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TOPIC PAPER

Epidemiological gender-specific aspects in urolithiasis

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Abstract
Purpose The incidence of urolithiasis is worldwide increasing and contributes to a rising economic and health care burden. The objective of this review is to identify gender differences in urolithiasis epidemiology in Europe and the USA as well as gender-specific risk factors for urolithiasis.
Evidence acquisition A systematic review of the present literature was performed including English journals without a time limit. The MeSH terms used were as follows: ("Sex Characteristics"[Mesh]) AND "Urolithiasis"[Mesh] or ("Epidemiology"[Mesh]) AND "Urolithiasis"[Mesh]. Additionally, reference search of retrieved papers identified additional references. The MEDLINE database was searched.
Evidence synthesis The prevalence of urolithiasis is rising worldwide including both genders in different age groups. Especially women face an increase in prevalence in the USA. Overweight seems to be an important cause for this development. Additionally insulin resistance and hypertonia, conditions present in the metabolic syndrome complex, contribute to this phenomenon.
Conclusion Stone prevalence across all age groups and both genders is increasing. Lifestyle changes along with increasing prevalence of obesity are key factors for this development. Female gender did significantly differ in the risk ratio of stone development in different variables including body mass index, hyperinsulinemia, and hypertension. It is important to inform the public on measures how to change lifestyle and dietary measures for preventing or lowering events of stone disease.

Keywords Gender · Urolithiasis · Epidemiology · Obesity · Diabetes mellitus

Introduction

A worldwide increasing incidence and prevalence of urolithiasis seems to be more pronounced in industrialized countries [1–3]. Studies from the United States and Europe found that the prevalence and incidence of urolithiasis have increased steadily during the last decades, especially among women, in parallel with an increase in animal protein intake, reflecting the gradual rise in living standards [4–7]. Observations indicate a changing incidence and composition of urolithiasis as well as a dynamic of gender- and age-related incidences [8–10]. US health care data suggest an up to three times higher incidence of symptomatic stone disease in men compared to women [11–13]. This incidence difference seems to be steadily narrowing with a male-to-female ratio of inpatient discharges from 1.7 (1997) to 1.3 (2002) in a study of the Nationwide Inpatient Sample database [14]. However, it is not clear whether those differences represent true stone epidemiology or gender differences in health care utilization [15].

Evidence acquisition

A systematic review of the present literature was performed including English journals without a time limit. The MEDLINE database was searched. The MeSH Terms used were as follows: ("Sex Characteristics"[Mesh]) AND

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"Urolithiasis"[Mesh] and ("Epidemiology"[Mesh]) AND "Urolithiasis"[Mesh]. Studies investigating gender differences in urolithiasis epidemiology in Europe and the USA as well as gender-specific risk factors for urolithiasis were included. Reference searches in retrieved papers identified additional references. Studies reporting wet chemical stone analyses were excluded.

Evidence synthesis

The Medline search ("Sex Characteristics"[Mesh]) AND "Urolithiasis"[Mesh] retrieved 38 articles, and 9 were eligible for inclusion. The term ("Epidemiology"[Mesh]) AND "Urolithiasis"[Mesh] retrieved 5 articles without eligible articles for inclusion. Additional 37 articles were retrieved from reference lists of searched papers. 46 articles were eligible for inclusion.

Urine concentration differences

Osmolality

Perucca et al. [16] performed a review to characterize possible gender differences in urine concentration that could influence gender distribution of urolithiasis. In all studies, whether involving healthy subjects, patients with diabetes mellitus (DM) or chronic kidney disease, urine osmolality, estimated urine osmolality, and the relative index of urine concentration (urine creatinine/plasma creatinine) were higher in men compared to woman. Urine osmolality increases after protein loading [17]. However, according to comparable urea proportions in the urine gender differences did not result from a higher protein intake in men [16]. Compared to females, urine osmolality is already higher in males before puberty. Therefore, it is unlikely that sex hormones directly influence urine concentration. Additionally, no variations in urine concentration were observed between genders at 4–15 years of age [18]. Finally, after the menopause, urine osmolality differences did not change significantly [19, 20].

