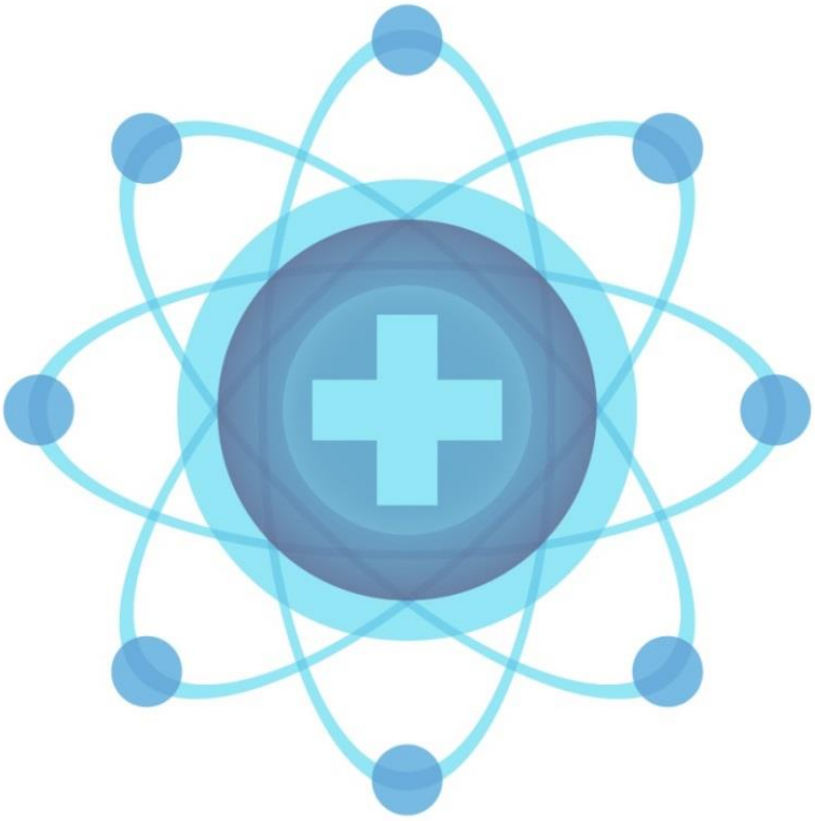

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# STATE OF KIDNEY FUNCTION IN DIABETES MELLITUS

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**Abstract:** A lot is said today about diabetes mellitus (DM) and its many complications, but these problems are still far from being solved. Cardiovascular complications and kidney damage are especially dangerous for a patient with diabetes. Diabetes mellitus is the leading cause of chronic kidney disease. Studies show that up to 40% of people with diabetes develop chronic kidney disease (CKD). In addition, more than 80% of end-stage CKD is due to diabetic involvement. There are 3 types of kidney damage in diabetes mellitus: diabetic kidney disease, diabetic nephropathy, and non-diabetic kidney damage.
Diabetic nephropathy - pathological changes in the kidneys that occur due to diabetes mellitus. It occurs in 70% of people with this endocrine disease. Gradually, the filtration capacity of the organ decreases, the kidney tissue becomes denser, degenerates into a connective tissue, chronic renal failure develops. Similar changes are noted 10-15 years after the onset of the underlying disease.
**Keywords:** diabetes mellitus, chronic kidney disease, diabetic nephropathy, microalbuminuria, glomerular filtration rate, hyperglycemia

The World Health Organization (WHO) and the International Diabetes Federation (IDF) have defined diabetes mellitus (DM) as an epidemic, chronic disease of non-infectious etiology. The incidence of diabetes has the nature of a pandemic, covering most economically developed countries. According to the IDF, the predicted number of diabetic patients among the adult population of the world will reach 625 million by 2045 [1,10].

Diabetic nephropathy (DN) is a serious complication of diabetes mellitus. The prevalence of DN in diabetes mellitus is up to 40.6% [2]. DN from the point of view of pathophysiology is a multicomponent process and can lead to a complete loss of filtration, nitrogen excretion and other functions of the kidneys, death of patients from terminal renal failure and cardiovascular "catastrophes" (primarily from myocardial infarction and stroke). Identification of this complication in the early stages is an important task, both in terms of prevention and a more favorable prognosis. The concept of chronic kidney disease (CKD), developed in 2002 by the Kidney Disease Outcomes Quality Initiative (KDOQI) expert group, allows clinicians to screen and monitor nephropathy based on laboratory data. [7,10].

