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Diabetes Mellitus and Chronic Kidney Disease: Achievements, Unsolved Problems and Treatment Prospects

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Annotation: Recent years have been marked by a dramatic increase in the number of patients with diabetes mellitus (DM) and chronic kidney disease (CKD) in the world. These two big medical problems are closely interrelated, as diabetes has taken a leading position among the causes of kidney disease. Diabetology and nephrology are very costly healthcare sectors. The burden of economic costs allocated to provide renal replacement therapy to patients with DM continues to grow. In this regard, the expediency of a renoprotection program in the early stages of diabetic nephropathy (DN), which can prevent or slow down the development of end-stage renal disease, is becoming more and more obvious. The implementation of the renoprotection program in patients with DM is based on a conceptual model of the development and progression of DN, which is the result of the combined effect of metabolic and hemodynamic factors modulated by genetic factors.

Keywords: diabetes mellitus, chronic kidney disease, diabetic nephropathy, renal replacement therapy.

Recent years have been marked by a dramatic increase in the number of patients with diabetes mellitus (DM) and chronic kidney disease (CKD) in the world. These two big medical problems are closely interrelated, as diabetes has taken a leading position among the causes of kidney disease. In European countries, a doubling of the number of patients suffering from diabetes with end-stage renal disease (ESRD) over a 9-year follow-up period is clearly defined - from 12.7 to 23.6 per 1 million populations [1]. According to the US Joint Donor Data System (USRDS), in 2008 the number of patients with DM (mainly type 2) with ESRD in this country reached 153 per 1 million populations [2]. Even in countries with a relatively low incidence of DM - Australia and New Zealand - there was an almost twofold increase in the number of patients with ESRD due to patients with type 2 DM (DM2) [3]. In connection with the westernization of the diet and the urbanization of lifestyle in Asia, the largest population of patients with DM with a high risk of renal pathology is expected to be associated with congenital nephron deficiency, defective production of the most important vasodilating factor - nitric oxide (NO), low efficiency of angiotensin-converting enzyme inhibitors (ACE inhibitors) due to for a common side effect - cough. In Japan, the most developed country in this part of the world, patients with diabetes predominate in terms of numbers in the structure of the dialysis service [4]. The cohort of DM patients with primary and moderate renal failure remains less accounted for and studied, which makes it difficult to predict the dynamics of the prevalence of ESRD and the need for renal replacement therapy (RRT).

Economic aspects. Diabetology and nephrology are very expensive healthcare sectors. The burden of economic costs allocated to provide RRT to patients with DM continues to grow. The amount of money spent on care for these patients affects the overall health budget of developed countries. In the

United States, the cost of treating patients with type 2 diabetes with ESRD is estimated at $39 billion annually [1]. In the countries of the European Union, according to an economic analysis within the framework of the REIN (Ramipril Efficacy In Nephropathy) study, it was shown that the cost of treating 1 patient on hemodialysis varies from 20,000 to 80,000 euros per year (average 48,170 euros as in Germany) [7]. In this regard, the expediency of a renoprotection program in the early stages of DN, which can prevent or slow down the development of ESRD, is becoming more and more obvious. Efforts to determine the time and cost of treating patients with a relatively low risk of developing ESRD (primarily with DN at the stage of microalbuminuria (MAU)) seem, at first glance, to be costly due to the large cohort. However, the analysis of early active interventions demonstrates an increase in life expectancy and a decrease in total costs compared with a late start of treatment - at the stage of severe DN [8]. In Russia, the cost of diagnosis and treatment of 1 patient with DN at the stage of renal failure for 1 year is 462,000 rubles. (From the calculations of the FGU ENTS on the standards of outpatient medical care, 2008).

Clinical and morphological classification of diabetic nephropathy.

