Acute effects of moderate dietary protein restriction in patients with idiopathic hypercalciuria and calcium nephrolithiasis[1,2]

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ABSTRACT

Background: High dietary protein intake is a potential risk factor for nephrolithiasis because of its capacity to increase urinary calcium and to facilitate lithogenesis through many other mechanisms.

Objective: Our aim was to verify the effects of moderate protein restriction in hypercalciuric patients.

Design: We studied 18 patients (10 men and 8 women aged 45.6 ± 12.3 y) with idiopathic hypercalciuria and renal calculi. Before and after 15 d of a diet with 0.8 g protein $\cdot kg^{-1} \cdot d^{-1}$ and 955 mg Ca, all patients were evaluated for the main serum and urinary measures of calcium metabolism as well as for urinary uric acid, oxalate, citrate, and prostaglandin E_2.

Results: Urinary excretion of urea fell after the diet ($P < 0.001$). Urinary calcium ($P < 0.001$), uric acid ($P < 0.005$), oxalate ($P < 0.01$), and hydroxyproline ($P < 0.01$) decreased after protein restriction, whereas urinary citrate increased ($P < 0.025$). Blood pH increased after the hypoproteic diet ($P < 0.05$). 1,25-Dihydroxycholecalciferol (calcitriol) concentration fell significantly ($P < 0.025$) and parathyroid hormone increased ($P < 0.001$). Creatinine clearance tended to decrease (106.4 ± 4.8 compared with 97.5 ± 5.7 mL/min) after the diet. The decrease in urinary uric acid after the diet correlated with calcitriol concentration ($r = 0.57$, $P < 0.05$) and the decrease in urinary urea correlated positively with that in hydroxyproline excretion ($r = 0.58$, $P < 0.01$).

Conclusions: In hypercalciuric patients, moderate protein restriction decreases calcium excretion, mainly through a reduction in bone resorption and renal calcium loss; both are likely due to a decreased exogenous acid load. Moreover, dietary protein restriction ameliorates the entire lithogenic profile in these patients. *Am J Clin Nutr* 1999;69:267–71.

KEY WORDS Idiopathic hypercalciuria, dietary proteins, nephrolithiasis, bone metabolism, 1,25-dihydroxycholecalciferol, parathyroid hormone, calcitriol, metabolic acidosis, oxalate, citrate

INTRODUCTION

Recurrent calcium nephrolithiasis is a multifactorial disease and idiopathic hypercalciuria is regarded as the most important risk factor for this condition, being present in 30–60% of patients with renal calculi (1). Although idiopathic hypercalciuria is generally believed to be related to increased intestinal calcium absorption (absorptive hypercalciuria) or to a possible primary shift of calcium from bone (fasting hypercalciuria) rather than to a renal calcium leak (renal hypercalciuria), the exact mechanisms underlying this common metabolic defect are still debated (2).

The effect of diet on kidney stone formation has been recognized for many years (3). From an epidemiologic point of view, a link has been observed between high protein consumption and nephrolithiasis, whereas this disease is relatively uncommon in vegetarians, in whom the consumption of animal proteins, if any, is low (4, 5). High dietary protein intake is associated with increased calcium excretion in healthy subjects as well as in patients with kidney stones (6). Protein-induced reduction in calcium resorption in the distal tubule and an increase in urinary sulfate excretion, which lead to a renal calcium leak, are among the possible mechanisms governing this association (7, 8). Furthermore, mild metabolic acidosis due to excessive protein intake might stimulate bone resorption, with a secondary increase in urinary calcium excretion (9). Increased dietary protein consumption also constitutes a risk factor for other conditions involved in the pathogenesis of nephrolithiasis; hyperuricosuria, hyperoxaluria, and hypocitraturia are frequently observed in patients with high dietary protein intakes (10, 11).

Prompted by these issues, we studied the acute effects of moderate dietary protein restriction on calcium metabolism in patients with idiopathic hypercalciuria and calcium nephrolithiasis. We also evaluated the effect of such a diet on other urinary factors involved in the pathogenesis of renal stone formation, such as uric acid, oxalate, and citrate.