Sarada and Satyanarayana [21] investigated urinary concentrations in healthy men and women (at four phases of the estrous cycle) to elucidate gender differences in the incidence of Urolithiasis. Calcium excretion was higher in men than in women during phase I (p less than 0.01) and phase II (p less than 0.05) of the estrous cycle. Oxalate excretion was marginally elevated in men compared to women during each phase. Urinary citrate was lower in men compared to women during each phase (p less than 0.05). The data suggest that low concentrations of calcium and oxalate with an elevated citrate excretion might reduce the risk of stone disease in women compared to men.

Parks et al. [22] studied seasonal variations of urine stone risk factors between genders. Both genders showed modest sodium depletion in summer with a corresponding decrease in urine calcium, but men showed a remarkable decrease in urine volume, causing high calcium oxalate supersaturation. Women had maximum calcium oxalate supersaturation in early winter because of decreasing urine volume and increasing urine calcium excretion. Urine pH was reduced during summer, but the decrease was far more marked in men, who had a uric acid supersaturation spike. Overall, men and women differ markedly in the timing of stone risk. Men show a dual summer calcium oxalate and uric acid high risk, while women show a high early winter calcium oxalate high risk.

Vasopressin

Gender differences in vasopressin thresholds may be an influential factor as some studies report higher values for plasma and urine vasopressin levels in men as well as higher sensitivity thresholds to osmotic stimuli in men [16]. Observations of animal experiments support the concept that there is a gender difference in antidiuretic responsiveness to endogenous vasopressin [23, 24]. Whether those differences in concentrating urine might contribute to higher male susceptibility to urolithiasis or chronic kidney disease and hypertension remains to be evaluated (Table 1).

Age

Two large studies from France and Germany demonstrate a clear gender correlation of urolithiasis formation [9, 10]. The overall male/female ratio in the study from Daudon was 2.28. The M/F ratio was the highest in young children,

Table 1 Urolithiasis male-to-female ratio

	Male/female ratio	
Daudon et al. [9]	2.28 (2001)	France
Knoll et al. [10]	2.4 (1977)	Germany
	2.7 (2006)	
Nowfar et al. [36]	1.6 (1998)	USA
	1.5 (1999)	
	1.4 (2000)	
	1.3 (2002)	
	1.2 (2003)	
Lieske et al. [7]	3.1 (1970)	USA
	1.3 (2000)	

whereas it was the lowest in teenagers, young adults, and in very old subjects. In the first decade of live, urolithiasis was more common in boys, whereas in the second decade, girls seemed to be affected more often [25]. A sex ratio of 2 was consistently observed in the age groups between 30 and 79 years. The highest number of calculi was observed in the age groups 40–49 and 30–39 years in males and females, respectively [9]. Trinchieri et al. determined the prevalence of stone formers in a village near Milan, Italy, during two time periods, with an interval of 12 years. The overall prevalence of stone formers at the age of 25 and older among males was 6.8 % in 1986 and 10.1 % in 1998 and that among females was 4.9 and 5.8 %, respectively. The yearly incidence was estimated at 0.4 %, with 0.6 and 0.18 % in men and women, respectively. According to the authors, this marked increase in renal stones could be the result of environmental factors such as dietary habits and lifestyle, in particular the influence of an increased consumption of animal protein [5]. Knoll et al. collected more than 200,000 urinary stone compositions to evaluate age and gender distributions in Germany from 1977 to 2006. The overall male-to-female ratio of 2.4:1 increased from 1977 (1.86:1) to 2006 (2.7:1). While stone formation in females had a peak from ages 60 to 69 years, males showed a stone formation plateau at ages 30–69 years [10].

