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Original Article

Age and gender-associated metabolic characteristics of urinary stone patients

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The aim of the present study was to investigate sex- and age-associated clinico-metabolic characteristics of urinary stone patients. A retrospective review was performed on data from 2,009 consecutive patients presenting with their first urinary stone episode between 2005 and 2013. Of the 2,009 patients, 1,426 (71.0%) satisfied the inclusion criteria and were enrolled in the study. Patients were grouped by age (<60, ≥60 years old) and sex. The medical history and 24 hr urinary chemistry results of each patient were obtained. The mean age of the 165 (11.6%) patients aged 60 or over was 65.5 ± 4.2 years. Body mass index was greater in elderly females than in younger females (*p*=0.031). After stratification by sex and age, lower urinary excretion of calcium and uric acid was a protective factor for both sexes among the elderly (*p*<0.05, each, respectively). Low urine pH was a common risk factor for both sexes among the elderly (*p*=0.013 in males, *p*=0.047 in females, respectively), whereas lower citrate excretion was a risk factor for only the elderly female group (*p*=0.004). With regard to urinary metabolic abnormalities, elderly females showed higher incidence of hypocitraturia compared to younger females (*p*=0.049). In conclusion, this study demonstrated the sex- and age-associated clinico-metabolic characteristics of urinary stone patients. Thus, it is important to tailor metabolic evaluation and medical prevention therapies for patient according to sex and gender characteristics.

Key words: urolithiasis, aged, sex, risk factors, body mass index

Introduction

The prevalence rate of urolithiasis has been reported to vary between 5% and 12% in men and between 4% and 7% in women in Unitied states [1, 2]. The increase in prevalence observed in the last quarter of the twentieth century in men and women was attributed to both improvements in radiology and changes in environmental factors [1-3].

Incidence of urolithiasis peaks in the fourth to fifth decades of life, with adult men more commonly affected than adult women, after which urinary stone occurrence decreases with age. However, contemporary studies have reported increased incidence of urolithiasis in elderly patients over 60 years old [4-6]. Women display a bimodal distribution of urinary stone disease at ages ranging from 30~39 and 60~69 years, whereas peak incidence in men occurs from 60~69 years [6]. As the number of elderly people continues to rise worldwide [7, 8], increasing prevalence of urinary stones in the elderly is responsible for significant economic costs and has a significant impact on quality of life [4]. Although numerous studies have identified predictive risk factors for urinary stone formation, such as obesity, diabetes or hypertension, family history, and urinary metabolic abnormalities (hypercalciuria, hyperoxaluria, hyperuricosuria, hypocitraturia, and low urinary volume) [8-11], little is known about the metabolic characteristics of elderly stone patients. Suitable preventive measures should be developed by performing metabolic evaluations to elucidate the presence of risk factors for urinary stone formation.

To address these questions, we assessed the clinico-metabolic characteristics of elderly urinary stone patients. Patients' clinico-metabolic parameters were categorized by sex to reduce confounding factors.

Materials and Methods

Study Population

We performed a retrospective, cross-sectional analysis of 2009 consecutive patients presenting with a first-time urinary stone episode who were diagnosed and treated

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between 2005 and 2013 at our institution. Data were collected on urinary stone history, body mass index (BMI), metabolic evaluation (including serum and 24 hr urine chemistry), and radiographic imaging of the urinary tract. Urinary stone formation was diagnosed based on radiologic modalities such as abdominal radiography, ultrasonography, and non-contrast computerized tomography. Exclusion criteria consisted of any of the following: incomplete data collection, age younger than 16 years, impaired renal function (serum creatinine greater than 1.5 mg/dL), presence of staghorn calculi, radiolucent stones, urinary tract obstruction, urological system anomalies, primary hyperparathyroidism, calcium-related medication, hypertension, gout, and other systemic diseases that might affect calcium and bone metabolism. In total, 583 patients were excluded, so analysis was conducted on 1,426 of the 2,009 (71%) original patients. Medications that could affect serum and 24 hr urine chemistry results were discontinued at least 2 weeks before complete metabolic evaluation. Metabolic evaluation was performed at least 4 weeks after completion of stone management.

