Kidney International, Vol. 60 (2001), pp. 272–276

Frequency of renal phosphate leak among patients with calcium nephrolithiasis

DOMINIQUE PRIÉ, VINCENT RAVERY, LAURENT BOCCON-GIBOD, and GÉRARD FRIEDLANDER

Department of Physiologie Explorations Fonctionnelles, and Department of Urology, Hôpital Bichat, Paris, France

Frequency of renal phosphate leak among patients with calcium nephrolithiasis.

Background. Nephrolithiasis is a frequent disorder affecting 10 to 15% of the population in Europe and the United States. More than 80% of renal stones are made of calcium oxalate and calcium phosphate. The main identified risks for calcium renal stone formation are hypercalciuria and urinary saturation. A urine phosphate (Pi) loss is often associated with hypercalciuria; furthermore, hyperphosphaturia increases urinary saturation.

Methods. To determine whether urinary phosphate loss is associated with calcium urolithiasis, we measured renal Pi threshold (TmPi) in 207 stone formers with normal parathyroid hormone (PTH) serum concentration and in 105 control subjects.

Results. The TmPi followed a normal distribution in both groups. The mean TmPi was significantly lower in stone formers versus controls (0.72 ± 0.13 vs. 0.87 ± 0.18 mmol/L, $P < 0.0001$) because of a shift to the left of the TmPi distribution curve in the stone former population, with no evidence for bimodal distribution. Five percent of the controls had a TmPi <0.63 versus 19% of the stone formers. Daily urinary calcium excretion was significantly higher in stone formers than in controls. Calcium excretion was also significantly higher in stone formers with TmPi <0.63 mmol/L compared with those with TmPi ≥ 0.63. Serum PTH and ionized calcium concentrations were not different in stone formers and in control subjects, whatever the TmPi value.

Conclusions. A low TmPi is more frequently encountered in stone formers with a normal PTH concentration than in control subjects and is associated with a high urinary Ca excretion. The hypophosphatemia induced by a renal phosphate leak may predispose the subject to calcium stone formation by increasing the serum calcitriol level, calcium excretion, and urinary saturation.

Nephrolithiasis is a common disorder affecting 10 to 15% of the population during their lifetimes in Europe and the United States [1–3]. Renal stones cause severe pain, lead to hospitalization for shock wave lithotripsy or surgery, and tend to recur at a rate of approximately 75% during 20 years [4, 5]. A better understanding of the mechanisms involved in stone formation should improve the prevention of their recurrence. More than 80% of renal stones are composed of calcium oxalate and calcium phosphate [5]. Hypercalciuria is one of the main risk factors for idiopathic calcium stone formation. Hypercalciuria in normocalcemic patients has been classified in absorptive hypercalciuria (types I and II), renal hypercalciuria, and renal phosphate leak (absorptive hypercalciuria type III) [6]. In the latter, it is postulated that the decrease of the renal capacity to reabsorb phosphate leads to hypophosphatemia that in turn increases $1,25(OH)_2$ vitamin D synthesis, increasing phosphate and calcium intestinal absorption responsible for hypercalciuria. Furthermore, hyperphosphaturia may by itself increase the risk of stone formation by increasing urinary saturation.

A decrease of the renal phosphate threshold normalized for the glomerular filtration rate (TmPi) in patients with calcium nephrolithiasis has been reported by several groups [7–12]. The frequency and characteristics of this disorder in a large population of calcium stone formers are, however, unknown. From January 1, 1996, to December 31, 1999, we investigated 230 patients with calcium renal stones. TmPi and renal function parameters were measured in these patients and in 105 control subjects with no history of nephrolithiasis. We compared the TmPi distribution in the two populations and showed that renal phosphate leak is a common disorder, affecting approximately 20% of calcium stone formers with normal parathyroid function (SF). In SF, calciuria was significantly higher in patients with a low TmPi than in those with normal urinary phosphate excretion.

METHODS

All investigations were performed in ambulatory subjects.

