

# ASSOCIATION OF UROLITHIASIS WITH OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN: RISK PREDICTORS FOR THE DISEASE

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**Abstract:** Urolithiasis and osteoporosis are two significant multifactorial diseases that cause the constant increase in the number of affected persons due to the increased age of population and negative effects of environmental factors, i.e. unhealthy lifestyle. Those affected by urolithiasis have an increased risk for osteoporosis. Association of urolithiasis and osteoporosis in postmenopausal women is still not completely understood, but it is certain that those diseases may cause serious consequences leading to the permanent disability and even death due to osteoporotic hip fractures. This is why those disorders remain very significant social, economic and health problems not only for those affected but for the whole society, due to very high treatment costs. Identification of risk factors for menopausal women aims at decreasing the rate of disease and improving of preventive measures. Since both disorders are preventable, preventive measures should be applied from young age, with identification of risk factors being extremely important for significant decrease of morbidity rate.

**Key words:** osteoporosis, urolithiasis, postmenopause, risk factors.

## INTRODUCTION

Urolithiasis and osteoporosis are two pathological entities that represent serious metabolic disorders and significantly contribute to increased disability rate of affected persons. Osteoporosis is metabolic bone disease causing very significant public health problems worldwide, with postmenopausal women being especially affected. Also, urolithiasis remains one of the biggest health problems, with its prevalence constantly increasing in the last two decades and its increased rate among female population; studies have shown that more than 7% of women had an episode of symptomatic urolithiasis in their middle age (1, 2).

This review article discusses different pathophysiological mechanisms contributing to development of those diseases, their age and sex distribution, overweight and obesity as important segments of metabolic syndrome, as well as bad lifestyle habits (smoking, drinking coffee and alcohol, insufficient physical activity) as strong predictors of those diseases. Timely preventive measures and educating population on risk factors may greatly reduce mortality and morbidity rates of those diseases.

## PATHOPHYSIOLOGICAL MECHANISMS

Association of urolithiasis and osteoporosis in postmenopausal women may be caused by several reasons. Clinical research revealed increased destruction and reduced bone mass in patients with calcium urolithiasis. Some studies indicated that hypercalciuria and increased excretion of potassium, which are present in majority of urolithiasis patients, turned out to be major risk factors for osteoporosis and bone fracture in postmenopausal women (3-7). In their study, Denburg et al. also concluded that urolithiasis is associated with high incidence of bone fracture, especially in women older than 70 (8). On the other hand, some studies found reduced bone density in patients with normal calciuria (9, 10).

Bone mass is reduced in all patients with urolithiasis, i.e. there is a reciprocal relationship between

urolithiasis and loss of bone mass, regardless of the value of some serum parameters (11). Patients with recurrent calcium urolithiasis and idiopathic hypercalciuria have reduced bone mineral density (BMD), i.e. they have increased incidence of osteopenia and osteoporosis measured by DEXA method (12). In postmenopausal women there may be some additional problems present: negative balance of calcium, which is doubled during menopause, increased values of parathyroid hormone (PTH) and low level of estrogen. All that may result in lower levels of serum calcium, with consequent formation of calcium calculi, reduced bone mineral density (BMD) and development of disease (13,14).

## AGE AND SEX

Regardless of numerous scientific studies, the association of urolithiasis and osteoporosis in women remains controversial (15). It should be emphasized that although urolithiasis and osteoporosis are two different pathological entities, both are characterized with high risk of complications (fracture of hip, spine), especially in older population, which may have severe consequences for the overall health of patients, leading to disability and even death (16). Scientific studies show increased presence of osteopenia and osteoporosis in older population, meaning that patient's age (over 60) represent important risk factor for urolithiasis and osteoporosis. Prevalence of osteoporosis increases with age; 2-8% of men and 9-38% of women over 50 who live in industrialized countries are affected by this disease. Results of numerous studies show that osteoporosis incidence increases with age, approximately by 20% (16, 17). Normal DEXA findings decrease with age, i.e. the percentage of those with abnormal findings is increased in older population (18). New studies by multiple regression show significant impact of age and daily calcium intake on bone mass loss in urolithiasis patients. Significantly reduced bone mass was found in urolithiasis patients compared to control group, and it was more prevalent in older population, especially women in menopause (19).

Urolithiasis prevalence is increased worldwide, including both sexes and different age groups. Women are especially affected in USA. Overweight is important risk factor in development of this disease, as well as insulin resistance and hypertension, conditions met in metabolic syndrome, and they contribute to this phenomenon (20). Recent scientific research revealed higher percentage of urolithiasis patients who also have osteopenia to be women in older age (over 60). Bone mineral density analysis by DEXA method show significantly higher percentage of women with osteopenia and urolithiasis (36.1%) compared to men (2.1%), which represent statistically very significant difference (21).

