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FREQUENCY OF OCCURRENCE AND RISK FACTORS FOR THE DEVELOPMENT OF CHRONIC KIDNEY DISEASE IN WOMEN OF FERTILE AGE

Monograph

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Ushbu monografiyada fertil yoshdagi ayollarda surunkali buyrak kasalligi uchrash darajasi, tarqalishi, xavf omillari yo'nalishida olib borilgan ilmiy izlanishlar haqida bayon etiladi. Monografiyada keltirilgan surunkali buyrak kasalligining tug'ish yoshidagi ayollar orasida uchrash chastotasi, qaysi xavf omillari ko'proq sabab bo'lishi ravon tilda bayon etilgan va ko'plab muammolarga urg'u berilgan. Qo'llanmadan tibbiyot institutlari, ordinatorlar, magistrlar, nefrolog, reabilitolog va terapevtlar uchun muhim qo'llanma sifatida amaliyotda foydalanish mumkin.

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Frequency of occurrence and risk factors for the development of chronic kidney disease in women of fertile age [text]/Jumayeva Madina Faxritdinovna

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This monograph describes the scientific research carried out in the direction of the incidence, prevalence, risk factors of chronic kidney disease in women of fertile age. The frequency of occurrence of chronic kidney disease among women of childbearing age listed in the monograph, which risk factors are the most likely cause, is stated in fluent language and emphasizes many problems. The manual can be used in practice as an important guide for medical institutes, interns, Masters, nephrologists, rehabilitologists and therapists.

Жумаева Мадина Фахритдиновна

Частота встречаемости и факторы риска развития хронической болезни почек у женщин фертильного возраста [текст]/ Жумаева Мадина Фахритдиновна /Бухара — 2024. — 60 с.

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В данной монографии описаны научные исследования, проведенные в направлении изучения заболеваемости, распространенности, факторов риска хронических заболеваний почек у женщин фертильного возраста. Перечисленная в монографии частота встречаемости хронических заболеваний почек среди женщин детородного возраста, факторы риска которых являются наиболее вероятной причиной, изложены доступным языком и подчеркивают многие проблемы. Руководство может быть использовано на практике в качестве важного руководства для медицинских институтов, интернов, магистров, нефрологов, реабилитологов и терапевтов.

LIST OF ABBREVIATED WORDS

AH- arterial hypertension

RRT – renal replacement therapy

IHD - ischemic heart disease

BMI- body mass index

HDL- high density lipoproteins

LDL- low density lipoproteins

MAU-microalbuminuria

NSAIDs - nonsteroidal anti–inflammatory drugs

GFR – glomerular filtration rate

CVC -cardiovascular complications

RFP- rural family polyclinic

TG – triglyceride

TRF – terminal renal failure

CKD - chronic kidney disease

CND - chronic non-communicable diseases

CKD-EPI-Chronic Kidney Desease Epidemiology Collaboration Index

KDOQI - Kidney Disease Outcomes Quality Initiative

MDRD - Modification of Diet in Renal Disease

INTRODUCTION

Today, chronic kidney disease (CKD) is a general medical problem with deep socio – medical and economic consequences associated with its widespread prevalence among the population, disability, mortality due to the development of kidney failure and cardiovascular complications.

In recent years, there has been a steady increase in patients with chronic renal disease. It was found that chronic kidney disease is observed in 12-80% of the population in countries with different ethnic composition and economic development, signs of chronic kidney disease of stages C3-C5, which are most unfavorable in 5.9-8.1% of residents, and in Japan up to 18.7%.

At the global level, a number of scientific studies are currently being conducted to achieve high reliability and efficiency in improving the early diagnosis, treatment and prevention of chronic kidney disease. In this regard, there is a sufficient number of scientific papers on the close, direct relationship of risk factors for the formation and development of chronic renal pathology with the level of complications and mortality among patients.

In research and medical centers of various countries, research works are carried out in the chosen field of research, but the features of early diagnosis and prevention, the importance of risk factors for the development and progression of chronic kidney disease, the assessment of the relationship between weight gain and the development of this pathology, the development of early biomarkers for diagnosis and an algorithm for early detection of chronic kidney disease are still being studied.

In our republic today, one of the priorities is to develop ways to improve the health care system, early detection and prevention of widespread non-communicable diseases, including nephrological diseases. The action strategy for 5 priority areas of

the Republic of Uzbekistan in 2017-2021 states that " ... one of the main tasks is to improve the convenience and quality of medical care, strengthen the material and technical base of medical institutions, further reform specialized and high-tech medical care, strengthen family health...". The current tasks that are waiting to be solved at this time are to reduce the growth of chronic kidney disease among the population, to determine the significance of risk factors for the development and progression of chronic kidney disease, to develop an algorithm for early detection of chronic kidney disease and an early urinary biomarker for determining.

CHAPTER I . THE CONCEPT OF CKD (Literature review)

§ 1.1 Prevalence, risk factors, and organization of medical care for chronic kidney disease

The development of clinical medicine in recent years allows to preserve the life, working capacity and social activity of patients, as well as to improve their quality of life. But it is not always possible to carry out timely diagnosis of some chronic diseases, including CKD, which leads to deterioration of the condition of patients, complications of the disease, disability and, unfortunately, death of patients [77; p. 22-26]

The development of the system of nephrological care and renal replacement therapy (RRT) is not able to solve the problem of treating patients and improving their quality of life. There is a need for a universal, simple and convenient methodological framework that allows you to combine the efforts of many clinicians-nephrologists, cardiologists, endocrinologists, therapists and others for the purpose of early diagnosis of chronic kidney pathology of different nature, timely appointment of nephroprotective therapy and nephroprophylaxis. [70; pp. 22-26;]

The initial attempt to address these issues was initiated at the beginning of the XXI century by the National Kidney Foundation of the United States (NationalKidneyFoundation-NKF). The analysis of the results of numerous studies on the diagnosis and treatment of kidney diseases, the prognostic role of a number of indicators, and terminological concepts formed the basis of the concept of CKD (Chron-ickidneydisease – CKD) [54; p. 4-26]. Later, experts from the European Kidney Association, the European Association for Dialysis and Transplantation (ERA-EDTA), and KDIGO (KidneyDisease:ImprovingGlobalOutcomes) participated in the development of this model [38; p 950-957].

Currently, the concept of CKD and its proposed classification have received

worldwide recognition by scientists and specialists in the field of nephrology.

In 2002, the National Kidney Foundation of the United States published practical recommendations for the identification and management of patients with CKD - K/DOQIGuideline (KidneyDiseaseOutcomesQualityInitiative). These recommendations address the assessment, classification and stratification of CKD risk [62; p 107-114]

Recommendations include the study of the degree of renal damage by determining the albumin / creatinine ratio, evaluating the glomerular filtration rate (GFR) by blood creatinine level using calculated formulas. Since the prevalence of early stages of CKD in the general population is quite high, the recommendations created are useful not only for nephrologists, but also for doctors of other specialties – cardiologists, endocrinologists and general practitioners [34; 48].

In 2008, in the UK, the National Institute for Health and Clinical Excellence (NICE - NationalInstituteforClinicalExcellence) established guidelines for the early diagnosis and management of CKD in adults in primary and secondary care [27; 53]

In 2012, Australia created its own CARI (CaringforAustralianswithRenalImpairment) recommendations [58; p 1-32].

CKD is a growing public health problem in all countries of the world due to the huge increase in its risk factors in recent years. Due to rapid lifestyle changes, there is a significant increase in the prevalence of risk factors that are the main causes of CKD.

Epidemiological assessment followed by prioritization of risk factors helps to determine the prevalence and incidence of CKD, and these studies are necessary for the development of prevention programs.

To this end, screening studies are being implemented worldwide to determine the local burden of chronic kidney disease and its contribution to public health.

According to studies conducted in different countries of the world, the following figures are determined: according to the results of the NHANES study conducted in 2005-2010, signs of CKD are observed in 14-20% of the US population, according to the KEEP epidemiological study conducted in 2000-2011,

the incidence of CKD among the adult population of the United States is 23.8%. According to the results of the national epidemiological study "Beijingstudy", conducted in China in 2008, CKD is observed in 14% of the country's residents.In 2013,such a national epidemiological study was implemented in India (SEEK – India, 2013). According to this survey, CKD occurs in 17.2% of Indian residents. The prevalence of CKD among residents of the Congo was 12.4%, with the most unfavorable stages of the disease observed in 8% of residents (in the United States - 15.7%).

In Russia, a huge epidemiological study on the definition of CKD has not been conducted, but scientific studies conducted in certain categories of the population confirm that in older age groups CKD was observed in 66.3%, among patients suffering from pathologies of the cardiovascular system, the incidence of CKD was 16%.

The first epidemiological study of kidney disease in Kazakhstan was conducted in 1980 and studied the incidence of nosological types of kidney diseases. The results of the screening survey conducted among students of Karaganda universities showed that 13.6 % of students have pathological changes in urine characteristic of the early stages of CKD. [36; p. 6-16].

According to the scientific literature, it is determined that large-scale epidemiological studies for the realization of the prevalence of CKD among the population of our Republic have not been conducted. However, a study was conducted in separate groups of patients with certain pathologies aimed at studying the clinical and genetic features of nephropathy in diabetes mellitus and metabolic syndrome and the development of CKD in patients with arterial hypertension.

According to Kamilov D. N. (2011), the average level of disability due to nephrological diseases in Tashkent is 0.5 per 10,000 population, the main part was made up of women of reproductive age (84.5%) and the working-age population (70.5%).

Scientific surveys of Daminova K. M. and Kayumov U. K. (2011) show that type 2 diabetes is a risk factor for the development of CKD. Analysis of the results of a

scientific study showed a high incidence of nephropathy in direct-line relatives of patients suffering from type 2 diabetes mellitus complicated by diabetic nephropathy. In families of patients with metabolic syndrome, nephropathy occurs in every third (35.5%).

Studies have shown that CKD is a serious medical and social problem that significantly affects the health of people and the economic condition of the country on all continents [28; 51]. The most obvious consequence of CKD is the high cost of life-saving RRT (dialysis and kidney transplantation), which places a heavy burden on the health system.

In the United States, 28.9% of Medicare's budget was spent on non-RRT CKD patients, who accounted for 12.7% of the total number of people covered by Medicare, in 2011. The need for hospitalization in patients with CKD is 38% higher compared to people without CKD, and mortality is 43% higher[39; pp. 39-44].

The high prevalence, adverse outcomes, and complications of CKD give reason to raise the issue of the feasibility of developing and implementing measures for its early detection, nephroprotection, and nephroprophylaxis [70; pp. 1-70].

CKD occupies a special place in the family of chronic non-communicable diseases (CKD). Most cases of CKD are secondary kidney lesions within other CKD diseases, such as diabetes mellitus and hypertension. This is one of the reasons that most of the risk factors for CKD are shared with the risk factors for these diseases, so programs for the prevention and early detection of diabetes mellitus and arterial hypertension play a crucial role in the prevention of CKD [60; p.71-87].

The results of the NHANESIII study [24; p. 601 - 609] demonstrated that in addition to arterial hypertension and diabetes mellitus, the main factors for the development of CKD are also the age of patients. Studies have found that, in 11% of people over 65 years of age without arterial hypertension and diabetes mellitus, CKD of stages III-V of development is determined [36; p. 6-16].

The characteristic general aging of the population in developed countries significantly affects the increase in the prevalence of CKD, which in most cases is associated with an increase in the number of patients with vascular kidney damage

[15; p.17-20].

Recent publications prove that a large number of patients with arterial hypertension, hyperlipidemia and diabetes mellitus have a high risk of developing kidney failure. This fact is proved by the research of Tangri, N. etal. [56; p. 514-520], which indicates that about 40% of the adult population has an increased risk of developing CKD and renal dysfunction.

The formation of a healthy lifestyle of the population reduces the risk of developing CKD, as well as other CKD. However, it is important to emphasize that the common risk factors for CKD - high blood pressure, dyslipidemia, smoking, poor nutrition, inactivity, reduced carbohydrate tolerance, obesity, alcohol consumption increases the risk of not only secondary nephropathies, but CKD in general. A decrease in the effect of these risk factors leads to a decrease in these pathologies and their complications. [65; pp. 7-17].

Playing a central role in the regulation of metabolism and the elimination of its end products from the body, exotoxins of the kidneys functionally and structurally suffer from an irrational diet and an unhealthy lifestyle of the population [68; p 117-124].

It should be emphasized that non - compliance with the diet, heavy consumption of fatty, salty and spicy foods directly correlates with the development of kidney pathology, especially in adults. In this regard, many authors agree that poor nutrition is also an important risk factor for the formation and development of CKD.

According to these national guidelines, risk factors for the progression of CKD include a number of chronic diseases, such as diabetes mellitus, arterial hypertension, autoimmune diseases, various pathogenic and opportunistic microbes, urinary tract stones, lower urinary tract obstruction, kidney surgery, frequent use of analgesics and other nephrotoxic drugs, acute renal failure, a history of nephropathy in pregnant women, obesity, hyperhomocysteinemia, a violation of calcium-phosphorus metabolism, which are divided into modifiable and non-modifiable.

The fifth stage of CKD corresponds to the term "end-stage renal failure," or "end-stage renal disease" (ESRD) used by English-speaking authors, and requires the initiation of renal replacement therapy (RRT). Earlier stages of CKD, i.e., stages I-IV, involve a set of measures aimed at either slowing the deterioration of kidney function or preparing the patient as best as possible for RRT. Despite the cautious approach of Russian nephrologists, the concept of CKD is gaining more supporters as its advantages become increasingly evident.

CKD is not merely a mechanical grouping of chronic kidney damage of various origins. This concept is based on the unity of the leading pathogenetic mechanisms behind the progression of the pathological process in kidney tissue, the commonality of many risk factors for the development and progression of kidney diseases, and the resulting similarity of therapeutic approaches, primary and secondary prevention [2]. It is possible that, in practical terms, CKD will occupy a similar place as coronary artery disease (CAD) or chronic obstructive pulmonary disease (COPD). The authors [1], along with the concept of CKD, believe it is necessary to retain the term "end-stage renal failure (ESRF)" in Russia. ESRF should refer to patients receiving RRT and individuals with stage V CKD, for whom renal replacement therapy has not yet started or is not being conducted due to organizational issues.

