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URINARY VOLUME, WATER AND RECURRENCES IN IDIOPATHIC CALCIUM NEPHROLITHIASIS: A 5-YEAR RANDOMIZED PROSPECTIVE STUDY

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ABSTRACT

Purpose: We define the role of urine volume as a stone risk factor in idiopathic calcium stone disease and test the actual preventive effectiveness of a high water intake.

Materials and Methods: We studied 101 controls and 199 patients from the first idiopathic calcium stone episode. After a baseline study period the stone formers were divided by randomization into 2 groups (1 and 2) and they were followed prospectively for 5 years. Followup in group 1 only involved a high intake of water without any dietetic change, while followup in group 2 did not involve any treatment. Each year clinical, laboratory and radiological evaluation was obtained to determine urinary stone risk profile (including relative supersaturations of calcium oxalate, brushite and uric acid by Equil 2), recurrence rate and mean time to relapse.

Results: The original urine volume was lower in male and female stone formers compared to controls (men with calcium oxalate stones 1,057 ± 238 ml./24 hours versus normal men 1,401 ± 562 ml./24 hours, $p < 0.0001$ and women calcium oxalate stones 990 ± 230 ml./24 hours versus normal women 1,239 ± 440 ml./24 hours, $p < 0.0001$). During followup recurrences were noted within 5 years in 12 of 99 group 1 patients and in 27 of 100 group 2 patients ($p = 0.008$). The average interval for recurrences was 38.7 ± 13.2 months in group 1 and 25.1 ± 16.4 months in group 2 ($p = 0.016$). The relative supersaturations for calcium oxalate, brushite and uric acid were much greater in baseline urine of the stone patients in both groups compared to controls. During followup, baseline values decreased sharply only in group 1. Finally the baseline urine in patients with recurrences was characterized by a higher calcium excretion compared to urine of the patients without recurrences in both groups.

Conclusions: We conclude that urine volume is a real stone risk factor in nephrolithiasis and that a large intake of water is the initial therapy for prevention of stone recurrences. In cases of hypercalciuria it is suitable to prescribe adjuvant specific diets or drug therapy.

KEY WORDS: urine, water, calcium, calculi

Prospective studies of patients with calcium nephrolithiasis followed since the first episode have shown that a large number of them present with recurrences within 5 years.[1-4] Urine factors that lead to idiopathic calcium nephrolithiasis and recurrences include a low urine volume, hypercalciuria, hyperoxaluria, hyperuricosuria, hypomagnesiuria, hypocitraturia and a low excretion of glycosaminoglycans.[5-7] The practice of increasing the urine volume with a high supply of water to prevent recurrences has been in use since the time of Hippocrates. Since the excretion of the promoters of calcium crystallization, with the possible exception of oxalate, is largely independent of urine flow,[7] any increase in urine volume should cause a decrease in the concentration of calcium, oxalate, phosphorus and uric acid, with subsequent reduction in the saturation of some of the salts that form stones. However, this protective effect of a high water intake may be counterbalanced by an increased dissociation of soluble complexes of lithogenous salts and by the simultaneous decrease of the concentration of the inhibitors of calcium crystallization (for example magnesium, pyrophosphate, citrate, glycosaminoglycans).[7,8]

In their investigation of this problem Pak et al showed that the dilution of urine, obtained in vitro with the addition of water to urine or in vivo with a sufficient intake of water to bring the urine volume to 2.5 l. a day, reduced the tendency to calcium crystallization by lowering urine saturation of calcium oxalate and brushite, and by increasing the limit of metastability of calcium oxalate.[9] Following these results the authors concluded that there was an objective protective effect of urine dilution. However, few authors have tested in a scientifically correct manner the actual preventive effectiveness of an increased water intake, except for Frank and De Vries who illustrated its importance in a general population living in a village in a hot desert region.[10]

Few studies have been published on stone formers that suggest a protective effect of a high urine volume[11-13] and no definite conclusions may be drawn since they present methodological limits, such as the absence of an adequate control group, concomitant cofactors, such as diet changes, a limited number of subjects or a followup that is too short for a condition characterized by a variable natural history. Another controversial element that has not been specifically studied concerns the baseline urine volume of calcium stone formers. Many authors have shown that patients exposed to chronic dehydration caused by a hot climate, working or sports activities performed at high temperatures and with abundant perspiration or scarce intake of liquids have a particularly high incidence of urolithiasis.[2,14-21] However, it has not been established whether subjects producing idiopathic calcium calculi have a reduced baseline urine volume compared to healthy subjects not producing calculi and com-

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parable in regard to age, sex, body weight, life-style and geographical area of origin.

