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Biochemical Alterations in Patients with Oxalocalcic Lithiasis, the Influence of Sex, Age, and Body Mass Index

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Abstract

Background: Urolithiasis is a disorder that has a high prevalence in the population. Also, lithiasic patients have biochemical alterations that predispose them to the formation of stones. The knowledge of these alterations may be useful for future preventive interventions.
Objectives: The objectives were to describe the metabolic characteristics of patients with oxalocalcic lithiasis, identifying the most frequent biochemical alterations, and their variation with different demographic variables. In this way, we can prevent the formation of the lithiasis before it appears, instead of treating it once established.
Methods: A descriptive cross-sectional study of serum and 24 hour-urine parameters in patients with oxalocalcic lithiasis was performed. The most frequent biochemical alterations were described, and their association with age, sex, and body mass index (BMI) were assessed.
Results: In this study, 100% of the 151 patients had biochemical alterations, the most frequent being hypocitraturia (84.7%), hypercalciuria (51.7%), and urinary pH decrease (44.4%). There were differences according to sex, age, and BMI with regard to the biochemical alterations. Hypouricemia, hypouricosuria, hypophosphaturia and hypomagnesuria were more frequent in women. Men had a higher percentage of hyperzinquemia, hyperphosphaturia, and excess of urinary urea. Urine density in men was slightly higher than in women. A higher percentage of hyperphosphaturia, excess urinary urea, and excess of serum urea was found in overweight patients. Patients not overweight showed a higher percentage of hypouricemia and hypomagnesuria. Urinary density was slightly higher in overweight patients. Urinary volume was higher in middle-aged subjects.
Conclusions: Patients with oxalocalcic lithiasis have biochemical alterations that may predispose to stone formation. These alterations vary with sex, age, and BMI.

Keywords: Metabolism, Sex, Body Mass Index (BMI), Lithiasis, Age Factors

1. Background

Urinary lithiasis is a disease known since ancient times, with a high prevalence in the general population, which has experienced an increase in recent decades (1). There has also been an increase in medical activities aimed at its treatment (2) and, consequently, in the costs associated with both the treatment itself and the sick leave secondary to the disease (3).

However, the medical treatment of urinary lithiasis has shown little evolution in recent decades. The significant improvements that have occurred in surgical treatment and extracorporeal lithotripsy have relegated it to the background (4).

The knowledge of epidemiological factors and biochemical alterations associated with urolithiasis could serve as a target for future interventions (5). In this way, we can prevent the formation of the lithiasis before it appears, instead of treating it once established.

On the other hand, there is a lack of homogeneity in the alterations reported by the literature, with a wide variation in the biochemical alterations found (6-11).

2. Objectives

The aim of the study was, therefore, to identify the biochemical alterations in patients with calcium oxalate lithiasis.

3. Methods

A cross-sectional study was carried out, consisting of the assessment of biochemical alterations that lithiasic patients presented. The sample selection was made consecutively, and the analysis was performed on the patients who attended the urolithiasis consultation (adult population) and who were diagnosed with oxalocalcic stones. All patients underwent a complete clinical evaluation.

The patients underwent a basal metabolic study, including analysis of urinary biochemical parameters, pH and urinary volume, as well as serum analysis of various parameters. A urine culture was performed to rule out concomitant urinary tract infection. All measurements were performed according to the standards of the hospital laboratory. Biochemical alteration was defined as a value outside the reference interval (95% of the population).

Patients under 18 years of age were excluded. Also, the appearance of nephritic colic can produce an alteration in the urinary and serum measurements due to the treatment (forced hydration, analgesics, etc.) Therefore, patients who had suffered from colic in the last month before the basal metabolic study were excluded from the study.

Regarding statistical analysis, categorical variables are expressed in absolute frequency and percentage, and quantitative variables as mean $\pm$ SD (standard deviation) or median (IQR, interquartile range). The Kolmogorov-Smirnov and Levene tests were used to verify the normality of the variable and the homogeneity of variances, respectively.

An analysis of the prevalence of each biochemical alteration in the sample of patients was performed. The comparison with the reference population was made by contrasting the proportion of patients who were above or below the reference interval with respect to the theoretical 0.025 using the binomial law. It was considered clinically relevant if the proportion of patients who were above or below the limits exceeded 0.10.

Body mass index (BMI) was categorized in patients not overweight (BMI $<$ 25) and overweight (BMI $>$ 25). Age was categorized as "young adult" ($<$ 40 years old), "middle adult" (40 - 60 years old), and "elderly adult" ($>$ 60 years old). The analysis of the different age categories in association with the presence of biochemical alterations was made by logistic regression (significance obtained with the likelihood ratio test). The comparative analysis of the parameters according to sex and BMI was performed using the Chi-square test (or Fisher's exact test when appropriate).

The difference between men and women in terms of urine density, volume, and pH was calculated by student's *t*-test (or Mann-Whitney U). These parameters were also studied according to BMI. The ANOVA test was used to assess urine density, pH, and volume in the different age groups. An analysis of vitamin D3 values was carried out to compare patients with PTH elevation with those who had normal levels using the student's *t*-test.

All analyses were carried out assuming a level of significance of 5% (Bonferroni correction); the contrasts are bilateral. The analyses were performed with the statistical package SPSS (version 20.0, SPSS Inc., Chicago, IL).

The study was carried out in accordance with the code of ethics included in the Declaration of Helsinki, and with the current Spanish legislation. All patients were informed and signed the written informed consent. The study was approved by the Ethics Committee of Ramon y Cajal University Hospital, code 65/10.

