

CLINICAL SCIENCE

Metabolic assessment of elderly men with urolithiasis

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OBJECTIVE: To assess the presence of metabolic disorders in elderly men with urolithiasis.

METHODS: We performed a case-control study. The inclusion criteria were as follows: (1) men older than 60 years of age and either (2) antecedent renal colic or an incidental diagnosis of urinary lithiasis after age 60 (case arm) or (3) no antecedent renal colic or incidental diagnosis of urolithiasis (control arm). Each individual underwent an interview, and those who were selected underwent all clinical protocol examinations: serum levels of total and ionized calcium, uric acid, phosphorus, glucose, urea, creatinine and parathyroid hormone, urine culture, and analysis of 24-hour urine samples (levels of calcium, citrate, creatinine, uric acid and sodium, pH and urine volume). Each case arm patient underwent two complete metabolic urinary investigations, whereas each control arm individual underwent one examination. ClinicalTrials.gov: NCT01246531.

RESULTS: A total of 51 subjects completed the clinical investigation: 25 in the case arm and 26 in the control arm. In total, 56% of the case arm patients had hypocitraturia (vs. 15.4% in the control arm; $p=0.002$). Hypernatruria was detected in 64% of the case arm patients and in 30.8% of the controls ($p=0.017$).

CONCLUSION: Hypocitraturia and hypernatruria are the main metabolic disorders in elderly men with urolithiasis.

KEYWORDS: Urolithiasis; Calculi; Citrate; Metabolism; Aging; Elderly.

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INTRODUCTION

The increase in male life expectancy has provoked many inquiries into health disorders and quality of life with respect to the natural aging process. Populational aging is characterized by a higher proportion of people who reach advanced ages combined with shrinking numbers of children and young people in that group. According to the World Health Organization (WHO), aging is defined as living beyond 60 years in a developing country or 65 years in a developed country. The number of aging people is increasing faster than is any other age group: in 2025, there will be an estimated 1.2 billion individuals over the age of 60, and this number could reach two billion by 2050 (1). Urolithiasis is a public health problem affecting approximately 300 men and 100 women out of every 100,000 people (2). At present, the incidence of urolithiasis in aging people is increasingly, particularly in industrialized countries (3-5). Little information is available about urolithiasis in older

individuals, especially with respect to metabolic disorders that may be helpful for the clinical treatment of these individuals.

MATERIALS AND METHODS

This project was approved by our Hospital Ethics Committee (protocol number 0688/07) in October 2007. It was also registered in Clinical Trials (www.clinicaltrials.gov): NCT01246531. All patients provided written informed consent for their participation in the study. We performed a case-control study with patients who were recruited from a database of the Urologic Clinic between January 2008 and January 2010.

The inclusion criteria for the case arm were applied to patients from the Urinary Lithiasis database: (I) men older than 60 years of age (II) who had a first episode of renal colic (lumbar or flank pain) or an incidental diagnosis of renal stones after age 60. The patients in the control arm were selected from a database of men with benign prostate hyperplasia (BPH). The inclusion criteria were as follows: (I) men older than 60 years of age and (II) with no diagnosis of renal stones at any point in their lives. All patients were asked about their stone disease history (renal colic, age at the first lithiasic episode, incidental urolithiasis diagnosis, antecedent shockwave lithotripsy or surgical therapies for renal and/or ureteral calculi), persistent

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No potential conflict of interest was reported.

urinary tract infection, family history of renal stones, clinical comorbidities (e.g., hypertension, diabetes, dyslipidemia, gout) and drug use (including alcohol consumption and smoking). All subjects underwent the following metabolic assessments:

- Blood tests: total calcium, ionized calcium, uric acid, phosphorus, glucose, creatinine, urea and parathyroid hormone (PTH) levels;
- Type I urinalysis and urine culture;
- 24-hour urine samples: calcium, citrate, creatinine, uric acid and sodium levels, pH and volume.

Each case arm patient underwent two complete metabolic urinary investigations, and the control arm patients underwent one metabolic urinary investigation with three 24-hour urinary samples, as described previously.

Imaging examinations, including abdominal X-rays, abdominal ultrasonography, and unenhanced abdominal computed tomography (CT) (if necessary), were conducted for documentation purposes.

