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UROLITHIASIS IN CHILDREN: PROGNOSIS AND EARLY DIAGNOSIS

MONOGRAPHY

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OVERVIEW

INTRODUCTION

Relevance of the problem. To date, urolithiasis is not only a medical, but also a serious socio-economic and demographic problem. The disease is currently detected in young children and even in newborns. According to the World Health Organisation (WHO) "...diseases of the urinary system (MUS) are the second most frequent pathology of childhood. In the last decade, the frequency of MUS diseases in children has increased 2.5-3 times and ranges from 20.6 to 106.0 per 1000 child population, depending on the region. Changes in the nature of nutrition and physical activity of children lead to changes in the metabolic status of the organism and predisposition factors to urolithiasis are realised already in childhood..." **.**

Globally, special attention is paid to scientific research on the study of etiology, risk factors, mechanisms of development, diagnosis and differential diagnosis, course of paediatric diseases, in particular urolithiasis, as well as effective methods of treatment and prevention. In this connection, conducting scientific research on early diagnosis, timely detection of risk factors of urolithiasis in children, characterisation of anamnestic and data features of the clinical course, indicators of laboratory, instrumental and immunogenetic methods of research, as well as improvement of the complex of preventive measures for early diagnosis of ICD in outpatient and polyclinic institutions is of no small importance. In addition, one of the most urgent issues of scientific research on this problem is the study of genetic markers of predisposition to the development of urolithiasis, which will allow to identify risk groups and contribute to the opening of opportunities for the application of algorithms for early diagnosis, as well as for personalised management of patients.

Our country implements complex measures aimed at the development of the medical sphere, in particular at early diagnosis of pathologies of the urinary system, improvement of methods of treatment and prevention of the disease with the achievement of certain results. In this regard, important tasks have been defined as "...improving the efficiency, quality and popularity of medical care provided to the population in our country, as well as supporting healthy lifestyles and disease prevention through the formation of a system of medical standardisation, the introduction of high-tech methods of diagnosis and treatment, the creation of effective models of patronage service and dispensary ..." . On this basis, in order to realise these objectives, it is important to identify risk factors for the spread of urolithiasis among the population in a timely manner and implement measures aimed at preventing complications, as well as the subsequent increase in the range of medical and social care, reducing disability and improving the quality of life.

The results of studies conducted to date on a global scale have shown that the problem of the occurrence of dysmetabolic nephropathies related to risk groups for the development of ICH in children is of great interest. Many authors in their works note the significance and prevalence of ICD in environmentally unfavourable regions and indicate the influence of endogenous factors on the development of urolithiasis (Voshchula V.I. et al., 2018). At the same time, many works identify polygenically inherited membranopathy as one of the factors in the development of dysmetabolic nephropathy associated with environmentally unfavourable environmental factors (Carmen Inés R.C. and all., 2020).

Numerous studies have shown that the detection of urolithiasis in children is characterised by the rapid development of complications and the risk of recurrence over the next few years (Kusumi K. and all., 2015). In this regard, the search for ways to predict the occurrence of urolithiasis, based on the detection of immunogenetic markers has certain prospects, it will allow to detect predisposition to the occurrence of the disease at any age, practically from birth, since the genotype does not have a feature to change during life. This becomes especially important when early diagnosis is possible in the absence of any clinical and biochemical manifestations (Alyaev Y.G., 2019).

The studies of Uzbek scientists Shamsiev A.M. (2021), Yusupov Sh.A. (2021), Shamansurova E.A. (2020), etc. deserve attention. to study the subtle mechanisms of pathophysiology of the disease, to analyse the prevalence and regional features of USD with the identification of endogenous and exogenous risk factors, wide application of clinical and laboratory methods, assessment of the composition of concretions, differentiated approach to the study of the role of infection against the background of urostasis in USD to improve diagnosis and increase the effectiveness of treatment and prevention of urolithiasis in children. However, there is limited information on the etiology of this disease and its connection with the study of aspects of immunogenetic changes occurring in this pathology in children.

In view of the accumulated experience and many scientific and practical studies of urolithiasis from the perspective of the development of immunogenetic methods of research with the definition of markers that allow predicting the risk of disease development, can be used for early diagnosis of the disease, justification of the choice of tactics of treatment and management of patients, prevention of the transition of the primary form of urolithiasis in recurrent. This will make it possible to compile an algorithm for early diagnosis of urolithiasis in children on the basis of the obtained data, which is of scientific and practical importance in paediatrics.

The aim of this work is to optimise the algorithm of early diagnosis of urolithiasis in children in outpatient and polyclinic conditions. In accordance with this, the following tasks were developed:

1. to analyse the role of endogenous and exogenous risk factors in the development of urolithiasis in children;

2. to identify age-specific clinical and laboratory data in the examined children to determine the early symptoms of urolithiasis;

3. to investigate the pathogenetic significance of immunogenetic predisposition in the development of urolithiasis;

4. to develop an algorithm for early diagnosis and prognosis of urolithiasis in children in outpatient and polyclinic centres.

This monograph provides information on the identified endogenous and exogenous risk factors for the development of USD, which can be used for early diagnosis and prediction of its development based on the assessment of epidemiological aspects of the disease in children; on the importance of immunogenetic factors in the pathogenesis of the development of urolithiasis in children, which are predictors of its development at the preclinical stage; on the role of immunogenetic method of predicting USD in identifying predisposition to the disease with the study of the distribution of polymorphisms in children; on the role of immunogenetic method of predicting USD in the study of the distribution of polymorphisms in children in Samarkand region.

This work is of great practical importance, as the main endogenous and exogenous risk factors for the development of urolithiasis in children in Samarkand region on the basis of epidemiological studies have been identified. Optimised screening of USD detection at the preclinical stage is proposed taking into account characteristic immunogenetic parameters responsible in the pathogenesis of its development and having a significant impact on the possibility of recurrence. New approaches to the diagnosis of urolithiasis in children were developed, which allowed to use an algorithm for effective and early detection of ICH taking into account the results of immunogenetic studies.

The scientific significance of the results of the study lies in the study of the prevalence of urolithiasis among children, determination of endogenous and exogenous factors, as well as the study of immunogenetic factors (genes of vitamin D receptor (VDR) and interleukin-1β), which will improve the efficiency of early detection of the disease at the level of primary health care with the inclusion of a diagnostic algorithm based on the obtained immunogenetic features of urolithiasis in children. The obtained results of complex research with the use of modern

epidemiological and immunogenetic methods of research allowed to reveal new aspects of pathogenetic mechanisms of USD development in children.

The practical significance of the work lies in the fact that the proposed algorithm helps to predict the development of urolithiasis in children and its early diagnosis at the preclinical stage of the disease. The developed algorithm can be recommended in practical healthcare for doctors of outpatient and polyclinic institutions.

The identification of endogenous and exogenous risk factors, taking into account the pathogenetic mechanisms of immunogenic predisposition, the development of a programme for early diagnosis of urolithiasis, its prognosis and prevention made it possible to prevent the development and complications of the disease and improve the quality of life of children.

Chapter I.
EPIDEMIOLOGY, RISK FACTORS AND DIAGNOSIS OF UROLITHIASIS IN CHILDREN (LITERATURE REVIEW)

§1.1. Prevalence of urolithiasis (world statistics).

The epidemiology of USD is constantly being studied and is in the field of attention of clinicians and health care organisers [59, p.49-50; 95]. The incidence of USD in children worldwide tends to increase, and it should be noted that the pathogenetic mechanisms and clinical picture of the disease in children differ from adults. That causes special interest to this problem and necessity to study regional epidemiological processes, including sex and age categories, with determination of etiological risk factors of urolithiasis. In the future, this will make it possible to develop diagnostic, therapeutic and preventive measures, the main purpose of which is the timely detection and reduction of morbidity [24, p.144-150; 171, p.2300-2305].

In recent years, reports of the Society of Urology have reported an increase in the prevalence of USD patients in those countries where previously the incidence was quite low - China, Laos, Japan. In this regard, there is a need for research and epidemiological analysis of morbidity rates with the search for risk factors of urolithiasis. Apparently, it is associated not only with endogenous but also exogenous factors, such as environment, ecological disturbance, climate change, with a shift towards global warming, presence of calcium salts in drinking water, excessive content of fats and proteins in food, high level of urbanisation, active migration of population.

Summarising the above, we can conclude that the incidence of USD is influenced by many different factors: race, geographical region, socio-economic and living conditions, dietary habits and eating habits [139, p.155-161].

According to the literature, USD is widespread throughout the world, but there are countries and regions where the incidence reaches high figures and is endemic - countries of the Middle East, North Africa, Turkey. The main causative factors in these countries are the hot climate, the high level of consanguinity, and the genetic and racial characteristics present. There is a lack of analysis of the studied full-fledged epidemiological factors in almost every country, therefore, these data have a significant difference, which is probably due to the lack of methodological approaches, as well as proper collection of information [148, p.639-645].

The indicators of USD morbidity and prevalence obtained from hospitalisation and physical examination data are not correct, and therefore these data cannot reliably reflect the

existing reality, so there is a need to conduct epidemiological population studies according to a well-established methodology. This circumstance leads to imperfection of available data on USD epidemiology, as the number of patients at the population level for a certain period cannot always be established.

USD can be characterised by stone formation with asymptomatic course of the disease, so for a long time the patient does not seek medical help at the preclinical stage and misses the opportunity for early diagnosis of the disease.

According to studies [45, p. 90-98; 77, p. 4-64], more than 30% of patients with urolithiasis require emergency surgical interventions due to the development of renal colic. But when examining these patients, earlier stones could be absent and/or their discharge was not noted by patients.

Most researchers [136; 166, p.688-709] note the presence of stone formation, which was determined by autopsy, which also indicates the fact of asymptomatic course of the disease in a large number of patients. This confirms the need to obtain reliable data on the prevalence of this disease through epidemiological and population studies.

The available controversial data once again prove the existence of interest in solving the problems of USD epidemiology, and explain the increase in research work on the part of scientists who are trying to approach this problem, analysing in detail the various risk factors for the development of this pathology.

Studies conducted in Uzbekistan have undoubtedly contributed to the study of this issue. The peculiarity of these studies was that they were of a sporadic nature and mainly concerned specific diagnostic or therapeutic tactics [2, pp. 13-17]. The analysis of prelithiasis prevalence among the rural population of the Khorezm region [23, p.60-61] showed that it averages 11.5% or from 1.9% to 21.7% in different regions.

A number of scientists have also studied the prevalence of urological diseases, in particular urolithiasis, in the Aral Sea region, taking into account the fact that this region is an ecological disaster zone. The authors note the need for special attention to the state of public health, diagnosis of early stages of the disease. And most importantly, they assign a great role in the development of treatment and preventive measures to the activities of outpatient and polyclinic services [2, p. 13-17].

Along with this, studies have been conducted to improve and increase the effectiveness of the results of diagnosis, treatment and prevention of ICD in children. Thus, A.M. Shamsiev et al. (2021) paid special attention to the study of subtle mechanisms of pathophysiology of urolithiasis, targeted application of clinical, laboratory and instrumental methods of research.

The questions of etiology of this disease were considered in connection with the studied aspects of immunogenetic changes arising in this pathology, which will prevent the occurrence of the disease in children [34, p.129-132; 35, p.46-48].

Along with this, Yusupov Sh.A. (2020) analysed the prevalence and regional features of ICD with the identification of endogenous and exogenous risk factors, differentiated approach to the study of the role of infection against the background of urostasis [182, p.322-328].

Thus, ICD is a widespread disease in the world, the number of cases of which continues to steadily increase. According to studies, most scientists believe that this is primarily due to changes in diet, the environmental situation in the world, and the quality of fluid and food intake [74, p.858-863; 108, p.1581-1585; 109, p.37-46; 187, p.1120-1124]. Some authors argue that lifestyle changes influence the increased incidence of ICD [86, p.1329-1339; 87, p.33-38; 124, p.839-846]. Other researchers in their conclusions insist that the reason for the sharp increase in the incidence of ICD in various populations is the increasing incidence of mutations and polymorphisms of certain genes [60, p. 2754-2758].

Traditionally, ICD was considered a disease of adults. However, there is now increasing evidence of a significant increase in this pathology in the paediatric population and in the general population. In statistical reports of most countries there are data on the growing financial burden of ICD. According to the authors, in economically developed countries the average cost of care for ICD patients in the adult population is more than 10 billion dollars per year [153, p.1305-1312]. The costs associated with hospital beds with ICD in children also tend to increase annually, for example, inpatient care costs on average more than $18,000,000 [107, pp.805-810].

Analyses of the causative factors and mechanisms causing the risk of ICD in the paediatric population have shown a number of gaps, despite the many hypotheses and theories (about 200) of urinary stone formation available [22, p.11-17; 53, p.1151-1156].

In the works of Tajik scientists on the study of etiological risk factors for the development of urolithiasis in children, it was noted that the polyetiology of urolithogenesis plays an important role in the process of urinary stone formation, as well as the participation of both general (including the influence of geographical environment) and local (constitutional) nephrogenic factors. In their opinion, this explains the development of the disease in a certain contingent of children in the conditions of an endemic region [22].

The studied epidemiological data on the prevalence of ICD prove the occurrence of this pathology on all continents, with different levels of morbidity. The etiological causative factors are the environment, certain chemical composition of soil, plants, degree of water mineralisation, climatic conditions, sex and age peculiarities, industrial and household conditions. The most

significant endogenous factors are: pathological-functional changes in kidneys, urinary tract infections, GI diseases, bone injuries with prolonged immobilisation, hyperfunction of parathyroid glands, genetic predisposition.

Summarising the available data, we can conclude that the incidence and prevalence of ICD is quite diverse in different regions of the world, with an uneven distribution and a wide range of indicators, and countries with a high level of economic development and urbanisation remain the leaders in terms of morbidity.

Thus, urolithiasis is a polyetiological disease, the development of which is associated with the presence of a number of endogenous and exogenous risk factors.

§1.2. Risk factors and pathogenetic mechanisms of ICD development

Realisation of the effects of exo- and endogenous factors leading to changes in the kidneys is carried out at the level of the nephron epithelium, which are the basis for stone formation [27, pp. 82-89; 28, pp. 28-32]. Endogenous factors in the development of urolithiasis include sex and age, ethnicity, family predisposition; exogenous factors include climatic conditions, environment, lifestyle, dietary habits, profession, level of education, etc. The most important and determinants of the risk of development, prevalence and morbidity, recurrence rate of ICD and stone composition are climate and nutritional characteristics.

One of the risk factors for the development of ICD is age, with peak incidence occurring between 30-60 years of age. According to most researchers, one of the causative factors of age dependence of the disease is heavy labour-intensive work, leading to reduced fluid intake and thus a high level of dehydration. Also age-related causative factors are unhealthy lifestyle, irregular irregular diet, sleep and rest disturbance, occupational stress [7, p.11]. According to literature data, in many countries men are more predisposed to urolithiasis than women, and the ratio is 5:1.3 [89, p.2158-2163; 91, p.630-637; 135, p.56-60]. According to the authors, this difference may be related to dietary habits [157, p.410-415], as men consume more alcohol, coffee, and meat compared to the female sex. The hormone testosterone may also contribute to stone formation, while estrogen apparently prevents this process through regulation of the synthesis of 1-25 - vitamin D dihydroxide [83, p. 143936; 97, p. 278-289]. Another factor contributing to stone formation in males is the anatomical peculiarity of the MVC. Most often a stone in men is detected in the bladder, with subsequent obstruction of the urethra, which in turn increases the risk of benign prostatic hyperplasia [38, p.31-34; 39, p.386-391; 41, p.200-203; 86, p.1329-1339; 123, p.309-314; 157, p.410-415; 169, p.80-85; 181, p.1899-1904].

According to a number of authors [58, p.2301-2311; 167, p.72-81], the change of dietary habits and nutritional characteristics is also of great importance in the development of urolithiasis.

Economic development and improvement of living standards in most countries, transition to proper nutrition and healthy lifestyle have significantly reduced the intersex ratio of ICD incidence. In studies of scientists conducted in India [80, p.39-46; 97, p.278-289], special attention was paid to lifestyle and diet: indigenous people ate cereals, vegetables with high levels of oxalate and its precursors. The second group in the study observed adherence to the Western lifestyle, their dietary preferences, which also contributed to stone formation due to the high content of proteins, lipids, calcium and sodium in the diet. According to scientists, all this has contributed to the dramatic increase in ICD in many Asian countries [38, p.31-34; 42, p.51-61; 80, p.39-46; 93, p.175-179; 149, p.73-82; 161, p.92-112; 180, p.104-111].

The main metabolic disorders contributing to the development of ICH are hyperuricaemia, hyperuricuria, hyperoxaluria, hypercalciuria, hyperphosphaturia, and changes in urine acidification [61, pp.1251-1260; 78, pp.715-734]. According to the majority of researchers [143, p.265-272], metabolic disorders cause renal-canalic acidosis, which plays a major role in the pathogenesis of urolithiasis [13, p.80-89]. Its development leads to an increase in the degree of ionisation of chemical substances from which stones are formed, and there is a dependence on pH, the level of free ions that determine the degree of saturation of urine. From the point of view of biochemistry, the solubility of substances that lead to the formation of stones in the urine has a correlation with the pH indicator.

In food, oxalate precursors are glycine, hydroxyproline [142, p.1330-1338]. Excessive meat consumption increases the risk of uric acid kidney stones [117, p.420], contributing to hyperuricaemia and oxidation of urine with the formation of calcium oxalate stones [126, p.189-202; 179, p.209-213], which is typical of Japan, where the prevalence of ICD due to dietary habits is still high [55, p.393-399]. Calcium in combination with hydroxyacetic acid and vitamin C can be metabolised to oxalates in the liver, increasing their concentration in the urine, with subsequent formation of oxalate stones. Some studies [134, p.155-163] have shown a role for the combination of lipids with calcium in the intestine, leading to the formation of insoluble substances with increased oxalate absorption. Another factor mechanism contributing to stone formation is the precipitation of crystals at the appropriate pH of urine. Stones in the urinary tract can form under a simultaneous combination of basic conditions - concentration of chemical ingredients and appropriate urine pH [88, p.1084-1089]. This hypothesis is confirmed by the high incidence of ICH in Southwest and South Asia, where rice is the main food crop, the

catabolism of carbohydrates of which creates a favourable urine environment - acidic, so necessary for the formation of stones [114, p.211-217; 145, p.687-694].

Reduced fluid intake plays a leading role in the development of ICH [55, p.393-399]. The quality of drinking water plays an important role, since an increase in the content of fluorine, sodium, calcium, magnesium and phosphate in it promotes the formation of oxalate stones [55, p.393-399; 96, p.383-391; 162, p.240-244; 168, p.39-46; 176, p.537-540]. At high content of fluoride in drinking water, exceeding the MPD, fluoride stones are formed, the mechanism of formation of which is closely related to the retention of fluoride in the intestine, with increased absorption of oxalates and formation of calcium fluoride [168, p.39-46].

The cause of ICD in oxalaturia was first reported in 1888 [68, p.64-68]. Acidification of urine due to low pH contributes to a decrease in the solubility of uric acid and cysteine, while alkalisation, at high pH, reduces the metastable zone of calcium phosphate and struvite. Hypercalciuria, reduction of the metastable zone, super saturation of urine with calcium phosphate and its crystallisation are considered to be one of the main factors in stone formation in children [125, p.1-6].

Increased oxalate excretion leads to the formation of insoluble calcium fluoride in the urine, forming a vicious circle in the form of oxidative stress in the renal system. Due to excess sodium, there is additional absorption of calcium into the blood, or inhibition of calcium from the urine into the epithelium of the renal tubules, which further enhances the deposition of kidney stones. Micronutrient deficiencies play a significant role in stone formation, as molybdenum and silicon play a key role in keeping crystals in solution.

One of the no less significant factors in the development of ICD is climate or environment: temperature regime, time of year, sunlight hours, ultraviolet light level, humidity, atmospheric pressure, precipitation and its level [97, p.278-289]. This dependence and significance of the above factors can be considered on the example of countries with tropical and subtropical climates. In these regions, the prevalence of ICD is significantly higher compared to countries with temperate and cold climates. Due to the hot and dry climate typical of West Asia, the level of water evaporation from the body increases, thus contributing to an increase in urine concentration, followed by the precipitation of salt crystals and the formation of stones of various origins.

With regard to occupational activity and level of education, their significance as risk factors for ICD remains controversial [48, p.119-126]. According to some researchers, the fact of development of urolithiasis among people with initially high level of education, intellectuals, whose main work is associated with sedentary lifestyle has been revealed, because there are

studies in which it was found that people with sedentary work in the office are more susceptible to morbidity [93, p.175-179; 167, p.72-81].

Nevertheless, there are studies among people with secondary education, in which heavy physical labour plays a significant role in the occurrence of pathology. The authors attach great importance to the temperature factor, as there are most professions that work outdoors or in workshops exposed to high temperatures (miners, steel workers, bricklayers, drivers). These individuals have twice the risk of developing ICH compared with people working at normal room temperature [80, p.39-46; 149, p.73-82; 169, p.80-85; 180, p.104-111]. The mechanisms for the development of ICH during exposure to high temperatures are primarily related to dehydration and limited access to drinking water. Prolonged sun exposure promotes increased production of vitamin D, with subsequent disruption of calcium absorption in the intestine and the development of stones of various structures.

The inheritability of ICD is 52-56%, the presence of monogenic mutations is determined among 2% of adults and 10% of children [66; 121, p.151-162], indicating a significant role of genetic factors in children and the influence of environmental factors in adults. Currently, there are many genes that are involved in the pathogenesis of urolithiasis. At least 17 genes are involved in the formation of renal tubule stones. There are also a large number of genes responsible for intestinal calcium absorption, intracellular metabolism of oxalates, purines, etc.

Another of the causative risk factors of ICH in children are abnormalities of MBC development, obstruction, urinary stasis, infection with urea-degrading microorganisms [44, p.2203-2209].

To date, despite the large number of available theories of pathogenesis, the process of kidney stone formation cannot be properly explained as it is quite diverse and complex. Excessive growth of interstitial apatite plaque is considered to be the main pathway of stone formation. It is formed in the basal membranes of the branches of the loop of Henle in the form of small particles, coloured black, which is not accompanied by tissue reaction, or cell damage. These particles are represented by microspheres, arranged in layers, of alternating apatite crystals and organic matrix, which merge to form a syncytium, where islets of crystals float in the organic component and easily migrate without crossing anatomical formations to the suburothelial space, where they can be detected externally, in the form of white plaque. Within the microspheres, plaques, osteopanthine is localised along the crystal-matrix boundary, and the third heavy chain inhibitor, interalfatrypsin, is located in the matrix [69, pp.1503-1511; 70, pp.145-154]. This process is characteristic of idiopathic calcium oxalate stones without any

disease, the exception being familial (idiopathic) calciuria. Plaques can be found in patients with primary hyperparathyroidism, ileostomy and small intestine resection.

The second pathway of lithogenesis is the deposition of crystals in the renal tubules. They appear as elongated yellowish elevations below the urothelium, they are easily distinguished from interstitial plaque localised below the urothelium, in which extensive and focal damage occurs and these deposits replace epithelial cells with the formation of interstitial fibrosis. The full pathogenesis of these processes remains a subject of research.

The third pathway of stone formation is crystallisation of free solution, in cystinuria a large number of stones are formed, massive in size, filling the renal pelvis, as cysteine is poorly soluble and is excreted in large quantities, oversaturating the urine, with the stones being free in the renal pelvis and never attached. Unlike apatite plugs, cysteine plugs cannot anchor stones, due to mobility and sliding.

Based on the mechanisms of stone formation, some substances cause metabolic disorders in the body, increasing the concentration of stone-forming components in the urine (oxalic and uric acids, calcium, phosphates), and others have a direct effect on the renal epithelium, causing "local" changes in them. Long-term use of citrate preparations containing citric acid and its salts may lead to oxalaturia, and vitamin A deficiency in the diet may indirectly contribute to the development of phosphaturia, with the formation of phosphate stones [63, p.1173-1184].

With the addition of infection, the acidic reaction of urine changes to alkaline, in which phosphates precipitate amorphous and crystalline, and against the background of inflammation and increase in uromucoid in the urine can activate the process of phosphate stone formation. The possibility of drug hypervitaminosis C, which is a risk factor for oxalate stone formation, was determined.

