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LITHOGENIC METABOLIC PROFILE RELATED TO GENDER IN PATIENTS WITH CALCIUM-CONTAINING URINARY STONES

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ABSTRACT

Purpose: Little information is available on the metabolic changes found in relation to gender in patients with urolithiasis. In this study a comparison has been made of the metabolic profiles in men and women with calcium-containing urinary stones in order to identify possibly significant differences.

Materials and Methods: In the past five years, a total of 500 patients with calcium-containing urinary stones, 226 male (45.2%) and 274 female (54.8%), have undergone comprehensive metabolic evaluation. The mean age of the males was 46.3 years and of the females 46.9 years, with a range of 20 to 75 years for both sexes. A comparison has been made of the frequency of metabolic changes, the urinary biochemical parameters and the supersaturation index [AP (Ca0x)] between a group of men and a group of women with calcium-containing urinary stones. The patients collected a 24-hour urine specimen after following a low calcium diet and the following measurements were made: total volume, creatinine, calcium, phosphate, uric acid, oxalate, magnesium and citrate. Specific gravity, pH and ammonia were determined in an isolated sample of urine. A calcium overload test was then performed in order to determine the calcium and creatinine in a 4-hour urine sample.

Results: Hyperoxaluria, hyperuricosuria and hypocitraturia were more common in men than in women, whilst in women, hypercalciuria and a low urinary volume were more frequent with respect to men, though the differences in hypercalciuria were not statistically significant. Men excrete higher levels of calcium, phosphate, oxalate, uric acid and magnesium than women do, though the differences in the calcium values were not statistically significant. On the other hand, women excrete higher levels of citrate than men. The AP (CaOx) index is significantly higher in men than in women do.

Conclusions: Differences were observed between the metabolic profiles of men and women with calcium-containing urinary stones. In women, the lower urinary excretion of calcium, phosphate, oxalate and uric acid together with the higher excretion of citrate compared to men, affords them a metabolic profile of lower lithogenic risk; this is consistent with the lower reported prevalence of lithiasis and the lower tendency to recurrence in women compared to men.

Key words: urolithiasis; metabolism; calcium; risk factors; gender
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INTRODUCTION

There is a clinical predominance of urolithiasis in men, with a ratio of 2-3: 1 compared to women (1). It has also been shown that a larger percentage of women than men suffer their first episode of urinary stone disease at over 50 years of age. Furthermore, the probability of recurrence of urinary stones is higher in men than in women, with a ratio of 1.5: 1 (2). All these observations appear to

suggest the existence of different lithogenic metabolic profiles in men and in women that could explain the different clinical presentations. The pathogenic mechanism leading to this higher morbidity from urinary stone disease in men is still not fully understood. Although there could be a relationship with lifestyle and dietary habits, it is thought that the sex hormones, testosterone and the estrogens, are the true causative factors. Up to now, very few studies that report on the metabolic alterations observed in urinary stone disease have taken gender into account. This paper presents a study of the relationship between the lithogenic metabolic risk factors and gender in a group of patients with calcium-containing urinary stones.

MATERIALS AND METHODS

Over the past 5 years, a metabolic evaluation has been carried out on a total of 500 patients, 226 male (45.2%) and 274 female (54.8%), with calcium-containing urinary stones (calcium oxalate and/or phosphate). The mean age of the males was 46.3 years and of the females 46.9 years, with a range of 20 to 75 years for both sexes (Table-1). The patients were included in the study consecutively. The women were more inclined to agree to a metabolic evaluation. Any patient in whom a methodological error occurred in any phase of the study was excluded from the statistical analysis, as were patients with renal insufficiency (serum creatinine > 1.5 mg %), patients who had received treatment to reduce the urinary stone formation in the previous 6 months, the presence of urinary infection at the time of metabolic evaluation, patients with calculi of > 30 mm largest diameter, the finding of morphological or functional changes of the urinary tract (congenital or acquired) which predispose to urinary stone formation, the presence of foreign bodies in the urinary tract, or patients with a history of reconstructive surgery of the urinary tract, surgical urinary derivation (internal or external) or renal transplant.