4. Results

A total of 151 metabolic studies were performed. The median age of the patients was 51 years old (18.6 - 84.8). 32 (21.2%) were younger than 40 years old, 86 (57%) between 40 and 60, and 33 (21.9%) older than 60. 64.9% of patients were male. The mean age of women was 48.3 years-old (SD 14.9), and mean age of men 51.5 (SD 11.8). The mean BMI was 25.9 (SD 3.7) kg/m^2. 81 patients (53.6%) were overweight.

The mean urinary volume was 1944.9 (SD 764.4) mL/24 h, and the mean urinary density was 1012, 4 (SD 5.7) mg/mL. The mean urinary pH was 5.74 (SD 0.58); 44.4% of the patients had a diminished pH and 6% had an elevated pH. The mean creatinine clearance was 91.4 (SD 20.0) mL/min.

Table 1 shows the biochemical alterations and their statistical significance according to binomial law. The percentage of patients with biochemical alterations in the study, including serum or urinary ions and PTH, was 100%. The measurement error of the 151 patients in the sample population is 0.5% (95% confidence interval).

The percentage of patients who had only one biochemical alteration was 0.7%, two or three alterations 8.6%, four 20.5%, five 19.2%, and six or more alterations 42.5%.

Figure 1 shows the percentage of patients who had biochemical alterations according to sex. Those with a statistically significant difference appear highlighted. A higher percentage of hypouricemia, hypouricosuria, hypophosphaturia, and hypomagnesuria were observed in women. Men had a higher percentage of hyperzinquemia, hyperphosphaturia, and excess of urinary urea.

The urine density in men was slightly higher (1013.1 mg/mL), than in women (1011.2 mg/mL, P = 0.008). Urinary volume was not statistically different between men and women (P = 0.842). The average pH in men was 5.69, and in women, it was 5.83, but this difference was not statistically significant.

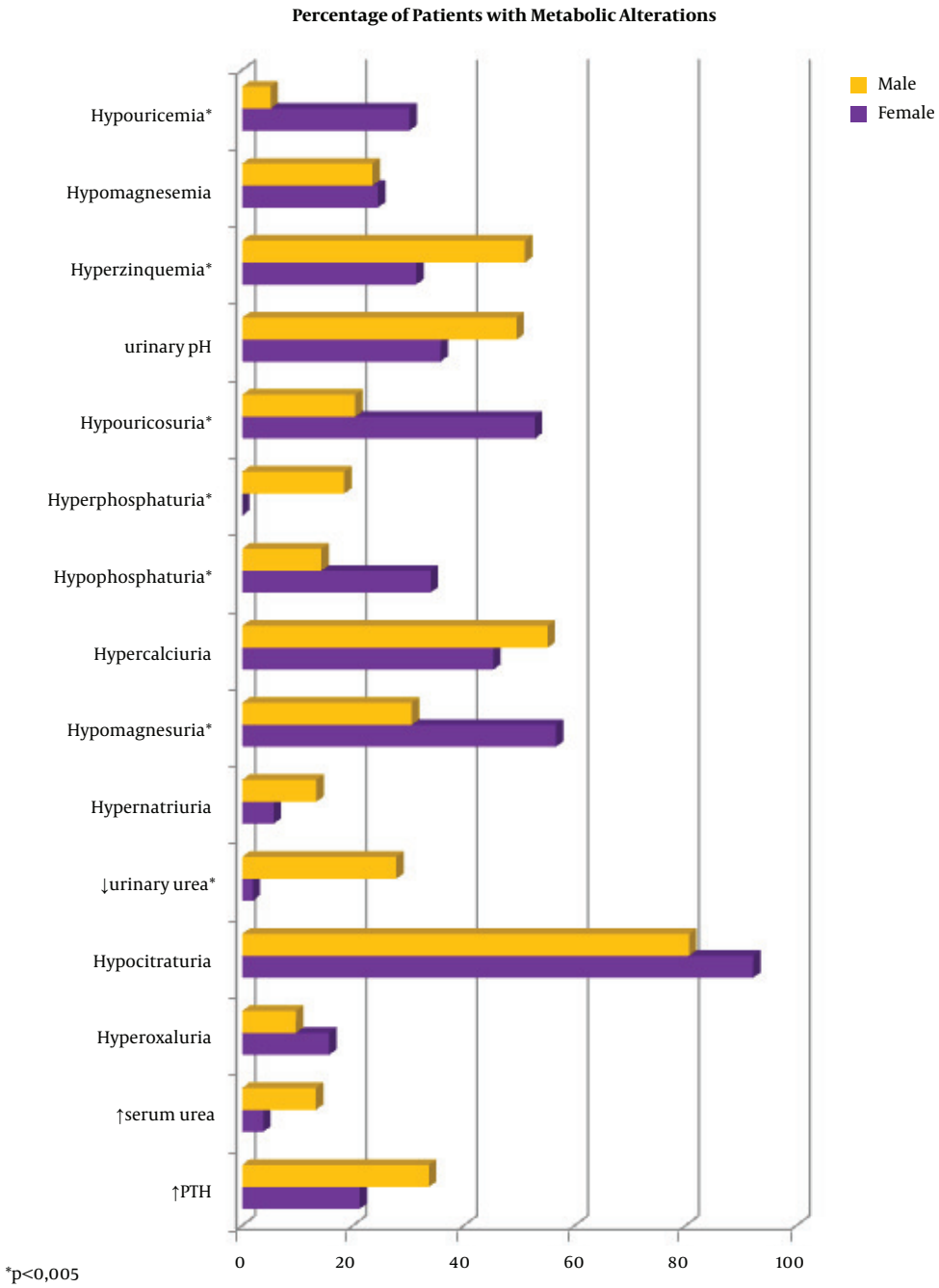

Figure 1. Biochemical alterations regarding sex

Biochemical alterations regarding BMI are shown in Figure 2. A higher percentage of hyperphosphaturia, excess of urinary urea, and excess of serum urea were observed in overweight patients. On the other hand, patients not overweight showed a higher percentage of hypouricemia and hypomagnesuria.

