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Diabetic Nephropathy: Modern Principles of Classification, Diagnostics and Features of Sugar-Reducing Therapy

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Abstract: The article is devoted to modern approaches to the treatment of diabetes mellitus complicated by kidney damage. Diabetes mellitus is the most important problem of modern medicine, which is primarily due to the high prevalence of the disease among the working-age population. Diabetic nephropathy is one of the severe chronic complications of diabetes, which increases the disability and mortality of patients. Diabetic nephropathy is the main cause of the development of end-stage renal failure in developed countries and eventually affects about 30% of patients. Kidney damage in patients with diabetes occurs in 6-7% of cases out of the total number of nephropathies in patients receiving treatment in a specialized nephrological department of a multidisciplinary hospital. The first manifestations of diabetic nephropathy develop 3-4 years after the onset of the disease, and reach their peak in 15-20 years. The concept of «chronic kidney disease» includes kidney damage regardless of the primary diagnosis and is characterized by such basic diagnostic criteria as urinary albumin excretion and glomerular filtration rate values, which are markers of kidney damage. Methods for preventing the progression of diabetic nephropathy include general measures to change the lifestyle, control of glycemia and blood pressure, correction of lipid metabolism disorders in combination with nephroprotective therapy. Currently, when choosing therapy in patients with type 2 diabetes mellitus in combination with chronic kidney disease, along with taking metformin, preference is given to sodium-glucose cotransporter type 2 inhibitors and glucagon-like peptide-1 receptor agonists with a nephroprotective effect.

Introduction. Currently, diabetes mellitus (DM) is one of the urgent problems of modern medicine. First of all, this is due to the high prevalence of the disease among the working population. By 2040, the number of people with diabetes aged 20-79 is projected to increase to 642 million [1, 2]. The socio-economic significance of the disease is also important. The development of chronic complications of DM significantly increases the early disability and mortality of patients [3]. The greatest danger, of course, is associated with the development of cardiovascular complications (CVS) in these patients. Diabetic nephropathy (DN) also occupies an important place in this series, which develops in approximately 20.1% and 6.3% of patients with type 1 and type 2 diabetes, respectively [4, 5].

The study of the problem of kidney damage in DM has a long history. Back in 1836, the British physician Richard Bright noted the presence of proteinuria (PU) in diabetic patients, which is a sign of kidney damage [6]. Later, in 1936, American pathologists P. Kimmelstiel and C. Wilson first described the pathomorphology of the kidneys in patients with DM [7].

In patients with type 2 diabetes, RD complications are the third leading cause of death after cardiovascular diseases (CVD) and malignant neoplasms [1]. In addition, to date, type 2 DM-associated nephropathy is the main cause of end-stage renal disease (ESRD) in Europe, the USA and Japan [8]. Early diagnosis and timely provision of therapeutic and preventive measures to patients with DM are the key to preventing the development of DN.

Definition, prevalence and pathogenesis of DN

DN is understood as a specific lesion of all structures of the kidneys (glomeruli, tubules, interstitium and vessels) that occurs with diabetes and is accompanied by the formation of nodular glomerulosclerosis, which can lead to the development of ESRD requiring renal replacement therapy (dialysis, transplantation). Glomerular damage is associated with thickening of their basement membrane, an increase in the volume of the mesangial matrix, and the subsequent development of nodular and/or diffuse intercapillary glomerusclerosis. Tubulointerstitial changes consist in dystrophy and atrophy of the tubular epithelium, fibrosis of the interstitium, and vascular changes in the development of arteriohyalinosis and arteriosclerosis. "Specific damage to the structures of the kidneys" means that in the absence of hyperglycemia, the structural changes in the kidneys characteristic of DM are not detected [9].