The metabolic evaluation is designed in stages, following a protocol established for outpatients that we have described in a previous publication (3). The patient is asked to follow a low calcium (400-mg calcium), purine-free diet for 3 days. A 24-hour urine sample is collected during the second and third days after starting the diet. One of the containers for the collection contains 20 ml of fuming hydrochloric acid at 37%. The patient is asked to drink similar volumes of water during the two days of the collection. On the fourth day after starting the low calcium diet, a fasting blood test is taken and a freshly voided urine sample is collected. After centrifugation of the blood sample, automatic analysis is carried out on an aliquot using a Technicon RA-1000 autoanalyser, measuring the creatinine, uric acid, calcium, phosphate and magnesium. In a second aliquot, using an apparatus with selective electrodes, the sodium, potassium, chloride and total carbonate are measured. A sample of the freshly voided urine specimen was used for determination of the pH, specific gravity, titratable acid, ammonium and study of the sediment; a second sample was cultured for microbiological examination.

Table 1 *- Series of patients with urolithiasis.*

	No. of Patients	Age (years) Mean	Range
Total	500	47.4	75-20
Males	226 (45.2%)	46.3	75-20
Females	274 (54.8%)	49.9	75-20

The total volume of the 24-hour urine specimen was measured. The calcium, phosphate, oxalate, magnesium and citrate were measured in a sample of urine from the acid containing collection bottle and the creatinine, sodium, potassium, chloride and uric acid were measured in the urine from the container with no added acid. The analytical methods used for these determinations were the same as those for the blood sample except for the determination of citrate that was carried out manually using the citrate lyase enzyme method (Boehringer Mannheim reagent). The magnesium was determined by non-deproteinised calmagite colorimetry (BioMérieux Mg-Kit reagent) and the oxalate by the oxalate oxidase-peroxidase enzyme method (Sigma Diagnostics Oxalate reagent). The same day on which the patient attended for the laboratory tests, and after extraction of the blood test and collection of the freshly voided urine sample, the patient underwent

an oral calcium overload (1 g) test, with collection of the urine produced during the following 4 hours; the patient was advised that he should drink 500-1000 ml of water during this period. The volume of urine passed is noted and the calcium and creatinine determined.

After recording the analyses carried out in the blood sample, the freshly passed urine and the 24-hour urine after the low calcium diet and the 4-hour urine after calcium overload, a series of indices and quotients are calculated automatically by the Emusys computer program, facilitating the laboratory work enormously. The following calculations are made in the 24-hour urine: excretion of creatinine, calcium, calcium/kg weight, phosphate, oxalate, uric acid, magnesium, citrate, sodium, potassium and chloride; creatinine and uric acid clearances; tubular reabsorption of calcium and phosphate; the calcium / creatinine, phosphate / creatinine, oxalate / creatinine, uric acid / creatinine, magnesium / creatinine, citrate / creatinine, sodium / creatinine, potassium / creatinine and chloride / creatinine ratios. In the 4-hour urine specimen, the excretion of creatinine and calcium, the calcium / creatinine quotient and the creatinine clearance are calculated. Finally, the super-saturation index for calcium oxalate [AP (CaOx)] proposed by Tiselius (4) is calculated.

The metabolic alterations evaluated are: hypercalciuria (males: > 300 mg/d, females >250 mg/d); hyperoxaluria (> 45 mg/d); hyperuricosuria (> 800 mg/d); hypocitraturia (< 320 mg/d), hypomagnesuria (< 35 mg/d), low urinary volume (< 1.200 ml/d), changes in the urinary pH and distal renal tubular acidosis. The hypercalciuria could be absorptive, renal or resorptive. The absorptive hypercalciuria is divided into Pak types I, II or III. The resorptive hypercalciuria could be secondary to primary hyperparathyroidism or of other origin. Hyperoxaluria is divided into absorptive and endogenous. Absorptive hyperoxaluria could be dietary or enteric. Hyperuricosuria is divided into entero-renal and endogenous. The changes in urinary pH could be of acid (pH < 5.3) or alkaline (pH > 6.0) tendency. The criteria used for the diagnosis of these metabolic changes have been described in previous publications (3). In dietary absorptive hyperoxaluria the oxalate decreases (< 45 mg/d) after dietary oxalate restriction. In enteric absorptive hyperoxaluria the oxalate keeps over 45 mg/d after dietary oxalate restriction with malabsorption syndrome. In endogenous hyperoxaluria the oxalate keeps over 45 mg/d after dietary oxalate restriction but without malabsorption syndrome. In entero-renal hyperuricosuria the serum uric acid is normal, but in endogenous hyperuricosuria is increased. In distal RTA the ammonium chloride loading test doesn't decrease urinary pH under 5.3.