Key words: stone formers, lithiasis, renal stones, hypercalciuria, hyperphosphaturia, urinary calcium excretion.

Received for publication July 7, 2000
and in revised form February 14, 2001
Accepted for publication February 16, 2001

Stone formers

From January 1996 to December 1999, 230 patients were investigated in our department for calcium urolithiasis. All patients were evaluated using an ambulatory protocol. All patients were asked to follow a diet restricted in calcium during the two days before the investigation. The investigation was conducted in the forenoon on fasting subjects and at least one month after a pain episode. Serum calcium, phosphate, and standard blood parameters were measured. To determine glomerular filtration rate (GFR), the patients were infused with inulin (Inutest 25%), and urine was collected every hour by spontaneous voiding during three hours. Blood samples were drawn at the same time. In all patients with normal parathyroid function, the biochemical markers of bone remodeling (serum osteocalcin concentration, urinary deoxypyridoline) were within the normal range.

Control subjects

One hundred five subjects were referred to our department for GFR assessment during the same period of time (from January 1996 to December 1999). These patients exhibited mild-to-medium lesions of psoriasis and were scheduled to receive low doses of cyclosporine A. These patients were investigated using the protocol described previously in this article, except for parathyroid hormone (PTH) and $1,25(OH)_2$ vitamin D concentrations, which were measured in only 28 subjects. None of the patients had received any medication during the month prior to the investigation, and none had a history of urolithiasis. All had a normal GFR.

All the investigations were conducted in the Department of Physiologie Explorations Fonctionnelles using our standard protocols in accordance with the French rules concerning research in humans.

All measurements were made on site using routine methods. PTH concentrations were determined by an immunoradiometric assay recognizing the intact 1-84 PTH (ELSA-PTH kit; CIS Biointernational, Gif-sur-Yvette, France). Normal values ranged from 11 to 62 pg/mL. Serum $1,25(OH)_2$ vitamin D concentrations were measured by radioimmunoassay (INCSTAR, Stillwater, MN, USA). Normal values ranged from 15 to 42 pg/mL.

The renal phosphate threshold normalized for GFR (TmPi; mmol/L) was calculated according to the nomogram of Walton and Bijvoet [13].

Statistical analysis

Data were compared using a two-way analysis of variance and a least-significant difference test when $P < 0.05$. All results were expressed as mean ± SEM.

RESULTS

Among the 230 patients referred to our department for urolithiasis, 10% (23 patients) exhibited high PTH and ionized calcium serum concentrations (PTH, 101 ± 18 pg/mL; Ca^{2+}, 1.33 ± 0.03 mmol/L). Since high PTH levels are known to decrease the tubular maximal threshold for phosphate reabsorption (TmPi), the data from these patients were not included in the rest of the study. The main characteristics of the remaining 207 stone formers with normal serum-ionized calcium and PTH concentrations (SF) and of the 105 control subjects (CS) are presented in Table 1. The mean age was similar between the two groups. As expected, the sex ratio was significantly different between the two groups. Males represented two thirds of the patients with urolithiasis and 50% of the control subjects.

Table 1. General characteristics of control subjects and patients with urolithiasis

	Urolithiasis	Controls
Number	207	105
Males/females	142/65	49/56
Age (mean ± SE)	42.2 ± 0.83	41.2 ± 1.33

Patients with hyperparathyroidism were excluded.

In the two populations, TmPi followed a normal distribution (Fig. 1). The mean TmPi, however, was significantly lower in SF than in controls (0.72 ± 0.13 vs. 0.87 ± 0.18 mmol/L, respectively, $P < 0.0001$; Fig. 1 A, C). The curve obtained from patients with urolithiasis was shifted to the lower values, with no evidence for bimodal distribution. Similarly, the mean serum phosphate concentration was significantly lower in SF than in controls (0.87 ± 0.12 vs. 0.96 ± 0.14, respectively, $P < 0.0001$). The fractional excretion of phosphate was significantly increased in SF compared with CS (19.6 ± 0.6 vs. 15.2 ± 0.7, $P < 0.0001$).