Examples of diagnosis formulation:

1. Hypertensive disease stage III, grade 3 arterial hypertension, very high risk of cardiovascular complications. Hypertensive nephrosclerosis. Chronic kidney disease stage III.

2. IgA nephropathy. Isolated urinary syndrome. Chronic kidney disease stage I or stage III.

3. Type 2 diabetes mellitus. Diabetic nephropathy. Chronic kidney disease stage II or stage III.

The introduction of the CKD principle required the use of a simple, reliable, and

inexpensive criterion for clinical practice. The developers of the National Kidney Foundation of the United States convincingly demonstrated that this criterion is the glomerular filtration rate (GFR): the degree of reduction in GFR is closely associated with other clinical and metabolic changes that occur as chronic nephropathies progress.

Among the many proposed methods for determining GFR, the "calculated" methods have gained the most recognition. In "adult" nephrology, the Cockcroft-Gault and MDRD formulas are used [2].

The most acceptable formula requires only the serum creatinine concentration from biochemical indicators (MDRD):

GFR, ml/min/1.73m² = 186 × $(Scr)^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 for women) × (1.210 for African Americans),

where Scr – serum creatinine concentration.

Note: Scr in mg/100ml = Scr in μmol/L ÷ 88.4;
Age–age in years;

women – for females

aa – for African Americans.

The diagnosis of CKD, including those stages characterized by a decrease in GFR, i.e., from stage III, requires the registration of the patient at a regional renal replacement therapy center [3]. Of course, the treatment of the underlying disease causing the reduction in GFR should continue, and in some cases, partial or complete restoration of kidney function can be achieved.

Over the past 20 years, the prevalence of CKD in the general population has remained consistently high [4,5]—at least 10%, and up to 20% in certain groups (elderly individuals, people with type 2 diabetes, African Americans). A link has been established between kidney pathology and cardiovascular diseases, which has

led to the concept of the cardiorenal continuum. It has been noted [6] that in individuals aged 65 and older, mortality increased by 26% for every 5 ml/min decrease in GFR. One of the key pathogenetic links in the cardiorenal continuum is arterial hypertension (AH). It is now proven that AH of any degree (not just severe, uncontrolled, as previously thought) is a leading risk factor for the development of end-stage renal failure.

Even at stage I AH, the formation of hypertensive nephropathy begins. The most significant risk factor for hypertensive kidney damage is an increase in systolic blood pressure, which is considered an independent risk factor for CKD [4]. Hypertensive kidney damage is most pronounced in older individuals, and moderate decreases in kidney function have been associated with an increase in the prevalence of AH (from 36% to 55%), coronary artery disease (from 13% to 26%), and heart failure (from 3% to 8%). In patients aged 50-75 years, the risk of cardiovascular diseases is characterized by progressively increasing global nephrosclerosis involving glomerular structures, tubulointerstitium, and maladaptive remodeling of the vascular bed. Hypertensive kidney damage develops in parallel with damage to other target organs.

In diagnosing hypertensive nephropathy, special attention is given to the detection of microalbuminuria (MAU). Table 5 provides the criteria for assessing MAU. Urine is collected either over a specific time interval (preferably over 24 hours) or from a single urine sample (in the latter case, the concentration of creatinine is also measured, and the albumin/creatinine ratio is calculated).

Microalbuminuria (MAU) reflects the presence of generalized endothelial dysfunction in the body. In large studies (PREVEND, LIFE), MAU was found in 20-30% of individuals with hypertension (AH). The presence of MAU is a serious sign and requires the initiation of renal and cardiovascular protection measures.

Among the risk factors for CKD, some of the most common are obesity, carbohydrate metabolism disorders, lipoprotein metabolism disturbances,

hyperuricemia, smoking, the use of non-narcotic analgesics and nonsteroidal anti-inflammatory drugs, HIV, and HBV and HCV infections. Advanced age is one of the leading risk factors for CKD. In addition to age-related involutional changes in kidney tissue, elderly individuals often have late stages of chronic nephropathy (such as diabetic or urate nephropathy) and chronic glomerulonephritis. Cardiovascular diseases, including atherosclerosis, heart failure, and hypertension, are also widespread.

At early stages of CKD, when GFR is normal, the diagnosis should primarily focus on urine test results (proteinuria, hematuria). A decrease in the relative urine density (Zimnitsky test), indicating loss of the kidney's concentrating function (primarily tubular dysfunction), often precedes a decrease in GFR. In patients with risk factors for CKD, MAU is commonly detected. To clarify the underlying cause of CKD, instrumental methods, particularly ultrasound, and, in some cases, computed tomography, are used. If CKD is suspected, repeated blood pressure measurements are essential.

The rate of CKD progression is variable. It largely depends on the underlying disease. However, CKD itself worsens the patient’s prognosis, not only due to the development of end-stage renal failure. Leading factors for an unfavorable prognosis in CKD patients are cardiovascular complications: stroke, myocardial infarction, and chronic heart failure. Given that hypertension is a significant risk factor for CKD, regular monitoring of GFR, MAU, urine analysis, creatinine levels, and kidney ultrasound is essential for patients with hypertension. Timely detection, prevention, and treatment of CKD are crucial directions for increasing the active life expectancy of the population.

Chronic kidney disease (CKD) is widespread in the population (over 10-13%), represents a significant medical and social problem, and holds a special place among all non-communicable diseases. Moreover, this condition leads to a significant decline in quality of life, increased mortality, and, at the terminal stage, requires the use of costly renal replacement therapies (dialysis, kidney transplantation) [7, 39].

Globally, the number of patients with end-stage renal disease is steadily increasing, which is associated with the rising prevalence of type 2 diabetes, hypertension, and other diseases that cause chronic kidney disease.

According to data from the Russian Dialysis Society, the availability of renal replacement therapy averages 246 patients per 1 million people. There are uneven growth rates among patients receiving hemodialysis compared to those undergoing peritoneal dialysis and kidney transplant recipients [7]. At the same time, the actual number of patients with chronic kidney disease requiring various extracorporeal blood purification methods is significantly higher.

At the beginning of 2014, approximately 10 million people worldwide were registered as needing renal replacement therapy, but only 32% of them were able to receive it [76].

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registered as needing renal replacement therapy, but only 32% of them were able to receive it [76].

At the current stage of medical development, increasing attention is being paid to the prevention of various diseases, which makes nephroprotective therapy particularly important for patients with therapeutic pathologies who are at high risk of developing chronic kidney disease (CKD).

To improve the organization of medical care for patients with chronic kidney disease, ensure the rational distribution of resources, and train medical personnel, epidemiological, clinical-statistical, and socio-medical studies are of great importance. These studies focus on assessing the prevalence of the disease, identifying predisposing risk factors that contribute to its development and progression, and implementing timely preventive measures. However, there is still a lack of research aimed at optimizing nephrology care in different regions.

Chronic kidney disease is one of the major medical and social problems , as the past decade has been marked by an increase in the number of such patients, especially in the terminal stage. This has led to a progressive rise in the number of patients requiring costly renal replacement therapy. Moreover, the potential prevalence of CKD may significantly exceed the actual figures reported in official statistics.

The lack of timely examinations, necessary treatment, and preventive measures for CKD leads to the rapid progression of the disease, increases disability and mortality rates in this patient population, and raises the overall cost of therapy for individuals with chronic kidney disease.

Currently, among chronic non-communicable diseases, chronic kidney disease (CKD) holds a key position due to its high prevalence, negative impact on patients' quality of life, high disability rates, and mortality [58, 131, 41, 107, 137]. The terminal stage of kidney damage necessitates the use of costly renal replacement therapies—hemodialysis and kidney transplantation [1, 113]. Chronic kidney

disease is not only a medical issue but also a significant economic and social problem [116].

The diagnosis of CKD is established based on the detection of anatomical or structural kidney damage and/or a decrease in the glomerular filtration rate (GFR) to less than 60 ml/min/1.73 m², documented for at least three months, regardless of the cause or etiology [51, 67, 100].

Chronic kidney disease is considered a supra-nosological concept, meaning it serves as a tool to assess the progression of kidney diseases of various etiologies and to initiate timely treatment [163]. CKD is particularly dangerous because it remains largely asymptomatic until the later stages. This often leads to late diagnosis, when nephroprotective therapy is no longer effective [67]. Another key feature of CKD is the predominance of secondary nephropathies in its etiology, causing patients to be monitored by different specialists over an extended period [86, 96].

Over the past two decades, several large epidemiological studies have been conducted, demonstrating a high prevalence of CKD [96]. A global meta-analysis by Hill et al. (2016) showed that approximately 13% of the world's population suffers from CKD. However, prevalence rates vary significantly across countries, likely due to differences in research methodologies. According to major epidemiological studies, CKD prevalence is estimated at 14-24% in the United States, 18% in the Netherlands, 14% in China, 17% in India, and 13% in Australia [65, 63, 160, 162].

An inevitable outcome of CKD is end-stage renal disease (ESRD), which is diagnosed in 0.1% of the population [122, 60]. In recent years, life expectancy for ESRD patients has significantly increased. However, even with effective and comprehensive treatment, their lifespan remains limited to 10–15 years [124, 131]. A concerning trend is the continuous rise in the number of ESRD patients. According to data from the Russian Dialysis Society Registry, the annual increase in the number of patients receiving various types of renal replacement therapy is 10.5% [44].

The high prevalence of CKD, the frequency of adverse outcomes, and the high rate of complications highlight the urgent need to improve medical care for such patients [167]. It is crucial to educate the population about CKD and its consequences, develop methods for early detection, and maintain statistical records of at-risk patients. A well-organized approach to addressing CKD-related challenges can improve public health on a population-wide scale.

The modern classification of chronic kidney disease (CKD) was developed by the National Kidney Foundation (USA) in 2002. It consists of five stages, which are categorized based on a combination of kidney function indicators, markers of kidney damage, and glomerular filtration rate (GFR) [100].

In Russia, the CKD classification (K/DOQI) was recommended for use by the VI Congress of the Scientific Society of Nephrologists (2005) and the plenary session of the Board of the Scientific Society of Nephrologists of Russia (2007). An important criterion for assessing kidney function decline is a GFR level, standardized for body surface area, that falls below 90 ml/min/1.73 m². A GFR of 60-89 ml/min/1.73 m² is considered an initial or mild reduction in kidney function [39]. End-stage renal disease (ESRD) is diagnosed when GFR drops below 15 ml/min/1.73 m². To diagnose CKD, the presence of kidney damage markers is also required; in their absence, CKD is not diagnosed [81].

CKD encompasses a range of pathological conditions characterized by persistent impairment of kidney function [27, 138].

Regardless of the site of initiation (glomeruli, tubules, or blood vessels), the development of chronic renal failure is driven by a decrease in the number of functioning nephrons and the predominance of fibroplastic processes, replacing nephrons with connective tissue [118, 148]. In the early stages of the disease, the following processes occur: inflammation, extracellular matrix synthesis (fibrogenesis), regeneration, and tissue remodeling [68].

An important aspect is that fibrogenesis initially begins as a necessary attempt

to stabilize kidney function by maintaining the structural integrity of the basement membranes [92]. However, if repair mechanisms are disrupted or the damaging stimulus persists, kidney damage can progress to a chronic condition characterized by irreversible organ remodeling and scar tissue formation. Histologically, this process manifests as glomerulosclerosis, vascular sclerosis, and tubulointerstitial fibrosis, with the latter being the primary predictor of declining kidney function, regardless of etiology [93].

Fibrosis exacerbates disease progression by reducing the capillary network and causing tissue hypoxia [70], while hypoxia itself directly stimulates further fibrogenesis. Renal parenchymal sclerosis represents the final common outcome of all progressive kidney diseases [36].

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functioning nephrons and the predominance of fibroplastic processes, replacing nephrons with connective tissue [118, 148]. In the early stages of the disease, the following processes occur: inflammation, extracellular matrix synthesis (fibrogenesis), regeneration, and tissue remodeling [68].

An important aspect is that fibrogenesis initially begins as a necessary attempt to stabilize kidney function by maintaining the structural integrity of the basement membranes [92]. However, if repair mechanisms are disrupted or the damaging stimulus persists, kidney damage can progress to a chronic condition characterized by irreversible organ remodeling and scar tissue formation. Histologically, this process manifests as glomerulosclerosis, vascular sclerosis, and tubulointerstitial fibrosis, with the latter being the primary predictor of declining kidney function, regardless of etiology [93].

Fibrosis exacerbates disease progression by reducing the capillary network and causing tissue hypoxia [70], while hypoxia itself directly stimulates further fibrogenesis. Renal parenchymal sclerosis represents the final common outcome of all progressive kidney diseases [36].

The primary factor stimulating glomerular damage is considered to be the development of intraglomerular hypertension and hyperfiltration. Intraglomerular hypertension arises as a result of the transmission of systemic arterial pressure or due to glomerular pathology [135].

Damaged and sclerotic glomeruli may retain a certain level of filtration function [27, 90]. The adaptive process occurs by increasing the function of the remaining nephrons, leading to hyperfiltration and further structural changes in the kidneys, which, in turn, contribute to the progression of renal failure.

Damaged tubules produce a range of profibrotic and pro-inflammatory factors that, under pathological conditions, can alter glomerular function and cause additional damage through paracrine mechanisms. Increased protein reabsorption in the proximal tubules due to glomerular hyperfiltration activates cytokine production

by tubular cells, which in turn promotes immune cell infiltration and the activation of an immune-inflammatory response [27, 110, 130].