Due to the increasing number of patients with renal failure resulting from various nosological forms, in 2002 the US National Kidney Foundation proposed to combine kidney diseases with a known cause, as well as with a pathology accompanied by a decrease in glomerular filtration rate (GFR) less than 60 ml / min / 1.73 m2 for 3 months or more, even in the absence of laboratory and instrumental signs of kidney damage, regardless of the diagnosis, in the term "chronic kidney disease" (KDOQI-2002) [9]. The level of GFR is now recognized as the best method for assessing kidney function in general, both in healthy individuals and in various diseases. The normal level of GFR correlates with age, gender, and body surface area. GFR less than 60 ml/min/1.73 m2 is a cut-off value indicating a loss of 50% of the filtration capacity of a normal kidney. The supra-nosological concept of CKD is especially relevant for patients with DM, given the importance and need for unification of approaches to the diagnosis, treatment and prevention of renal pathology, especially in cases of minimal severity and difficult to establish the nature of the disease. In addition, one should remember about the universality of the molecular-cellular and hemodynamic mechanisms of the progression of nephrosclerosis. The adoption of a new classification of CKD required the correction of the formulation of the diagnosis of DN, indicating the stage of CKD:

- DN, stage of microalbuminuria (MAU), CKD 1 (2, 3 or 4);
- DN, proteinuria stage, CKD 2 (3 or 4);
- DN, CKD 5 (treatment with renal replacement therapy);
- DM 1 or 2, CKD 3 or 4 (with GFR less than 60 ml/min and in the absence of MAU or proteinuria).

Active screening of patients with DM1 and DM2 in the regions of the Russian Federation revealed the frequency of CKD only by the level of GFR<60 ml/min/1.73 m2 without taking into account the level of albuminuria in 11.6% of cases [10]. The introduction of the concept of CKD into the practice of diabetology service is an important strategic approach aimed at reducing cardiovascular and overall mortality, since the relationship between kidney dysfunction and changes in the cardiovascular system in patients with diabetes is based on the commonality of population risk factors that determine the commonality of many methods of primary and secondary prevention. Until now, there has been no unified morphological classification of structural changes in the renal tissue in DM. In 2010, the Scientific Committee of the Society for Renal Pathology (USA) for the first time developed a morphological classification of kidney pathology in DM [11]. The authors subdivide changes in DN into four classes of glomerular lesions with a separate assessment of the involvement of the interstitium and vessels (Fig. 2). Class I includes thickening of the basement membrane and small nonspecific changes on light microscopy. In class II, mesangial expansion is determined (moderate - IIa or severe - IIb), but without nodular sclerosis or glomerular sclerosis, more than 50% of the glomeruli. Class III morphological changes correspond to the picture of nodular sclerosis (Kimmelstiel-Wilson changes). Class IV - a picture of advanced diabetic glomerulosclerosis (sclerosis of more than 50% of the glomeruli). The earliest method for diagnosing DN is the

determination of MAU, i.e. highly selective excretion of protein in the urine in an amount of 30 to 300 mg / day or 20 to 200 μg / min in a nightly portion of urine. MAU is also diagnosed by the ratio of albumin / creatinine in morning urine, which eliminates errors in daily urine collection. Urinalysis for MAU is performed 5 years after the onset of DM1 and at the time of diagnosis of DM2, then annually. It should be taken into account that DM2 is often diagnosed 5–10 years after its true onset, and along with diabetes, most patients with DM2 may have a number of comorbidities (arterial hypertension (AH), obesity, atherosclerosis of the kidney vessels, disorders of purine metabolism, etc.), that contribute to kidney damage and the progression of kidney failure.

It is important to consider MAU as a harbinger of the development of not only DN, but also cardiovascular diseases. From this point of view, MAU is an indication for screening for possible cardiovascular pathology and aggressive therapy aimed at reducing risk factors (extension of physical activity, smoking cessation, use of antihypertensive and lipid-lowering agents).

Significant progress has been made in recent years in determining the molecular mechanisms and ultrastructural changes leading to MAU, complementing previous concepts of the glomerular barrier function. The important role of changes (quantitative and functional) in podocytes and nephrin expression in the formation of the structure of the slit diaphragm, the main component of the renal filter, has been determined [13]. The results of recent studies allow us to consider MAU as the result of damage to the entire nephron, and the violation of tubular reabsorption as the main component of the increase in albuminuria [14].

