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SYMPOSIUM PAPER

Role of overweight and obesity on the urinary excretion of promoters and inhibitors of stone formation in stone formers

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Abstract In recent decades there has been an increasing prevalence of urolitithiasis in many western countries and at the same time there has been an increasing progression of obesity that has reached epidemic proportions. The aim of the present study was to assess the influence of overweight/obesity on the metabolic risk factors for renal stone formation. We studied 799 renal stone formers (462 men and 337 women) who came to the clinic for metabolic risk factors evaluation. They were all studied with a standard protocol (two 24-h urine collections and serum parameters). They were divided according to their BMI in normal (BMI < 25) overweight (BMI 25–29.9) and obese (BMI > 30). Low-weight individuals were excluded. Overall, 487 of 799 (60.9%) patients had a BMI > 25, including 40.6% overweight and 20.3% obese. Among women 55.2% had normal weight, 25.5 were overweight, and 19.3% were Obese; among men 27.3% had normal weight, 51.7 were overweight, and 21% were obese. Age increased significantly with increasing BMI both in men and women. In women there was a significant increase in the excretion of oxalate, uric acid, phosphorus, creatinine, and sodium with increasing BMI, but no change was observed in calcium, magnesium, citrate, and urine pH. In men there was a significant increase in the excretion of oxalate, uric acid, creatinine, phosphorus, sodium, magnesium, and citrate with increasing BMI, no change in urinary calcium and significant progressive decrease in urinary pH. In this population of stone formers there was a high prevalence of overweight/obesity (60.9%). Both in men and women we found a significant increase in the urinary excretion of two promoters of stone formation, oxalate, and uric acid but no change in urinary calcium. There was either no change or increase in magnesium and citrate, inhibitors of crystallization, and a significant decrease in urine pH only in men.

Keywords Renal lithiasis · Metabolic risk factors · Body size · Overweight

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Introduction

In recent decades there has been an increasing prevalence of urolitithiasis in many western countries [1, 2]. At the same time there has been a growing epidemic of overweight/obesity in industrialized nations [3, 4]. This temporal parallelism of increased stone formation and overweight/obesity has suggested a possible relationship between them. Several epidemiologic studies have shown an association between body size and nephrolithiasis

[5–8]. However, the mechanisms that relate greater body size to increased stone risk are not yet clarified.

Several studies have analyzed the relationship between the urinary excretion of stone promoters and inhibitors and body size in normal subjects and stone formers. A study in healthy subjects has indicated that body size is a major determinant of urinary oxalate excretion [5]. In a study of nearly 6,000 stone formers, those heavier than 120 kg excreted more calcium, oxalate, and uric acid compared to those weighting less than 100 kg, but because of differences in urinary volume, urinary calcium and oxalate concentrations were similar [9]. 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 (10). Taylor and Curham [10] analyzed the 24-h urinary excretion of promoters and inhibitors of stone formation in big cohorts of stone-forming and non-stone forming subjects divided in several categories of body size. Participants with greater BMIs excreted more urinary oxalate, uric acid, sodium, and phosphate than participants with lower BMIs. The positive associations they found between BMI and urinary calcium excretion did not persist after adjustment for sodium and phosphate excretion. Urinary supersaturation for uric acid increased with BMI but not for calcium oxalate. This was probably due to the fact that urinary pH decreased as BMI increased both in non-stone formers and stone formers. This inverse association between urinary pH and body weight had been previously shown in more than 4,500 patients with history of kidney stones [11].

In this study we evaluated the relation between body size and the urinary excretion of promoters, and inhibitors of renal stone formation in a large population of stone formers.

Materials and methods

Study population

We retrospectively reviewed the charts of 799 renal stone formers (462 men and 337 women) with a mean age of 43.9 ± 12.6 years, who came to the clinic for metabolic risk factor evaluation. Patients with renal failure, prolonged immobilization, or those who were taking drugs that could affect mineral metabolism (corticosteroids, diuretics, and anticonvulsants) were not included. They were grouped according to their sex and BMI. BMI was calculated as weight in kilograms divided by the square of height in meters. BMI was categorized as normal (BMI, 18.6–24.9) overweight (BMI, 25–29.9), and obese (BMI > 30). Low-weight individuals (BMI < 18.5; 21 cases, 90.5% women) were excluded as well as patients with cystine stones. Urine stones were analyzed from 275 of these patients (34.4%): 89.1% were calcium stones (calcium oxalate or calcium phosphate stones), 10.9% were uric acid stones.

Study protocol

Patients were studied with a standard ambulatory protocol while taking their usual diet.

Two 24-h urine samples were obtained, followed by a 2-h fasting urine sample collected by spontaneous voiding on the morning of the following day. During the collection period, the urine was kept refrigerated. Following the collection of the urine samples, a blood sample was drawn. Blood samples were analyzed for creatinine, uric acid, calcium, and magnesium. Urine samples were analyzed for calcium, creatinine, uric acid, citrate, oxalate, cystine, and magnesium. Urine volume was measured for both 24-h urine collections. Values for analytes are the average of the two urine collections. Urinary sediment and pH were determined in the 2-h fasting sample. The patients were studied at least 1 month after the episode of renal colic.