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The frequency of detection of DN is closely dependent on the duration of DM. This dependence is more studied in type 1 diabetes due to a more accurate determination of the onset of the disease. The incidence of DN in patients with a duration of type 1 diabetes up to 10 years is 5–6%, up to 20 years - 20–25%, up to 30 years – 35–40%, up to 40 years – 45%, and the maximum peak in the development of DN occurs for a period of 15 to 20 years of existence of the SD. It is important to note that, along with classical diabetic glomerulosclerosis, patients with type 2 diabetes often develop kidney damage of non-diabetic origin (chronic pyelonephritis, urolithiasis, ischemic nephropathy, etc.). The possibility of a combination of several forms of nephropathy significantly increases the risk of irreversible deterioration in kidney function. It has been established that in patients with newly diagnosed type 2 diabetes, microalbuminuria (MAU) is already detected in 15-40% of cases, PU in 7-10%, and chronic renal failure (CRF) in 1%. Most likely, this reflects the late diagnosis of DN due to the low awareness of primary care physicians. With a relatively accurate determination of the onset time of type 2 diabetes, the same as in type 1 diabetes, the dependence of the incidence of DN on the duration of the disease can be traced: 7-10% with a duration of DM of 5 years, 20-35% with a duration of 20-25 years and 50-57% - with longer periods of the disease [11].

According to the GVKG them. N. N. Burdenko, the proportion of patients with DN among all patients receiving treatment in the nephrology department averages 6.4% (Fig. 1).

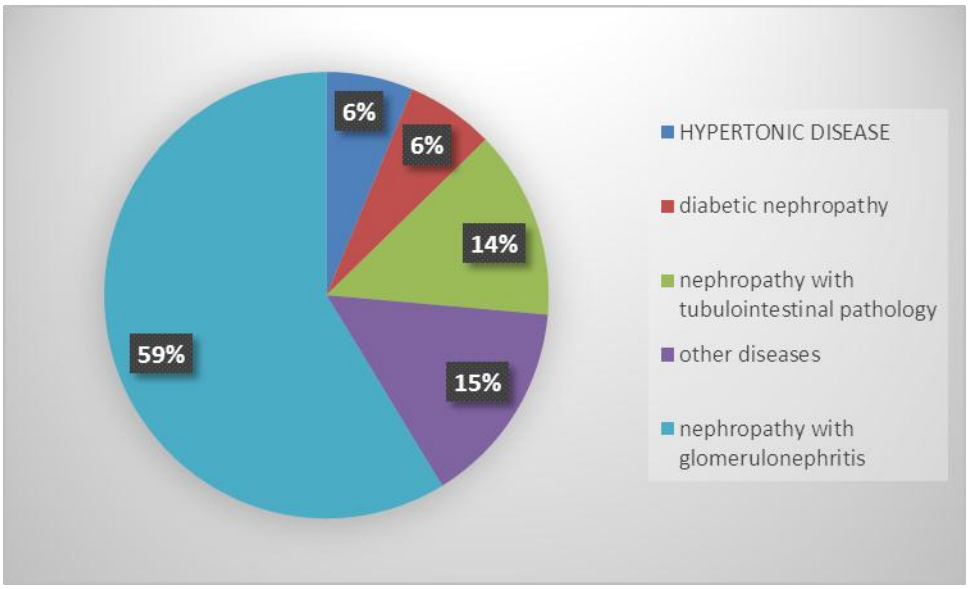


Fig. 1 Prevalence of different types of nephropathy

At the same time, the examination of patients of the endocrinological department of the GVKG named after. N. N. Burdenko showed that DN is diagnosed in 35.6% of patients with type 1 diabetes and 43.1% - type 2 diabetes (Fig. 2) with a disease period of 25 years. The first signs of DN are detected after 3-4 years from the onset of DM, and its frequency reaches a maximum after 20 years of the course of the disease.