It was assumed that MAU is unambiguously associated with a decrease in GFR in patients with DM2, as well as in patients with DM1. More recent studies have shown that this is predominantly characteristic of patients with typical diabetic glomerular lesions and MAU. Moreover, heterogeneous structural changes or even no changes were found in DM2 patients with MAU [15]. According to modern concepts, MAU is a manifestation of generalized dysfunction of the vascular endothelium, which can explain not only renal pathology, but also the known correlation between MAU and cardiovascular events.

Currently, there is a discussion about recognizing the presence of kidney damage already in the detection of MAU more than 15 mg/day. The role of "high normal" levels of albuminuria was previously shown in a study conducted at the Steno Memorial Hospital (Denmark) in 1982-1988. It demonstrated the presence of a high risk of the formation of the microalbuminuric stage of DN already at an albuminuria value of 15–23 mg/day. Analysis of randomized trials (HOPE (Heart Outcomes Prevention Evaluation), LIFE (Losartan Intervention For Endpoint reduction in hypertension), PREVEND (Prevention of Renal and Vascular END-stage Disease), Copenhagen Community Cohort, Copenhagen City Heart Study, Framingham Heart Study Offspring, Nord-Trondelag Health Study) shows that the level of urinary albumin excretion below the diagnostic threshold ("low-grade microalbuminuria") is closely associated with an increased risk of cardiovascular events and mortality from any cause, even in the population of the population without DM and AH [16 -18].

Thus, the simultaneous assessment of the main indicators - GFR and albuminuria - is necessary for the primary diagnosis of renal dysfunction, as well as for monitoring therapy, the rate of progression of the pathological process and determining the prognosis.

Development mechanism. The implementation of the renoprotection program in patients with DM is based on a conceptual model of the development and progression of DN, which is the result of the combined effect of metabolic and hemodynamic factors modulated by genetic factors. A "breakthrough" moment in understanding the pathogenesis of DN was the discovery by Brenner BM of the phenomenon of hyperfiltration and intraglomerular hypertension [25]. This mechanism is activated by chronic hyperglycemia, causing first functional and then structural changes in the kidneys, which proceed silently and lead to the appearance of MAU. Prolonged exposure to a powerful hydraulic press ("shear stress") initiates mechanical irritation of the adjacent structures of the glomerulus, which contributes to the hyperproduction of collagen and its accumulation in the

mesangium, initial sclerotic processes, disruption of the architectonics and permeability of the basal membrane of the glomerulus.

Another important discovery was the determination of the ultrahigh activity of the local renin-angiotensin-aldosterone system (RAAS) in DM. It has been established that the local renal concentration of the key component of the system, AII, is 1000 times higher than its content in plasma [26]. The mechanisms of the pathogenic action of AII in DM are due not only to its powerful vasoconstrictor action, but also to its proliferative, prooxidant and prothrombogenic activity. In the kidneys, AII causes intraglomerular hypertension, promotes sclerosis and fibrosis of the renal tissue indirectly through the release of cytokines and growth factors. There has been a long debate about the specificity of the manifestation of DN in DM1 and DM2. There is now fairly convincing evidence that the underlying pathophysiological mechanisms leading to the development and progression of DN are the same in both types of diabetes. However, in T2DM, there are additional preexisting factors of kidney damage, such as obesity, hyperuricemia, dyslipidemia, and others responsible for complex renal pathology. Pathophysiological changes before the development of T2DM, classified as a metabolic syndrome, can already create conditions for the development of renal damage, regardless of hyperglycemia. Hyperglycemia plays a leading role in the development of micro- and macrovascular complications. It induces non-enzymatic protein glycation, oxidative stress, activates protein kinase C, mitogen-activating protein kinase, the action of growth factors, vasoactive factors, cytokines that cause kidney damage at the cell level. This leads to the development of renal hypertrophy and accumulation of the extracellular matrix, preceding such irreversible changes as glomerulosclerosis and tubulointerstitial fibrosis. Today, there is no doubt about the need to achieve optimal glycemic control to prevent the development and increase in the severity of DN. The largest study that confirmed the possibility of preventing the development of DN in patients with DM1 with ideal compensation of carbohydrate metabolism was the DCCT study (Diabetes Control and Complication Study), in patients with DM2 - the UKPDS study (United Kingdom Prospective Diabetes Study) and the ADVANCE study (The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation). Compensation of carbohydrate metabolism, which plays a key role in the initial stages of the disease, continues to retain its importance even in advanced stages of complications. However, kidney pathology imposes serious restrictions on the choice of hypoglycemic drug in patients with DM [27]. The ADVANCE study convincingly demonstrated that in patients with type 2 diabetes over 60 years of age with a high cardiovascular risk and a long course of the disease, the appointment of such a hypoglycemic drug as Gliclazide MB (Diabeton MB) in routine practice is safe and highly effective, since it reduces the risk of developing and progressing renal pathology and cardiovascular mortality [28]. In this study, the use of Gliclazide MB reduced the risk of developing:

- microalbuminuria by 9% ($p=0.018$);
- macroalbuminuria (proteinuria) by 30% ($p<0.001$);
- New cases of nephropathy and its progression by 21% ($p=0.006$).

Hyperlipidemia is another metabolic factor in the progression of DN. Patients with DM have complex lipid disorders: reduced levels of high-density lipids (HDL), elevated levels of triglycerides (TG), low-density lipids (LDL), which are especially pronounced in DN. The existence of a complete analogy between the process of formation of glomerulosclerosis and atherosclerotic plaque of the vascular wall has been established [29]. This is facilitated by the structural similarity of the mesangial cells of the glomeruli with the smooth muscle cells of the arteries. Oxidized LDL, growth factors and cytokines increase the synthesis of mesangial matrix components, accelerating glomerular sclerosis. In addition, lipids filtered into the primary urine can also damage the cells of the renal tubules. Proteinuria is most often regarded as the most important non-hemodynamic predictor of the progression of DN. When the structure of the renal filter is disturbed, large molecular proteins come into contact with the mesangium and with the cells of the renal tubules, which leads to toxic damage to the mesangial cells, accelerated sclerosis of the glomeruli, and the development of an inflammatory process in the interstitial tissue. The results of recent studies allow us to consider the violation of tubular reabsorption as the main component of the progression of

albuminuria. The mechanisms of proteinuric remodeling of tubulointerstitium in DN substantiate the need for measures aimed at reducing the high level of protein loss in the urine in complex therapy.

The RENAAL study (Reductions of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan study), which included patients with DM2 and DN at the stage of initial renal failure, showed proteinuria as the most significant risk factor for cardiovascular events and progression of DN, regardless of BP level [30].

Arterial hypertension plays a key role in the development and progression of DN, as well as in the development of macrovascular pathology. As DN progresses, the role of metabolic factors decreases, and the role of hemodynamic factors (AH, intraglomerular hypertension) increases. It is possible to prevent the development and progression of vascular complications (including DN) only by maintaining blood pressure at a level of no more than 130/80 mm. rt. Art. Tighter blood pressure control in individuals with renal disease may lead to hypoperfusion of other target organs.

Anemia is one of the main manifestations of a decrease in kidney function in DN and, at the same time, a factor in the progression of kidney pathology. An epidemiological study organized by the Federal State Institution ERC to detect anemia in patients with DM, which included 2015 patients with DM1 (807 people) and DM2 (1208 people), showed a high prevalence of anemia in patients with DN. Thus, anemia in patients with DM1 with DN was detected 2.5 times more often than without kidney damage (41.9% and 16.6%, respectively), and in DM2 patients it was 2.1 times more often (25.7% and 12.0%, respectively) [31]. An assessment of the prevalence of anemia in patients with DN, depending on the stage of CKD and the severity of kidney damage, revealed that the frequency of anemia proportionally increases with increasing albuminuria and decreasing GFR, reaching 89.5% at the pre-dialysis stage of CKD. The leading link in the pathogenesis of anemia in patients with DN is inadequate production of the hormone erythropoietin (EPO) by the kidneys in response to anemia (hypoxia) - the level of EPO in the blood remains within normal values, i.e. does not correspond to a low Hb value. This phenomenon is called functional or relative EPO deficiency. It has been established that in progressive kidney diseases, the production of EPO by the kidneys in response to anemia can be maintained at a GFR level of more than 40 ml/min/1.73 m2.