Vitamin D and its metabolites - D2, D3 - play an important role in the regulation of calcium and phosphate metabolism in the body. Prolonged hypervitaminosis D (6 months - 2 years) leads to irreversible changes in the kidneys, due to overload and disruption of calcium and phosphate transport, nephrocalcinosis develops, in which salt deposition occurs in the cortical substance and tubular apparatus of the kidney. In some patients, renal papillae calcinosis is observed, calyx stones are formed with the development of ICH and the formation of calcium phosphate stones.

§1.3. The role of clinical diagnostic and immunogenetic methods in the diagnosis of urolithiasis

In the standard examination at the initial stages of diagnosing urolithiasis, a detailed history and physical examination are performed. Urolithiasis is characterised by low back pain, vomiting, sometimes increased body temperature, and an asymptomatic course [82, p.401].

Laboratory diagnostics. In the diagnosis of ICH, general urine and blood analysis, biochemical studies of urine and blood with determination of creatinine, uric acid, calcium, sodium, potassium, phosphorus are carried out. To determine the function of the kidneys are used Zimnitsky test. When planning surgical intervention - coagulogram. In cases of high risk of recurrence of ICD prescribe a thorough examination, with a specific assessment of metabolism, taking into account the composition of stones.

The simplest way to make an accurate diagnosis is to analyse the withdrawn nodule using an analytical method that determines the mineral composition of the stone. Given that children with ICD have a high risk of recurrent stone formation, standard diagnostic methods are recommended for them.

Instrumental methods of investigation. Among the diagnostic methods for ICD, imaging is one of the most important. The choice of investigation methods depends on the clinical situation, and it may be different in patients with suspected ureteral or renal stones. Ultrasound is recommended as the initial diagnosis, without delaying pain management and other urgent measures until the imaging procedure is performed. Ultrasound is a safe, reproducible and inexpensive method that can be used to detect stones in the calyx, pelvic ureter, and vesicoureteral segments as well as diagnose upper urinary tract (UUT) dilatation. According to the literature [62, p.958; 140, p.371], ultrasound has a sensitivity of 45% and specificity of 94% for ureteral stones, and 45% and 88% for renal stones, respectively [122, p.1557-1565]. The disadvantage of ultrasound is the inability to detect stones in more than 40% of children with ICH [64, pp.352-363; 131, pp.583-591], as well as incomplete information on renal functional activity.

When planning a computed tomography (CT) scan without contrast, review urography, which can differentiate between radiopaque and radiopaque stones, is not indicated [175, pp.582-594]. The data obtained by CT examination can be used for dynamic follow-up and monitoring. In patients with a single kidney and complaints of high body temperature, if the diagnosis of ICH is doubtful, immediate imaging is a direct indication.

Standard diagnostic methods for renal colic include CT scan without contrast. This method has replaced excretory urography, as it is more informative and allows differential

diagnosis with other diseases causing abdominal pain in the absence of a stone. In addition, with the use of modern CT devices, the need for sedation and anaesthesia is virtually eliminated. With the help of CT it is possible to diagnose X-ray negative stones containing uric acid and xanthine, but the stones formed by the drug indinavir in this method are not visualised [79, p.268-273]. This method allows to clearly determine the density of stones, their size, structure, distance from the stone to the skin, anatomical features, i.e. those parameters that have a direct impact on the choice of treatment [46, p.565-570; 111, p.205-212; 174, p.1341-1351]. It should be noted that this technique has its own disadvantages - it is impossible to judge the renal function and anatomy of the TMJ, and also its performance is associated with high-dose load and radiation. Radiation exposure can be reduced by using low-dose CT [158, p.1413-1419]. Among this imaging method, spiral CT without contrast is the most sparing in children, but it is impossible to diagnose about 5% of stones. According to the results of prospective studies, the sensitivity of low-dose CT in the diagnosis of ICD is 96.6% and specificity is 94.9% [144, p.375-381].

The use of colour Doppler ultrasonography allows a comparative assessment of ureteral discharge, evaluation of the resistive index of the arch arteries of both kidneys with determination of the degree of their obstruction [141, p.11-23].

The sensitivity and specificity of review urography are 44-77% and 80-88%, respectively [122, p.1557-1565]. Review urography as an imaging method allows to detect stones, to determine their X-ray contrast, with subsequent observation in dynamics. Excretory urography is also informative, but the disadvantage is the necessity of contrast agent administration [63, p.1173-1184].

Magnetic resonance urography is not recommended in the diagnosis of ICH, but it allows obtaining detailed information about the anatomy of the CSF, localisation of ureteral obstruction or stenosis, morphology and renal parenchyma.

Thus, ultrasound is the preferred diagnostic method of choice in children with suspected ICH. If the ultrasonographic method of investigation fails to provide the necessary information, it is recommended to perform review urography or low-dose CT [116, p.2791-2803].

Modern urology has a significant arsenal of methods to get rid of kidney and urinary tract stones in most patients. However, removal of a stone does not mean getting rid of urolithiasis. That is why the problems of metaphylaxis (prevention of recurrence) of ICH are extremely important. Treatment of most conditions in which stones form in the urinary tract is currently based primarily on symptoms rather than causes. In this regard, it is relevant to study the distribution of genotypes of polymorphic markers of vitamin D receptor (VDR), interleukin-1β, interleukin-18 genes in children with ICD [188, p.107-114].

It is of great importance in the diagnosis of ICD to identify the degree of involvement of genetic factors. According to available literature data [177, p.1-7], hereditary predisposition in combination with environmental factors has a significant influence on the occurrence of metabolic disorders characteristic of urolithiasis [94, p.263]. A complete understanding of the causative factors of immunogenetic changes in ICH, with the identification of mutant genes and their products will contribute to the development of rational protocols for early diagnosis, treatment and prevention of urolithiasis.

ICD development is genetically determined by structural and functional features of metabolism, neurohumoral regulation, and local factors. In epidemiological and clinical studies, foreign scientists [56, p.234] suggest the existence of certain genes responsible for the occurrence of ICD, one of which, studied at present, is the VDR gene (vitamin D receptor) [119, p.913908]. The most significant polymorphisms of the VDR gene involved in the development of urolithiasis are considered to be Bsm I, Fok I, Taq I. Thus, there are data demonstrating the significance of the ApalAA genotype, which determines sensitivity to vitamin D, in the development of calcium stones in the urinary tract [112, p.249-255]. It is also reported about the higher frequency of occurrence of HLA genes B13, B22 and B35 in patients with urolithiasis in comparison with healthy individuals [29, p.114-116]. There is also evidence that in all metabolic disorders there were very high levels of the active product of vitamin D, 1,25-dihydroxyvitamin D, increasing calcium absorption through the gastrointestinal tract, reducing the synthesis and secretion of parathyroid hormone. These changes in calcium homeostasis lead to hypercalciuria with subsequent formation of kidney stones [90, p.193].

Despite many population-based immunogenetic studies, these markers, which play a major role in the development of ICD in children, are still poorly understood. The possibility of predicting the occurrence of ICD based on the detection of immunogenetic markers has some promise. Knowledge of a possible predisposition to the development of ICD, which can be determined using immunogenetic markers at an early preclinical stage, will allow timely prevention of the disease.

Determining the genetic contribution to urolithiasis is difficult, due to its multifactorial nature. This is confirmed in the formation of stones composed entirely or partially of calcium oxalate. There are quite a few parameters that contribute to calcium oxalate crystallisation in the kidney or urinary tract, such as high urinary concentration of calcium oxalate and crystallisation promoters (urates) and low concentration of crystallisation inhibitors (citrate, uromodulin (MsK 191845), osteopontin (MsK 166490) and nephrocalcin). Most of these changes are genetically determined or determined by environmental factors [119, p.913908]. The health status of

parents, pregnancy and postnatal period also require attention, as they influence the increase in the prevalence of anomalies of the MBC structure in children.

Conclusions of the chapter

Thus, ICD in children is a polyetiological disease, the formation of which is influenced by various factors: exogenous and endogenous. As exogenous risk factors for the development of the disease are identified such as environmental disorders, increased concentration of calcium salts and heavy metals in drinking water, poor quality, excessive consumption of vegetable and protein food, high level of urbanisation, active migration of population, climate change, with a shift towards global warming. Endogenous factors also play an important role in the pathogenesis of ICD development: developmental anomalies of the urinary system organs, metabolic diseases, genetic predisposition.

To diagnose urolithiasis in children, a complex of clinical, laboratory and instrumental methods of investigation is used, each of which has its own advantages and disadvantages. Immunogenetic method of research has a certain superiority among other methods of research, because it has the ability to diagnose urolithiasis at the preclinical stage, while other diagnostic methods work in the presence of uroliths in the urinary tract.

Insufficient study of genetic risk factors for the development of ICH in children necessitates further research.

Chapter II. CHARACTERISATION OF CLINICAL MATERIAL AND RESEARCH METHODS USED

This research work was carried out within the framework of the applied project "Development of new methods of treatment and prevention of urolithiasis in children taking into

account the genetic factor" (scientific supervisor - Professor A.M. Shamsiev) of the Committee for Coordination of Science and Technology Development under the Cabinet of Ministers of the Republic of Uzbekistan.

The research was carried out in Samarkand province in order to study the epidemiological features of the regions with regard to the prevalence of ICD in children. Search data were analysed to characterise the geographical, epidemiological and demographic features that play a role as causal risk factors for the development and prevalence of urolithiasis in this region.

The chapters provide descriptive epidemiological, medico-geographical features, with their significance and contribution to ICD prevalence and territorial specificity.

§2.1. General characteristics of the examined children

The study of the prevalence of urolithiasis in children was carried out according to the data of referral to the Specialised Children's Surgical Clinic of Samarkand State Medical University in the period from 2012 to 2019. The work was carried out in two stages.

At the first stage, anamnestic analysis and clinical and laboratory examination of 652 children with ICH aged from 1 to 17 years were conducted to study the prevalence of urolithiasis, as well as to determine risk factors: of them 439 (67.3%) boys and 213 (32.7%) girls ($\chi2=2104$; $p<0.001$). Meanwhile, 99 (15.2%) children were in the urban group and 553 (84.8%) in the rural group; 75 (17.1%) boys were in the urban group and 364 (82.9%) in the rural group; 34 (15.96%) girls were in the urban group and 179 (84.04%) in the rural group ($\chi2=0.01$; $p>0.05$). The total length of hospital stay ranged from 2 to 28 days (13.59±0.11). The children's height ranged from 69 to 170 cm (122.3±0.3) and body weight ranged from 8.5 to 71 kg (26.01±0.1).

The study of distribution of our patients with ICH by regions of the Republic of Uzbekistan is shown in Table 2.1 (n=652).

Table 2.1

Distribution of patients with ICD by region (by treatment)

Region, district, city	2012	2013	2014	2015	2016	2017	2018	2019	Всего
Bukhara region									
Bukhara district	-	-	-	-	1	-	-	-	**1**
Karakul district	-	-	-	-	-	1	-	-	**1**
Romitan district	-	-	-	-	-	-	1	-	**1**
Jizzak region									
Arnasay district	-	-	-	-	1	-	-	-	**1**
Bakhmal district	4	1	2	2	1	2	1	-	**13**
Gallaaral district	-	-	-	1	-	1	1	1	**4**
Jizzak district	-	-	1	2	1	-	-	-	**4**
Jizzakh city	-	-	1	2	-	-	-	-	**3**

Zarbdor district	-	-	1	-	-	-	-	-	**1**
Farish district	1	1	-	1	1	-	-	1	**5**
Kashkadarya region									
Dehkanabad district	-	-	-	3	1	-	-	-	**4**
Guzar district	1	-	-	-	-	1	-	-	**2**
Karshi district	1	-	1	1	-	1		1	**5**
Karshi city	1	-	-	1	4	2	2		**10**
Kasbiy district	-	-	-	-	-	-	-	1	**1**
Kitab district	1	1	-	2	-	1	1		**6**
Kasan district	1	-	-	-	2	-	-	1	**4**
Mirishkor district	-	-	-	2	1	-	-	-	**3**
Muborak district	-	1	-	1	-	-	-	-	**2**
Nishon district	1	-	1	-	2	-	-	-	**4**
Chirokchi district	4	4	2	4	4	1	8	4	**31**
Shakhrisabz district	-	2	1	2	6	-	1	-	**12**
Shahrisabz city	-	1	-	1	1	-	1	-	**4**
Yakkabagh district	-	-	-	-	1	-	-	-	**1**
Navoi region									
Zarafshan district	-	-	-	-	-	-	1	-	**1**
Karmana district	1	1	-	2	-	-	1	-	**5**
Kizilteppa district					1	-	1	1	**3**
Navbahor district	-	1	-	-	-	-	-	-	**1**
Navoi city	-	-	-	3	3	-	-	-	**6**
Nurata district	-	-	1	1	2	1	-	1	**6**
Konimeh district	1	-	-	-	-	-	-	-	**1**
Khatyrchi district	1	-	-	-	1	1	1	-	**4**
Samarkand region									
Bulungur district	2	2	2	1	-	-	2	1	**10**
Jambay district	-	1	1	2	1	1	-	-	**6**
Ishtikhan district	4	1	2	5	1	1	9	-	**23**
Kattakurgan district	1	6	3	3	3	1	10	2	**29**
Kattakurgan city	2	-	-	-	3	2	3	1	**11**
Kushrabat district	2	-	1	2	2	3	1	1	**12**
Narpai district	1	3	2	2	3	4	8	1	**24**
Nurabad district	4	4	2	8	5	1	6	-	**30**
Akdarya district	1	-	2	-	1	2	-	-	**6**
Payaryk district	1	-	3	3	4	-		1	**12**
Pastdargom district	5	1	10	8	6	2	12	6	**50**
Pakhtachi district	1	-	-	2	4	2	6	-	**15**
Samarkand district	2	3	2	8	5	2	4	2	**28**
Samarkand city	-	4	6	14	9	8	23	6	**70**
Taylak district	3	2	1	4	3	1	7	-	**21**
Urgut district	18	12	19	25	17	12	24	6	**133**
Urgut city	-	-	1	1	-	-	-	-	**2**
Surkhandarya region									
Baysun district	-	-	-	-	-	1	-	1	**2**
Denav district	-	-	1	1	-	-	-	-	**2**
Jarkurgan district	-	1	1	-	-	-	-	-	**2**

Kumkurgan district	-	1	-	-	1	-	-	-	**2**
Muzrabat district	-	-	-	-	-	1	-	-	**1**
Sariosi district	-	-	1	2	1	1	-	-	**5**
Termez city	-	-	-	-	-	1	-	-	**1**
Uzun district	-	-	-	-	-	-	1	-	**1**
Tashkent region									
Tashkent city	-	-	-	-	1	-	1	-	**2**
Republic of Karakalpakstan									
Nukus city	-	-	-	-	1	-	-	-	**1**
Panjikent district	-	-	-	-	-	-	1	-	**1**
Total	**65**	**54**	**71**	**122**	**105**	**58**	**138**	**39**	**652**

The sex and age distribution of ICD patients is shown in Tables 2.2 and 2.3.

Table 2.2

Distribution of patients by sex during the study period

Sex	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**	**Total**	
									abs.	**%**
boys	47	35	58	81	72	38	82	26	**439**	**67,3**
girls	18	19	13	41	33	20	56	13	**213**	**32,7**
Total	**65**	**54**	**71**	**122**	**105**	**58**	**138**	**39**	**652**	**100,0**

Table 2.3

Distribution of patients by age during the study period

Age	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**	**Total**	
									abs.	**%**
1-11 month	1	-	2	5	3	2	4	1	**18**	**3,0**
1 y - 4 y	13	15	17	38	23	16	38	10	**170**	**26,0**
5 y - 9 y	20	18	28	48	54	26	59	18	**271**	**42,0**
10 y -14 y	20	12	17	17	17	10	18	7	**118**	**18,0**
15 y -17 y	11	9	7	14	8	4	19	3	**75**	**12,0**
Total	**65**	**54**	**71**	**122**	**105**	**58**	**138**	**39**	**652**	**100,0**

The study population was divided by place of residence, urban or rural ratio (Table 2.4).

Table 2.4

Distribution of children with urolithiasis by place of residence

Location	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**	**Total**	
									abs.	**abs.**
City	1	5	8	22	19	11	27	6	**99**	**15,2**
District	64	49	63	100	86	47	111	33	**553**	**84,8**

Total	**65**	**54**	**71**	**122**	**105**	**58**	**138**	**39**	**652**	**100,0**

The socio-hygienic risk factors were studied using a questionnaire (Appendix 1), including data on objective examination, ultrasound findings, and clinical and biochemical analyses.

At the second stage of the study, in order to fulfil the set tasks of studying the immunogenetic predisposition to the development of ICD in children, a clinical examination of 200 children who were divided into two groups was carried out.

The first (main) group consisted of 100 patients with urolithiasis who underwent comprehensive examination (clinical, haematological, biochemical, bacteriological, immunogenetic, ultrasound, radiological) and treatment. ***The second (control) group*** consisted of 100 children without ICH and hospitalised for minor planned surgical interventions (circumcision, herniorrhaphy) in the Specialised Children's Surgical Clinic of Samarkand State Medical University.

To solve the set tasks, a patient examination card was developed, on the basis of which the peculiarities of the course and diagnosis of ICH in children of different ages were studied. According to the examination plan, the necessary laboratory and instrumental investigations were carried out with the subsequent registration of the obtained data in journals, with the compilation of an electronic database in Excel. On the basis of the collected material, the nature of the course of urolithiasis was identified by qualitative and quantitative composition of crystals by laboratory and diagnostic studies of urinary sediment; the frequency of complications and recurrences of stone formation in children with ICH of different age groups was determined.

Table 2.5 presents data on the age distribution of patients according to the WHO classification (2021).

Table 2.5 shows that among the patients, the majority of children with ICH were of school age, more often 5-9 years old - 45 (45%). This is due to the fact that it is at this age that metabolic disorders associated with the transition of children to general nutrition, drinking disorders, etc. are most often manifested, while in the younger group nutrition remains relatively rational and metabolic changes are manifested to a lesser extent.

Table 2.5

Distribution of children with and without urolithiasis according to WHO age grading (2021)

Age	**Control group (n = 100)**	**Main group (n = 100)**	**Total (n = 200)**

	abs	%	abs	%	abs	%
1-11 month	-	-	1	1	**1**	**1**
1 y - 4 y	31	31	26	26	**57**	**57**
5 y - 9 y	18	18	45	45	**63**	**63**
10 y -14 y	33	33	21	21	**54**	**54**
15 y -17 y	18	18	7	7	**25**	**25**

Table 2.6 shows the distribution of those surveyed in both groups according to gender.

Table 2.6

Distribution of patients depending on sex

Indicator	Control group (n = 100)		Main group (n = 100)		Total (n = 200)	
	abs.	%	abs.	%	abs.	%
girls	3	3,0	32	32,0	**35**	**17,5**
boys	97	97,0	68	68,0	**165**	**82,5**

The data presented in Table 2.6 shows that in terms of sex distribution in the main group, ICD is more common among boys 68 (68.0%) children than among girls 32 (32.0%).

§ 2.2. Examination methods for children with urolithiasis

According to the set objectives, we carried out a common list of clinical investigations, which first of all included the analysis of patients' complaints, detailed family, hereditary and obstetric history, assessment of living conditions, previous and concomitant diseases, and objective examination data. In addition, all patients underwent clinical, laboratory and instrumental methods of investigation.

Laboratory methods of research were performed in the department of clinical and laboratory diagnostics of the Specialised Children's Surgical Clinic of SamSMU. All 200 patients underwent general blood and urine analysis, biochemical blood tests (determination of calcium, phosphorus, alkaline phosphatase, creatinine, residual nitrogen, urea, and total protein levels), and bacteriological examination of urine according to standard methods.

Laboratory investigations of blood and urine were performed according to standard methods described in the manual of I.E. Tareeva (2000). The functional concentration capacity of the kidney was judged by the Zimnitsky test with collection of daily urine. The number of urine sediment formate elements was also determined by the Kakovsky-Addis method.

Blood biochemical parameters (residual nitrogen, urea, creatinine, total protein, calcium, inorganic phosphate) were investigated on the analyser Merilyzer AutoQuant 100i (India) according to the methodological guidelines for the use of unified clinical laboratory methods of research.

Bacteriological study of urine. Microbiological examination of urine was carried out by sowing on accumulation medium according to Gold's method. For identification of coccus culture from the accumulation medium we made sowing on yolk-salt agar, Endo agar and Sabouraud's medium. In the course of bacteriological examination of urine, the sensitivity of microbial strains to antibacterial drugs was also determined.

Instrumental methods of research: ultrasound sonography (USS), review and excretory urography were performed.

Ultrasound sonography (USS) of retroperitoneal organs was performed in all 200 patients on ALOKA-500-SSD (Japan) and SIEMENSE SONOLINE SI-450 (Holland) devices using linear transducers 3.5; 5.5 and 7.5 MHz, in real time mode.

Radiological studies were performed in 100 patients with urolithiasis on EDR 750B apparatus with X-ray television unit (produced in Hungary). Along with review and excretory urography (OU, EU) antegrade urography, infusion excretory urography were performed according to the indications. All radiological studies were performed according to the generally accepted methods.

Computed tomography (CT) was performed on General electronics 2 all. Model HI Speed (USA) in patients with ICD only in those cases when traditional radiological studies were not informative enough (12 patients with multiple or multilocular urolithiasis).

Immunogenetic study of genes. The studies were carried out in the laboratory of genomics of the Institute of Bioorganic Chemistry (IBOCH) of the Academy of Sciences of the Republic of Uzbekistan (AS RUz).

Blood samples of patients were collected from all 200 patients of both groups. Sampling was performed with the consent of the probands. Venous blood in the amount of 1ml was collected in 0.5ml of sodium citrate solution and stored at -20^0C.

DNA extraction. The material for DNA was venous blood from the ulnar vein in the volume of 1 ml. Vacutainers or disposable plastic tubes with 0.5 ml anticoagulant (preservative) were used for blood collection, storage and transport. Blood for further processing was stored at a temperature of at least +40 C.

DNA extraction from whole blood was performed using Diatom™ DNA Prep 200 reagent kit (manufactured by IsoGen Laboratory LLC, Moscow, Russia). This reagent set is based on the use of lysing reagent with guanidinedithiocyanate, which is designed for cell lysis, solubilisation of cell derbis, and denaturation of cellular nucleases. In the presence of the lysis reagent, DNA is actively sorbed on NucleoS™, a sorbent. DNA eluted from the sorbent with

ExtaGene E™ or pure water was directly used for further analysis. DNA extraction was performed according to the standard DNA extraction protocol using Diatom™ DNA Prep 200 reagent kit (Appendix 2).

§2.3. Statistical processing of the results of the study

The data obtained in the study were subjected to statistical processing on a personal computer using the Microsoft Office Excel-2021 software package, including the use of built-in functions of statistical processing. The methods of variation parametric and nonparametric statistics with calculation of the arithmetic mean of the studied index (M), standard error of the mean (m), relative values (frequency, %) were used. Statistical significance of the obtained measurements when comparing mean values was determined by Student's criterion (t) with calculation of the probability of error (P) when checking the normality of distribution (by the kurtosis criterion) and equality of general dispersions (F - Fisher's criterion). The level of reliability $P<0.05$ was taken as statistically significant changes.

Categorical features were assessed by the nonparametric chi-square test ($\chi 2$).

Data on the prevalence of ICD were obtained from statistical reports of the State Statistics Committee of the Republic of Uzbekistan and the official website: //http: www.stat.uz.

Chapter III.

EPIDEMIOLOGICAL ANALYSIS OF RISK FACTORS FOR THE DEVELOPMENT OF UROLITHIASIS IN CHILDREN

§3.1. Epidemiological studies of the prevalence of urolithiasis in children in Samarkand province of the Republic of Uzbekistan

Epidemiological study involves in its basis the study and search for patterns of development and prevalence of any pathology, in this case urolithiasis in a particular area, region or country, taking into account the available features. Analytical epidemiology studies the relationship between the occurrence of the disease and any existing risk factors, with the possibility of their subsequent consideration and implementation of appropriate preventive and metaphylactic measures. Significant factors in the development of ICD are considered to be age and gender aspects, social status (occupation, family prosperous or problematic), climate and seasons, diet and food habits, drinking water (sources of water supply, quantitative and qualitative characteristics of water), the presence of genetic factors of predisposition to the development of ICD and many others, which are detected at the same time conducted epidemiological studies. At the same time, it is difficult to clearly identify a single factor that determines the occurrence of ICD, as the causative factors represent a rather complex interrelated complex.