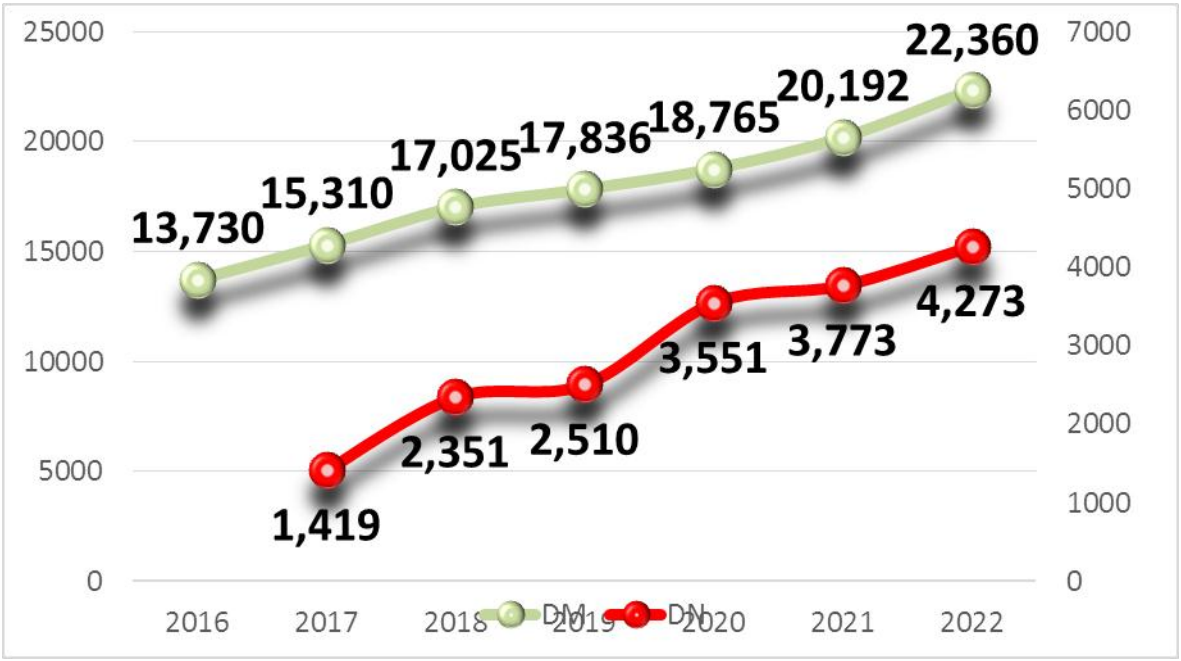


Fig. 2 Increase in the incidence of DM and diabetic nephropathy over the past 7 years in the Bukhara region

DN develops under the influence of a huge number of reasons. But of all the variety of mechanisms of its development, the most studied and proven are metabolic (hyperglycemia, hyperlipidemia) and hemodynamic (intraglomerular hypertension, arterial hypertension (AH)).

By far, one of the most important metabolic factors initiating kidney damage is hyperglycemia. Under conditions of hyperglycemia, stable glycosylation products are formed, which lead to disruption of the glomerular membrane configuration, proliferation of arteriolar smooth muscle cells, and increased lipid peroxidation. Ultimately, there is a thickening of the glomerular basement membrane and the development of glomerulosclerosis. In addition, the expression of vascular endothelial growth factor in podocytes increases, which autocrine enhances its activity and leads to damage to kidney tissue [12].

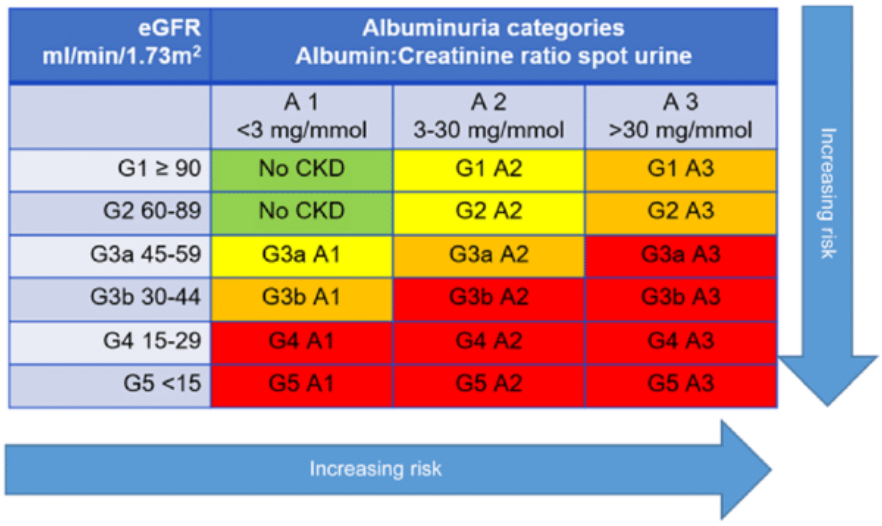
Hyperlipidemia plays an important role in the development of DN. Oxidized low density lipoproteins, growth factors and cytokines increase the synthesis of mesangial matrix components, accelerating glomerular sclerosis. In turn, lipids filtered into the primary urine can lead to damage to the cells of the renal tubules [13].

