glycemia, but also for other risk factors for CKD: arterial hypertension, obesity, hyperuricemia, dyslipidemia, infectious and inflammatory processes in the kidneys, and taking nephrotoxic drugs.

CONCLUSION. In conclusion, it should be noted that type 2 diabetes mellitus is a trigger of CKD. By applying measures for the prevention and treatment of this pathology, it is possible to prevent the development of CKD, thus, the methods used in modern medicine for assessing kidney function (creatinine level, creatinine GFR, albuminuria) detect violations already at the stage of glomerular damage and cannot in all cases serve as predictors of development CKD. This leads to the search for new biochemical and genetic markers at the preclinical stage, which will prevent or delay the development of renal pathology in patients with DM, initiate timely nephroprotective therapy and reduce the economic costs of renal replacement therapy.

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