Significant problems of disease occurrence have a connection with both endogenous factors, i.e. processes directly occurring in the body, and exogenous factors - environment, living and living conditions, social status, genetically determined components and others. Thus, a clear representation of the causal-pathological, pathogenetic links of the disease, knowledge of the mechanisms of environmental factors, assessment of adaptive capabilities, individual approach will reveal the prospects and possibilities of risk factors assessment, their specific weight for subsequent prospective development of effective therapeutic and preventive measures, which are of direct importance for a certain region, in this work - Samarkand region and its districts.

§ 3.1.1. Geo-economic characterization of Uzbekistan

The assessment and epidemiological study of regional features involves a stage of medico-geographical studies:

at the first stage - characterisation of the region with its geographical location, economic components and current state today;

at the second stage - analytical assessment of medical and geographical components of risk factors with the assessment of population health, occurrence and prevalence of the main pathological conditions - diseases;

at the third stage - medical and sanitary assessment and search for causal risk factors for the development of ICD, with the aim of early detection of urolithiasis in children, and the development of an algorithm with subsequent personalised mashrutisation of patients.

Uzbekistan is a state located in the central part of Central Asia with an area of 448,924 km². The population, according to the estimates of the State Statistics Committee as of 1 December 2022, is 36,006,008 people, which increased by 2.1 per cent compared to the previous year. The number of women increased by 346,600 (2.0 per cent) and men by 365,700 (2.1 per cent), respectively, and it should be noted that about half of them live in rural areas.

The number of births in the Republic of Uzbekistan in 2021 increased by 63.4 thousand people or, compared to 2020, by 7.5 per cent; the number of deaths decreased by 1.1 thousand people, which, compared to 2020, decreased by 0.6 per cent.

The number of registered marriages increased by 8.3 thousand people or, compared to 2020, by 2.8%; and the number of divorces increased by 11.0 thousand people or by 39.0%, which means that the number of single-parent families increased, which may also be one of the risk factors for the development of the disease [https://www.unfpa.org/data/world-population-dashboard].

The country is divided into 14 administrative units: 12 provinces (Viloyats), one autonomous republic (Karakalpakstan, in the north-west of the country) and one administrative city, the capital Tashkent.

Life expectancy at birth, according to official statistics, is 70.7 years for men and 75.5 years for women. However, according to World Bank estimates, these figures are lower - for men life expectancy at birth is 64.8 years and for women life expectancy is 71.5 years. This discrepancy is due to a number of factors, in particular, underreporting of infant mortality, as well as differences in definitions, methodology and sources (World Bank estimates are based on survey data).

As of 1 January 2022, the population of the Republic was 78.6 persons per km2, which is 1.6 persons more than in the same period of 2021 (77.0 persons per km2 at the beginning of

2021). A special situation should be noted by regions of the Republic. Thus, in terms of regions, the highest population density is determined in Tashkent city, which is 8035.1 people; in Andijan region - 756.6; Fergana region - 576.4; Namangan region - 394.0; Samarkand region - 240.4. The lowest indicators were recorded in Kashkadarya region - 119.3; Jizzak region - 68.1; Navoi region - 9.3; Bukhara region - 49.1 and the Republic of Karakalpakstan - 11.7.

That is, if we analyse the situation Samarkand after Fergana, Namangan, Andijan valleys, stands on the 2nd place in terms of population density, which is also one of the unfavourable factors for the development of various pathologies.

Throughout the Republic, 905.2 thousand children were registered, with a birth rate of 25.90/000 (per 1000 population), which increased by 1.30/000 compared to the period of 2020 (for 2020 - 24.60/000).

For the same period, the analysis of the number of deaths showed that it was 174.5 thousand for the country, the mortality rate per 1000 population was 5.00/000, for January-December 2020 it was 5.10/000.

After Tashkent city, regionally Samarkand region also leads in the number of deaths, which also indicates the presence of risk factors for the development of diseases of various genesis, which requires epidemiological study and control. The number of deaths in Samarkand region was 18.9 thousand people.

A stepwise study from the point of view of epidemiology must necessarily take into account the geographical features of the region, a section that belongs to descriptive epidemiology. Thus, the territory of Uzbekistan is one of the flat countries of Central Asia, as 4/5 of its area is represented by plains, and in the extreme east - by mountains. The main water basins of the country are the Central Asian rivers: the Amu Darya and the Syr Darya. Territorially Uzbekistan can be divided into 3 parts: mountainous and foothill areas, semi-deserts and deserts, foothill plains, the total area of which is no more than 25% of the total, where the main population lives and large industrial cities with developed infrastructure - Tashkent, Samarkand, Bukhara, Fergana and other smaller ones - operate. 2/3 of the territory of Uzbekistan is represented by semi-deserts and deserts - the central part is occupied by the Kyzylkum desert, with the Amu Darya and Syr Darya rivers in between. This also has a certain significance in terms of the development and prevalence of various diseases, as the climatic conditions in this territory are quite complex - dry and hot in summer and cold in winter. In terms of climatic peculiarities, the territory of Uzbekistan has a hot, dry, sharply continental climate, i.e. rapid change of hot air with cold air, with sharp temperature changes.

This is due to the absence of oceans and other bodies of water that would affect the climatic features of the territory of Uzbekistan. Thus, the average annual temperature fluctuates from $+9^0$C in the north to $+16^0$C in the south, soil temperature reaches $+60^0$C and above, and in the desert zone - up to $+80^0$C, air humidity is low - on average it decreases to 20-30%. The annual solar energy input averages 100-200 thousand calories per 1 cm^2 of horizontal area, which is 2-3 times more than in Moscow, St. Petersburg and Crimea. Available regional geographical and climatic conditions and peculiarities, with different characteristics of natural-climatic zones should be taken into account in epidemiological studies.

§ 3.1.2. Geo-economic characterisation of Samarkand region

The city of Samarkand is located in the heart of the Central Zone of Uzbekistan, at the junction of historical routes and modern railway, road and air connections. Occupying a favourable economic and geographical position, it developed intensively, forming as the centre of the whole region - the Zarafshan river basin.

Samarkand oblast is located in the middle part of the Zarafshan river basin, the Zarafshan catchment basin within Samarkand oblast is a large-sized tectonic depression with surrounding mountain ranges, in the axis of which the river valley is laid, to the north stretches the spurs of the Turkestan range, the southern part of which is continued to the west by the Zarafshan range [21].

In the present study, which is devoted to the study of the epidemiological features of USD, it should be noted that a particular importance in the development of this disease, plays a disturbance in the system of geo-ecological biocenosis and water resources.

Proceeding from the set tasks the study of analytical reports, which are engaged in analysis and research of natural resources, geo-economy, climatic and water sources, was carried out. So, according to the data of analytical reports at present the state of natural resources of Samarkand region is subject to the influence of various factors that have a direct role in the formation of diseases: the chemical composition and properties of soils, climatic features, the presence of large industrial facilities, water resources. Climatic features of the region create a background that determines the balance of heat and moisture, influencing the formation of soils, vegetation and chemical composition of natural water sources. Climate - sharply continental, average annual air temperature - 12,90C - 140C. The coldest month is January, with minimum temperature up to minus 90C, the hottest month is July - temperature - 40-420C, annual precipitation - no more than 204-414 mm, soil composition is hydrocarbonate-sulphate, the soil is slightly saline.

Analysis of the hydrochemical regime of the Zarafshan River in the zone of melt water formation depends on the quality of water entering the river, groundwater and surface water [1]. The Zarafshan River in Uzbekistan crosses Samarkand, Navoi and Bukhara provinces (Figure 3.1). Since some districts of neighbouring provinces (Kasan, Mubarek, Jizzak) also use the waters of the Zarafshan River, it is worth mentioning the boundaries of the provinces through which the Zarafshan River flows. Samarkand province is located in the Zarafshan River basin, in the central part of Uzbekistan. In the north it borders with Nurata district of Navoi province; in the north-west - with Khatyrchi and Karmanan districts of Navoi province; in the west it borders with Kyzylteppa district of Navoi province; in the south has borders with Kashkadarya oblast, in particular with Kasan, Mubarek, Kitab and Chirakchi districts; in the east with Penjikent district of Sughd oblast of the Republic of Tajikistan; in the north-east has borders with Jizzak oblast (Bakhmal, Galliaaral and Farish districts).

Figure 3.1. Map of the Zarafshan River basin

The Zarafshan River originates in Tajikistan from the Zarafshan Glacier, at the confluence of Mount Koksu at the intersection of the Turkestan and Zarafshan Ranges, at an altitude of about 2,800 metres. The length of the river is more than 870 kilometres. The highest water consumption is in July (250-690 m3/s) and the lowest in March (28-60 m3/s) [96, p.17-26]. For effective utilisation of water from the Zarafshan River. Zarafshan was built a number of hydrosystems and such reservoirs as Kattakurgan and Kuyimazar [1]. Zarafshan is connected with the Kashkadarya River through the Eski Ankhor canal and with the Sanzar River through the Iskituyatartar canal.

Analysis of groundwater quality data conducted by the Institute of Hydrogeology in Samarkand, Navoi and Bukhara regions for the Zarafshan river basin revealed that in Samarkand region groundwater mineralisation ranges from 0.118 to 1.032 g/l, i.e. the water is suitable for supplying drinking water to the population of the region. In Navoi oblast, groundwater quality is not suitable for drinking water due to high salinity; the highest salinity is observed at the tailing pond of GMZ-1 (hydrometallurgical plant) and sedimentary layer of Navoiazot JSC, where water salinity reaches 4 MPC (maximum permissible concentration); groundwater salinity reaches 4.2 MPC in Bukhara oblast. The chemical composition of water is mainly sulphate-chloride, which is not suitable for drinking water supply in terms of total mineralisation and hardness [104, p.17-26].

In Samarkand province, the use of river water for irrigation during one year is 2.4-2.5 km3. According to the Ministry of Water Resources and Agriculture, the volume of collector-drainage and wastewater discharges in 2002 was 1.23 km3; in 2003 - 1.46 km3; and in 2004 - 1.50 km3. - 1.50 km3. [104, p.17-26]. This indicates an annual increase in wastewater discharge and pollution, with people being the main consumers of these resources. As is known, industrial wastewater (waste, etc.), which is intended for injection into underground formations, usually contains dissolved minerals and salts, organic compounds, mechanical impurities and pathogenic organisms (bacteria).

Assessment of surface water quality showed that in the analytical review of the data obtained, the use of water of the Zarafshan River should be viewed in the dynamics of pollution, as it affects the quality of water in the river [85, p.2988-95]. Dynamics of water pollution along the Zarafshan River channel by oil products is shown in Figure 3.2.

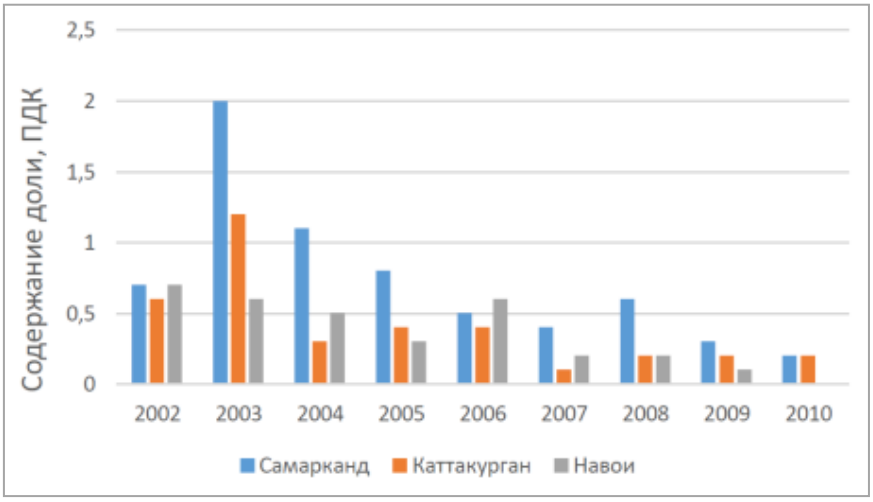

Figure 3.2. Dynamics of water pollution along the Zarafshan river channel

As can be seen from Figure 3.2 and according to the analysis of the Samarkand oblast reporting, the level of oil pollution of Zarafshan river water was earlier, in 2003-2004, much higher, but by now the dynamics of reduction has been determined. Nevertheless, the level of phenol in samples taken below the city of Samarkand remains 1.2-2 times higher than the MAC. In general, pollution of river water with oil products is relatively stable and regular, but sometimes can increase significantly.

Over the last twelve years the situation has changed, but not for the better. Thus, the quality of surface water in the area of the Kattakurgan reservoir does not meet the requirements, as there is pollution from the Anzob mining and processing plant, which discharges into the Zarafshan effluent containing antimony and mercury compounds (background antimony content is 0.4-0.02 mg/kg) [30, p.109, 112, 114; 33, p.25-30]. The ingestion of antimony in food and water resources can lead to various pathological health conditions, especially in children.

Environmental factors, such as the presence of heavy metal salts in wastewater at high MAC, may have a prenatal influence on the incidence and severity of USD, as they cause the development of immune abnormalities, zinc deficiency, maternal diabetes on the background of increased stress, toxins and parental age. There is now a high level of evidence supporting the association between many prenatal environmental factors and the increased incidence of USD.

Toxic metals are among the likely environmental factors that may contribute to the development of ICD both intrauterine and postnatally. This likelihood appears to be increasing due to the worldwide trend towards industrialisation and the consequent increase in human exposure to toxic metals. There are multiple sources of toxic metals in different areas depending on the industrial activities. The major sources of toxic metal inputs are air, soil, plants, water and sewage sludge. In addition, as shown by the literature data reviewed, materials associated with primary sources can also be contaminated with toxic metals [146, p.562-577].

Numerous reports mention technogenic pollution of natural resources with oil products, which are carcinogenic and promote mutations in the body, with subsequent development of pathological conditions in the body, including USD.

This is confirmed by studies conducted by the staff of HydroINGEO, according to the reports of which in the water of the Zarafshan River in Samarkand the content of phenol is 0.6 MAC, oil products - 1.0 MAC, chromium - 1.5 MAC, copper - 2.0 MAC, nitrate nitrogen - 2.5 MAC [104, p.17-26].

Thus, the analysis of reports conducted by experts on the study of natural and water sources [9; 18, p.38-49] shows the presence of harmful substances and impurities in ground and

surface waters, which are associated with human activity, the work of various enterprises of chemical, timber and oil refining industries.

Changes in climate and water availability, socio-economic aspects have a significant impact on the overall health of the population. The global ecological drop in the level of the Aral Sea and salinisation of its waters have led to an increase in the amplitude of annual water temperature fluctuations and a shift in the temperature regime, which have contributed to a decrease in the quality of the living environment and deterioration of socio-economic conditions [31, p.79-111].

Thus, the health of the population is primarily significantly affected by the use of drinking water with excessive salt content, presence of toxic chemicals; dust storms, which year after year become a common phenomenon. Such climatic changes have led to various demographic processes and affected the state of health of the population, which subsequently caused an increase in migration of the population to more decent working and living conditions.

§ 3.2. Demographic indicators for Samarkand province

The population of Samarkand region according to the State Statistics Committee for 2022 is 4,033,300 people, of which: urban - 1,483.1; rural - 2,548.2 thousand people; population density - 240.3 people/km². Statistical data for the last 10 years revealed that the population has tended to increase. Starting from 2013 it was 3,380,900 with predominance of rural population and increasing density, which was 201.6 people/km². The area of Samarkand region is 16,770 km². The region consists of 14 districts (tumans) and 4 cities of regional subordination. The largest cities are Samarkand, Aktash, Juma, Kattakurgan and Urgut. In the structure of the balance of the territory, a significant share - 51.8% of the total area - is made up of non-settlement territories occupied by external transport, Afrosiab archaeological reserve, industrial enterprises, special territories, etc. Residential areas occupy an area of 42.57%.

Housing construction and further urban development of the city require an increase of the city area by 4,841 ha. Samarkand has large industrial enterprises of machine-building, chemical and light industries, as well as enterprises of construction materials and structures. A number of enterprises are the only ones in the republic. The city has a significant number of joint ventures with foreign partners, such as ‘Uzbat’. ‘SamAvto’, “Samarkand-Praga”, “Samarkand-California”, tomato plant “Chele-Baltimore”, “Singapore-Samarkand” and others.

The analysis of the current state of the environment presented in the paper shows that the environmental situation on the territory of the city is characterised as tense, which is explained by both natural and anthropogenic factors. The natural conditions contributing to the adverse

situation include: various engineering and geological processes (erosion, gullies, landslides, dumps, suffosion, destruction of banks, increase in the planting of soils); high level of groundwater table, waterlogging, waterlogging and salinisation of the territory; aridity, stagnant phenomena in the vital layer of the atmosphere.

Anthropogenic factors include: low level of sanitary cleaning of the city, lack of an equipped city rubbish dump; construction of ravines, cutting of slopes, increased load on slopes (vibration, etc.); unregulated surface runoff, insufficient coverage of the population by centralised sewerage (63%), lack of water protection zones of collectors and canals, high level of surface water pollution, poor condition of water intakes and lack of sanitary protection zones, low level of landscaping (3 m2/person).

Sources of atmospheric air pollution are industrial and communal facilities, motor transport, airport. Most of the enterprises are located in the western and northern parts of the city, many of them have no sanitary protection zone, are surrounded by residential buildings and are located near architectural monuments. The Samarkand airport, which occupies an area of 225 hectares directly adjacent to the residential part of the city in violation of urban planning norms, poses a major problem, creating uncomfortable conditions for the population. The high level of air pollution is also formed by mobile sources. The impact on the atmospheric air is aggravated by the emissions of transit flows of motor vehicles, which account for 92.5% of the total amount of pollutant emissions into the atmosphere.

To ensure a safe and clean environment of the city and reduce the level of anthropogenic loads, it is necessary to carry out engineering, urban planning and environmental protection measures. These include: protection of the territory from dangerous exogenous processes (clearing and reconstruction of watercourse beds, drainage and irrigation systems, terracing and strengthening of landslide-prone areas and ravines, etc.).); organisation of water protection zones of rivers and canals; sanitary cleaning of the territory, reconstruction of the city road and transport system, redistribution of traffic flows, re-profiling or removal of 33 industrial and motor transport facilities that have a negative impact on the health of the population. Reduction of air pollution is forecasted as a result of reconstruction of the transport system and urban planning measures, including closure and re-profiling of industrial, motor transport and warehouse facilities on the territory of 172.5 ha, located in densely populated areas and near architectural monuments. Reduction of surface water pollution level is envisaged through closure of industrial facilities discharging untreated wastewater (leather factory, leather raw materials plant of ‘Alpamysh’, etc.) and construction of treatment facilities. Vertical and horizontal drainage is designed to reduce groundwater level.

According to the World Health Organisation (WHO), socio-economic and environmental conditions, such as housing, employment, health care, water quality and so on, influence the health of the population.

According to WHO, a quarter of all existing diseases develop as a result of environmental influences. WHO identifies the main diseases, the appearance of which is associated with poor ecology and unfavourable climate: these are diseases of the upper respiratory tract (URT), blood, gastrointestinal (GI) and urinary tract (UT), endocrine system (ES), immunological. The analysis of epidemiological situation of Samarkand city. Samarkand and its regional centres, which showed the existing environmental and epidemiological problems influencing the development of USD. Accordingly, the possible ways of their overcoming are defined, which are of recommendatory character and are justified on the data of numerous literature sources, as well as the available studies conducted earlier, in order to search for causal risk factors of USD development, especially in children.

§ 3.3. Epidemiological analysis of the general morbidity of children (1-14 years) and adolescents (15-17 years) in Uzbekistan regionally and in Samarkand province

According to the State Statistics Committee of the Republic of Uzbekistan, the total population of Samarkand province (as of 1 July 2022) was 4,069.3 thousand people, of whom: women - 2,021.4 thousand people and men - 2,047.9 thousand people. There were 1,496,900 people living in urban areas and 2,572,400 in rural areas. The number of births was 49.9 thousand; the number of deaths was 8.9 thousand; the number of marriages concluded during this period was 11.5 thousand, while the number of divorces was 2.6 thousand. As for the problem of population movement (migration) - the total number of departures was 4.7 thousand people, arrivals - 7.6 thousand people.

An analysis of statistics among the child population has shown that the incidence of morbidity among children aged 1 to 14 years in the Republic of Uzbekistan for the period from 2015 to 2020 was in 2015. - 5376,1; 2016 г. - 5647,0; 2017 г. - 5478,2; 2018 г. - 5105.6; 2019 - 5030.9; 2020. - 4767.8 thousand cases. By the main classes of diseases the leading places were occupied by diseases of respiratory organs, diseases of digestive organs, blood, hematopoietic organs, injuries, poisonings, infectious and parasitic diseases, endocrine pathology, diseases of urogenital system.

According to the latest statistics, the morbidity of children (1-14 years old) with pathology of the urogenital system was in 2015. - 186,3; 2016 г. - 194.1; 2017 - 186.5; 2018. -

175.6; 2019 - 175.8; 2020. - 172.4 thousand cases; incidence rate per 100 thousand children: 2015. - 2104,0; 2016 г. - 2142,5; 2017 г. - 2015,6; 2018 г. - 1853.7; 2019 - 1805.8; 2020. - 1720.0 (Figure 3.3).

In Samarkand oblast, the incidence of childhood morbidity (1-14 years) for the period from 2015 to 2020 was: 2015 - 539.7; 2016 - 556.4; 2017 - 479.2; 2018 - 495.7; 2019 - 530.5; 2020 - 439.3 thousand cases. In terms of dynamics, the total number of cases has slightly decreased between 2015 and 2020. Per 100,000 children, the figures were: 2015 - 51,015; 2016 - 5,135.4; 2017 - 43,208.8; 2018 - 43,491.3; 2019 - 45,125.7; 2020 - 36,301.3. The incidence of adolescents aged 15-17 years in Uzbekistan for the period 2015-2020 was 1378.9 in 2015; 1469.8 in 2016; 1329.9 in 2017; 1247.8 in 2018; 1836.9 in 2019; and 1637.9 in 2020. Per 100,000 adolescents, the incidence rates were: 85499.5 in 2015; 94315.6 in 2016; 86526.7 in 2017; 81799.1 in 2018; 119816.1 in 2019; 105697.9 in 2020.

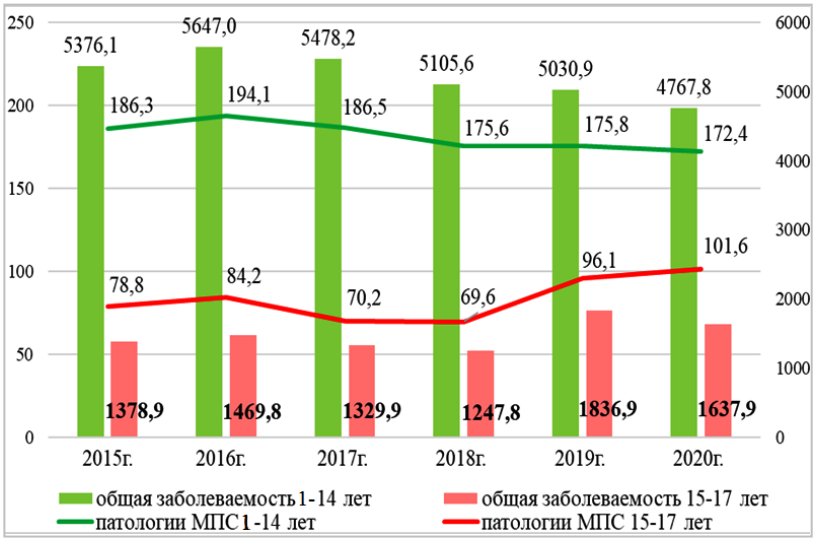

Figure 3.3. Total morbidity of children and adolescents versus diseases of the genitourinary system in the Republic of Uzbekistan (thousand cases)

According to statistics, the morbidity rate of adolescents (15-17 years old) with pathology of the urogenital system in the Republic of Uzbekistan was: 2015 г. - 78,8; 2016 г. - 84.2; 2017 - 70.2; 2018. - 69.6; 2019 -96.1; 2020. - 101.6 thousand cases; incidence rate per 100 thousand adolescents: 2015. - 4887,7; 2016 г. - 5400,2; 2017 г. - 4564,6; 2018 г. - 4563.4; 2019 - 6268.3, 2020. - 6557,6.

For Samarkand region, the incidence of adolescents (15-17 years old) for the period from 2015 to 2020 was: 2015 г. - 170,9; 2016 г. - 177,3; 2017 г. - 132.4; 2018 - 134.0; 2019 - 116.9; 2020. - 135.5 thousand cases. The incidence per 100,000 adolescents for these periods was:

2015 г. - 90030,5; 2016 г. - 96408,5; 2017 г. - 72172,1; 2018 г. - 73297.8; 2019 - 63742.5; 2020. - 73558.5 (Figure 3.4).