Hypertension in patients with DM is the most powerful factor in the progression of chronic kidney disease (CKD), which is many times greater than hyperglycemia and hyperlipidemia in its influence. Intraglomerular hypertension is the main hemodynamic factor in the development of DN, which occurs due to the toxic effect of hyperglycemia and activation of vasodilatory hormones with the development of dilatation of the afferent glomerular arteriole, on the one hand, and on the other hand, due to the activation of local angiotensin II with constriction of the efferent renal arteriole [14].

Classification and clinical manifestations of DN

For the first time, a detailed classification of the stages of DN was developed by the Danish researcher S. E. Mogensen in 1983. It was based on indicators of functional and structural changes in the kidneys (changes in the glomerular filtration rate (GFR), thickening of the glomerular basement membranes, the presence of MAU or PU) [15]. Until recently, the classification of DN from 2000 was used in the Russian Federation, which included the following stages: microalbuminuria, PU with preserved nitrogen excretion function of the kidneys, and CRF [16]. Serum creatinine has been used for a long time as the main marker of impaired nitrogen excretion of the kidneys. Thanks to recent studies, it has become clear that, due to the compensatory capabilities of the kidneys, its numbers can correspond to normal values for many years, while GFR is already reduced. The modern classification of DN is based on the principles of CKD staging, which can be diagnosed if there are deviations in the anatomical and morphological structure or function of the kidneys for three or more months, regardless of the nosological diagnosis [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. It is its level that determines the various stages of CKD

eGFR ml/min/1.73m²	Albuminuria categories Albumin:Creatinine ratio spot urine		
	A 1 <3 mg/mmol	A 2 3-30 mg/mmol	A 3 >30 mg/mmol
G1 ≥ 90	No CKD	G1 A2	G1 A3
G2 60-89	No CKD	G2 A2	G2 A3
G3a 45-59	G3a A1	G3a A2	G3a A3
G3b 30-44	G3b A1	G3b A2	G3b A3
G4 15-29	G4 A1	G4 A2	G4 A3
G5 <15	G5 A1	G5 A2	G5 A3



Adapted from National Institute for Health and are Excellence. Clinical guideline (CG182)

Assessment of the degree of kidney damage in patients with DM has changed significantly. There has been a transition from an isolated assessment of AU/PU as a classic marker of DN to the determination of the stage of DN depending on the level of GFR, supplementing it with an index of AU/PU. AC/PU are considered as markers of kidney pathology, which reflect the degree of damage to the glomerular apparatus of the kidneys (Table 2).

According to international clinical and epidemiological studies, CKD is registered in 40-60% of patients with type 2 diabetes. According to the federal registry, in 2016, on average in the Russian Federation, CKD was detected in patients with type 1 diabetes in 23% of cases and in type 2 diabetes

in 6.9% of cases. GFR less than 60 ml/min in patients with type 1 DM with DN occurs in 50–60% of cases in the presence of persistent PU and in 70–80% of cases in patients with type 2 DM [2].

DN has no specific symptoms, the clinical picture is determined by the actual manifestations of DM, its complications and manifestations of CKD. The main clinical manifestations of CKD are AU/PU, AH, anemia, electrolyte disturbances, acidosis, disorders of phosphorus-calcium metabolism, edematous syndrome may be present due to the formation of nephrotic syndrome and/or fluid retention in the body.

Diagnosis of DN

When PU appears in a DM patient with a long history of the disease (more than 10 years), with severe diabetic retinopathy and other signs of micro- and macrovascular complications, the diagnosis of DN is beyond doubt. To detect it, mandatory methods of laboratory diagnostics are performed: determination of the albumin / creatinine ratio in the morning portion of urine, general clinical analysis of urine with an assessment of protein content, daily PU, examination of urine sediment, determination of serum concentrations of creatinine, urea and potassium. If necessary, ultrasound examination of the kidneys and sonographic examination of the renal arteries are performed.