The term DN is understood as various degenerative changes in the vessels, glomeruli and tubulointerstitial apparatus of the kidneys in patients with diabetes

mellitus. In 1983 C.E. Mogensen et al. proposed a classification of DN, including preproteinuric stages, which made it possible to reverse the development of functional and structural changes in the kidneys at the early stages of the development of this complication with the help of adequate therapy. In accordance with this classification, several stages of DN are distinguished:

Stage I is characterized by the development of hyperfunctional hypertrophy, which is accompanied by an increase in the size of the glomeruli and the kidney as a whole [3,5]. Microalbuminuria is reversible, glomerular filtration rate (GFR) is high, but also reversible. In stage II DN, kidney damage is observed without clinical manifestations. There is a thickening of the basement membrane and an increase in the volume of the glomerular mesangium. Microalbuminuria (urinary albumin excretion in the range from 20 to 200 mg/l) is detected only with diabetes decompensation and physical activity, while the glomerular filtration rate (GFR) increases significantly. At stage III - initial nephropathy - patients have persistent microalbuminuria against the background of still high GFR. Blood pressure tends to rise, especially during exercise. Stage IV (clinical nephropathy) is characterized by persistent proteinuria (urine protein is determined by standard methods), GFR decreases by an average of 1 ml / min. In stage V, the terminal stage of CKD, patients have low GFR due to sclerosis of the renal tissue. [6,8].

Giving credit to this classification, it should be noted that more than 25 years have passed since its creation, and in addition, this unit of the NAM has “vulnerabilities”. First, in the above classification, stage I and II DN are based on morphological criteria, stages III and IV are based on urinary protein excretion, and stage V is based on glomerular filtration rate. Secondly, in real clinical practice it is difficult to diagnose stage I and II DN. Thirdly, in this classification there is no conservative stage of CKD that does not require replacement therapy. Fourth, it does not give a quantitative gradation of the glomerular filtration rate, which largely determines the nephrological prognosis. [4,7].

In connection with the above circumstances, the introduction of the term "chronic kidney disease" (CKD) into clinical practice in 2002 by specialists from the National Kidney Foundation (USA) and experts from the Kidney Disease Outcome Quality Initiative (KDOQI) seems appropriate and timely. Some time later, this concept was adopted by the European Medical Community. Subsequently, the concept of CKD was adopted and began to be actively used in the practice of endocrinologists. [5,10]. So, if earlier in the State Standard there was only a formula for calculating GFR, then already in 2006 the table "Characteristics of the level of GFR" was introduced into the Algorithms for the provision of specialized medical care to patients with diabetes mellitus, and in 2009 the classification and formulation of the diagnosis of DN in these algorithms were supplemented by the characteristic stages of CKD. Apparently, the widespread use of the terminology and classification of CKD among domestic specialists will occur in 2010.

It is necessary to take into account different interpretations of this term. In a broad sense, CKD is a supranosological concept that combines all primary and secondary kidney lesions. Obviously, different nephropathies have the same risk

factors, mechanisms of development and progression, clinical and laboratory manifestations, common approaches to treatment and outcome. In addition, the path of development of any nephropathy is the same: from the presence of risk factors to the natural outcome - the end stage of renal failure. Thirdly, in the narrow sense, CKD is a diagnosis in the absence of a confirmed nosological form of kidney pathology, but with signs of kidney damage. [9,11].

Criteria for chronic kidney disease are (5):

• the presence of any clinical markers of kidney damage, including changes in the composition of urine and blood, confirmed at intervals of at least 3 months;

• any markers of irreversible structural changes in the kidneys, detected once during an intravital morphological study of the organ or during its visualization;

• decrease in GFR less than 60 ml/min./1.73 m2 for 3 or more months, regardless of the presence of other signs of kidney damage.