Frequency analyses and descriptive statistics i.e., mean and standard deviation (SD), were performed. The Student's t-test was used to compare the case and control arms. The associations between the independent data from the case and control arms were tested using the chi-squared test. If the expected value in any category was less than or equal to five, Fisher's exact test was performed instead of the chi-squared test. Independent variables that demonstrated statistically significant differences were tested by univariate logistic regression analyses. Multiple logistic regression analysis evaluated the relationship between hypocitraturia and hypernatruria, adjusting for thiazide use based on our theoretical understanding of the effects of thiazide diuretics on renal metabolism (6). Statistical significance was set at $p < 0.05$. All statistical analyses were conducted using SPSS for Windows 18.0 software (Chicago, IL).

RESULTS

After applying the inclusion criteria, 70 patients were selected to participate in the clinical protocol. Nineteen patients did not complete the clinical study, with seventeen lost to follow-up (eight patients from the case arm and nine from the control arm). Two individuals were diagnosed with prostate cancer during the study and were discharged for oncologic management (one from each arm). In total, 51 men completed the protocol: 25 in the case arm and 26 in the control arm.

The two groups were statistically comparable in terms of their demographics, comorbidities, smoking and alcoholic beverage consumption habits, and thiazide use (Table 1).

Twenty patients from the case arm had comorbidities: systemic arterial hypertension (n=11), diabetes mellitus (n=7), and gout (n=3). In the control arm, there were 21 men with comorbidities: systemic arterial hypertension (n=13), diabetes mellitus (n=4), and gout (n=1).

The blood metabolic assessments revealed no significant disorders (Table 2).

The urinary metabolic assessments revealed hypocitraturia in 56.0% of the case arm patients and 15.4% of the control arm patients ($p = 0.002$). Hypernatruria was detected in 64.0% of the case arm patients and in 30.8% of the controls ($p = 0.017$). No additional statistically significant differences were present for the remaining variables (Table 3). These findings were confirmed by the univariate analyses and multiple logistic regressions. Hypocitraturia and elevated urinary sodium levels were independent risk factors for urinary lithiasis, even when adjusted for thiazide use (Table 4), which would be considered a confounding factor in the analysis. Another notable observation was the presence of an altered urinary pH in 11 patients of the case arm compared with five individuals from the control arm, a difference that approached statistical significance ($p = 0.057$).

Table 1 - Demographics, comorbidities, smoking and alcohol consumption habits and thiazide use.

Variable	Cases		Controls		p-value
	\bar{x}	(SD)	\bar{x}	(SD)	
Age (years)	68.3	(5.4)	67.8	(5.9)	0.750*
	(60 - 78)		(60 - 83)		
Weight (kg)	79.2	(11.7)	74.9	(11.0)	0.177*
	(59 - 103)		(60 - 100)		
	n	(%)	n	(%)	p
Race					
Caucasian	22	(88.0)	24	(92.3)	0.668 [†]
Non-Caucasian	3	(12.0)	2	(7.7)	
Alcohol consumption					
No	17	(68.0)	20	(76.9)	0.475
Yes	8	(32.0)	6	(23.1)	
Smoker					
No	23	(92.0)	21	(80.8)	0.419 [†]
Yes	2	(8.0)	5	(19.2)	
Medical disorders					
No	5	(20.0)	6	(23.1)	0.789
Yes	20	(80.0)	20	(76.9)	
Thiazide use					
No	22	(88.0)	20	(76.9)	0.465 [†]
Yes	3	(12.0)	6	(23.1)	
Total	25	(100)	26	(100)	

*Student's T-test; [†]Fisher's exact test; SD = standard deviation.

Table 2 - Metabolic assessment (blood tests).

Variable	Cases		Controls		p-value
	n	(%)	n	%	
Total calcium (RV: 8.6 – 10.2 mg/dl)					
Normal	22	(88.0)	25	(96.2)	0.350 [†]
High	3	(12.0)	1	(3.8)	
Ionized calcium (RV: 4.6 – 5.3 mg/dl)					
Normal	22	(88.0)	24	(92.4)	0.668 [†]
High	3	(12.0)	2	(7.7)	
Uric acid (RV: 3.4 – 7.0 mg/dl)					
Normal	20	(80.0)	20	(76.9)	0.789*
High	5	(20)	6	(23.1)	
Phosphorus (RV: 2.7 – 4.5 mg/dl)					
Normal	20	(80.0)	20	(76.9)	0.789*
Low	5	(20.0)	6	(23.1)	
Glucose (RV: 65 – 99 mg/dl)					
Normal	10	(40.0)	9	(34.6)	0.691*
High	16	(60.0)	17	(65.4)	
Urea (RV: 10 – 50 mg/dl)					
Normal	22	(88.0)	25	(96.2)	0.350 [†]
High	3	(12.0)	1	(3.8)	
Creatinine (RV: 0.6 – 1.5 mg/dl)					
Normal	23	(92.0)	25	(96.2)	0.610 [†]
High	2	(8.0)	1	(3.8)	
PTH (RV: 16 – 87 pg/dl)					
Normal	22	(88.0)	18	(69.2)	0.103*
High	3	(12.0)	8	(30.8)	
Total	25	(100)	26	(100)	