The difference in TmPi values between the two groups was not due to a difference in the sex ratio (Table 1). Within each group, TmPi was not significantly different in males and females; furthermore, comparing the males and females separately between the two groups showed that the mean TmPi was lower in the SF of both genders as compared with controls (Fig. 2).

Ninety-five percent of the subjects in the control group had a TmPi greater than 0.63 mmol/L (Fig. 1D). This value of TmPi (0.63 mmol/L) was used to define further the group of patients with urolithiasis and normal serum PTH and ionized calcium concentrations. Thirty-nine of these patients (19% of all SF) exhibited a TmPi lower than 0.63 mmol/L (Fig. 1A). In this subgroup, designated as low TmPi SF, the serum phosphate concentration was lower than that in SF with a TmPi ≥0.63 mmol/L (Table 2). This latter group was designated as "normal" TmPi SF.

Hypercalciuria, regardless of its mechanism, is one of the main risk factors for stone formation [14]. Furthermore, it has been postulated that renal phosphate leak-

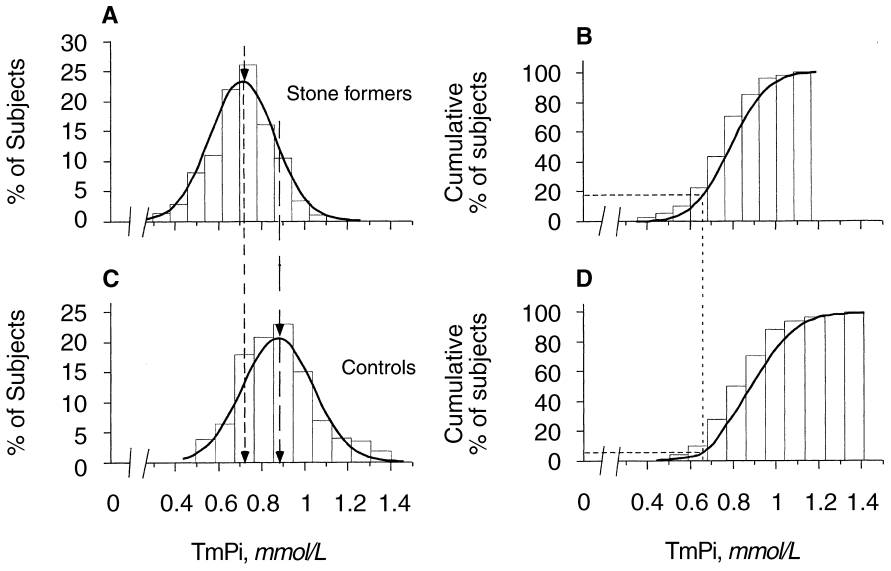

Fig. 1. Distribution of the renal phosphate threshold (TmPi) expressed as histogram and cumulative curves in stone formers (SF) with normal parathyroid function (*A*) and in control subjects (*C*). The distribution is normal in both populations, but the curve is shifted to the lower values of TmPi in stone formers (A) compared with that in controls (C). TmPi is lower than 0.63 mmol/L in 5% of controls (*D*) versus 19% in SF (*B*).

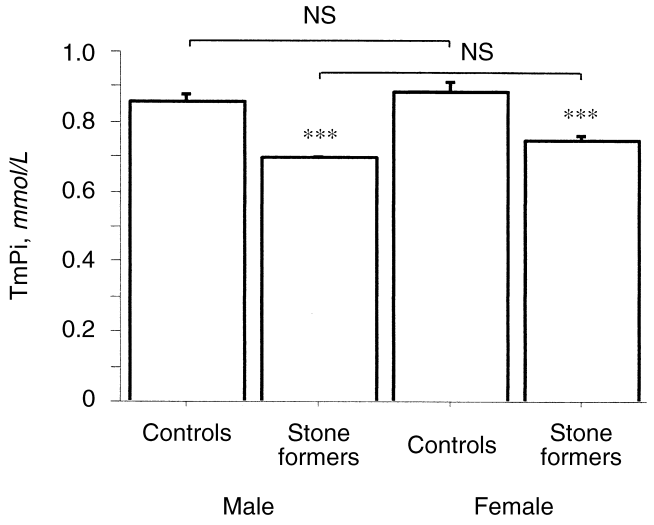

Fig. 2. Values of TmPi in stone formers and in controls according to gender. TmPi were significantly lower in male stone formers compared with male control and in female stone formers vs. female controls (***$P < 0.0001$). There was no difference in TmPi according to gender in stone formers and in controls.

