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Gender aspects of urolithiasis development in patients with metabolic syndrome

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ABSTRACT

The review summarizes and analyzes the results of domestic and major foreign studies of recent years concerning gender characteristics of the epidemiology and development mechanisms of metabolic syndrome and urolithiasis as an associated disease. A deep understanding of gender aspects in the pathogenesis of these pathologies can form the basis for development of high-quality diagnostic algorithms and pathogenetically grounded approaches to treatment.

Key words: metabolic syndrome, urolithiasis, gender characteristics.

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Гендерные аспекты развития уролитиаза у пациентов с метаболическим синдромом

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РЕЗЮМЕ

В обзоре обобщены и проанализированы результаты отечественных и крупных зарубежных исследований последних лет, касающиеся гендерных особенностей эпидемиологии и механизмов развития метаболического синдрома и мочекаменной болезни как ассоциированного с ним заболевания. Глубокое понимание гендерных аспектов в патогенезе данных патологических процессов может лечь в основу разработки качественных диагностических алгоритмов и патогенетически обоснованных подходов к лечению.

Ключевые слова: метаболический синдром, уролитиаз, гендерные особенности.

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INTRODUCTION

For four decades, the interest of many clinicians and researchers in the problem of metabolic syndrome (MS) has continued to grow. First of all, this is determined by the growth of its social and medical importance associated with its high prevalence and negative consequences. The results of the latest epidemiological studies on all continents of the world make it possible to establish a global trend towards an increase in the spread of MS in the adult world population, a significant part of which are people of working age.

The concept of MS, which united the interests of therapists, cardiologists, and endocrinologists at the end of the last century, is to recognize the existence of a cluster of factors that have a common pathogenetic basis. This symptom complex, according to most researchers, is a combination of risk factors for the development, severe course, and complications of a large number of socially sensitive diseases, which currently determine the structure of morbidity, disability, and mortality among the population. MS and its components (abdominal obesity, arterial hypertension, impaired lipid, carbohydrate, and purine metabolism, and low-grade inflammation) are known to negatively affect the quality of life in patients, which further increases its social significance [1, 2]. The list of diseases and pathological conditions, the development of which is based on modifiable factors united under the concept of MS, continues to grow. Among the pathological conditions associated with MS, in addition to diseases of the cardiovascular system and type 2 diabetes mellitus (DM), urolithiasis should be also mentioned.

Urolithiasis is considered one of the most common chronic diseases. According to a number of recent epidemiological studies, its prevalence varies from 3.5 to 9.6% [3–6] and accounts for about 40% of all diseases of the urinary tract. At the same time, attention is paid to significant differences in this parameter not only in different countries, but also in different social groups. There is a persistent trend towards an increase in the incidence of urolithiasis among the population, which does not depend on age, gender, and race [5]. The social significance of this disease is determined not only by its big share in the structure of morbidity, but also by its propensity for a recurrent course and high frequency of emergency conditions and disability, while the existing methods for removing calculi do not save patients from recurrent urolithiasis [7, 8].

There is still no single point of view on the pathogenesis of urolithiasis. The development of this disease is explained by complex physicochemical processes occurring both in the body as a whole and directly in the urinary tract and kidneys. Urolithiasis is currently considered a multifactorial pathological process resulting from disorders of urodynamics and genetic, hormonal, and metabolic disorders [9]. In the etiology of urolithiasis, the so-called non-modifiable factors, such as gender, ethnic and genetic characteristics, as well as geographic location, play an essential role [6]. However, it is the increasing role of modifiable risk factors in the increase in the urolithiasis incidence that

currently explains the great interest of researchers in studying the influence of such factors as obesity, DM, and MS on the formation of kidney stones to improve the quality of diagnosis and develop effective methods of drug and non-drug correction [10].

For the first time, data on the relationship between urolithiasis and MS were published in 2008 by American researchers, who demonstrated a close correlation between the severity of MS symptoms and cases of urolithiasis. At the same time, the simultaneous presence of four or more components of MS, diagnosed according to the National Cholesterol Education Program (NCEP) criteria, almost doubled the risk of developing urolithiasis [11].

Later, the results of a large-scale study conducted in South Korea at the Asan Medical Center were presented. 34,895 people were examined: they underwent general screening tests, which included anthropometry, blood and urine tests, chest X-ray, respiratory function test, and ECG. The presence of MS was also determined according to the NCEP criteria. The presence of kidney stones was assessed using computed tomography or ultrasound.