Currently, in clinical practice, the following calculation formulas are used to calculate GFR in the adult population: Cockcroft-Gault 1976, MDRD 1999, CKD-EPI 2011.

It is generally recognized that the most accurate calculation method for determining GFR is the CKD–EPI formula [17].

СКФ = 141 × min(СКР/k, 1)a × max(СКР/k, 1) – 1,209 × 0,993 age [× 1,018 for women] [× 1,159 for people of the black race],

where TFR is serum creatinine (mg/dl); k - 0.7 (for women) or 0.9 (for men); a - coefficient equal to - 0.329 (for women) or - 0.411 (for men).

Since the value of creatinine in the Russian Federation is measured in μmol / l, it is necessary to convert it to mg / dl, for this the value must be divided by a factor of 88.4 (i.e. 100 μmol / l corresponds to 1.13 mg / dl).

Compensation of carbohydrate metabolism plays a key role in preventing the development and slowing down the progression of CKD in patients with DM. A number of clinical studies have shown that strict glycemic control can not only prevent the development of DN in individuals who do not suffer from it, but also slow down the progression of this complication in patients with AU and PU. This statement is true both for patients with type 1 DM (DCCT study) and for patients with type 2 DM (UKPDS study) [11].

The progression of azotemia, manifested in a decrease in GFR, significantly narrows the range of possible use of oral hypoglycemic drugs (Table 4). The KDIGO (Kidney Disease Improving Global Outcomes Quality Initiative) clinical practice guidelines consider glycemic control as part of a multifactorial intervention strategy to control BP and CV risk. They define target levels of HbA1c in individuals with DM and CKD, taking into account existing risks. HbA1c < 7.0% (< 53 mmol/mol) is recommended to prevent the development and progression of microvascular complications, including DN. In patients at risk of hypoglycemia, a target HbA1c < 7.0% (< 53 mmol/mol) is not recommended. For patients with severe complications, comorbidities, short life expectancy, risk of hypoglycemia, the target HbA1c value is < 8.0% [9, 17]. In recent decades, the principles of prescribing drugs used in the treatment of patients with diabetes have changed significantly. Currently, the main requirements for therapy are an individualized, personalized approach that provides nephro- and angioprotection, cardiovascular safety, and strict glycemic control [9].

The beginning of this century was marked by a rapid increase in the number of hypoglycemic drugs (SSPs) and the emergence of new classes of antidiabetic drugs with fundamentally new mechanisms of action: dipeptyl peptidase-4 (iDPP-4) inhibitors, glucagon-like peptide-1 receptor agonists (arGLP-1), sodium- glucose cotransporter type 2 (SGLT-2).

In completed large-scale randomized controlled trials evaluating the cardiovascular risks of these drugs, there was convincing evidence that SGLT-2 inhibitors reduce all-cause mortality to a greater extent than arGLP-1, while DPP-4 i did not show CVD. -vascular benefits compared to placebo and were inferior to SGLT-2 and arGLP-1 inhibitors in terms of mortality. Moreover, the obtained results of studies indicate the ability of SGLT-2 inhibitors to improve cardiovascular prognosis and renal outcomes in patients with type 2 diabetes. Both SGLT-2 and arGLP-1 inhibitors have a pronounced hypoglycemic effect, contributing to a significant improvement in glycemic control, favorably affect body weight and blood pressure, and are not associated with an increased risk of hypoglycemia. Both classes of drugs exhibit cardio- and nephroprotective properties not only due to direct hypoglycemic action, but also due to numerous direct and indirect pleiotropic metabolic and hemodynamic effects [19]. It should be noted that these qualities are not class effects. Empagliflozin has the most pronounced and proven cardio- and nephroprotective properties of SGLT-2 inhibitors.

The results of the EMPA-REG OUTCOME study showed that empagliflozin significantly reduced the onset or progression of MAU (39% and 38% risk reduction, respectively). In the empagliflozin group, there was a 46% reduction in serum creatinine doubling and a 55% reduction in initiation of renal replacement therapy compared with placebo. Patient follow-up demonstrated long-term stabilization of renal function in the empagliflozin group. At the same time, a similar level of GFR did not affect the nephroprotective effects of empagliflozin therapy [20]. The CANVAS study (the effect of canagliflozin on cardiovascular outcomes) showed a 27% reduction in the progression of AU when the drug was prescribed, as well as a slowdown in the decline in GFR and a 40% decrease in deaths from renal causes [21].