Measurement and Definition of Parameters

Patients were divided into two groups based on their age at first-time stone episode (≤60 and >60 years old), and within-group comparisons by sex were made. Group allocation for patients with recurrent stones was based on their age at first-time stone episode. The metabolites in 24 hr urine samples were classified into five categories, according to Lifshitz *et al*., in order to assess prevalence of urinary metabolic abnormalities. The groups were as follows: low urine volume (urine volume <2000 mL), hypercalciuria (urinary excretion of calcium >300 mg in men and 250 mg in women), hyperoxaluria (urinary excretion of oxalate >45 mg), hyperuricosuria (urinary excretion of uric acid >800 mg in men and 750 mg in women), and hypocitraturia (urinary excretion of citrate <320 mg) [9].

Statistical Analyses

Patients' clinical characteristics and metabolic parameters according to age and sex were investigated. Summary statistics for continuous variables were presented as mean ± standard deviation. The differences in parameters of urine characteristics between elderly and younger patients were assessed by Student's *t*-test. Categorical variables were compared using the chi-square test or Fisher's exact test. All statistical analyses were performed using SPSS 21.0 software (IBM, Armonk, NY, USA). All tests were performed with 2-tailed analyses, and $p<0.05$ was considered statistically significant.

Results

Baseline Characteristics

Baseline characteristics of study populations (n=1,426) are presented in Table 1. Age categorization resulted in 165 (11.6%) patients in the elderly group (>60 years old) and 1,261 (88.4%) patients in the younger group (≤60 years). Mean (± standard deviation) age of the elderly

Table 1. Clinical characteristics of patients presenting with first-time stone episodes according to sex and age

	Total (n=1426)			Male (n=903)			Female (n=523)		
	≤60 years	>60 years	p	≤60 years	>60 years	p	≤60 years	>60 years	p
No. of patients (%)	1261 (88.4)	165 (11.6)		841 (93.1)	62 (6.9)		420 (80.3)	103 (19.7)	
Mean age ± SD (years)	42.4 ± 10.5	65.5 ± 4.2	<0.001	40.8 ± 10.2	64.6 ± 3.7	<0.001	45.4 ± 10.5	66.0 ± 4.5	<0.001
BMI ± SD (kg/m^2)	24.0 ± 3.2	24.3 ± 3.2	0.302	24.3 ± 3.2	24.5 ± 2.5	0.758	23.5 ± 3.1	24.2 ± 3.6	0.031
Family history of stones (%)			0.772			0.285			0.440
Yes	236 (18.7)	29 (17.8)		157 (18.7)	15 (24.2)		79 (18.8)	16 (15.5)	
No	1025 (81.3)	134 (82.2)		684 (81.3)	47 (75.8)		341 (81.2)	87 (84.5)	
Diabetes mellitus (%)			0.003			<0.001			0.229
Yes	27 (2.1)	11 (6.7)		19 (2.3)	7 (11.3)		8 (1.9)	4 (3.9)	
No	1234 (97.9)	154 (93.3)		822 (97.7)	55 (88.7)		412 (98.1)	99 (96.1)	
Hypertension (%)			0.002			0.005			0.172
Yes	57 (4.5)	17 (10.3)		32 (3.8)	7 (11.3)		395 (94.0)	93 (90.3)	
No	1204 (95.5)	148 (89.7)		809 (96.2)	55 (88.7)		25 (6.0)	10 (9.7)	
Stone size (mm)	7.6 ± 6.6	9.8 ± 7.6	0.001	7.7 ± 6.4	8.2 ± 5.9	0.535	7.3 ± 7.1	10.7 ± 8.3	<0.001

Data are presented as the mean ± standard deviation or the number of patients, with the percentage in parentheses.
The patients' numbers for category of family history and stone episodes included only data from responders of questions.

group was 65.5 ± 4.2 years (range: 60~79 years). There was moderate evidence that BMI was higher in elderly females than in younger females (24.2 ± 3.6 vs 23.5 ± 3.1 kg/m^2, p<0.031). Moreover, the elderly group showed a larger stone size than the younger group at presentation of initial episode (9.8 mm vs. 7.6 mm, p=0.001). Family history of urolithiasis did not differ between the two age groups (p=0.772). Prevalence of diabetes mellitus (19/841, 2.3% vs 7/62, 11.3%, p<0.001) and hypertension (32/841, 3.8% vs 7/62, 11.3%, p<0.005) was significantly higher in elderly men than in younger men.