The development of an early deficiency of EPO production by the kidneys in DN also suggests an early onset of correction of anemia with erythropoiesis-stimulating agents (ESS).

In 2007, an addendum to the latest NKF K/DOQI recommendations for the treatment of anemia in CKD, NKF K/DOQI Update of Hb Target [32], was released, which defined target Hb values in CKD patients receiving ESAs in the range of 11.0– 12.0 g / dl and not more than 13.0 g / dl (maximum level). The tactics of the European Working Group on anemia (Anemia Working Group of European Renal Best Practice (ERBP)) has also changed, indicating special care in the treatment of anemia by ESA in patients with type 2 diabetes with CKD and who have had a stroke.

Optimization of correction of anemia ESA, including the use of a new promising ESA with prolonged action CERA (continuous erythropoesis receptor activator), a long-acting erythropoietin receptor activator (MIRCERA), is one of the main tasks of the complex treatment of patients with DM and CKD. The most acceptable Hb level in patients with DN receiving ESA should be determined individually, taking into account concomitant cardiovascular pathology, possible benefits and risks of therapy and be based on recommendations based on the results of large clinical studies in evidence-based medicine.

Variety of kidney pathology in diabetes mellitus.

The stereotypical view of DN can mask various other kidney diseases in DM: unilateral or bilateral atherosclerotic renal artery stenosis (RAS), tubulointerstitial fibrosis, urinary tract infection, interstitial nephritis, drug nephritis, etc. Renal artery stenosis introduces a number of features into the clinical course of nephropathy and can radically change approaches to the treatment of kidney pathology. In a study conducted at the FGU ENTS together with the Scientific Center for Cardiovascular Surgery. A.N. Bakuleva, according to duplex ultrasound of the renal vessels, was detected and subsequently confirmed by contrast diagnostic methods, unilateral SPA in 30% of

patients with type 2 diabetes over the age of 50 years, and bilateral - in 7% [33]. The high prevalence of RAS in T2DM may be seen as a result of the early involvement of the renal arteries in accelerated generalized atherosclerosis. In turn, chronic ischemia of the kidneys, superimposed on DN, certainly accelerates the development of renal failure in patients with type 2 diabetes. Patients with SPA had severe atherosclerosis of the coronary and brachiocephalic arteries, more often had myocardial infarction, had isolated systolic hypertension, which required 3 or more antihypertensive drugs to control, and abused nicotine.

A Kaplan-Meier survival analysis of these patients confirmed the role of SPA in achieving the combined endpoint defined as patient death, ER, heart failure, myocardial infarction, creatinine doubling, and ESRD at 24 months of follow-up. The data obtained indicate that SPA in patients with type 2 diabetes is one of the significant risk factors for the progression of renal and cardiac pathology, as well as increased mortality.

According to a retrospective analysis, patients with type 2 diabetes who underwent coronary angiography (CA) and angiography of the renal arteries showed more widespread vascular pathology compared with the control group without DM. At the same time, coronary artery lesions in individuals with SPA were predominantly 2- and 3-vascular in nature and amounted to 92.3% [33]. The results obtained showed, in addition, that every third patient with DM had lesions of all major vascular beds: renal, brachiocephalic, peripheral and coronary.

Contrast-induced nephropathy (CIN) occupies a special place among toxic kidney lesions, which has become an important clinical problem that develops in parallel with the widespread use of diagnostic and therapeutic procedures using contrast agents due to the main route of their elimination through the kidneys.

When conducting a retrospective analysis of the study on the basis of the FGU ENTS and the Scientific Center for Cardiovascular Surgery. A.N. Bakuleva, the incidence of CIN in DM2 patients who underwent CAH was 2.5 times higher than in the control group of persons without DM with a comparable initial level of renal function, a dose of a contrast agent and a similar hydration regimen [34]. The risk of developing CIN in patients with type 2 diabetes was associated with NYHA class III–IV heart failure, anemia, dose of contrast agent, diuretics in the periprocedural period, multivessel coronary artery disease, and the need for intervention. In patients with type 2 diabetes with a history of CIN, renal function declined faster, serious cardiovascular events more often developed, and survival rates were worse during 24 months of follow-up. The high probability of development and prognostic significance of CIN in patients with type 2 diabetes determine the need to assess individual risk in order to take preventive measures during contrast procedures.