Overweight patients had a slightly higher urinary density than those not overweight (1,013.4 vs. 1011.3 mg/mL, P = 0.002). The volume was rather lower in overweight patients (1,845 vs. 2,060 mL/24 h), but this difference was

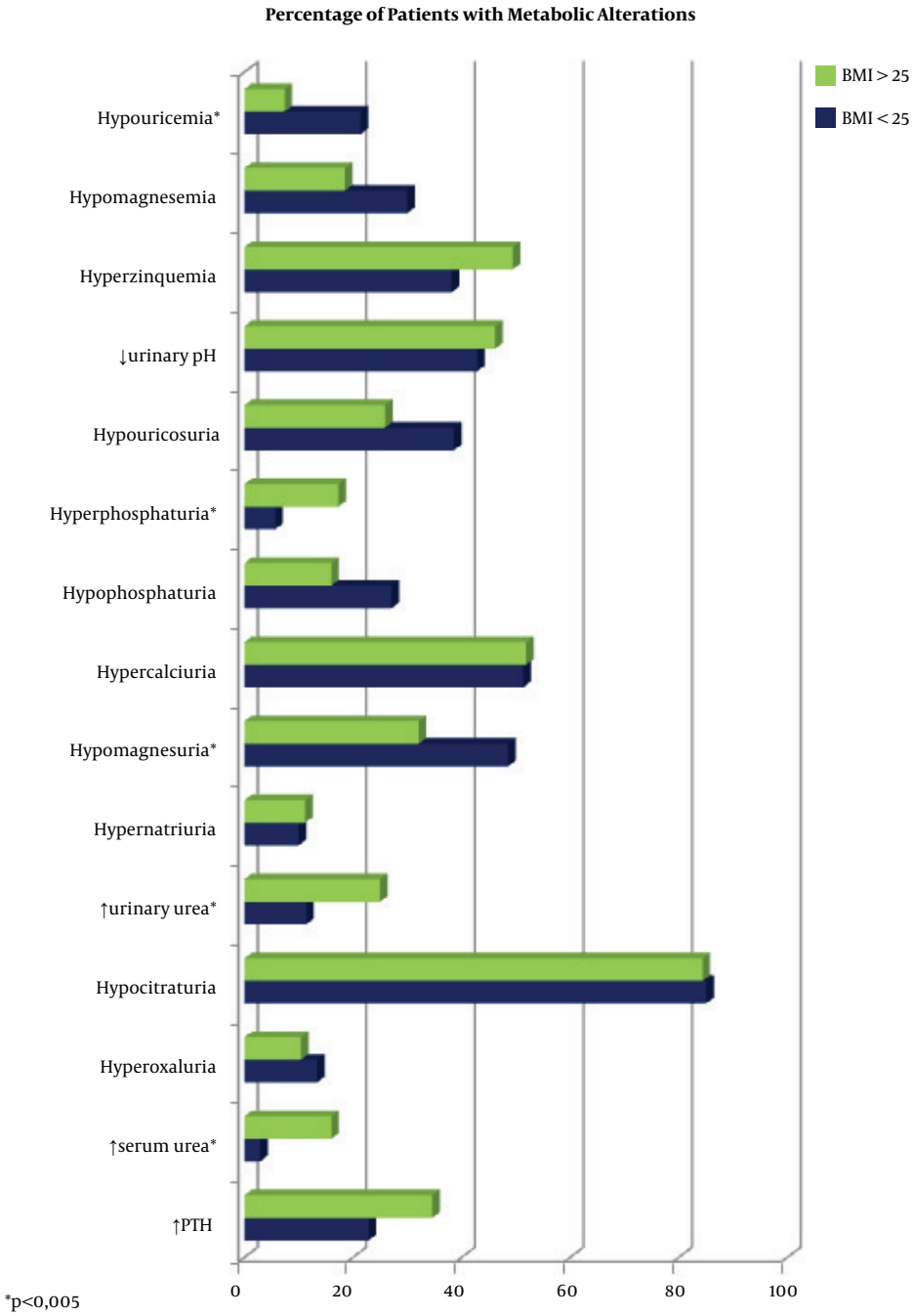

Figure 2. Biochemical alterations regarding BMI

not significant (P = 0.086). Patients not overweight had a slightly higher mean pH than those overweight (5.8 vs. 5.7), but it was not statistically significant.

Table 2 indicates the percentage of patients who presented biochemical alterations according to the age groups. No statistically significant differences were found in the biochemical alterations, according to age groups.

Urinary volume was higher in the middle-aged pa-

Table 1. Biochemical Alterations (Statistical Significance According to Binomial Law)

	Percentage of Patients, %	P
Urine parameters		
Hypocitraturia	84.7	0.000
Hyperoxaluria	11.8	0.000
Elevated urinary urea	18.7	0.000
Decreased urinary urea	5.3	0.036
Hypercreatinuria	6	0.014
Hypocreatinuria	0.7	0.107
Elevated pH	6	0.014
Decreased pH	44.4	0.000
Hyperuricosuria	2.6	0.523
Hypouricosuria	31.8	0.000
Hyperphosphaturia	11.9	0.000
Hypophosphaturia	21.2	0.000
Hypercalciuria	51.7	0.000
Hypermagnesiuria	3.3	0.327
Hypomagnesiuria	39.7	0.000
Hypernatriuria	10.7	0.000
Hyponatriuria	2.7	0.518
Hyperkaliuria	0.7	0.109
Hypokaliuria	4.7	0.084
Serum parameters		
Hypercreatininemia	6	0.014
Hypocreatininemia	15.2	0.000
Hyperuricemia	4.6	0.086
Hypouricemia	13.9	0.000
Hyperphosphatemia	4	0.178
Hypophosphatemia	9.9	0.000
Hypercalcemia	9.3	0.000
Hypocalcemia	8.6	0.000
Hypermagnesemia	1.3	0.269
Hypomagnesemia	23.8	0.000
Hypernatremia	2	0.477
Hyponatremia	4.6	0.086
Hyperkalemia	1.3	0.269
Hypokalemia	0.7	0.107
Hyperzinquemia	44.2	0.000
Hypozinquemia	2.7	0.502
Elevated PTH	29.1	0.000
Decreased PTH	7	0.107