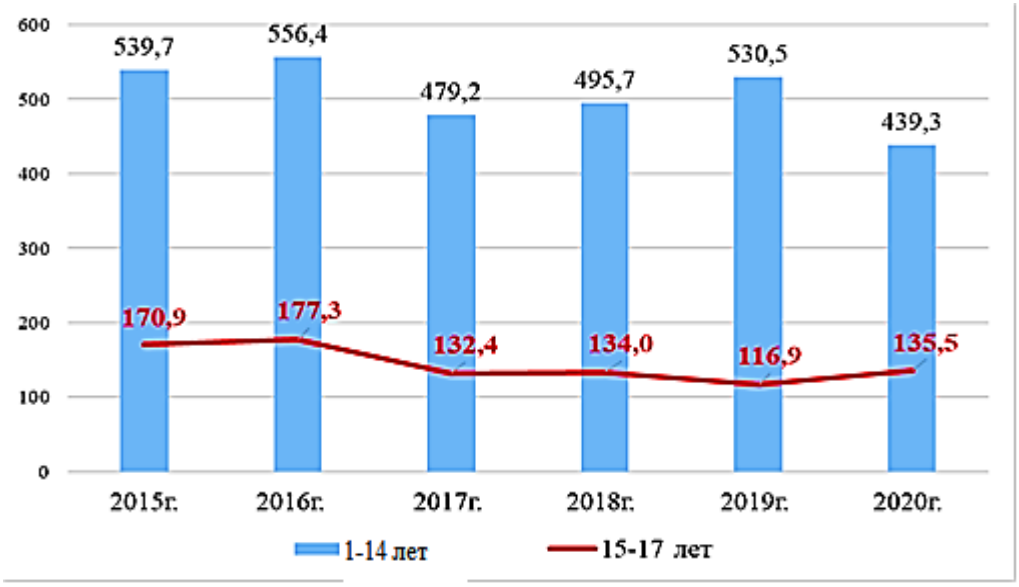

Figure 3.4. Morbidity among children and adolescents in Samarkand province (thousand cases)

In Uzbekistan as a whole, the structure of morbidity in 2020 was as follows: respiratory diseases ranked first (29.8 per cent), digestive diseases second (13.9 per cent), injuries and poisonings third (6.8 per cent) and genitourinary diseases fourth.

As can be seen from the analysis, the problem of morbidity among children and adolescents both in Uzbekistan and in Samarkand province, including diseases of the urogenital system, is an urgent one and requires large-scale epidemiological studies to examine it in the population.

Analyses of morbidity rates for the past 2020 by region for children aged 1 to 14 years have shown considerable variability. Thus, in Uzbekistan as a whole, morbidity rates tend to decrease, while they remain high in Tashkent city, Andijan, Fergana, Tashkent, Kashkadarya, Samarkand provinces and the Republic of Uzbekistan.

Observations of morbidity indicators in dynamics by years allow to note both their increase and decrease in different periods of the study. This indicates that there are regional peculiarities of certain risk factors observed in each region, including ICD morbidity, which are directly related to climatic, medical and geographical features of the territory and regions of the Republic of Uzbekistan.

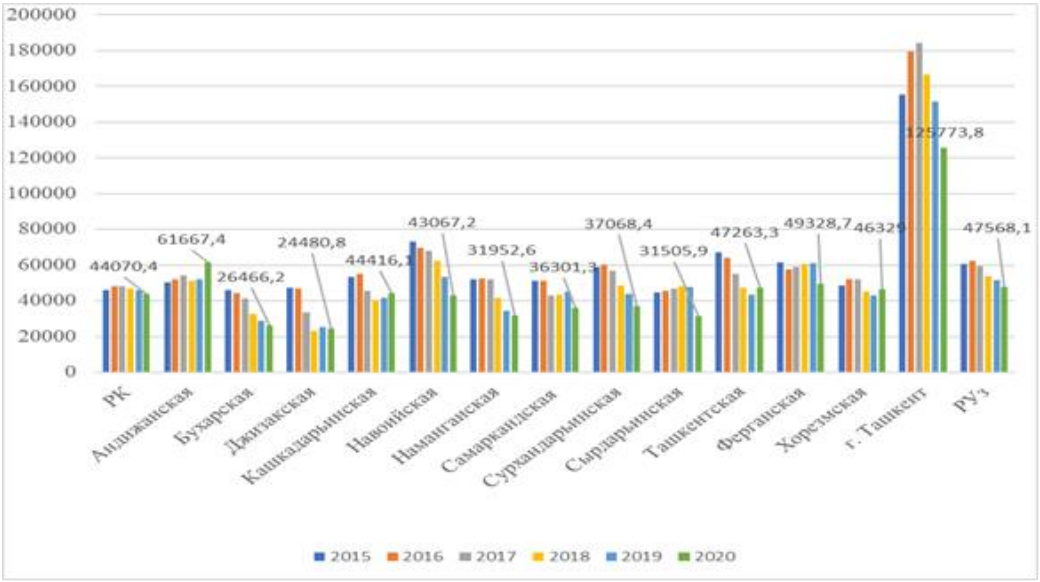

Figure 3.5. Dynamics of morbidity rate for 2015-2020 among the child population of the Republic of Uzbekistan and by region

Samarkand region needs special attention in terms of consideration of existing anthropogenic problems, for the possibility of making management decisions on the part of subordinate organisations and the Ministry of Health, in order to address the issues of prevention and metaphylaxis of urolithiasis, as well as the problems of the current environmental situation, pollution of water and land resources, transport routes, etc.

§ 3.4. Клинико-эпидемиологический анализ результатов исследования детей с мочекаменной болезнью

To present the situation about the prevalence of ICD in children in Samarkand region, the analysis of data on referral for the period from 2012-2019 to the Samarkand Specialised Children's Surgical Clinic of SamSMU was conducted. The study group comprised 652 patients. The analysis of patients' length of stay in hospital showed that the total length of stay ranged from 2 to 28 days (average 13.59±0.11 days). The anthropometric data studied showed that the patients' height ranged from 69 to 170 cm (mean height 122.3±0.3 cm) and body weight ranged from 8.5 to 71 kg (mean weight 26.01±0.1 kg). BMI in our observed patients ranged from 15.3

to 46.1 kg/m2 (27.22±0.10 kg/m2). This index was 22.3 to 42.5 kg/m2 (27.08±0.11 kg/m2) in boys and 25.8 to 45.8 kg/m2 (27.49±0.19 kg/m2) in girls.

To conduct epidemiological studies, patients were distributed by region and place of residence - urban and rural residents, sex and age structure, clinical form, and localisation of urolithiasis.

Analysis of the distribution of children with urolithiasis (n=652) referred to this institution by region showed that the largest number of admissions was from Samarkand region - 73.92% (n=482). Somewhat fewer were from Kashkadarya Province - 13.65% (n=89), followed by patients from Jizzak Province - 4.75% (n=31), Navoi Province - 4.14% (n=27) and Surkhandarya Province - 3.07% (n=20) (Figure 3.6).

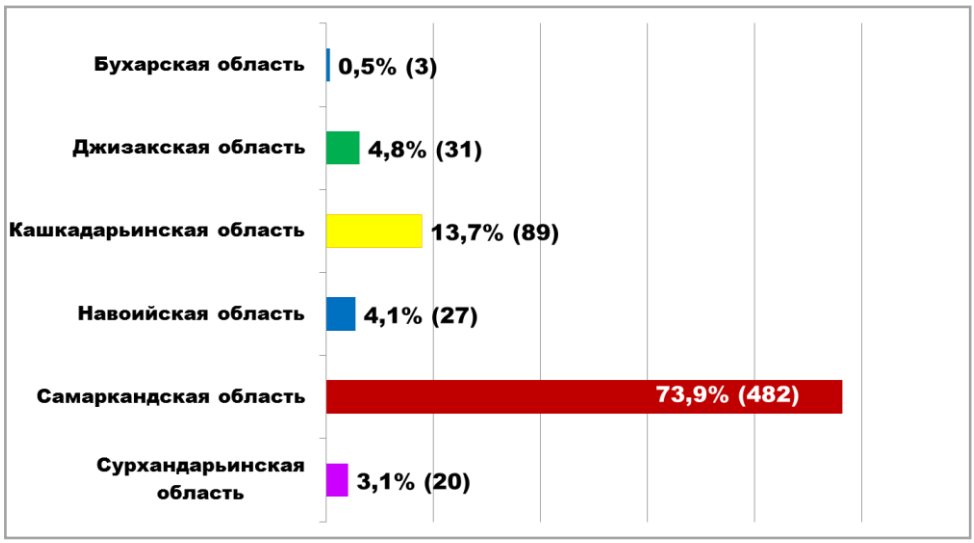

Figure 3.6. Distribution of patients with urolithiasis by regions of the Republic (by turnover)

The sex distribution of patients with USD was as follows: boys 67.33% (n=439) and girls 32.67% (n=213) were the highest, the M/D ratio was - 2.1:1.0 (Figure 3.7).

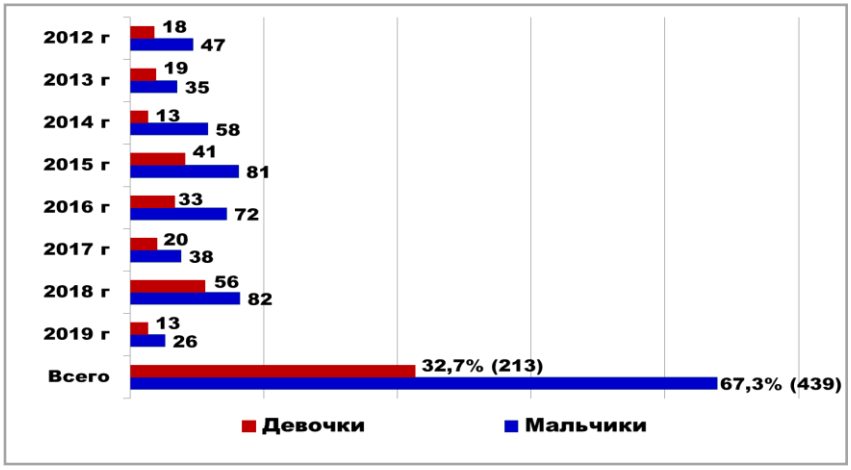

Figure 3.7. Distribution of patients by gender

By age, the study groups included children aged 1 to 17 years (n=652). The smallest number of children with ICD were in the group under 1 year of age, 2.8% (n=18); the largest number of children were between 1 and 9 years of age: 1-4 yrs. - 26.1% (n=170); 5-9 years - 41.5% (n=271); 10-14 years - 18.1% (n=118); 15-17 years - 11.5% (n=75). This indicates an early development of stone formation processes in the urinary tract (UTS) in children, which is also due to certain epidemiological risk factors (Fig. 3.8).

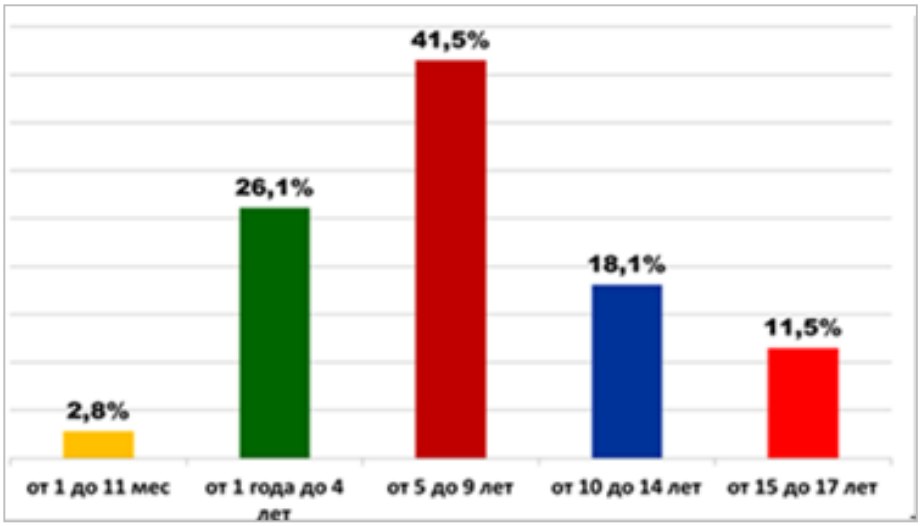

Рисунок 3.8. Распределение пациентов по возрасту

Next, the place of residence of the selected population for the study was studied, with a division by urban or rural population (Fig. 3.9). As can be seen from the diagram, the majority of those hospitalised were from rural areas - n=553 (84.82%), urban dwellers - n=99 (15.18%).

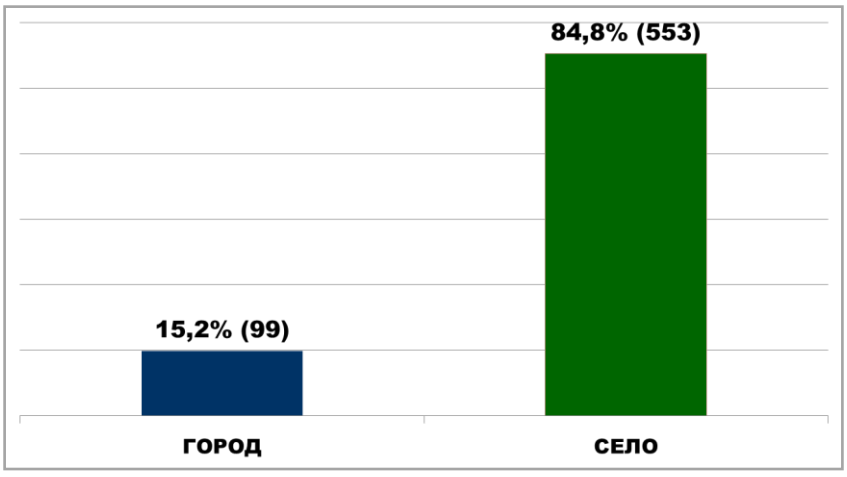

Figure 3.9. Distribution of patients by place of residence - city/village

As can be seen from the diagram (Fig. 3.10) on the prevalence of ICD directly in Samarkand region, the highest number of people who applied was in Urgut (28.01%),

Samarkand city (14.52%), Pastdargom (10.37%), Nurabad (6.22%) and Kattakurgan (6.02%) districts.

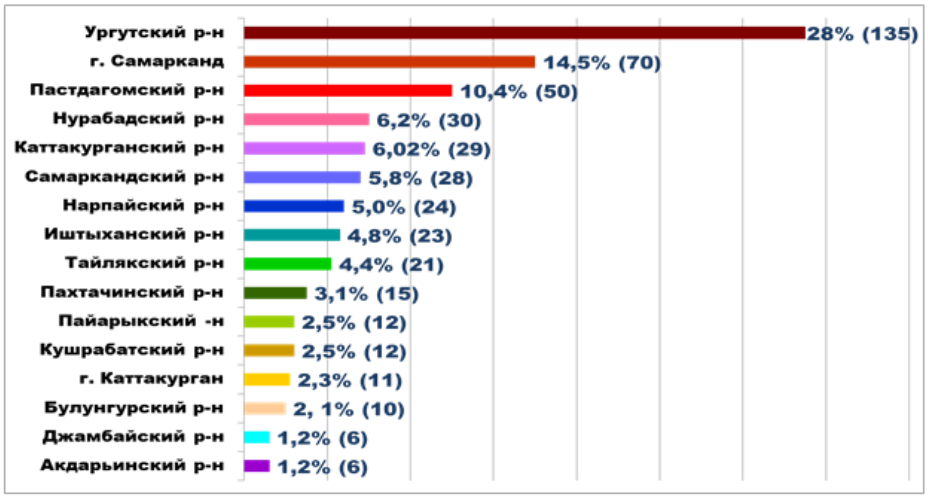

Figure 3.10. Distribution of patients by district of residence in Samarkand region

Taking into account that the largest number of people diagnosed with urolithiasis was in Urgut and Pastdargom districts, as well as in Samarkand city, it was decided to conduct epidemiological studies in these districts.

According to the results of the studies, urolithiasis was diagnosed in 3.5 per cent of residents of Urgut district, 4.5 per cent of residents of Samarkand city and 2.7 per cent of residents of Pastdargom district, or 35, 45 and 27 cases per 1,000 inhabitants, respectively. Boys predominated by sex, with a ratio of 2.1:1.0, i.e. the prevalence of urolithiasis was twice as high in boys as in girls. Among children in Samarkand city, the ratio was 1.8:1.2; in Pastdargom district - 2.1:1.5. Overall, children with USD in the 2 districts and Samarkand city accounted for 39.11% (n=255).

In order to study the prevalence of urolithiasis, such signs of the disease as kidney/ureter stones; presence of salt conglomerates in the kidneys; salt crystals in the urine sediment; anamnestic data that may indicate ICH; surgical interventions in the history or spontaneous removal of stones were taken into account. To determine the causative risk factors and prevalence of signs of urolithiasis, regional epidemiological studies were carried out based on the collection of information by means of a questionnaire. It studied socio-hygienic factors, data of objective examination, ultrasound findings, clinical and biochemical analyses, with their comparative evaluation.

In order to study the causal risk factors for the development of USD in children, a survey was conducted among residents of the above-mentioned regions, which revealed a higher

prevalence of the disease in the Samarkand region. Fluid volumes and types of drinks consumed were studied.

As can be seen from Figure 3.11, it was determined that the volume of liquid consumed by most patients in the study districts and Samarkand city was less than 1 litre per day, with 12.6% consuming tea and milk, and 87.4% consuming water, mainly tap water, in boiled or raw form.

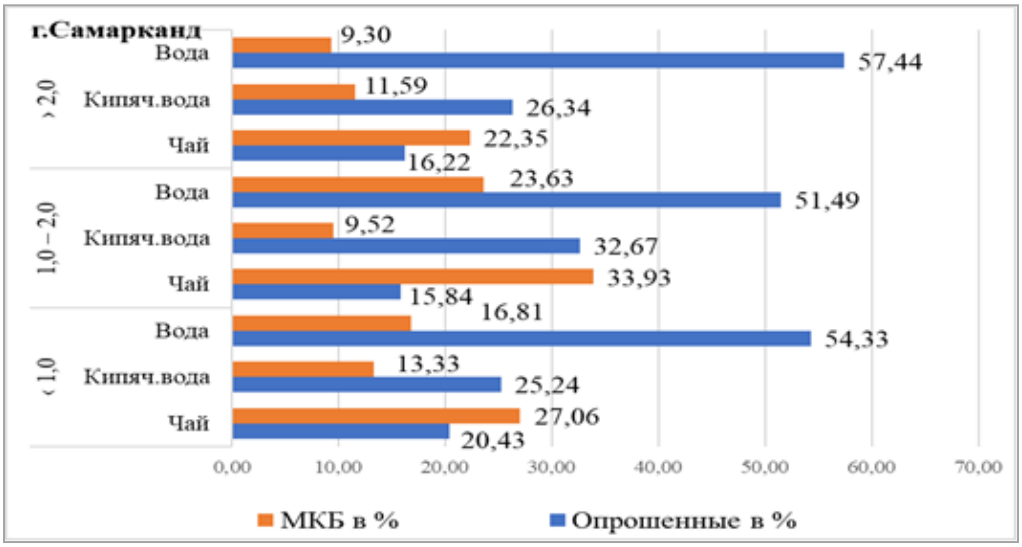

Figure 3.11. Study of volumes of consumed liquid, its types and occurrence of ICD in the interviewees in Samarkand city

In Samarkand city most of all tap water is consumed, which by volume is: less than 1 litre - 54.3%; 1.0-2.0 litres. - 51.5%; more than 2.0 litres. - 57.4%; boiled water was consumed by: 25.3% - less than 1 litre, 32.7% - 1.0-2.0 litres, 26.3% - more than 2.0 litres; tea - 20.4%, 15.8%, 16.2%, respectively.

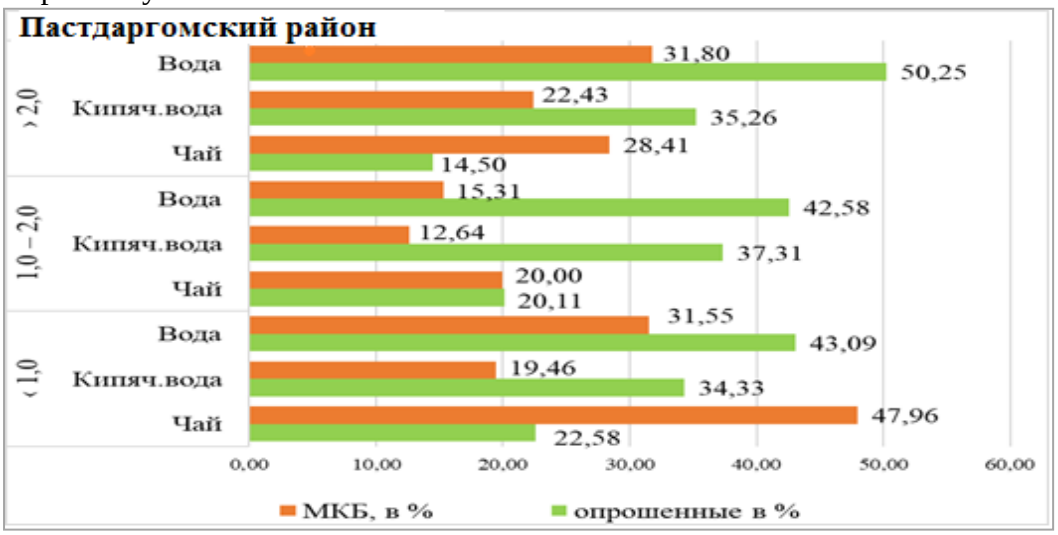

Figure 3.12. Study of fluid intake, types of fluid consumed and the occurrence of ICD in respondents in Pastdargoma district

In Pastdargom district by volume of water consumed, the situation is as follows: less than 1.0 litre. - 43,1%; 1,0-2,0 л. - 42.6%; more than 2.0 litres. - 50.3%; boiled water - 34.3% (1.0 litre); 37.3% (1.0-2.0 litres); 35.3% (more than 2.0 litres); tea - 22.6%; 20.1%; 14.5% respectively (Figure 3.12).

In Urgut district the most endemic for IBC incidence, the population consumed natural water the most, with less than 1.0 litres. - 59,8%; 1,0-2,0 л. - 28.3%; more than 2.0 litres. - 51.7%; boiled water, 20.9%; 23.4%; 13.2%; tea, 19.2%; 48.2%; 35.1%, respectively, in volumes of 1.0 litres; 1.0-2.0 litres; and more than 2.0 litres. (Fig.3.13).

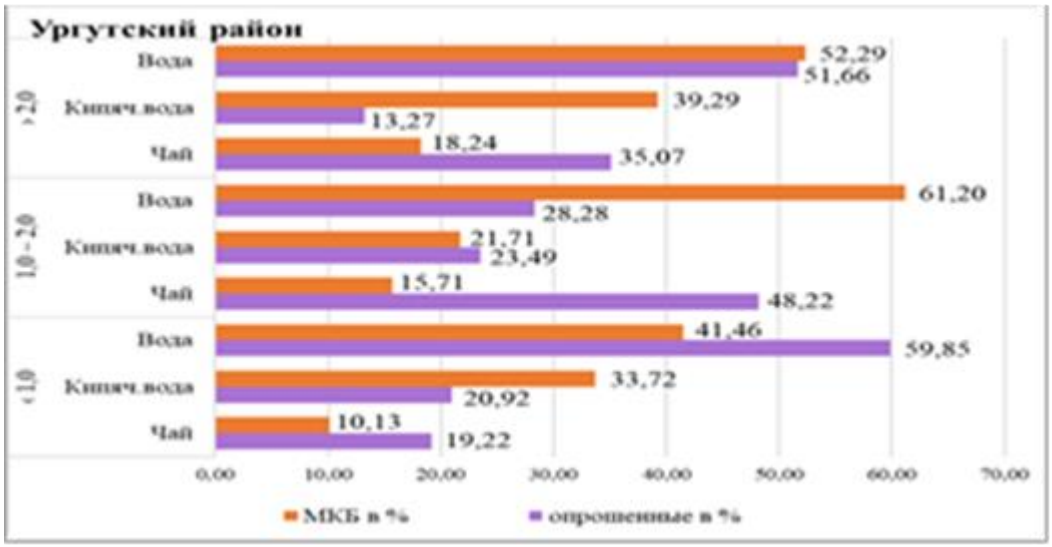

Figure 3.13. Study of fluid intake volumes, types of fluid consumed and occurrence of USD in the respondents in Urgut district

The analysis of studies conducted among the population of Samarkand region and 3 endemic areas on the prevalence of USD has shown the presence of such risk factors for the development of the disease as the use of small 1.0 litre volumes of liquids, as well as preference in the use of natural water and its boiling. Given the presence of various impurities in the water used by residents of the Samarkand region, we can assume their long-term cumulative effect. The presence of various substances in the composition of water, its increased salinity, high doses exceeding MPC of salts, heavy metals, mercury, cadmium, industrial waste from oil refineries, as well as existing corrosive changes in the soil, represent a serious problem that needs to be addressed on a global scale, not only in the case of already arisen disease, but also in the absence of changes in the health of the population. It becomes especially important in case of health disorders of children and adolescents - the future potential of our Republic.