Tubulointerstitial fibrosis (TIF) is just as important a mechanism for the loss of functional capacity in DM as is glomerulosclerosis. The role of complex processes of intercellular interactions, which are activated under the influence of immune and non-immune factors, has been determined in the development of tubulointerstitial damage. Potential mechanisms of tubulointerstitial damage in primary glomerular pathology (diabetic glomerulosclerosis, glomerulonephritis) include the toxic effect of filtrating plasma proteins, activation of tubular epithelial cells by cytokines secreted in the glomeruli, a decrease in peritubular blood flow leading to increasing tubulointerstitium ischemia, and overload of functioning tubules. In turn, progressive interstitial fibrosis can increase the resistance of pre- and post-glomerular arterioles, which exacerbates intraglomerular hyperfiltration. Progressive tubular stenosis in TIF determines an increase in intratubular pressure, which ultimately leads to a decrease in GFR, and their obstruction leads to a decrease in the number of functioning nephrons. The spectrum of possible tubulointerstitial injury factors is quite wide: proteinuria, transforming growth factor-β (TGF-β), angiotensin II (AT II), monocytic chemoattractant protein (MCP-1), activity regulator of normal expression and secretion of T cells (RANTES), adhesion factors (intracellular adhesion molecule (ICAM 1), vascular cell adhesion molecule (VCAM-1)), endothelial vascular growth factor (VEGF), acute phase proteins (C-reactive protein (CRP), fibrinogen), interleukin-6 (IL 6), asymmetric dimethylargenin (ADMA), homocysteine (HCYST), metalloproteinases (MMPs), von Willebrand factor (FW), plasminogen activator inhibitor (PAI-I), etc.

In a study conducted at the FGU ERC, an increased level of profibrogenic cytokines (MCP-1, TGF-β1 and IL-6), as well as extracellular matrix degradation factor (MMP-9) in the blood of patients with DM with CKD was detected when compared with individuals with DM2 without renal pathology and the control group, regardless of the type of diabetes and the cause of nephropathy, which shows the involvement of these molecular mediators in kidney damage, mainly due to the universal mechanism of TYF formation. Activation of profibrogenic cytokines in diabetic patients with kidney pathology was closely associated with endothelial dysfunction, determined by increased blood production of adhesive, angiogenic, thrombogenic factors (FW, PAI, VICAM, sICAM, VEGF), as well as endothelial damage factors (ADMA, homocysteine), which gives the processes a mutually inducing character, aggravating renal damage. The involvement of mediators of inflammation and fibrogenesis in the processes of tubulointerstitial damage in patients with DM and CKD was determined, confirmed by their negative correlation with GFR and positive with albuminuria, the main markers of renal dysfunction. The study indicated a high risk of reducing GFR in patients with DM and CKD with an increase in TGF-β1, ADMA, MCP-1 in the blood, along with traditional risk factors [35].

Treatment of CKD in diabetes mellitus and its prospects

The mechanisms of the development of DN and the decisive role of RAAS in the development of renal pathology determine the choice of antihypertensive agents - ACE inhibitors, angiotensin II receptor blockers (ARBs). ACE inhibitors and ARBs are used as basic antihypertensive therapy. The expediency of their use is determined by reno- and cardioprotective effects, regardless of the effect on systemic hemodynamics. ACE inhibitors are first-line drugs for patients with type 1 diabetes, starting from the earliest stages. Three major studies (IRMA2, IDNT, RENAAL) on the use of ARBs in patients with type 2 diabetes with kidney pathology suggest their advantage as drugs of choice, which is reflected in the general ADA recommendations for the control of hypertension [36].

