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FACTORS AFFECTING FASTING URINARY CALCIUM EXCRETION IN STONE FORMER PATIENTS ON DIFFERENT DIETARY CALCIUM INTAKE

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Abstract

The effects of variable calcium content on daily and fasting urinary calcium and other lithogenic solutes excretion, on the bone turnover index (fasting hydroxyproline urinary excretion) and on the calciotropic hormones were studied in 312 stone former patients with an outpatient protocol and 15 stone former patients in an inpatient study. Furthermore in 60 of these patients, 30 while on a low calcium diet (LCD) and 30 on a free calcium home diet (FCD), the effects of an oral calcium load (OCL) on bone turnover index, calciotropic hormones and calcium excretion were evaluated. The results demonstrate that an LCD is effective in reducing daily calcium excretion. Fasting calcium excretion is apparently not affected by changes in dietary calcium content. On the other hand, LCD induces a marked increase in bone resorption, without apparent signs of increased parathyroid activity. This may explain the failure to reduce fasting urinary calcium excretion by the LCD. The OCL greatly reduced bone resorption rate, without any change in calciotropic hormones, especially in patients on LCD. In conclusion, the LCD induces a reduction in the lithogenic factors in the urine of stone formers, but induces a marked increase in bone resorption. The lack of any change in fasting urinary calcium excretion in conditions of different dietary calcium intake may be due to an opposite change in the intestinal and osseous components that affect this parameter, and is therefore of little value.

Key Words: Hypercalciuria, hydroxyproline, bone turnover, calcium, diet, citrate, oxalate, parathyroid hormone, calcitonin, vitamin D, nephrolithiasis.

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Introduction

Hypercalciuria, usually defined by a 24-hour urine calcium excretion rate above 4 mg/kg/day, is a common feature in stone former patients (8, 23). Among hypercalciuric patients, an increased excretion of calcium in fasting urine is also frequently found and this finding has long been considered an index of a renal tubular calcium leak (4, 7, 16, 24-26). However, this form of so-called "renal hypercalciuria" has been a matter of controversy, because most authors were not able to find any clear sign of secondary hyperparathyroidism in association with fasting hypercalciuria, as one would expect in a calcium-wasting nephropathy (5, 9, 16, 19).

On the other hand, calcium excretion in the fasting urine of normal subjects has been shown to correlate with the urinary excretion of hydroxyproline, a reliable marker of bone turnover rate (17).

Indeed, fasting hypercalciuria in stone former patients has also been found in association with signs of increased bone turnover rate (20) and reduced bone mineral content (1). Furthermore, a reduced basal secretion rate of parathyroid hormone (30) and reduced responsiveness of the parathyroid glands to induced hypocalcemia (21) was also found in nephrolithiasic patients presenting fasting hypercalciuria.

These findings have suggested the hypothesis that fasting hypercalciuria in stone formers could be secondary to a primary increase in bone turnover rate. However, other studies clearly demonstrated that an increased dietary calcium content may cause not only greater daily urinary calcium excretion, but also a proportional increase in fasting calcium excretion (29), especially when high levels of calcitriol are present (18).

Stone former patients have been reported by many authors to have high levels of circulating calcitriol (6, 12), so that it is in theory possible that fasting hypercalciuria in this condition could be of intestinal origin.

The present study faced the problem of fasting hypercalciuria in nephrolithiasic patients in relation to dietary calcium intake, bone resorption rate and calciotropic hormones.

Patients and Methods

Four hundred and thirty-two patients were subjected to the study in our stone clinic because of a history of recurrent passage of renal stones. Of them, 120 were excluded from the present investigation because they were affected by primary hyperparathyroidism, or infected calculi or mild renal failure. The remaining 312 patients (196 males, aged 18-69 yrs) were submitted to the following study protocol.

Summary of the whole protocol

- Outpatients basal evaluation: all patients studied after a free calcium diet (FCD) or a low calcium diet (LCD) (see below).

- Diet cross-over study: 15 of these patients were shifted from LCD to FCD (or vice-versa).

