

## Different dietary calcium intake and relative supersaturation of calcium oxalate in the urine of patients forming renal stones

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- 1. Dietary calcium restriction, an efficient practice in reducing urinary calcium excretion, has been reported to induce either an increase or no change in oxalate excretion, questioning its use in hypercalciuric stone-forming patients. In addition, calcium restriction has been previously demonstrated to induce other urinary changes which might influence the relative supersaturation of calcium oxalate. So the overall effect of calcium deprivation on the relative supersaturation of calcium oxalate is unpredictable.**
- 2. The aim of the study was to evaluate the effect of dietary calcium restriction on the relative supersaturation of calcium oxalate in the urine of stone-forming patients utilizing a computer methodology which takes into account the main soluble complex species of oxalate.**
- 3. We studied 34 stone-forming patients on both a free-choice diet, whose Ca and oxalate content (24 and 1.2 mmol respectively) was assessed by dietary inquiry, and after 30 days on a prescribed low-calcium and normal oxalate diet (11 and 1.1 mmol respectively). Under both conditions, the excretion of the main urinary parameters related to dietary composition, electrolytes, oxalate and daily citrate urinary excretion, were measured. The relative supersaturation of calcium oxalate was calculated by means of an iterative computer method which takes into account the main soluble complex species on which the solubility of calcium oxalate is dependent. In addition, intact parathyroid hormone and 1,25-dihydroxyvitamin D blood levels were also evaluated. In 13 of the patients intestinal calcium absorption was evaluated during both a free- and a low-calcium diet, utilizing kinetics methodology.**
- 4. The low-calcium diet induced, together with an expected reduction of calcium excretion, a marked increase in oxalate urinary output. This finding was**

**independent of the presence or otherwise of hypercalciuria and of the serum levels of parathyroid hormone and vitamin D. Intestinal calcium absorption was also stimulated by calcium deprivation and its levels were well correlated with oxalate excretion. Minor changes in magnesium and citrate excretion were also observed. The overall effect on the relative supersaturation of calcium oxalate consisted in a substantial increase in this parameter during the low-calcium diet.**

- 5. In conclusion, our data reinforce the concept that dietary calcium restriction has potentially deleterious effects on lithogenesis, by increasing the relative supersaturation of calcium oxalate.**

### INTRODUCTION

Hypercalciuria (HC), a common metabolic finding in patients forming renal stones (SF), is often related to increased dietary intake and/or intestinal absorption of calcium [1–3]. It is also accepted that HC is one of the most important factors affecting the urinary supersaturation of calcium oxalate, the most common constituent of urinary calculi [4]. For all these reasons the prescription of dietary calcium restriction has been used for a long time as an obvious intervention in SF and suffering from hypercalciuria.

However, much experimental and epidemiological evidence has put into question this practice. In fact, some studies reported increased urinary oxalate excretion in patients consuming a calcium-restricted diet, which could be explained by the increased amount of oxalate available for absorption in the colon, secondary to the reduced intestinal calcium concentration [5, 6]. However, these results were not found universally, and a study by Galosy et al. [7] was not able to confirm the finding of increased oxa-

**Key words:** bone, bone resorption, calcium oxalate, diet, urolithiasis.

**Abbreviations:** FCD, free-choice diet; HC, hypercalciuria; ICA%, fractional intestinal absorption of calcium; i-PTH, intact parathyroid hormone; LCD, low-calcium diet; NHC, non-hypercalciuric; SF, renal stone-forming patients; 1,25-vitD, 1,25-dihydroxyvitamin D.

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late excretion secondary to a reduction in calcium dietary intake.

A recent prospective study [8] seems to indicate that calcium supplementation even has beneficial effects on the risk of development of kidney stones, adding more confusion and concern to the dietary calcium prescription.

In addition to these findings, in a previous study [9] we found that dietary calcium restriction induces changes in the urinary excretion of other constituents which might have some direct or indirect effect on the calcium oxalate lithogenic process, owing to the fact that the relative supersaturation of calcium oxalate in urine is dependent on the concentration of a large number of soluble complex species [10].

