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ORIGINAL PAPER

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Renal phosphate leak in patients with idiopathic hypercalciuria and calcium nephrolithiasis

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Abstract Although urine phosphate loss has been associated with hypercalciuria, it is debated how frequently renal phosphate leak is present in hypercalciuric patients. We reviewed the records of 100 consecutive adult patients who were diagnosed with idiopathic hypercalciuria and calcium urolithiasis, searching for the presence of renal phosphate leak. The renal phosphate threshold, normalized for the glomerular filtration rate (TmPO4/GFR), of the hypercalciuric patients followed a normal distribution and had a good correlation with serum phosphate ($r = 0.77$; $p < 0.0001$). There were no correlations between TmPO4/GFR and urinary calcium or between serum phosphorus and urinary calcium. We found only nine patients (9%) with renal phosphate leak. These patients had a mean TmPO4/GFR of 2.19 mg% (0.70 mmol/l) and serum phosphorus of 2.65 mg% (0.85 mmol/l). Nevertheless, urinary calcium was not significantly different between patients with or without low TmPO4/GFR. We conclude that renal phosphate leak is an infrequent finding in patients with idiopathic hypercalciuria and is not associated with a higher urinary calcium loss.

Keywords Hypercalciuria · Renal phosphate leak · Renal stones · Hyperphosphaturia · Calcium lithiasis

Introduction

Idiopathic hypercalciuria has long been recognized as the most frequent disorder associated with recurrent calcium nephrolithiasis [6]. At present idiopathic hypercalciuria is thought to be constituted by several entities of distinct pathogenetic origin: absorptive hypercalciuria, fasting hypercalciuria and renal hypercalciuria [2, 9, 10, 13]. Williams et al. [15] have proposed that all hypercalciuria is due primarily to a renal phosphate leak. Phosphate excretion leads to increases in the renal synthesis of calcitriol with the consequent increase in intestinal absorption of calcium. Although some studies favour this theory [5], others were unable to find evidence supporting a renal leak of phosphate [8]. In an ambulatory evaluation of 1,270 patients with recurrent nephrolithiasis, Barilla et al. [1] found that 60.9% of patients had hypercalciuria but only 2–4% of them had renal phosphate leak. In a more recent study, Prié et al. [12] found a low renal phosphate threshold in 5% of controls and in 19% of stone formers with normal PTH; they also found that it was associated with a high urinary calcium excretion.

Because of the great discrepancies among studies, we decided to evaluate how frequently renal phosphate leak was seen in patients with calcium nephrolithiasis due to idiopathic hypercalciuria who come to our stone clinic.

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Materials and methods

Patients and methods

We reviewed the records of 100 consecutive patients who were diagnosed as having idiopathic hypercalciuria and normal creatinine clearance on metabolic evaluation performed at our institute for calcium urolithiasis. All these patients were evaluated using an ambulatory protocol: they were asked to follow a 7-day diet containing 1,000 mg calcium and 100 mEq sodium. On the last 2 days, two 24-h urine samples were obtained followed by a 2-h fasting urine sample collected by spontaneous voiding on the morning of the 8th day. At the end of that collection a blood sample was obtained. Blood and urine samples were analyzed for creatinine, calcium, phosphorus and other analytes using automated analyzers. The patients were studied at least 1 month after the episode of renal colic. Our historical control population had been analyzed with the same protocol.

Serum calcium was measured by Synchron CX3 automated analyzer (Beckman Instruments Inc, USA). The coefficient of variation was 1.3% at 8 mg% and 1.5% at 14 mg%. Serum and urine creatinine were measured by a Jaffe kinetic method using an automated analyzer. The serum coefficient of variation (CV%) was 7% at 0.8 mg% and 1.8% at 4.2 mg%. The urine CV% was 2.9% at 43 mg% and 3% at 87 mg%. Phosphate was measured by UV using a CCX Spectrum automated analyzer (Abbott Laboratories, USA). The urine CV was 2.9% at 43 mg% and 3% at 87 mg% and the serum CV was 6.5% at 2.4 mg% and 2.8% at 4.5 mg%.

Patients were considered as having idiopathic hypercalciuria if the urinary calcium excretion was more than 4 mg/kg/d (0.1 mmol/kg/d) or more than 220 mg/24 h in women or 300 mg/24 h in men, with normal serum calcium. The renal phosphate threshold normalized for glomerular filtration rate estimated by creatinine clearance (TmPO4/GFR; normal range 2.5–4.2 mg%) was calculated according to the nomogram of Walton and Bijvoet [14]. Patients were diagnosed as having renal phosphate leak if they had hypophosphatemia (serum phosphorus <2.8 mg%) and a renal phosphate threshold of less than 2.4 mg%.