However, long-term (more than 25 years) use of ACE inhibitors has shown that in real clinical practice, the nephroprotective effect of their use develops in 50% of patients with DN [37]. When studying this issue, it turned out that there are other alternative pathways for the formation of AII, controlled by chiamase, cathepsin G, tonin, etc. When these enzymes are activated, the so-called ACE effect occurs; a decrease in its antihypertensive and antiproteinuric action, since the synthesis of AII is preserved. Other reasons for the ineffectiveness of ACE inhibitors as nephroprotectors may be the abuse of table salt and genetic determinism. Incomplete blockade of the RAAS may be responsible for the progression of renal and cardiac pathology, since it does not provide optimal organ protection. Causes, mechanisms, time of development of the phenomenon, as well as its clinical significance are still conjectural and little covered in the literature. In the Department of Diabetic Nephropathy of the Federal State Institution of Energy Research Center, work has been carried out for a long time to study the nature of the phenomenon of escaping from the action of ACE inhibitors. In a retrospective analysis of the progression of DN in patients with DM1 and DM2 against the background of a stable intake of an effective dose of ACE inhibitors for 6 years, 2 groups of patients were identified: a group of people with stable filtration function of the kidneys during all years of observation (50% of patients with DM1 and 47% of patients with DM2) and a group of patients in whom, despite the stable use of ACE inhibitors, GFR continued to decline steadily (50% of patients with type 1 diabetes and 53% of patients with type 2 diabetes).Исходные клинико-лабораторные характеристики этих пациентов не различались, в том числе и по состоянию СКФ, уровню гликемического контроля, потреблению соли, диуретиков и другим показателям [38]. When studying the concentration of RAAS hormones in patients who received ACE inhibitors for a long time, it was possible to establish that the phenomenon of escape clinically begins to manifest itself when the concentration of AII in the blood is more than 50 pg/ml. When AII secretion is suppressed to 50 pg/ml or less, the high nephro- and cardioprotective efficacy of ACE inhibitors remains. Otherwise, therapy adjustment and switching to alternative drugs (ARBs) were required [39]. A new class of drugs - direct renin inhibitors (aliskiren) - demonstrate effectiveness in blockade of the RAAS and give hope for the possibility of long-term nephroprotection in DM without the phenomenon of escape. The role of this group of drugs in long-term renoprotection in

diabetic patients will be determined upon completion of large multicenter studies currently underway (ALTITUDE - The Aliskiren Trial in Type 2 Diabetic Nephropathy). The search for markers of early diagnosis of CKD in patients with DM and methods of active influence on them would make it possible to prevent or delay the progression of the loss of renal function. Modern approaches to nephroprotection include drugs that specifically affect mediators of inflammation and fibrosis (anti-inflammatory agents, TGF β antagonists, kinin receptor activators, inhibitors of DDR1 collagen receptors, inhibitors of intracellular signaling pathways, etc.). Suppression of inflammation, which plays an important role in the initiation of renal pathology, is possible in the early stages. Rapamycin, used primarily as an immunosuppressant, has been experimentally shown to reduce tubular dilatation, interstitial volume, and collagen deposition. Similar effects are observed with the introduction of inhibitors of the nuclear factor (NF) - kappaB. TGF-β is the most important activator of extracellular matrix (ECM) synthesis. To suppress its fibrogenic activity, bone morphogenic protein 7 (BMP 7), hepatocyte growth factor (HGF), an ALK5-mediated Smad3 inhibitor, and monoclonal antibodies are used in the experiment. BMP 7 in rats with streptozotocin diabetes reduces proteinuria, inflammation, the severity of sclerosis of the glomeruli and interstitium, and prevents a decrease in the number of podocytes [40]. The antifibrotic potential of HGF has been described, leading to a slowdown in the development of glomerular and tubulointerstitial fibrosis in diabetic mice [41]. In addition, HGF stimulates cell regeneration, reduces inflammation, and NF-kappaB activation. Studies are underway on an ALK5 inhibitor mediated by Smad3 that prevents the TGF-β action cascade [42]. The use of growth factor receptor antagonists is a promising direction in antifibrotic therapy. However, the severity of side effects with long-term use requires further research to improve its safety. Inhibitors of protein kinase C, the most important intracellular signaling agent for proliferation, hypertrophy, and apoptosis, help preserve kidney function by reducing glomerulosclerosis, interstitial fibrosis, and tubular atrophy [43]. These data need further study, given the very complex regulatory pathway involving protein kinase C, before the agents of the discussed action.

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