The main criterion for the classification of CKD is an indicator of the functional state of the kidneys (GFR). This indicator reflects the mass of active nephrons. The value of this parameter for adult patients should be calculated using the Cockcroft-Gault formula, which, using the SI system, has the form:

• GFR = K x [(140 - Age (years)) x Body weight (kg)]/Ser. Creatinine (μmol/l), where K = 1.23 for men or 1.05 for women;

• or according to the MDRD equation:

• GFR = 186 x (serum creatinine, mg/dL) - 1.154 x (age, years) - 0.203 x 0.742 (for women).

The MDRD equation takes precedence. It should be noted that in some cases calculation methods cannot be used. Thus, incorrect results can be obtained when using formulas for calculating GFR in patients over 80 years of age, after limb amputation, with severe malnutrition or, conversely, overweight, with skeletal muscle diseases, paraplegia and quadriplegia, against the background of acute and rapidly progressive nephrotic syndrome, acute renal failure, treatment with nephrotoxic drugs when deciding on renal replacement therapy and the patient's vegetarian diet [11].

The classification of CKD has now been developed: at stage III, two sub-stages began to be distinguished - IIIA and IIIB. This division is justified, since patients with stage IIIA CKD (GFR in the range of 45-59 ml/min/1.73 m2) have a high risk of developing cardiovascular disorders with a moderate rate of progression of renal failure. In patients with stage IIIB CKD (GFR in the range of 30-44 ml/min/1.73 m2), the risk of developing ESRD is higher than the risk of death from cardiovascular disease.

Urinary albumin/protein excretion is an important physiological parameter and clinical symptom as it reflects the state of glomerular filter permeability and proximal tubular reabsorption capacity. In connection with the above, it is proposed to index each of the first four stages of CKD depending on the severity of albuminuria / proteinuria: normoalbuminuria (N), microalbuminuria (M), proteinuria (P) or macroalbuminuria [3,11]. At the same time, it is believed that the gradation of levels of urinary albumin excretion, despite proposals to revise the lower level of the microalbuminuric range, should be left generally accepted.

Taking into account the new classification, the patient's diagnosis should be formulated as follows: “Moderate type 2 diabetes mellitus, subcompensated. Diabetic nephropathy, CKD II degree (CPN 0 Art. L.)”. Bracketing of the stage of chronic kidney disease remains necessary during the transitional period until the term "chronic kidney disease" is introduced into the guidance documents. Taking into account the concept of CKD in the national standards for the diagnosis and treatment of diabetes, it seems that the algorithm for diagnosing DN should be adjusted depending on the time of confirmation of the microalbuminuric and proteinuric stages of this complication. So, if it is currently recommended to re-examine for microalbuminuria and proteinuria 3 times a month, then it is proposed to increase this period to 3 or more months.

The development of DN can be thought of as a cascade of interactions between a triggering cause (hyperglycemia), progression factors (intraglomerular hypertension, systemic hypertension, hyperlipidemia, proteinuria, etc.) and progression "mediators" (growth factors, vasoactive factors, vascular endothelium), proteoglycans, oxidative stress, cytokines) kidney damage. The interaction of all these factors is under genetic control, which determines the greater or lesser sensitivity of the kidneys to the effects of pathological agents [6,7].

In accordance with the above scheme of the pathogenesis of DN, therapeutic efforts can be directed to the triggering cause, factors and mediators of progression, and genetic predisposition to this disease. The last direction has not been developed today. At the same time, the first two directions are actively used, and the third is promising. It is important to note that the treatment of DN at any stage should be active, multicomponent and complex [2,3].

Let us consider in more detail some aspects of the first two directions of treatment. The impact on the triggering factor for the development of DN implies the achievement of compensation for carbohydrate disorders. The importance of maintaining strict glycemic control in relation to the development of DN in patients with type 2 diabetes has long been known. Thus, the 8-year KUMAMOTO study showed that in the group of patients with initially uncomplicated type 2 diabetes, intensive control (the HbA1c level was reached - 7.1%) reduced the incidence of microalbuminuria by 4 times (11.5% vs. 43.5%). proteinuria - 3 times (11.5% vs. 32%) compared with a group of patients with a traditional approach to diabetes control, which reached an HbA1c value of 9.4%.