tients (2085.4 mL/24 h) than in young patients or those over 60 years (1699.1 and 1817.3 mL/24 h. respectively). There were no statistically significant differences in terms of urinary pH and density by age groups.

Patients with high PTH showed values up to a maximum of 100 pg/mL. except from 3. The highest of the latter reached a value of 122.6 pg/mL. In patients who had an increase in PTH, the average vitamin D3 was 17.74 ng/mL (below the lower limit for vitamin D3). In those without PTH increase, the mean value of vitamin D3 was 23.08 (P = 0.136) ng/mL. Although the mean levels of vitamin D3 were lower in those patients who had elevated PTH, differences were not statistically significant.

5. Discussion

In the presented study, sex distribution was similar to what is published in the literature for lithiasic patients in most studies, where the prevalence in men is usually reported two times higher than in women (6). The ages of the patients in this study were distributed between 18 and 84 years, but most were within the intermediate ages of life, forming a normal distribution. Our data coincide with the distribution reported by the literature (6, 7).

Moreover, 53.6% of the patients presented overweight. The association between urolithiasis and obesity is well known (12-15), and is likely to be one of the risk factors for the increase in the incidence of lithiasis in developed countries.

The percentage of urolithiasic patients with biochemical alterations ranges between 90.5% and 96.8% in the literature (8-10, 16-18). In addition, usually, more than one biochemical alteration was found in each patient (8-10, 16-18). In our study, 100% of the patients presented biochemical alterations. The most frequent one was hypocitraturia (84.7%), followed by hypercalciuria (51.7%), and a decreased urinary pH (44.7%).

The role of citrate is fundamental in the genesis of urolithiasis, since it has been observed that crystallization decreases with citrate, so it potentially has a protective role for all types of lithiasis. The majority of the studies coincide in a decrease of urinary citrate in patients with urolithiasis, ranging from 10.55% to 57.2% (8, 9, 16, 17, 19, 20). This circumstance has been used to treat patients with substances rich in citrate, and this has become one of the most used medical treatments.

Hypercalciuria was the second metabolic disorder in frequency, reaching 51.7%. This data is in the range of hypercalciuria that is described in the literature, between 14.5% and 74%. Hypercalciuria has been associated with an increase in the formation of urinary stones, both calcium oxalate and calcium phosphate, as well as mixed (21-24).

Table 2. Biochemical Alterations Regarding Age Groups

Biochemical Alterations	Percentage of Patients with Biochemical Alterations			P
	Young Adult (< 40 Years)	Middle Adult (40 - 60 Years)	Elderly Adult (> 60 Years)	
Hypouricemia	12.5	17.4	6.1	0.225
Hypomagnesemia	25	23.3	24.2	0.979
Hyperzinquemia	25.8	48.8	50	0.059
↓ Urinary pH	46.9	45.3	40.6	0.864
Hypouricosuria	40.6	30.2	27.3	0.467
Hyperphosphaturia	12.5	10.5	15.2	0.780
Hypophosphaturia	25	18.6	24.2	0.670
Hypercalciuria	56.2	54.7	39.4	0.276
Hypomagnesuria	43.8	34.9	48.5	0.349
Hypernatriuria	9.4	12.8	6.2	0.549
↑ Urinary urea	15.6	19.8	18.8	0.873
Hypocitraturia	87.1	86.9	75.9	0.367
Hyperoxaluria	16.1	9.5	13.8	0.589
↑ Serum urea	9.4	8.2	15.2	0.554
↑ PTH	18.8	29.1	39.4	0.182

The decrease in pH was the third most frequent biochemical alteration in the patients. Although the presence of alterations in pH in lithiasic patients has previously been described, the proportion is usually lower than in the study (16).

Hypomagnesuria, with 39.7% of subjects, was the fourth metabolic disorder in frequency. The decrease in urinary magnesium is also a frequent finding in metabolic studies performed in patients with urinary lithiasis, ranging from 12.9% to 30.7%. This may be due to the fact that magnesium forms complexes with oxalate, thereby reducing the supersaturation of calcium oxalate. In addition, magnesium oxalate complexes reduce the intestinal absorption of oxalate. At physiological concentrations of oxalate, magnesium reduces both nucleation rates and the growth of calculus (8, 9, 16-18).

Hypouricosuria was the fifth metabolic disorder in the frequency of this study, being present in 31.8% of patients. This data is striking since hyperuricosuria is a risk factor classically associated with the formation of urinary stones, not only uric lithiasis, but also oxalocalcic lithiasis. However, in this study, hyperuricosuria was present in only 2.6% of patients. In the literature, the percentages of hyperuricosuria range between 12.9% and 30.7% (8, 9, 16-20). This higher percentage may be explained because the referred studies comprise all types of stones, including uric acid stones, which are more frequently associated with hyperuricosuria, unlike the present study, which is limited to calcium oxalate lithiasis.

Hyperoxaluria was present in 11.8% of our patients. The presence of hyperoxaluria reported in the literature ranges between 2.6% and 64.1% (8, 10, 16-20, 25), being the most frequent biochemical alteration found in some cases (10).