- Oral calcium load test: 60 of these patients (30 on LCD and 30 on FCD) were submitted to an oral load of calcium.

Outpatients basal evaluation

Seventy-four of the above patients were studied while on a free calcium home diet (FCD), the other 238 patients after 15 days of a diet containing: calcium 400 mg, phosphate 1100 mg, sodium 100 mmol, potassium 50 mmol, caloric content 40 kcal/kg body weight (LCD). Compliance with the diet was assessed by the evaluation of urinary content in urea, sulphate and electrolytes (see results).

The protocol consisted in two 24-hour urine collections where the following parameters were evaluated: calcium, phosphate, sodium, potassium, chloride, magnesium, citrate, oxalate, uric acid, sulphate, creatinine, urea, ammonium.

In all the patients, after a 12-hour overnight fast, a 2-hour urine sample was collected for the measurement of: creatinine, calcium, phosphate, hydroxyproline, c-AMP.

On the same morning, a blood sample was collected for measurement of: calcium, phosphate, sodium, potassium, chloride, magnesium, uric acid, creatine, urea, acid-base balance, PTH (intact molecule). In 38 of these patients (18 on FCD and 20 on LCD, randomly chosen among the overall stone former group), calcitriol and calcitonin (CT) were measured.

Diet cross-over inpatient study

Fifteen patients were randomly allocated to a high-normal calcium diet (HCD: containing 1000 mg of calcium and comparable to the LCD for the other constituents, see "Outpatients evaluation" paragraph) or to LCD (calcium 400 mg) and, after 15 days of stabilization, were studied with the same protocol used for outpatients. Thereafter, they were shifted to the other diet and after a further 15 days the same study was repeated.

Calcium load test (OCL)

Sixty patients (30 on FCD and 30 on LCD) were also submitted to an OCL (1 gram of elemental calcium) and in urine samples, collected 2 hours before and 4 hours after the calcium challenge, the following parameters were evaluated: calcium, creatinine, hydroxyproline, c-AMP. Furthermore, before and 2 hours after the OCL, blood samples were collected for measurement of: calcium, acid-base balance, PTH (intact molecule). In 38 randomly chosen patients (18 on FCD and 20 on LCD) CT was also measured before and after the OCL.

Tubular threshold of phosphate (TTPi) was calculated by urinary excretion of phosphate and creatinine in fasting urine, according to Walton and Bijvoet (31).

Urinary anion gap was calculated as: (Na + K + Ca + Mg mEq) - (Cl mEq + 1.8 x phosphate mmol).

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

Urinary oxalate and citrate were measured in urine collected under HCL by gas-chromatography, performed by a capillary column, after extraction and derivation with BSTFA; calibration was made with a 4 points curve.

Hydroxyproline in urine was estimated by resin catalyzed hydrolysis method (11).

PTH was measured by INCSTAR intact-PTH immunoradiometric assay (IRMA), utilizing two different policlonal antibodies, purified by affinity chromatography, specific for two different regions of the PTH molecule (normal values 7-55 pg/ml).

Calcitonin was analyzed by INCSTAR radioimmunoassay, utilizing an antibody produced in a goat against pure synthetic human calcitonin (normal values 20-70 pg/ml).

Calcitriol was determined by a competitive binding assay, following separation with Sephadex chromatography (TechnoGenetics) (normal values 15-60 pg/ml).

Urinary cyclic AMP was determined by radioimmunoassay, using rabbit antiserum (International CIS-France).

Statistics were calculated utilizing t-test for paired data, anova, chi-square test, simple and multiple regression analysis and non parametric tests, when appropriate, using a statistic package (BMDP) implemented on an IBM AT computer.

Results

Outpatient basal evaluation

The two groups of patients studied in basal condition on the 2 different diets were substantially identical as regards the major clinical data (Table 1).