For all these reasons, the final effect of dietary calcium restriction on the calcium oxalate lithogenic process is unpredictable, without assessing the effect of the overall urinary changes secondary to calcium restriction.

Given that dietary Ca restriction has a deleterious effect on bone [9, 11], especially in the subgroups of patients characterized by fasting hypercalciuria, known to have a basically increased bone resorption rate [12], it seems relevant to prove, or otherwise, whether this kind of dietary prescription plays any role, at least in the reduction of the lithogenic risk.

The aim of the present investigation was to evaluate the effect of dietary calcium restriction on the urine relative saturation index of calcium oxalate, using a computer method which takes into account the main soluble complex species of oxalate, in a group of SF kept on both a free-choice diet (FCD) and a low-calcium diet (LCD).

## MATERIALS AND METHODS

### Patients

Thirty-four patients (10 female), aged 22–54 years, who had experienced at least two episodes of calcium oxalate stone formation in the previous 3 years, were enrolled in the study. None of them was affected by primary hyperparathyroidism, medullary sponge kidney disease or tubular acidosis, and their renal function was in the normal range, as judged by serum creatinine  $<130 \mu\text{mol/l}$  and creatinine clearance  $>90 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$  of BSA. Patients with primary hyperoxaluria were also excluded. The female patients were all in premenopausal period. All subjects gave informed consent to be submitted to the study protocol and ethics committee approval was obtained for the study.

The patients were first evaluated while on a home FCD. The calcium and oxalate content of the FCD were indirectly estimated by dietary inquiry performed by our dietitians. In particular, the patients were invited to record the quality and quantity of all food consumed during or out of main meals, for five consecutive days. Thereafter, the average Ca and

oxalate content of the diet consumed was assessed, utilizing the Ciba-Geigy diet composition tables [13]. The calculated Ca and oxalate content was about 24 and 1.2 mmol/day respectively. Dietary content in salt and proteins was evaluated by both dietary inquiry and daily urinary excretion of NaCl and urea respectively; this double method served as a control of the quality of dietary records by patients. While our SF patients were on this FCD, two 24 h urine collections were performed on two occasions separated by at least 1 week. Each daily collection was obtained in a double-chamber container which allows for the simultaneous separation of each urine output into two equal parts. One of the two chambers contained 6 mol/l HCl. The urine collected in the acid-containing chamber was utilized for the measurements of oxalate, citrate, sulphate and Ca. In the other urinary sample the following parameters were evaluated: Na, K, Mg, inorganic phosphate, Cl,  $\text{NH}_4$ , uric acid, urea, creatinine and pH.

In one urine sample, collected on the morning after a 12 h fast, creatinine, Ca, inorganic phosphate and hydroxyproline were measured.

In a blood sample, collected on the same morning, calcium, phosphate, creatinine, total alkaline phosphatase, 1,25-dihydroxyvitamin D (1,25-vitD) and intact parathyroid hormone (i-PTH) were measured.

In 13 of the patients, the fractional intestinal absorption of calcium (ICaA%) was evaluated by kinetic methodology, utilizing stable strontium as tracer. These 13 patients were chosen on their compliance to perform the extended study. However, they were very representative of the global groups as regards gender distribution (M/F 9/4), age (22–48 years) and the presence of HC (7/13).

Thereafter, all the patients were kept on an LCD. This LCD, composed by our dietitians utilizing the Ciba-Geigy dietary content tables [13], was studied in order to change the calcium content only, maintaining almost the same amount of the other constituents (and in particular of oxalate), with respect to a normal diet habitually consumed by north-eastern Italian people. In particular, the LCD consisted of about 11 mmol calcium, 35 mmol phosphate, 100 mmol sodium chloride, 50 mmol potassium, 1.1 mmol oxalate, 80 g of proteins, 85 g of lipids and 320 g of carbohydrates, with a total caloric content of about 167.36 kJ/kg of body weight. Compliance with the diet was indirectly assessed by the evaluation of urinary content in urea, sulphate and electrolytes (see Results).