induced hypophosphatemia may induce hypercalciuria by increasing the serum calcitriol concentration, resulting in increased intestinal calcium absorption and bone resorption. Urinary calcium excretion per 24 hours in stone formers with and without low TmPi was significantly increased compared with that in controls. In addition, daily calcium excretion in stone formers with low TmPi was significantly higher than that in stone formers with "normal" TmPi (Fig. 3). We also found that calcium excretion was higher in stone formers with TmPi $\geq$0.63 than in control subjects.

Parathyroid hormone is a major determinant of TmPi. Serum PTH levels were compared in stone formers and in controls according to the TmPi values. Serum PTH values were not significantly different in SF with low and normal TmPi and in controls (Table 2); serum-ionized calcium concentrations were also similar in SF and in controls. Serum 1,25$(OH)_2$ vitamin D concentrations were not different between the two groups of SF, but were significantly higher in SF than in 28 controls.

DISCUSSION

The data reported in this study indicate that a decrease in the capacity of kidney to reabsorb phosphate is not an unusual finding, and is more frequently observed in patients with urolithiasis with normal PTH and ionized calcium concentrations than in control subjects.

Hyperphosphaturia in patients with urolithiasis has been reported by several authors [7–12]; however, the frequency of a low TmPi among SF with normal parathyroid function is unknown, and the distribution of TmPi in this population has never been reported to date. We observed that TmPi is distributed across the entire bell-shaped curve in SF with a normal PTH concentration and in the control population. In both populations TmPi values are distributed following a normal distribution, that is, a bell-shaped curve. The lower values of TmPi in SF were not due to a specific subgroup, since no bimodal distribution was observed. This suggests that low TmPi is a complex trait controlled by multiple factors.

The cause of the decreased TmPi in SF is not elucidated. None of these patients had a history of rickets, and there were no arguments in favor of familial hypophosphatemia, such as those encountered in familial X-linked or autosomal-dominant hypophosphatemic rickets [15].

Table 2. Serum concentrations of parathyroid hormone (PTH), ionized calcium, calcitriol, and phosphorus in stone former patients (SF) according to renal Pi threshold (TmPi) values and in controls

	Stone formers *TmPi <0.63 mmol/L*	Stone formers *TmPi ≥0.63 mmol/L*	Controls
N	39	168	105
Phosphorus *mmol/L* (Nl range, 0.85–1.44 *mmol/L*)	0.73 ± 0.01^{b}	0.91 ± 0.01^{c}	0.96 ± 0.01
Ionized calcium *mmol/L* (Nl range, 1.15–1.25 *mmol/L*)	1.22 ± 0.01	1.22 ± 0.01	1.21 ± 0.01
PTH *pg/mL* (Nl range, 11–62 *pg/mL*)	33.8 ± 2.2	34.6 ± 1.0	33.5 ± 2.4^{d}
$1,25(OH)_2$ vitamin D *pg/mL* (Nl range, 10–42 *pg/mL*)	45.4 ± 3.9^{a}	44.7 ± 1.9^{a}	32 ± 2.7^{d}

Patients with hyperparathyroidism were excluded. Nl is normal.
Serum PTH and ionized calcium concentrations were not statistically different between the three groups. *N* is the number of patients in each group.
[a] $P < 0.05$ compared to control
[b] $P < 0.0001$ vs. control and stone formers with TmPi ≥0.63 mmol/L
[c] $P < 0.005$ vs. control
[d] PTH and $1,25(OH)_2$ vitamin D were measured only in 28 patients

