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Low Urine Citrate Excretion as Main Risk Factor for Recurrent Calcium Oxalate Nephrolithiasis in Males

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Key Words
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Abstract
To better define the relative role of metabolic factors in the recurrence of stone formation, we studied the 24-hour urinary excretion of calcium (uCa), citrate (uCit), oxalic acid (uOx) and uric acid (uUa) in 73 male patients with primary calcium oxalate urolithiasis. According to the episodes of stone formation per year, we identified 51 recurrent stone formers (RSF) and 22 single stone formers (SSF). 20 normal adult males constituted the control group (C). uCa and uOx were higher in RSF than in C, but quite similar in SSF and RSF. The only difference between RSF and SSF was uCit, significantly lower (2.06 ± 1.04 mmol/24 h) in RSF than in SSF (3.22 ± 1.18 mmol/24 h, $p < 0.001$) and in C (3.42 ± 1.33 mmol/24 h, $p < 0.001$). Hypocitraturia (uCit < 1.5 mmol/24 h) was found in 16 of 51 RSF (31.4%) and in 1 of 22 SSF (4.5%). These data confirm that high levels of uCa and uOx represent a risk factor for lithogenesis, but also strongly indicate the low uCit excretion as the most important urinary abnormality accounting for the recurrence of calcium oxalate stones.

Introduction

Idiopathic calcium oxalate nephrolithiasis is a multifactorial disease with likelihood of recurrence [1, 2]. Some metabolic abnormalities have been identified as risk factors: hypercalciuria [3–5], hyperoxaluria [6–8] and hyperuricuria [9]. A very important role in the lithogenic process, even in absence of these conditions, was attributed to a defective production of urinary inhibitors of stone formation, mainly hypocitraturia [10, 11]. Both in normal and stone former males, the total amount of urinary calcium (uCa), oxalic acid (uOx) and uric acid (uUa) was higher than in females, while urinary citrate (uCit) excretion was lower [12]. Therefore, males have a higher risk for calcium oxalate stone formation than females.

The aim of this investigation was to verify the role of abnormalities in urine chemistry, as cause of recurrent nephrolithiasis, for the practical purpose of identifying the patients who need diet and/or medication to prevent stone recurrences [13, 14]. The study was performed in adult males to avoid sex-linked differences [12, 15, 16].

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Table 1. Results of 24-hour urinary excretion in male RSF, SSF and C

	RSF	SSF	C
uV, ml/24 h	2,021 ± 968*	1,897 ± 1067	1,495 ± 776
uCa, mmol/24 h	6.55 ± 2.82*	6.80 ± 2.72*	5.17 ± 1.77
uOx, mmol/24 h	0.31 ± 0.09*	0.28 ± 0.08	0.25 ± 0.09
uUa, mmol/24 h	3.60 ± 0.98	3.18 ± 0.81	3.45 ± 0.69
uCit, mmol/24 h	2.06 ± 1.04**/***	3.20 ± 1.18	3.42 ± 1.33
uCr, mmol/24 h	13.6 ± 3.1	13.7 ± 2.9	14.1 ± 2.3

The results are expressed as mean ± SD.
*$p < 0.05$; **$p < 0.001$ vs. C; ***$p < 0.001$ vs. SSF. uV = Urinary Volume.

Table 2. Prevalence of metabolic abnormalities in male RSF, SSF and C

	RSF 51		SSF 22		C 20	
	n	%	n	%	n	%
Hypercalciuria (uCa > 7.5 mmol/24 h)	16	31.4	6	27.6	2	10
Hyperoxaluria (uOx > 0.5 mmol/24 h)	4	7.8	0	0	0	0
Hyperuricuria (uUa > 4.2 mmol/24 h)	10	19.6	2	9	2	10
Hypocitraturia (uCit < 1.5 mmol/24 h)	16	31.4	1	4.5	0	0

Table 3. uCit excretion in male hypercalciuric (uCa > 7.5 mmol/24 h) and normocalciuric (uCa < 7.5 mmol/24 h) patients

	uCa mmol/24 h	uCit mmol/24 h	p value
Hypercalciuric patients			
RSF (n = 16)	10.0 ± 2.0	2.42 ± 1.12	< 0.01
SSF (n = 6)	10.4 ± 2.3	4.21 ± 1.11	
Normocalciuric patients			
RSF (n = 35)	4.8 ± 1.6	1.90 ± 0.97	< 0.01
SSF (n = 16)	5.4 ± 1.1	2.84 ± 1.00	

Patients and Methods

73 male patients suffering from primary calcium oxalate urolithiasis were examined. According to the clinical history, they were divided into two groups: 51 patients, aged 40 ± 11 years, who had formed 2 or more stones in the 3 years preceeding the study and defined as 'recurrent stone formers' (RSF), and 22 subjects, aged 45 ± 14 years, who had had a single episode more than 2 years before, defined as 'single stone former' (SSF).