SUBJECTS AND METHODS

Eighteen patients who arrived consecutively at our unit for treatment of idiopathic hypercalciuria and recurrent calcium

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nephrolithiasis were enrolled in the study. There were 10 men and 8 women ($\bar{x}$ ± SE: height, 169 ± 1 cm; weight, 67 ± 10 kg) aged 26–61 y (45.6 ± 12.3 y). Hypercalciuria was defined as a urinary calcium excretion >0.1 mmol (4 mg)·kg^{-1}·d^{-1} at ≥2 different determinations while consuming a diet containing 955 mg Ca/d and 140 mmol Na/d.

Patients with conditions known to affect calcium metabolism, such as endocrine diseases, osteomalacia, Paget's disease of bone, renal tubular acidosis, medullary sponge kidney, intestinal malabsorption, and liver diseases were excluded from the study. All patients had normal renal function and no one was being treated with drugs that modify calcium-phosphate homeostasis. All patients gave their informed consent to the study, which was approved by our Ethical Committee.

After 15 d of a free diet controlled only for calcium and sodium intake, blood and 24-h urine specimens were obtained from all patients. Fasting blood samples were analyzed for calcium (Atomic Absorption Spectrophotometer 3100; Perkin Elmer, Norwalk, CT), phosphate (colorimetric method; Boehringer Mannheim, Mannheim, Germany), creatinine, urea, uric acid, and total alkaline phosphatase (Automatic Analyzer, Technicon Instruments Corporation, Tarrytown, NY). Blood pH and bicarbonate concentration were determined by using an ABL 520 apparatus (Radiometer, Copenhagen). Intact parathyroid hormone (PTH) was evaluated by a commercial immunoradiometric assay (Nichols Institute, San Juan Capistrano, CA), with an intraassay CV of 5.8%. 1,25-Dihydroxycholecalciferol (calcitriol) was assayed by using a nonequilibrium, competitive protein-binding assay (Nichols Institute) on plasma samples previously extracted with acetonitrile and then purified on C_{18}-OH columns. The intra- and interassay CVs were 7.9% and 10.8%, respectively. Urine samples were evaluated for calcium, phosphate, creatinine, urea, uric acid, and hydroxyproline (resin-catalyzed hydrolysis and colorimetric method; Hypronosticon, Organon Teknika, Boxtel, Netherlands). Hydroxyproline data were then expressed as a ratio with urinary creatinine excretion. Patients were specifically requested to follow a collagen-free diet 2 d before urine collection. Citrate was measured with a kit from Boehringer-Mannheim. Urinary oxalate concentration was determined by a colorimetric method as previously described by Hodgkinson and Williams (12). Prostaglandin E_2 (PGE_2) was evaluated by radioimmunoassay after extraction of urine with organic solvents and silica gel column chromatography according to the method of Remuzzi et al (13).

To assess the composition of the basal diet, a validated dietetic questionnaire (Institute of Nutrition, University of Perugia, Italy) was administered to all patients. Nutrient composition was evaluated with specific tables provided by the National Institute of Nutrition. According to the data collected, the mean nutrient intakes were as follows: 54 ± 6% of energy as carbohydrate, 14 ± 3% as protein (59% from animal sources and 41% from vegetables), and 32 ± 4% as lipid. In particular, protein intake was estimated as 86.5 ± 6.1 g/d with a phosphate intake of 1268 ± 62 mg. The main sources of animal protein were red meat (calf, beef, horse, and pork), white meat (chicken, turkey, and rabbit), fish (trout and pike), dairy products (Bel Paese cheese, mozzarella cheese, taleggio cheese, Asiago cheese), and milk. The main sources of vegetable protein were pasta, rice, bread, crackers, biscuits, Mediterranean fruit, and various types of vegetables (artichokes, spinach, tomatoes, green peppers, green beans, carrots, Swiss chard, and lettuce).

After the basal evaluation and for the next 15 d, all patients were given an isoenergetic (to avoid weight loss), moderately protein-restricted (0.8 mg·kg^{-1}·d^{-1}), diet containing 955 mg Ca, 140 mmol Na, and 9% protein (43% animal protein and 57% vegetable protein), 60% carbohydrate, and 31% lipid. The sources of dietary protein remained substantially unchanged and the patients purchased their food at the local marketplace.