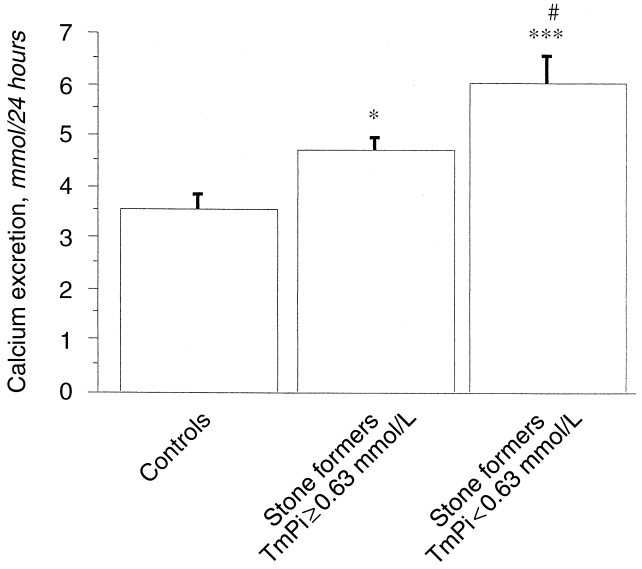

Fig. 3. Daily excretion of calcium in controls and in stone formers with TmPi ≥0.63 mmol/L or <0.63 mmol/L. $*P < 0.05$, $***P < 0.0005$ compared with controls; $\#P < 0.05$ stone formers with TmPi <0.63 vs. ≥0.63 mmol/L.

Similarly, the clinical and biochemical presentations were very different from those observed in oncogenic hypophosphatemic osteomalacia [16]. Recently, an inactivating mutation in the *CLCN5* gene, a gene implicated in X-linked nephrolithiasis/Dent's disease, has been reported in one patient with isolated idiopathic hypercalciuria [17]. However, the *CLCN5* mutation is a very rare finding among patients with urolithiasis [17]. The decrease of TmPi in SF was not secondary to an increase in PTH or PTH hypersensitivity, since serum PTH and ionized Ca concentrations were normal and similar in SF with low or normal TmPi as well as in controls. These results are in line with our previous report showing that urinary cAMP excretion was normal in patients with an idiopathic renal phosphate leak [18].

It is interesting to note that a dissociation between serum PTH values and TmPi is also observed in humans during a low-phosphate diet. In normal subjects, phosphate deprivation increases TmPi and serum $1,25(OH)_2$ vitamin D concentrations, but does not significantly decrease serum PTH concentration and nephrogenic cAMP excretion and does not modify serum calcium concentration [19, 20]. The PTH-independent mechanisms that influence phosphate reabsorption by the kidney are still largely unknown. Hypercalciuria is present in a phosphate-deprived diet and in a renal phosphate leak; however, the low urinary phosphate excretion in the former state may protect against stone formation, as discussed later in this article.

The decrease of TmPi in SF was associated with hypophosphatemia. Hypophosphatemia is known to increase $1,25(OH)_2$ vitamin D synthesis [20]. In agreement with that study, $1,25(OH)_2$ vitamin D concentrations in SF were close to or above the upper normal values of our laboratory. However, $1,25(OH)_2$ vitamin D concentrations were not significantly different between SF with normal and low TmPi, although hypophosphatemia was lower in the latter group than that in the former group. These observations suggest that high calcitriol levels in stone formers may be due to various mechanisms, one of them being hypophosphatemia secondary to the renal phosphate leak. Some stone formers with an increased serum $1,25(OH)_2$ vitamin D concentration did not exhibit a renal phosphate leak and hypophosphatemia. This observation has also been reported by different investigators [21–23]. The cause of the increase of $1,25(OH)_2$ vitamin D concentration in stone formers is still unknown. The search for linkages between renal stone formation and polymorphisms of the genes of the vitamin D receptor [24] or the 1α hydroxylase [25] has been unsuccessful to date.