After at least 30 days on the LCD, the complete basal evaluation was repeated (the ICaA% was evaluated again only in the patients for whom it was checked on the FCD).

### Methods

The urine saturation index relative to calcium oxalate monohydrate ( $\beta_{\text{CaOx}}$ ) was calculated by

means of an iterative computer method which calculates free concentrations by simultaneously solving a system of multiple mass-balance equations, taking into account the main soluble complex species of the measured ions in the 24 h urine collections. This method, produced by Marangella and co-workers, has been validated by a large series of data, published elsewhere [4, 14, 15].

ICaA% was evaluated by means of kinetic methodology, with stable strontium as a tracer. Strontium is recognized to be a good tracer for calcium kinetics assessment, on condition that no substantial amount of calcium is simultaneously introduced [16, 17]. Briefly, the methodology of ICaA% assessment was as follows: on the first day 1.25 mmol of SrCl<sub>2</sub> was given by mouth, after at least 12 h of complete fasting, and blood samples were collected at 0, 30, 60, 120, 180, 240, 360, 480, 680 and 1440 min for the measurement of strontium concentration; the patients were allowed to eat after the 360th minute. At least 2 days after, but not later than 1 week, the same amount of SrCl<sub>2</sub> was infused in an antecubital vein in 2 min; blood samples were collected from the controlateral arm at 0, 5, 15, 30, 60, 120, 180, 240, 360, 480, 600 and 1440 min for evaluation of the strontium concentration. The ICaA% was calculated according to the deconvolution method described by Tothill et al. [18]. The normal values of ICaA% assessed by the above method in our normal population (a historical control group) range from 25 to 50%.

#### Analytical and statistical methodology

Electrolytes, creatinine, uric acid and urea in serum and urine were measured by standard methodology (autoanalyser, absorption spectrophotometry, flame photometry).

Urinary oxalate and citrate were measured by column gas chromatography (Hewlett-Packard 5894 II; Supelco SPB-5), in urine collected under 6 mol/l HCl. Gas chromatography was performed after urine extraction with N,O-bis(trimethylsilyl)trifluoroacetamide/1% trimethylchlorosilane, on a capillary column (capillary diameter 0.32 mm, type DB-5). Quality control was performed utilizing control urine (Bio-Rad). The intra- and inter-assay coefficients of variation were 4.5 and 5.5% for citrate and 5.6 and 6.3% for oxalate respectively,

with linearity maintained up to 10 mmol and 1 mmol for citrate and oxalate respectively. The normal range in our laboratory was: 2–5 mmol/day and 0.100–0.500 mmol/day for citrate and oxalate respectively. Hydroxyproline in urine was determined by liquid chromatography (Beckman System Gold), after acid hydrolysis.

Strontium in serum was measured by atomic absorption spectrophotometry (Perkin-Elmer Zeeman 5000).

PTH and 1,25-vitD were measured by methods described elsewhere [19]. Briefly, PTH was measured by intact-PTH immunoradiometric assay (IRMA, Nichols Institute Diagnostic, San Juan Capistrano, CA, U.S.A.), with intra-assay and inter-assay coefficients of variation respectively of 2.4% and 5.6%. The normal range for i-PTH was 5–55 pg/ml.

For 1,25-vitD determination, a radioreceptorial method was utilized (RRA, Nichols Institute Diagnostic), with a recovery of between 60 and 80% (each sample was corrected for its own recovery) and intra- and inter-assay coefficients of variation respectively of 10.0 and 14.0%. The normal range for 1,25-vitD was 20–45 pg/ml.

Statistics were calculated by analysis of variance, paired *t*-test and linear-regression analysis utilizing a BMDP computer statistical package on a Pentium-100 PC.

#### RESULTS

The daily urinary excretion of the substances related to the proteic and saline content of the diet in the 34 SF patients, studied on both FCD and LCD, are shown in Table 1.

The compliance with the prescribed LCD is indirectly demonstrated by: (1) the excretion of an amount of urea nitrogen consistent with 80 g of protein intake (if faecal loss is also taken into consideration); (2) the excretion of phosphate very close to 60% (the normal percentage of intestinal absorption) of the prescribed dietary intake; and (3) sodium chloride excretion quite similar to the prescribed amount. The accuracy in the urine collection is indirectly demonstrated by the constancy of the values of creatine excretion during the two different diets.