The purpose of the study was explained in advance to all subjects; in particular, the patients were instructed to strictly adhere to the 15-d dietary regimen. Moreover, after 1 wk all of them were telephoned to encourage continued compliance with the prescribed diet. After 15 d, blood and 24-h urine specimens were collected from all subjects and the same assays described for the basal study were performed again.

Statistical analysis

The results are expressed as means ± SEs. Paired *t* tests were used when appropriate. Linear regression analysis was performed to evaluate relations between variables. The α level for significance was set at <0.05. The analyses were performed by using the STATGRAPHICS program (version 5.01; STSC, Inc, Rockville, MD).

RESULTS

The mean protein intake during the 15-d follow-up period was 54 g/d (range: 44–70 g/d). As shown in **Table 1**, the initial mean values of all serum variables considered were in the normal range (as defined in our own laboratory), with the exception of pH, which was slightly low. After 15 d of moderate dietary protein restriction, serum urea decreased significantly compared with basal values ($P < 0.03$) whereas venous blood pH values rose significantly ($P < 0.005$) without any substantial modification in bicarbonate concentration. Both calcitriol (reduced, $P < 0.025$) and parathyroid hormone (increased, $P < 0.01$) were significantly modified by decreasing protein intake.

The urinary variables considered in this study are reported in **Table 2**. As expected, in basal conditions urinary calcium was >0.1 mmol (4 mg)·kg^{-1}·d^{-1} in all subjects. Mean urinary urea was in the normal range; however, after the 15-d period of protein restriction values fell significantly ($P < 0.001$). Although not completely normalized, urinary calcium excretion decreased after the protein-reduced diet ($P < 0.001$), as did urinary uric

TABLE 1
Serum variables in subjects with idiopathic hypercalciuria and nephrolithiasis before and after moderate protein restriction

	Before diet (n = 18)	After diet (n = 18)	Normal range
Creatinine (mmol/L)	88.4 ± 2.65[1]	89.2 ± 2.65	61–122
Urea (mmol/L)	5.8 ± 1.6	4.9 ± 1.0[2]	2.5–7.5
Calcium (mmol/L)	2.41 ± 0.02	2.42 ± 0.03	2.1–2.6
Phosphate (mmol/L)	0.97 ± 0.04	0.96 ± 0.03	0.83–1.48
Uric acid (mmol/L)	0.29 ± 0.06	0.28 ± 0.06	0.2–0.38
Alkaline phosphatase (U/L)	65.0 ± 2.7	61.6 ± 3.4	10–51
Venous blood pH	7.34 ± 0.01	7.37 ± 0.01[3]	7.35–7.43
Bicarbonate (mmol/L)	28.2 ± 0.5	27.6 ± 0.5	22.0–28.0
Parathyroid hormone (ng/L)	25.4 ± 2.8	31.1 ± 2.1[4]	10–55
Calcitriol (ng/L)	34.2 ± 1.9	28.6 ± 2.2[5]	20–60

[1] $\bar{x}$ ± SE.
[2–5] Significantly different from before diet (paired *t* test): [2] $P < 0.03$, [3] $P < 0.005$, [4] $P < 0.001$, [5] $P < 0.025$.

TABLE 2
Urinary variables in subjects with idiopathic hypercalciuria and nephrolithiasis before and after moderate protein restriction

	Before diet (n = 18)	After diet (n = 18)	Normal range
Creatinine (mmol/d)	11.2 ± 0.7[1]	10.3 ± 0.63	7.1–17.7
Calcium (mmol/d)	9.35 ± 0.3	6.45 ± 0.3[2]	2.7–7.5
Phosphate (mmol/d)	25 ± 1.9	19 ± 1.6[3]	12.9–42
Sodium (mmol/d)	184 ± 9.8	177 ± 9.6	40–220
Uric acid (mmol/d)	3.1 ± 0.1	2.5 ± 0.1[4]	1.48–4.43
Urea (mmol/d)	370 ± 10	280 ± 10[2]	330–700
Oxalate (mmol/d)	0.59 ± 0.09	0.31 ± 0.03[3]	0.25–0.45
Citrate (mmol/d)	3.42 ± 0.3	5.34 ± 0.9[5]	2.6–5.36
Hydroxyproline:creatinine ($mmol \cdot mol^{-1} \cdot d^{-1}$)	20.8 ± 2.2	15.5 ± 1.1[3]	5–17
Creatinine clearance (mL/min)	106.4 ± 4.8	97.5 ± 5.7	80–130
Prostaglandin E_2 (ng/d)	334.4 ± 57.2	333.7 ± 33.7	228–491