It is known that urinary calcium excretion is higher in stone formers than in controls, although the mechanisms involved are not unequivocal. Our results show that stone former patients with a lower TmPi had greater daily urinary calcium excretion than patients with normal TmPi. This observation suggests a link between renal phosphate leak and hypercalciuria in these stone formers.

It is impossible to conclude from this study whether renal stones recur more frequently in SF with a low TmPi and normal parathyroid function versus SF with a normal TmPi. It is also unknown whether the rate of stone occurrence is higher in subjects with low TmPi than in a control population. However, the shift of TmPi distribution to the lower values and the high frequency of patients with low TmPi in SF compared with controls suggest that hyperphosphaturia may be a factor facilitating or increasing the risk of stone formation. It has been reported recently that in hypercalciuric rats, a low-phosphate diet decreased phosphaturia, preventing stone formation, although hypercalciuria was augmented further [26]. These results together with those of our study suggest that regardless of the mechanism involved, the increase of phosphate excretion may augment urine saturation, and hence promote calcium stone formation. Conversely, decreasing phosphaturia may contribute to the prevention of calcium renal stone recurrences. We have shown that dipyridamole was able to increase renal phosphate reabsorption and serum phosphate concentration and to normalize calciuria and $1,25(OH)_2$ vitamin D in patients with idiopathic renal phosphate leak [18], and we recently extended these results to patients with urolithiasis and low TmPi presented here (unpublished personal data). It will be interesting to study the effect of dipyridamole on stone recurrence in larger cohorts of treated and untreated patients.

In conclusion, low TmPi is more frequently observed in stone formers without hyperparathyroidism than in control subjects. Hyperphosphaturia, by increasing urinary calcium excretion and urinary saturation, may predispose the patient to calcium stone formation.

ACKNOWLEDGMENTS

This work was supported by grants from Association des Laboratoires de Recherche en Physiologie and from the CEGETEL Foundation. We acknowledge Pr. D. Leguludec and Dr. A. Meulemans, Nuclear Medicine Department at the Hôpital Bichat, for measuring the PTH and $1,25(OH)_2$ vitamin D concentrations. We are thankful to Dr. Caroline Silve for her helpful comments and advice during the preparation of the manuscript.

Reprint requests to Dominique Prié, M.D., Ph.D., Department of Physiologie Explorations Fonctionnelles, Hôpital Bichat, 48 rue Henri Huchard, 75018 Paris, France.
E-mail: dprie@bichat.inserm.fr