Of all the examined individuals, kidney stones were detected in 839 (2.4%) people, MS was diagnosed in 4,779 (13.7%) people. The likelihood of calculi formation grew with an increase in the waist circumference quintile and the level of systolic / diastolic blood pressure ($p < 0.001$). Age, gender, arterial hypertension, and metabolic status were independent risk factors for urolithiasis. The presence of MS had a probability coefficient of 1.25 (95% confidence interval (CI), 1.03–1.50) for the formation of urolithiasis. In subjects with arterial hypertension, the probability coefficient for the presence of kidney stones was 1.47 (95% CI, 1.25–1.71) compared with that for people without arterial hypertension after adjustment for other variables [12].

In the Iranian population, the prevalence of urolithiasis was 14.53%, while patients with this disease were significantly younger and had higher body mass index and blood uric acid levels compared with the average values in the general population [13]. Chinese researchers found that in the presence of urolithiasis, MS was detected 1.74 times more often. A statistically significant relationship was found between these pathological processes, the strength of which increased with a rise in the number of MS components [14].

Currently, contribution of the following factors to the pathogenesis of urolithiasis in MS has been proven: insulin resistance, hyperuricemia, and high levels of free fatty acids. Hyperuricemia is quite common in the clinical practice of a doctor. An asymptomatic increase in the concentration of uric acid in the blood is observed in 5–8% of the population. A close relationship between the level of this parameter in the blood and MS components allowed to consider hyperuricemia one of the manifestations of this symptom complex [15, 16]. Much more often in patients with MS, calculi originating from uric acid salts are found. In individuals with type 2 diabetes, the incidence of uric acid nephrolithiasis is 6 times higher than in patients from the general population [17].

One of the key mechanisms of the uric acid stone formation, along with a decrease in urine output and hyperuricosuria, is the acidic reaction of urine, which is a consequence of insulin resistance. Insulin resistance reduces production and transport of ammonium, which leads to a change in urine pH towards oxidation. Free fatty acids (FFA) are released from adipose tissue in visceral obesity, which contributes to an increase in production of glucose, triglycerides, very low-density lipoproteins (VLDL) and low-density lipoproteins (LDL) and a decrease in production of high-density lipoproteins (HDL) in the liver. It underlies the development of insulin resistance and characterizes dyslipidemia.

Calcium oxalate urolithiasis is the most common type of urolithiasis [17], and its pathogenetic relationship with MS is very complex. The role of MS as a risk factor for calcium oxalate stone formation is often considered insignificant. The pathogenesis of calcium oxalate nephrolithiasis includes increased excretion of lithogenesis predictors, such as oxalates, calcium, uric acid, etc., against the background of a decrease in the excretion of citrates, which act as inhibitors of kidney stone formation. It is followed by a decrease in urine acidity, increased formation of Randall's plaques, and inflammation in the renal tubular epithelium due to oxidative stress associated with insulin resistance [18].

In addition, in the mechanisms of calcium oxalate urolithiasis in patients with MS, the presence of obesity and associated lipid metabolism disorders with chronic low-grade inflammation is of greater importance, in contrast to uric acid lithiasis, where insulin resistance is considered the main pathogenetic factor. Experimental studies and clinical observations indicate a negative effect of dyslipidemia on renal tubular function with the development of hypercalciuria, hyperoxaluria, and hyperphosphaturia with a decrease in the level of citrates in the urine, which characterizes

an increase in its lithogenic properties. Data were also obtained confirming the relationship between other MS components and oxalate urolithiasis. A positive correlation was described between body mass index (BMI) and calcium and oxalate excretion, and a negative correlation – between BMI and citrate excretion.

In the study of the epidemiology, clinical presentation, and pathogenesis of MS and urolithiasis as an associated disease, the attention of some researchers was drawn to gender characteristics in the development of metabolic disorders, understanding of which would make it possible to more effectively select pathogen-specific therapy for patients. Gender differences in the epidemiological parameters of MS are characterized by earlier (from the age of 30 years) appearance of abdominal obesity in men and, as a consequence, a risk of atherosclerosis of different localization and other pathological conditions. For women, the problem of MS and the emergence of related diseases become more relevant during menopause. On the one hand, these features are associated with the influence of sex hormones: the stimulating effect of estrogens and progesterone and the suppressive effect of testosterone. On the other hand, they are related to the peculiarities of adipose tissue distribution, since the morphofunctional features of the adipose tissue in the subcutaneous fat are well known. According to the lipokine theory, white adipose tissue is considered an endocrine organ that synthesizes a large amount of biologically active substances – adipokines, which realize their systemic action by participating in the regulation of various body functions [19–25].