[1] $\bar{x}$ ± SE.
[2–5] Significantly different from before diet (paired t test): [2] $P < 0.001$, [3] $P < 0.01$, [4] $P < 0.005$, [5] $P < 0.025$.

acid ($P < 0.005$), phosphate ($P < 0.01$), and oxalate ($P < 0.01$). On the contrary, urinary citrate increased significantly ($P < 0.025$). Urinary sodium excretion and urinary PGE_2 did not change after the diet, whereas creatinine clearance showed a tendency toward reduction. Finally, urinary hydroxyproline tended to be high in basal conditions and fell significantly at the end of the 15-d study period ($P < 0.01$).

After the diet, we observed a positive correlation between the changes in urinary urea and hydroxyproline excretion (**Figure 1**; $r = 0.58$, $P < 0.01$). Furthermore, the changes in PTH concentration correlated negatively with those in urinary calcium (**Figure 2**; $r = -0.70$, $P < 0.01$). Finally, there was a positive relation between the change in urinary uric acid and calcitriol (**Figure 3**; $r = 0.57$, $P < 0.05$) and between urinary uric acid and oxalate ($r = 0.57$, $P < 0.05$).

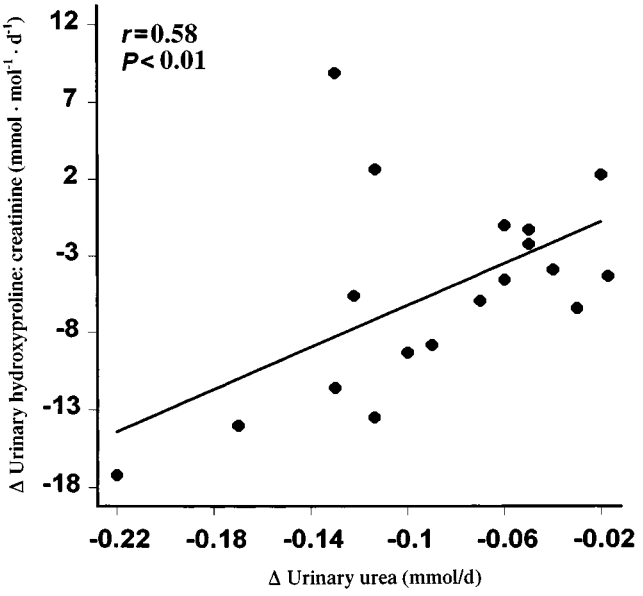

FIGURE 1. Correlation between the change in urinary urea and hydroxyproline excretion after protein restriction.

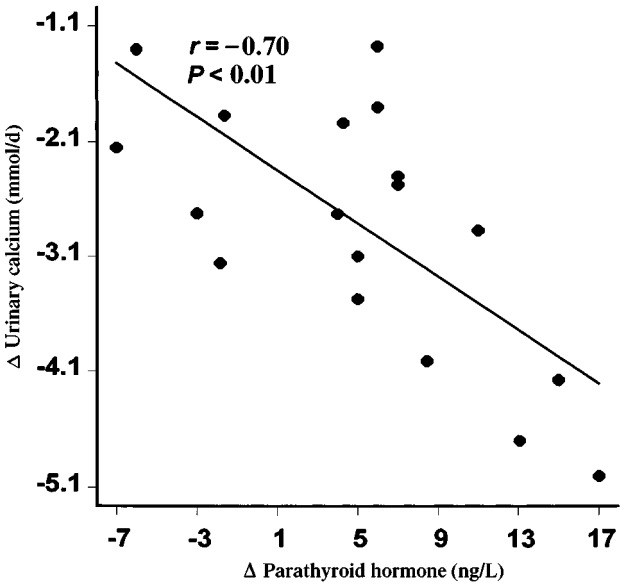

FIGURE 2. Correlation between the change in serum parathyroid hormone and urinary calcium excretion after protein restriction.