Also, 11.9% of the patients had hyperphosphaturia. This finding correlates with what has been previously published. The reduction of renal reabsorption of phosphates takes place basically at the level of the proximal tubule and is closely related to the reabsorption of sodium through the sodium-phosphate cotransporter so that phosphaturia is favored with the ingestion of diets rich in sodium (17). In this study, 10.7% of the patients presented an elevation of urinary sodium. The association of urinary sodium with urinary volume, pH, Oxalate, and citrate has also been described in the literature (9, 26, 27).

With regard to urinary volume, the observed median of 1.860 mL/24 h can be considered high. These findings can be explained because of the popular knowledge in lithiasic patients of an abundant intake of fluids. Urinary volume was not statistically different between men and women (P = 0.842), which contrasts with what is published by other authors (25), who observed a lower diuresis in women. Nevertheless, the decrease in diuresis has been reflected in the literature as a clear lithogenic risk factor by increasing the relative concentration of solutes in the urine (28).

Urinary density and osmolarity vary in a parallel manner, while there is no high molecular weight substance in the urine. In this study, urine density was evaluated. It was observed that urine density in men was slightly higher (1013.1 mg/mL), than in women (1011.2 mg/mL), this difference being statistically significant. This is consistent with that published by Perucca et al. (29), who describes an increase in men's urine osmolality with respect to women.

In this study, a significant percentage (29.1%) of patients with parathormone levels above the upper limit of the reference interval was found. In these patients, the concentration of vitamin D3 was analyzed secondarily. It was observed that they had, on average, lower levels of vitamin D3 than patients without PTH elevation; however, the difference was not statistically significant. This deficit of vitamin D3 could lead to a decrease in serum calcium, which reactivates serum levels of PTH as a compensatory way to raise serum calcium (30, 31).

Different prevalence of lithiasis has been described by both sex and age (32-34). In order to explain this circumstance, the metabolic differences existing in the different populations have been studied. Lancina Martin et al. (35) described a greater presence of hyperoxaluria, hyperuricosuria and hypocitraturia in men and a higher presence of hypercalciuria and decreased urinary volume in women. This lower presence of hyperoxaluria in women may be due to the effect of oestrogen. Ferraro et al. (20), in contrast, found a lower urinary calcium excretion in women, but also a reduction in the excretion of uric acid (20, 35). Another study describes the changes that have occurred in women in recent times, confirming an increase in the excretion of oxalate and urinary calcium, and a decrease in urinary magnesium. However, an increase in the urinary excretion of citrate was also found. The excretion of phosphorus and uric acid decreased. Calcemia decreased, whereas serum phosphorus and magnesium increased, and serum uric acid did not show any variation. The authors of the study relate these changes in the parameters with the modifications in the lifestyle of recent years (36). Sanchez-Martin et al. (25) in 2017, published a review on differences in metabolic parameters by sex. A greater excretion of calcium, phosphorus, magnesium, oxalate and uric acid was observed in men and a greater excretion of citrate in women. On the other hand, it should be noted that there are papers that describe the absence of metabolic differences between sexes (19).

In the present study, it was observed that women had a higher percentage of hypouricemia, Hypouricosuria, hypophosphaturia and hypomagnesuria. Higher percentages of hyperzinquemia, Hyperphosphaturia, and excess urinary urea were found in men. Besides, urine density in men was slightly higher (1013.1 mg/mL), than in women (1011.2 mg/mL, P = 0.008). The findings in this regard are very heterogeneous, and no conclusions can be drawn regarding the relationship of sex with biochemical alterations. Therefore, the relevance of some of these values in the development of urolithiasis remains to be determined. No specific analysis was performed on menopausal women as the sample was small (9 older than 60, 15 between 50 and 60 years old). Some authors have found different patterns in this group of patients (37).

Regarding age, a greater presence of hyperoxaluria, hyperuricosuria, and decreased urinary volume in patients older than 60 years are described in the literature, but with a higher prevalence of biochemical alterations in those under 60 years of age. Besides, a lower hypocitraturia in older women is reported. Other authors found that increases in age lead to an increased BMI and also decreased urinary pH, calcium, uric acid, ammonium, and creatinine, as well as a supersaturation of calcium oxalate and calcium phosphate. In a study with young patients, a higher prevalence of hypercalciuria and hypocitraturia was observed (38-40). In contrast, an increase in hypercalciuria, hyperuricosuria and increased calcium oxalate saturation in patients under 60 years old has also been described. Also, a decrease in urine volume in patients under 40 years is reported (35). In this study, the only difference found was a higher urinary volume in middle-aged patients. Therefore, also, in this case, the findings are disparate and do not allow us to draw clear conclusions regarding the biochemical alterations between different ages and their influence on lithogenesis.

With regard to BMI, overweight patients had a higher percentage of hyperphosphaturia, excess urinary urea, hyperglycemia and excess of serum urea. On the other hand, patients not overweight showed a higher percentage of hypouricemia and hypomagnesuria. In the published literature, a higher prevalence of biochemical alterations has been found in obese patients, with an increase in the excretion of lithiasis promoters (oxalate, calcium, uric acid), and a decrease in pH. With respect to the excretion of lithogenesis inhibitors (citrate), in some papers, an increase of excretion is described in overweight patients, while a decrease of citrate is shown in others (15, 41-43).

Regarding the limitations of the study, a single determination was made in the 24-hour urine. However, there are groups that recommend performing two separate determinations in time (8, 44). Parks et al. (45) observed that the metabolic characteristics of the patients varied according to the season of the year in which the metabolic study was carried out. In the present study, the season of the year in the assessment of the metabolic study has not been taken into consideration. Neither has been the influence of diet.