Methods

Serum calcium was measured by the ISE method using a Synchron CX3 Delta automated analyzer (Beckman, Beckman Instruments, Brea, CA); the same method was used for urinary calcium determination (performed on an acidified aliquot). Urinary magnesium was measured by Magnesium Reagent Synchron Systems (calmagite) with a Synchron CX4 automated analyzer. Serum and urine creatinine were measured using a Jaffe kinetic method with the same automated analyzer. Urinary uric acid was measured in an alkalinized aliquot to prevent precipitation. Urinary citrate was determined by an enzymatic procedure using reagents from Sigma-Aldrich (St Louis, MO). Urinary oxalate (measured in an acidified aliquot) was determined by an enzymatic procedure (Trinity Biotech, Bray Co., Wicklow, Ireland). Urinary pH was measured with a pH electrode in the 2-h fasting urine sample immediately post-voiding. Brand's reaction was used for the qualitative determination of cystine. We did not calculate the relative super saturation values or analyze urinary acidification defects.

Statistical analysis

The results are expressed as mean (X) ± the standard deviation (SD). The differences in the urinary excretion of analytes among groups in both sexes were analyzed by ANOVA. When differences were detected, significance was established by pot-Hoc test of Bonferroni. Significance was set at $p \leq 0.05$.

Results

Prevalence of overweight and obesity among stone formers

Overall, 487 (60.95%) patients had a BMI > 25, including 40.6% overweight and 20.2% obese. There were significantly more overweight subjects among men compared to female stone formers with equal proportion of obese subjects. Age increased significantly with increasing BMI both in men and women (Table 1).

Table 1 Age and prevalence of overweight and obesity among stone formers

	Normal	Overweight	Obese
Females			
Frequency %(n)	55.2% (186)	25.5% (86)	19.3% (65)
BMI (Kg/height^2)	22.0 ± 1.7	26.9 ± 1.3	34.7 ± 5.3
Age (years)	40.3 ± 12.0	47.1 ± 14.7	49.6 ± 10.7
Males			
Frequency %(n)	27.3% (126)	51.7% (239)	21.0% (97)
BMI (Kg/height^2)	23.1 ± 1.3	27.3 ± 1.4	33.2 ± 3.4
Age (years)	38.3 ± 11.5	45.9 ± 11.9	49.3 ± 9.9

Excretion of promoters and inhibitors of stone formation according to BMI

In women (Table 2) there was a significant increase in the excretion of oxalate, uric acid, phosphorus, creatinine, and sodium with increasing BMI. No change was observed in calcium, magnesium, citrate, and urine pH. In men (Table 3) there was a significant increase in the excretion of oxalate, uric acid, creatinine, phosphorus, sodium, potassium, urea, magnesium, and citrate with increasing BMI; there was a tendency for increasing calcium excretion with increasing BMI and a significant progressive decrease in urinary pH.

Discussion

The unadjusted urinary excretion of promoters and inhibitors of stone formation are of primary interest in

Table 2 Twenty-four hour urine composition according to BMI categorization in stone-forming females

Variable	Normal	Overweight	Obese	*P* for trend
Oxalate (mg)	25.5 ± 8.2	27.5 ± 6.7	29.1 ± 9.1	0.004
Citrate (mg)	618.0 ± 258.4	633.2 ± 263.9	628.8 ± 311.0	0.90
Calcium (mg)	210.7 ± 81.4	224.6 ± 88.9	230.6 ± 92.5	0.197
Uric Acid (mg)	487.8 ± 143.2	558.6 ± 164.7	570.3 ± 192.1	<0.001
Magnesium (mg)	88.1 ± 28.3	93.1 ± 29.3	91.2 ± 32.8	0.40
Phosphate (mg)	541.3 ± 194.9	634.0 ± 232.1	660.3 ± 194.0	<0.001
Creatinine (mg)	1,196.4 ± 434.8	1,230.0 ± 218.5	1,331.0 ± 262.3	0.036
Sodium (mEq)	123.4 ± 52.1	140.9 ± 53.0	155.9 ± 55.2	<0.001
Potassium (mEq)	53.7 ± 19.5	59.5 ± 18.8	56.9 ± 20.2	0.056
Urea (g)	20.4 ± 2.7	20.8 ± 6.2	21.1 ± 6.4	0.97
Volume (ml)	1,950.3 ± 904.7	2,113.9 ± 759.4	1,862.7 ± 745.4	0.16
pH (units)	5.7 ± 0.5	5.7 ± 0.5	5.7 ± 0.5	0.57

Table 3 Twenty-four hour urine composition according to BMI categorization in stone-forming males