The patients, when studied on the FCD, tended to have a higher urinary excretion of the substances

Table 1. Daily urinary excretion of diet-related substances in the 34 SF studied on the FCD and the LCD. Results are given as means  $\pm$  SD; ns, not significant.

	Urea nitrogen (mmol/day)	Sulphate (mmol/day)	Na (mmol/day)	Phosphate (mmol/day)	Creatinine (mmol/day)
FCD	218 $\pm$ 329	19.6 $\pm$ 8	171 $\pm$ 72	26.2 $\pm$ 10	13.7 $\pm$ 4.3
LCD	198 $\pm$ 49	18.9 $\pm$ 7	124 $\pm$ 66	23.5 $\pm$ 7	12.8 $\pm$ 3.6
P	ns	ns	< 0.05	ns	ns

related to protein and saline intake than on the LCD, however none of these differences, with the exception of Na, were statistically significant.

Table 2 shows excretion of the urinary substances more directly related to the lithogenesis process on both FCD and LCD. When the SF patients consumed the LCD they eliminated, as expected, significantly lower amounts of calcium than on FCD. Seventeen of the patients studied were non-hypercalciuric (NHC) (urinary-Ca < 7.5 mmol/day) on either the FCD or LCD. Of the remaining seventeen SF, 10 were hypercalciuric only on the FCD (HC1, diet-dependent hypercalciuria), the other 7 on both the diets (HC2, diet-independent hypercalciuria).

Urinary oxalate excretion was substantially greater in SF on the LCD than on the FCD, whether subjects were considered as a whole (Table 2) or separated according to their calcium excretion (Table 3). Oxalate excretion was higher in both diet-dependent (HC1) and diet-independent (HC2) hypercalciuric SF, when compared with NHC SF on the FCD. On the other hand, no significant difference was evident between the groups when considered on the LCD.

Mg and citrate urinary excretion tended to be higher during the LCD than on the FCD, even if the differences were not significant.

Figure 1 shows the overall effect of the urinary changes produced by the two diets on the relative supersaturation of CaOx. The RS of CaOx is consistently and significantly higher in the SF, considered as a whole, when studied on an LCD.

When the RS of CaOx was considered in the three groups separated according to calcium excretion, it was found that, on the FCD, both hypercalciuric groups had greater values than NHC patients; this difference was no longer evident while the

patients consumed the LCD, where all the patients experienced a dramatic increase in RS values.

Table 4 shows the serum concentrations of i-PTH and 1,25-vitD, the levels of ICaA% and hydroxyproline urinary excretion in the SF patients studied on both the LCD and the FCD.

The values of i-PTH and 1,25-vitD overlapped on both diets. No correlation was found between the 1,25-vitD levels and either urinary excretion or relative supersaturation of oxalate.

ICaA% was found to be higher in SF studied on an LCD, compared with SF on an FCD. Furthermore, when all the data collected on both FCD and LCD were taken together, a significant correlation was found between ICaA% and both urinary oxalate excretion and RS of CaOx (Figure 2).

Hydroxyproline urinary excretion, an index of bone resorption, was found to be substantially increased in SF studied on an LCD. Total alkaline phosphatase tended to be higher on LCD than on FCD, however the difference did not reach a statistically significant level (Table 4).

## DISCUSSION

Previous studies demonstrated that calcium restriction might induce increased oxalate excretion, which might potentially counteract the positive effect on lithogenesis secondary to the reduction of calcium excretion [5, 6]. However, these results were not confirmed by another study [7] which could not demonstrate any difference in oxalate excretion after changing from a random to a low-calcium diet.