The SPSS statistical package was used for the statistical analysis of the data. The Chi-squared (χ^2) test was used to compare the frequencies of the categorical variables between the study groups, calculating the Pearson p-value and the p-valu11e of the likelihood ratio. The Yates correction and the Fisher test were applied when necessary. A one-way analysis of variance (one-way ANOVA) was used to compare the values of the different continuous variables between the study groups. When a significant difference was detected between any of the numerical variables using this test, the Scheffé test was used to demonstrate in which study groups these differences had occurred. When comparison of the variables between the study groups gave rise to statistically significant differences, these are expressed by a p-value of $p < 0.05$, $p < 0.01$ or $p < 0.001$. If no statistically significant difference was found, this is expressed as NS.

RESULTS

The most frequent metabolic alterations observed were, in decreasing order of frequency: hypercalciuria, acid pH, hyperuricosuria, hyperoxaluria, and hypocitraturia (Table-2). In the males, the changes were hypercalciuria, hyperuricosuria, acid pH, hyperoxaluria and hypocitraturia. In the females, the changes were hypercalciuria, acid pH, hyperuricosuria, hyperoxaluria and low urinary volume. Hyperoxaluria, hyperuricosuria and hypocitraturia were more frequent in the males than in the females, whilst hypercalciuria and low urinary volume were

Table 2 - *Frequency of metabolic changes.*

	Total (%)	Males (%)	Females (%)	p (χ^2)
Hypercalciuria	45.0	42.0	47.4	NS
Hyperoxaluria	16.0	20.4	12.4	< 0.05
Hyperuricosuria	23.6	31.4	17.2	< 0.001
Hypocitraturia	9.2	12.8	6.2	< 0.05
Hypomagnesuria	4.8	5.3	4.4	NS
Acid pH	27.8	27.4	28.1	NS
Alkaline pH	2.8	2.2	3.3	NS
Distal RTA	8.2	7.1	9.1	NS
Low Urinary Volume	6.8	4.0	9.1	< 0.05
Normal	17.2	16.4	17.9	NS

RTA: renal tubular acidosis; p (χ^2): p value of the Chi-squared test.

more frequent in the females, however, the difference in the frequency of hypercalciuria was not statistically significant. The frequency of hypomagnesuria, acid pH, alkaline pH and distal renal tubular acidosis was similar in males and females.

With respect to hypercalciuria, the absorptive form was the most frequent presentation for both sexes (Table-3). In the males, there was a predominance of Pak types III and I whilst, in the females, type II was more frequent. Renal and resorptive hypercalciuria were more frequent in the females, though a statistically significant difference compared to the males was only found for the resorptive form. All forms of hyperoxaluria were more frequent in the males though only the absorptive form showed statistical significance. Both the entero-renal and the endogenous forms of hyperuricosuria were more frequent in the males.

Of the urinary biochemical parameters analyzed, it was shown in the 24-hour urine sample that the males excreted higher levels of calcium,

Table 3 - *Frequency of the subtypes of metabolic changes.*

	Total (%)	Males (%)	Females (%)	p (χ^2)
Absorptive hypercalciuria	35.2	36.3	34.3	NS
Type I	9.4	14.6	5.1	< 0.01
TypeI	19.4	11.1	26.3	< 0.001
Type III	6.4	10.6	2.9	< 0.01
Renal hypercalciuria	3.4	1.8	4.7	NS
Resorptive hypercalciuria	6.6	4.0	8.8	< 0.05
PHPT	3.4	1.8	4.7	NS
Other types	3.2	2.2	4.0	NS
Absorptive hyperoxaluria	9.8	12.8	7.3	< 0.05
Dietary	9.6	12.4	7.3	NS
Enteric	0.2	0.4	0.0	NS
Endogenous hyperoxaluria	6.2	7.5	5.1	NS
Entero-renal hyperuricosuria	21.0	26.2	16.8	< 0.05
Endogenous hyperuricosuria	2.6	5.3	0.4	< 0.01

