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Modern pathogenetic aspects of urolithiasis development

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Abstract: World experience accumulated in the study of the problem from the standpoint of various fields of knowledge indicates that urolithiasis is probably the most polyetiological disease with a very complex pathogenesis. Despite the successes achieved in the treatment of urolithiasis, relapses of the disease within 5 years can occur in 50% of patients. Today, some genetic polymorphisms associated with urolithiasis are of particular interest: uromodulin, which is involved in the regulation of vitamin D metabolism and calcium metabolism. The study of the problem of urolithiasis has reached a qualitatively new level in recent years due to the use of a multidisciplinary approach and the principles of evidence-based medicine. The expansion of the study of the etiology and pathogenesis of the disease, the development and application of high-tech diagnostic and treatment methods have made it possible to solve many problems.

Keywords: Urolithiasis, gene polymorphism, pathogenesis, etiological factor, diagnostics, morbidity.

Introduction: Urolithiasis (urolithiasis) is one of the most pressing health problems worldwide, as its prevalence increases annually by 0.5–5.3%. The significant prevalence of urolithiasis in the population (at least 5% of the population of industrialized countries) forces us to constantly study the etiology and pathogenesis, look for effective mechanisms for prevention and metaphylaxis, improve diagnostic methods, and develop new technologies for

conservative and surgical treatment [1]. The incidence varies greatly in different countries of the world, averaging: 1–5% in Asia, 5–9% in Europe, 13% in North America, and up to 20% in Saudi Arabia [2].

The importance of urolithiasis has become especially relevant in recent years due to global demographic shifts. The constant shift in the age pyramid of society in developed countries towards an increase in the proportion of elderly and old age groups leads to an increase in the incidence of urolithiasis, which is 8.8% in men and 5.6% in women in the 65–69 age group, compared to 3.7% and 2.8%, respectively, in the 30–34 age group [3]. The prevalence of urolithiasis in countries such as the USA, Italy, Germany, Spain, and Japan has doubled over the past 20 years, and has increased especially rapidly in recent years [4]. Despite the advances made in the treatment of urolithiasis, relapses of the disease within 5 years may occur in 50% of patients. World experience accumulated in the study of the problem from the perspective of various fields of knowledge indicates that urolithiasis is probably the most polyetiological disease with a very complex pathogenesis. There is still no unified concept of the pathogenesis of urolithiasis. The development of the disease is associated with a number of complex physicochemical processes occurring both in the body as a whole and in the kidney and urinary tract. Currently, urolithiasis is considered a multi-etiological disease resulting from dysfunction of the urinary system, gastrointestinal tract, genetic, hormonal and metabolic disorders [5]. Although the so-called "non-modifiable" factors such as gender, ethnicity, geographic location, and genetic characteristics play a significant role in the etiology of urolithiasis [6], however, the importance of "modifiable" risk factors for urolithiasis, such as obesity, diabetes mellitus and metabolic syndrome (MS), is attracting increasing interest from researchers.

Currently, urolithiasis is recognized as a polyetiological disease. The causes of its occurrence are traditionally divided into exogenous and endogenous. Sometimes they are closely interconnected, in some cases it is possible to clearly identify one of the causes. Exogenous causes include climate, biogeochemical characteristics of soils, water, nutritional factors; social and other causes [7]. Endogenous etiological factors are inherent in the human body. They can be genetic, congenital and acquired during a person's life [8]. In the scientific literature, special attention is paid to the role of exogenous factors in the etiology of urolithiasis. These include climatic and geographical, dietary, iatrogenic, socio-economic factors, professions and others [9, 10]. Climate (air temperature, humidity, precipitation, insolation) can contribute to an increase or decrease in the incidence of nephrolithiasis. Biogeochemical characteristics of the territory in which the indigenous population permanently resides also affect the incidence of urolithiasis to one degree or another. The main causes here are the physicochemical state of the soil, drinking water and local food products depending on the level of micro-, macroelements and vitamins [11, 12].

Endogenous etiological factors include changes in kidney tissue [13], pathological changes in the kidneys, urinary tract and urodynamics [14, 15], impaired microcirculation in the kidneys and the presence of infection in them [16], changes in the composition of urine, increased excretion of lithogenic substances [1].

Among the leading endogenous etiological factors in the development of nephrolithiasis, great importance is attached to genetic factors, which can cause the development of polygenically inherited membranopathy, congenital and acquired enzymopathies, tubulopathies and metabolic nephropathies, as well as some monogenic forms of lithogenic substance metabolism disorders [17]. In the last decade, the main direction of studying the genetic risk factors for the development of urolithiasis has been the identification of its association with polymorphic variants of a particular gene. In foreign studies, an association was found between the occurrence of urolithiasis and the polymorphism of some genes, such as KL [18], VDR [20], CASR [19], ORAI1 [21]. The N. A. Lopatkin Research Institute of Urology and Interventional Radiology is also conducting studies on the association of urolithiasis with polymorphisms of various candidate genes. A relationship was found between the occurrence of urolithiasis in the Russian population and the polymorphism of the VDR and ORAI1 genes. No such dependence was found for the TNFRSF11B, TNFSF11, ESR1, KL, CASR, SLC26A6 genes [22]. An association was found between the polymorphism of the ORAI1 gene and the development of calcium oxalate urolithiasis [23]. A relationship was established between the non-recurrent form of the disease and the ORAI1 gene polymorphism, and between the recurrent form and the CASR gene polymorphism [24]. Comparison of the obtained data with the results obtained by Y. Chou [21] in the only foreign work on this gene, conducted in the Chinese population, indicates that the relationship between urolithiasis and the ORAI1 gene was identified in the Russian and Chinese populations. In the only foreign work [21] on the ORAI1 gene, conducted in the Chinese population, an association of urolithiasis with the ORAI1 gene was also established. It is worth noting that the Chinese work, with a similar volume of the main and control groups, included only patients with calcium

urolithiasis and did not study the possible relationship between the formation of multiple urinary stones and the polymorphism of this gene.

An analysis of the literature showed that various genetic risk factors for the formation of calcium, including calcium oxalate, stones were identified in studies by different authors for a number of populations. And these hereditary factors in most cases differ from those found in the present work. An association of calcium oxalate urolithiasis with the Klotho gene polymorphism (KL, rs3752472) was established in the Chinese population [21], and a link was also found with another polymorphism of the specified gene (KL, rsG395A) and the development of calcium urolithiasis in the Turkish population [25]. Polymorphisms of the CASR promoter 1 and CASR (rs R990G) genes are considered a hereditary risk factor for calcium oxalate urolithiasis in the Italian and Iranian populations, respectively [26, 27]. As for the ORAI1 gene (rs7135617), its association with the development of calcium urolithiasis in the population of Taiwan has been shown [26]. Thus, urolithiasis is a multifactorial disease, the development of which is based on the interaction of a number of genes and factors such as high consumption of carbohydrates, sodium, proteins, physical inactivity, etc. In the last ten years, according to foreign literature, studies have been conducted to study the association of one or another gene polymorphism with urolithiasis. Today, some genetic polymorphisms associated with urolithiasis are of particular interest: those involved in the regulation of vitamin D metabolism and uromodulin in the regulation of calcium metabolism. The study of the problem of urolithiasis has reached a qualitatively new level in recent years due to the use of a multidisciplinary approach and the principles of evidence-based medicine. Expanding the study of the etiology and pathogenesis of the disease, the development and application of high-tech diagnostic and treatment methods have made it possible to solve many problems and raise new ones, to identify prospects for future scientific and practical work.

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