Similar results regarding the risk of developing microangiopathies were obtained in approximately 4000 patients with newly diagnosed type 2 diabetes without vascular complications, as well as in another large-scale long-term study UKPDS (UK Prospective Diabetes Study). It was shown that after 10 years of observation in the group of patients receiving intensive treatment with oral hypoglycemic drugs or insulin, a decrease in HbA1c levels to an average of 7% led to a significant reduction in the relative risk of developing microalbuminuria by 24%, proteinuria by 33%, and microvascular complications in general. by 25% compared with the diet-only group, in which the achieved HbA1c level was 7.9% [5,8].

However, in the UKPDS study, intensive glycemic control did not lead to a significant reduction in the risk of macrovascular complications. Moreover, the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study was prematurely terminated due to higher mortality (by 22%, p = 0.04) in the group of patients with type 2 diabetes receiving intensive glucose-lowering therapy (target HbA1c ≤ 6.0%)) compared with patients receiving standard therapy.

It has been established that markers of kidney damage in diabetes - micro- and macroalbuminuria - are not only harbingers of the progression of renal pathology and the development of terminal chronic renal failure, but also independent risk factors for the formation of cardiovascular pathology [10,11]. The relationship between the pathology of the cardiovascular system and kidney damage is called cardiorenal syndrome. Currently, when timely nephrological care is provided, diabetic patients die not from uremic intoxication, but from cardiovascular complications. Only 5% of deaths in patients with type 2 diabetes are caused by end-stage chronic renal failure, while the leading causes of death are cardiovascular diseases [2].

Therapeutic goals in patients with type 2 diabetes are achieved through the combined use of dosed physical activity, a rational diet, the use of oral hypoglycemic agents and insulin therapy. These activities should be carried out continuously from the moment the underlying disease is detected.

At the same time, until recently, a number of unresolved questions remained before clinicians: to what levels should the HbA1c level be reduced in order to prevent diabetic nephropathy, how intensively should the blood glucose level be lowered, and, finally, whether it is necessary to lower the blood glucose level, currently used antihyperglycemic drugs. Are the drugs equally effective and safe in terms of nephro- and cardioprotection? The answers to these questions were received after the publication of the results of the largest of the international studies completed to date on the study of type 2 diabetes - ADVANCE (Action in Diabetes and Vascular disease: Preterax and Diamicron MR Controlled Evaluation). The results of the study showed that in the intensive glycemic control group (n=4828), the HbA1c level decreased after 5 years of treatment from 7.5 to 6.5%, and the incidence of serious micro- and macrovascular complications significantly decreased. by 10% (p=0.013), microvascular complications - by 14% (p=0.01), microalbuminuria - by 9% (p=0.018), proteinuria - by 30% (p<0.001), development of new cases of nephropathy and its progression - by 21% (p=0.006). In addition, there was a trend towards a 12% reduction in CV mortality (p=0.12) compared with the standard glycemic control group (n=4741), in which the HbA1c level decreased after 5 years of treatment from 7, 5. up to 7.3%.

The positive results of the ADVANCE study are attributed to various factors, the most important of which is the optimal target HbA1c ≤ 6.5% in terms of efficacy/safety ratio in the intensive treatment group. In this case, the coefficient of the safe rate of decrease in the level of HbA1c was used, not exceeding 0.5-0.6% per year [5,10].

The second direction, which is necessary for the prevention of kidney damage in patients with diabetes mellitus, is the correction of the factors of progression of

DN, that is, the mechanisms, the elimination of which may slow down, but can no longer completely stop or cause the reverse development of DN. The most important of these factors is hypertension. According to current guidelines, the therapeutic goal in patients with diabetes mellitus, regardless of the stage of DN, is to achieve a blood pressure level below 130/80 mmHg. Moreover, this indicator in patients with diabetes mellitus should not be lower than 110/70 mm Hg. Art., since excessively tight control of blood pressure in individuals with kidney pathology can lead to hypoperfusion of target organs [2]. Of course, the doctor needs to be aware of the benefits of non-drug treatments for arterial hypertension: limiting salt intake (no more than 3g / day), exercise, reducing excess body weight, smoking cessation, moderation in alcohol consumption and reducing mental stress, however, early pharmacotherapy is indicated for most patients with DN and arterial hypertension. In patients with diabetes mellitus with normal albuminuria, it is recommended to start antihypertensive therapy from the moment blood pressure is detected ≥ 130/80 mm Hg. Art., and in persons with microalbuminuria - and at a lower level of blood pressure. Achieving the recommended target levels of blood pressure in patients with diabetes mellitus should occur gradually, in stages, taking into account the level of blood pressure indicators before the start of treatment.