PHPT: Primary hyperparathyroidism; p (χ2): p value of the Chi-squared test.

phosphate, oxalate, uric acid and magnesium than females, though the difference in the calcium values were not statistically significant (Table-4). However, the calcium / creatinine ratio is significantly higher in the females. On the other hand, the females excreted higher levels of citrate than males in the 24-hour urine sample. Though the females show a tendency towards a more alkaline urinary pH, no significant difference was found compared to the males. The urinary volume was higher in the males than in the females but without showing statistically significant differences. The AP (CaOx) index is significantly higher in males.

Table 4 *- Biochemical parameters in urine and supersaturation index.*

	Total	Males	Females	p
Diuresis, ml/24 h	1938 ± 479	1974 ± 445	1708 ± 504	NS
pH	5.6 ± 0.6	5.5 ± 0.6	5.6 ± 0.6	NS
Calcium, mg/24 h	184 ± 92	191 ± 99	178 ± 85	NS
Calcium, mg/Kg weight/d	2.7 ± 1.3	2.6 ± 1.3	2.8 ± 1.3	NS
Calcium/Creatinine	0.15 ± 0.08	0.13 ± 0.06	0.17 ± 0.08	< 0.001
TRCa	98.1 ± 0.9	98.2 ± 0.9	98.0 ± 1.0	NS
Phosphate, mg/24 h	876 ± 364	926 ± 371	835 ± 353	< 0.01
Phosphate/Creatinine	0.73 ± 0.30	0.64 ± 0.26	0.81 ± 0.31	< 0.001
TRP	76.9 ± 11.4	77.0 ± 11.6	76.8 ± 11.2	NS
Oxalate, mg/24 h	32.4 ± 16.8	34.7 ± 17.0	30.6 ± 16.4	< 0.01
Oxalate/Creatinine	0.02 ± 0.01	0.02 ± 0.01	0.03 ± 0.01	< 0.001
Uric acid, mg/24 h	633 ± 250	688 ± 263	588 ± 228	< 0.001
Uric acid/Creatinine	0.52 ± 0.18	0.47 ± 0.16	0.56 ± 0.18	< 0.001
Cua, ml/minute	10.3 ± 5.0	9.3 ± 4.2	11.2 ± 5.5	< 0.001
Citrate, mg/24 h	630 ± 263	600 ± 256	656 ± 267	< 0.05
Citrate/Creatinine	0.55 ± 0.27	0.42 ± 0.19	0.65 ± 0.28	< 0.001
Magnesium, mg/24 h	90.3 ± 38.5	95.6 ± 4.6	85.9 ± 35.3	< 0.01
Magnesium/Creatinine	0.07 ± 0.03	0.06 ± 0.02	0.08 ± 0.03	< 0.001
AP (CaOx) index	0.89 ± 0.61	0.95 ± 0.63	0.83 ± 0.59	< 0.05

Values expressed as mean and standard deviation; TRCa: Tubular reabsorption of calcium; TRP: Tubular reabsorption of phosphate; Cua: Uric acid clearance; p: p value for the one-way analysis of variance.

DISCUSSION

In most series published, it has been found that urolithiasis is more common in males than females though, to date, it has not been possible to give a satisfactory explanation of why this difference exists. This information may not be valid as almost all of the available publications are case control studies; this could lead to a selection bias by including a smaller number of women. In epidemiological studies carried out on large population samples, Yoshida (5), in Japan, found that lithiasis is more frequent in males than in females with a ratio of 2.4: 1. Ljunghall (6), in Sweden, found a prevalence of the urinary lithiasis of 8.9% in males and of only 3.2% in females. However, Rousaud & Pedrajas (7), in Spain, found a prevalence of 4.5% in males, only slightly higher than the 3.8% observed in females. In an epidemiological study on a population in the North of Italy, Trinchieri et al. (8) found an increase in frequency of lithiasis between the years 1986 and 1998, both in males and females, though this increase

was only statistically significant in males (a rise from 6.8% to 11.9%, $p < 0.01$), not in females (a rise from 4.9% to 6.7%). Thus, from this study, it may be deduced that urinary lithiasis is not only more frequent in males but also that this higher frequency is now more significant than in previous years.