RV = reference value.

DISCUSSION

Urinary lithiasis in elderly people has an estimated prevalence of 10–12% and an estimated incidence of 0.1–2% (7). In Japan, the prevalence reaches almost 9.6% and predominantly affects men (71.7%) (8). No consensus exists on the worldwide prevalence of urolithiasis in aging individuals, and even given the recent increase in incidence, there are few studies on this subject in the urological literature.

Urolithiasis is a disorder that may cause a higher morbidity rate in older people than in younger people, mainly due to urinary obstruction related to stone migration and infectious complications (9). Recently, some authors have assessed the aspects and outcomes of extracorporeal shock wave lithotripsy (SWL) (10-14), percutaneous nephrolithotomy (15-17) and ureteroscopy (18) for elderly patients with renal or ureteral stones. However, no recent studies have involved metabolic assessments of urinary lithiasis in aging subjects.

We performed a case-control study that was initially designed as a pilot study with 70 patients. Unfortunately, we lost almost 25% of our sample, which is higher than the normal attrition rate of 10% reported in a majority of studies. Most patients who stopped the study cited the 24-hour urine gathering protocol and transportation to the clinical laboratory as their main reasons for withdrawal. A case-control study design was selected because the sample size was small (because urinary lithiasis is not common in aging people) and no comparative studies existed on

Table 3 - Metabolic assessment: 24-hour urine samples and urine culture.

Variable	cases		Controls		p-value
	n	(%)	n	%	
Calcium (RV: 100 – 240 mg)					
Normal	22	(88.0)	18	(69.2)	0.103*
High	3	(12.0)	8	(30.8)	
Citrate (RV: > 290 mg)					
Normal	11	(44.0)	22	(84.6)	0.002*
Low	14	(56.0)	4	(15.4)	
Creatinine (RV: 1.04 – 2.35 g)					
Normal	25	(100)	26	(100)	
High	0	(–)	0	(–)	
Sodium (RV: 40 – 220 mEq)					
Normal	9	(36.0)	18	(69.2)	0.017*
High	16	(64.0)	8	(30.8)	
Uric acid (RV: 0.2 – 0.75 g)					
Normal	20	(80.0)	23	(85.5)	0.465 [†]
High	5	(20.0)	3	(11.5)	
Volume 24 hours (RV: >or= 20 ml/kg/day)					
Normal	17	(70.8)	21	(80.8)	0.411*
Low	7	(29.2)	5	(19.5)	
pH (RV: 6 – 7)					
Normal	14	(56.0)	21	(80.8)	0.057*
Altered	11	(44.0)	5	(19.2)	
Urine culture (RV: Negative)					
Negative	23	(92.0)	22	(84.6)	0.668 [†]
Positive	2	(8.0)	4	(15.4)	
Total	25	(100)	26	(100)	

RV = reference value; *Chi-square test; [†]Fisher's exact test.

metabolic assessments in aging men with urolithiasis. Another advantage of the case-control design is its ability to evaluate the feasibility of more complex and expensive future projects.

The control arm did include individuals with BPH, which could have introduced possible selection bias (e.g., limited fluid intake due to nocturia and/or urinary frequency). Patients from the control arm presented with higher urinary volumes than did those in the case arm: 80.8% vs. 70.8%, although this difference was not significant.

We did not include women in this study because of the potential effects of postmenopausal physiology and hormonal replacement therapy (HRT), which could produce questionable outcomes in the metabolic assessments. Maalouf et al. investigated 25,000 postmenopausal women and documented an association between hormonal replacement therapy and the development of urinary lithiasis (19), which was mediated by exacerbated calcitriol production (an estrogenic effect) leading to an increase in the intestinal absorption of calcium. Another clinical study assessing women undergoing HRT over the course of ten years found no increase in urinary lithiasis events (20).