On the other hand, a recent clinical study by Curhan et al. [8] provided evidence that increased, and not decreased, calcium supply with diet is effective

**Table 2. Daily urinary excretion of the main substances involved in lithogenesis in the SF patients studied on the FCD and the LCD. Results are given as means  $\pm$  SD; ns, not significant.**

	Ca (mmol/day)	Mg (mmol/day)	Oxalate (mmol/day)	Citrate (mmol/day)	Urate (mmol/day)	pH	Urinary volume (litres/day)
FCD	6.8 $\pm$ 3.2	4.1 $\pm$ 1.6	0.328 $\pm$ 0.119	2.8 $\pm$ 1.5	4.8 $\pm$ 5.8	5.8 $\pm$ 0.7	2.1 $\pm$ 0.9
LCD	5.3 $\pm$ 2.5	4.5 $\pm$ 1.4	0.566 $\pm$ 0.197	3.1 $\pm$ 2.0	4.5 $\pm$ 4.3	5.9 $\pm$ 0.8	1.9 $\pm$ 0.9
P	< 0.05	ns	< 0.001	ns	ns	ns	ns

**Table 3. Oxalate excretion and RS of CaOx values in SF, separated according to urinary calcium excretion on FCD and LCD (NHC = non-hypercalciuric SF on both diets; HC1 = hypercalciuric SF on FCD only; HC2 = hypercalciuric SF on both diets). Results are given as means  $\pm$  SD.  $\alpha$  =  $P$  < 0.02 NHC compared with HC1+HC2;  $\beta$  =  $P$  < 0.01 NHC compared with HC1+HC2. a =  $P$  < 0.05 NHC compared with FCD; b =  $P$  < 0.01 LCD compared with FCD.**

	n	FCD		LCD	
		Oxalate (mmol/day)	RS of CaOx	Oxalate (mmol/day)	RS of CaOx
NHC	17	0.274 $\pm$ 0.106 <sup>a</sup>	3.41 $\pm$ 1.81 <sup><math>\beta</math></sup>	0.556 $\pm$ 0.317 <sup>a</sup>	9.73 $\pm$ 6.14 <sup>a</sup>
HC1	10	0.356 $\pm$ 0.104	6.46 $\pm$ 2.95	0.542 $\pm$ 0.288 <sup>b</sup>	11.24 $\pm$ 8.86
HC2	7	0.416 $\pm$ 0.116	7.22 $\pm$ 3.52	0.624 $\pm$ 0.274 <sup>b</sup>	11.1 $\pm$ 2.67 <sup>b</sup>

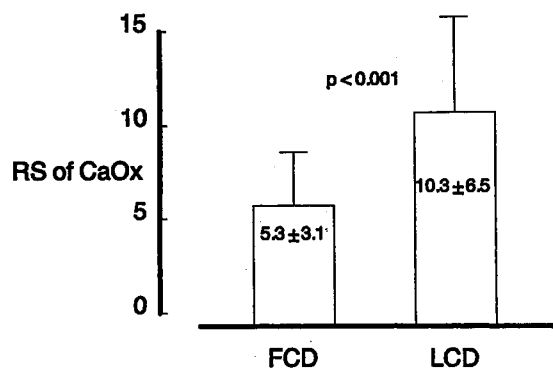


Fig. 1. Effect of calcium restriction on relative supersaturation of calcium oxalate. LCD induced a clear-cut increase of relative supersaturation (RS) of CaOx (means  $\pm$  SD).

in reducing stone-forming events. It has been claimed, however, that the results of this latter study might be due in part to the criteria used for patient selection, owing to the possibility that a large percentage of patients with hyperoxaluria and absorptive hypercalciuria had been excluded.

The patients included in the present study were very representative of a common population of SF patients: about 50% having hypercalciuria of both diet-dependent and -independent type and about 30% reduced urinary citrate. In this study primary iperoxaluric SF, or SF with daily oxalate excretion above 0.650 mmol, were deliberately excluded.

The composition of the diet freely consumed by our SF patients, assessed by dietary inquiry and urinary excretion of the main diet-related compounds, was representative of a common north-eastern Italian diet.

The oxalate excretion of the studied SF patients, studied on the FCD, ranged from 0.105 to 0.620 mmol/day. When these patients were shifted to an LCD, apart from an expected significantly lower excretion of calcium, a substantially higher oxalate excretion was evident.