On the other hand, one study performed a urinalysis to patients with oxalocalcic lithiasis at various times throughout the day, observing that the pH oscillated, such that it decreased in the morning, increased at midday and returned to decrease at night (46). In this study, the possible variations of the pH throughout the day have not been taken into account since the pH analysis was carried out in fresh urine, always collected in the morning between 8.30 and 10 h.

There are research groups that, in the basal metabolic study of patients with urolithiasis, include a urine acidification test in order to identify those with renal tubular acidosis (8). In the current study, a urinary acidification test was not performed. However, this disorder is frequently associated with calcium phosphate stones, which are not the ones studied in this case. Other parameters analyzed occasionally in metabolic studies are urinary saturation indexes, both calcium oxalate, and calcium phosphate or other substances (47). In this study, the saturation indices have not been analyzed.

Also, despite some groups that have assessed metabolic differences between calcium oxalate monohydrate and dehydrate lithiasis (48, 49), in this study, they were considered altogether. Nevertheless, stones with other minor components that had different patterns in some studies (50) were excluded.

5.1. Conclusions

Patients with oxalocalcic lithiasis had biochemical alterations in 100% of the cases. The most frequent were hypocitraturia (84.7%), hypercalciuria (51.7%), and urinary pH decrease (44. 4%). These biochemical alterations varied according to sex, age, and BMI. Considering these data, it is advisable to perform a metabolic evaluation of patients with urolithiasis to carry out interventions to reduce recurrences.

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Footnotes

Authors' Contribution: SA and AS contributed to the study conception and design. Material preparation and data collection were performed by AS, FA, and IL. Statistical analysis was performed by IL. The first draft of the manuscript was written by VG, FB, and IL. All authors read and approved the final manuscript.

Conflict of Interests: The authors declare there is no conflict of interest.

Ethical Approval: The study was carried out in accordance with the code of ethics included in the Declaration of Helsinki, and with the current Spanish legislation. The study was approved by the Ethics Committee of Ramon y Cajal University Hospital, code: 65/10.

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Informed Consent: All patients were informed and signed the written informed consent.

References

1. Boyce WH, Garvey FK, Strawcutter HE. Incidence of urinary calculi among patients in general hospitals, 1948 to 1952. *J Am Med Assoc*. 1956;**161**(15):1437–42. doi: 10.1001/jama.1956.02970150005002. [PubMed: 13345602].
2. Turney BW, Reynard JM, Noble JG, Keoghane SR. Trends in urological stone disease. *BJU Int*. 2012;**109**(7):1082–7. doi: 10.1111/j.1464-410X.2011.10495.x. [PubMed: 21883851].
3. Saigal CS, Joyce G, Timilsina AR; Urologic Diseases in America Project. Direct and indirect costs of nephrolithiasis in an employed population: opportunity for disease management? *Kidney Int*. 2005;**68**(4):1808–14. doi: 10.1111/j.1523-1755.2005.00599.x. [PubMed: 16164658].
4. Astobieta A, Rodriguez JM, Resel L. Tratamiento médico de la litiasis urinaria. *Tratado Farmacoter en Urol*. 2001:753–98.
5. Scales CJ, Smith AC, Hanley JM, Saigal CS; Urologic Diseases in America Project. Prevalence of kidney stones in the United States. *Eur Urol*. 2012;**62**(1):160–5. doi: 10.1016/j.eururo.2012.03.052. [PubMed: 22498635]. [PubMed Central: PMC3362665].
6. Daudon M, Dore JC, Jungers P, Lacour B. Changes in stone composition according to age and gender of patients: A multivariate epidemiological approach. *Urol Res*. 2004;**32**(3):241–7. doi: 10.1007/s00240-004-0421-y. [PubMed: 15127165].
7. Novak TE, Lakshmanan Y, Trock BJ, Gearhart JP, Matlaga BR. Sex prevalence of pediatric kidney stone disease in the United States: An epidemiologic investigation. *Urology*. 2009;**74**(1):104–7. doi: 10.1016/j.urology.2008.12.079. [PubMed: 19428065].
8. Amaro CR, Goldberg J, Amaro JL, Padovani CR. Metabolic assessment in patients with urinary lithiasis. *Int Braz J Urol*. 2005;**31**(1):29–33. doi: 10.1590/s1677-55382005000100006. [PubMed: 15763005].
9. Amaro CR, Goldberg J, Damasio PC, Leitao VA, Turney B, Padovani CR, et al. An update on metabolic assessment in patients with urinary lithiasis. *World J Urol*. 2015;**33**(1):125–9. doi: 10.1007/s00345-014-1271-z. [PubMed: 24623379].
10. Ahmad I, Pansota MS, Tariq M, Tabassum SA. Frequency of metabolic abnormalities in urinary stones patients. *Pak J Med Sci*. 2013;**29**(6):1363–6. doi: 10.12669/pjms.296.4007. [PubMed: 24550954]. [PubMed Central: PMC3905383].
11. Spivacow FR, Negri AL, Polonsky A, Del Valle EE. Long-term treatment of renal lithiasis with potassium citrate. *Urology*. 2010;**76**(6):1346–9. doi: 10.1016/j.urology.2010.02.029. [PubMed: 20399488].
12. Ahmed MH, Ahmed HT, Khalil AA. Renal stone disease and obesity: What is important for urologists and nephrologists? *Ren Fail*. 2012;**34**(10):1348–54. doi: 10.3109/0886022X.2012.723777. [PubMed: 23013150].
13. Asplin JR. Obesity and urolithiasis. *Adv Chronic Kidney Dis*. 2009;**16**(1):11–20. doi: 10.1053/j.ackd.2008.10.003. [PubMed: 19095201].