It is currently believed that in the pathogenesis of MS and associated pathological conditions, adipokine imbalance is of great importance, the main manifestations of which are hypoadiponectinemia, hyperleptinemia, and leptin resistance. At the same time, adipokine imbalance has also gender characteristics [26]. There are literature data confirming the statistically significant predominance of the concentrations of adiponectin [27, 28], leptin [29, 30], and resistin [31] in women. Meanwhile, some researchers established gender characteristics of the relationship between some adipokines and both insulin resistance [32] and other clinical and metabolic parameters, including markers of the acute phase of inflammation [26].

Inflammation and oxidative stress, which significant role in the mechanisms associated with MS in pathological conditions has been proven, are also regulated by adipokines. The relationship of clinical and laboratory symptoms of MS (the severity of abdominal obesity, arterial hypertension, impaired carbohydrate metabolism), the intensity of inflammation, and activation of free radical oxidation with adipokine imbalance has gender characteristics. For men, hypoadiponectinemia is crucial in this relationship, and for women – hyperleptinemia [26]. Gender characteristics of urolithiasis development are multifaceted.

Researchers studied gender differences in urine concentration, which may affect the prevalence of urolithiasis in men and women. It was found that both in healthy individuals and in patients with diabetes and / or chronic kidney disease, urine osmolality, calculated urine osmolality, and relative urine concentration index (urine creatinine / plasma creatinine) were higher in men than in women [33]. Urine osmolality increases after protein loading [34]. Urine osmolality in men is already higher before puberty, which is not found in women. Therefore, it is unlikely that sex hormones directly affect urine concentration. A comparative analysis of the concentration of some electrolytes in urine showed that excretion of calcium and oxalates was significantly higher in men, and the level of citrate – in women ($p < 0.05$). These data suggest that lower calcium and oxalate concentrations and higher citrate excretion may reduce the risk of kidney stone formation in women [35].

Seasonal fluctuations of risk factors for the formation of urolithiasis were found. In summer, both men and women had moderate sodium depletion with a corresponding decrease in urinary calcium, while men had a significant decrease in the volume of urine with an increase in calcium oxalate concentration. In women, the level of calcium oxalate was at its highest at the beginning of winter, both due to a decrease in the urine volume and an increase in urinary calcium excretion. A decrease in urine pH in both gender groups was observed in summer, but the pH level in men was significantly lower, mainly due to a high concentration of uric acid [36]. Thus, the risk of kidney stone formation is seasonal. In men, an increase in the concentration of calcium oxalate and uric acid was noted in summer, while in women, a high level of calcium oxalate was noted at the beginning of winter.

Gender differences in the level of vasopressin were determined. They were characterized by higher values for this parameter in the blood plasma and urine of men, as well as by higher threshold of sensitivity to osmotic stimuli in this group [33]. On a biological animal model, the concept of gender differences in antidiuretic reactivity to endogenous vasopressin was confirmed [37, 38]. Higher values of urine con-

centration may be a risk factor for the development of urolithiasis and / or chronic kidney disease and arterial hypertension in men, which requires in-depth study.

Two large studies from France and Germany demonstrate a clear gender correlation of urolithiasis formation in relation to age [39, 40]. In the first decade of life, urolithiasis is more common in boys, while in the second decade, girls, according to these data, suffer from it more often [41]. The largest number of people with urolithiasis was observed in the age groups of 40–49 years and 30–39 years, regardless of gender [39]. Italian researchers found that the process of kidney stone formation can be the result of environmental factors, such as dietary habits and lifestyle. In particular, they noted the influence of increased consumption of animal protein [42].

In Germany, a large-scale study of more than 200,000 urinary stone compositions was carried out for almost 30 years (from 1977 to 2006). The overall ratio of men and women with urolithiasis was 2.4 : 1, and throughout the study, it changed: in 1977 – 1.86 : 1, and in 2006 – 2.7 : 1. At the same time, the peak of kidney stone formation in women was in the age group of 60–69 years, while in men, a plateau at the age of 30–69 years was observed [40]. It was also found that calcium stones were widespread regardless of gender (84% of men, 81% of women). However, in the age group of 60–69 years, the proportion of men among patients with urolithiasis with calcium stone formation was 3 times higher than among women.

Calcium phosphate in the form of carbonate apatite was twice as common in women than in men; it was the third most common calculi after calcium oxalate monohydrate and calcium oxalate dihydrate. Hyperuricemia was more common in men with a 4 : 1 ratio [40]. The incidence of uric acid lithiasis remained steady, with an overall rate of 11.7% in men and 7.0% in women and a peak at an older age in both groups [40]. It was found that 0–9.6% of all analyzed kidney stones were cystine. The level of cystine stone formation remained low; this type of urolithiasis occurred in 0.4% of men and 0.7% of women. The peak incidence in women was between 20 and 29 years of age, while in men, the peak incidence occurred 10 years later, between 30 and 29 years, respectively [40].