Urinary Parameters

Urinary excretion of sodium, calcium, and uric acid as well as urine pH were significantly lower in the elderly group than in the younger group (p=0.01, p<0.001, p<0.001, p=0.003, respectively). After stratification by sex and age, lower urinary excretion of calcium and uric acid was a protective factor for both sexes among the elderly (p<0.05, each, respectively). On the other hand, low urine pH was a common risk factor for both sexes among the elderly (p=0.013 in males, p=0.047 in females, respectively), whereas lower citrate excretion was a risk factor for only the elderly female group (p=0.004) (Table 2).

Tables 3 lists the prevalence of urinary metabolic abnormalities by age and sex. Prevalence of hypocitraturia in the elderly female group was significantly higher than in younger female group (p=0.049). In the elderly male group, prevalence of hyperoxaluria was significantly lower than in the younger age group (1.7% vs 12.5%, p=0.006).

Discussion

Recent studies in Germany, the USA, and Japan have

Table 2. Comparison of 24 hr urinary excretion of metabolites for each sex by age group

	Total (n=1426)			Male (n=903)			Female (n=523)		
	≤60 years	>60 years	p	≤60 years	>60 years	p	≤60 years	>60 years	p
Sodium (mEq/d)	201.3 ± 82.5	183.8 ± 83.1	0.010	209.5 ± 84.2	197.0 ± 72.4	0.260	185.0 ± 78.8	176.1 ± 88.2	0.322
Calcium (mg/d)	209.4 ± 100.9	166.7 ± 88.0	<0.001	219.1 ± 102.1	172.8 ± 99.8	0.001	189.8 ± 95.7	162.9 ± 80.2	0.009
Uric acid (mg/d)	647.9 ± 218.2	531.6 ± 193.2	<0.001	689.2 ± 222.8	606.5 ± 209.9	0.005	565.1 ± 182.4	486.0 ± 167.6	<0.001
Magnesium (g/d)	0.01 ± 0.05	0.09 ± 0.04	0.122	0.10 ± 0.05	0.10 ± 0.14	0.791	0.09 ± 0.04	0.09 ± 0.04	0.256
Oxalate (mg/d)	26.6 ± 23.8	23.4 ± 16.4	0.092	26.8 ± 21.8	23.07 ± 10.2	0.191	26.3 ± 27.6	23.5 ± 19.1	0.342
Citrate (mg/d)	374.2 ± 217.7	355.1 ± 206.2	0.289	353.7 ± 203.7	379.2 ± 219.5	0.352	415.6 ± 238.5	340.8 ± 197.6	0.004
Urine pH	5.9 ± 0.7	5.6 ± 0.8	0.003	5.9 ± 0.6	5.6 ± 1.0	0.013	5.9 ± 0.7	5.7 ± 0.7	0.047
Volume (mL/d)	1718.4 ± 666.2	1747.4 ± 779.4	0.601	1755.0 ± 656.9	1677.6 ± 752.2	0.371	1643.5 ± 678.9	1790.1 ± 796.0	0.058

Data are presented as the mean ± standard deviation or the number of patients, with the percentage in parentheses.

Table 3. Prevalence of urinary metabolic abnormalities for each sex by age group

	Total (n=1426)			Male (n=903)			Female (n=523)		
	≤60 years	>60 years	p	≤60 years	>60 years	p	≤60 years	>60 years	p
Low urine volume (%)	42.5	45.5	0.262	40.5	48.4	0.232	38.6	47.6	0.116
Hypercalciuria (%)	27.2	16.0	0.054	21.0	14.5	0.257	23.0	16.8	0.226
Hyperuricosuria (%)	23.1	11.0	<0.001	27.9	17.7	0.103	13.4	6.9	0.089
Hyperoxaluria (%)	11.9	4.9	0.007	12.5	1.7	0.006	10.8	6.9	0.273
Hypocitraturia (%)	44.2	44.2	1.000	47.0	38.7	0.236	38.6	47.6	0.049

*Low urine volume: urine volume less than 2000 mL/day; hypercalciuria: calcium excretion greater than 300 mg/day in men and 250 mg/day in women; hyperoxaluria: oxalate excretion greater than 45 mg/day; hyperuricosuria: uric acid excretion greater than 800 mg/day in men and 750 mg/day in women; and hypocitraturia: citrate excretion less than 320 mg/day.