According to literature data, by 2080 the number of population suffering from water deficit will increase by 16-44 million people. Water flows will decrease by up to 80 per cent during summer periods, leading to freshwater shortages and an increased risk of water pollution.

The condition of marine coastal waters is also threatened, posing a risk of infection during sea bathing and when consuming seafood. Access to safe sport and sanitation, which is already uneven across the region, may deteriorate further. In Central Asia, about 70 per cent of the total population has access to centralised water supply, but only 25 per cent in rural areas. This problem, in particular, is a factor in diarrhoea-related mortality - 13,500 deaths among children each year. Even in countries with adequate water supplies, water does not always meet WHO standards for its microbiological and chemical characteristics.

Ensuring water security is key to climate change adaptation. The implementation of international instruments such as the 'Protocol on Water and Health' will contribute to improved access to safe drinking water and sanitation and a corresponding reduction in the burden of disease and mortality. Necessary measures include disease surveillance and timely detection of outbreaks, vaccination, safe drinking water supply. Many water providers in the Region are already using WHO-recommended water safety plans that ensure safe drinking water from the source to the end user.

As can be seen from the charts below, the majority of patients in the study areas were diagnosed with USD. According to the data obtained, among the inhabitants of endemic districts who consumed the same drinks but in different volumes, there were dependences both on the volume of the consumed liquid and its type. In each of the neighbourhoods, advantages in the liquids consumed were identified. For example, where the amount consumed was less than 1 litre; or in larger volumes, but from natural water, without boiling. It is in these districts that a statistically significant increase in the number of people who became ill was observed, which is possibly explained by the impact of the risk factors mentioned earlier, such as the contamination of groundwater, which fulfils the main function of nourishing living beings, being considered a protected repository of quality water.

Because of its rapid availability and normal protection against microbial contamination, it is used as global key sources for ingestion, agricultural and industrial purposes in many countries [132, p.7898; 129, p.13706]. But, a variety of pollution factors such as climate change, excessive groundwater abstraction, surface water characteristics, subsurface geochemical reactions, geological location, characteristic precipitation and human activities are the main important factors directly or indirectly affecting its quantity and quality [105, p.736495]. Reports from a number of scientists indicate that groundwater can be contaminated with pathogenic viruses

penetrating through aquifer cracks [106, p.236-244], which, once in the body, can cause various diseases, including inflammatory diseases of the urinary system, which are one of the factors in the occurrence of USD. Groundwater pollution factors have a serious impact on human health due to their toxicity, persistence and carcinogenic risk in the environment [127, p.449-453; 138, p.104]. Consumption of unsafe water can contribute to various water-related diseases that affect millions of people - diarrhoea, cholera, typhoid and parasitic diseases [102, p.522]. It has been found that consumption of salt water can also lead to the risk of developing serious pathologies of the urinary system, as well as hypertension, skin diseases, infertility and others.

§ 3.5. Regional risk factors and early predictors of urolithiasis in children

The epidemiological study of the development of ICD involves studying the prevalence of kidney and urinary tract stones to determine the causative factors of the initial stages of stone formation (prelithiasis). Criteria for orpelation of signs of prelithiasis are ultrasound examination, where conglomerates of salts in the cavity of the calyx-lochanous system are visually identified, as well as the presence of crystalluria (oxaluria, uraturia, mixed crystalluria, etc.), determined by microscopy of urine sediments.

In children, the most common are disorders of metabolism of Ca and oxalate (the precursor is oxalic acid and vitamin C), which manifests itself as an increase in the excretion of these salts - hyperoxalaturia. In the formation of this type of crystalluria, the composition of the diet plays a major role. Increased excretion of urates or uric acid with urine - hyperuraturia is an endothelial ‘poison’ and leads to a decrease in the level of urokinase in the urine with inhibition of renal processes of fibrinolysis.

In hyperphosphaturia, the formation of sodium and potassium phosphate salts is rare. They are formed at any urine reaction and are characterised by the fact that these salts are well soluble. Increased excretion of phosphate salts, along with the alimentary factor, is aggravated by the layering of urinary tract infection caused by the microorganism Proteus mirabilis, which produces urease and significantly affects the reaction of urine by alkalising it.

Changes in urine tests are characterised by small leukocyturia (10-15 p/view) in the absence of bacteriuria, microhaematuria (up to 5-7 p/view), trace proteinuria, which may be transient. More permanent character is the detection of oxalate, urate or phosphate salts of varying degrees of severity in the general urine analysis. Renal function in prelithiasis remain intact. In the absence of adecate therapy, the disease may progress with the formation of signs of urolithiasis.

According to the data obtained in the studied groups, the signs of prelithiasis were topographically detected only in the kidney, both in the kidney and in the urine sediment, or only in the urine sediment. Renal ultrasound and microscopy of urine sediment were used in diagnostics of prelithiasis signs. In case of prelithiasis signs and detection of CS in urine sediment, their mineral belonging was determined by the type of crystals - calcium oxalate, calcium phosphate, uric acid and tripelphosphate crystals.

As shown by clinical and laboratory analysis, signs of prelithiasis were determined in 477 (23.0±0.6) inhabitants or 230 per 1000 population in Samarkand region; in Urgut district - 214 (24.7±0.8), 247 per 1000 population; in Pastdargom district - 106 (18.3±1.6) or 183 per 1000 population; in Samarkand city - 157 (19.7±1.1) or 197 per 1000 population. It should be noted that the indicator in Urgut district was reliable ($p<0.001$).

According to the topographic location of prelithiasis signs, the examined residents were divided into three groups: the first - CGS in kidneys; the second - CGS+CS in urine sediment; the third - only CS in urine sediment (Fig.3.14).

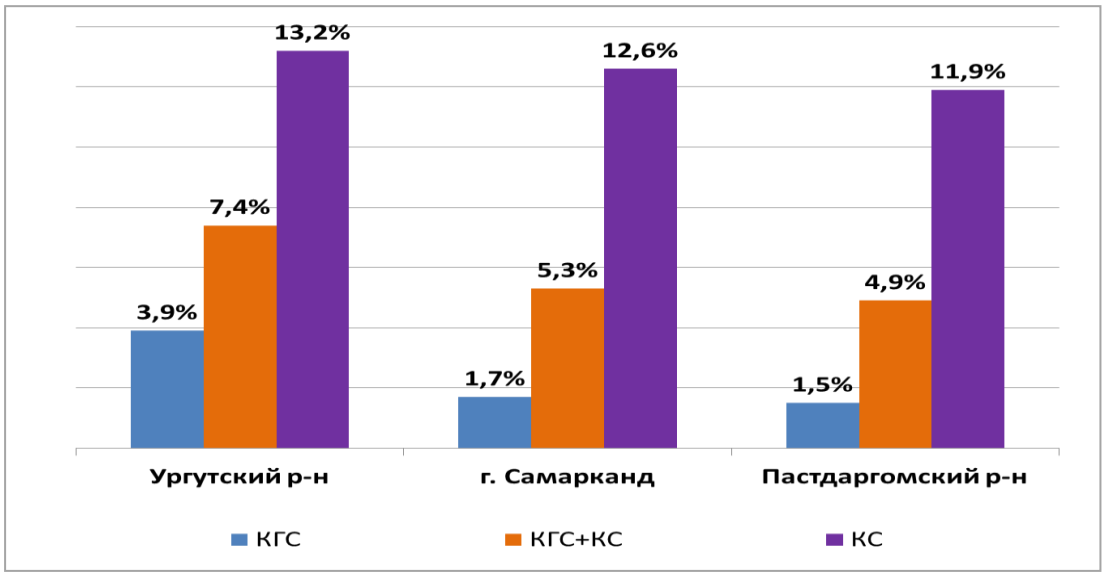

Figure 3.14. Prevalence of prelithiasis signs in the population of the study areas

Analysis of the obtained data showed that CGS was detected in the majority of residents of Urgut district - 3.9; least of all in Pastdargom district - 1.5; average values were detected in residents of Samarkand city - 1.7. The share of residents with CGS was 32 (2.4±0.2). The combination of CGS+CC was revealed in 155 (5,9±0,4), i.e. 59 per 1000 inhabitants of the investigated territories, so in Urgut district this combination of signs was determined in 57 (7,4±0,6), i.e. 74 per 1000 inhabitants; in Samarkand city - 51 (5,3±0,6), 53 per 1000 inhabitants and in Pastdargom district - 47 (4,9±0,7), 49 per 1000 inhabitants ($p<0,05$). The most frequently

determined signs of urolithiasis by CW type were 290 (12,5±0,4) patients, in rare 125 per 1000 population; at distribution by districts in Urgut - 145 (13,2±0,6); in Samarkand - 95 (12,6±0,8); Pastdargom - 50 (11,9±0,6) (p>0,05).

Summarising the obtained data we can conclude that in Urgut district prevalence of prelithiasis is significantly higher in comparison with Samarkand city and Pastdargom district. The analysis of the obtained data shows that prelithiasis is most often manifested by signs of CS in the urine residue, less often by CGS in the calyx-lochanous system, even less in combination of these two signs.

It is necessary to point out that this trend persists in all endemic areas for the development of urolithiasis in Samarkand region. Urgut district, Samarkand city, is the most widespread in terms of USD incidence; this is likely to be due to risk factors for its development, which were mentioned earlier in the previous subchapters when conducting epidemiological and geographic-economic characteristics of endemic districts of Samarkand region.

Conclusions of the chapter

Based on the results obtained on the study of epidemiological features of IBC prevalence in Samarkand region, it can be stated that territorial features, urbanisation, presence of large industrial facilities, a large number of emissions both into the atmosphere and groundwater sources are bioecological factors in the development of urolithiasis.

The analysis of the data obtained during the study shows that prelithiasis is most often manifested by signs of CS in the urine residue, less often by CGS in the calyx-lochanous system, even less in the combination of these two signs. It should be noted that this tendency is maintained in all endemic areas for USD development in Samarkand region, which, as studies have shown, are Urgut district and Samarkand city.

Chapter IV. CLINICAL AND EPIDEMIOLOGICAL AND IMMUNOGENETIC MECHANISMS OF UROLITHIASIS IN CHILDREN

§ 4.1. Clinical and epidemiological assessment of the morbidity of urolithiasis of children in the Samarkand region

In the process of epidemiological assessment of USD morbidity in the context of districts of Samarkand region, 200 patients were divided into 2 groups: main group - 100 sick children diagnosed with USD; control group - 100 children without urolithiasis. At the next stage the qualitative and quantitative composition of crystals was analysed by laboratory-diagnostic study

of urine sediment. Then the character of the course of urolithiasis in children of different age groups was analysed.

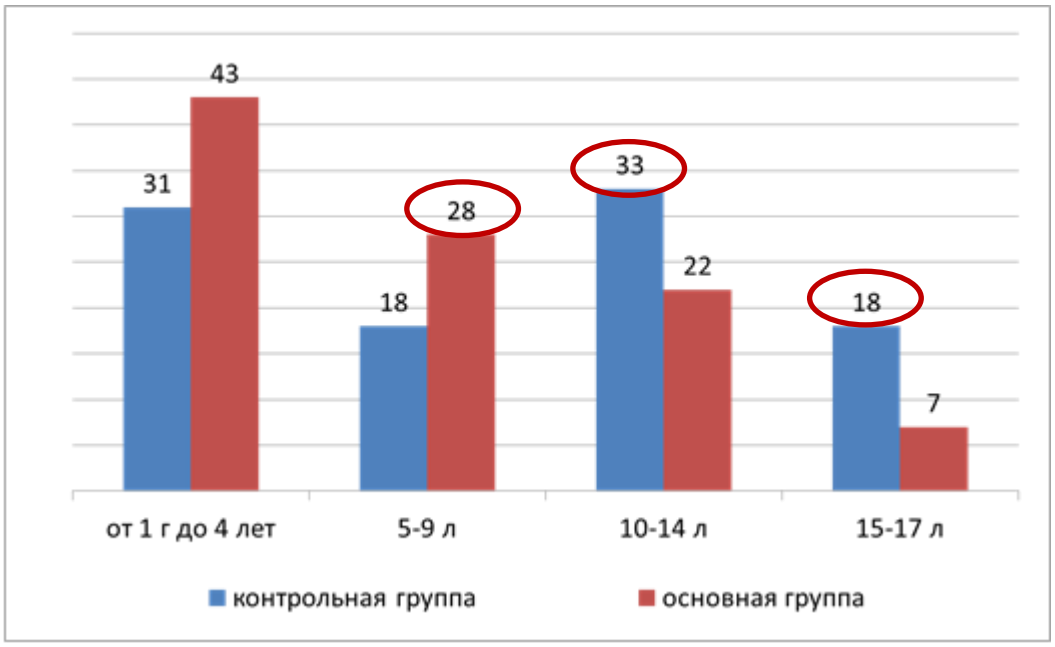

Figure 4.1. Distribution of patients according to age

The age distribution of patients in both study groups is presented in Figure 4.1. The analysis of ICD incidence rate in the main group depending on age showed that school-age patients prevailed among children with diagnosed urolithiasis in more than half of observations - n=57 (57%). This is due to the fact that this is the age when metabolic disorders associated with the transition of children to general nutrition, non-compliance with drinking regime, activation of metabolic processes due to the peak of hormonal activity are most often manifested. Since in the younger age group nutrition remains relatively rational, metabolic changes are manifested to a lesser extent.

Along with this, in the development of urolithiasis in children there is also activation of hereditary predisposition and the impact of existing risk factors.

According to the data obtained by analysing the sex distribution of ICH patients, boys accounted for 67.2% of children, girls for 32.8%, and their sex ratio was 2.1:1.0, which is due to the anatomical features of the urogenital system in males (Fig. 4.2).

Figure 4.2. Distribution of children with ICD by sex

Having analysed the obtained results of questionnaire survey of patients with ICD (n=100) it was revealed that in one third of cases (33%) the detection of urolithiasis in school-age children was noted during preventive examination, somewhat less frequently during medical examination of children - in 10%, while in 24% of patients the disease was diagnosed due to initially detected irregularities in urine tests and subsequent in-depth examination.

It is worth noting that clinical manifestations of ICH, such as pain, dysuria, haematuria, and increased body temperature, were detected in only 7% of children, while in the remaining cases the diagnosis of urolithiasis was detected during treatment and ultrasound and clinical and biochemical examinations or was an incidental finding - 26% (Fig. 4.3).

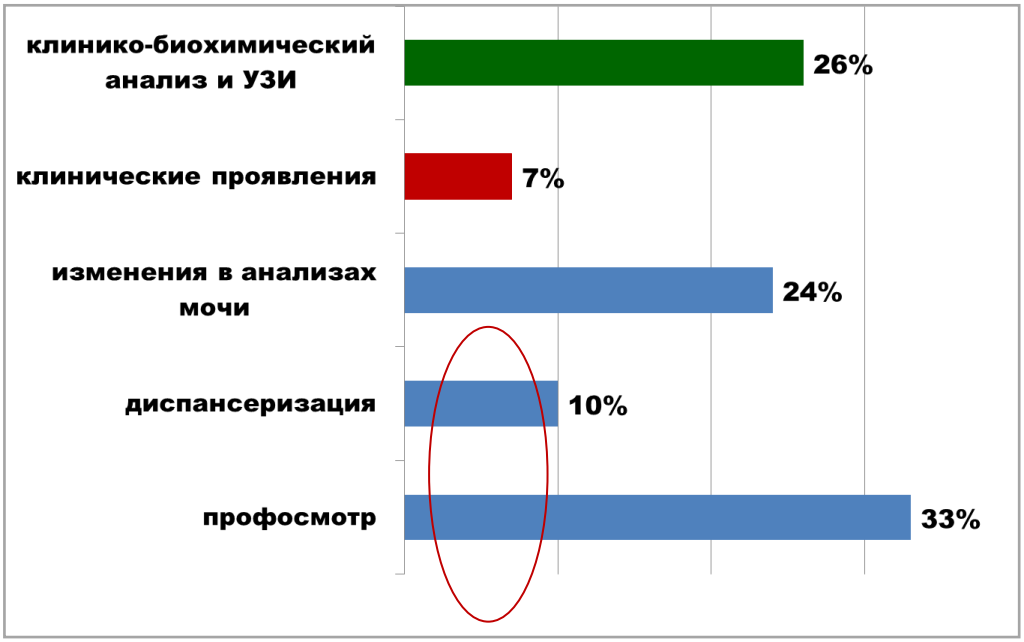

Figure 4.3. Detectability of urolithiasis according to the questionnaire

According to the literature (Pulatov A.T., 1990; Yusupov S.A., 2022) the most significant indicators in children with USD are the following main symptoms of the disease: pain, leukocyturia, proteinuria, hematuria, bacteriuria, leukocytosis, dysuria, acceleration of COE, periodic increase in body temperature, poor appetite, the frequency of which we studied in the main group of patients. All symptoms of the disease were divided into two groups by significance and specificity: main (pain, leukocyturia, proteinuria, haematuria, bacteriuria, dysuria) and additional (leukocytosis, COE acceleration, temperature reaction, poor appetite) (Table 4.1).

Таблица 4.1

Частота регистрации (ЧР) основных и дополнительных симптомов мочекаменной болезни у детей с учётом возраста

Клинические признаки болезни	**Возрастные группы**				
	Всего (n=100)	**Ранний возраст, 1-4 года (n=35)**	**Старший возраст, 5-9 лет (n=36)**	**Подростки младшего возраста, 10-14 лет (n=22)**	**Подростки старшего возраста, 15-17 лет (n=7)**
	ЧР, %	**ЧР, %**	**ЧР, %**	**ЧР, %**	**ЧР, %**
Основные симптомы					
Боль	89,0	77,2	94,4	90,9	100,0
Лейкоцитурия	85,0	80,0	91,6	86,3	85,7
Протеинурия	73,0	42,8	97,2	81,8	71,4
Гематурия	48,0	60,0	27,7	59,0	57,1
Бактериурия	43,0	54,2	33,3	22,7	100,0
Дизурия	27,0	42,8	16,6	18,1	28,5
Дополнительные симптомы					
Ускорение СОЭ	43,0	42,8	33,3	59,0	42,8
Плохой аппетит	39,0	60,0	25,0	36,3	14,2
Лейкоцитоз крови	35,0	51,4	22,2	31,8	28,5
Повышение температуры тела	29,0	34,2	30,5	22,7	14,2

The results of the study in Table 4.1 show the frequency characteristics of the main and additional symptoms of urolithiasis in children by age. It can be seen that pain (89.0%) was the most frequent symptom in the entire group of sick children. However, the diagnostic value of this indicator changes with age groups. Thus, in young children (from 1 to 4 years of age) this indicator is in the 2nd place, and in the group of older adolescents (15-17 years of age) - in the first place.

Before the age of 5 years (77.2%), frequent and characteristic clinical signs of the disease were attacks (1-2 times a month) of restless crying due to abdominal pain, usually associated

with the discharge of small concretions accompanied by macrohaematuria. Parents reported poor appetite somewhat less frequently - 60.0%. In 34.2% of cases USD was accompanied by elevations of body temperature to subfebrile against the background of ‘relative’ somatic well-being.

Parents paid attention to the pain syndrome mainly in children starting from the age of 5 years (94.4%), when the child could clearly voice his/her complaints about painful sensations associated with the passage of stones or sand. In the age group of children older than 7 years of age, the increase in pain was due to displacement of concrements, which increased with active physical activity, up to the onset of renal colic - 7.0%. Renal colic was accompanied by attack-like pain in the lower back with irradiation along the ureter and genitals, with nausea, vomiting and increased body temperature. In most cases, the pain was wavy in nature.

The second sign is leucocyturia. In the general age group, it was found in 85.0% of cases. In the older age group leucocyturia was more frequent than in the younger group. In the group of children older than 5 years of age, leucocyturia ranged from insignificant (up to 40 leucocytes) to pronounced leucocyturia (more than 100 in the field of view), which indicates a long course of urolithiasis.

The third sign is proteinuria. It was detected in 73.0% of patients. In all age groups proteinuria had close values, but in the middle age group it is in the first place.

If in the whole group of patients haematuria was 48.0%, in young children this indicator was much higher (60.0%), which, apparently, is associated with the highest detectability of haematuria in children of this age group. The incidence of haematuria increases with age, as haematuria, both macro- (more than 200 erythrocytes per vision) and microhaematuria (no more than 20 erythrocytes per vision) is associated with the size of the urolith. In fifth place is bacteriuria. Its frequency of detection depends on the age of patients. So in children of early and older adolescence bacteriuria is detected more often (54, 2% - 100,0%) than in older children and young adolescents. The older the age of the child, the dysuric phenomena tend to decrease, and is detected in 2/3 of children of early age, 1/4 of older and younger adolescents and 1/3 of patients - older adolescents.

Consequently, frequency analysis of the main signs of urolithiasis shows significant differences depending on the age of patients. For example, in children of older age groups, pain is in the first place, while in young children it is in the fourth place. In contrast, haematuria and dysuria come first in young children.

Of the additional symptoms of the disease as a whole for the whole group, acceleration of COE was most often observed (43.0 %). In young adolescents it was in the first place, in

children of early and older adolescence - in the second place and in older children - in the third place.

Poor appetite was observed in approximately equal numbers of examined children, except for young children. This sign is in the first place (60, %).

Elevated blood leucocyte counts were most frequently detected in infants (51.4%) and young adolescents (31.8%), ranking first and second, respectively.

Increase in body temperature was 29.0 per cent of the group as a whole in terms of its informative value. In young children - 34.2 %, in older children - 30.5 % and in adolescents of younger and older age - 22.7 % and 14.2 %, respectively.

Consequently, additional symptoms were detected with different frequencies depending on the age groups. The highest percentages of these symptoms were observed in young children, when they were registered in half or more of the patients. In children aged 5 to 17 years, these symptoms were detected much less frequently - in about 1/3 of patients.

Figure 4.4. Clinical manifestations of ICD in children (n=100)

Summarising the results of anamnestic interview and clinical examination, it should be noted that pain is the most frequent symptom of ICH - 89.0 %. The results of the study, shown in Figure 4.4, represent the most frequent clinical symptoms of the disease. It is well seen that no less rare sign of urolithiasis is urine opacity, which is found in 73.0% in the group of sick children. And to a lesser extent haematuria (48,0%), signs of intoxication (42,0%), dysuria (27,0%) were noted, which in 29,0% of children were accompanied by body temperature

increase. Due to urinary tract obstruction, acute urinary retention was observed in 5.0% of patients.

In bacteriological examination of urine, monoinfection was isolated from the total number of strains in 49.0% of patients, including E. coli in 30.0%, Proteus in 9.0%, Pseudomonas in 4.0%, and epidermal and Staphylococcus aureus in 6%. Microbial association was detected in 9% of the patients, the most frequent association being Escherichia coli + Proteus (5%); somewhat less frequent were Escherichia coli + Pseudomonas coli (2%) or Pseudomonas coli + Proteus (2%) (Fig. 4.5). The isolated strains were most sensitive to beta-lactams: amoxicillin with clavulanate (100%), cephalexin (95%), ampicillin and sulbactan (91%) - with low sensitivity to ampicillin alone (33%) - and 3rd and 4th generation cephalosporins had 85% and 87% sensitivity.