The arGLP-1 drug liraglutide in the LEADER trial resulted in a statistically significant reduction in the combined microvascular complication rate (HR, 0.84; 95% CI, 0.73 to 0.97; p = 0.02). Moreover, this decrease was mainly due to the lower incidence of nephropathy in the liraglutide group compared with the placebo group (1.5 and 1.9 cases per 100 person-years of follow-up, respectively; RR 0.78; 95% CI 0.67 to 0.92; p = 0.003). In the SUSTAIN-6 study, patients treated with semaglutide, as well as in LEADER, had a lower risk of developing or progressing nephropathy, mainly due to a decrease in AC, but a higher risk of complications of diabetic retinopathy than patients in the placebo group [22].

According to the results of studies, iDDP-4 showed their safety in relation to CVD, and when assessing kidney function, a decrease in AU was observed within 3–6 months, while GFR remained stable during the entire follow-up period [22].

The results of the studies have led to a revision of recommendations for the treatment of type 2 diabetes and the prevention of CVD in this category of patients. Currently, both international and domestic clinical guidelines suggest that when choosing therapy in certain categories of patients with type 2 diabetes with CVD, CKD, along with metformin, preference should be given to arGLP-1 and SGLT-2 inhibitors [9]. An important difference of the updated clinical guidelines is the focus on the early use of SGLT-2 or arGLP-1 inhibitors in the treatment of type 2 diabetes in order to prevent adverse cardiovascular and renal outcomes, regardless of the achievement of glycemic control during metformin therapy.

Conclusion. Thus, kidney damage in DM occurs in 6-7% of patients treated in a specialized nephrology department of a multidisciplinary hospital, however, these are mainly patients with stage 3-5 CKD, who have high risks of CVE and progression of renal failure. The first manifestations of DN develop 3–4 years after the onset of the disease and reach their maximum in 15–20 years. Early diagnosis of DN, based on the detection and assessment of the severity of albuminuria and/or PU and the dynamics of GFR, is the key to effective treatment. The most important link in the treatment of patients with DN is the appointment of hypoglycemic drugs with a proven nephroprotective effect.