reported increased urinary stone occurrence in elderly patients over 60 years of age [4-6]. Annual incidence of urinary stone formation as well as age of peak occurrence in Japan rose from 1965~2005 over that time period in both men (from 20~49 years in 1965 to 30~69 years in 2005) and women (from 20~29 years in 1965 to 50~79 years in 2005) [4]. As the number of elderly people has risen worldwide [7, 8], increasing prevalence of urinary stones in the elderly has significant economic costs and a significant impact on quality of life [4]. In our results, the elderly group showed a larger stone size than the younger group at presentation of initial episode (p=0.001). Krambeck *et al.* previously reported a larger urinary stone size in elderly patients, and stones in elderly patients were less likely to pass spontaneously and more likely to require surgical intervention (p<0.001) [10]. Thus, initial stone management in elderly patients should be carried out in light of all risk factors. Metabolic abnormalities such as hypercalciuria, hyperoxaluria, hyperuricosuria, and hypocitraturia as well as low urine volume are some well-known risk factors for stone formation. Amaro et al. previously reported hypercalciuria and hypocitraturia as risk factors for stone formation [11]. However, lithogenic risk factors such as urinary excretion of calcium, sodium, and uric acid were significantly less prevalent in the elderly group than in the younger group. This suggests that the elderly group exhibited greater protective characteristics against stone formation than the younger group, which might explain the lower frequency of stone episodes in the elderly group. Other than metabolic abnormalities, known risk factors for stone formation include obesity [12-15]. Additionally, risk of stone formation in obese patients, especially women, might be elevated as a result of increased mean urinary calcium excretion and lower citrate excretion [13, 14]. Obesity is associated with also changes in environmental factors, such as lifestyle and dietary habits and particularly increased consumption of animal protein. In addition, postmenopausal status may render elderly female patients more prone to a high BMI since menopause is associated with altered patterns of fat deposition and distribution of body fat. Therefore, estrogen deficiency after menopause has a negative influence on fat metabolism, leading to central obesity [16, 17]. Our observation of increased BMI in elderly women partially reinforces previous reports that a high BMI in elderly female patients is associated with abnormalities in urinary metabolites and stone composition [10, 13, 15, 18]. As urine pH is negatively related to BMI [11], obese patients may have a lower urine pH in addition to insulin resistance [19]. Insulin acts as the proximal renal tubule Na/K exchanger and is involved in transport or ionic trapping of ammonium in the tubular lumen [20]. Thus, patients displaying insulin resistance may have hyper-acidic urine owing to an impaired ability to excrete ammonium [21]. Persistence of hyper-acidic urine induces formation of uric acid nephrolithiasis [22, 23] and is usually associated with low urinary excretion of citrate [24] leading to hypocitraturia [25, 26]. Citrate inhibits growth of calcium oxalate and phosphate stones [27]. Thus, hypocitraturia is a major risk factor for calcium stone formation. In the present study, increased levels of risk factors for stone formation, namely a low urine pH and reduced excretion of urinary citrate, were identified in elderly female patients. These results suggest that dietary modification and weight control to correct these lithogenic risk factors in elderly patients may help to reduce stone formation. Dietary modification is very important to reduce risk of stone formation. Alkaline diets rich in potassium, fruits, and vegetables are associated with elevated citrate excretion [28]. Therefore, patients with hypocitraturia could prevent urinary stone formation by consuming greater amounts of these foods. Further, weight control through adequate physical activity, balanced nutrition, and sufficient fluid intake has been shown to improve low urine pH. Thus, appropriate dietary behaviors and weight control might reverse abnormal urine metabolite formation and reduce stone formation in elderly patients. Lastly, our study had two weaknesses. First, not all patients presenting with a first-time stone episode were enrolled in this study, owing to incomplete data. Second, this study was cross-sectional in design, and the study population was collected over a short period. To overcome these concerns, we plan to collect more metabolic profiles of elderly urinary stone patients over a longer period.

Our results demonstrate that elderly urinary stone patients displayed both protective and risk factors for stone formation. Lower urinary excretion of calcium and uric acid was a protective factor for both sexes among the elderly. Low urine pH was a common risk factor for both sexes among the elderly, whereas lower citrate excretion was a risk factor for only the elderly female group. Thus, it is important to tailor metabolic evaluation and medical prevention therapy for patients according to sex and gender characteristics.

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