Variable	Normal	Overweight	Obese	*P* for trend
Oxalate (mg)	22.7 ± 6.3	26.3 ± 7.9	29.7 ± 7.4	<0.001
Citrate (mg)	533.3 ± 218.3	630.44 ± 245.0	694.3 ± 287.0	<0.001
Calcium (mg)	230.0 ± 85.3	243.9 ± 93	258.3 ± 117.7	0.097
Uric Acid (mg)	622..0 ± 176.1	682.2 ± 205.7	784.5 ± 260.1	<0.001
Magnesium (mg)	94.0 ± 38.8	107.4 ± 34.2	116.3 ± 41.5	<0.001
Phosphate (mg)	735.8 ± 206.9	8,446.2 ± 254.3	992.1 ± 249.5	<0.001
Creatinine (mg)	1,716.2 ± 278.1	1,887.3 ± 326.3	2,069.5 ± 376.7	<0.001
Sodium (mEq)	152.9 ± 61.9	175.5 ± 63.7	206.9 ± 80.0	<0.001
Potassium (mEq)	59.8 ± 20.7	71.0 ± 23.8	74.6 ± 23.7	<0.001
Urea (g)	22.7 ± 6.3	26.3 ± 7.9	29.7 ± 7.4	<0.001
Volume (ml)	1,882.1 ± 773.6	2,000.0 ± 788.6	1,973.3 ± 683.6	0.37
pH (units)	5.71 ± 0.50	5.61 ± 0.50	5.45 ± 0.49	0.001

renal nephrolithiasis, as their concentrations affect kidney stone formation [12]. In this study we found that with increasing BMI, both in men and women, there was a significant increase in the urinary excretion of two promoters of stone formation, uric acid, and oxalate but no change in urinary calcium. There was either no change or increase in magnesium and citrate, inhibitors of crystallization, and a significant decrease in urine pH only in men.

In our population of stone formers there was a great prevalence of overweight/obesity (60.95%). This prevalence is much higher than found by Daudon in France, where 34.8% of 672 stone formers had a BMI ≥ 25 [13], but similar to that found by Siener in Germany among 363 men and 164 women calcium oxalate stone formers where 59.2% of men and 43.9% of women had overweight and obesity [14]. In USA, Ekeruo et al. found that 140 of 1,021 stone patients (14%) were identified as obese (BMI > 30) [15].

There have been several studies of the effect of body size on 24 h urine composition in stone formers. In a study of nearly 6,000 stone formers, Powell et al. found that those heavier than 120 kg excreted more calcium, oxalate, and uric acid compared to those weighing less than 100 kg, but because of differences in urinary volume, urinary calcium and oxalate concentrations were similar [9]. 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 (10).Taylor and Curhan studied this relationship in stone forming and non-stone forming participants in the Health Professionals Follow-up study that included only men, the Nurses's Health study that included older women and the Nurses's Health Study II that included younger women [10]. Male stone former participants with greater BMIs excreted more urinary oxalate, calcium, uric acid, sodium, and phosphate than the participants with lower BMIs and they had an inverse relation between BMI and urine pH. Women stone formers with greater BMIs also excreted more urinary oxalate, uric acid, sodium, and phosphate than the participants with lower BMIs, but increased urinary calcium was seen only in younger women. An inverse relation between BMI and urine pH was seen also in both groups of women.

The principal discrepancy among studies is with respect to calcium excretion. Most studies have found increased calcium excretion with increasing body size [9, 16]. We found a trend towards increased excretion of calcium in men but no increase in calcium excretion in women. Taylor and Curhan found positive associations between BMI and urinary calcium excretion in men and stone-forming young women, but not in older women. The positive association between BMI and calcium excretion in men and younger women did not persist after adjustment for urinary phosphate and sodium excretion [10]. Siener et al. found in overweight/obese calcium oxalate stone formers that BMI was associated with urinary calcium excretion only in men [14]. Finally, Nouvenne et al. recently found that in women with idiopathic calcium nephrolithiasis (mean age 40 ± 14 years), but not in control women, there was a linear increase in hypercalciuria with increasing BMI [17].

The other interesting finding in our study is the progressive decrease in urinary pH with increasing BMI that we saw only in men. Maalouf et al. have found in 4,883 patients with nephrolithiasis at two stone clinics in Dallas and Chicago that urinary pH had a strong graded inverse association with body weight [11].Urinary creatinine and age were both found to be significant covariates of urinary pH while gender was not a significant independent variable after adjustment for urinary creatinine. In the study by Taylor and Curhan, urinary pH decreased significantly with increasing BMI in men, older and younger women. Contrary to these studies, Nouvenne et al. found that neither in 420 stone former women nor in 290 matched healthy control women urinary pH significantly changed with increasing class of BMI [17].

In conclusion our study shows a high prevalence of overweight/obesity (60.95%) in this population of stone formers. Both in men and women we found a significant increase in the urinary excretion of two promoters of stone formation, oxalate and uric acid, with a trend for increased urinary calcium excretion in men but not in women. There was either no change or increase in magnesium and citrate, inhibitors of crystallization, and a significant decrease in urine pH only in men.

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