Patients with primary hyperparathyroidism, medullary sponge kidney disease and other diseases causing secondary urolithiasis (obstructive uropathy, enteric hyperoxaluria, prolonged immobilization, sarcoidosis, renal tubular acidosis and Paget's disease) were excluded. 20 normal males aged 35 ± 11 years formed the control group (C). All the patients had normal renal function and no evidence of urinary tract infections.

All subjects were studied as outpatients at the time of the entry in our Center, with their usual diet and habits, and in absence of any drug which might interfere with the studied parameters. While almost all stone formers were given advice to increase their fluid intake by the family physician, their dietary calcium, oxalate and purine intake did not change.

uCa, uOx, uUa, uCit and creatinine (uCr) excretion was measured on 2 consecutive days by using 24-hour urine collections. uCa was measured with a Kontron autoanalyzer, uUa by enzymatic-colorimetric assay, uOx and uCit by the enzymatic methods previously described [17, 18]. Relative supersaturation (RS) for calcium oxalate was calculated using Marshall's nomograms [19].

Results were expressed as mean ± SD. Statistical analysis was performed by using the Student 't' test for unpaired observations. Values of $p < 0.05$ were regarded as statistically significant.

Results

The mean values of the studied urinary parameters are reported in table 1. The prevalence of metabolic abnormalities is shown in table 2.

The only significant difference between RSF and SSF was the daily uCit excretion (2.06 ± 1.04 and 3.22 ± 1.18 mmol/24 h, respectively; $p < 0.001$; table 1). uCit concentration was also significantly lower in RSF than in SSF (fig. 1). A significant difference ($p < 0.001$) was found between RSF and C, while the difference in uCit concentration between SSF and C was not statistically significant (fig. 1).

Hypocitraturia (uCit < 1.5 mmol/24 h) was present in 16 of 51 RSF (31.4%) whereas it was found only in 1 of 22 SSF (4.5%) and in none of the controls (table 2).

Even when hypercalciuric and normocalciuric patients were examined, the differences in uCit excretion were still maintained. RSF showed lower uCit excretion than SSF, suggesting an imbalance between uCa and uCit excretion in the former (table 3). In fact, uCa/uCit ratio was markedly higher in RSF (4.1 ± 2.8 mmol) than in SSF (2.3 ±

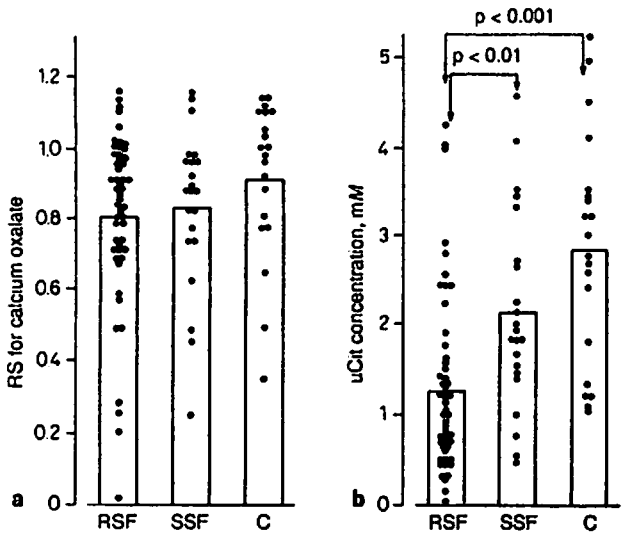

Fig. 1. RS for calcium oxalate in RSF, SSF and C (**a**) and uCit concentrations in the same groups (**b**).

0.8 mmol, $p<0.005$) and C (1.7 ± 0.8 mmol, $p<0.001$). A statistically significant difference was also detected between SSF and C ($p<0.05$).

RS for calcium oxalate salt was similar in both RSF and SSF, indicating no difference in urinary saturation, whereas uCit concentration was much lower in RSF than in SSF, as it appears in figure 1. In C, the mean values of RS and uCit concentration were higher (because of the smaller urinary volume) than in RSF, but a statistically significant difference was observed only for uCit concentration.

uCa was similar in RSF and SSF, being in both groups higher than in C (table 1); the prevalence of hypercalciuria (uCa > 7.5 mmol/24 h) was quite similar in RSF and SSF. Hypercalciuria was also present in 10% of C (table 2).

uOx was higher in RSF than in C, but no difference was detected versus SSF (table 1). The prevalence of hyperoxaluria was 7.5% in the RSF group.