Most studies on idiopathic calcium urolithiasis report urine volumes that are on average higher in stone patients than in normal subjects but this seems to be a logical consequence of the common recommendation to increase the intake of liquids for therapeutic reasons. Robertson et al proposed including urine volume in the computerized assessment of the probability of calculi formation, suggesting that a lower urine volume was found in stone patients than in the controls, but this result was not explicitly reported in these studies.[7,22,23]

In 1986 we began a study to quantify the urine volume "at the origin" for idiopathic calcium stone formers, assess the actual effectiveness of simple high water treatment without any diet changes in preventing recurrences and identify any biochemical urine factors to predict recurrences. The results of this study are reported.

MATERIAL AND METHODS

Since 1986 a uniform study protocol reported elsewhere[24] was applied to all stone patients who were referred to our stone center. At our center all patients with renal colic are hospitalized for a few days. They receive appropriate medical treatment for the colic pain, and a complete clinical, laboratory and radiological evaluation, including flat plain abdominal x-ray, renal echography, infusion excretory urography (IVP), serum concentrations of sodium, potassium, calcium, phosphorus, magnesium, urea, glucose, uric acid, creatinine, cholesterol, triglycerides, intact parathyroid hormone and bicarbonate, and urinalysis and culture, to define any established cause of stone formation. When necessary patients undergo shock wave lithotripsy or other urological procedures and then they are followed as outpatients. In 3 years 750 patients were subjected to this protocol, of whom 220 were found suitable for this study. Inclusion criteria were first episode of idiopathic calcium nephrolithiasis (calculus found at the chemical examination to be composed of pure calcium oxalate or mixed with traces of calcium phosphate), absence of other retained calculi (renal echography and IVP) and absence of arterial hypertension or other metabolic pathology that requires regular dietary measures or drug therapy.

Once the lithiasic episode had been resolved (through spontaneous expulsion of the calculus, shock wave lithotripsy, percutaneous techniques or other procedures), each patient was then thoroughly encouraged to resume the normal diet and high water intake as before the lithiasic episode. Each patient was informed of the importance of having a urine collection that would reflect the situation before the calculosis. After 3 months each patient collected urine for 24 hours to determine the baseline stone risk profile, which includes at our laboratory urine volume, pH, excretion of creatinine (Jaffè method), sodium and potassium (flame photometer), calcium and magnesium (atomic spectrophotometer), chloride (coulomb metric titration), uric acid (uricase method), phosphorus, sulfate and oxalate (ion chromatography), citrate (citrate lyase method) and ammonium (colorimetric method). Relative supersaturations for calcium oxalate, brushite and uric acid were obtained with the Equil 2 computerized program.[25]

After the basic urine collection patients were randomly placed in 2 different followup programs lasting 5 years. Program 1 has as its only measure a high water intake, which would give a urine volume that was equal to or greater than 2 l. a day (all patients received water that was not too mineralized and they were all instructed to measure the urine volume at home every 2 to 3 months). Each year for the 5-year followup period a 24-hour urine collection was brought to the stone center to determine the urine stone risk profile and patients received a complete physical examination, a flat plain abdominal x-ray and renal echography. Program 2 did not provide for any high water treatment and patients were told that, since it was an isolated stone episode, it was not necessary at least at that time to follow any special procedures. The rest of program 2 was identical to program 1.

All patients were invited to contact the stone center immediately in case of colic or expulsion of calculi during followup, and they would no longer be included in the study but would be placed on a personalized therapeutic program. The appearance of a silent calculus at the yearly followup identified by renal echography or x-ray also resulted in exclusion from the study, and the interval to recurrence was calculated to the date on which echography and x-ray were performed. This method made it possible to know the number of patients with recurrences in both groups as well as the mean time to recurrences in the 5-year followup period.

In the last 5 years of the study period 6,000 citizens residing in the same geographical area as the stone patients were contacted directly by mail and 101 healthy volunteers who were well matched in regard to age, sex, body weight, social class and working activity were enrolled as controls in our study (table 1). The controls had normal findings on all objective examinations, and normal values for arterial pressure and the serum parameters of urea, creatinine, glucose, uric acid, sodium, potassium, calcium, phosphorus and magnesium. The presence of silent renal calculi was excluded by renal echography and flat plain abdominal x-ray. The controls were also adequately instructed not to change their eating or high water habits, and a 24-hour urine collection was done to determine the urine stone risk profile, as in the stone formers.