The daily urinary excretion of urea nitrogen, sulfate, phosphate, uric acid and ammonium, indirect indices of proteic content and acidic load of the diet, were not significantly different in the 2 groups of patients; however, urinary anion gap was significantly higher in patients on LCD (Table 2).

Table 3 shows the pattern of daily urine composition as regards calcium, sodium, oxalate and citrate excretion and calcium/citrate index in the 2 groups. As expected, calcium excretion was higher on FCD; sodium

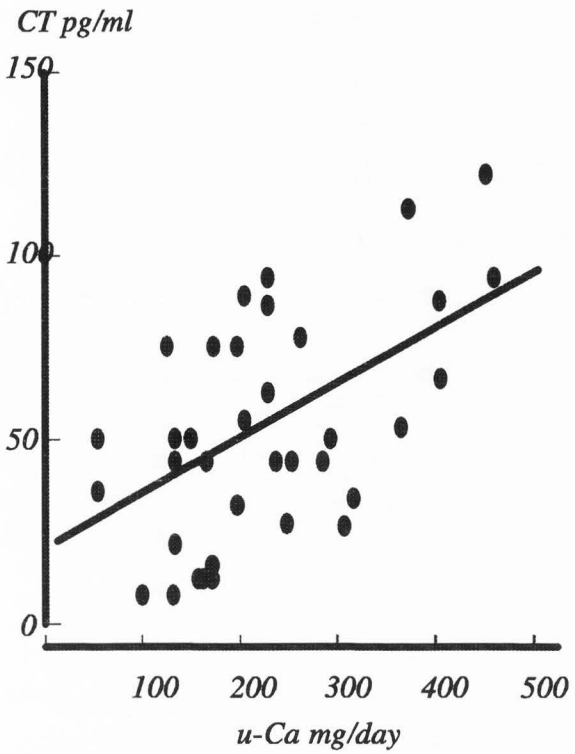

Figure 1. Relationship between daily urinary calcium excretion and calcitonin serum levels in stone former patients. A good linear direct correlation is evident ($y = 17.6 + 0.15\ x$; $r = 0.502$; $p < 0.001$).

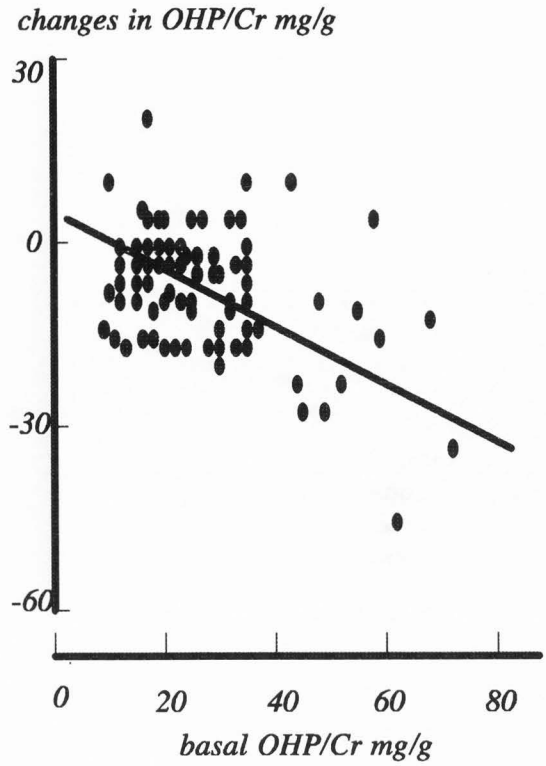

Figure 2 . Relationship between changes in hydroxyproline excretion and its basal values (changes OHP/Cr = 4.34 - 0.43 x basal OHP/Cr; $r = 5.13$, $p < 0.001$)

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daily urine output was also higher during FCD, while no difference in oxalate excretion was observed between the two diets. A very impressive increase in citrate excretion accompanied the LCD, with a consequent significant reduction of calcium/citrate index.