Statistical analysis

All analyses were performed using CSS: Statistica software (StatSoft, Inc, Tulsa, OK). Results are expressed as mean ± SD. Correlations between variables were assessed by linear regression analysis. Continuous variables were compared by Student *t*-test for independent samples. The chi-square test was used for categorical data. $P<0.05$ was considered significant.

Results

The main characteristics of the population studied are presented in Table 1. Males had a higher urinary calcium excretion in 24 h than females, but renal phosphate threshold was similar in both sexes.

The TmPO4/GFR of the hypercalciuric patients followed a normal distribution and we observed a good correlation between TmPO4/GFR and serum phosphate ($r=0.77$; $p<0.0001$) (Fig 1). There were no correlations between TmPO4/GFR and urinary calcium or between serum phosphorus and urinary calcium.

We found only nine patients (9%), four females and five males, with renal phosphate leak. The proportion of patients with low TmPO4/GFR in both sexes was 5/33 (15.1%) in males and 4/67 (5.9%) in females (chi square, 0.13). These patients had a mean TmPO4/GFR of 2.19 mg% (0.70 mmol/l) and serum phosphorus of 2.65 mg% (0.85 mmol/l) Table 2. Nevertheless urinary calcium was not significantly different between patients with or without low TmPO4/GFR.

Table 1 Characteristics of the population studied

	Females	Males
N	67	33
Age (years)	42.5 ± 12.4	43.1 ± 12.1
Weight (kg)	60.8 ± 8.8	79.2 ± 9.1
Serum Phosphate mg%	3.5 ± 0.49	3.3 ± 0.49
Serum calcium mg%	9.6 ± 0.33	9.7 ± 0.33
Cr clearance ml/min	100.9 ± 20.2	105.7 ± 15.2
TmPO4/GFR mg%	3.42 ± 0.76	3.26 ± 0.67
UCa mg/day	287.0 ± 57.4	363.2 ± 50.2
UCa/KgBW mg/kg	4.77 ± 1.15	4.69 ± 0.90

Discussion

We found that renal phosphate leak is an infrequent finding in patients with idiopathic hypercalciuria and nephrolithiasis. In a recent study, Prié et al. [12] found that a low renal threshold for PO4 was more frequently encountered in calcium stone formers with normal PTH compared to control subjects and that this was associated with a high urinary Ca excretion. Prié used a TmPO4 of <0.63 mmol/l (1.95 mg%) as a cut off for renal phosphate leak. With this cutoff value, she found that 19% of calcium stone formers had renal phosphate leak, and only 5% of controls. We used instead a cutoff value of <2.4 mg% (<0.77 mmol/l), as this is below the 95% confidence limit of our normal historical controls. This is the same threshold that Michaut et al. [8] considered as abnormal. Serum phosphate in our historical controls is higher (1.13 mmol/l or 3.62 mg%) than Prié's

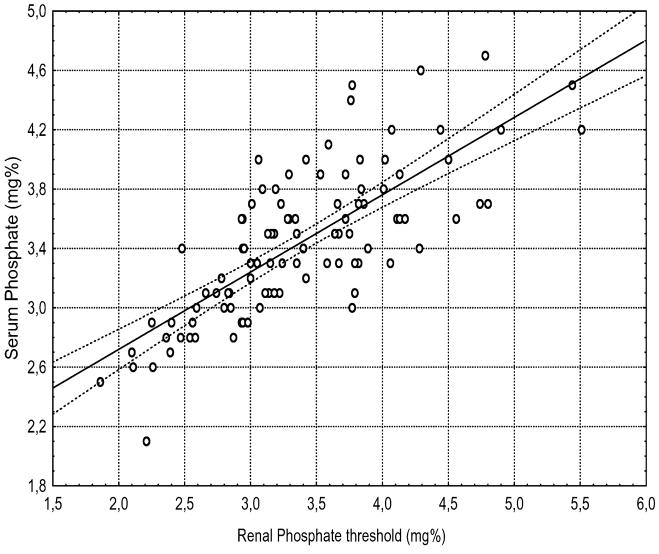

Fig. 1 Correlation between renal phosphate threshold and serum phosphate

Table 2 Comparison of patients with and without low renal phosphate threshold

	With low TmPO4/GFR	Without low TmPO4/GFR
N	9	91
Age (years)	42.5 ± 11.8	42.8 ± 12.4
Weight (kg)	65.5 ± 8.8	67.0 ± 12.7
Serum Phosphate mg%	2.65 ± 0.24	3.5 ± 0.44
Serum calcium mg%	9.5 ± 0.43	9.6 ± 0.33
Cr clearance ml/min	96.9 ± 11.4	103.0 ± 19.2
TmPO4/GFR mg%	2.19 ± 0.15	3.48 ± 0.66
UCa mg/day	305 ± 73.7	312 ± 65.2
UCa/KgBW mg/kg	4.76 ± 0.98	4.74 ± 1.08