Results were expressed as mean plus or minus standard deviation. The differences between the groups and in the various times of the followup were assessed by analysis of variance and Student's t test for unpaired data, with $p < 0.05$ considered significant. The frequency of stone events was compared by chi-square statistical analysis. All statistical analyses were performed with a computerized program.

RESULTS

Of the 220 patients enrolled in the program 199 completed the study, including 99 in group 1 and 100 in group 2. There were 11 dropouts during followup in group 1 and 10 in group 2. Table 1 shows that age, sex, body weight and type of working activity were similar in normal subjects as well as in stone patients randomly placed in groups 1 and 2. The baseline urine volume was lower in male and female stone patients compared to normal subjects, with a highly significant difference (fig. 1). Table 2 shows that the stone risk profile in the baseline urine was similar in groups 1 and 2 after randomization.

TABLE 1. *Patient characteristics*

	Controls	Idiopathic Calcium Stone Pts.	
		Group 1	Group 2
Age (yrs.)	40.9 ± 10.6	42.2 ± 11.6	40.4 ± 13.2
Sex (M/F)	71/30	70/29	64/36
Body wt. (kg.)	68 ± 10	71.2 ± 11.5	68.4 ± 13
Occupation:			
Civil servants	32	30	34
Tradesmen	17	15	13
Artisans	9	8	11
Farmers	6	4	2
Entrepreneurs	4	3	4
Managers	4	1	2
Practitioners	8	10	6
Retired	5	13	8
Housewives	16	15	20

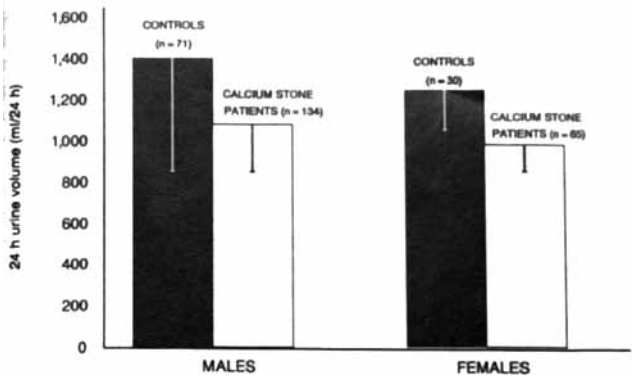

FIG. 1. Native urine volume in idiopathic calcium stone patients and controls. Male controls 1,401 ± 562 ml./24 hour versus male patients 1,057 ± 238 (p <0.0001). Female controls 1,239 ± 440 versus female patients 990 ± 230 (p <0.0001).

TABLE 2. *Baseline urinary stone risk profile in groups 1 and 2 after randomization*

	Group 1	Group 2
Vol. (ml./24 hrs.)	1068 ± 240	1008 ± 231
Creatinine (mg./24 hrs.)	1471 ± 322	1463 ± 401
Urea (gm./24 hrs.)	23 ± 8.1	23.4 ± 7
Sodium (mmol./24 hrs.)	158 ± 52	162 ± 55
Potassium (mmol./24 hrs.)	47 ± 14	47 ± 15
Calcium (mg./24 hrs.)	244 ± 109	266 ± 112
Phosphorus (mg./24 hrs.)	707 ± 250	670 ± 255
Magnesium (mg./24 hrs.)	85 ± 31	88 ± 33
Chloride (mmol./24 hrs.)	160 ± 53	159 ± 55
Uric acid (mg./24 hrs.)	588 ± 183	572 ± 211
Citrate (mg./24 hrs.)	512 ± 207	530 ± 259
Oxalate (mg./24 hrs.)	28.7 ± 9.5	28.6 ± 10.5
Sulfate (mmol./24 hrs.)	20.5 ± 5.8	20.4 ± 6.1
Ammonium (mmol./24 hrs.)	35 ± 10	34 ± 12
pH (24 hrs.)	5.91 ± 0.49	5.9 ± 0.5
Relative supersaturation:		
Calcium oxalate	10.1 ± 4.9	11.2 ± 5.3
Brushite	1.6 ± 1.24	1.82 ± 1.67
Uric acid	3.4 ± 2.9	3.6 ± 3.1

p value not significant.