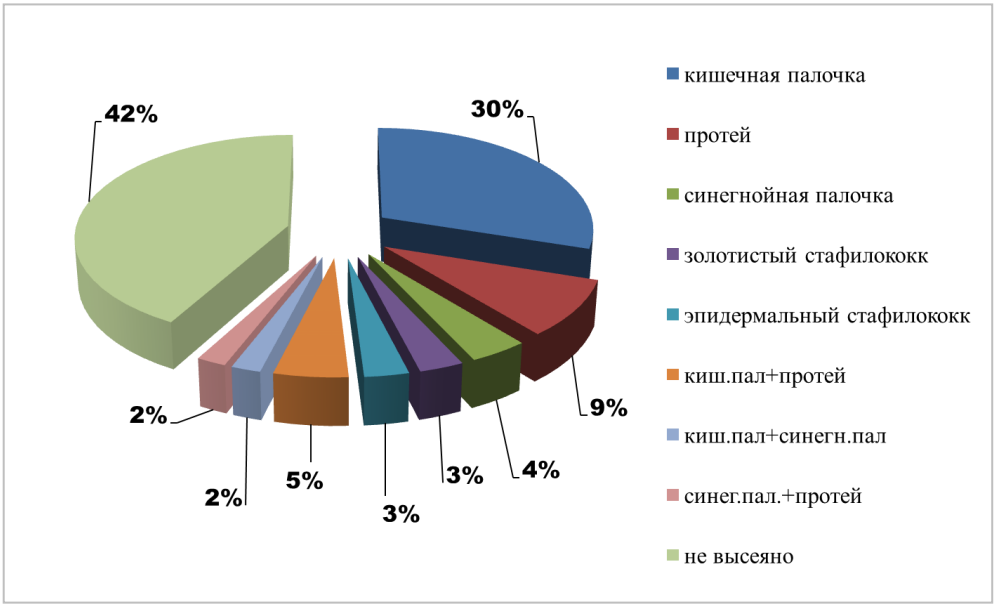

Figure 4.5. Bacteriological examination of urine in children with urolithiasis

The analysis of case histories (n=100) of ICD patients examined and treated during the period from 2012-2014 at the Samarkand Specialised Children's Surgical Clinic of SamSMU showed that surgical interventions were performed in 87.0% of children; 11.0% of patients had spontaneous removal of concretions, and 2.0% refused surgery due to family circumstances. Stones removed during surgical intervention were studied according to their composition and nature of origin. Depending on the composition of stones in the majority of patients they were simple - 73.6%, in 26.4% - complex. Their division by chemical composition showed that

oxalate stones predominated - 80.4%, while other stones accounted for 19.6%, including: urate stones (6.5%); cystine stones (2.2%); infectious stones (2.2%); mixed stones (8.7%).

Topographic characteristics of concrements showed predominance of their localisation in the upper parts of the urinary tract: kidney stones in 43 patients (21 on the right, 13 on the left, 9 on both sides). Ureteral stones were detected in 12 patients (upper third of the ureter - 1, middle third of the ureter - 1, lower third of the ureter - 10); bladder stones - 9 patients (1 of them recurrent bladder stone); urethral protrusion stone in 4 patients; multilocular urolithiasis in 10 patients. The combination of urolithiasis with developmental anomalies of the urinary system was detected in 22 children.

Using the developed questionnaire in the main group, an in-depth analysis was performed to assess the life history of children and their parents, taking into account the course of pregnancy in the mother, the presence of chronic diseases of the parents, as well as retrospective biochemical analyses of blood and urine with the study of the status of stone-forming substances.

In the course of our study, the main group of children with ICH was divided into two subgroups: subgroup A included 39 (39.0%) children whose parents were diagnosed with ICH; subgroup B included 61 (61.0%) patients with ICH whose parents had no clinical, laboratory and instrumental signs of urolithiasis. The control group consisted of 100 (100.0%) children with parents in whom urolithiasis was excluded by anamnestic and clinical and laboratory investigations.

According to the objectives, a detailed study of anamnestic data was carried out with questionnaires to the parents and the study of social and living conditions, the nature of the work performed, the health status of the parents, the presence of hereditary risk factors for the development of ICH, perinatal anamnesis, concomitant chronic diseases, and others.

According to the obtained data of the questionnaire, it should be noted that 17.0% of families of subgroups A and B lived in ecologically unfavourable conditions, the largest number of technogenic enterprises, factories, industrial facilities, whose emissions exceeded the MPC, which influenced the formation of anomalies of the urinary system, contributing to the development of urolithiasis.

10.3% of parents of subgroup A had work related to harmful industries (with chemical reagents), field work; about 5.1% of parents had bad habits, 10.3% had a sedentary lifestyle.

Questionnaire survey on the presence of chronic diseases among parents identified them among fathers in 16 (41.0%) cases and among mothers - 24 (61.5%). Analysis of the above-mentioned diseases among parents showed predominance of respiratory system diseases among mothers in 4 (10.3%), gastrointestinal tract diseases in 3 (7.7%), genital organs diseases in 2

(5.1%), nervous system diseases in 9 (23.1%), endocrine system diseases in 3 (7.7%), cardiovascular system diseases in 3 (7.7%). Whereas among male parents, chronic diseases of the respiratory, endocrine and cardiovascular systems were most often determined.

Heredity on USD in parents revealed its presence in: fathers - 19 (48,7%), mothers - 24 (61,5%), at that in 7 (17,9%) couples urolithiasis was determined in both parents. In subgroup A, 3 (7.7%) parents underwent surgery for USD, others were characterised by the presence of small kidney calculi, and 5 (12.8%) parents had persistent discharge of small calculi with the development of chronic pyelonephritis.

Analysis of the course of pregnancy in subgroup A indicated a complicated pregnancy with pre-eclampsia of various degrees in 76.9% of mothers; 71.8% had anaemia; 25.6% had multiple pregnancy, threat of termination, and 59.0% had oedema and arterial hypertension. In subgroup B, these anamnestic parameters were detected in 70.5%, 59.0%, 18.0% and 16.4% of cases, respectively. Pregnancy complications were significantly lower in the control group (Figure 4.5).

Pearson's χ^2 test showed a direct correlation between the presence of chronic diseases and complicated pregnancy in mothers and the development of USD in children of subgroups A and B (χ^2=10.12; p=0.0013).

Figure 4.5. Analysis of the course of pregnancy in mothers

Since some drugs, such as antiviral and antibacterial drugs, vitamins and dietary supplements can influence the formation of urolithiasis, a study of their use by women with pathological course of pregnancy was carried out. The study of the frequency of occurrence of Urolithiasis and the relationship of the disease with the intake of drugs by mothers during

pregnancy showed a direct correlation between the use of antiviral, antibacterial, vitamins, dietary supplements and hypotensive, with $\chi 2=10.13$, $p=0.024$ (Fig.4.6).

Thus, the analysis of the incidence of urolithiasis and the relationship of the disease with maternal drug intake during pregnancy in subgroup A showed a direct correlation between the use of antiviral and antibacterial drugs, hypotensive drugs, vitamins and dietary supplements. In subgroup B, analyses of the incidence of urolithiasis in children in relation to the use of medicines showed an association only with the use of vitamins and supplements.

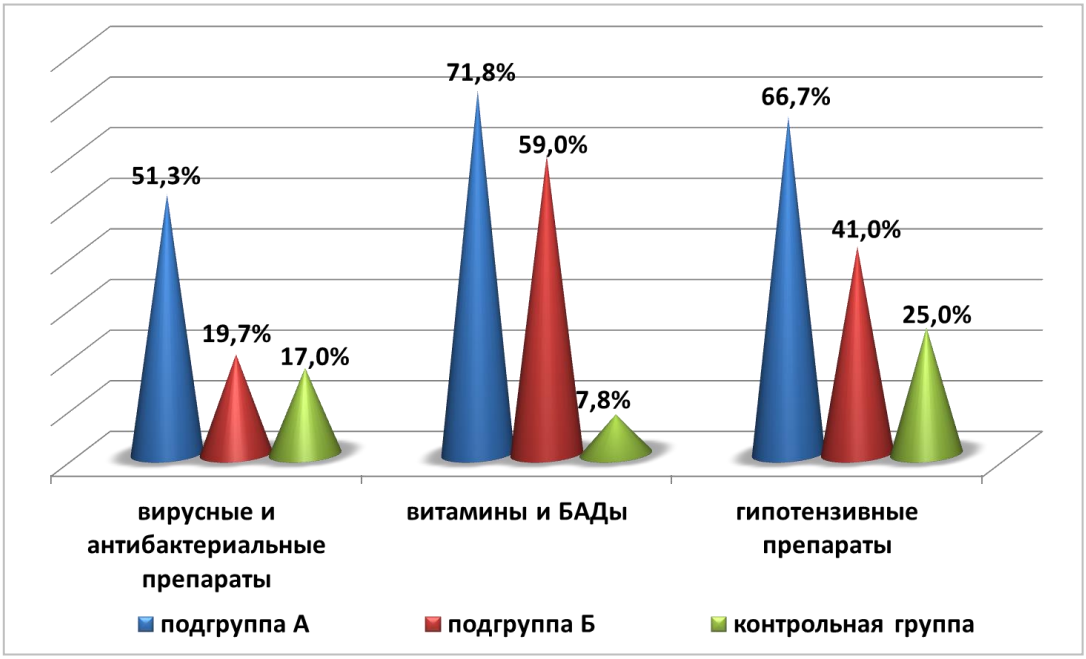

Figure 4.6. Frequency of development of urolithiasis depending on maternal drug use during pregnancy

It is well known that such a risk factor as irrational nutrition is of great importance in the development of urolithiasis. The study of this factor showed that in subgroup A, the majority of children and their parents favoured vegetable food (46.3%) and protein food (34.4%), while the consumption of dairy and mixed food was 16.1% and 3.2%, respectively. Subgroup B favoured plant and protein food with 47.5% and 33.2%, dairy food with 15.5% and to a lesser extent mixed food with 3.8%. In the control group, however, mixed food predominated with 61.0%, somewhat less frequently mixed with a preference for dairy (27.0%) or protein (12.0%) food (Figure 4.7).

Thus, in subgroups A and B, vegetable and protein meals were predominant. Whereas in the control group, parents favoured more mixed foods in their children's diet. In the children of this group, when the daily dietary intake was assessed, it was determined to be regular, complete and balanced. It can be stated that irrational and unbalanced diet with predominance of vegetable

and protein food is a great risk in formation of urolithiasis in children. And the use of a varied diet significantly reduces the risks of developing this pathology.

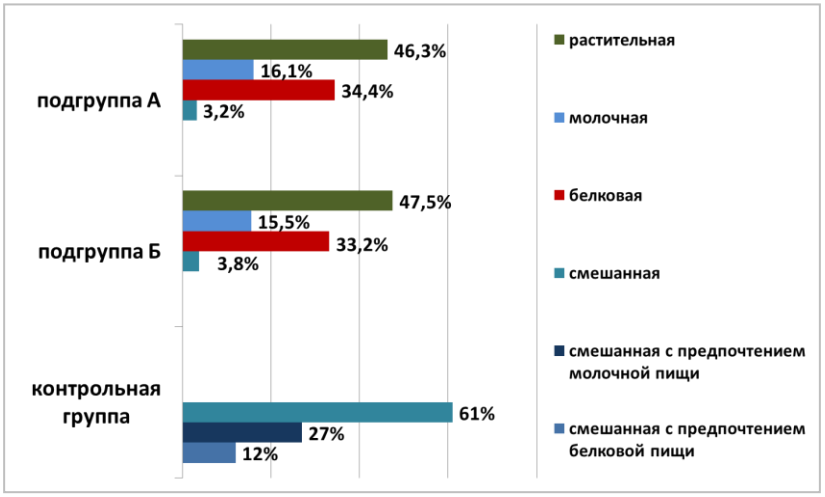

Figure 4.7. Comparative characterisation of nutritional features in the observation groups

The study of drinking habits showed that more than half of the respondents in subgroups A and B - 52.0% - had no information about the quality of the liquid consumed. Most of them - more than 63% - used natural water, while the remaining 37% used water from centralised water supply sources. At the same time, children using water from natural water bodies had a significant tendency and higher incidence of urolithiasis. Pearson's criterion calculation revealed a direct correlation between the quality of water consumed and the development of USD in children (χ^2=2.74; p=0.022).

The analysis of drinking regimen revealed that the risks of urolithiasis development increased when the volume of fluid intake decreased to less than 1-1.5 litres per day.

§4.2 Clinical and biochemical indicators of urolithiasis in children by region

In order to determine the functional activity of the kidneys in the study groups, the results of urine biochemical indicators were studied for the presence of oxalates, uric acid, calcium, and phosphorus. Distribution of crystalluria by frequency of their detection by region is presented in Figure 4.8, from which it follows that dysmetabolic disorders were more frequent in patients of Urgut district and Samarkand city than in Pastdargom district.

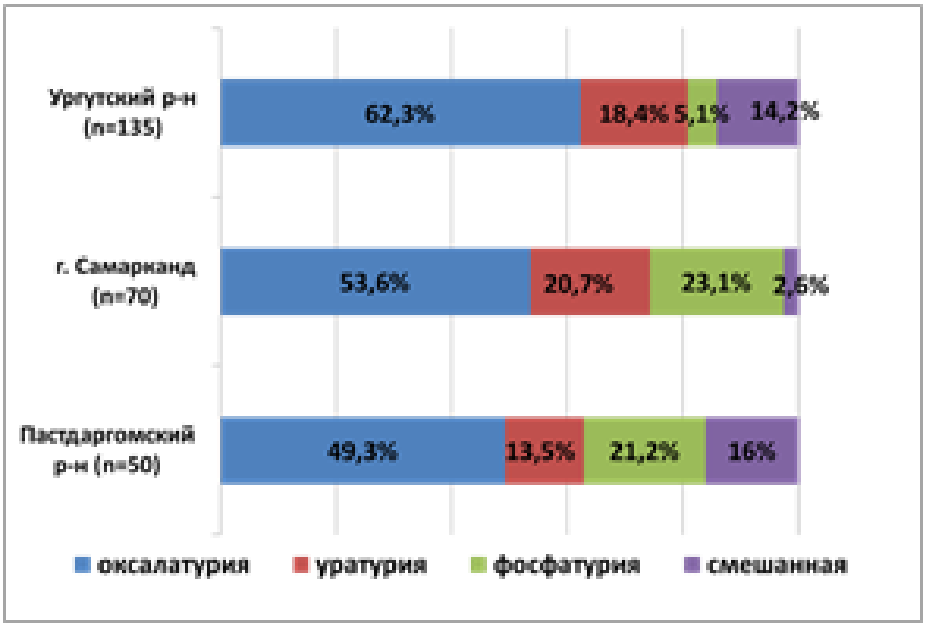

Figure 4.8. Frequency characteristics of crystalluria in the studied groups by region

Patients from Urgut and Samarkand had a significant increase in oxalate excretion compared to those from Pastdargom district. Whereas the concentration of phosphorus in urine was significantly higher in children from Samarkand city and Pastdargom district compared to children from Urgut district. There were no significant differences in uric acid content in urine in all the studied areas, however, the average values of this indicator were higher in patients from Urgut district and Samarkand city compared to patients from Pastdargom district. These data indicate the impact on the functional apparatus and activity of the UT of the levels of excretion of oxalates, phosphorus, uric acid, both exogenous risk factors for the development of USD and endogenous (hereditary), prevailing in Urgut district and Samarkand city.

Thus, statistical analysis of the obtained data allowed to reveal the presence of links between the frequency of metabolic disorders and the development of urolithiasis, as well as the place of residence. Prevalence of prelithiasis and USD among children of Urgut district was more frequent than in Pastdargom district and Samarkand city (75.3±2.13 versus 66.82±3.32 and 52.30±4.91 respectively).

Urine analysis of children with urolithiasis in subgroup A (n=39) revealed the following facts: urinary protein was detected in 4 (10.3%) (0.3g/l); urinary infection was detected in some patients; bacteriuria - 8 (20.5%) and leucocyturia - 6 (15.4%) were characteristic, in connection with which patients were treated with antibacterial therapy (Fig. 4.9). The majority of patients had crystalluria - 24 (61.5%), mainly oxalates, phosphates and uric acid.

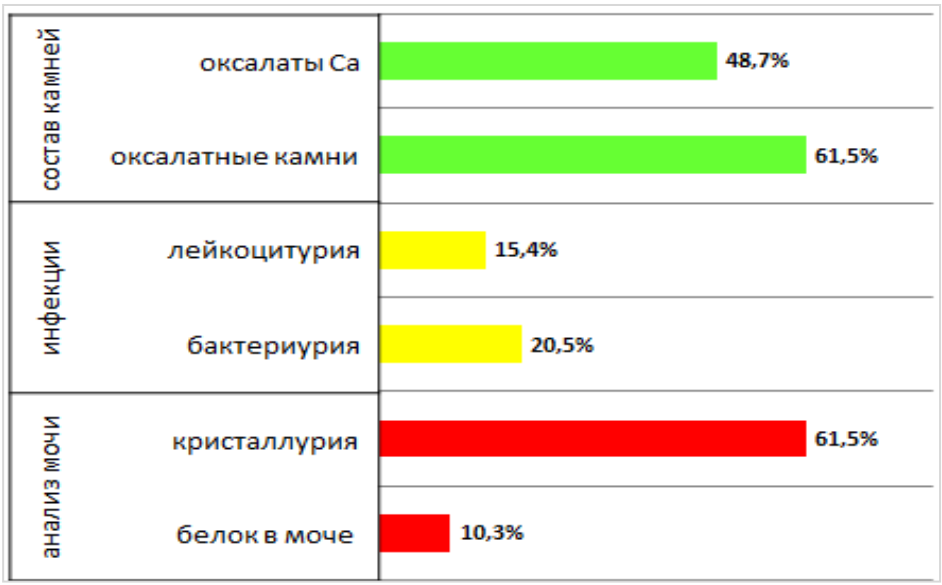

Figure 4.9. Clinical and biochemical parameters (urinalysis)

The study of urine pH in pre- and postoperative periods showed that it depends on the number of urease-producing bacteria, the increase in which contributes to the increase in the activity of the infectious-inflammatory process, which is an additional factor in the pathogenesis of stone formation and recurrence of urolithiasis.

The study of urine analysis and stone composition determined the presence of the following facts: oxalate stones prevailed in the composition of stones – 61,3%, among which mainly Ca oxalates - 48,7%.

The analysis of metabolic processes both in blood and urine among patients with urolithiasis revealed the most frequent metabolic disorders associated with hyperphosphatemia - 36 (92,3%), hypercalciuria and hyperuricuria were found in 32 (82,1%) and 26 (66,7%) cases respectively. Hypercalcaemia was determined in 19 (48,7%) children, hypocalcaemia in 1 (2,6%), increased uric acid level - hyperuricaemia was determined in 14 (35,9%), hyperphosphaturia and hypouricuria in 5,1% of cases each. Hypophosphatemia, hypocalciuria, hypophosphaturia with impaired excretion of oxalates were determined in 2,6% of patients. A characteristic feature of metabolic processes in children with USD was a combined violation of two types of metabolism (Fig. 4.10).

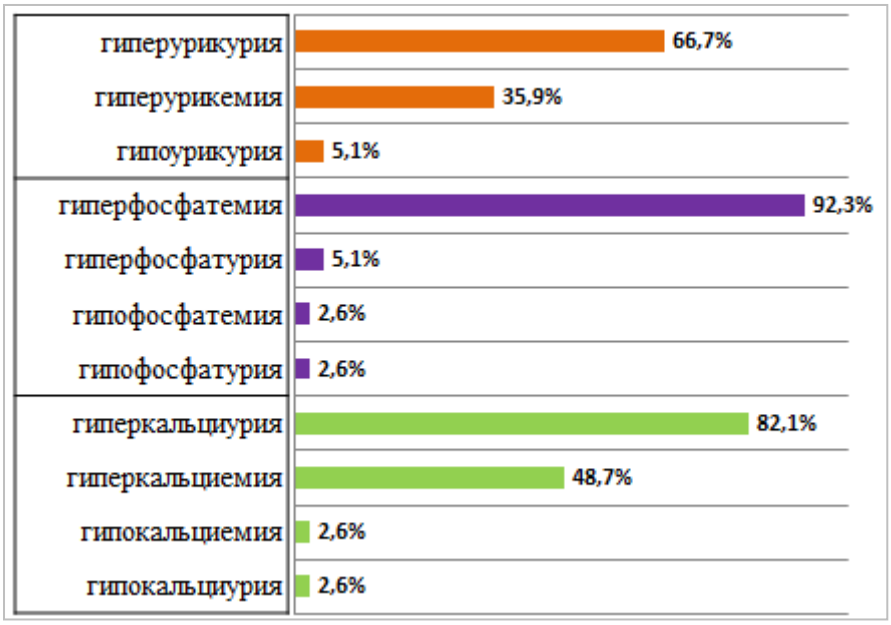

Figure 4.10. Stone-forming substance metabolism in children with urolithiasis

Parents' questionnaires showed that a quarter (28,2%) of the children were born earlier than the gestational age (34±1,2 weeks), which accordingly affected the child's weight; the average birth weight of the children was from 2000 to 2500 gr. It can be assumed that this factor has an important role in the pathogenesis of metabolic disorders in paediatric patients.

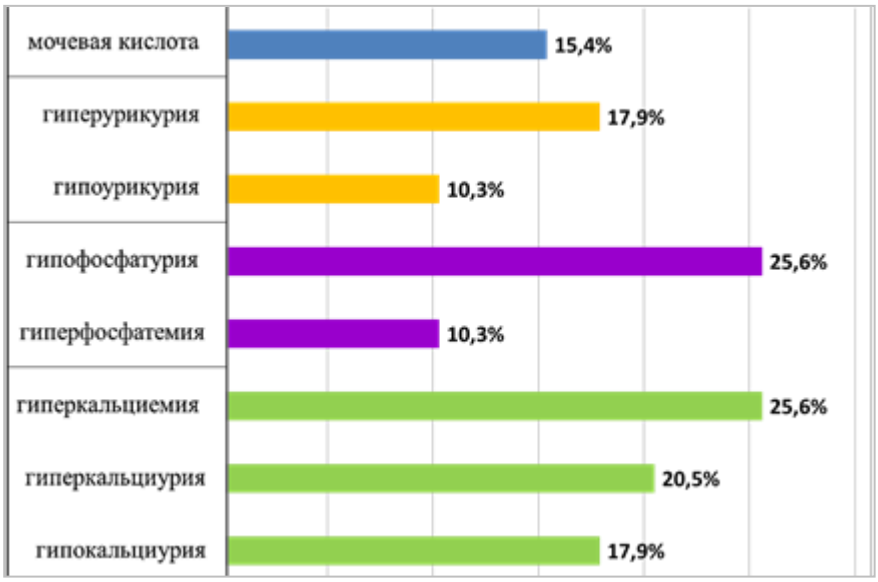

Figure 4.11. Exchange processes of stone-forming substances

in parents in subgroup A

When analysing metabolic disorders in parents in subgroup A, hypercalcaemia and hypophosphaturia were determined in 25,6%, hypercalciuria, hypocalciuria and hyperuricuria were 17,9% each, high levels of uric acid in the blood were determined in 15,4%, and hyperphosphatemia and hypouricuria were determined equally often in 10,3%. This indicates a

hereditary predisposition to the development of metabolic changes in children with urolithiasis (Fig. 4.11).

Thus, in children with urolithiasis in subgroups A and B, the presence of any congenital anomalies of the UT was found in 22% of cases. Whereas in children without congenital anomalies of the UT (78%), the development of urolithiasis was due to metabolic disorders, which were also detected in 39% of the parents of the respondents. This allows us to conclude that in the presence of congenital anomalies of the urinary tract the leading factor of lithogenesis is disorders of urodynamics of the upper urinary tract, and in patients with primary stones the leading factor is hereditary, which allows us to recommend immunogenetic studies with the study of VDR, IL-1β, IL-18 gene expression.

In conclusion, it can be determined that the development of urolithiasis in children has territorial variability associated with the environment, as well as the main risk factors affecting the formation of prelithiasis and urolithiasis are geoanthropotechnogenic factors, i.e. endemic spread is associated with environmental factors, drinking water composition, climatic conditions, geographical location, as well as the presence of technogenic objects that pollute both land, soil, water and atmosphere.

Thus, the trigger mechanism contributing to the formation of USD in children are unfavourable environmental factors, exogenous factors, heredity, directly affecting the stability of cell membranes, biochemical biogeocenosis processes that reduce antioxidant activity, hormonal instability with the development of endogenous toxaemia.

§ 4.3. Study of genotypic features and gene polymorphism in children with urolithiasis

Currently, the development of immunogenetic studies provides an opportunity to search for genetic markers that contribute to and are directly involved as risk factors for stone formation, with subsequent development of urolithiasis. A complete understanding of the immunogenetic causes of these conditions, including the identification of mutant genes, may facilitate early diagnosis and prevention of urolithiasis, as well as the implementation of more rational treatment protocols.