The fasting urine excretion of calcium and hydroxyproline, corrected by creatinine excretion, and the fasting values of urinary c-AMP, corrected by creatinine clearance, and of TTPi are shown in Table 4. The values of urinary calcium in fasting urine did not differ in the 2 groups of patients. On the other hand, hydroxyproline excretion was strikingly greater in patients on LCD. It is worth noting that urinary c-AMP was reduced and TTPi increased during LCD.

The serum concentrations of calcium, phosphate, bicarbonate and calciotropic hormones are reported in Table 5. No significant difference resulted in serum calcium concentration, PTH and vit D in the 2 groups. Phosphate levels were slightly, but significantly higher in patients on LCD. CT concentration was significantly higher during FCD. Furthermore, the serum levels of CT were directly correlated with the amount of daily urinary calcium (Fig. 1).

Diet cross-over inpatients study

Table 6 shows the effects of shifting from HCD to LCD, or vice-versa, in 15 inpatients, after 15 days of stabilization with each diet, on daily urinary calcium excretion, fasting calcium and hydroxyproline urine output. On the LCD, together with an expected reduction of daily calcium excretion in urine, a marked increase in bone resorption index was evident. Fasting calcium excretion also increased, but this change did not reach a statistically significant value.

OCL test

The changes in calcium and hydroxyproline fasting urinary excretion and serum calcium concentration after an OCL, in 30 patients on FCD and 30 on LCD, are shown in Table 7. OCL induced an increase in calcium excretion in both groups, but this effect was significantly greater in the FCD group. On the other hand, the OCL induced a significant reduction in the excretion of hydroxyproline only in the LCD group. No substantial differences resulted between the 2 groups as regards serum calcium changes.

The changes in calciotropic hormone after OCL are shown in Table 8. Again the basal values of CT and c-AMP were higher in the FCD group. However, the changes observed after the OCL were wholly comparable. PTH was markedly inhibited by OCL, but no significant difference was evident between the 2 groups.

Figure 2 shows how the changes in hydroxyproline urinary excretion were negatively correlated with its basal values.

Table 1. Most relevant clinical data of the stone former patients studied on a free calcium home-diet (FCD) or on controlled low calcium diet (LCD; Ca 400 mg). Values are expressed as mean ± se (standard error).

	Number	Sex (M/F)	Age (years)	Body weight (kg)	Stone Activity (no.stone/ 2 last yrs.)	Creat.Clear. (ml/min)
FCD	74	50/24	42.2±1.7	72.1±2.0	3.2±0.5	105.0±3.6
LCD	238	146/92	39.6±0.9	70.2±1.2	2.8±1.2	105.6±1.8
p		n.s.	n.s.	n.s.	n.s.	n.s.

Table 2. Daily urinary excretion of dietary proteic content related products in stone former patients on FCD and LCD. (mean ± se).

	Urea N. (g)	Sulphate (mEq)	Phosphate (mg)	Ammonium (mEq)	Uric Acid (mg)	An.Gap. (mmol)
FCD	10.7±0.4	20.4±1.0	826±38	33.0±2.9	598±26	22.9±10.8
LCD	8.6±1.1	20.8±1.7	754±18	30.2±2.5	612±14	32.0±1.5
p	n.s.	n.s.	n.s.	n.s.	n.s.	0.05

Table 3. Daily urinary excretion of calcium, sodium, oxalate and citrate and calcium/citrate index values during FCD and LCD. (mean ± se).

	Calcium mg	Sodium mEq	Oxalate mmol	Citrate mmol	Ca/Cit mmol/mmol
FCD	245±15	171±8	0.48±0.03	2.7±0.2	2.70±0.02
LCD	184± 6	114±4	0.52±0.04	3.7±0.4	1.69±0.02
p	< 0.001	< 0.001	n.s.	< 0.01	< 0.01
normal values	< 300 M; < 250 F		< 0.50	1.8-4.8	

Table 4. Values of calcium and hydroxyproline excretion (corrected by creatinine), of c-AMP (corrected by GFR), and of TTPi in fasting urine collected during FCD and LCD. (mean ± se)