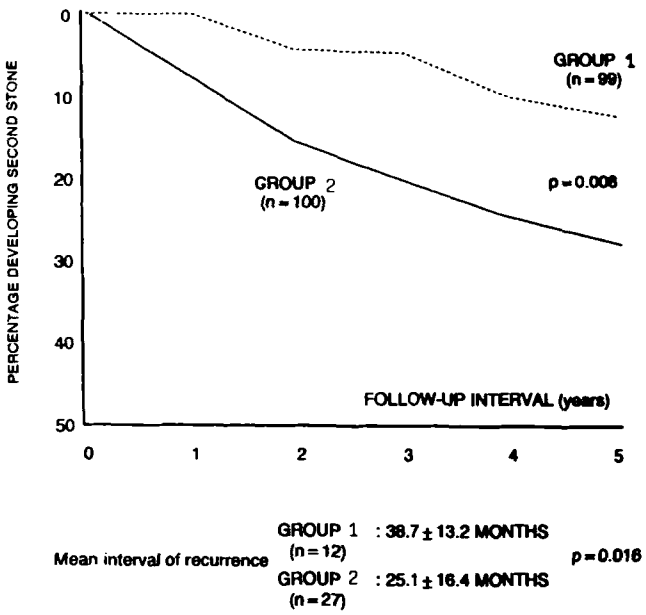

FIG. 2. Percentage of patients with relapse during followup and mean interval of recurrence. Group 1 treated with high water intake. Group 2 untreated.

During the 5-year followup period 12 of 99 patients in protocol 1 and 27 of 100 in protocol 2 had a second episode of calculosis (p = 0.008, fig. 2). The mean time for recurrence was 38.7 ± 13.2 months in group 1 and 25.1 ± 16.4 months in group 2 (p = 0.016). Urine volume and supersaturation of lithogenous salts (calcium oxalate, brushite, acid, uric acid), which were similar in both groups of stone formers in the baseline situation, were profoundly different at each annual visit during the 5-year followup (table 3). The baseline urine for stone formers was distinctly oversaturated compared to that of normal subjects, and during the followup period oversaturation of group 1 decreased to normal levels. Table 4 compares baseline stone risk parameters between patients with and without recurrences in groups 1 and 2. Baseline urine for patients with recurrences contained larger quantities of calcium in both groups, while no differences were observed in the other parameters examined.

DISCUSSION

In this study we have shown that patients with idiopathic calcium nephrolithiasis have a urine volume at the first episode that is lower than the volume of healthy control subjects, and that a simple but adequate increase in water intake, without any changes in diet, can prevent recurrences in a large number of subjects.

Many studies have shown that chronic dehydration, whatever the cause, was associated with increased urolithiasis[2,14-21] but it was not definitively established whether the formers of idiopathic calcium calculi originally had a urine volume that was reduced compared to healthy control subjects. To obtain an assessment of urine volume that was as similar as possible to the original volume we studied exclusively subjects with idiopathic calcium nephrolithiasis at the first episode of urolithiasis and followed them subsequent to the onset of symptoms. After resolution of the lithiasic event, we explained to each patient the importance of having a urine collection with eating, hydration and living conditions that were absolutely identical to those preceding the lithiasic episode. After 3 months the urine was collected to study the urine baseline stone risk profile. Healthy control subjects were identified in the same geographical area as the stone formers, and they were accurately matched in regard to age, sex, body weight and working activity.

We were able to document in subjects who had produced a calculus a decreased urine volume in both sexes. In man the mean difference compared to controls was 344 ml./24 hours, and in women it was 249 ml./24 hours (in both cases p <0.0001). These differences were close to those observed by Frank and De Vries, who studied the effect of a training program for hydration in the population of the desert town of Arad compared to the population of the nearby town of Beershiba, where no hydration training program was held.[10] After 3 years of training the urine volume for the population of Arad was significantly higher (p <0.01) in men (mean 263 ml./24 hours) and women (mean 278 ml./24 hours), and the incidence of nephrolithiasis was significantly, lower (p <0.001) compared to Beershiba (0.28% versus 0.85%). This comparison suggests that the difference in urine volume observed in our study may also represent a real stone risk factor.

There are many reasons for this result, some of which (sport, certain types of working activities that involve profuse perspiration, the presence of chronic gastrointestinal losses) have been analyzed by Embon et al who described chronic dehydration in 19% of 708 patients who formed calculi.[20] Although clinical experience suggests it, we do not have sufficient evidence to claim that idiopathic stone formers have some form of genetically determined reduced sense of thirst or insensitive loss of extra urinary water greater than normal, and such studies would be helpful.