Compensation of lipid metabolism disorders is also one of the most important areas of treatment, preventing the development and progression of DN. The goal of therapeutic intervention, regardless of the type of diabetes mellitus, is to reduce total cholesterol to less than 4.5 mmol/l, triglycerides to less than 1.7 mmol/l, low-density lipoprotein cholesterol to less than 2.5 mmol/l, high-density lipoprotein cholesterol should be more 1.2 mmol/l in women and more than 1.0 mmol/l in men. These goals are achieved by combining a rational diet with the intake of lipid-lowering drugs from the group of statins and fibrates. Therapeutic measures should be carried out continuously from the moment of detection of dyslipidemia.

It should be understood that the contribution of hyperglycemia, hypertension and hyperlipidemia to kidney injury is different and may vary depending on the stage of DN. Thus, our previous factor analysis showed that in patients with type 2 diabetes with normoalbuminuria (NAU), the value of GFR depended primarily on lipid, and then carbohydrate and hemodynamic factors. At the microalbuminuric (MAU) stage - hemodynamic, lipid, carbohydrate and at the proteinuric (PU) stage of DN, the distribution of the studied factors was of a different order: lipid, hemodynamic and carbohydrate. A similar pattern was found in patients with type 2 diabetes. According to some authors, after the development of proteinuria, the pathological process in the kidneys already loses its direct dependence on the level of hyperglycemia and acquires an independent course from the metabolic causes that caused it. As a rule, at the stage of proteinuria, there is no longer a correlation between the rate of decrease in glomerular filtration rate, an increase in blood creatinine, and the level of glycated hemoglobin. It should be noted that this point of view is consistent with the above scheme of the pathogenesis of DN.

The results obtained are of great practical importance, since they allow to correctly determine the priorities of nephroprotective therapy in patients with

diabetes mellitus. It can be assumed that in patients with type 2 diabetes in the absence of kidney damage or against the background of the proteinuric stage of DN, the main direction in preventing the progression of DN should be the correction of lipid metabolism, and in the microalbuminuric stage of DN, the normalization of blood pressure.

A similar approach is required when considering issues of cardioprotection. It is known that the ADVANCE study did not show a significant reduction in cardiovascular mortality among patients with type 2 diabetes in the intensive control group compared with patients in the standard therapy group.

As mentioned above, the ACCORD program was stopped due to the fact that intensive treatment aimed at achieving an HbA1c level of <6% resulted in a 20% increase in mortality in type 2 diabetic patients screened. These facts indicate that hyperglycemia is not a determining factor in the development of cardiovascular events, and achieving the target level of HbA1c is the only goal in the treatment of patients with type 2 diabetes mellitus.

Obviously, these data are not a reason to underestimate the importance of glycemic control in the effective prevention of diabetic angiopathy, but they are a strong argument in favor of the fact that on the verge of "mild" hyperglycemia and normoglycemia, additional benefits cannot be obtained due to tighter control over carbohydrate metabolism. Multifactorial treatment of the disease is required, including the control of other factors, the main of which are dyslipidemia and arterial hypertension. This position is confirmed by the results of a number of large studies that have shown the benefits of complex treatment of diabetes, based on the impact on all risk factors, not just hyperglycemia.

Thus, constant monitoring of glomerular filtration rate values, early diagnosis of microalbuminuria, constant monitoring of albuminuria, a complex effect on the initiating damaging factor, as well as factors and mediators of the progression of kidney damage determine the effectiveness of prevention and treatment of such a formidable complication of diabetes mellitus as diabetic nephropathy.

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