	Ca/Cr (mg/mg)	OHP/Cr (mg/g)	c-AMP (nmol/dl GFR)	TTPi (mg/dl)
FCD	0.124±0.008	18.8±1.0	4.9±4.1	2.85±0.09
LCD	0.118±0.003	25.0±0.9	3.9±5.0	3.24±0.04
p	n.s.	< 0.001	< 0.01	< 0.001
normal values	< 0.110	< 25	< 4.5	2.2-4.4

Table 5. Serum values of calcium, phosphate, bicarbonate and calciotropic hormones during FCD and LCD (the values of $1,25(OH)_2$ Vit D and CT are referred only to 42 patients, see patients and methods). (mean ± se).

	Ca (mg/dl)	Pi (mg/dl)	HCO_3 (mEq/l)	PTH-int (pg/ml)	$1,25(OH)_2$ (pg/ml)	CT (pg/ml)
FCD	9.71±0.06	3.05±0.07	24.2±0.3	20.4±1.6	38.4±2.3	67.3±9.6
LCD	9.66±0.03	3.27±0.04	23.9±0.4	16.7±3.8	31.0±2.2	33.7±5.2
p	n.s.	< 0.01	n.s.	n.s.	n.s.	< 0.01
normal values	8.9-10.4	2.4-4.5	22-26	< 50	20-75	20-70

Table 6. Effects of shifting from HCD to LCD, or vice-versa, in 15 inpatients, on urinary daily and fasting calcium excretion and fasting hydroxyproline urinary output. (mean ± se).

	u-Ca/day (mg)	u-Ca/Cr (mg/mg)	OHP/Cr (mg/g)
HCD	304±36	0.141±0.015	17.8±1.5
LCD	192±26	0.180±0.028	29.6±3.4
p	< 0.002	n.s.	< 0.002
normal values		< 0.110	< 25

Table 7. Effects of OCL on fasting calcium and hydroxyproline urinary excretion and on serum calcium concentration in 2 groups of patients studied respectively on FCD and LCD. (mean ± se). (The "p" values for the differences in each group between basal and after load values are represented as ** = p < 0.001 and * = p <0.05; the "p" values in the last row are related to the differences between the 2 groups).

	Ca/Cr (mg/mg)			OHP/Cr (mg/g)			s-Ca (mg/dl)		
	fast	OCL	change	fast	OCL	change	fast	OCL	change
FCD	0.124 ±0.008	0.204** ±0.015	+0.08 ±0.01	18.9 ±1.1	16.9 ±1.2	-2.0 ±1.3	9.62 ±0.06	9.95** ±0.08	+0.43 ±0.09
LCD	0.116 ±0.003	0.159** ±0.008	+0.06 ±0.01	24.7 ±0.9	17.9** ±1.2	-6.6 ±1.2	9.57 ±0.03	10.01** ±0.07	+0.55 ±0.07
p	n.s.	< 0.01	< 0.02	< 0.01	n.s.	< 0.02	n.s.	n.s.	n.s.

Table 8. Effects of OCL on PTH and CT serum concentrations and urinary excretion of c-AMP in the FCD and LCD patients. (mean ± se). (The "p" values for the differences in each group between basal and after load values are represented as ** = p < 0.001; the "p" values in the last row are related to the differences between the 2 groups).

	PTH (pg/ml)			CT (pg/ml)			c-AMP (nmol/dl GFR)		
	fast	OCL	change	fast	OCL	change	fast	OCL	change
FCD	22.3 ±1.4	11.4** ±0.5	-10.1 ±2.1	67.2 ±10.5	70.9 ±8.1	+3.37 ±4.42	5.04 ±0.35	4.40* ±0.46	-0.63 ±9.50
LCD	17.8 ±4.1	6.29** ±1.1	-11.63 ±9.8	32.0 ±5.4	32.8 ±6.2	+0.96 ±5.07	3.99 ±0.16	3.51* ±0.27	-0.59 ±12.50
p	n.s.	n.s.	n.s.	< 0.001	< 0.001	n.s.	< 0.01	< 0.01	n.s.