TABLE 3. *Values of urine volume and relative supersaturation of lithogenous salts during the baseline and followup interval in groups 1 and 2*

	Baseline	Followup Interval (Yrs.)				
		1	2	3	4	5
Vol. (ml./24 hrs.):						
Group 1	1,068 ± 240	2,127 ± 546 p < 0.0001	2,261 ± 575 p < 0.0001	2,611 ± 683 p < 0.0001	2,654 ± 587 p < 0.0001	2,621 ± 443 p < 0.0001
Group 2	1,008 ± 231	1,258 ± 292	1,183 ± 271	1,032 ± 256	1,005 ± 183	1,014 ± 195
Calcium oxalate, relative supersaturation:						
Group 1	10.1 ± 4.9	5.2 ± 3.2 p < 0.0001	4.4 ± 2.9 p < 0.0001	4.0 ± 2.4 p < 0.0001	3.5 ± 2.0 p < 0.0001	2.6 ± 0.8 p < 0.0001
Group 2	11.2 ± 5.3	8.1 ± 5.2	9.5 ± 5.2	10.2 ± 4.7	10.2 ± 3.3	9.9 ± 3.4
Brushite, relative supersaturation:						
Group 1	1.6 ± 1.24	0.97 ± 0.99	0.84 ± 0.72 p < 0.001	0.65 ± 0.58 p < 0.0001	0.54 ± 0.36 p < 0.0001	0.48 ± 0.24 p < 0.0001
Group 2	1.82 ± 1.67	1.22 ± 1.06	1.33 ± 1.16	1.60 ± 1.14	1.60 ± 0.90	1.58 ± 0.99
Uric acid, relative supersaturation:						
Group 1	3.48 ± 2.95	1.72 ± 1.49 p < 0.001	1.29 ± 1.19 p < 0.0001	1.15 ± 0.93 p < 0.0001	0.80 ± 0.52 p < 0.0001	0.60 ± 0.35 p < 0.0001
Group 2	3.64 ± 3.08	2.66 ± 2.3	3.02 ± 2.72	3.54 ± 2.96	3.19 ± 2.40	3.46 ± 3.31

Control values of the relative supersaturations in 101 healthy controls were 5.87 ± 4.1 for calcium oxalate, 0.83 ± 0.73 for brushite and 2.65 ± 2.19 for uric acid.

TABLE 4. *Urinary stone risk profile during the baseline period in calcium stone patients with and without relapse in groups 1 and 2*

	Group 1			Group 2		
	No Relapse (87 pts.)		Relapse (12 pts.)	No Relapse (73 pts.)		Relapse (27 pts.)
Vol. (ml./24 hrs.)	1,051 ± 232		1,191 ± 275	987 ± 242		1,064 ± 189
Creatinine (mg./24 hrs.)	1,450 ± 308		1,623 ± 397	1,419 ± 407		1,584 ± 365
Urea (gm./24 hrs.)	22.8 ± 7.9		24.4 ± 9.8	23.3 ± 7.2		23.7 ± 6.7
Sodium (mmol./24 hrs.)	156 ± 53		175 ± 43	158 ± 49		175 ± 69
Potassium (mmol./24 hrs.)	47 ± 14		45 ± 12	46 ± 15		50 ± 16
Calcium (mg./24 hrs.)	233 ± 100	p = 0.005	326 ± 140	249 ± 107	p = 0.01	313 ± 113
Phosphorus (mg./24 hrs.)	705 ± 220		708 ± 331	673 ± 273		661 ± 201
Magnesium (mg./24 hrs.)	84 ± 31		96 ± 35	86 ± 32		94 ± 35
Chloride (mmol./24 hrs.)	159 ± 55		173 ± 36	153 ± 51		177 ± 63
Uric acid (mg./24 hrs.)	579 ± 162		659 ± 294	565 ± 189		591 ± 264
Citrate (mg./24 hrs.)	517 ± 212		478 ± 173	529 ± 262		532 ± 255
Oxalate (mg./24 hrs.)	28.5 ± 8.8		30.1 ± 13.9	28.1 ± 10.1		30.2 ± 11.6
Sulfate (mmol./24 hrs.)	19.8 ± 5.1		24.6 ± 8.4	20.2 ± 5.6		21 ± 7.3
Ammonium (mmol./24 hrs.)	35 ± 10		38 ± 12	34 ± 13		36 ± 11
pH (24 hrs.)	5.92 ± 0.48		5.80 ± 0.53	5.91 ± 0.54		5.88 ± 0.42
Relative supersaturation:						
Calcium oxalate	10.1 ± 4.9		10.9 ± 5.0	10.9 ± 5.1		12.2 ± 5.9
Brushite	1.56 ± 1.15		1.88 ± 1.81	1.81 ± 1.58		1.85 ± 1.93
Uric acid	3.38 ± 2.93		4.24 ± 3.08	3.82 ± 3.38		3.16 ± 2.03