Stone composition

Calcium-containing stones

The same study from Knoll et al. [10] including more than 200,000 urinary stones found that calcium-containing calculi were most common in each gender (84 % males, 81 % females). The predominance of male calcium stone formers was even higher among elderly patients with a 3.13:1 ratio at ages 60–69. During the study period, the proportion of calcium stones increased from 82 to 86 % in males and 79–84 % in females. Similarly, the study from Daudon et al. [9] including almost 28,000 stones found calcium oxalate to be the predominant stone component in males 64 % and females 55 %. Calcium oxalate monohydrate (COM) was more prevalent in males than in females. Calcium phosphate (CaP) as carbonate apatit was twice more common in females than in males and was the third most common stone composition after COM and calcium oxalate dihydrate (COD).

Uric acid stones

The fourth most common stone composition is uric acid (UA) being more prevalent in males with a ratio of 4:1 [10]. The incidence of uric acid calculi remained stable with an overall rate of 11.7 % in males and 7.0 % in females with a peak at higher ages. In contrast to investigators, who reported a significant increase in the incidence of uric acid stones, the rate of this stone composition remained stable in the German series. This series relied on stone analysis data derived from stones gathered after spontaneous passage or intervention; therefore, a substantial number of uric acid stones that was treated with chemolitholysis might have been missed [10].

Cystine stones

Daudon et al. [9] found 0–9.6 % of all stones analyzed to be cystine. The rate of cystine stones remained rare at 0.4 % in males and 0.7 % in females [10]. The peak incidence in females was found between 20 and 29 years in females compared to males with a peak incidence 10 years later between 30 and 29 years [10].

Infection stones

While the rate of infection stones constantly decreased, infection stones were significantly more common in eastern parts of Germany with a rate of 14 versus 2.9 % in males and 26.7 versus 8 % in females ($p < 0.001$). One possible explanation for this finding could be that the higher incidence of infection stones in eastern parts may result from patients coming from eastern European countries with a lower standard of medical care [10].

Infection stones were rare in the series Daudon et al. [9] and Knoll et al. [10] with a clear decrease in the past decades attributable to improved medical care. Similarly, Trinchieri et al. [26] reported a series of stone analyses from Italy during 15 years with a low number of infection stones. Marickar and Vijay [27] reported a decrease in infection stones in females despite an overall increase in urinary stone formation. The decreasing number of staghorn stones in Europe is in agreement with this observation as infections are the most common cause for staghorn development [28].

Stone recurrence

Approximately 60 % of German and Danish stone formers experienced one stone episode only, whereas 40 % reported stone recurrences [3, 29]. Of patients with stone recurrences, 18 % experienced two, 10 % three, 2 % four, and 10 % $\geq$5 stones episodes [3]. Stone recurrences depend on the study populations investigated. Siener et al. [30] found a stone recurrence in 43 % of 134 recurrent stone formers, whereas Ahlstrand and Tiselius [31] found only a recurrence rate of 26 % in patients consisting of first-time stone formers. No gender differences were observed.

Obesity

Sarica et al. evaluated the possible role of being overweight on stone-forming risk factors in children. 94 children (male/female ratio 1:1.8) who were taking no medication or dietary modifications before stone treatment were included [32]. The overweight children demonstrated hypocitraturia, hypercalciuria, and hyperoxaluria compared with the normal weight children. The evaluation of the stone-forming risk factors in both groups supports that the overweight status might be responsible for stone formation in both sexes. Similarly, Negri et al. [33] found that with increasing BMI, in both genders, there was a significant increase in the urinary excretion of uric acid and oxalate, but a significant decrease in urine pH only in men. In another study of more than 500 calcium oxalate stone formers, there was a positive association between BMI and urinary oxalate excretion in women, and with urinary calcium excretion in men [34].

Taylor et al. investigated stone-forming and non-stone-forming participants in the Health Professionals Follow-up study that included only men, the Nurses's Health study (I) that included older women, and the Nurses's Health Study (II) that included younger women. They found a rising stone incidence with increasing obesity [34, 35]. A greater BMI in males was associated with an increased urinary oxalate, calcium, uric acid, sodium, and phosphate excretion and an inverse relation between BMI and urine pH. In females with greater BMIs compared to lower BMIs, similarly more urinary oxalate, uric acid, sodium, and phosphate excretion were noted again with an inverse relation between BMI and urine pH. An increase in urinary calcium was seen only in younger women. The higher percentage of body fat in women compared with men might explain these findings (Table 2).