Finally, with the pooled data from all our patients, we considered the influence of both daily urinary calcium excretion and hydroxyproline urinary output on fasting urinary calcium, by a multiple step-wise correlation analysis, reported in Figure 3.

It is evident that both the independent variables play a substantially identical role in affecting the values of fasting calcium excretion.

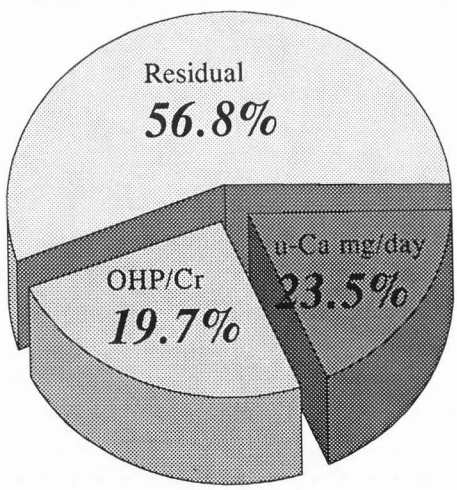

Figure 3. Multiple step-wise regression analysis of fasting calcium/creatinine on daily urinary calcium excretion, fasting hydroxyproline/creatinine and fasting Na excretion (r = 0.655; p < 0.001).

Discussion

Evaluation of calcium excretion in fasting urine plays a critical role in the classification of stone former patients. Three main hypotheses have been proposed to explain this finding in stone formers: a renal tubular calcium leak (4, 7, 10, 24-26); an increased input from intestine affecting urinary calcium excretion even after a long fasting period (18, 23, 29); and finally an increase in bone resorption, not dependent on parathyroid gland hyperactivity (1, 20, 21, 30).

The hypothesis of a tubular leak has been proved true only in a minority of cases, mainly represented by sponge kidney disease (13), while no real direct or indirect evidence of a calcium wasting nephropathy has been found in the majority of stone former patients with fasting hypercalciuria (5, 9, 16, 19, 22).

On the other hand, both the other two hypotheses could be true. However, if this is the case, one would expect to find an increase of fasting calcium either in a condition of calcium repletion, for the intestinal calcium supply, or in condition of calcium deprivation, if,as found by other authors (17), increased bone resorption ensues.

It is already known that a moderate restriction in dietary calcium content is frequently prescribed or spontaneously chosen by patients who experienced a stone event, with an increased risk for bone demineralization.

Indeed, our data show that an LCD is effective in reducing daily urinary calcium excretion, when compared with both an FCD and an HCD, without affecting fasting calcium excretion. This first set of results confirms that a calcium rich diet, independently of its proteic content, can result in increased calciuria; in fact, no significant difference of protein related product was evident in the urine of FCD and LCD patients, even if a slightly greater amount of urea, ammonium and phosphate was evident in the urine of FCD patients. The possibility that the difference in daily urinary excretion of calcium could be dependent on different dietary sodium content exists, but is of secondary importance in our opinion because the same difference in calcium excretion resulted in the inpatient study between the HCD and LCD, containing the same amount of sodium.

The LCD also resulted in a considerable increase in citrate excretion, with a consequent marked amelioration of the calcium/citrate index (27), resulting in a reduction of the potential risk of stone formation.

In fact, as mentioned above, a slightly higher proteic content of FCD might be the cause of increased acidic load and reduced citrate excretion. On the other hand, the greater urinary anion gap of LCD patients, in the absence of significant differences in ammonium excretion, might be indicative of a different quality in dietary proteic content, with a larger amount of organic metabolizable anions contained in LCD, and a potentially greater alkaline supply which could explain the increased citrate excretion.