14. Leslie SW. Comment on: Kidney stone incidence and metabolic urinary changes after modern bariatric surgery: Review of clinical studies, experimental models, and prevention strategies. *Surg Obes Relat Dis*. 2014;**10**(4):742. doi: 10.1016/j.soard.2014.04.004. [PubMed: 25224169].
15. Semins MJ, Shore AD, Makary MA, Magnuson T, Johns R, Matlaga BR. The association of increasing body mass index and kidney stone disease. *J Urol*. 2010;**183**(2):571–5. doi: 10.1016/j.juro.2009.09.085. [PubMed: 20018330]. [PubMed Central: PMC3375596].
16. Spivacow FR, del Valle EE, Negri AL, Fradinger E, Abib A, Rey P. Biochemical diagnosis in 3040 kidney stone formers in Argentina. *Urolithiasis*. 2015;**43**(4):323–30. doi: 10.1007/s00240-015-0778-0. [PubMed: 25958053].
17. Hussein NS, Sadiq SM, Kamaliah MD, Norakmal AW, Gohar MN. Twenty-four-hour urine constituents in stone formers: A study from the northeast part of Peninsular Malaysia. *Saudi J Kidney Dis Transpl*. 2013;**24**(3):630–7. doi: 10.4103/1319-2442.111090. [PubMed: 23640651].
18. Menditto VG, Lucci M, Polonara S. [The role of hypomagnesiuria in urolithiasis and renal colic: results from a prospective study of a metabolic evaluation protocola]. *Minerva Med*. 2012;**103**(5):377–82. Italian. [PubMed: 23042373].
19. Ossandon Salas E, Storme Cabrera O, Ledesma R, Marchant Gonzalez F, Palma Ceppi C, Recabal Guiraldes P. [Metabolic study results of 54 patients with high risk of recurrent urolitiasis]. *Actas Urol Esp*. 2009;**33**(4):429–32. Spanish. doi: 10.1016/s0210-4806(09)74170-1. [PubMed: 19579895].
20. Ferraro PM, Robertson WG, Johri N, Nair A, Gambaro G, Shavit L, et al. A London experience 1995-2012: demographic, dietary and biochemical characteristics of a large adult cohort of patients with renal stone disease. *QJM*. 2015;**108**(7):561–8. doi: 10.1093/qjmed/hcu251. [PubMed: 25524906].
21. Zilberman DE, Yong D, Albala DM. The impact of societal changes on patterns of urolithiasis. *Curr Opin Urol*. 2010;**20**(2):148–53. doi: 10.1097/MOU.0b013e3283353b6d. [PubMed: 19940772].
22. Shoag J, Tasian GE, Goldfarb DS, Eisner BH. The new epidemiology of nephrolithiasis. *Adv Chronic Kidney Dis*. 2015;**22**(4):273–8. doi: 10.1053/j.ackd.2015.04.004. [PubMed: 26088071].
23. Robertson WG, Peacock M, Heyburn PJ, Hanes FA. Epidemiological risk factors in calcium stone disease. *Scand J Urol Nephrol Suppl*. 1980;**53**:15–30. [PubMed: 6937991].
24. Penniston KL, Nakada SY. Health related quality of life differs between male and female stone formers. *J Urol*. 2007;**178**(6):2435–40. discussion 2440. doi: 10.1016/j.juro.2007.08.009. [PubMed: 17937947].
25. Sanchez-Martin FM, Angerri O, Emiliani E, Moncada E, Carpio J, Millan F, et al. [Epidemiology of urolithiasis in Spain: Review of published demographic data in the period 1977-2016]. *Arch Esp Urol*. 2017;**70**(2):294–303. Spanish. [PubMed: 28300034].
26. Damasio PC, Amaro CR, Berto SJ, Cunha NB, Pichutte AC, Padovani CR, et al. Urinary lithiasis and idiopathic hypercalciuria: The importance of dietary intake evaluation. *Int Braz J Urol*. 2010;**36**(5):557–62. doi: 10.1590/s1677-55382010000500005. [PubMed: 21044372].
27. Yun SJ, Ha YS, Kim WT, Kim YJ, Lee SC, Kim WJ. Sodium restriction as initial conservative treatment for urinary stone disease. *J Urol*. 2010;**184**(4):1372–6. doi: 10.1016/j.juro.2010.06.019. [PubMed: 20723924].
28. Curhan GC, Willett WC, Knight EL, Stampfer MJ. Dietary factors and the risk of incident kidney stones in younger women: Nurses' Health Study II. *Arch Intern Med*. 2004;**164**(8):885–91. doi: 10.1001/archinte.164.8.885. [PubMed: 15111375].
29. Perucca J, Bouby N, Valeix P, Bankir L. Sex difference in urine concentration across differing ages, sodium intake, and level of kidney disease. *Am J Physiol Regul Integr Comp Physiol*. 2007;**292**(2):R700–5. doi: 10.1152/ajpregu.00500.2006. [PubMed: 16990487].
30. Johri N, Jaeger P, Ferraro PM, Shavit L, Nair D, Robertson WG, et al. Vitamin D deficiency is prevalent among idiopathic stone formers, but does correction pose any risk? *Urolithiasis*. 2017;**45**(6):535–43. doi: 10.1007/s00240-016-0954-x. [PubMed: 27981376]. [PubMed Central: PMC5656695].
31. Souberbielle JC, Brazier F, Piketty ML, Cormier C, Minisola S, Cavalier E. How the reference values for serum parathyroid hormone concentration are (or should be) established? *J Endocrinol Invest*. 2017;**40**(3):241–56. doi: 10.1007/s40618-016-0553-2. [PubMed: 27696297].