Abnormally filtered bioactive macromolecules interact with the epithelial cells of the proximal tubules, activating signaling pathways involving **NF-κB**. The albumin-receptor complex (megalin-cubilin) mediates the uptake of certain proteins by proximal tubular epithelial cells. Albumin may also serve as a source of potential antigenic peptides produced by kidney dendritic cells [27, 136, 38].

A critical factor in CKD progression is **proteinuria**. In cases of severe proteinuria, tubular cells accumulate vacuoles containing proteins. In response, chemokines are produced, immune cells migrate, inflammatory infiltrates form, and ultimately, tubular cell apoptosis occurs [23, 64]. Additionally, when glomeruli are damaged, elements of the basement membrane, immune complexes, complement components, inflammatory cytokines, and lipids enter the urine, further contributing to interstitial inflammation and fibrosis [23, 42].

Regardless of the initial cause of kidney dysfunction, disease progression triggers compensatory mechanisms, which can further drive the pathological process. These reactions include arterial hypertension and hyperactivation of the peripheral or renal sympathetic nervous system [27, 107]. Thus, the disease continues to progress even in the absence of the initial triggering factor [61, 121].

1.2. Risk factors for CKD-a medical and social problem.

It is known that CKD is a supranosological concept that unites all patients with signs of kidney damage that persist for 3 or more months according to laboratory and instrumental studies and / or a decrease in function estimated by the value of GFR [66; pp. 89-115].

For the diagnosis of CKD, in addition to clinical and instrumental studies, it is necessary to determine the markers of renal damage and the state of renal function. The most accessible, simple and cheap laboratory method for the study of markers of renal damage is a general urinalysis, which allows detecting proteinuria,

hematuria, leukocyturia and other indicators of the pathological process in a single portion of urine [46; pp. 89-115, 62; c17-28]. Along with the advantage of this method, there are certain disadvantages associated with the imperfections of this method. The imperfections of this method include insufficient accuracy, especially when the level of proteinuria is below 0.5 g/l. A normal result of the general analysis of the patient's urine does not exclude the presence of CKD [52; p.38-43]. All the diagnostic criteria developed to date for determining kidney pathology are aimed at determining two components of signs – kidney damage and a decrease in GFR.

It is important to emphasize that at the beginning of the development of CKD, kidney function can remain intact for a long time, despite the presence of pronounced signs of damage. In normal or elevated GFR, as well as in patients with its initial decrease (60 < GFR<90 ml / min/1.73 m2), the presence of signs of kidney damage is a prerequisite for the diagnosis of CKD[35; pp. 727-733].

The detection of GFR in patients with more than 120 ml / min/1.73 m2 is also considered a deviation from the normal parameters for the kidneys, since in individuals suffering from diabetes mellitus and obesity, it may reflect the phenomenon of hyperfiltration caused by their increased perfusion with the development of glomerular hypertension, which leads to their functional overload, damage with further sclerosis of the structure [44; pp. 16-27].

However, to date, increased glomerular filtration (GFR > 120 ml / min/1.73 m2) is not included by specialists among the independent diagnostic criteria for CKD, but is considered a risk factor for its development [47; p.5-8].

The presence of CKD in diabetes mellitus and obesity is indicated by markers of renal damage, primarily increased albuminuria in patients[52; pp. 38-43].

There are 5 stages of CKD, depending on the level of GFR. Patients with stage III CKD are the most common among the population, while this group is heterogeneous in terms of the risk of cardiovascular complications, which increases with a decrease in GFR. Therefore, stage III of CKD was proposed to be divided into two sub - stages-IIIA and IIIB. [47; pp. 5-8].

If we talk about the classification of CKD, we want to highlight the fact that

there were numerous classifications of various pathological conditions of the kidneys. These classifications emphasized the nature of the pathology, the form of the disease, the duration of the pathological process, and so on, but they did not give a complete picture of the course and outcome of the disease.

Currently, clinicians use a single classification of CKD, given in the International Classification of Diseases 10-revision (ICD-10) 2007.

CKD in ICD-10 (2007) is presented as follows:

18.1 CKD - C1 stage, GFR level>90 ml / min/1.73 m2

18.2 CKD - C2 stage, GFR level 60-89 ml / min/1.73 m2

18.3 CKD - C3a stage, GFR level 45-59 ml / min/1.73 m2

18.3 CKD - C3b stage, GFR level 30-44 ml / min/1.73 m2

18.4 CKD - C4 stage, GFR level 15-29 ml / min/1.73 m2

18.5 CKD - C5 stage, GFR level<15 ml / min/1.73 m2

18.9 Unspecified CKD

If we talk about the strategy for identifying chronic kidney disease, a deep analysis of modern domestic and foreign literature sources, as well as clinical practice, shows that there is no consensus among specialists on this issue. There are numerous recommendations that are not perfect.

But a large number of researchers are inclined to believe that screening studies are the most optimal and recommend this method to be more acceptable for the detection of CKD. In this regard, various strategies have been proposed to identify it [23; 32, 62].

However, not all researchers share a common view and screening programs in their CKD studies are accepted not everywhere The published evidence base for CKD compared to that for cardiovascular disease and diabetes mellitus is limited, and to date there are not enough randomized controlled trials to compare the effectiveness of CKD screening with its effectiveness.

The goal of screening programs has almost always been to identify CKD at an early stage of the pathological process, which will allow for a timely final diagnosis and start appropriate nephroprotective treatment.

A great help in assessing the need for laboratory tests is provided by special questionnaires that the subjects fill out independently or with the help of secondary medical personnel. The most well-known questionnaire created in the United States for the KEEP study [162; p. 107-114], dedicated to the screening and monitoring of individuals with CKD risk factors. Based on the data of the American epidemiological study NHANES in the USA, an improved questionnaire SCORED (SCreeningforOccultREnalDisease) was developed [33; 38].

It should be noted that currently in many countries of the world there are so - called screening centers for CKD, created with the support of the state or charitable foundations, in which everyone who wants to be examined can pass a free questionnaire and interview for the presence of risk factors for CKD, in addition, they can pass the necessary laboratory tests.

With the introduction of modern means of informatization of IT technologies in medicine, this way of detecting CKD becomes more accessible. The prospects of using IT technologies for screening studies are shown by the results of the analysis of 1032 case histories in one of the central district hospitals of the Moscow region of the Russian Federation, which showed that among working-age patients undergoing examination and treatment in therapeutic departments and without a diagnosis of kidney disease, GFR < 60 ml/min/1.73 m2, that is, CKD 3a-5, was observed in 16% of cases. And in a sample of patients with cardiovascular diseases

A prerequisite after the completion of screening studies, according to many experts, is not only the identification of the patient with CKD, but also the inclusion of him in the risk group. In the future, these patients should undergo a mandatory primary consultation with a nephrologist in order to make a nosological diagnosis, select etiotropic, pathogenetic and nephroprotective therapy, as well as carry out secondary preventive measures for the progression of this pathology.

1.3 Diagnostic criteria and current strategies for the detection of chronic kidney disease

Practice shows that laboratory indicators or markers of kidney damage in patients

most often include proteinuria, changes in urine sediment, blood and urine tests, changes in functional and imaging methods of research, characteristic of violations of certain partial kidney functions [54; p .4-26].

At the same time, it is known that the early (preclinical) stages of chronic kidney dysfunction, corresponding mainly to stages 1-2, and sometimes to stages 3 of CKD, are characterized by an asymptomatic or low-symptom course in the current NKF classification [136; p.33-40]. Obvious clinical changes, including detected proteinuria, as well as structural changes in the organ during its ultrasound imaging, as a rule, indicate a far-reaching, irreversible pathological process [24].

According to the overwhelming majority of authors, in clinical practice, in the absence of any other signs of chronic kidney damage, the level of albuminuria is the only and relatively early indicator that allows us to exclude or confirm the presence of a subclinical course of CKD, especially in conditions of preserved GFR [52; pp. 38-43].

Studies have shown that albuminuria / proteinuria in the concept of CKD-K / DOQI is considered as a marker of renal dysfunction [16; p. 89-115, 17; c19-21].

At the KDIGO London Conference in 2009, the previous gradations of the severity of albuminuria ("stages of albuminuria") were left:

- less than 30 mg of albumin in the urine
- 30-299 mg of albumin in the urine
- 300 mg or more of albumin in the urine [56; pp. 89-115].

To assess albuminuria/proteinuria as part of a screening study, an albuminuria test or a general urinalysis can be used from laboratory parameters, which includes determining the concentration of total protein in the urine. The albuminuria test has an advantage for the early detection of CKD, since it is more sensitive and allows us to differentiate all 3 categories of albuminuria in the examined patients [30; pp. 33-38].

The albuminuria test is of particular value in the early diagnosis of CKD in the examined patients with hypertension, diabetes mellitus and obesity, in which the appearance of significant proteinuria is observed only at the late stages of the

pathological process [30; p.33-38, 65; p. 7-17].

The analysis of the literature showed that albuminuria is detected in 20-30% of people with arterial hypertension, in 25-40% of patients with type I or II diabetes, in 5-7% of people in the general population of the conditionally healthy population [59; pp. 1517-1523]. The development of albuminuria is associated with almost all components of the metabolic syndrome and is also noted in tobacco smoking [11].

The most rational and reliable way to determine GFR in routine laboratory practice is to automatically calculate it in biochemical laboratories, which should produce 2 results – serum creatinine concentration and calculated GFR [11].

The formulas proposed for practical health care take into account the peculiarities of creatinine kinetics due to age, different muscle mass and increased tubular creatinine secretion in the late stages of CKD. When the creatinine level falls within the reference (normal) laboratory values, GFR can be reduced to a level corresponding to the 3a and even 3b stages of CKD [63];

To date , the CKD-EPI method of GFR calculation is used for screening, taking into account the level of creatinine in the blood serum, gender and age of the patient. There are nomograms for determining GFR by this method. Electronic calculators are available for calculating GFR on-line or using separate applications for personal computers and mobile devices. Currently, the use of the old Cockcroft - Gault equations is not recommended for calculating GFR in practical medicine [64; 1-70].

Thus, our in-depth analysis of the literature sources of domestic and foreign authors has shown that the prevalence of CKD in the world is quite high, which leads to a deterioration in the quality of life of patients and high mortality among patients. For the early detection of CKD, the authors proposed screening studies and successfully carried out these works. Optimal classification introduction optimal methods of clinical examination and laboratory diagnostics are given. In addition, a strategy for the detection of CKD is proposed and risk factors for the progression of this pathology are described. Attention is drawn to the work devoted to the determination and evaluation of albuminuria glomerular filtration rate in the

diagnosis of CKD. It is proved that a successful solution to the problem of CKD only by RRT is impossible.

At the same time, the problems of early diagnosis of CKD with the help of screening studies in rural areas, the determination of risk factors for the development and progression of CKD in this category of individuals, modern methods of early diagnosis and prediction of the course of CKD with the help of ST-technologies have not yet been solved, an algorithm for preventing the formation and development of CKD in the adult population has not been developed.

In connection with the above, the continuation of research work in this area is relevant and in demand. In the 21st century, the global community has faced a major challenge— a pandemic of chronic non-communicable diseases, which have not only medical but also significant socio-economic implications related to loss of working capacity and the need for high-cost treatment [14, 15].

Diabetes mellitus (DM) and chronic kidney disease (CKD) hold a crucial place among diseases whose growth rates have taken on the character of non-communicable epidemics due to their significant prevalence in the population, sharp decline in quality of life, and high patient mortality.

According to the latest data from the International Diabetes Federation (IDF), the global prevalence of diabetes reached 463 million people in 2019 (approximately 8% of the world's population) [16]. These figures have surpassed previously projected growth rates by 10–12 years, and by 2045, the number is expected to increase by 51% to 700 million people.

In the Russian Federation (RF), as in many other countries, the prevalence of diabetes continues to rise. From 2000 to 2019, the number of registered diabetes patients doubled, reaching 4.58 million, which corresponds to 3.1% of the Russian population [17]. At the same time, the results of a large-scale national epidemiological study (NATION) showed that the actual prevalence of type 2 diabetes, based on active screening using HbA1c levels, is twice as high as the registered figures, reaching 5.4% [18].

The global prevalence of chronic kidney disease (CKD), according to the

Global Burden of Disease study, is estimated to be 8–16% [19], making it comparable to other socially significant diseases such as hypertension, diabetes mellitus (DM), and obesity. Signs of kidney damage and/or a decrease in glomerular filtration rate (GFR) are detected in at least one in ten individuals in the general population [1]. Similar figures have been observed across countries with different income levels, including both developing nations with low and middle incomes and high-income countries.

According to recent meta-analyses, CKD affects 13.4% of the global population (95% CI: 11.7%–15.1%) [20, 21] and is significantly more common—affecting 40–50%—in high-risk groups, particularly among patients with DM [2]. Data from the U.S. National Health and Nutrition Examination Survey (NHANES) indicate that CKD prevalence among diabetes patients exceeds 40%, while in the general population, it is 11.3% [22].

It is important to note that diabetic kidney disease is currently the leading cause of end-stage kidney disease (ESKD) worldwide, accounting for approximately 40% of new patients requiring renal replacement therapy (RRT) [23]. This underscores the importance of studying not only the epidemiological aspects of kidney disease but also its specific manifestations in diabetes.

Epidemiological studies conducted in the Russian Federation have shown that CKD is also a pressing issue for the country. According to domestic researchers, CKD is observed in one-third of patients with chronic heart failure (CHF), with its prevalence increasing to 26% in individuals with cardiovascular disease (CVD). Additionally, reduced kidney function is found in 36% of individuals over the age of 60 [24, 25]. These findings necessitated a fundamental restructuring of the healthcare system for this patient category and led to a reassessment of the traditional perception of kidney diseases as relatively rare among the population. This primarily affected the criteria for diagnosing CKD, as well as the definition and stratification of kidney disease severity [6].