It is worth noting that while oxalate excretion was greater in both diet-dependent (HC1) and diet-independent (HC2) hypercalciuric SF than in NHC SF on an FCD, this difference was no longer evident when both NHC and hypercalciuric patients were shifted to the LCD. A possible explanation for this finding might be that when calcium supply is in the

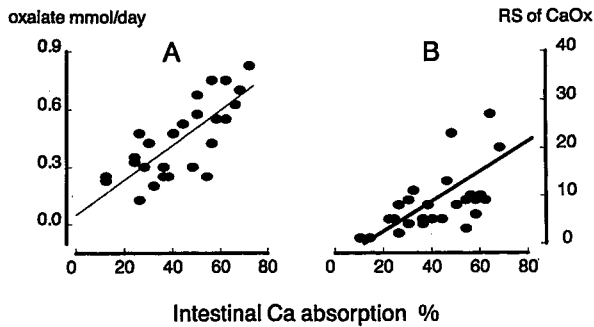
normal range or higher, by far exceeding the maximal calcium transport capacity of the intestine, the patients with higher values of intestinal calcium transport capacity (i.e. SF with hypercalciuria) are more prone to have lower calcium load in the distal intestine and, as a consequence, oxalate hyperabsorption. On the other hand, when dietary calcium is reduced to levels much closer to the intestinal maximal transport rate, the reduction of calcium load in the distal intestine is almost the same in both hyperabsorbers and normoabsorbers. These findings are in substantial agreement with previous data from Marangella et al. [20] who found increased oxalate intestinal absorption in hypercalciuric patients when compared with both controls and normocalciuric SF, and an increase in oxalate intestinal absorption after the dietary calcium intake was lowered.

In addition, we found that the fractional intestinal absorption of calcium was increased when the patients studied were shifted from the FCD to the LCD. Furthermore, when the data obtained on both FCD and LCD were pooled, the levels of ICaA% were significantly related to oxalate excretion. These data further reinforce the hypothesis that the intestinal transport of calcium is an important variable in controlling oxalate absorption and, as a consequence, urinary excretion. According to our data, no relationship was found between 1,25-vitD levels and oxalate excretion, either when results for both diets were considered as a whole or separately. These results are at variance with a previous study by Giannini et al. [21] who found a direct relationship between these two variables. It is possible that different inclusion criteria might explain the different results: in fact, in our study, primary hyperoxaluric and grossly hyperoxaluric patients (urinary oxalate >0.65 mmol/day) were deliberately excluded, while a large number of patients in Giannini's study had consistently high oxalate excretion values. In addition, the proportion of hypercalciuric patients was far higher in this latter study than in ours.

Another unexpected result was the increase in ICaA% after moderate dietary calcium deprivation in the absence of changes in 1,25-vitD levels. A possible explanation for this finding might be that, at least over a short period of time, the increase in intestinal calcium transport is induced independently of an increase of 1,25-vitD serum levels, possibly due to an increase in the number and/or affinity of 1,25-vitD receptors in the enterocytes, induced by

Table 4. Serum concentration of PTH and 1,25-vitD, levels of intestinal Ca absorption, hydroxyproline (OHP) urinary excretion (expressed as mmol/mol of urinary creatinine) and serum total alkaline phosphatase (AP) in the SF patients studied on the FCD and the LCD. ICaA% was measured in only 13 of the patients. Results are given as means  $\pm$  SD; ns, not significant.

	PTH (pg/ml)	1,25-vitD (pg/ml)	ICaA (%)	OHP/Cr (mmol/mol)	AP (units/l)
FCD	26.2 $\pm$ 12.5	36.7 $\pm$ 12.3	32.6 $\pm$ 10.3	15.8 $\pm$ 9.9	80.6 $\pm$ 65
LCD	25.1 $\pm$ 12.6	36.3 $\pm$ 10.8	52.7 $\pm$ 13.8	24.9 $\pm$ 8.7	104 $\pm$ 119
P	ns	ns	<0.01	<0.01	ns



**Fig. 2.** Interrelationships between intestinal calcium absorption and oxalate urinary excretion (A) and RS of CaOx (B), when the data from patients studied on both FCD and LCD were pooled. ICaA was highly significantly correlated with oxalate excretion:  $Ox = 42.9 + 9.57(ICaA)$ ;  $r = 0.733$ ,  $P < 0.0001$  (A). ICaA was also correlated with RS of CaOx, even if at lower levels of significance:  $RS = -3.2 + 0.26(ICaA)$ ;  $r = 0.545$ ,  $P < 0.001$  (B).

calcium deprivation, as demonstrated in the rat by Favus et al. [22].