32. Prezioso D, Illiano E, Piccinocchi G, Cricelli C, Piccinocchi R, Saita A, et al. Urolithiasis in Italy: An epidemiological study. *Arch Ital Urol Androl*. 2014;**86**(2):99–102. doi: 10.4081/aiua.2014.2.99. [PubMed: 25017588].
33. Lieske JC, Pena de la Vega LS, Slezak JM, Bergstralh EJ, Leibson CL, Ho KL, et al. Renal stone epidemiology in Rochester, Minnesota: an update. *Kidney Int*. 2006;**69**(4):760–4. doi: 10.1038/sj.ki.5000150. [PubMed: 16518332].
34. Daudon M, Lacour B, Jungers P. High prevalence of uric acid calculi in diabetic stone formers. *Nephrol Dial Transplant*. 2005;**20**(2):468–9. doi: 10.1093/ndt/gfh594. [PubMed: 15673704].
35. Lancina Martin JA, Rodriguez-Rivera Garcia J, Novas Castro S, Rodriguez Gomez I, Fernandez Rosado E, Alvarez Castelo L, et al. [Metabolic risk factors in calcium urolithiasis according to gender and age of the patients]. *Actas Urol Esp*. 2002;**26**(2):111–20. Spanish. doi: 10.1016/s0210-4806(02)72742-3. [PubMed: 11989423].
36. Marickar YM, Vijay A. Female stone disease: The changing trend. *Urol Res*. 2009;**37**(6):337–40. doi: 10.1007/s00240-009-0216-2. [PubMed: 19779708].
37. Caudarella R, Vescini F, Buffa A, Stefoni S. Citrate and mineral metabolism: Kidney stones and bone disease. *Front Biosci*. 2003;**8**:s1084–106. doi: 10.2741/1119. [PubMed: 12957820].
38. Yagisawa T, Hayashi T, Yoshida A, Kobayashi C, Okuda H, Ishikawa N, et al. Comparison of metabolic risk factors in patients with recurrent urolithiasis stratified according to age and gender. *Eur Urol*. 2000;**38**(3):297–301. doi: 10.1159/000020296. [PubMed: 10940703].
39. Spivacow FR, Negri AL, del Valle EE, Calvino I, Zanchetta JR. Clinical and metabolic risk factor evaluation in young adults with kidney stones. *Int Urol Nephrol*. 2010;**42**(2):471–5. doi: 10.1007/s11255-009-9623-0. [PubMed: 19653114].
40. Friedlander JI, Moreira DM, Hartman C, Elsamra SE, Smith AD, Okeke Z. Age-related changes in 24-hour urine composition must be considered in the medical management of nephrolithiasis. *J Endourol*. 2014;**28**(7):871–6. doi: 10.1089/end.2014.0002. [PubMed: 24571654].
41. Rendina D, De Filippo G, De Pascale F, Zampa G, Muscariello R, De Palma D, et al. The changing profile of patients with calcium nephrolithiasis and the ascendancy of overweight and obesity: A comparison of two patient series observed 25 years apart. *Nephrol Dial Transplant*. 2013;**28 Suppl 4**:iv146–51. doi: 10.1093/ndt/gft076. [PubMed: 23595293].
42. Lee SC, Kim YJ, Kim TH, Yun SJ, Lee NK, Kim WJ. Impact of obesity in patients with urolithiasis and its prognostic usefulness in stone recurrence. *J Urol*. 2008;**179**(2):570–4. doi: 10.1016/j.juro.2007.09.040. [PubMed: 18078957].
43. Ekeruo WO, Tan YH, Young MD, Dahm P, Maloney ME, Mathias BJ, et al. Metabolic risk factors and the impact of medical therapy on the management of nephrolithiasis in obese patients. *J Urol*. 2004;**172**(1):159–63. doi: 10.1097/01.ju.0000128574.50588.97. [PubMed: 15201761].
44. Healy KA, Hubosky SG, Bagley DH. 24-hour urine collection in the metabolic evaluation of stone formers: Is one study adequate? *J Endourol*. 2013;**27**(3):374–8. doi: 10.1089/end.2012.0216. [PubMed: 22967013].
45. Parks JH, Barsky R, Coe FL. Gender differences in seasonal variation of urine stone risk factors. *J Urol*. 2003;**170**(2 Pt 1):384–8. doi: 10.1097/01.ju.0000071721.91229.27. [PubMed: 12853781].
46. Murayama T, Sakai N, Yamada T, Takano T. Role of the diurnal variation of urinary pH and urinary calcium in urolithiasis: A study in outpatients. *Int J Urol*. 2001;**8**(10):525–31. discussion 532. [PubMed: 11737477].
47. Negri AL, Spivacow R, Del Valle E, Pinduli I, Marino A, Fradinger E, et

al. Clinical and biochemical profile of patients with "pure" uric acid nephrolithiasis compared with "pure" calcium oxalate stone formers. *Urol Res*. 2007;**35**(5):247–51. doi: 10.1007/s00240-007-0109-1. [PubMed: 17786420].

48. Maurice-Estepa L, Levillain P, Lacour B, Daudon M. Advantage of zero-crossing-point first-derivative spectrophotometry for the quantification of calcium oxalate crystalline phases by infrared spectrophotometry. *Clinica Chimica Acta*. 2000;**298**(1-2):1–11. doi: 10.1016/s0009-8981(00)00224-2.
49. Trinchieri A, Castelnuovo C, Lizzano R, Zanetti G. Calcium stone disease: A multiform reality. *Urol Res*. 2005;**33**(3):194–8. doi: 10.1007/s00240-004-0459-x. [PubMed: 15714335].
50. Kustov AV, Strelnikov AI. Quantitative mineralogical composition of calculi and urine abnormalities for calcium oxalate stone formers: A single-center results. *Urol J*. 2018;**15**(3):87–91. doi: 10.22037/uj.v0i0.3910. [PubMed: 29277881].