Nowfar et al. [36] reviewed the Nationwide Inpatient Sample Database to examine the relationships between obesity, gender, and nephrolithiasis. Approximately 180,000,000 hospital stays with the diagnosis of urolithiasis from 1998 through 2003 were analyzed with a total number of over 898,000 discharges. The male/female ratio of inpatients with stones decreased steadily, from 1.6:1 in 1998 to 1.5:1 in 1999, 1.4:1 in 2000, 1.3:1 in 2001 and 2002, and 1.2:1 in 2003. Male gender, younger age (40 years), and Caucasian race were associated with an increased risk of stone disease even after controlling for gender, race, age, diabetes mellitus, and hypertension. Although diabetes mellitus and hypertension did not increase the risk of urinary stones in the absence of obesity, they did increase the stone risk in obese patients by 32 and 28 %, respectively [36].

To determine whether the relationship of urinary stones and obesity existed across all domains, a subanalysis confirmed that obesity was a risk factor for urinary stones in all ages, both genders, in hypertensive and diabetic individuals. Within this subanalysis, obesity in females demonstrated the largest magnitude of effect: Obese females were significantly more likely to develop stones than non-obese females (OR 1.35, 95 % CI 1.33–1.37). This effect was less pronounced in males (OR 1.04, 95 % CI 1.02–1.06). Being an obese female increased the stone risk more than any other parameter by 35 % [36].

Gillen et al. [37] hypothesized that the association between stone history and blood pressure varies with respect to BMI and gender. Data from over 900 patients with a history of stones and more than 19.000 persons without stones from the Third National Health and Nutrition Examination Survey were analyzed. In women, it was estimated that stone formers experienced a 69 % increase in odds of self-reported hypertension. No significant difference was found in men. Their findings support the link between urolithiasis and hypertension, and suggest that obese women may be at significantly increased risk of hypertension [37].

Semins et al. [38] evaluated a national private insurance database (2002–2006) to identify over 95,000 subjects diagnosed with kidney stones of which over 33.000 had a BMI > 30. Of the 3,257 stone formers, 42.9 % were male and 57.1 % female. Obesity (BMI > 30) was associated with a significantly greater likelihood of being diagnosed with a kidney stone. However, after stratification by BMI, there were no significant differences observed, suggesting a steady risk state once a BMI of 30 is achieved. It is not clear why there was no continuous increase in concert with an increasing BMI. The urinary milieu may be contributory, in that, an increasing BMI is associated with an increase in the excretion of promoters and inhibitors of calcium oxalate stone formation [39, 40]. The finding of increasing stone incidence especially in obese patients provides a potential explanation for the narrowing gender prevalence of urolithiasis.

A similar gender narrowing for symptomatic urolithiasis has been found by Lieske et al. [7]. They collected

Table 2 Gender-specific stone compositions [10]

Stone composition	Male/female ratio	M	W	*p* value
Calcium	2.7:1	84 %	81%	<0.001
Uric acid	3.9:1	11.7 %	7 %	<0.05
Struvite	0.9:1	3.8 %	11 %	<0.001
Cystin	0.95:1	0.4 %	0.7 %	>0.05

epidemiology data for the Rochester population over the years 1970–2000. Age-adjusted incidence of new onset symptomatic stone disease for men was 155.1 (±28.5) and 105.0 (±16.8) per 100,000 per year in 1970 and 2000, respectively. For women, the corresponding rates were 43.2 (±14.0) and 68.4 (±12.3) per 100,000 per year, respectively. On average, rates for women increased by about 1.9 % per year ($p = 0.064$), whereas rates for men declined by 1.7 % per year ($p = 0.019$). The overall man-to-woman ratio decreased from 3.1 to 1.3 during the 30 years ($p = 0.006$). Incident stone rates were highest for men aged 60–69 years, whereas for women, they plateaued after age 30. The reasons could involve changes in diet and lifestyle.