REFERENCES

1. Sierakowski R, Finlayson B, Landes RR, *et al:* The frequency of urolithiasis in hospital discharge diagnoses in the United States. *Invest Urol* 15:438–441, 1978
2. Johnson CM, Wilson DM, O'Fallon WM, *et al:* Renal stone epidemiology: A 25-year study in Rochester, Minnesota. *Kidney Int* 16:624–631, 1979
3. Norlin A, Lindell B, Granberg PO, *et al:* Urolithiasis. A study of its frequency. *Scand J Urol Nephrol* 10:150–153, 1976
4. Sutherland JW, Parks JH, Coe FL: Recurrence after a single renal stone in a community practice. *Miner Electrolyte Metab* 11: 267–269, 1985
5. Asplin JR, Favus MJ, Coe FL: Nephrolithiasis, in *The Kidney*, edited by Brenner BM, Philadelphia, W.B. Saunders, 2000, p 1774
6. Levy FL, Adams-Huet B, Pak CYC: Ambulatory evaluation of nephrolithiasis: An update of a 1980 protocol. *Am J Med* 98:50–59, 1995
7. Tieder M, Modai D, Samuel R, *et al:* Hereditary hypophosphatemic rickets with hypercalciuria. *N Engl J Med* 312:611–617, 1985
8. Tieder M, Modai D, Shaked U, *et al:* "Idiopathic" hypercalciuria and hereditary hypophosphatemic rickets: Two phenotypical expressions of a common genetic defect. *N Engl J Med* 316:125–129, 1987
9. Lau YK, Wasserstein A, Westby GR, *et al:* Proximal tubular defects in idiopathic hypercalciuria: Resistance to phosphate administration. *Miner Electrolyte Metab* 7:237–249, 1982
10. Williams CP, Child DF, Hudson PR, *et al:* Inappropriate phosphate excretion in idiopathic hypercalciuria: The key to a common cause and future treatment? *J Clin Pathol* 49:881–888, 1996
11. Jaeger P, Portmann L, Ginalski JM, *et al:* Tubulopathy in nephrolithiasis: Consequence rather than cause. *Kidney Int* 29:563–571, 1986
12. Pabico RC, McKenna BA, Freeman RB: Renal threshold phosphate concentration in patients with idiopathic nephrolithiasis: Correlations with tubular functions, serum parathyroid hormone and $1,25(OH)_2D_3$. *Proc Eur Dial Transplant Assoc* 20:450–454, 1983
13. Walton RJ, Bijvoet OL: Nomogram for derivation of renal threshold phosphate concentration. *Lancet* 2:309–310, 1975
14. Scheinman SJ: Nephrolithiasis. *Semin Nephrol* 19:381–388, 1999
15. Agarwal R, Knochel JP: Hypophosphatemia and hyperphosphatemia, in *The Kidney* (vol 1), edited by Brenner BM, Philadelphia, W.B. Saunders, 2000, pp 1071–1125
16. Cai Q, Hodgson SF, Kao PC, *et al:* Brief report: Inhibition of renal phosphate transport by a tumor product in a patient with oncogenic osteomalacia. *N Engl J Med* 330:1645–1649, 1994
17. Scheinman SJ, Cox JP, Lloyd SE, *et al:* Isolated hypercalciuria with mutation in CLCN5: Relevance to idiopathic hypercalciuria. *Kidney Int* 57:232–239, 2000
18. Prie D, Blanchet FB, Essig M, *et al:* Dipyridamole decreases renal phosphate leak and augments serum phosphorus in patients with low renal phosphate threshold. *J Am Soc Nephrol* 9:1264–1269, 1998
19. Insogna KL, Broadus AE, Gertner JM: Impaired phosphorus conservation and 1,25 dihydroxyvitamin D generation during phosphorus deprivation in familial hypophosphatemic rickets. *J Clin Invest* 71:1562–1569, 1983
20. Portale AA, Halloran BP, Morris RC Jr: Physiologic regulation of the serum concentration of 1,25-dihydroxyvitamin D by phosphorus in normal men. *J Clin Invest* 83:1494–1499, 1989
21. Coe FL, Favus MJ, Crockett T, *et al:* Effects of low-calcium diet on urine calcium excretion, parathyroid function and serum $1,25(OH)_2D_3$ levels in patients with idiopathic hypercalciuria and in normal subjects. *Am J Med* 72:25–32, 1982
22. Shen FH, Baylink DJ, Nielsen RL, *et al:* Increased serum 1,25-dihydroxyvitamin D in idiopathic hypercalciuria. *J Lab Clin Med* 90:955–962, 1977
23. Gray RW, Wilz DR, Caldas AE, *et al:* The importance of phosphate in regulating plasma $1,25\text{-}(OH)_2$-vitamin D levels in humans: Studies in healthy subjects in calcium-stone formers and in patients with primary hyperparathyroidism. *J Clin Endocrinol Metab* 45: 299–306, 1977
24. Scott P, Ouimet D, Valiquette L, *et al:* Suggestive evidence for a susceptibility gene near the vitamin D receptor locus in idiopathic calcium stone formation. *J Am Soc Nephrol* 10:1007–1013, 1999
25. Scott P, Ouimet D, Proulx Y, *et al:* The 1 alpha-hydroxylase locus is not linked to calcium stone formation or calciuric phenotypes in French-Canadian families. *J Am Soc Nephrol* 9:425–432, 1998
26. Bushinsky DA, Parker WR, Asplin JR: Calcium phosphate supersaturation regulates stone formation in genetic hypercalciuric stone-forming rats. *Kidney Int* 57:550–560, 2000