Nonetheless, when approaching the problem of the risk for calcium oxalate stone formation after dietary manipulation, it must be taken into account that other urinary changes, able to affect the lithogenic process, may occur, such as changes in citrate, magnesium and sodium chloride excretion [9]. In fact, although no changes were observed apart from the calcium and oxalate variations, there was a trend toward higher citrate and magnesium excretion after the patients were shifted to the LCD.

Therefore, to properly evaluate the change in the risk for calcium oxalate stone formation induced by dietary calcium restriction, the global impact of the changes in all the urinary components potentially affecting the relative supersaturation of oxalate must be considered.

In the present study, the relative supersaturation of calcium oxalate in SF on both a calcium-free or low-calcium diet has been evaluated by means of an iterative computer method produced by Marangella et al. [4], which calculates the RS of calcium oxalate, taking into account the main soluble species on which the solubility of calcium oxalate is dependent. This method has been shown to provide quite similar results to those obtained by the Equil-2 programme, produced by Finlayson [10], and has been validated by a large number of experimental and clinical applications [4, 14, 15].

From our results, a marked increase in RS for CaOx was evident after the patients, considered as a whole, were shifted from the FCD to the LCD. When the data were analysed after grouping the patients according to their calciuric characteristics, we found that hypercalciuric patients, especially those of the diet-independent type, had substantially higher RS values for CaOx while on the FCD. On the other hand, no significant inter-group difference of this parameter was evident while the patients consumed the LCD. Owing to the prevailing role of

oxalate excretion in determining the RS values, the same considerations as taken into account above to explain the finding of the different change of urinary oxalate in the three groups, can be maintained.

Recently Marangella et al. [15] found that a substantial increase in the calcium content in mineral water supplied to a group of SF patients, although effective in increasing calcium excretion, induced a reduction in oxalate excretion, with a final null effect on the values of RS for CaOx. These results are in partial agreement with the present data, concurring with the finding of the hyperoxaluric effect of a low calcium intake. The apparent discrepant finding of a null effect of the LCD on RS for CaOx in Marangella's data might be explained, as stated in their study [15], by the increased urine volume, secondary to the imposed water supply, which was responsible for particularly low RS values. As a further consideration, it is possible that calcium supplied by water is much more easily absorbable than calcium contained in food, explaining the greater difference in calcium excretion between the low and high calcium supply found in the SF patients studied by Marangella's group than in our patients studied on the FCD and LCD. Furthermore, the difference in oxalate excretion between the two kinds of calcium intake was more marked in our study than in Marangella's: again, the modality of calcium supply might have played a predominant role in these results, owing to the contemporary intake of oxalate and calcium through the diet in our study, while calcium supply was independent and presumably not always contemporary with the food intake in the latter study.

As an additional result, the excretion of hydroxyproline in fasting urine, a marker of bone resorption, was strikingly increased by calcium deprivation. This result too is in agreement with that found in a previous study of ours [9] and in the more recent one by Marangella et al. [15]. This is of particular concern, in consideration of the frequent basal increased bone resorption rate previously found in at least some hypercalciuric patients [12] and of the reduced bone mineral density reported in hypercalciuric SF [23, 24].

In conclusion, from our results, dietary calcium restriction not only does not give any advantage to lithogenesis, but on the contrary it increases the relative supersaturation of CaOx in the urine of SF, mainly because of a marked increase in oxalate excretion. This finding, in addition to the known deleterious effect on bone metabolism, warns against the prescription of a calcium-restricted diet in stone forming patients.

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