The results of the study and literature data have shown that the occurrence of metabolic disorders characteristic of urolithiasis is significantly influenced by hereditary predisposition in combination with environmental factors. The studies show a possible correlation between the increased risk of USD development and polymorphisms of the vitamin D receptor (VDR) gene

[4, p.56-60; 150, p.277-83; 167, p.587-593]. Vitamin D receptor (VDR) is present in most cells of the body. It participates in the regulation of calcium haemostasis, as well as in the renal regulation of citrate levels [65, p.4937-40; 90, p.447-54; 104, p.249-55]. Numerous studies in experimental animal models show that the increase in VDR expression in tissues is genetically determined, resulting in an increase in 1,25(OH)2-D dependent membrane calcium transport, with subsequent development of idiopathic hypercalciuria [90, pp.447-54]. The vitamin D receptor is encoded by the VDR gene, which is characterised by genetic polymorphism, i.e. the existence of different allelic variants of this gene in the population [162, p.87]. The most significant polymorphisms of the VDR gene involved in the development of diseases were Bsm I, Fok I, Taq I [84, p.s75; 162, p.87].

Interleukin-1β (IL-1β) is a cytokine with a wide range of biological and physiological effects including fever generation, prostaglandin synthesis, T-lymphocyte activation and IL-2 production. The IL-1 family genes are localised on chromosome 2. When studying the structure of the genes, it was found that the number and distribution of exons indicates striking conservativeness of their structural organisation. The IL-1β gene contains 22 exons, 20 of which are alternative (i.e. have structural variants) and 9 introns, of which 8 are alternative. The balance between production, expression and inhibition of IL-1 family proteins synthesis plays one of the key roles in the development, regulation and outcome of the inflammatory process. Prior to the identification of associations of increased IL-1β production with specific alleles, it was known that some individuals produce higher levels of IL-1β. Moreover, the propensity for higher production of this cytokine persists in later measurements and also tends to be inherited.

§4.3.1. Immunogenetic study of polymorphism of vitamin D receptor, interleukin-1β, interleukin-18 genes

In order to study the polymorphism of VDR, Interleukin-1β (IL-1 β), Interleukin-18 (IL-18) genes, genomic DNA was isolated from whole blood of patients of the main group (n=100) and control group (n=100) according to the standard protocol using Diatom™ DNA Prep 200 reagent kit (manufactured by IsoGen Laboratory LLC). The principle of action of this kit is based on the use of a lysing agent with guanidinedithiocyanate, which is designed to disrupt cells, solubilise cellular debris, and denature cellular nucleases. In the presence of the lysing reagent, DNA was sorbed on NucleoS™ sorbent, then washed of salts and proteins with alcohol solution. DNA eluted from the Extra Genome™ sorbent was directly used for further analysis. Primer design for polymorphisms of VDR, Interleukin-1β (IL-1 β), and Interleukin-18 (IL-18) genes. The design of primers and selection of restrictionases for polymorphisms of VDR,

Interleukin-1β (IL-1 β), Interleukin-18 (IL-18) genes based on their nucleotide sequences was performed (Fig.4.12). Bioinformatic search of nucleotide sequences of these genes was performed in the Ensemble Genome Browser genomic database.

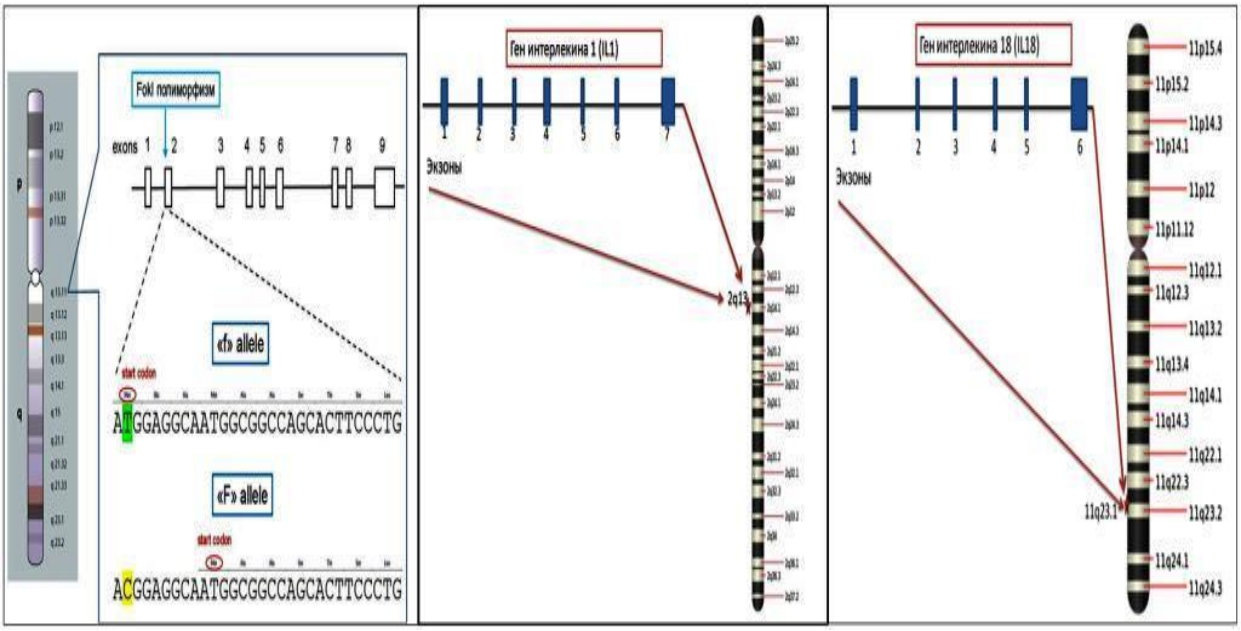

Figure 4.12: Fok-I polymorphisms of the VDR (Vitamin D receptor) gene, interleukin-1β (IL-1 β) and interleukin-18 (IL-18) genes

Table 4.2

Chromosomal localisation and structure of genes under study

Gene and polymorphism	Name of primers	Nucleotide sequence	Restrictases
Vitamin D receptor Fok-I polymorphism	Pr_VDR_F	AGCTGGCCCTGGCACTGACTCTGCTCT	Fok I
	Pr_VDR_R	ATGGAAACACCTTGCTTCTTCTCCCTC	
Interleukin-1β (IL-1 β) promoter region (-511) polymorphism	Pr_IL-1_F	TGGCATTGATCTGGTTCATC	Ama87I
	Pr_IL-1_R	GTTTAGGAATCTTCCCACTT	
IL-18 +105A/C polymorphism	Pr_ IL-18_F	TGTTTATTGTAGAAAACCTGGAATT	Taq I
	Pr_ IL-18_R	CCTCTACAGTCAGAATCAGT	
	Pr_OPN_R	GTTGTCAATTTAGTGGAGGGAAGTA	

Visualisation and photo-documentation of PCR-PDRF results. The obtained restriction products were separated by electrophoresis in 8% polyacrylamide gel, subsequently stained with

ethidium bromide and visualised in transmitted ultraviolet light using a WiseDoc WGD-30 transilluminator (DAIHAN, Korea). Interpretation of genotypes of polymorphisms of VDR, IL-1β, IL-18 genes was performed on the basis of different band patterns on the electrophoregram (Figs. 4.13 and 4.14).

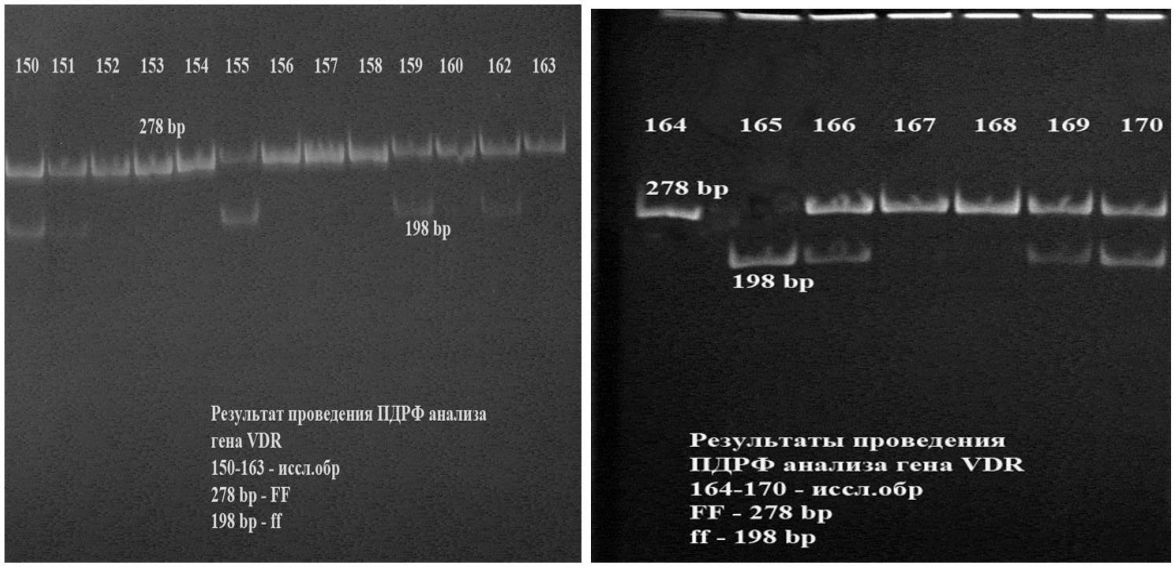

Figure 4.13. PDRF analysis of the Fok1 polymorphism of the VDR gene

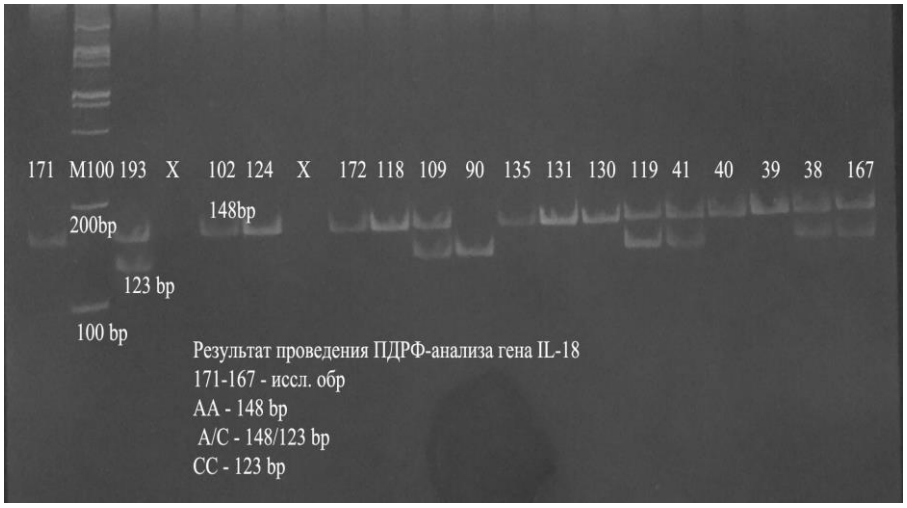

Figure 4.14. PDRF analysis of the IL-18 gene

Results of VDR gene polymorphism study in the study groups. VDR gene polymorphism was studied in 2 study groups (n=200), where the distribution of patients by sex and age was equal. The study of VDR gene polymorphism showed its prevalence in patients of both groups (Fig. 4.15).

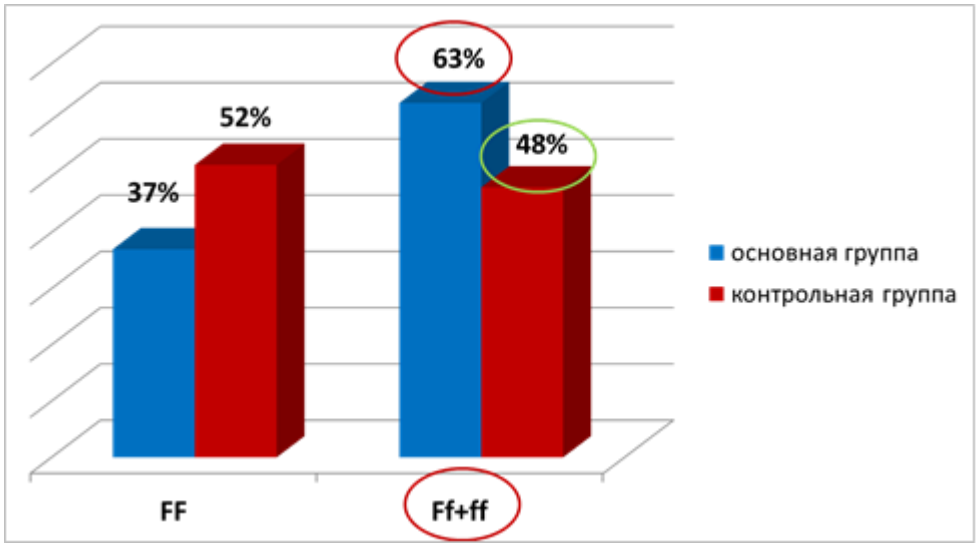

Figure 4.15.VDR gene polymorphism in the main and control groups

The results of immunogenetic testing showed the following distribution of genotypes of the FokI polymorphic marker of the VDR gene: 37 (37.0%) children in the main group were carriers of FF-genotype, 57 (57.0%) children were carriers of Ff-genotype, 6 (6.0%) children were carriers of ff-genotype, whereas in the control group 52 (52.0%) children were carriers of FF-genotype, 41 (41.0%) children were carriers of Ff-genotype, 7 (7.0%) children were carriers of ff-genotype. Thus, the frequency of F allele in the main group was - 65.0% and f allele - 35.0%, and in the control group - 73.0% and 27.0%, respectively.

A significantly significant association of F/f+f/f VDR (Fok1) genotype was revealed in the studied groups, which was 1.3 times more frequent in the main group than in the control group ($\chi2=4.55$; p=0.05; df=1). However, in the control group, the frequency of occurrence of the F/f+f/f genotype was 48.0%, indicating that the frequency of occurrence of the allelic variants under study also occurred in children without urolithiasis, thereby influencing the formation of predisposition to the disease in this group (Table 4.3).

Table 4.3

Distribution of VDR gene association with ICD development according to dominant inheritance model (χ^2 test, df=1)

Genotypes	Main group, n=100	Control group, n=100	χ^2_{emp}	χ^2_{kr}	p
Генотип F/F	37	52	4,6	3,84	0,05
Генотип F/f+f/f	63	48			

Note: p - statistical significance of differences between the main and control groups (according to the χ^2 criterion)

Thus, a comparative analysis of the frequency distribution of Fok1 genotypes of the VDR gene polymorphism revealed a statistically significant association of the f allele in children with urolithiasis, compared to children in the control group. This fact indicates that the presence of Ff+ff genotypes proves a significantly high risk of USD development in children. This indicator can serve as a criterion for predicting the development of urolithiasis.

Results of the study of IL-1β gene polymorphisms in the study groups. We also performed genotyping of IL-1β gene in the main (n=100) and control (n=97[1]) groups with subsequent comparative analysis of the results obtained.

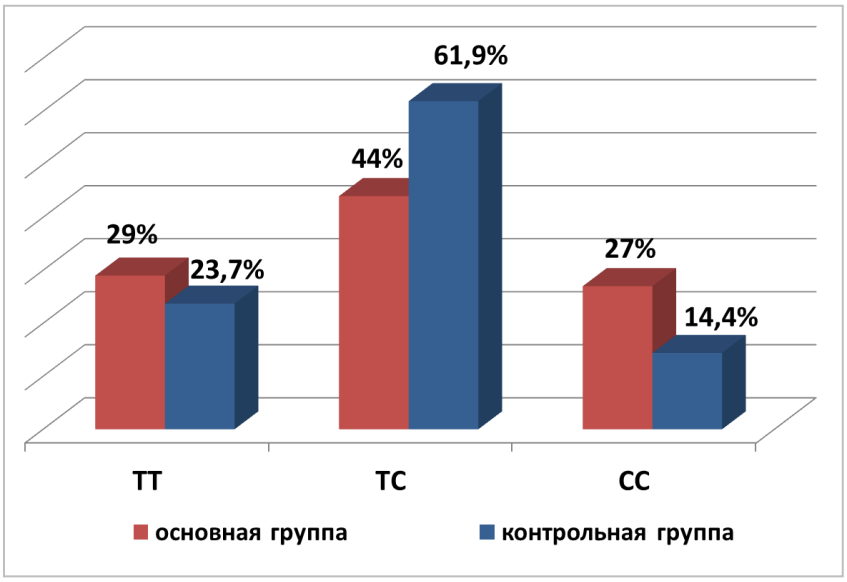

Figure 4.16. Distribution of IL-1β genotype frequency in the main and control groups

The results of immunogenetic testing showed that the distribution of IL-1β genotypes in the main group carriers of T/T-genotype were 29 (29,0%), T/C-genotype - 44 (44,0%), C/C-genotype - 27 (27,0%) children, and in the control group carriers of T/T-genotype - 23 (23,7%), T/C-genotype - 60 (61,9%), C/C-genotype - 14 (14,4%) children. As a result, the frequency of T allele in the main group was - 51.0%, and the frequency of C genotype was 49.0%, and in the control group - 54.6% and 45.4%, respectively (Fig. 15).

Thus, when determining the polymorphism of IL-1β gene in the control group the most frequent genotype T/C – 61,9%. Whereas the detection rate of T/T genotype was higher in the main group compared to the control group, being 29,0% versus 23.7%. The most significant marker in the development of stone formation in children was the C/C genotype, which was 1,9 times more frequent in children with USD than in children in the control group.

Table 4.4

Results of the distribution of the association of the IL-1β gene with the development of USD

Genotypes	Main group (n=100)	Control group (n=97*)	χ^2_{emp}	χ^2_{kr}	*p*
General inheritance model (χ^2 test, df=2)					
Genotype T/T	29	23	7,2	5,99	0,05
Genotype T/C	44	60			
Genotype C/C	27	14			
Recessive inheritance model (χ^2 test, df=1)					
Genotype T/T+T/C	73	83	4,72	3,84	0,05
Genotype C/C	27	14			

*Note: p - statistical significance of differences between the main and control groups (by the χ2 criterion for arbitrary tables); * - in the study of this gene, the number of children in the control group was 97, which is due to the technical aspects of immunogenetic analysis*

Further statistical analysis of the distribution of IL-1β gene genotypes with the development of ICH according to the common model of inheritance in the observation groups also showed a difference only in the C/C genotype: in the main group, a significantly significant C/C-genotype of IL-1β was detected (χ^2=7.2; p=0.05; df=2). The same trend persisted with recessive inheritance pattern (χ2=4.72; p=0.05; df=1) (Table 4.4).

Thus, analysis of the frequency distribution of IL-1β gene polymorphism in the study groups revealed a statistically significant association of the C/C genotype with urolithiasis compared to the control group. This indicates that the C/C genotype of IL-1β influences the formation of predisposition to the development of urolithiasis in children in any inheritance model.

Results of IL-18 gene polymorphism study in the study groups. Comparative results of IL-18 gene polymorphism in the studied groups showed the following genotype distribution: main group - AA-genotype carriers - 57 (57.0%), AC-genotype carriers - 41 (41.0%), CC-genotype carriers - 2 (2%) children; control group - AA-genotype carriers - 51 (51.0%), TC-genotype carriers - 41 (41.0%), CC-genotype carriers - 8 (8.0%) children (Fig. 4.17).

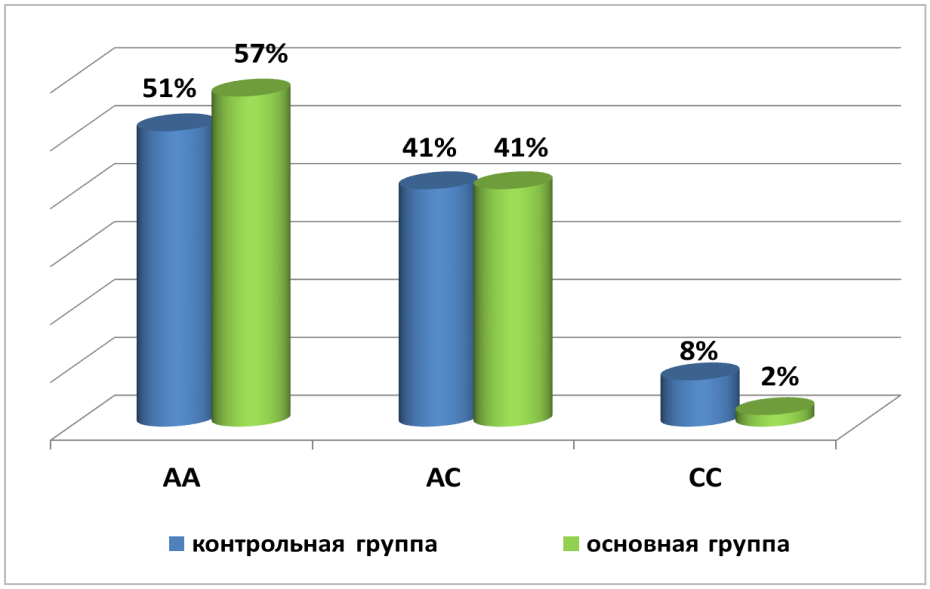

Figure 4.17. Frequency distribution of the +105A/C polymorphism of the IL-18 gene in the main and control groups

Further comparative analysis of the frequency distribution of the IL-18 -+105A/C gene polymorphism according to the common inheritance model revealed no significant differences between the patient group and the control group ($\chi 2=3.93$; $p>0.05$; $df=2$) (Table 4.5).

Table 4.5

Results of the distribution of the association of the IL-18 gene with the development of ICD according to the common inheritance model (χ^2 test, df = 2)

Genotypes	**Main group n=100**	**Control group n=100**	χ^2_{emp}	χ^2_{kr}	**p**
Генотип A/A	57	51	3,93	5,99	0,05
Генотип A/C	41	41			
Генотип C/C	2	8			

Note: p - statistical significance of differences between the main and control groups (by the χ2 criterion for arbitrary tables)

As the results of the study (Table 4.6) show, analysis of the association of IL-18 -+105A/C gene polymorphism with susceptibility to USD development in children under different inheritance models, particularly dominant ($\chi^2=3,79$; $p>0.05$; $df=1$) and recessive ($\chi^2=0.72$; $p>0.05$; $df=1$), also showed no statistically significant.

Table 4.6

Results of the distribution of the association of the IL-18 gene in the development of USDs

Genotypes	Main group n=100	Control group n=100	χ^2_{emp}	χ^2_{kr}	p
Dominant inheritance model (χ^2 test, df = 1)					
Genotype A/A+A/C	98	92	3,79	5,99	0,05
Genotype C/C	2	8			
Recessive inheritance model (χ^2 test, df = 1)					
Genotype A/A	57	51	0,72	3,84	0,05
Genotype A/C+C/C	43	49			

Note: p - statistical significance of differences between the main and control groups (by the χ2 criterion with Yates correction - values less than 10 in 2 fields)

The allele frequency distribution of IL-18 -+105A/C gene polymorphism practically did not differ between the main and control groups and, accordingly, did not influence the formation of predisposition to USD development in children.

Thus, the revealed polymorphism of VDR and interleukin-1β genes indicates a high risk of urolithiasis formation in children. At the same time genetic markers of predisposition to USD development in children are genotype Ff+ff of VDR gene and alleles C/C of interleukin-1β gene. Therefore, these indicators can serve as immunogenetic criteria for predicting the development of USD in children at the preclinical stage of the disease.

§4.4. Development of an algorithm for early diagnosis of urolithiasis in children taking into account risk factors and immunogenetic predisposition

Based on the results of the research work and to solve the problem, we developed an algorithm (Appendix 3) for early diagnosis and prediction of urolithiasis development in children at the preclinical stage of the disease in outpatient and polyclinic conditions, taking into account risk factors and immunogenetic predisposition.

According to the algorithm, risk assessment of urolithiasis in the first step is based on anamnestic data and analysis of risk factors. For this purpose, 10 basic questions are developed, on the basis of which the risk degree can be identified individually for each child on a 10-point scale. By summarising the results obtained, the risk of urolithiasis is predicted:

- 1 to 3 points - low risk of developing urolithiasis
- 4 to 6 points - medium risk of developing urolithiasis
- 7 to 10 points - high risk of urolithiasis.

When performing the second step of the developed algorithm, the patients are routed depending on their attribution to one or another degree of risk of USD development.