The second part of our study clearly defined the preventive role of a considerable increase in water intake on stone recurrences. To overcome several methodological deficiencies that were observed in studies on prevention of stone recurrences,[26] we used a prospective protocol with an adequate control group, and we obtained a followup that was sufficiently long compared to the natural history of the disease. The 2 groups of patients were homogeneous in regard to age, sex, body weight, type of occupation and urine parameters of lithogenous risk after randomization. In group 1, treated with a high intake of water without any diet changes, the percentage of subjects with recurrence was 12.1% in 5 years, while in group 2, untreated, it was clearly greater at 27% ($p = 0.008$). Furthermore, the interval before the onset of a recurrence in the treated group was statistically greater than in the control group (mean 38.7 ± 13.2 months versus 25.1 ± 16.4 months, $p = 0.016$). These data indicate the truly protective role of a high water intake versus recurrence after the first idiopathic calcium stone episode.

The percentage of recurrences (27%) we observed in the 100 patients in group 2, expression of the natural history of the disease, is slightly less than that observed in a previous prospective study by Ljunghall and Danielson on 54 patients with idiopathic calcium nephrolithiasis at the first episode and followed for 8 years.[4] Our mean interval before a recurrence was 25 months, which is in agreement with that of others who have underlined the importance of a particularly careful and timely preventive treatment in the 3 years following the first lithiasic episode.[3] During the 5-year followup we monitored our patients by levels of relative supersaturation obtained through the Equil 2 computerized program, as suggested by others.[27] In fact, it is well known that idiopathic formers of calcium calculi tend to have a greater excretion of calcium, oxalate and uric acid and, thus, the urine is more oversaturate with monohydrate calcium oxalate,[28,29] brushite,[28,30] monosodium urate[31] and uric acid.[32] In our patients the mean baseline value of relative supersaturation for calcium oxalate and brushite was double that of the controls, indicating a strong tendency to calcium lithogenesis (calcium oxalate 10.1 ± 4.9 in group 1, 11.2 ± 5.3 in group 2 and 5.87 ± 4.1 in controls, $p < 0.0001$ and brushite 1.6 ± 1.24 in group 1, 1.82 ± 1.67 in group 2 and 0.83 ± 0.73 in controls, $p < 0.0001$).

The high water intake in group 1 caused a strong increase in urine volume throughout the followup period, accompanied by a considerable decrease in the supersaturation values for calcium oxalate and brushite to below the values recorded for the controls (table 3). On the other hand, only marginal variations were recorded in group 2 compared to baseline values. This different urine supersaturation caused by the high water treatment probably represented the physical chemical basis for the lower incidence of recurrences in the

group that was treated. The relative supersaturation of uric acid was also higher as a baseline value in patients versus the controls (uric acid 3.48 ± 2.95 in group 1, 3.64 ± 3.08 in group 2 and 2.65 ± 2.19 in controls, $p < 0.003$) and there was a distinct decrease during followup only in the treated group (table 3).

To identify any urine factors that predict recurrences, we compared urine parameters for baseline lithogenous risk in groups 1 and 2 for subjects with and without recurrences. We observed that baseline urine for patients with recurrences contained greater amounts of calcium in groups 1 (326 ± 140 versus 233 ± 106 mg./24 hours, $p < 0.005$) and 2 (313 ± 113 versus 249 ± 107 mg./24 hours, $p < 0.01$). No other difference was observed for the other parameters of lithogenous risk. This result is in agreement with other studies that underlined the importance of urine levels of calcium in predicting stone recurrences in untreated patients[4] and in patients undergoing prophylactic treatment.[33]

CONCLUSIONS

The urine volume in patients with idiopathic calcium nephrolithiasis at the first episode is lower than that of normal subjects, and adequate water intake, even when not accompanied by changes in diet, may exert a protective effect against recurrences in a large number of patients. A high water intake results in a strong reduction of saturations of lithogenous salts which, if chronically maintained, represents the physical chemical basis for preventing recurrences. However, when hypercalciuria is present, it is necessary to introduce dietary and/or pharmacological measures to reduce the excretion of urinary calcium.

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