The first classification criteria were established by the National Kidney Foundation

(NKF) in the United States in 2002, allowing for a universal assessment of kidney function impairment [26]. The concept of CKD was based on published research regarding diagnosis, treatment, prognostic significance of various indicators, and relevant terminology. Subsequently, experts from the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) [27] and KDIGO (Kidney Disease: Improving Global Outcomes) [28, 29, 30] contributed to the development of the CKD model.

Currently, the glomerular filtration rate (GFR) is recognized as the best method for assessing kidney function in both healthy individuals and those with various diseases. GFR is correlated with age, sex, and body surface area, with a value below 60 ml/min/1.73m² indicating a 50% loss of filtration capacity [31].

Currently, the concept of CKD and its classification have gained widespread recognition. The integration of the CKD framework into the national healthcare system should be regarded as a key strategic approach to reducing overall and cardiovascular mortality, increasing life expectancy, and lowering costs associated with hospitalization for kidney function impairment complications and renal replacement therapy (RRT).

Thus, the rapid increase in the number of patients with impaired kidney function is not merely a specialized concern but a general medical and interdisciplinary issue with serious socio-economic consequences [6]. The CKD concept provides a foundation for addressing critical healthcare challenges by standardizing approaches to the diagnosis, prevention, and treatment of kidney disease of various etiologies.

There is a growing need for the integration of efforts among endocrinologists, nephrologists, primary care physicians, and other specialists to implement extensive preventive measures. These initiatives should focus on the early detection of kidney damage, the efficient allocation of healthcare resources, and the continuity of care for CKD patients.

A growing hypothesis in recent years suggests the existence of two distinct CKD phenotypes—the classic albuminuric and the non-albuminuric variants [8, 33]. In addition to the traditional albuminuric phenotype, two new phenotypes have been

identified: “non-albuminuric CKD” and “progressive decline in kidney function”. These suggest that the progression of DKD toward end-stage kidney disease (ESKD) in both type 1 and type 2 diabetes may follow two different paths—either through increasing albuminuria (AUR) or declining glomerular filtration rate (GFR).

The pathogenesis of kidney disease differs significantly between type 1 diabetes (T1D) and type 2 diabetes (T2D).

- In T1D, kidney damage typically follows the classical diabetic nephropathy (DN) pathway, characterized by glomerulosclerosis. The main marker of this condition is the increase in urinary protein excretion, starting with microalbuminuria (MAU) and progressing to proteinuria (PU).
- In T2D, kidney pathology is more multifactorial, making it difficult to differentiate classical DN solely based on protein excretion [10]. Unlike the classic glomerulosclerosis seen in T1D, T2D is often associated with structural changes in renal parenchyma rather than in the glomeruli themselves. These changes can occur even in the absence of MAU [34].

Given this, GFR assessment in T2D is particularly important for evaluating kidney function. MAU is considered a marker of generalized endothelial dysfunction, which may explain the link between kidney disease and cardiovascular risk. The ADVANCE study demonstrated that both MAU and GFR are independent risk factors for kidney damage and cardiovascular disease [35].

Classic kidney damage in diabetes is characterized by the development of diabetic nephropathy (DN)—a microvascular complication of diabetes that leads to either nodular or diffuse glomerulosclerosis [37]. Clinically, it manifests as proteinuria, arterial hypertension, edema, and declining kidney filtration function, eventually progressing to end-stage CKD, which requires renal replacement therapy (RRT).

According to modern understanding, DN and CKD development is a multifactorial process, with metabolic, hemodynamic, and genetic factors playing key roles [38].

There is no doubt that chronic hyperglycemia is the leading cause of all vascular complications of diabetes, including CKD. It initiates pathological reactions such as

oxidative stress, non-enzymatic glycosylation of proteins, and the polyol pathway of glucose oxidation, which ultimately trigger kidney damage [39, 40]. Additionally, hyperglycemia indirectly affects intrarenal hemodynamics, causing dilation of the afferent arteriole, which results in renal hyperperfusion [41].

The consequence of intraglomerular hypertension is an increased permeability of the basement membrane, allowing various plasma components (proteins, lipids) to accumulate in the mesangial space. This induces the overproduction of pro-inflammatory cytokines, stimulates mesangial cell activity, and increases the production of type IV collagen, ultimately leading to glomerulosclerosis [42].

The role of hyperglycemia as a risk factor for kidney damage is undisputed. The critical importance of glycemic control has been repeatedly confirmed in large-scale studies such as UKPDS, DCCT, and others [43, 44, 45].

Along with hyperglycemia, lipid profile abnormalities play a significant role in the development of diabetic microangiopathies. Dyslipidemia in diabetes is characterized by:

- Increased production and concentration of very low-density lipoproteins (VLDL)
- Reduced high-density lipoproteins (HDL)
- Hypertriglyceridemia
- Elevated levels of free (non-esterified) fatty acids (NEFA) [12]

Beyond diabetes-related causes of dyslipidemia, the world is also facing non-infectious epidemics of obesity and excess body weight, with the kidneys being recognized as a direct target organ of obesity. Kidney damage in obesity is now considered an independent risk factor for chronic kidney disease (CKD) [46]. Between 1978 and 2013, the global percentage of adults with overweight and obesity (BMI $\geq$25 kg/m^2) increased from 28.8% to 36.9% in men and from 29.8% to 38.0% in women [47].

Obesity-related kidney damage is a complex, multifactorial process that includes both direct and indirect mechanisms.

- Direct mechanisms involve the development of a specific obesity-associated

glomerulopathy (O-GP).

- Indirect mechanisms include various obesity-related conditions, such as:
    - Insulin resistance
    - Metabolic syndrome
    - Dyslipidemia
    - Hyperuricemia
    - Arterial hypertension
    - Type 2 diabetes

These factors predispose individuals to CKD and contribute to its progression.

Obesity-associated glomerulopathy (O-GP) is a specific type of kidney damage characterized by glomerular hypertrophy and the development of adaptive focal segmental glomerulosclerosis (FSGS). These changes occur due to podocyte maladaptation in the setting of insulin resistance.

In response to obesity-induced increases in:

- Glomerular filtration rate (GFR)
- Renal plasma flow
- Filtration fraction
- Tubular sodium reabsorption

the glomerulus enlarges, leading to intrarenal hemodynamic disturbances and the development of a “hyperfiltrating” kidney.

The damaging effects of obesity-related hormones further exacerbate renal dysfunction, including:

- Hyperleptinemia
- Activation of the renin-angiotensin-aldosterone system (RAAS)
- Reduced adiponectin production
- Ectopic lipid deposition in the kidney

Morphological Features of O-GP

- Low glomerular density (oligonephronia) → leads to glomerular and tubular hypertrophy
- Perihilar focal segmental glomerulosclerosis (FSGS)

- Severe podocyte damage
- "Fatty kidney" changes

Clinical Presentation of O-GP

- Gradual onset of albuminuria, typically not exceeding A3 stage (300–1999 mg/day)
- Approximately 1/3 of patients develop incomplete nephrotic syndrome (severe proteinuria but without edema or hypoalbuminemia)
- Full nephrotic syndrome occurs in no more than 6% of O-GP patients [49].

Endothelial Dysfunction in Chronic Kidney Disease and Diabetes

Role of the Endothelium in Vascular Tone Regulation

The endothelium plays a key role in regulating vascular tone, adjusting the vessel lumen in response to blood flow and systemic pressure. The significance of the endothelium was first highlighted in Nature (1980) [51], where researchers discovered that isolated arteries could independently alter muscle tone in response to acetylcholine, without neurohumoral mechanisms. This led to the concept of endothelial cells as a cardiovascular endocrine organ, mediating communication between blood and tissues.

The endothelium releases vasoactive mediators, primarily nitric oxide (NO), which is critical in maintaining vascular tone [52].

Endothelial Dysfunction and Its Mechanisms

Chronic hyperglycemia and hemodynamic overload contribute to endothelial dysfunction, characterized by:

- Reduced NO bioavailability due to impaired endothelial NO synthase (eNOS) activity
- Increased angiotensin-converting enzyme (ACE) activity on the endothelial surface
- Excess production of vasoconstrictors (angiotensin II, endothelin)

As endothelial compensatory vasodilatory capacity diminishes, the dominant vascular responses become:

1. Vasoconstriction

2. Vascular smooth muscle proliferation

This progressive endothelial dysfunction significantly contributes to hypertension, kidney damage, and cardiovascular complications in diabetes and chronic kidney disease (CKD) [53].

Hypertension and Chronic Kidney Disease (CKD) in Diabetes

Hypertension as a Key Factor in CKD Progression

Elevated blood pressure (BP) is recognized as a major contributor to kidney disease progression, similar to hyperglycemia [55]. Hypertension in diabetes is linked to intrarenal hemodynamic disturbances, leading to glomerular hypertension, which develops in the early stages of diabetes. If glucose metabolism remains uncontrolled, these changes can exacerbate kidney damage and accelerate hypertension progression.

- Type 1 Diabetes (T1D): Early blood pressure elevation is associated with CKD, and kidney damage eventually becomes the leading cause of hypertension in T1D [56].
- Type 2 Diabetes (T2D): Hypertension often precedes diabetes diagnosis, serving as a predictor of kidney disease. At the onset of T2D, BP correlates with microalbuminuria (MAU), reflecting the extent of endothelial dysfunction [57].

Physiological Mechanisms of Hypertension in Diabetic Kidney Disease

Blood pressure regulation depends primarily on two factors:

1. Systemic vascular resistance
2. Cardiac output

Diabetes-associated kidney damage contributes to both:

- Increased cardiac output: Driven by aldosterone-induced sodium reabsorption, leading to hypervolemia.
- Endothelial dysfunction: Caused by hyperactivation of the renin-angiotensin system (RAS), hyperglycemia, oxidative stress, and increased vasoconstriction. This results in:
    - Elevated total peripheral vascular resistance

- Increased intraglomerular pressure [58]

Together, these mechanisms promote the onset and progression of hypertension, further exacerbating diabetic kidney disease and increasing cardiovascular risk.

Glycemic and Blood Pressure Control in Diabetic Kidney Disease (DKD)

Nephroprotective Strategies to Delay DKD Progression

Effective management of blood glucose and blood pressure (BP), combined with early initiation of nephroprotective medications, plays a crucial role in slowing the progression of diabetic kidney disease (DKD). The key pharmacological agents include:

- Angiotensin-converting enzyme inhibitors (ACE inhibitors, ACEi)
- Angiotensin II receptor blockers (ARBs)

Both classes provide renal protection by reducing glomerular hypertension, proteinuria, and intraglomerular pressure.

Evidence from Large-Scale Studies

1. WHO MSVDD Study (2001) [59]
    - A multicenter study including 3,500 patients with Type 1 and Type 2 Diabetes (T1D and T2D) over 8.4 years.
    - Findings:
        - In T1D: Elevated BP was a predictor of diabetic nephropathy (DN), increasing risk by 50%.
        - In T2D: Besides hypertension, dyslipidemia (elevated triglycerides) was an additional risk factor for chronic kidney disease (CKD) progression.
2. RENAAL Study (2001) [60]
    - Included 1,500+ patients with T2D and CKD.
    - Findings:
        - ARB therapy reduced the risk of end-stage kidney disease (ESKD) by 20%.
        - Creatinine doubling was reduced by 25%.
        - Need for dialysis or kidney transplantation was lowered by 28%.

Conclusion

Hypertension is a strong determinant of diabetic kidney disease progression. Effective BP management significantly reduces the risk of microvascular and macrovascular complications in diabetes. Early intervention with ACE inhibitors or ARBs, along with optimal glycemic and lipid control, is crucial in preserving renal function and preventing end-stage kidney disease.

Role of the Renin-Angiotensin System (RAS) in Diabetic Kidney Disease (DKD)

The renin-angiotensin system (RAS) is a key regulatory mechanism responsible for maintaining blood pressure (BP) and circulating blood volume [61].

Mechanism of RAS Activation

- Renin, secreted by the juxtaglomerular apparatus of the kidneys, converts angiotensinogen (produced in the liver) into angiotensin I.
- Angiotensin-converting enzyme (ACE) then converts angiotensin I into angiotensin II, which is one of the most potent vasoconstrictors.
- Angiotensin II effects:
    - Increases BP via vasoconstriction.
    - Stimulates aldosterone secretion, promoting sodium and water retention in the distal renal tubules.
    - Enhances thirst mechanism and antidiuretic hormone (ADH) release, further increasing circulating blood volume.

Dysregulation of RAS in Diabetes Mellitus (DM)

- In diabetes, systemic RAS activity is reduced, but local RAS activation in the kidneys, vascular endothelium, brain, and heart is significantly increased.
- Renal levels of renin and angiotensin II can be 1,000 times higher than their plasma concentrations [62].

Pathophysiological Impact of RAS Hyperactivity in DKD

1. Intrarenal Hemodynamic Changes:
    - Angiotensin II causes constriction of the efferent arteriole, leading to intraglomerular hypertension.

- Intraglomerular hypertension, combined with systemic hypertension, contributes to glomerular damage and proteinuria.

2. Progression of Chronic Kidney Disease (CKD):
    - Persistent glomerular hypertension and systemic hypertension are major drivers of diabetic nephropathy progression.
    - This leads to glomerulosclerosis, podocyte injury, and eventual renal failure.

Clinical Implications

Given the role of RAS hyperactivity in DKD, RAS inhibitors—ACE inhibitors (ACEi) and angiotensin II receptor blockers (ARBs)—are fundamental in nephroprotection for diabetic patients.

Genetic Factors in the Development of Chronic Kidney Disease (CKD) in Diabetes

Diabetes mellitus (DM) is characterized by vascular damage, leading to microvascular (nephropathy, retinopathy) and macrovascular complications (ischemic heart disease, atherosclerosis). The rate and severity of these complications depend not only on modifiable factors (hyperglycemia, hypertension, dyslipidemia) but also on genetic predisposition.

Genetic Susceptibility to CKD in Diabetes

- Genetic variations may influence an individual's sensitivity to damaging pathological factors, contributing to the onset and progression of CKD.
- Despite advances in medicine and pharmacology, CKD remains one of the most expensive conditions to treat, highlighting the need for genetic research to identify early risk markers.
- Genetic screening could enable early risk stratification, potentially preventing disease progression to end-stage renal disease (ESRD).