Thus, children who scored 1 to 3 points according to a 10-point scale constituted a group with a low risk of developing urolithiasis. This category of patients underwent clinical and

laboratory investigations (general blood analysis, urine, blood biochemistry), as well as ultrasound sonography of the UT. As a rule, children in this group do not have clinical-laboratory and ultrasonographic manifestations of urolithiasis. Therefore, they are observed by a doctor in outpatient and polyclinic conditions according to the approved calendar of preventive examinations.

Children who scored from 4 to 6 points and entered the group of average risk, also require clinical, laboratory and instrumental studies. Patients found to have clinical and/or laboratory and instrumental changes in urolithiasis should be referred to a paediatric urologist in a specialised clinic for further comprehensive examination and treatment. If the results of clinical, laboratory and instrumental methods of investigation do not reveal signs of USD, immunogenetic analysis is recommended. If the results of testing for immunogenetic predictors do not indicate their polymorphism, the child should be under the supervision of a doctor in outpatient and polyclinic conditions. Detection of VDR and interleukin-1β gene polymorphisms in this group of patients requires an appropriate set of measures to prevent the development of urolithiasis, including metaphylaxis.

Analyses of studies have shown that patients at high risk of developing USD (7 to 10 points) require special attention. If clinical signs of the disease are detected in children, as a rule, they are referred to a paediatric urologist of a specialised clinic. In the absence of clinical signs of urolithiasis, laboratory (general urine, blood, biochemical tests) and instrumental studies (ultrasound) should be performed. Children with relevant changes in laboratory tests and ultrasonography of the US should be referred to a paediatric urologist in a specialised clinic. In the absence of changes in laboratory tests and ultrasonography data, immunogenetic testing is performed. Children with a high risk of developing USD and in the presence of gene polymorphism there is a need for a set of measures to prevent the development of urolithiasis. In cases where changes at the gene level are not detected, children should be under the supervision of a doctor in an outpatient clinic.

Thus, the developed algorithm for early diagnosis of USD in children and their subsequent routing according to the risk group (low, medium or high) will contribute to the detection of urolithiasis at the preclinical stage in outpatient and polyclinic conditions.

Conclusions of the chapter

The conducted research showed that of the total number of children with urolithiasis, this disease was detected most of all in Urgut, Pastdargom districts and Samarkand city. Among the patients, the majority of ICD patients were of school age - 69.0 per cent.

Irrational and unbalanced diet with predominance of vegetable and protein food is a great risk in formation of urolithiasis in children. And the use of a variety of food significantly reduces the risk of developing this pathology.

The study of drinking regime showed that more than half of the respondents - 52.0% had no information about the quality of the consumed liquid. Most of the respondents - more than 83.0% - used water from natural sources, the remaining 17.0% - specialised drinking water of satisfactory quality.

Taking into account the high prevalence and incidence of ICH in children, specific risk factors are identified: The presence in anamnesis among relatives of pathologies and urological diseases, including ICD with characteristic metabolic disorders of stone-forming substances (55.1%); various anomalies of the MBC in children (22.0%); residence in environmentally unfavourable and geotechnogenic conditions (17.0%); parents' bad habits (5.1%); pathological course of pregnancy complicated by pre-eclampsia (76.9%), antiviral and antibacterial drugs (51.3%), vitamins and dietary supplements (71.8%).

These studies have shown a possible association of increased risk of ICD development with polymorphisms of vitamin D receptor (VDR) and interleukin-1. Genetic markers of predisposition to urolithiasis are genotypes Ff+ff of VDR gene (63,0%), genotype CC of interleukin-1β gene (27,0%). Consequently, it is reasonable to include testing for the presence of these genotypes in a comprehensive screening programme for urolithiasis in children at high risk of urolithiasis in outpatient and polyclinic institutions.

The developed algorithm and routing of children according to the risk group (low, medium or high), helps to detect urolithiasis at the preclinical stage and thus will prevent its development, various complications, recurrence, reducing disability and mortality among children in this category.

CONCLUSION

According to WHO, diseases of the urinary system are the second most frequent pathology of childhood. In the last decade, their frequency has increased 2.5-3 times and ranges from 21 to 106 per 1000 children, depending on the region. Today urolithiasis is not only a medical, but also a serious socio-economic and demographic problem. The disease, previously first detected or developing in adolescence, is now detected in young children and even in newborns. Urolithiasis of children is characterised by rapid development of complications up to organ-killing interventions. And the frequency of recurrence of urolithiasis within the next few years after surgical treatment is up to 38.0 % of observations.

Outpatient clinic is the leading and most important, but, unfortunately, at the moment, a weak link in both early diagnosis and conservative complex treatment of patients with urolithiasis, primarily due to the lack of standardised personalised approach.

All the above-mentioned determined the aim of our study, which is to develop an optimal algorithm for early diagnosis of urolithiasis in children in outpatient and polyclinic conditions.

The study of the prevalence of urolithiasis in children was carried out according to the data of treatment in the Specialised Children's Surgical Clinic of SamSMU (chief physician - Professor J.A. Shamsiev) in the period from 2012 to 2019. The work was performed in two stages from 2012 to 2019.

At the first stage, to study the prevalence levels of ICD, as well as to determine the risk factors, the selection of the contingent of the studied children among 652 patients with urolithiasis was carried out on the basis of in-depth assessment of anamnestic data on risk factors, clinical and laboratory analysis of the enrollees, ultrasound findings. Socio-hygienic risk

factors with input of objective examination data were studied using a questionnaire.

At the second stage, in connection with the set tasks of studying immunogenetic predisposition to the development of urolithiasis, a quantitative and qualitative analysis of the main clinical and laboratory parameters, instrumental methods of research, and immunogenetic methods of research was carried out in 100 children with urolithiasis, who made up the main group, and 100 children without urolithiasis, who made up the control group. Inclusion criteria for the study were the age of children from 1 to 17 years, and the established diagnosis of urolithiasis N20 according to ICD-10.

All patients underwent general clinical and laboratory examination methods, including general blood and urine analysis, blood biochemical examination, bacteriological examination of urine and immunogenetic study, as well as instrumental methods of investigation: ultrasound and X-ray examination.

The in-depth assessment conducted at the first stage showed that the overall morbidity of children and adolescents compared to the morbidity of diseases of the urinary system in the Republic of Uzbekistan from 2015 to 2020 tends to decrease slightly. Unfortunately, while the incidence of urinary system pathology in children aged 1 to 14 years has a slight downward trend, children aged 15 to 17 years have an increase in the detection of this pathology.

According to statistical data in Samarkand region from 2015 to 2020 the morbidity of children aged 1 to 14 years again tends to decrease, while among children aged 15 to 17 years there is an increase in morbidity.

It follows that the problem of morbidity among children and adolescents, including pathology of the urinary system, both in Uzbekistan and in the Samarkand region, is relevant and requires large-scale epidemiological studies to address it at the population level.

The analysis of 652 case histories of children with urolithiasis carried out at the first stage showed a 2-fold predominance of boys among the patients. At the same time, about 85.0% of children with urolithiasis lived in rural families.

The distribution of those who came to the clinic with a diagnosis of urolithiasis by region (n=652) of the Republic of Uzbekistan showed that the largest number of patients came from Samarkand region (74.0%); somewhat less frequently from Kashkadarya region (14.0%), followed by patients from Jizzak, Navoi and Surkhandarya regions.

According to the data by region, patients from Urgut, Samarkand and Pastdargom regions prevailed in Samarkand, accounting for 28, 15, and 10.0%, respectively.

The sex structure of the distribution of patients with urolithiasis revealed a predominance of morbidity among boys, with an average boy/girl ratio of 2.1:1.0.

Patients aged 5-9 years (45.0%) prevailed among the examined children with urolithiasis, which indicates the early development of stone formation in the urinary system in children and is caused by certain risk factors.

At the second stage, in order to fulfil the set tasks of studying the predisposition, including immunogenetic, to the development of urolithiasis in children, an in-depth examination of 200 patients who were divided into two groups was carried out.

The first (main) group consisted of 100 patients with urolithiasis who underwent complex examination (clinical, haematological, biochemical, immunogenetic, ultrasound, radiological) and treatment. 100 children without urolithiasis and hospitalised for minor planned surgical interventions (circumcision, herniorrhaphy) in the Specialised Children's Surgical Clinic of SamSMU constituted the second (control) group.

In the age groups under consideration, the predominance of school-age children among patients with urolithiasis was revealed. This is due to the fact that it is at this age that metabolic disorders associated with the transition of children to general nutrition, drinking disorders, activation of metabolic processes due to the peak of hormonal activity are most often manifested. This is also favoured by the activation of hereditary predisposition and the impact of existing risk factors. In the younger age group, nutrition remains relatively rational and metabolic changes manifest themselves to a lesser extent. In terms of gender, boys prevailed almost twice as much among children with urolithiasis, with a proportion of 68.0%.

In order to identify risk factors for the development of ICH and the subsequent derivation of an algorithm for early diagnosis of urolithiasis in children, a questionnaire survey was carried out using a specially designed questionnaire-questionnaire. It included an in-depth analysis of the life history of children and their parents, taking into account the peculiarities of the course of pregnancy, the presence of chronic diseases in the parents, as well as an assessment of the status of stone-forming substances on the basis of biochemical parameters of blood and urine.

Analysis of the data on the detection of urolithiasis in children according to the results of the questionnaire showed that only 43% of children were diagnosed during occupational examination and medical examination, while more than half of the respondents pointed to the accidental detection of the disease when visiting a doctor with other pathologies.

The analysis of clinical manifestations of ICH revealed a very variable picture. The most typical complaints were pain (89.0%) of different localisation and intensity, urine turbidity (73.0%), increased body temperature (29.0%), haematuria (48.0%), increased or decreased urination (27.0%). In some cases, acute urinary retention was noted (5.0%). Intoxication

(42.0%), manifested by headache, poor appetite, and drowsiness, was characteristic for patients with chronic renal failure.

General clinical urine analysis in admitted patients with urolithiasis was characterised by leukocyturia (85,0%), proteinuria (73,0%), presence of erythrocytes in urine up to macrohaematuria (48,0%) and bacteriuria (43,0%).

Of the additional symptoms of ICH, the most frequent were acceleration of COE (43.0%), poor appetite (39.0%), blood leucocytosis (35.0%) and increased body temperature (29.0%).

In urine microbiological examination, monoinfection was isolated in 49.0% of patients, of which 30.0% had Escherichia coli, 9.0% had Proteus, 4.0% had Pseudomonas bacillus, and 6.0% had epidermal and Staphylococcus aureus. Microbial association was detected in 9.0% of the examined patients. The seeded uromicroflora was most sensitive to beta-lactams: amoxicillin with clavulanate (100.0%), cephalexin (95.0%), ampicillin and sulbactan (91%), 3rd and 4th generation cephalosporins had 85.0% and 87.0%.

Detection of urolithiasis in children required surgical treatment, which was eventually performed in 87.0% of patients. The duration of preoperative preparation depended on the localisation and number of concrements, the presence of obstruction and morphological changes in the kidneys. The choice of the method of surgical intervention depended on the localisation of the process, concomitant diseases, the function of the opposite kidney and the general condition of the patients. In 11.0% of children spontaneous removal of concrements was observed, and 2.0% of patients refused surgical treatment due to family circumstances.

Depending on the composition of the stones, the majority of patients had simple stones (73.6%) and 26.4% had complex stones. The basis of the chemical structure of uroliths in 80.4% of cases were oxalates, in 6.5% - urates, in 2.2% - cystine stones, in 8.7% - of mixed composition and in 2.2% - of infectious nature.

In 43% of cases, the predominant localisation of stones in ICH in children was the kidneys. It was the localisation of the nodule that influenced the choice of surgical intervention. In multilocular urolithiasis, the kidney with more pronounced morphofunctional changes was subject to priority sanation. In 3 patients there was a complete loss of function of one kidney with irreversible morphofunctional changes; in these cases nephroureterectomy was performed. In 22 children, reconstructive plastic surgery was performed along with removal of the urolith in case of urinary tract malformations on the side of the intervention.

To study risk factors in the development of urolithiasis, the children of the main group were divided into two subgroups: subgroup A included 39 (39.0%) children with parents in

whom the diagnosis of urolithiasis was confirmed; subgroup B included 61 (61.0%) patients with urolithiasis whose parents had no clinical, laboratory and instrumental signs of ICD. Children with parents in whom ICD was excluded by anamnestic and clinical and laboratory investigations constituted the control group (100).

According to the data obtained from the questionnaire, 17.0% of families in subgroups A and B lived in environmentally unfavourable conditions.

For example, 10.3% of parents of subgroup A had labour activity connected with harmful industries and field work. About 5.1 per cent of parents had bad habits, and 10.3 per cent had sedentary lifestyles.

Questionnaire survey on the presence of chronic diseases in parents identified them among fathers in 16 (41.0%) and among mothers in 24 (61.5%) cases.

Hereditary aggravation for ICD was identified in 73.1% of parents, among which fathers - 19 (48.7%), mothers - 24 (61.5%), while in 7 (17.9%) couples urolithiasis was identified in both parents. It should be noted that 3 (7.7%) parents in subgroup A had undergone surgical interventions for ICH, 5 (12.8%) parents had permanent discharge of small concretions with the development of chronic pyelonephritis (CP), and others were characterised by the presence of small concretions in the kidneys.

Complicated pregnancy was most characteristic of mothers in subgroup A, who also had urolithiasis. According to the questionnaire, 76.9% of the mothers had complicated pregnancy with preeclampsia of varying severity; 71.8% had anaemia, oedema and arterial hypertension in 59.0% of cases, and multivaginal oedema and threat of termination in 25.6%.

Analysis of the incidence of urolithiasis and the relationship of the disease with the use of drugs by the mother during pregnancy in subgroup A showed a direct correlation between the use of antiviral and antibacterial drugs, vitamins and dietary supplements. The dependence of the incidence of ICD in children in subgroup B on maternal use of vitamins and dietary supplements only was determined.

Irrational and unbalanced nutrition has an important role in the development of ICD. While children and parents in the control group consumed predominantly mixed food (61.0%), somewhat less frequently mixed food with preference for dairy (27.0%) or protein (12.0%), subgroups A and B were characterised by consumption of vegetable (46.3% and 47.5%, respectively) or protein (34.4% and 33.2%, respectively) food, whereas consumption of dairy (16.1% and 15.5%) and mixed (3.2% and 3.8%) food was observed only in every fifth child.

Thus, while in the control group parents favoured mixed foods in their children's diet, the diet in subgroups A and B was dominated by vegetable and protein foods, and the daily ration

was irregular, incomplete and unbalanced. It follows that an unbalanced diet with a predominance of vegetable and protein food is a great risk in the development of urolithiasis in children.

Analysis of drinking habits revealed a direct correlation between the quality of water consumed and the development of ICH in children ($\chi 2=2.74$; $p=0.022$). In addition, more than half of the respondents in subgroups A and B - 52% - not only had no information about the quality and quantity of fluid consumed, but most of them (more than 63%) used water from natural water bodies. According to the drinking regimen, the risks of developing urolithiasis increased when the volume of fluid consumed decreased to less than 1-1.5 litres per day.

More than half of the respondents from Urgut district and Samarkand city analysed frequency characteristics of crystalluria revealed predominance of oxaluria. At the same time, according to the data of Samarkand city. Samarkand, compared to Pastdargom district, also had significantly higher concentration of phosphorus in urine. The mean values of uric acid in patients from Urgut district and Samarkand city were higher compared to Pastdargom district, but without statistically significant differences.

Qualitative analysis of urine in subgroup A showed predominance of oxalate stones - 61.3%, among which mainly Ca oxalates - 48.7%; crystalluria (mainly oxalates, phosphates and uric acid) was noted in more than half of patients (61.5%). Less characteristic symptoms were urinary infection, manifested by bacteriuria - 20.5% and leucocyturia - 15.4%, and proteinuria (10.3%). The study of urine pH in pre- and postoperative periods showed its alkalinisation due to the increase in the number of urease-producing bacteria, contributing to the increase in the activity of the infectious-inflammatory process, which is a significant factor in the pathogenesis of stone formation and recurrence of urolithiasis.

The study of metabolic processes both in blood and urine among children with urolithiasis revealed the most frequent metabolic disorders manifested by hyperphosphatemia (92.3%), hypercalcemia (48.7%), hyperuricemia (35.9%), hypercalciuria (82.1%) and hypouricuria (66.7%).

Early gestational age (34±1.2 weeks) is important in the mechanism of development of metabolic disorders in urolithiasis in children, which accordingly affects the further development of the child.

The analysis of metabolism in parents in subgroup A revealed its disorders in the form of hypercalcaemia and hypophosphaturia in 25.6%, hypercalciuria in 20.5%, hypocalcaemia and hyperuricuria in 17.9%, hyperuricaemia in 15.4%, hyperphosphatemia and hypouricuria in

10.3%, respectively. This fact indicates a hereditary predisposition to the development of metabolic changes in children with urolithiasis.

Thus, in children with urolithiasis in subgroups A and B, the main pathogenetic factor in the development of the disease is metabolic disorders (78.0%), also detected in 39.0% of the parents of the respondents. Whereas the presence of any congenital anomalies of the MBC, detected in 22.0% of children, is one of the predisposing factors for the development of urolithiasis. Since metabolic disorders are a genetically determined condition, it allows us to conclude that it is advisable to conduct immunogenetic studies to examine the expression of VDR, IL-1β, IL-18 genes.

All patients of the main and control groups underwent immunogenetic analysis of blood samples for DNA extraction and PCR analysis for vitamin D receptor (VDR), IL-1β and IL-18 genes with subsequent interpretation of the results.

Comparative analysis of the frequency distribution of Fok1 genotype frequencies of the VDR gene polymorphism in the studied groups revealed a significantly significant association of Ff+ff alleles of the VDR gene (Fok1 genotype), which was 1.3 times more frequent in the main group than in the control group ($\chi 2=4.55$; $p=0.05$; $df=1$). But it was found that in the control group, 48% of patients were also found to have Ff+ff allelic variants of the VDR gene (Fok1 genotype). This indicates that the study of this genotype also revealed a predisposition to the formation of urolithiasis in children of the control group.

When determining the polymorphism of the IL-1β gene, the most indicative marker in the formation of uroliths in children of the main group was the C/C allele, which occurred 1.9 times more often than in patients of the control group.

In the comparative analysis of genotype frequency distribution of IL-18 -+105A/C polymorphism genotypes, no significant differences were found between the patients of the main and control groups ($\chi 2=3.93$; $p>0.05$; $df=2$).

Thus, the high risk of ICD formation in children is due to the presence of polymorphism of VDR and interleukin-1β genes. The genetic markers of predisposition to the development of urolithiasis in children are genotype Ff+ff of VDR and genotype C/C of interleukin-1β. Consequently, the above genotypes may serve as immunogenetic predictors of predicting the development of ICH in children at the preclinical stage of the disease.

Based on the above mentioned, it is advisable to test for the presence of markers of Ff+ff VDR genotype and C/C genotype of interleukin-1β in children with high and medium risk of ICH development in outpatient and polyclinic conditions.

In order to predict the possible development of urolithiasis and the formation of appropriate groups of patients, as well as to build a personalised approach to the management of children at the stages of observation, an algorithm for early diagnosis of ICD with regard to risk factors, consisting of 10 points, was developed. According to the first action of the algorithm (on a 10-point scale), the total score allows to distinguish 3 risk groups: 1-3 points - low risk, 4-6 points - average and 7-10 points high risk of urolithiasis development.

When performing the second step of the developed algorithm, an individual routing programme is recommended for children depending on their risk group, including a set of clinical, laboratory, instrumental and immunogenetic methods of investigation for early diagnosis of ICH. Children in the low-risk group (total score from 1 to 3 points) undergo in-depth clinical, laboratory and ultrasonographic examinations and are recommended for follow-up in outpatient clinics according to the approved calendar of preventive examinations.

The average risk group consists of children with a score of 4 to 6 points. Patients with clinical and/or laboratory, instrumental (ultrasound) signs of ICD are referred to a paediatric urologist in a specialised clinic for further comprehensive examination and treatment. In the case when the results of clinical, laboratory and instrumental methods of investigation (ultrasound) do not reveal signs of urolithiasis in children from the average risk group, immunogenetic testing is recommended. If the results of genotyping do not indicate in favour of genetic predisposition to urolithiasis, patients in this group are sent under medical supervision in outpatient and polyclinic conditions. If polymorphisms of VDR and interleukin-1β genes are detected, a set of measures to prevent the development of ICD is carried out.

Particular attention should be paid to the group of children at high risk of developing urolithiasis who scored 7 to 10 points according to the first step of the algorithm. In accordance with the routing scheme we have developed, patients at high risk of developing ICH who have clinical and/or laboratory-instrumental signs of the disease are referred to a paediatric urologist at a specialised clinic. Patients without clinical, laboratory and instrumental signs of urolithiasis are subjected to immunogenetic testing. When immunogenetic testing is performed on children at high risk of developing ICD and in the presence of gene polymorphisms, measures are taken to prevent the development of urolithiasis. In cases when changes at the gene level are not detected in this category of patients, the children are under the supervision of a doctor in an outpatient clinic.

Thus, the algorithm of early diagnosis and prediction of urolithiasis development in children developed by us implies their subsequent routing depending on the risk group (low, medium or high). The measures taken in accordance with the actions of this algorithm will

contribute to the detection of ICD at the preclinical stage, thus preventing its development, various associated complications, recurrence, and, as a consequence, will lead to a reduction in disability and mortality among children in this category.

CONCLUSIONS

1. An epidemiological assessment of the prevalence of urolithiasis in children in Samarkand region has shown that the disease is endemic with the highest zonality in Urgut (28.0%), Pastdargom (10.4%) districts and Samarkand city (14.5%). Territorial variability is associated with geoanthropotechnogenic risk factors (dietary habits, water regime, residence in an environmentally unfavourable zone, presence of urinary tract infection) that influence the formation of prelithiasis and urolithiasis in children. Changes in nutrition and drinking disorders determine the frequency of its diagnosis at school age - 7-16 years.
2. Among endogenous risk factors for the development of urolithiasis in children, gender, genetic predisposition and developmental anomalies of the urinary system organs are of particular importance. The frequency of urolithiasis in boys compared to girls is 2.1:1, which indicates the role of frequent concomitant pathology of the urinary system in the development of urolithiasis in boys.

3. In age groups of patients with urolithiasis there are significant differences in the frequency of the main symptoms: in children under 4 years of age, leukocyturia (77.2%), dysuria (42.8%), haematuria (60.0%) are more frequently registered, and in groups of children aged 5-17 years - pain (95.1%), leukocyturia (87.9%) and haematuria (47.9%). Which necessitates further in-depth examination of children for urolithiasis when the above symptoms are detected.
4. Genetic markers of predisposition to urolithiasis in children are the Ff+ff VDR genotype, which are 1.3 times more frequent in the main group than in the control group ($\chi 2=4.55$; $p=0.05$; $df=1$) and the CC genotype of interleukin-1β, which exceeds 1.9 times the parameters of children in the control group ($\chi 2=7.2$; $p=0.05$; $df=2$). At the outpatient and polyclinic level it is reasonable to include testing for the presence of Ff+ff genotypes and CC polymorphism of VDR (Fok1) and IL-1β genes in the complex programme of early preclinical diagnostics of urolithiasis.
5. The developed algorithm of early diagnosis and prediction of ICD development in children in outpatient and polyclinic institutions will allow to identify the risk group with the construction of a personalised approach to patient routing at the stages of observation.

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LIST OF ABBREVIATIONS

DS	- dietary supplements
URT	- upper respiratory tract
UUT	- upper urinary tract
WHO	- World Health Organisation
DIT	- gastrointestinal tract
IBCh	- Institute of Bioorganic Chemistry
BMI	- body mass index
SC	- salt conglomerates
SCr	- salt crystals
CT	- computed tomography
PMC	- preventive medical centre
USD	- urinary stone disease
US	- urinary system
RU	- review urography
MPD	- maximum permissible dose
MPC	- maximum permissible concentration
RFLP	- restriction fragment length polymorphism
RUS	- renal urothelial stones
PCR	- polymerase chain reaction
SamSMU	- Samarkand State Medical University
USE	- ultrasound examination
USS	- ultrasound sonography
UV-radiation	- ultraviolet radiation
ChP	- chronic pyelonephritis
ES	- endocrine system
EU	- excretory urography
IL-1β	- interleukin-1β
IL-18	- interleukin-18
VDR	- vitamin D receptor