## OVERWEIGHT AND OBESITY

Numerous studies indicated overweight as significant factor contributing to development of urolithiasis. According to the estimate of World Health Organization (WHO), 1.7 billion people worldwide are affected by obesity (BMI > 30 kg/m<sup>2</sup>) and overweight (BMI 25-29 kg/m<sup>2</sup>), and increased urolithiasis incidence -- higher than 75% was found in overweight and obese patients compared to persons of normal body weight (22-24). Numerous studies revealed that overweight and increasing body mass directly correlated with increased risk of kidney disease like urolithiasis, where increased risk had the tendency of being higher in women than in men (25). Wrobel et al. indicated association of overweight and kidney disease, like calcium-oxalate calculi, with significant results related to BMI, urine pH and urine citrates, but overweight was not found to be risk predictor for recurrent calcium-oxalate calculi (26). Recent studies have shown association between increased BMI and urolithiasis by age groups, i.e. there is statistically significant correlation between older age (over 60) and urolithiasis (27).

For years overweight and obesity have been considered protective factors for bones and osteoporosis development. Nevertheless, new studies show that obesity, being one of main components of metabolic

syndrome, has negative effects on bones despite normal values of bone mineral density (BMD) measured by DEXA method, which is considered to be the consequence of increased mechanical pressure on the bone (28, 29). Ong et al. think that higher BMD is not protective factor for osteoporotic fractures, for significant number of such fractures occurs in obese women due to body habitus or mechanism of injury (30). Research in this area found obesity to be very significant risk factor affecting reduction of bone mineral density and occurrence of vertebral fractures (27, 31). Adipose tissue functions as endocrine organ and releases more adipokines that modulate metabolism, inflammatory reactions, insulin resistance and disrupts normal homeostasis of bone cells, which may cause reduced bone mineral density and disease (32-34). Reference data indicate that overweight and obesity are more prevalent in men with urolithiasis than in women, while the results of linear regressive analysis show significant positive relationship between increased BMI among men and women with urolithiasis ( $p = 0.015$ ) (25, 35).

Data on longitudinal correlation between BMI and bone mineral density from early childhood (early adolescence), being the period in life when bone density is mostly formed, and during its later variations, are very scarce. Also, association of adipose and muscle tissues with bone mineral density in postmenopausal women may be the result of many factors working together, mainly genetic components and different effects of environmental risk factors, which should be within the scope of some future studies.

## GENETIC PREDISPOSITION AND ENVIRONMENTAL FACTORS

There are numerous factors that increase the risk of urolithiasis and osteoporosis. The data indicate increase of urolithiasis prevalence by 70% in the last 15 years, affecting all age and ethnic groups, especially women (36), where it is associated with osteoporosis. Scientists agree that those two diseases represent the consequence of different factors working together, including genetic predisposition, environmental factors (dietary habits, different lifestyles, bad habits), lack of physical activity and sedentary lifestyle.

Despite all the efforts, *genetic predisposition* for urolithiasis has not been clearly identified so far. Genome-wide association studies are widely used for identification of genetic risk factors for different diseases, for they lighten the load of DNA sequence examination with the aim of finding mutations, variants and single nucleotide polymorphisms (SNPs) (37). Such polymorphisms play very important role in determining the genes associated with urolithiasis, and understanding ways of their association might aid in interpretation of genomic initiators of lithogenesis. Also, understanding responsible genes might lead to more effective and directed genetic therapy and better prevention of this disease in the future (38).

The reference data indicate that different environmental factors, together with adopted bad lifestyle habits, may be important predictors of development of diseases like urolithiasis and osteoporosis in postmenopausal women. Increased intake of salt (6, 39), calories (40), animal proteins (41), lower calcium intake (4) and decreased intake of fluids (41) are significant risk factors that individually or in synergism may lead to stone formation. *Smoking* is an independent risk factor for osteoporosis in postmenopausal women (42) and many studies indicate much higher osteoporosis prevalence in group of smokers (31.3%) compared to former smokers (28.6%) or non-smokers (7.5%) (43-45). Also, *excessive consumption of alcohol and coffee* may lead to rapid bone loss in lumbar spine in older postmenopausal women (46-48), which is related to increased risk of fractures. Research revealed that daily consumption of large amounts of alcohol has negative effects on mechanisms of bone remodeling, i.e. has direct negative effects on bone homeostasis (49, 50), thus representing significant risk factor for osteoporosis and bone fracture (51, 52).

*Physical activity* is significant protective factor for bones; more active women are more rarely affected by osteoporosis. It is a known fact that increased bone density results from increased mechanical load on bones and increased activity of bone cells osteoblasts (53). Studies show that recreational sports or

active walking for 30-60 minutes more than twice a week reduces the risk of osteoporosis in women (54). Exercising improve the balance and movement coordination, as well as functional muscle activity, which reduces the risk of falls and fractures (55, 56). That is why regular exercises are required for healthy bones, but physical activities should be adjusted individually.

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