Family History and Genetic Studies

- The first study discussing the familial inheritance of diabetic nephropathy (DN) was published in 1989 [63].
- It demonstrated that the risk of diabetic kidney disease is significantly higher

in individuals with a family history of nephropathy or diabetes among close relatives [64].

- However, CKD is a multifactorial disorder, making the identification of specific genetic markers challenging [65].

Challenges in Genetic Research on CKD

- CKD progression is polygenic, involving multiple genes that influence phenotypic traits such as hyperglycemia, hypertension, and dyslipidemia.
- These interacting factors complicate the identification of individual genetic contributions.

Future Perspectives

- Genome-wide association studies (GWAS) and precision medicine approaches may help uncover key genetic variants associated with CKD risk in diabetes.
- Identifying genetic biomarkers could facilitate personalized interventions to slow CKD progression before irreversible damage occurs.

Candidate Genes and Genetic Markers in CKD Development

A candidate gene is defined as a gene whose expression product is potentially involved in the development of a particular disease. Within these genes, polymorphic markers—variable nucleotide sequences with unique localizations—are identified in the DNA structure [66].

Role of Polymorphic Markers in CKD and Diabetes

- The presence of a polymorphic marker associated with disease susceptibility does not necessarily result in disease manifestation, especially in multifactorial disorders like diabetes and CKD.
- The impact of polymorphic markers is weak or moderate, meaning that other environmental and genetic factors play a role in disease progression.
- The frequency of these genetic variants varies significantly across different ethnic groups, leading to differences in population-based CKD risk [67, 68].
- Therefore, one of the primary objectives in studying genetic factors of complex diseases is to identify susceptibility genes and polymorphic markers

specific to different ethnic populations.

Genetic Complexity of CKD in Diabetes

- CKD development is not influenced by a single gene, but rather by a complex network of multiple candidate genes [69].
- Recent research highlights that genes involved in key pathogenic pathways play a critical role in diabetic kidney disease.
- These include genes regulating:
    - Vasoactive endothelial factors
    - Lipid metabolism
    - Inflammatory processes
    - Insulin secretion and resistance [70].

Future Directions

- Genome-wide association studies (GWAS) may help identify genetic risk variants more accurately.
- Understanding these genetic mechanisms can aid in developing targeted therapies to prevent CKD progression in diabetic patients.

Genes of the Renin-Angiotensin-Aldosterone System (RAAS) in CKD Development

As discussed earlier, RAAS hyperactivation plays a key role in the hemodynamic disturbances in diabetes, leading to increased production of vasoactive factors that contribute to kidney damage. Genes encoding RAAS components are considered major candidate genes for CKD development in diabetes.

Angiotensinogen (AGT) Gene

- Chromosomal location: 1q42-43
- Function: Encodes the protein angiotensinogen, the precursor of angiotensin I.
- Key polymorphisms:
    - M235T and T174M – well-studied variants [71].
    - These polymorphisms correlate with plasma angiotensinogen levels [72].

- A meta-analysis of European populations (45,000+ participants) showed that the TT genotype of M235T is associated with 11% higher plasma angiotensinogen levels [73].
- AGT gene variants are linked to:
  - Hypertension (HTN)
  - Atherosclerosis
  - Cardiovascular diseases (CVD), including ischemic heart disease (IHD) and myocardial infarction (MI).
- T allele of M235T is associated with diabetic nephropathy (DN) in studies on Canadian patients with type 2 diabetes (T2D) and in mixed diabetes populations [74].

Angiotensin-Converting Enzyme (ACE) Gene

- Function: Encodes angiotensin-converting enzyme (ACE), which converts angiotensin I into angiotensin II (AT II).
- Key polymorphism: I/D variant
  - Insertion (I) allele – associated with lower ACE levels
  - Deletion (D) allele – associated with higher ACE levels
- Clinical significance:
  - Individuals with the DD genotype have higher ACE levels in plasma, leading to increased AT II concentration and its detrimental effects [75].
  - I/D polymorphism is linked to:
    - CVD
    - Vascular complications of diabetes [76, 71].
  - A 2012 meta-analysis found that the D allele is significantly associated with end-stage CKD in T2D, particularly in Asian populations, compared to Europeans [77].

Implications for CKD Risk Assessment

- Understanding AGT and ACE gene variants may help in identifying high-risk individuals for CKD in diabetes.

- Personalized treatment approaches (e.g., ACE inhibitors, angiotensin receptor blockers) could be tailored based on genetic predisposition.

CHAPTER II. SCOPE AND DESIGN OF RESEARCH, MATERIALS AND METHODS

To study the assessment of diagnostic predictors of the formation and development of chronic kidney disease, it is necessary to conduct not only clinical, but also laboratory and socio-medical studies. In this regard, the research will have to be carried out in several stages. Given this, we have described the design of the study and selected a sufficient amount of research.

§ 2.1. Research design

The implementation of this research work was carried out in 3 stages:

Stage 1. Selection of the research object, determination of the research volume and population, distribution into representative groups, organization of randomized trials.

Stage 2. Conducting screening studies in selected localities of urban areas with the help of a specially developed "Questionnaire for identifying the risk of developing chronic kidney disease".

Stage 3. In-depth clinical, instrumental and laboratory studies of patients in whom diagnostic predictors (criteria) were identified during screening studies) CKD. Statistical processing, comparative analysis of the material and development of ways to prevent the progression of CKD.

§ 2.2. Research materials

At the first stage, the object, the contingent, and the scope of research were

selected. To achieve this goal, the studies were conducted in the city family polyclinics No. 3, No. 5 and No. 11 of the city of Bukhara

87 women of childbearing age were involved in the research work. The medical examination of the population and the survey-interview of this contingent were carried out in an outpatient setting located on this territory.

At the second stage of the study, screening studies were conducted. The medical examination of the population was accompanied by a survey-interview and the completion of a specially developed goal "Questionnaire for identifying the risk of developing chronic kidney disease" and the determination of microalbumin in a single portion of urine by a semi-quantitative method using test strips.

The questionnaire consists of 2 parts: the passport part and the main part. The passport part consists of 6 questions that include materials about this person. The main part consists of 40 questions that are designed to identify risk factors for the formation and development of CKD. Questions related to age, gender, place of work, the presence of concomitant diseases and conditions, adherence to a healthy lifestyle, anthropometric data, and other aspects.

The occurrence of various pathologies of other organs leading to the formation and development of CKD as risk factors for the development of this pathology is analyzed.

At the third stage of the study in this selected contingent(n=87), which included: identification of anamnesis of life and illness; determination of height and weight indicators-height (cm), weight (kg), waist circumference (OT), hip circumference (OB), waist-to – hip ratio (OT/OB), waist-to-height ratio (OT/height), body mass index (BMI) according to the Kettle formula (depending on why the normal body weight was allocated BMI18,5-24,9 kg/m2, excess weight). weight-BMI 25-29. 9 kg/m2 and obese BMI $\geq$ 30 kg/m2.

The basis for the diagnosis of CKD, as a consequence of structural or functional disorders, is cases of deviation in the laboratory and functional results of the study, which were preserved for more than 3 months after the initial detection of the disease by the method of the most detailed examination.

Microalbuminuria (MAU> 10 mg/L) was detected in 61 of these patients in this group. In 23 (37.7±4.52%), the glomerular filtration rate (GFR) < 90 ml / min was 1.73 m2, which allowed us to state the I-III stages of CKD (K/DOOL, 2002).

The design of this study is presented in Table 2.1.

Table 2.1.

Stages and scope of research in the surveyed population permanently residing in urban areas (n=87)

Stages	I	II	III
Informed consent of the patient to the study	+	+	+
Anamnesis of life and illness		+	+
Physical examination		+	+
Filling out the questionnaire		+	
Determination of BMI		+	
Clinical and biochemical blood tests		+	+
General urinalysis		+	+
Determination of microalbumin and creatinine in urine		+	+
Clinical blood test			
Biochemical blood analysis (ALT,AST, total protein, lipid fraction, glucose)			+
Determination of urea, serum creatinine and GFR			+
Determination of coagulogram parameters			+
Ultrasound of the genitourinary system and pelvis			+

Patients who have identified diagnostic criteria for CKD (microalbuminuria, low GFR) were examined for 2-3 months after a comprehensive examination to clarify the diagnosis of CKD in a specialized clinic in the city of Bukhara.

When performing the research, we followed all the ethical principles of human-assisted medical research adopted by the Helsinki Declaration of the World Medical Association in 1964 (the latest addition at the 59th General Assembly of the World

Medical Association in 2008 in Seoul).

The research was carried out on the basis of the Department of Faculty and Hospital Therapy of the Bukhara State Medical Institute in the period from 2011 to 2017.

§ 2.3. Research methods

General clinical examination: Traditional clinical examinations were conducted to examine therapeutic patients. Anthropometric indicators were evaluated: height, weight, OT, OB, BMI according to the Kettle formula: BMI (kg/m2)= weight (kg)/height (m2) (Table 2.2).

Table 2.1.

Classification of obesity by BMI (WHO, 1997)

Types of body weight	BMI, kg / m2	Risk of comorbidities
Body weight deficit	<18,5	Low (increased risk)
Normal body weight	18,5-24,9	Usual
Overweight	25,0-29,9	Elevated
Grade I obesity	30,0-34,9	Tall
Grade II obesity	35,0-39,9	Very high
Grade III obesity	>40	Extremely high

- Measurement blood pressure (BP) was measured in the morning, in the patient's sitting position at least 3 times, with the calculation of the average value of systolic blood pressure and diastolic blood pressure. The criteria for arterial hypertension were systolic blood pressure ≥ 140 mmHg and diastolic blood pressure ≥ 90 mmHg, or normal blood pressure levels against the background of constant antihypertensive medication. The severity of arterial hypertension was determined according to the classification of hypertension according to the recommendations of the

IOC:

- 1 degree of AH – 130-159 and / or 80-100 mm Hg
- 2 degree-160-180 and / or 100-109 mm Hg
- 3 degree -180 and/or 100 mm Hg and above.

Ultrasound examination: All the examined patients underwent ultrasound examination of the kidneys using special equipment of the company "ToshibaSSA-340" (Japan) with a sensor frequency of 3.5 MHz.

The purpose of ultrasound is to determine the location of the kidneys and their mobility, shape, contours, linear and volumetric parameters; to determine the clarity of the image, the thickness of the fibrous capsule and adipose tissue; the state of the parenchyma - the thickness, density, clarity of differentiation of the cortical, medullary layers, parenchyma and renal sinus; the state of the cavity system - expansion or deformation, the degree of dilation, the thickness of the walls of the upper, middle and lower groups of cups; to determine the paranephral fiber, own vessels and main retroperitoneal, adjacent organs - the adrenal glands, ureter and bladder.

Determination of the main parameters of hemostasis

The device "HumanClotJunior" coagulometer, manufactured in 2013, by "HumanGesellschaftBiochemicaundDiagnostica" (Wiesbaden, Germany) was used. Conducting a study of clotting with the structure of fibrin, using the endpoint method. The following tests were performed: PV (Prothrombin Time) - expressed in seconds, can be converted to % and the calculated method is determined by INR; APTT (Activated Partial Thromboplastin Time) - expressed in seconds; Fibrinogen-expressed in seconds, automatically converted to mg/dl concentration in peripheral blood plasma.

Determination of hematological parameters

To determine the parameters of peripheral blood, an automatic hematological analyzer BC-5800 from MindrayCo.Ltd (China) was used, which is able to determine 29 parameters + 2 histograms +2 scategrams, differentiation of white blood cells by 5 parameters.

Determination of biochemical parameters

For this purpose, an automatic biochemical analyzer VS - 200 from MINDRAY (China) was used.

Creatinine was determined using a photocolorimetric test for kinetic measurement, without deproteinization. The principle of the method: creatinine in an alkaline solution of orange-red color in a complex with picric acid. The absorption of this complex is proportional to the creatinine concentration in the sample (Test "HumanGesellschaftBiochemicaundDiagnostica", Wiesbaden, Germany).

Urea was determined using the enzyme colorimetric method. The test "HumanGesellschaftBiochemicaundDiagnostica" (Wiesbaden, Germany) was used.

Albumin was determined by using bromocresol green. Bromocresol green forms a colored complex with albumin in the citrate buffer. The absorption of the resulting complex is proportional to the albumin concentration in the sample. (Test «HumanGesellschaftBiochemicaundDiagnostica»,Wiesbaden, Germany).

Glucose was determined after its conversion under the action of hexokinase to gluconate-6-phosphate and subsequent interaction of glucose-6-phosphate with NAD in the presence of glucose-6-phosphate dehydrogenase. The increase in the optical density of the solution is proportional to the concentration of glucose in the sample. (Test «HumanGesellschaftBiochemicaundDiagnostica»,Wiesbaden, Germany).

Cholesterol was determined after enzymatic hydrolysis and oxidation. The H2O2 formed as a result of these reactions reacts under the action of peroxidase with 4-aminophenazone and phenol to form a colored product-quinonimine (Test "HumanGesellschaftBiochemicaundDiagnostica", Wiesbaden, Germany).

The concentration of triglycerides was determined after enzymatic hydrolysis under the action of lipase. Formed as a result of a series of enzymatic reactions, H2O2 reacts with 4-aminoantipyrine and 4-chlorophenol under the action of peroxidase to form a colored quinonimine(Test "HumanGesellschaftBiochemicaundDiagnostica",Wiesbaden, Germany).

Low - density lipoprotein (LDL) - the quantitative determination of LDL cholesterol consists of two stages: the first stage is the removal of the chylomicrons of VLDL cholesterol and HDL cholesterol from the reaction zone under the action of enzymes.

Determination of urine parameters

A general urine analysis was performed using Combina 13 test strips on a Combineyzer urinary analyzer (Germany).