The urinary excretion of uUa was similar in RSF, SSF and in C (table 1). Hyperuricuria was found in 23.5% of RSF, 9% of SSF and 10% of C, respectively (table 2).

Urinary volume was higher in RSF than in C (table 1). A possible explanation may be the suggestion of a high fluid intake by the family physician [20]. A slight, but not statistically significant difference in urinary volume was present between SSF and C (table 1).

Discussion

Stone formation is a complex and dynamic process involving nucleation, growth and aggregation of crystals [21, 22]. Abnormalities of metabolism and ion transport in the kidney and intestine can modify urinary solute composition and favor stone formation.

Hypercalciuria, hyperoxaluria and hyperuricuria are frequently associated with calcium nephrolithiasis [23]. However, these abnormalities do not necessarily cause urinary stone formation. On the contrary, stone patients often do not have any of these abnormalities.

The 24-hour excretion of uCa, uOx, uUa and urinary volume were not different between RSF and SSF, as it appears from our results, whereas lower uCit concentration and absolute excretion were the only feature that distinguished male RSF from SSF, with a prevalence of hypocitraturia of 31.4% in the former versus 4.5% in the latter.

In RSF, urinary volume, uCa and uOx excretion were higher than in C, while uCit was lower. In SSF, higher uCa excretion was the only difference in comparison to normal subjects.

These data confirm that high uCa and uOx excretions are risk factors for calcium nephrolithiasis. Our results point out also that a low excretion of uCit is the only difference between recurrent and single calcium oxalate stone formers. Subjects with a well-known cause of hypocitraturia, such as renal failure, complete tubular acidosis, urinary tract infections or malabsorption syndrome were excluded from our study, and the diet was quite similar in all the studied groups. Indeed, the mechanism of hypocitraturia in RSF may be an enhanced tubular resorption of citrate, as it was recently described (11, 24).

The urinary saturation for calcium oxalate salt was quite similar in RSF, SSF and C. The mean values of RS in the three groups was at the upper limit of metastability (fig. 1). The reason may be the high water intake of RSF patients, which, on the other hand, decreases uCit concentration, worsening the inhibitory defect derived from the lower daily uCit excretion. Theoretically, high fluid intake decreases urinary concentration of inhibitors and it could eliminate the beneficial effect of reduced saturation. Instead, it has been demonstrated that high fluid intake exerts a protective effect in the management of kidney stone disease, because urinary dilution reduces calcium oxalate crystal formation by lowering urinary saturation of component ions, without any decrease in formation-product ratio [20].

It is well known that one of the protective actions of citrate on the calcium oxalate lithogenetic process is the

complexation of calcium ions which decreases the calcium oxalate activity product [15]. Moreover, uCit exerts an inhibitory activity on crystal growth and aggregation that is a major mechanism of stone formation [25].

The importance of a calcium-citrate imbalance in urine emerges also from the results shown in table 3, where uCit in RSF is lower than in SSF, both in hypercalciuric and in normocalciuric patients. Consequently, these results suggest that a low uCit level is a serious risk factor not only in absolute, but also in relation to uCa excretion [15].

In the present study, uUa excretion seems not to be a major risk factor. As a consequence of the high fluid intake, its urine concentration is low, as well as the risk of uric acid crystal formation. This finding is consistent with the observations of some clinical trials which failed to demonstrate a real protection of allopurinol treatment against calcium oxalate stone recurrences [14].

Oxalic acid concentration is of critical importance in causing oversaturation for calcium oxalate in urine [8]. In this study, however, no statistical difference was found between RSF and SSF in uOx, although its mean value in the former resulted higher than in the latter.

In conclusion, our results suggest that the measurement of uCit excretion is of great importance in the study of patients with calcium oxalate nephrolithiasis, and that dietary and/or pharmacological measures should be used to correct hypocitraturia. Hypercalciuria is a common finding in calcium oxalate urolithiasis, but its role as risk factor of stone formation seems not to be critical [8], unless relatively low uCit levels are not associated [15]. In this respect, it may be reasonable to start thiazide therapy [26, 27] when high uCa excretion is associated with low uCit levels and, in any case, to use therapeutic measures to increase citraturia. Potassium citrate may represent a new and reasonable way to prevent calcium nephrolithiasis, alone or in association with thiazides [28].