DISCUSSION

In industrialized countries, an increased incidence of kidney stones has been observed; one of the possible explanations proposed is high consumption of dietary protein (14–16). There is a large body of evidence indicating that high dietary protein intake raises urinary calcium excretion (mainly because bone tissue is a buffering system for the increased exogenous acid load) and increased excretion of nonreadily resorbable inorganic sulfate, which is abundant in animal proteins (17–19). On the contrary, only few and contradictory data on the effects of reducing protein consumption and the risk of kidney stone formation are available (20).

This study was aimed primarily at evaluating the effects of moderate protein restriction on calcium metabolism in patients with idiopathic hypercalciuria and renal calculi. After the diet, serum and urinary urea values were significantly reduced. In particular, the percentage decrease in urinary urea after the diet was quite close to the percentage reduction in protein intake prescribed with the test diet. This was convincing evidence that patients complied with our instructions. Indeed, urinary excretion of urea is an accepted marker of protein consumption, at least under controlled conditions (21).

Moreover, although calcium excretion still remained high after the diet, we observed a significant and relevant decrease after the 15 d of protein restriction. Several explanations could be proposed for these findings. First, blood pH increased after the diet because of the decrease in exogenous acid load. This, in turn, could have decreased the proton-mediated bone resorption and consequently the shift of calcium from bone, thus resulting in a reduction in urinary calcium. This hypothesis is strengthened by the concomitant fall in the excretion of hydroxyproline, a marker of bone resorption that correlated with the decrease in urinary urea. Second, although we did not measure sulfate excretion in our patients, a reduction in protein intake (especially animal protein) may have lowered urinary sulfate excretion and therefore also calcium excretion, as has been suggested by others (19, 22).

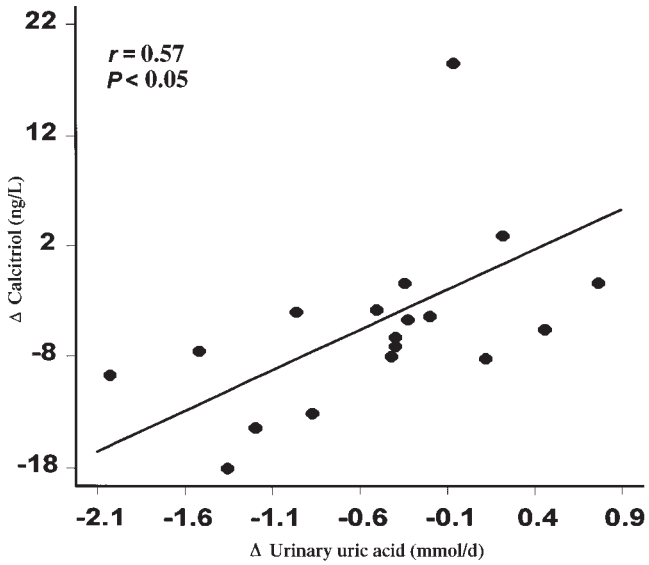

FIGURE 3. Correlation between the change in urinary uric acid and serum calcitriol after protein restriction.

Another possible mechanism contributing to the decrease in calcium excretion might be an increase in intraluminal pH in the renal tubule. Indeed, a high urinary acid load inhibits tubular calcium reabsorption while it decreases citrate excretion by increasing its tubular reuptake. Urinary citrate excretion rose significantly after the protein-restricted diet in the present study; the most likely explanation for this is an increase in intratubular pH, thus confirming the role of a different intraluminal milieu on calcium excretion.