Test strips for determining the biochemical parameters of urine, 13-parameter. The principle of the test: reflective photometry (visual evaluation) of the result on a color scale. Test parameters: blood (hemoglobin), bilirubin, urobilinogen, ketones, protein, nitrites, glucose, pH, specific gravity, white blood cells, ascorbic acid, microalbumin, creatinine, albumin/creatinine ratio . Lower limit of determination: blood – 10 red blood cells/mcl, bilirubin – 1 mg/dl, urobilinogen – 0.2 mg/dl, ketones – 5 mg/dl, protein – 30 mg/dl, glucose – 50 mg/dl, white blood cells - 15 white blood cells/mcl, ascorbic acid – 10 mg/dl, microalbumin – 10 mg/dl, creatinine – 10 mg/dl Test strips are used for rapid determination (determination time 1 minute) in the urine, bilirubin, urobilinogen, ketones, glucose, protein, blood (red blood cells/hemoglobin), pH, nitrites, white blood cells, specific gravity/density, ascorbic acid, creatinine, microalbumin.

Determination of the concentration of albumin in the urine was carried out using test strips Combina 13 manufactured by "Humang GmbH" (Germany) and Urine-2AC manufactured by "CypressDiagnostics" (Belgium). Diagnostic strips are designed for semi-quantitative measurement of the concentration of albumin in the urine using the analyzer "Combineyzer 13". The test for measuring albumin in urine is based on the binding of a dye using sulfonephthalene. The resulting color ranges from pale green to the color of a blue moon.

The level of albuminuria was assessed on the following scale: 10 mg/l-optimal or slight increase, 10-29 mg/l – moderate increase, 30-80 mg/l – high, > 150 mg / l – very high.

In order to clarify the diagnostic reliability of test strips for urine analysis in 20 patients at the same time, proteinuria was determined using two methods: the determination of microalbumin in daily urine and the determination of microalbumin in a single morning portion

of urine. The difference between the indicators of these methods was as follows: MAU in daily urine averaged 69.16 mg / day. MAU in a single urine morning portion averaged 64.66 mg/day.

Determination of creatinine concentration in the urine. This test is based on the reaction of creatinine with a dye-metal complex. In an alkaline environment, creatinine reacts with the dye-metal complex to form a purple-brown complex.

Statistical methods

Statistical analysis of the obtained results was carried out using the methods of variation statistics. The reliability of the differences in the mean values was estimated on the basis of the Student's test (t) with the calculation of the probability of error (P) when checking the normality of the distribution and the equality of the general variances (F – Fisher's test). The correlation analysis was performed using Spearman (Rs) and Pearson (r) methods.

In conclusion, I would like to emphasize that for this purpose, the object and the research contingent were correctly selected in compliance with all the rules of the general and sample population.

Almost all selected respondents and survey groups were representative, and all studies were randomized.

Statistical methods are also carried out in accordance with the high requirements of statistical analysis.

All of the above allows you to indicate that the results obtained are reliable, and the conclusions are true.

CHAPTER III ANALYSIS OF THE RESULTS OF THE STUDY BY FREQUENCY PREVALENCE OF CHRONIC KIDNEY DISEASE IN WOMEN OF FERTIL AGE

About 10% of the world's adult population suffers from CKD , including nearly 200 million women worldwide. The diagnosis is made in the presence of any chronic kidney damage, even if their function is not impaired. The progression of CKD does not always occur, but in many cases, deterioration of kidney function is observed for several years or even months and leads to the need for dialysis [56; p. 52-56].

Screening is a secondary prevention measure aimed at identifying a specific disease in the preclinical stage. During screening, a mass examination of a contingent from certain risk groups is carried out, who do not consider themselves sick, do not seek medical help and, accordingly, do not receive specific treatment. The main purpose of screening is to detect the disease before specific clinical symptoms appear and to completely cure the pathology [46; p. 52-56, 124; p.601-609].

It should be emphasized that the results of screening studies in rural areas of our republic are rare. In this regard, we considered it appropriate to conduct a survey of the population living permanently in rural areas for the early detection of CKD.

The methods of screening examination and the place of residence of patients were described in detail in chapter II, so we did not consider it appropriate to dwell on this.

The main selection criterion was microalbuminuria (MAU >10 mg / L), which persisted for 3 months or more, considering this parameter a diagnostic predictor of CKD development. Among the examined patients, this criterion of CKD was detected in 27 persons (31±4.9%) out of 87 examined patients.

On the basis of clinical materials, parameters of laboratory and instrumental

studies, the diagnosis was established in some subjects, the number of examined and identified nosological units differed from each other, as in 1 examined patient, sometimes there were 2 or 3 established diagnoses of the disease. Thus, in 87 patients with diagnoses established on the basis of outpatient records, there were 101 diseases (1.15 nosologies per 1 examined person). The contingent with the diagnosis established after our examination (n=27) had 50 nosologies – 1.86 per 1 examined person.accordingly, the data in Table 3.1. are calculated from the total number of identified nosological units.

Table 3.1

Indicators of the frequency of occurrence of various pathologies that were risk factors for the development of chronic kidney disease,%

Nosological units	DIAGNOSIS	
	established on the basis of outpatient charts of 101 nosology n=87	installed after the survey 50 nosology n=27
Arterial hypertension	37/42,5±4,93	9/33,33±4,72* ↓
Coronary heart disease	13/15,4±3,60	4/14,81±2,53 ↔
Diabetes mellitus	5/5,74±2,83	2/7,4±2,13* ↓
Rheumatological diseases	7/7,71±2,66	2/7,4±2,13 ↔
Anemia of various degrees	11/12,64±2,57	1/3,7±1,86* ↔
Endemic goiter	3/3,51±1,66	4/14,81±2,53 ↔
Obesity	11/12,5±1,18	5/18,55±3,88* ↑

Note: in the numerator absolute, in the denominator relative (%) indicators: * - a sign of a significant difference in the parameter; ↑ ↓ and ↔ - an increase, decrease or absence of a difference in the indicator from the compared group

Among the established diagnoses, both on the basis of outpatient records and after examination, diseases of the cardiovascular system were often encountered,

with arterial hypertension, respectively, 42.5±4.93%, (n=37) and 33.33±4.72%, (n=9), coronary heart disease, respectively, 15.4±3.60%, (n=13) and 14.81±2.53%, (n=4)

Other established diagnoses were less frequent - diabetes mellitus, respectively, 5.74±2.83%, (n=5) and 7.4±2.13%, (n=2), rheumatic diseases, respectively, 7.71±2.66%, (n=27) and 7.4±2.13 % (n=2), anemia, respectively, 12.64±2.57%, (n=11) and 3.7±1.86%, (n=1), endemic goiter, respectively, 3.51±1.66%, (n=3) and 14.81±2.53%, (n=4), obese, respectively, 12.5±1.18%, (n=11) and 18.55±3.888%, (n=5).

We can say that among the above-mentioned diseases, the level of diagnosis of obesity as a nosological unit is very low - the difference between the groups is 6.2 times. This indicates that health professionals do not assess obesity as an unfavorable risk factor for the development of various pathological conditions, including CKD.

Given the importance of urinary tract diseases as risk factors for CKD, we decided to give the frequency of these nosological units separately (Table 3.2)

Table 3.2.

Indicators frequency of occurrence of urinary tract diseases as risk factors for CKD in the examined population

Nosological units	Диагноз	
	established on the basis of outpatient card data, n=21	established after the survey, n=40
Pyelonephritis	10/47,06±4,99	22/55,17±4,97*↑
Cystitis (acute and chronic)	7/35,29±4,77	9/24,14±4,27* ↓
Urolithiasis	3/13,73±3,44	9/20,69±4,05 ↔
Glomerulonephritis	1/3,92±1,94	0

Note: in the numerator absolute, in the denominator relative (%) indicators: * - a sign of a significant difference in the parameter; ↑ ↓ and ↔ - an increase, decrease or absence of a difference

in the indicator from the compared group

It should be noted that among the examined patients, who were diagnosed on the basis of outpatient records, the diagnosis of CKD as a nosological unit was not detected. After the examination, this diagnosis was established in 29.1% (n=21) of the respondents from the general subjects.

In our studies, each separately, the role of these nosological units listed in Table 3.2. as a risk factor for CKD is insignificant, so we decided to use the general group of urinary tract diseases to determine the groups at risk for CKD.

The conducted scientific studies prove that hypertension, diabetes mellitus, and obesity are traditional factors of CKD development [4; pp. 82-87]. But in the development of chronic kidney damage, non-traditional factors of CKD development are of great importance. The results of our research show that these factors include the place of residence, ethnic customs of the people, the way and standard of living of the population, the effectiveness of preventive measures carried out by medical institutions of widespread non - communicable chronic diseases, the use of poor-quality drinking water, violation of the rules of rational nutrition, constant consumption of high-calorie food by the population.

According to ValerieA and KathrinR [2017], which conducted studies in Switzerland, many of the factors we mentioned were the main causes of the spread of CKD in the population.

Thus, it was found that there is a significant difference between the established diagnoses based on the outpatient records of rural family clinics and after our examination. Arterial hypertension, diabetes mellitus, obesity and urinary tract diseases, which were among the main risk factors for the development of CKD, were not sufficiently identified in the primary and repeated treatment of patients for medical care.

Based on this , to determine the frequency of non-traditional risk factors that affect the development and progression of CKD, the following factors were analyzed using the integration method:

- abuse of nephrotoxic drugs that are usually sold without a prescription in our

country - analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), some antibiotics;

- abuse of salty and bitter foods;
- bad habits - smoking, drinking alcohol;
- non-controlling pathological conditions and diseases with a history of history (proteinuria, dysuria, nephropathy of pregnant women, arterial hypertension of pregnant women, acute allergic reactions, acute bleeding with hypovolemia);
- chronic foci of infection - chronic tonsillitis, chronic otitis media, dental caries;

When analyzing the frequency of occurrence of these factors, we paid attention to the level of identification and / or elimination of these factors as the cause of the development of other diseases (Table 3.3)

Table3.3

The frequency of occurrence of non-traditional factors as a risk factor for CKD among the examined patients

Non-traditional factors		Diagnosis	
		established on the basis of outpatient card data, n=21	established after the survey, n=40
Abuse of nephrotoxic drugs		13/58,57±4,92	25/62,61±4,83↔
Abuse of salty and bitter foods		7/33,80±4,73	17/42,99±4,95↔
A history of proteinuria		4/20,95±4,16	15/38,31±4,86*↑
Nephropathy of pregnant womenˆ		12/60,90±4,87	24/60,0±4,89 ↔
Arterial hypertension in pregnancyˆ		8/39,09±4,87	16/40,0±4,89 ↔
The presence	Chronic tonsillitis	6/31,90±4,66	15/38,31±4,86 ↔

of chronic foci of infection	Chronic otitis media	1/1,90±1,36	1/5,60±2,29 ↔
	Dental caries	12/58,57±4,92	25/64,48±4,78 ↔

Note: ˆ-indicators are calculated based on the number of women examined in the groups n=21 and n=60, respectively; * - a sign of a significant difference in the parameter; ↑ ↓ and ↔ - an increase, decrease or absence of a difference in the indicator from the compared group

Among non-traditional risk factors for CKD are often met abuse of nephrotoxic drugs (analgesics, NSAIDs, antibiotics), respectively 58,57±4,92% (n=13) and 62,61±4,83% (n=25); the presence of chronic foci of infection, of which a large number of identified caries 58,57±4,92% (n=12) and 64,48±4,78% (n=25), and in the next place chronic tonsillitis work at 31.90±4,66% (n=6) and 38,31±4,86% (n=15); among surveyed women residing in the rural municipality of residence of non-traditional factors in the development of CKD identified nephropathy pregnant women in history, respectively 60,90±4,87%(n=12) and 60,0±4,89% (n=24).

Analysis of the results shows that the above factors are not fully evaluated as a risk factor for CKD and the effectiveness of preventive measures for non-communicable chronic diseases among the rural population is quite low.

Thus, the frequency of non-traditional CKD risk factors among the subjects varies, ranging from 1.90±1.36% (chronic otitis media) to 58.57±4.92% (abuse of nephrotic drugs). Of the 10 non-traditional risk factors studied, the most significant in the group of patients diagnosed on the basis of outpatient records were abuse of nephrotoxic drugs (58.57%) , dysuria of unclear etiology (43.80%), abuse of salty and bitter foods (33.40%), bad habits (21.42%), proteinuria in the anamnesis (20.95%) and nephropathy of pregnant women in the anamnesis (60.90%). Almost the same trend in the occurrence of non-traditional risk factors was observed in the group with established diagnoses during screening tests. From the findings, it follows that, first, the population permanently living in rural areas generally have the same non-traditional risk factors for CKD; second, the population is not a traditional risk factor for CKD.

For each identified patient, there are 0.51 undiagnosed conditionally ill individuals with the same non-traditional risk factors for CKD. The detectability of non-traditional risk factors per patient is from 3.40 to 4.58 risk factors, respectively.