controls (0.96 mmol/l or 2.97 mg%), so most probably there is a difference in the method of phosphate measurement. Thus the values of controls and patients are pushed downwards in her study. The other major difference between our study and hers is that we measured phosphate threshold after a 7-day diet of 1000 mg calcium while Prié's patients followed a calcium-restricted diet for only 2 days before the investigation. The shorter fixed diet period prior to the renal phosphate threshold determination could lead to greater variations in renal phosphate handling. Nevertheless, these differences do not explain the different proportion of patients with low renal phosphate threshold we found, which is half what Prié et al. found. The other major difference between our study and Prié's study is that she studied patients with calcium urolithiasis, which may be produced by more than one physiopathologic entity and not purely hypercalciuric patients as we studied. Mean calcium excretion in 24 h in her stone-former patients with normal TmPO4 was 4.7 mmol in 24 hours (188 mg/24 h), and those with low TmPO4, 6 mmol in 24 h (240 mg/24 h), both within the normal range. Patients in our study were predominantly female as opposed to most studies in kidney stones formers in which gender distribution is predominantly male. This may be part of the reason why our results differ from those of Prié, who had predominantly male patients. The renal phosphate threshold was slightly but not significantly lower in male than in female hypercalciuric stone formers; the proportion of patients with low TmPO4/GFR was higher in males than in females, although in did not reach statistical significance.

Prié found that daily calcium excretion in stone formers with low TmPO4/GFR was significantly higher than in stone formers with normal TmPO4/GFR. On the contrary, we could not find greater calcium excretion in hypercalciuric patients with low TmPO4/GFR. This is likely to be due to the inclusion of only hypercalciuric patients. If calcium stone formers with a full range of urine calcium excretion had been studied, as Prié did, we would probably have found higher urinary calcium in patients with low TmPO4/GFR.

The importance of phosphaturia or hypophosphatemia in the increased risk of stone formation is debated. Bushinsky et al. [3] recently reported that hypercalciuric rats given a low-phosphate diet decreased phosphaturia, preventing stone formation, although hypercalciuria was augmented further. They suggest that variations in calcium phosphate super saturation regulates stone formation in hypercalciuric stone-forming rats. Lerolle et al. [7], studying risk factors for nephrolithiasis in patients with familial idiopathic hypercalciuria, found that lower serum phosphate and higher vitamin D levels were associated with stone formation in these patients. However, when they analyzed odds ratios for stone formation in a multivariate model, only age, 24-h urinary calcium and uric acid excretion were found as independent risk factors for stone formation but not serum phosphate or calcitriol concentrations.

If the renal phosphate threshold were an important risk factor for increased stone formation it would be interesting to manipulate renal phosphate excretion to see if stone formation varies accordingly. It has been demonstrated that dipyridamole, a well-known antiaggregate and vasodilator drug, can lower phosphate excretion in rats [4] and humans [8]. Prié et al. [11] recently showed with chronic dipyridamole treatment at a dose of 75 mg four times daily increased TmPO4/GFR in 80% of 64 patients who had a low renal phosphate threshold. The maximal values were reached at 9 months of treatment, and in 51 patients the increase in TmPO4/GFR was substantial enough to improve serum phosphorus. The serum1, 25(OH) 2 vitamin D concentration was initially increased in 28 patients and decreased towards normal within 9 months of treatment. With dipyridamole treatment, 24-h calcium excretion decreased only in patients with initially high vitamin D levels and in patients with renal stones. There are still no studies on the effect of dipyridamole on stone recurrence in large cohorts of treated and untreated patients.

In conclusion, renal phosphate leak was found in only 9% of our patients with idiopathic hypercalciuria and calcium nephrolithiasis. Patients with low TmPO4/GFR did not have higher urinary calcium excretion than those who had a normal one. Further studies are needed to determine the importance of renal phosphate leak and its pharmacological manipulation in calcium stone recurrence.

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