Литература/References

1. World Health Organization 2019. URL: https://www.who.int/diabetes/global-report/en/.

2. Джураева А. Ш., Бадридинова Б. К. Сравнительный Анализ Качества Жизни Больных Принимающих Программный Гемодиализ //Центрально Азиатский Эндокринологический Журнал. – 2022. – Т. 2. – №. 2.
3. Badridinova B. K. Comparative Analysis Of Program Hemodialysis Efficiency And Impact On Quality Of Life //Uzbek Scholar Journal. – 2022. – Т. 11. – С. 186-192.
4. Bommer C., Heesemann E., Sagalova V., Manne-Goehler J., Atun R., Bärnighausen T. et al. The global economic burden of diabetes in adults aged 20-79 years: a cost-of-illness study // Lancet Diabetes Endocrinol. 2017; 5: 423-430. URL: https://doi.org/10.1016/S2213-8587(17)30097-9.
5. Badridinova B. K. Comparative Analysis Of Program Hemodialysis Efficiency And Impact On Quality Of Life //Uzbek Scholar Journal. – 2022. – Т. 11. – С. 186-192
6. Badridinova B. K. Risk factors for the development of diabetic nephropathy In patients with type 1 diabetes //ДОКТОР АХБОРОТНОМАСИ ВЕСТНИК ВРАЧА DOCTOR'S HERALD. – 2020. – С. 40.
7. Яхёева Х. Ш. //Сахарный Диабет 2-Го Типа У Детей И Подростков Бухарской Области
8. Биология и интегративная медицина, 139-145, 2021Kimmelstiel P., Wilson C. Intercapillary lesion in the glomeruli of the kidney // Am. J. Pathol. 1936; 12: 82-97.
9. Remuzzi G., Schieppati A., Ruggenenti P. Clinical practice. Nephropathy in Patients with Type 2 Diabetes // N. Engl. J. Med. 2002; 346 (15): 1145-1151.
10. Алгоритмы специализированной медицинской помощи больным сахарным диабетом: клин. рек. / Под ред. И. И. Дедова, М. В. Шестаковой, А. Ю. Майорова // Сахарный диабет. 9-й вып. М.: 2019. 212 с. [Algorithms of specialized medical care for patients with diabetes mellitus: wedge. rivers. / Pod red. I. I. Dedova, M. V. Shestakovoy, A. Yu. Mayorova // Sakharnyy diabet. 9-y vyp. M.: 2019. P. 212.]
11. Худоёрова Д. Р. Прогноз И Профилактика Диабетической Нефропатии //Research Journal Of Trauma And Disability Studies. – 2023. – Т. 2. – №. 4. – С. 75-84.
12. Шестакова М. В., Шамхалова М. Ш., Ярек-Мартынова И. Я. и др. Сахарный диабет и хроническая болезнь почек: достижения, нерешенные проблемы и перспективы лечения // Сахарный диабет. 2011; 1: 81-88. [Shestakova M. V., Shamkhalova M. Sh., Yarek-Martynova I. Ya. i dr. Diabetes Mellitus and Chronic Kidney Disease: Achievements, Unresolved Issues and Treatment Prospects // Sakharnyy diabet. 2011; 1: 81-88.]
13. Orzikulova Sh. A. (2022). Relationship Of New Markers Of Kidney Damage And Vascular Status In Patients With Arterial Hypertension. Eurasian Medical Research Periodical, 7, 161–166.
14. Захарьина О. А., Тарасов А. А., Бабаева А. Р. Актуальные аспекты медикаментозной профилактики и лечения диабетической ангиопатии // Лекарственный вестник. 2012; 5 (45): 14-22. [Zakhar'ina O. A., Tarasov A. A., Babayeva A. R. Actual aspects of drug prevention and treatment of diabetic angiopathy // Lekarstvennyy vestnik. 2012; 5 (45): 14-22.]
15. М.Ш. Тоиров, Ш.А. Орзикулова. Таълим Ва Ривожланиш Таҳлил. Анализ Роли Артериальной Гипертонии И Нарушений Липидного Обмена В Развитии И Прогрессировании Хронической Болезни Почек У Больных Гипертонической Болезнью. Volume: 02 Issue: 10 |Oct- 2022 ISSN: 2181-2624
16. Mogensen C. E., Christensen C. K., Vittinghus E. The stages in diabetic renal disease. With emphasis on the stage of incipient diabetic nephropathy // Diabetes. 1983; 32 (2): 64-78.
17. Шестакова М. В. Диабетическая нефропатия: фатальное или предотвратимое осложнение? // Рус. мед. журнал. http://www.rmj.ru/2007/3. [Shestakova M. V. Diabetic nephropathy: a fatal or preventable complication? // Rus. med. zhurnal. http://www.rmj.ru/2007/3.]

18. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury // Kidney Int Suppl. 2012; Issue 1: 1-126.
19. Lim S., Eckel R. H., Koh K. K. Clinical implications of current cardiovascular outcome trials with sodium glucose cotransporter-2 (SGLT2) inhibitors // Atherosclerosis. 2018; 272: 33-40.
20. Handelsman Y. Rationale for the early use of sodium-glucose cotransporter-2 inhibitors in patients with type 2 diabetes // Advances in Therapy. 2019; 36 (10): 2567-2586.
21. Wanner C., Inzucchi S. et al. Empaglifozin and progression of kidney disease in type 2 diabetes // N. Engl J. Med. 2016; 375: 323–334.
22. Jakher H., Chang T. I., Tan M., Mahaffey K. W. Canagliflozin review – safety and efficacy profile in patients with T2DM // Diabetes Metab. Syndr. Obes. 2019; 12: 209-15. DOI: 10.2147/DMSO.S184437.
23. Prischl F. C., Wanner C. Renal Outcomes of Antidiabetic Treatment Options for Type 2 Diabetes-A Proposed MARE Definition // Kidney Int. Rep. 2018; 3 (5): 1030-8. DOI: 10.1016/j.ekir.2018.04.008.