None of the patients had undergone gastric bypass surgery, another potential cause of hyperoxaluria, which could have resulted in confounding. All individuals from the case arm were asymptomatic during the study, and radiologic examinations did not reveal any obstructive

Table 4 - Multiple logistic regression.

Variable	OR _{adjusted}	IC _{95%}	p-value
Urine citrate			
Normal	1.0		
Low	7.12	1.74 – 29.21	0.006
Urine sodium			
Normal	1.0		
High	4.0	1.07 – 14.96	0.039
Thiazide use*			
No	1.0		
Yes	0.79	0.15 – 4.27	0.782

*adjusted variable.

ureteral calculi or other complication(s) or sign(s) of urolithiasis.

Despite the theoretical importance of some comorbidities in the pathophysiology of nephrolithiasis, the small sample size did not allow us to draw any conclusions on these kinds of associations. However, no significant differences were observed between the cases and controls in terms of the occurrence of comorbidities.

Hypocitraturia and hypernatruria were the main metabolic disorders identified in our study. Urinary citrate is an important inhibitor of calcium oxalate/phosphate lithogenesis. The prevalence of hypocitraturia has been estimated at 20–50%, mostly in association with other metabolic disorders (21). No established data exist on the prevalence of hypocitraturia in aging people with urolithiasis. In a retrospective study, Usui et al. found that 5% of the subjects had low urinary citrate levels, but they did not exclude subjects with a prior urolithiasis diagnosis before the age of 60 (8). In another retrospective study, Gentle et al. found that 29% of elderly individuals were hypocitraturic, and 40% of these individuals were first diagnosed with urinary lithiasis before the age of 50. In both studies, the authors were most likely analyzing chronic stone-formers who had had this condition since their third and fourth decades of life in addition to individuals who started having symptoms after 60 years of age (22). One explanation for the predominance of hypocitraturia in this age group could be specific dietary habits, including high protein and salt intake. The resultant acidotic state would promote low urinary citrate excretion through proximal convoluted tubule reabsorption, balancing the intracellular pH (23). Another consequence of acidosis is bone calcium mobilization with transitory hypercalciuria, which increases the lithogenic risk of developing calcium kidney stones (24,25).

High levels of urinary sodium reduce calcium reabsorption via the proximal convoluted tubules, promoting mild systemic acidosis that increases the risk of calcium lithogenesis (26). An association often exists between high salt intake and hypocitraturia because of the resulting acidotic state (27). We identified nine patients in the case arm with hypocitraturia associated with hypernatruria, as suggested above. The ingestion of a sodium rich diet plays an important role in the formation of calcium oxalate stones, and this association may also explain the high occurrence of hypernatruria in the case arm patients.

The hypercalciuria levels did not differ between the case and control arms. Hypercalciuria is the most common metabolic disorder in chronic stone-formers (approximately 60%) (28). The low occurrence of hypercalciuria serves as additional evidence that aging people have distinct

pathophysiological features compared with younger subjects, including features related to urinary lithiasis.

Our study has several limitations. First, we did not analyze urinary oxalate levels in the 24-hour urine samples because it is not a standardized test in our clinical laboratory. Taylor et al. performed a retrospective study based on three cohorts, totaling 3,348 subjects and including both urolithiasis formers and non-formers (29), to evaluate the relationship between dietary oxalate and urinary oxalate. Diabetics and obese people presented with high levels of urinary oxalate, but an assessment of the age factor revealed that the older the individual, the more minor his/her urinary oxalate levels; in other words, an inversely proportional relationship exists between age and urinary oxalate levels (29).

The association between urolithiasis and the metabolic syndrome was not approached in this study. At the time of the conception of this study, that association had not yet well established. However, the metabolic syndrome in patients with urolithiasis seems to be more common in aging individuals than in younger individuals (30).

In conclusion, hypocitraturia and hypernatruria are the main metabolic disorders found in aging men with urolithiasis.

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AUTHOR CONTRIBUTIONS

Freitas Jr CH conceived the study, defined and organized the database, evaluated the outcomes and statistical assessment, and was responsible for the literature review (discussion). Mazzucchi E conceived the study, defined and organized the database, evaluated the outcomes and statistical assessment. Danilovic A and Brito AH were responsible for critical analysis of the materials, methods and results. Srougi M was responsible for final analysis and approval of the manuscript for submission.

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