Another important result was that no real change was observed in oxalate excretion between the two diets, although the mean excretion values remained on the high-normal range. This result is at variance with other data present in the literature (2) and the only apparent explanation for this difference might be that an increased absorption of oxalate during LCD could be counteracted by reduced dietary content. However, subsequent studies have given more insight into the role of oxalate stemming from the diet in causing hyperoxaluria, owing to a very low real bioavailability of dietary oxalate (3) and a major role for endogenous sources of this salt (28). Whatever the cause of this difference, the LCD was really effective in reducing the main risk factors for stone formation in our patients.

On the other hand, the LCD resulted in a marked increase in hydroxyproline excretion in fasting urine, a well known index of bone resorption. This finding was evident not only in the outpatient study, but also in crossover inpatient protocol, with values almost completely overlapping for the two studies. The increased bone resorption was not accompanied by signs of secondary hyperactivation of the parathyroid glands, as serum PTH remained substantially the same.

On the other hand, a reduced urinary c-AMP level and increased TTPi values were evident during LCD, as though reduced parathyroid activity was present. No difference in calcitriol serum concentration was found which could explain the finding of reduced PTH activity. We have no convincing explanation for this finding. It is possible however that the duration and the degree of calcium deprivation (15 days) were not sufficient to stimulate the PTH-Vit D system, and that other as yet unexplored factors might have induced the observed minor changes in PTH activity. In fact, the increased bone turnover was certainly not dependent on PTH stimulation. On the other hand, a very impressive difference in CT serum levels was present between patients on LCD and FCD. Moreover the CT values appeared well related to daily calcium excretion in urine, confirming the possibility that an increased dietary calcium content can stimulate, and conversely a calcium reduction in the diet can reduce, CT levels. With the present data we cannot be sure that this finding is the explanation for the reduced PTH activity found, because only a small number of our patients were checked for CT. However, this finding could be at least a partial answer to the question posed by Liberman and De Vriers nearly 20 years ago (15).

It is also difficult to propose a primary role for CT in modulating bone resorption rate in relation to variable dietary calcium content, because the striking reduction in hydroxyproline excretion that we found after OCL, was not accompanied by any change in CT levels.

From our data, no clear explanation is evident for this "primary" increased bone turnover rate: further studies, directed to investigating bone receptor sensitivity to calciotropic hormones and/or local calcium-regulating factors, might provide new insights into this issue.

Indeed, OCL resulted in a normalization of hydroxyproline excretion in patients studied on LCD. This reduction was accompanied by a lesser increase in calcium excretion after OCL in these patients. This finding could be explained by reduced intestinal calcium absorption in the LCD, but this explanation does not seem tenable because it is well known that calcium transport in the intestine is increased by an LCD (14). Furthermore, in our previous study we did not find any difference in intestinal calcium absorption, measured by kinetics methodology, in relation to different calciuric response to OCL (20).

It is thus possible that the greater reduction in bone turnover together with a reduced calciuric response to the OCL could represent a greater uptake by "hungry" bone secondary to dietary calcium deprivation. That this could be the explanation is indirectly demonstrated by the relationship between the level of basal values of bone turnover rate and the degree of its reduction after the OCL.

In fact, reviewing our data as a whole, calcium excretion in fasting urine was not apparently affected by change in calcium intake. This may be because, while reducing the intestinal component, the increase in bone turnover could compensate for it, resulting in an invariate figure.

Indeed, the multiple regression analysis demonstrates that the two components, intestinal and osseous, play an almost equal role, so in evaluating the fasting levels of urinary calcium, both these variables have to be considered.

In conclusion, an LCD is effective in reducing the major risk factors for stone formation, reducing daily calcium excretion, increasing citrate in urine, without major modifications in oxalate urinary output. However this beneficial effect is balanced by an increased bone turnover rate. It is worth stressing that a LCD, especially if maintained over a long period, could be dangerous for bone.

Finally, the evaluation of fasting urinary calcium excretion is a low reliable index because affected by variables that change in the opposite direction with the changing of dietary calcium intake, so that any pathogenetic classification based on this parameter has to be considered with extreme caution.

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Editor's Note: All of the reviewer's concerns were appropriately addressed by text changes, hence there is no Discussion with Reviewers.