Diabetes mellitus and hypertension

There is growing body of evidence suggesting a relationship between insulin resistance or type 2 diabetes mellitus and urolithiasis. To evaluate this relation, a study of three large cohorts including over 200,000 participants was performed: the Nurses' Health Study (I) (older women), the Nurses' Health Study (II) (younger women), and the Health Professionals Follow-up Study (men) [1]. The association between DM and incident nephrolithiasis was studied over combined 44 years of follow-up. Because insulin resistance can precede the diagnosis of DM by decades, the relation between kidney stones and the diagnosis of incident DM was also observed. The review of the Health Professionals Follow-up Study (HPFS), the Nurses Health Study (I) (NHS I), and the Nurses Health Study (II) (NHS II) showed a relative risk of prevalent urolithiasis of 1.67 in younger diabetic women, 1.38 in older diabetic women, and 1.31 in diabetic men. The relative risk of incident urolithiasis in participants with DM compared to participants without was 1.60 in younger women, 1.29 in older women, and 0.81 in men [1]. It seems not only that type 2 DM is associated with an increased risk of urolithiasis but that a history of urolithiasis increases the probability of being diagnosed with a type 2 DM later in life. Therefore, it might be reasonable to screen new stone formers for diabetes [1]. This proposal is supported by Daudon et al. [41] who found the proportion of uric acid stones to be 2.2 times higher in diabetic than in non-diabetic stone formers, with strikingly more marked difference in women than in men with a ratio of 3.8 versus 1.7 ($p = 0.003$).

Dietary factors

In men and older women, increased intakes of dietary calcium, potassium, alcohol, and total fluid are associated with a reduced risk of stone formation, while supplemental calcium, sodium, animal protein, and sucrose may be associated with an increased risk [42, 43]. In younger women, higher intake of dietary calcium decreases the risk of kidney stone formation, but supplemental calcium does not [44]. Phytate intake was associated with a reduced risk of stone formation. Compared with women in the lowest quintile of phytate intake, the relative risk for those in the highest quintile was 0.63 (95 % confidence interval, 0.51–0.78) [44]. Curhan et al. [42, 43] reported that among men without a history of nephrolithiasis, those with a high intake of calcium (>26.2 mmol per day) had a 34 % lower risk of stone formation than did those with a low-calcium intake (<15.1 mmol per day) a finding which was later confirmed in women. Borghi et al. compared in a 5-year randomized trial the effect of two diets in 120 men with recurrent calcium oxalate stones and hypercalciuria. One diet was a traditional low-calcium diet compared with a diet containing a normal amount of calcium but reduced amounts of animal protein and salt. Increased consumption of water was recommended with both regimens [45]. They concluded that in men with recurrent calcium oxalate stones and hypercalciuria, restricted intake of animal protein and salt, combined with a normal calcium intake, provides greater protection than the traditional low-calcium diet. Recently, Taylor and Curhan [46] conducted prospective studies in the Health Professionals Follow-up Study, the Nurses' Health Study (I) ($N = 94{,}164$ women), and the Nurses' Health Study (II) ($N = 101{,}701$ women). They found that in all groups, higher dietary calcium from either non-dairy or dairy sources is independently associated with lower kidney stone risk.

Conclusion

Stone prevalence across all age groups and both genders is increasing. Lifestyle changes along with increasing prevalence of obesity are key factors for this development. There seems to be an age and gender relationship between stone formation and stone composition. Gender did significantly differ in the risk ratio of stone development in different variables including body mass index, hyperinsulinemia, and hypertension. The evaluation of the stone-forming risk factors in both groups supports that the overweight status might be responsible for stone formation in both sexes. Obese females seem more likely to develop stones than non-obese females, an effect less pronounced in males. A finding provides potential explanation for the narrowing gender prevalence of urolithiasis. It is important to inform the public on measures how to change lifestyle and dietary measures for preventing or lowering events of stone disease.

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