The most intriguing and unexpected result of this study is that after a 15-d period of moderate dietary protein restriction calcitriol concentrations fell significantly, whereas PTH increased. This suggests that the primary effect of the diet was on calcitriol production, with a secondary stimulation of parathyroid gland activity. Why a reduced protein intake reduced calcitriol synthesis is less clear. Calcium intake was identical before and after the 15-d period of the diet; thus, it is unlikely that the fall in serum calcitriol depended on differences in dietary calcium. Prostaglandins might change in response to different protein intakes (23) and PGE_2 may stimulate calcitriol synthesis in hypercalciuric patients (24). Nevertheless, in our patients PGE_2 concentrations did not change after protein restriction. Additionally, there was a trend toward a similar correlation between the changes in urinary urea and calcitriol after the diet, but this was not significant; this supports the hypothesis that the decrease in calcitriol values was induced by protein restriction itself.

High protein intake is responsible for increased renal size and function (25–27) and a close correlation between calcitriol production and renal size has been shown in pigs (28). Hess et al (29) observed that overconsumption of protein induced an increase in renal mass and function in stone-forming patients with hypercalciuria. This in turn would raise the number of 1-α-hydroxylase–producing cells, leading to an overproduction of calcitriol. Furthermore, a rapid reduction in renal size after the discontinuation of previous intravenous hyperalimentation with amino acids was reported (27). Although not significant, we also noticed a clear tendency toward a decrease in creatinine clearance after protein restriction, which could reflect a reduction in renal mass. We did not measure renal size before or after the protein-restricted diet, but the most likely explanation for our data is that a slight decrease in glomerular filtration rate, together with a possible reduction in renal size and thus in renal 1-α-hydroxylase activity, reduced transformation of calcidiol into calcitriol. This process, in turn, also contributed to the reduction in calcium excretion through an increase in PTH concentrations, as shown by the inverse correlation between PTH and urinary calcium after the protein-reduced diet.

In the present study, urinary citrate excretion rose significantly after the protein-reduced diet. Several factors might contribute to the control of citrate excretion (30). For example, urinary citrate decreases after protein loading because of a reduction in intracellular pH. This, in turn, activates the citrate pumps into the proximal tubular cells, resulting in increased tubular citrate reuptake (31). Thus, an increase in blood pH because of the decrease in dietary protein intake might result in a reduction in tubular citrate reabsorption and consequently in augmented urinary citrate excretion.

Urinary oxalate concentration is regarded as a major risk factor for nephrolithiasis, because ≈20% of patients with calcium nephrolithiasis have elevated urinary excretion of this substance (11). The relation between protein consumption and urinary oxalate excretion is still controversial. Although some authors observed no correlation between protein intake and oxalate excretion (32), many others have suggested that increased consumption of dietary protein leads to hyperoxaluria (10, 33). In our study, we observed a significant reduction in oxalate excretion after moderate protein restriction. Because of the amount of vegetables included in our dietary protocol, it is unlikely that the reduction in oxalate excretion could be related to a decreased intake of oxalate. Furthermore, it is well-known that dietary oxalate contributes to 10–20% of urinary oxalate, whereas endogenous metabolism accounts for ≥40–50% of the total excretion of this substance (11).

Elevated excretion of glycolate, a precursor of oxalate, has been observed in most subjects with renal calculi and hyperoxaluria, and some authors have proposed that dietary protein may be the most important contributing factor (34, 35). Although urinary glycolate was not measured in this study, the correlation between urinary uric acid and oxalate strongly suggests that the reduction in oxalate excretion was due to a decrease in endogenous production.

Hyperuricosuria and hypercalciuria in patients with kidney stones seems to be the typical consequence of excessive intake of dietary purines rather than of abnormal metabolism of these substances (36). Thus, it is not surprising that there was a decrease in urinary uric acid after a moderate restriction of protein intake.

In conclusion, this study showed that moderate dietary protein restriction in patients with hypercalciuria and calcium nephrolithiasis reduced calcium excretion. This phenomenon may be secondary to an effect on the calcitriol-PTH axis, although the reasons for this still need to be elucidated fully. In addition, the beneficial effects can also be seen in a reduction of the entire lithogenic potential of these patients. Thus, controlling dietary protein intake may be an effective tool in a more complex strategy aimed at renal stone prevention.

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