3.2. The significance of microalbuminuria/ proteinuria as a predictor of diagnosis and risk factor for the development of chronic kidney disease

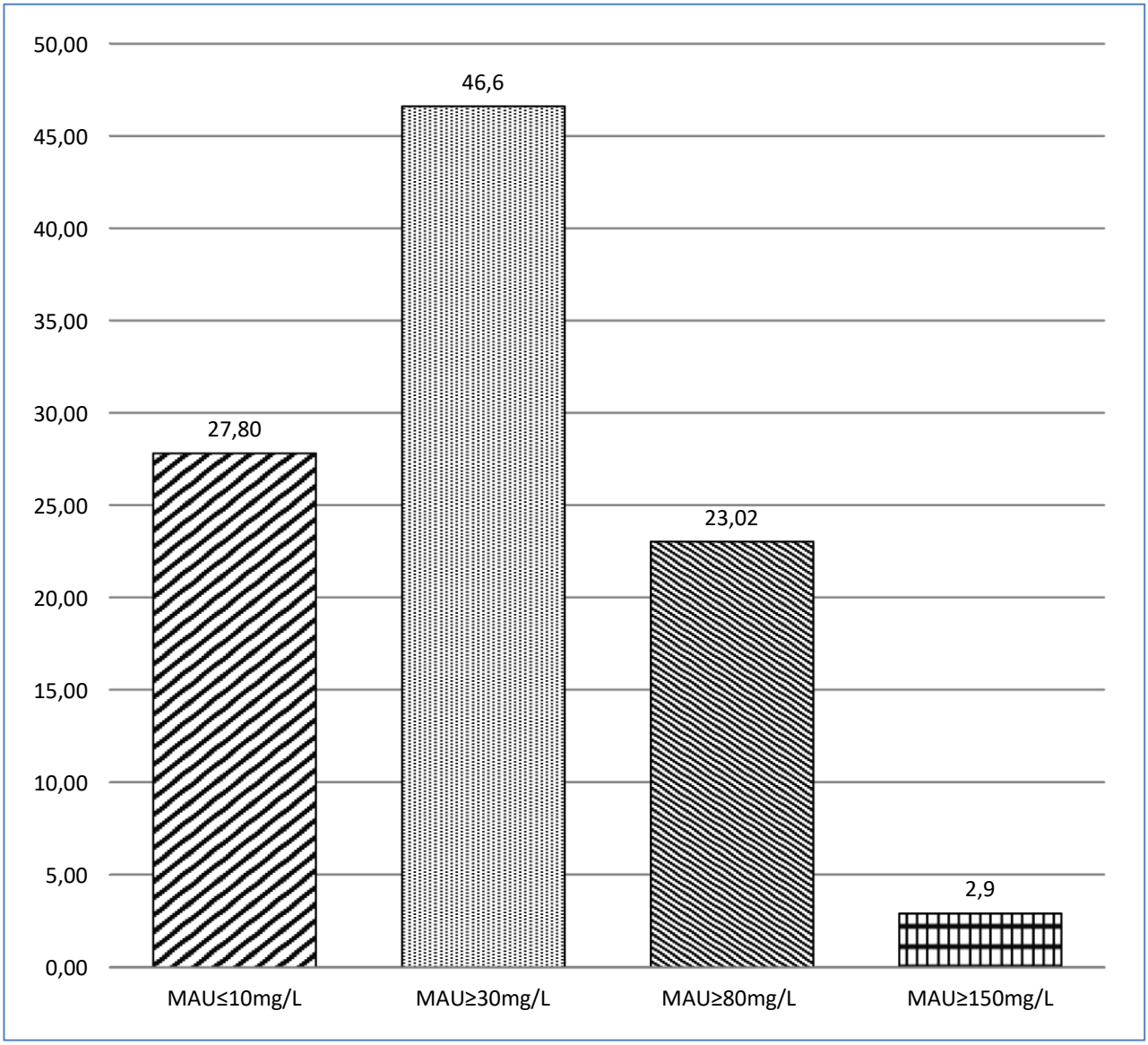
The main diagnostic method for CKD is a urine test, where proteinuria and changes in urine sediment are detected. But these changes are usually detected in stages 4-5 of CKD, when specific clinical symptoms of kidney damage appear. In the asymptomatic current stages of CKD and in the absence of clinically obvious proteinuria, a urine test for microalbuminuria allows diagnosis in the early stages of chronic kidney damage.

A reliable value of proteinuria is the determination of its amount on the daily urine of the subjects, which is more than

0.5 g per day, which usually corresponds to a MAU of ≤300 mg per day.

The determination of proteinuria in daily urine requires special conditions for the collection of urine. Currently, a system of test strips for urine analysis is widely used in the clinical laboratory, which simultaneously contain the ability to determine microalbumin and creatinine in the urine of the examined individuals.

To clarify the probability of MAU, the albumin/creatinine ratio (ACR) was determined. This ratio was evaluated on the following scale: Normal - normal; Abnormal - pathology; Highabnormal-pronounced pathology.

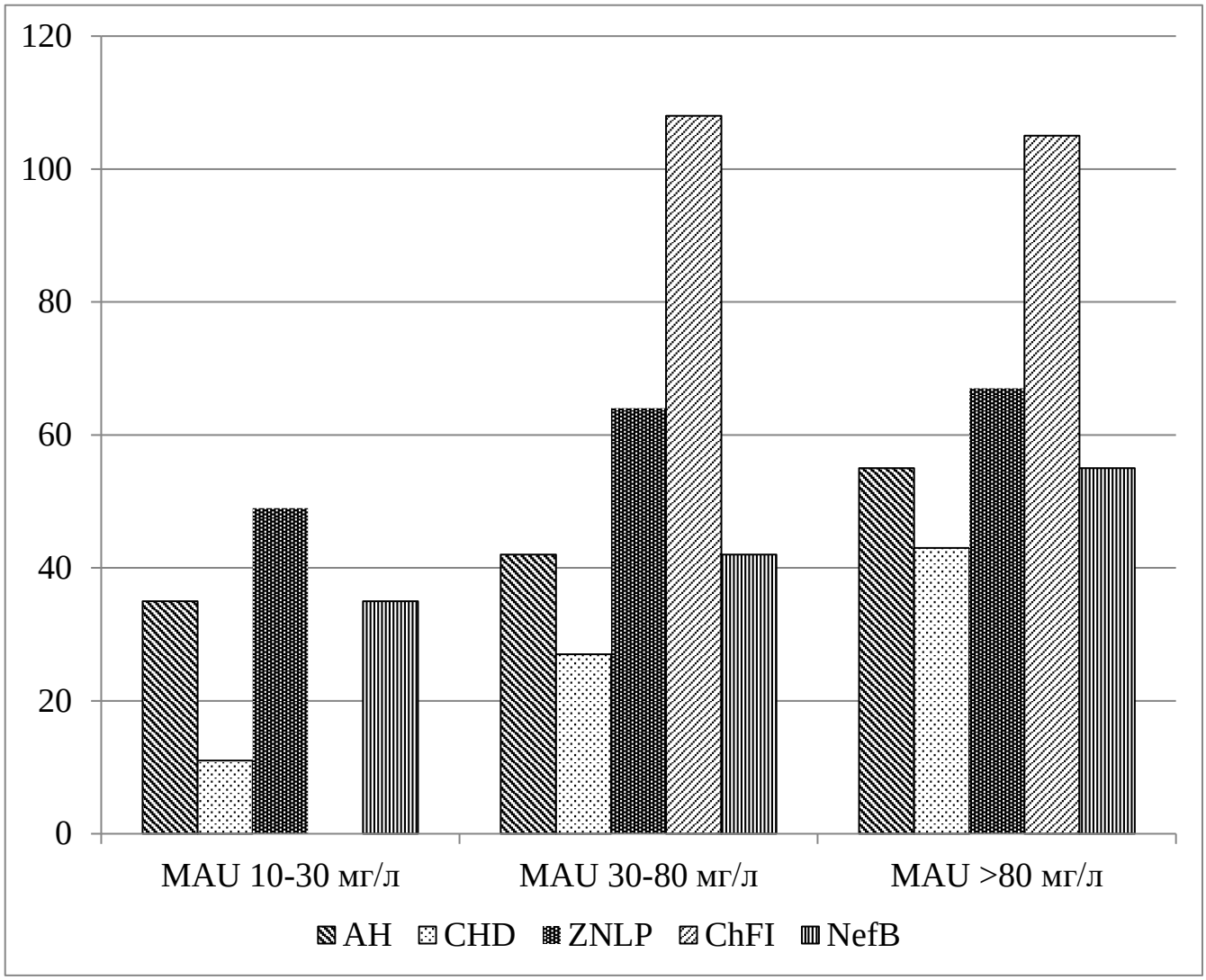


3. 1. The prevalence of albuminuria in the examined patients, depending on the degree of MAU (in %)

The initial increase in microalbuminuria (MAU=10-30 mg/l) was determined in 46.33±4.98% (n=40), the average increase (30-80 mg/l) in 23.03±4.20% (n=20)and the high level of MAU (80-150 mg/l) in 2.84±1.66% (n=2) cases. (Fig. 3. 1.)

Studies have shown that there is a direct proportional relationship between the frequency of CKD risk factors and a certain level of microalbuminuria (Figure 3.2).

It was found that with an increase in the level of UIA, the detection of risk factors also increases. This proven relationship is especially noticeable when studying such a risk factor as arterial hypertension: 18.64±3.64% with MAU=10-30



mg/l; 37.74±4.84% with MAU=30-80mg/l and 43.62±4.95% with MAU>80mg/l; in addition, the same picture was observed with the incidence of coronary heart disease: 13.75±3.43% with MAU=10-30 mg/l; 32.51±4.68% with MAU=30-80mg/l and 53.75% with±4.98% at MAU>80mg/l. The same data were obtained for the risk factor of abuse of nephrotoxic drugs 21.78±4.37% for MAU=10-30 mg/l, 33.68±4.72% for MAU=30-80mg/l and 35.26±4.77% for MAU>80mg/l; Similar indicators were obtained for the presence of chronic foci of infection with the following indicators: 21.78±4.37% for MAU=10-30 mg/l; 33.68±4.72% for MAU=30-80mg/l and 35.26±4.77% at MAU>80mg/l. It is especially necessary to mention such a risk factor as, nephropathy of pregnant women in the anamnesis in women, where the following parameters were obtained: 26.51±4.41% with MAU=10-30

Figure 3.2. Frequency of occurrence of risk factors in the examined patients

depending on the level of microalbuminuria

Note: MAU – microalbuminuria; AH - arterial hypertension; CHD – ischemic heart disease; ZNLP-abuse of nephrotoxic drugs; NKHOI – the presence of chronic foci of infection; NefB b A-nephropathy of pregnant women in the anamnesis.

In the examined patients, whose MAU level is within the normal range (MAU= 10 mg / l), but a pathological deviation of the creatinine/microalbumin ratio (ACR-abnormal) is determined, the frequency of detection by a risk factor for CKD development showed the following parameters:

- arterial hypertension in 18.64±3.64% (n=16) cases;
- coronary heart disease in 13.75±3.43% (n=10) cases;
- abuse of nephrotoxic drugs in 25.87±4.37% (n=22) cases;
- the presence of chronic foci of infection in 18.38±3.87% (n=16) cases;
- a history of nephropathy in pregnant women in 26.51±4.41% (n=23) cases

.It is known that albuminuria is used as an early marker of glomerular filter damage, but in proteinuria and / or MAU, the renal tubules are also damaged at the same time. Proteins that enter the primary urine have a toxic effect on the cells of the tubular epithelium and activate the development of tubulointerstitial fibrosis [Nats. recom.CKD, RF 2012].

To determine the value of MAU as a risk factor for the development and / or progression of CKD, we analyzed the relationship between the level of microalbuminuria and the stage of CKD (Figure 3.3.).

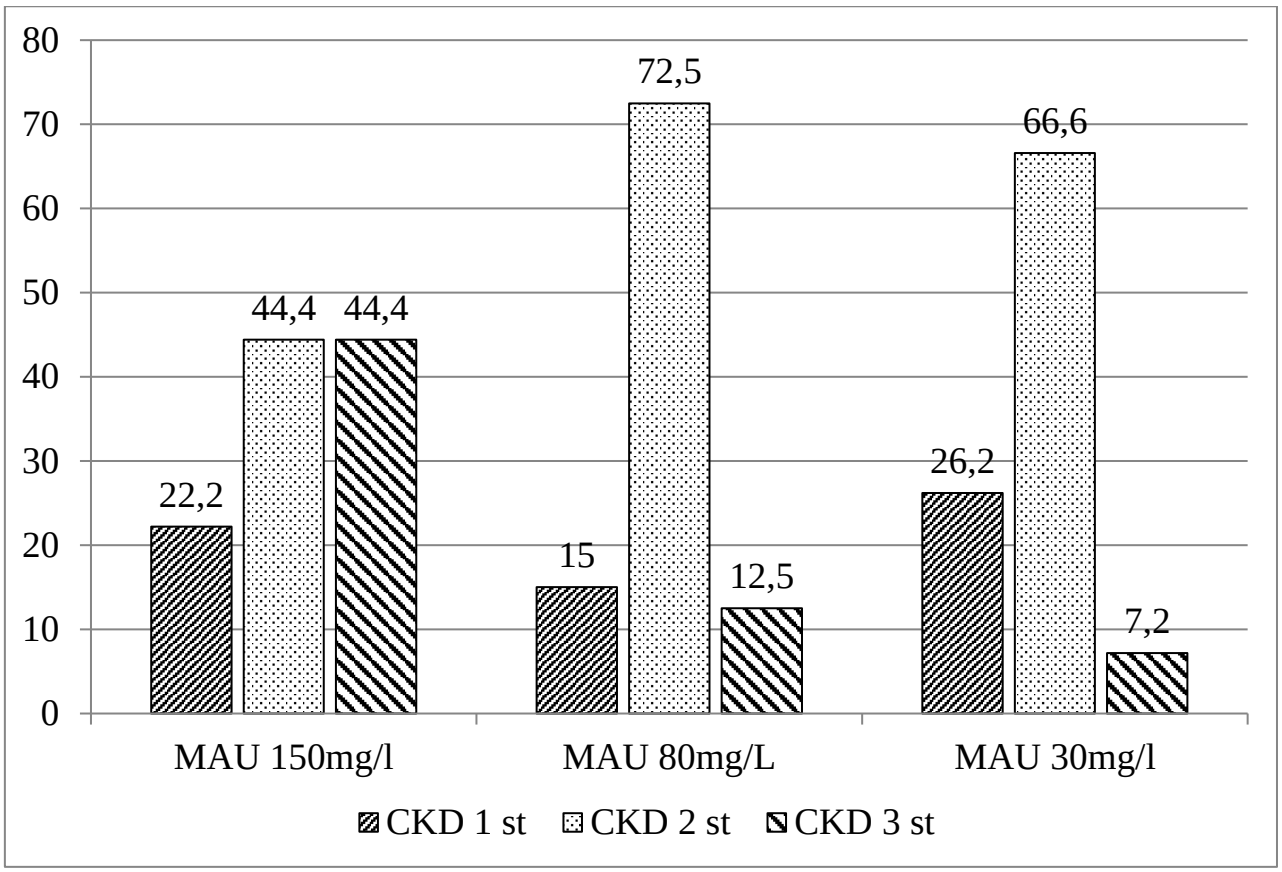


Figure 3.3. Prevalence of microalbuminuria depending on the stage of CKD in the examined patients

Among the examined persons (n=87) with an established diagnosis of CKD, 28.7±4.52% were found. The distribution of MAU by CKD stages was as follows: with an initial increase in MAU (30 mg / l), the occurrence of stage 3 CKD was in 7.14±2.57% of cases, stage 2 in 66.66±4.71% and stage 1 in 26.19±4.39% of cases ($p<0.001$).