References

1 Goldwasser B, Weinerth JL, Carson CC: Calcium stone disease: An overview. J Urol 1986; 135:1-9.
2 Ljunghall S: Incidence of upper urinary tract stones. Miner Electrolyte Metab 1987;13: 220-227.
3 Sutton RAL: Disorders of renal calcium excretion. Kidney Int 1983;23:665-673.
4 Nordin BEC, Peacock M, Wilkinson R: Hypercalciuria and renal stone disease. Clin Endocrinol Metab 1972;1:169-183.
5 Broadus AE, Burtis WJ, Oren DA, Sartori L, Gay L, Ellison AF, Insogna KL: Concerning the pathogenesis of idiopathic hypercalciuria. Contrib Nephrol 1987;58:127-136.
6 Larsson L, Tiselius HG: Hyperoxaluria. Miner Electrolyte Metab 1987;13:242-250.
7 Baggio B, Gambaro G, Favaro S, Borsatti A: Prevalence of hyperoxaluria in idiopathic calcium oxalate kidney stone disease. Nephron 1983;35:11-14.
8 Robertson WG, Peacock M: The cause of idiopathic calcium stone disease: Hypercalciuria or hyperoxaluria? Nephron 1980;26:105-110.
9 Coe FL: Hyperuricosuric calcium oxalate nephrolithiasis. Kidney Int 1978;13:418-426.
10 Nicar MJ, Skurla C, Sakhaee K, Pak CYC: Low urinary citrate excretion in nephrolithiasis. Urology 1983;21:8-14.
11 Rudman D, Kutner MH, Redd SC, Waters WC, Gerron GG, Bleier J: Hypocitraturia in calcium nephrolithiasis. J Clin Endocrinol Metab 1982;55:1052-1057.
12 Hesse A, Classen A, Klocke N, Vahlensieck W: The significance of sexual dependency of lithogenic and inhibitory substances in urine; in Schwille PO, Smith LH, Robertson WG, Vahlensieck W: Urolithiasis and Related Clinical Research. New York, Plenum Press, 1985, pp 25-27.
13 Pak CYC, Britton FB, Peterson R, et al: Ambulatory evaluation of nephrolithiasis. Am J Med 1980;69:19-30.
14 Churchill DN: Medical treatment to prevent recurrent calcium urolithiasis. Miner Electrolyte Metab 1987;13:294-304.
15 Parks JH, Coe FL: A urinary calcium-citrate index for the evaluation of nephrolithiasis. Kidney Int 1986;30:85-90.
16 Hesse A, Klocke K, Classen A, Vahlensieck W: Age and Sex as factors in oxalic acid excretion in healthy persons and calcium oxalate stone patients, Contrib Nephrol 1987;58: 16-20.
17 Chiriboga J: Some properties of an oxalic oxidase purified from barley seedlings. Biochem Biophys Res Commun 1963;11:277-290.
18 Mollering H, Gruber W: Determination of citrate with citrate lyase. Anal Biochem 1968; 17:369-376.
19 Marshall RW, Robertson WG: Nomograms for the estimation of the saturation of urine with calcium oxalate, calcium phosphate, magnesium ammonium phosphate, uric acid, sodium acid urate, ammonium acid urate and cystine. Clin Chim Acta 1976;72:253-260.
20 Pak CYC, Sakhaee K, Crowther C, Brinkley L: An objective evidence for the beneficial effect of a high fluid intake in the management of nephrolithiasis. Ann Intern Med 1980;93: 36-39.
21 Finlayson B: Physiochemical aspects of urolithiasis. Kidney Int 1978;13:344-360.
22 Smith LH: Pathogenesis of renal stones. Miner Electrolyte Metab 1987;13:214-219.
23 Robertson WG, Peacock M, Heyburn PJ, Marshall DH, Clark PB: Risk factors in calcium stone disease of the urinary tract. Br J Urol 1978;50:449-454.
24 Minisola S, Rossi W, Pacitti MT, et al: Studies on citrate metabolism in normal subjects and kidney stone patients. Miner Electrolyte Metab 1989;15:303-308.
25 Kok DJ, Socrates E, Papapoulos SE, Bijvoet OLM: Crystal agglomeration is a major element in calcium oxalate urinary stone formation. Kidney Int 1990;37:51-56.
26 Churchill DN, Taylor DW: Thiazides for patients with recurrent calcium stones: Still an open question. J Urol 1985;133:749-751.
27 Yendt ER, Cohanim M: Prevention of calcium stones with thiazides. Kidney Int 1978;13: 397-409.
28 Nicar MJ, Peterson R, Pak CYC: Use of potassium citrate as potassium supplement during thiazide therapy of calcium nephrolithiasis. J Urol 1984;131:430-433.