A higher incidence of the disease has also been seen in males. Curhan et al. (9) found an annual incidence of 0.31% in cohort of 45,289 adult males with no previous history of lithiasis, followed up for a period of 6 years. In another study by the same authors (10), an annual incidence of 0.10% was found in 91,731 adult females, also with no previous history of lithiasis, followed up for a period of 12 years. It has also been reported that the risk of recurrence is higher in males. In a prospective study of 54 patients presenting a first episode of lithiasis, Ljunghall & Danielson (2) found that 53% of the patients had repeat episodes during the follow-up period of 8 years. However, whilst repeat episodes occurred in 63% of the males, they were only seen in 18% of the females ($p < 0.01$). In another prospective study of patients with lithiasis, Marshall et al. (11) also found a higher recurrence rate in males. On the other hand, Lonsdale (12), in an autopsy study, found similar frequencies of lithiasis in both sexes, without being able to explain adequately the reason for the lower clinical expression of the urinary stone disease in the females.

There is still insufficient knowledge on the pathogenic mechanisms that determine the higher morbidity from urinary stones seen in males. Without excluding completely the possible contribution of dietary and lifestyle factors, it is suspected that the sex hormones may be the truly determining factor. There is very little information on the influence of these hormones on the pathogenesis of the urinary stones. The higher frequency of urinary stone disease found in males, when considering the adult population, is not seen in children (13). Research in rats found that an increase in the serum levels of testosterone led to an increase in the endogenous production of oxalate due to an increase in the activity of the enzyme glycolate oxidase in the liver (14). Castrated male rats formed fewer calculi when hyperoxaluria was induced by the administration of ethylene glycol (15) but formation increased when testosterone was given subcutaneously (16). These observations suggest that low levels of serum testosterone may contribute to protecting females and male children against the formation of calcium oxalate stones.

Similarly, it has been observed that estrogens reduce the production of oxalate (17) and also appear to affect calcium metabolism, favoring the tubular reabsorption of calcium and inhibiting bone resorption. On the other hand, it has been shown that the estrogens cause an increase in the urinary excretion of citrate (18). Lee et al. (16) showed that the excretion of citrate falls significantly after oophorectomy in rats. These investigators also observed that the formation of calculi is higher when these castrated rats are administered testosterone subcutaneously. All these actions of the estrogens, therefore, should have a marked reducing effect on urinary stone formation. However, doubt was cast on the protective role of the estrogens by previous studies by these same investigators (15) as they did not observe a higher frequency of stone formation induced by ethylene glycol in female rats after oophorectomy.

There is very little research on the different metabolic changes observed in males and females separately. Tiselius (4), in a series of patients with calcium-containing stones, found a higher frequency of hyperoxaluria and hypomagnesuria in females with similar frequencies of hypercalciuria, hypocitraturia, low urinary volume and AP (CaOx) index in males and females. Teodosio et al. (19), in a series of 65 patients with urinary stones, found no significant differences in the frequencies of hypercalciuria, hyperuricosuria or hypocitraturia. However, of the different types of hypercalciuria, these authors found differences in the renal form ($p < 0.05$), more frequent in females, but not in the absorptive or unclassified forms. Yagisawa et al. (20), in a series of 181 patients with recurrent calcium-containing urinary lithiasis, showed that the males had a significantly higher number of metabolic disturbances than females (2.12 versus 1.65, $p < 0.05$). In males, hypercalciuria, hyperoxaluria, hyperuricosuria and hypocitraturia were more frequent and in the females, low urinary volume; however, only the hypocitraturia showed

statistical significance for the group of patients below 45 years of age. In the present study, hyperoxaluria, hyperuricosuria and hypocitraturia were significantly more frequent in the males. On the other hand, low urinary volume was more frequent in the females. There is a particularly high frequency of Pak type II absorptive hypercalciuria in females; this could be related to a degree of incompetence in females of the entero-renal mechanisms, which regulate urinary calcium after exogenous calcium overload. Further research is needed into this disturbance as, if it is confirmed, a more strict control to avoid excessive dietary calcium in females may be advisable due to the higher risk of stone formation compared to males. The predominance of resorptive hypercalciuria in females is explained by the higher frequency of bone pathology affecting females, particularly from the fifth decade of life onwards, and which also occurs in primary hyperparathyroidism (21).