Among the examined population with an increase in the level of MAU to 80 mg / l, the incidence of stage 3 CKD was 12.5±3.3%; stage 2 72.5±4.96% and stage 1 15.0±3.5% ($p<0.01$); with a level of MAU greater than 150 mg/l, stage 3 CKD was found in 38.9±4.87%, stage 2 38.9±4.87%; stage 1 CKD in 22.22±4.15% ($p<0.01$) of the examined patients.

Thus, the definition of MAU has diagnostic value and allows earlier identification of patients of different risk groups with CKD. The determination of MAU on an outpatient basis will allow for early diagnosis of CKD, in addition, this method will allow for effective primary and secondary prevention.

Microalbuminuria, which is a predictor of early diagnosis of CKD, is also a risk factor for CKD. An increase in the level of proteinuria / microalbuminuria worsens the prognosis of CKD. Given the close, direct relationship between the amount of albumin excreted in the urine and the degree of CKD development, it can be concluded that MAU is particularly important in the development and progression of CKD in the examined patients.

From the above, we can conclude that the early detection of UIA in screening examinations has several features:

- first, microalbumin is an early diagnostic predictor, when it is detected in the urine, which is 8-10 years earlier will allow the diagnosis of CKD before the manifestation of specific clinical symptoms of kidney damage in addition, in this sense, MAU is of great importance as a prognostic risk factor for CKD, cardiovascular pathologies and diabetes mellitus;
- second, early detection of UIA will allow to determine CKD in the initial stages, which improves the quality of life of patients and reduces the cost of RRT in ESRD;
- Third, the definition of UIA allows for secondary prevention of CKD and reduces the likelihood of CKD progression.

§ 3.3. The algorithm optimizes the tactics of early detection of chronic kidney disease and ways to prevent progression.

Effective policies for the prevention of chronic kidney disease rely on indicators of the incidence and prevalence of this disease, as well as on the frequency of distribution and the burden of risk factors for development.

The most modern method of identifying the prevalence of risk factors and the significance of their effect on the development of CKD is screening.

Screening is a purposefully organized secondary prevention measure to detect the disease at the preclinical stages and the main goal is to detect the disease earlier before the onset of clinical symptoms. Under screening.also understand the mass survey of the population from a certain risk group or "conditionally healthy" who do not go to doctors. At the same time, the goal of screening is to reduce morbidity, disability and death from their complications.

- Based on the conducted scientific research, we propose the following measures of primary and secondary prevention of CKD:

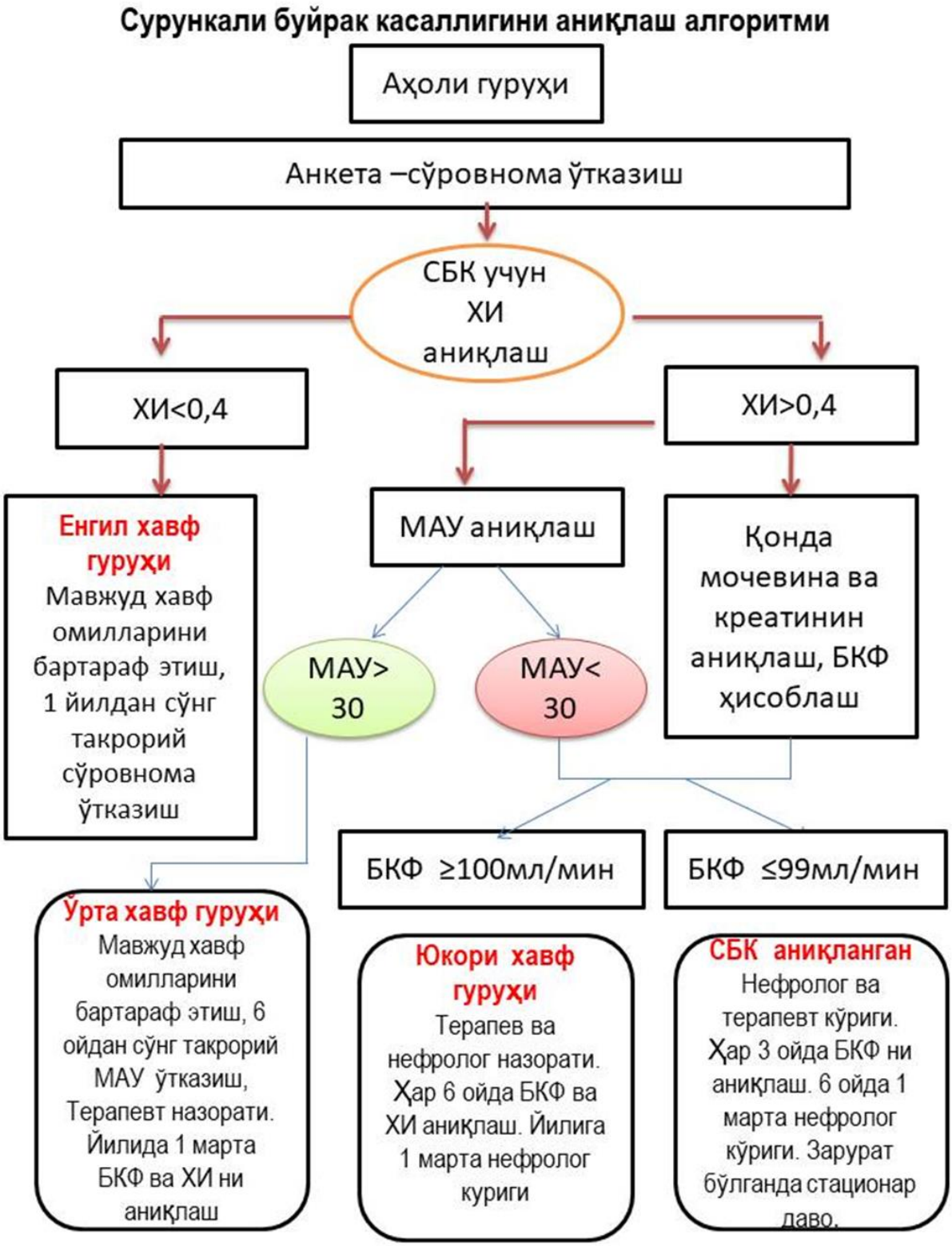
Conducting a screening survey of the population to identify risk factors and determine the risk group for CKD (including the age from 18 to over 45 years.

Taking into account the difficulties and inexpediency of continuous screening of the population for the detection of CKD, as well as the high cost and labor intensity of laboratory tests during mass surveys among the population (representatives of the conditionally healthy population and the active working population), the first place is proposed to conduct a questionnaire to identify prognostically significant risk factors for chronic kidney disease.

At the same time, people who fill out the questionnaire are informed about the causes of development and clinical symptoms of CKD. This provides two-way benefits: first, increasing the medical education of the population, and second, they try to create a healthy lifestyle based on this information.

- Create an electronic register of the population at risk of developing CKD;
- Given the diagnostic value of microalbuminuria for the early detection of CKD, it is advisable to determine this parameter for the diagnosis of CKD once a year in people at risk on an outpatient basis;
- Create an information sheet in outpatient records that contains complete information about non-traditional CKD risk factors (body mass index, OT, OB, bad habits, information about frequently used medications, the presence of chronic foci of infection, about diseases of direct line relatives that are an unfavorable risk factor for CKD) and systematically updates this data to determine the effectiveness of prevention and/or treatment measures;
- Repeated blood and urine tests with the determination of creatinine and urea, calculation of GFR, microalbumin in the urine in women with nephropathy and hypertension during pregnancy, 1 time per year;
- Appropriate planning of consultations with nephrologists 1 and / or 2 times a year (based on the degree of the risk group Annex 2) for the population

at risk for the timely and effective detection and treatment of CKD in the early stages.



SUMMERY

Numerous clinical and socio-medical studies conducted in the world over the past decades provide a complete picture of the scale of CKD problems that have spread to all countries of the world. The prevalence of CKD is high and is not inferior to the prevalence of such socially significant diseases as diabetes mellitus, hypertension, and heart failure

The literature data of recent years show that the prevalence of CKD and its range varies from 10-18%. This is due to the different criteria that are used for screening for CKD, as well as the place of residence (city or village), ethnic customs, lifestyle and standard of living, the effectiveness of preventive measures, the spread of chronic non-communicable diseases among the population.

In our study, we raised the question of determining the prevalence of chronic kidney disease at its various stages in the population..

Developed national and international recommendations from different countries offer a number of markers for the early diagnosis of CKD. With a decrease in GFR of 60 ml / min, the functional and structural damage to the kidneys will undoubtedly be irreversible, however, it is possible to identify earlier-reversible-stages, which should first be paid attention to.

To date, the study of albuminuria is of paramount importance for the early diagnosis of CKD, when there is no proteinuria and a decrease in GFR, as well as for assessing the risk of its progression and the development of complications – both in the early and later stages. The simplicity and accessibility of this method of diagnosing CKD is an important advantage that is necessary for conducting screening studies.

In our studies, the diagnosis of CKD was established in accordance with international recommendations and the available diagnostic capabilities of each treatment and prevention institution.

A microalbuminuria test and GFR calculation using the CKD-EPI formula for creatinine and MDRD were performed in the health care unit. When comparing these two GFR markers, the advantages of either of them were not revealed, which makes it possible to use them interchangeably.

Until recently, serum creatinine concentrations were considered to be the main estimates of GFR in practical medicine all over the world.

The introduction of these two methods in the diagnostic standards at the primary health care level (in outpatient settings) increases the chance of early diagnosis of the development and progression of CKD.

Our data on the prevalence of chronic kidney disease in certain population groups suggest that its occurrence in general is not lower than in the world. According to our data, the prevalence of CKD among women of the active working population was 28.7%. The distribution by stages of CKD was as follows: 1 st. - 12.6%, 2 st. - 13.2%, 3 st. - 2.8%. The high prevalence of stages 1 and 2 was associated with a high frequency of risk factors: arterial hypertension, overweight, obesity, the presence of chronic foci of infection, abuse of nephrotoxic drugs.nephropathy of pregnant women in the anamnesis in women.

In outpatient settings, where it is not possible to study daily urine, we examined the level of albumin in a single portion of urine in patients using test strips. The criterion for CKD was AU $\geq$ 30 mg/l. As a result, high albuminuria was detected in 29.2% of the examined patients.

The results of our study showed that the questionnaire plays an important role in identifying risk factors for chronic kidney disease.

In our study, the division of the questionnaire into blocks containing complaints characteristic of CKD, nephrological history data, indications of metabolic disorders and family predisposition to them, information about maintaining a healthy lifestyle allows us to more accurately identify risk factors for CKD and determine indications for laboratory examination, which is important both for improving the detection of CKD, especially in its early stages, and for the rational appointment of laboratory tests.

The second set of questions in the questionnaire concerned the presence of patient complaints. The most specific complaints were those directly related to kidney damage and uremia, such as dysuria, nocturia, pain and discomfort in the lower back. However, their sensitivity to the risk of MAU ≥ 30 mg/L was relatively low. The most sensitive predictors were complaints such as swelling of the limbs and eyelids. Complaints of edema, which can be observed both in independent kidney disease and in cardiovascular pathology, are characterized by a combination of high sensitivity and specificity.

Among the representatives of the conditionally healthy population, there was a difference in complaints in different sex and age groups. In younger people, there were complaints of edema, and among women of this age, pain in the lower back, dysuria with nocturia. The older age group was characterized by thirst and dysuria. The most common risk factors for CKD in our study were arterial hypertension, overweight, obesity, the presence of chronic foci of infection, and the abuse of nephrotoxic drugs.

Attention is drawn to the revealed association of high MAU with the presence of nephropathy in women with a history of pregnancy.

We found a significant association of high albuminuria with the abuse of analgesics. Frequent use of analgesics poses an immediate threat to the kidneys, since these drugs can have a toxic effect on the epithelium of the renal tubules, and also contribute to their ischemic damage by suppressing the production of prostaglandins.

In our studies, it was noticeable that there is a large difference in the indicators of kidney changes according to ultrasound studies, the frequency of MAU ≥ 30 mg/l in the examined patients is significantly higher than certain pathological changes in the kidneys during ultrasound.

To date, the place of ultrasound in the diagnosis of CKD remains not fully defined. Population studies for the detection of CKD were based on laboratory data – the determination of GFR and MAU, but, as a rule, did not include ultrasound data.

In our studies, only anamnesis data was taken into account and does not give an idea of what specific symptoms of structural changes in the kidneys during ultrasound were observed in the examined patients.

It seems important that by filling out the questionnaire and passing a subsequent interview with a doctor, the subject gets an idea of the factors that adversely affect the kidneys, he develops a more conscious attitude to the need to lead a healthy lifestyle in order to prevent CKD and an understanding of the need for regular preventive medical examinations. These questionnaires allow not only to assess the risk of CKD, but also to create an individual program of nephroprophylaxis and nephroprotection, taking into account the characteristics of the patient's condition.

CONTENT

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