In order to study the influence of the MS components on kidney stone formation in relation to gender aspects, a study was carried out in the child population. The study included 94 children (the ratio of boys and girls was 1 : 1.8) who did not take any medications and did not follow a diet prior to treatment for urolithiasis [43]. Overweight children were found to have hypocitraturia, hypercalciuria, and hyperoxaluria compared with children with normal weight.

An assessment of risk factors for kidney stone formation in both groups confirms that being overweight can cause stone formation in both sexes. Likewise, A.L. Negri et al. [44] found that with an increase in BMI in both sexes, there was a significant increase in the excretion of uric acid and oxalate, but a significant decrease in urine pH was noted only in men. In another study of more than 500 people with calcium oxalate stones, a positive relationship was found between BMI and urinary oxalate excretion in women and urinary calcium excretion in men [45].

To determine a possible relationship between urolithiasis and obesity, a subanalysis was carried out. It showed that obesity was a risk factor for the development of urolithiasis in all age groups and in both gender groups, in persons with hypertension and diabetes mellitus. In this subanalysis, obesity in women showed the greatest effect: women with obesity were significantly more susceptible to stone formation than nonobese women (odds ratio (OR) 1.35, 95% CI 1.33–1.37). This effect was less pronounced in men (OR 1.04, 95% CI 1.02–1.06). Being overweight in women increased the risk of urolithiasis by 35% compared with any other parameter [46].

A. Trinchieri et al. conducted a study aimed at assessing the impact of overweightness and obesity on the risk of kidney stone formation in the population following a Mediterranean diet, as well as elucidating the mechanisms underlying the increased risk of urolithiasis observed in obese individuals [47]. A retrospective analysis of data from 1,698 patients with urolithiasis (average age of 45.9 ± 14.6 years; 984 men and 714 women) attending outpatient clinics in Milan and Florence from January 1986 to June 2014 was carried out.

Italian scientists reviewed the records and collected data regarding age, sex, body weight, height, calculus composition, association with type 2 diabetes or gout, and daily urine metabolic profile. In the studied population, overweightness and obesity occurred in 40.7% and 8% of men, respectively, and in 19.9% and 8.7% of women, respectively [47]. The average BMI in patients with urolithiasis was 24.5 ± 7.5 kg / m^2 [47]. BMI values positively correlated with age (p = 0.000), and the average BMI was higher in men than in women (25.5 ± 8.9 versus 23.2 ± 4.4 kg / m^2) [47]. In men with urolithiasis, the rates of overweightness and obesity were higher than in the general population

of Italy in 2004 for the age group of 25–44 years alone [47].

The rates of overweightness and obesity varied significantly in patients with different chemical composition of calculi. In particular, patients with uric acid stones had higher rates of overweightness and obesity than patients with calcium or other types of stones [47]. Additionally, the rates characterizing type 2 diabetes and gout were significantly higher in overweight and obese patients. Besides, in this category of patients, urinary excretion of risk factors for stone formation (calcium, oxalates, and urates) and inhibitory substances (citrate) was significantly higher than in patients with normal weight or who were underweight. The prevalence of overweightness and obesity in patients with urolithiasis in a country following a Mediterranean diet is no higher than in the general population [47].

There is a growing body of evidence suggesting a relationship between insulin resistance or type 2 diabetes and urolithiasis. To assess this correlation, a study was conducted including three large cohorts of over 200,000 participants: the Nursing Health Study (I) (older women), the Nursing Health Study (II) (young women), and the Health Professionals Follow-Up Study (men) [48]. The relationship between diabetes and nephrolithiasis was studied for over 44 years of follow-up. Analysis of the results in the groups listed above showed a relative risk of urolithiasis prevalence: 1.67 in young women with diabetes, 1.38 in older women with diabetes, and 1.31 in men with diabetes.

The relative risk of urolithiasis in participants with diabetes compared with participants without diabetes was 1.60 in young women, 1.29 in older women, and 0.81 in men [48]. It was found that not only type 2 diabetes is associated with an increased risk of urolithiasis, but also a history of urolithiasis increases the likelihood of type 2 diabetes in the future. The authors consider it relevant to diagnose diabetes mellitus in new patients with urolithiasis [48]. This opinion is confirmed by a study which found that the proportion of uric acid stones is 2.2 times higher in patients with diabetes mellitus than in patients with urolithiasis without diabetes, with statistically significant predominance in women compared with men (3.8 versus 1.7) ($p = 0.003$) [49].

CONCLUSION

This literature review showed that gender aspects are of significant importance in the mechanisms of development of MS and urolithiasis as an associated disease. Their further study and understanding are necessary for the development of high-quality diagnostic algorithms and pathogenetically grounded approaches to treatment.

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