Nor is there sufficient information on the levels of the urinary excretion of calcium, phosphate, oxalate, uric acid, citrate and magnesium observed separately in males and females. Hesse et al. (22) report that the urinary levels of calcium, oxalate and uric acid are higher in males than in females, whilst the levels of citrate are lower, both in patients with urinary stones and in normal subjects. Parks & Coe (23), in a series of 330 patients with calcium oxalate stones, found that the males had a higher 24-hour urinary volume (1,626 ml in males versus 1,370 ml in females, $p < 0.05$) and higher levels of oxalate per litter of urine (25 mg/l in males versus 23 mg/l in females, $p < 0.05$), whilst the females had higher levels of citrate per litter of urine (349 mg/l in males versus 463 mg/l in females, $p < 0.001$). The urinary levels of calcium, phosphate, uric acid and magnesium are higher in males than in females but without these differences reaching statistical significance. Trinchieri et al. (24), in a series of 104 patients with recurrent idiopathic calcium urinary stones, found that up to 20 years of age there was no significant difference in the urinary excretion of citrate and magnesium between males and females. In older patients, the differences were still not significant but the citrate/creatinine ratio was higher in females. Yagisawa et al. (20) found that males had a higher AP (CaOx) index and higher levels of calcium, phosphate, oxalate, uric acid, magnesium and urinary volume in a 24-hour urine sample and that the females had higher levels of citrate; the significance levels of these data were not calculated. The observations in the present study are in total agreement with those reported by the above authors, finding statistical significance for the higher levels of phosphate, oxalate, uric acid, magnesium and the AP (CaOx) index in the males and for the higher levels of citrate in females. These data are supported by data from experimental studies in which it has been shown that testosterone favors and increase in urinary oxalate and that the estrogens favor an increase in urinary citrate whilst also having a reducing effect on the urinary excretion of oxalate and calcium.

CONCLUSIONS

The present study shows differences in the metabolic alterations observed in men and women with calcium-containing urinary stones. In females, the lower urinary excretion of calcium, oxalate and uric acid and the higher excretion of citrate produce a metabolic profile of the lower lithogenic risk. The higher prevalence, incidence and recurrence of urinary stone disease that have been reported in males compared to females could well be related to this low lithogenic risk metabolic profile in the latter. On the other hand, the greater response of women to an oral calcium overload, increasing urinary calcium excretion, could make stricter control of possible excesses in the calcium content of the diet in women compared to men advisable due to the higher risk of stone formation.

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EDITORIAL COMMENT

Although differences between the sexes with regards to the incidence of nephrolithiasis may be decreasing, why women form less stones than men remains an interesting clinical observation. The main focus of studies related to this issue has been to identify a biophysical parameter(s) in urine that is (are) less lithogenic in women. Various processes in the stone formation cascade: urine supersaturation, crystal nucleation and aggregation, crystal-tissue interaction, and/or crystal retention may be altered between the sexes. In addition to the concentrations of crystal components (calcium, oxalate, phosphate), micromolecular inhibitors (magnesium, citrate) and several macromolecular inhibitors have been looked at previously.

This study evaluates the 24-hour urine excretions of various chemicals in the urine from a Stone Clinic in calcium stone formers. The present study confirms that women excrete more citrate, and perhaps at a higher urine concentration, than men. Although the concentrations of the various chemicals are not given, women were found to have a higher calcium/creatinine, oxalate/creatinine, and uric acid/creatinine rations than men. As women also had a lower AP (CaOx) index than men did, this implies that the reduced urine concentration of magnesium and/or the higher urine concentration of citrate in women overrode the effects of higher calcium, and oxalate urine concentrations in women.

As concentrations of chemicals determine the crystallization process, it is hoped that future reports would focus on concentration rather than the amount of the chemical excreted over a 24 period even though this parameter may be normalized with the patient's weight or creatinine excretion.

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