International Urology and Nephrology 29 (5), pp. 523–528 (1997)

Markers of Bone Turnover in Patients with Nephrolithiasis

M. KUCZERA, A. WIĘCEK, F. KOKOT

Department of Nephrology, Silesian University School of Medicine, Katowice, Poland

(Accepted May 30, 1997)

A total of 19 patients with active nephrolithiasis, 14 patients with non-active nephrolithiasis and 17 healthy subjects were examined under standardized intake of calcium, phosphorus, purine and protein. In patients with both active and non-active renal stone disease the following abnormalities were found: elevated plasma levels of PTH and osteocalcin, increased activity of the bone isozyme of alkaline phosphatase, low plasma levels of phosphate and increased urinary excretion of calcium and oxalic acid. These abnormalities were more marked in patients with active than non-active nephrolithiasis. No correlation was found between plasma PTH levels and parameters of bone turnover as well as calciuria and oxaluria. Results presented in this paper suggest that (a) Smith's criteria of active renal stone disease are of minor pathogenetic and therapeutic value and (b) patients with active nephrolithiasis differ from non-active renal stone formers by more elevated oxaluria and markers of bone turnover and more marked abnormalities in calcium-phosphate metabolism related parameters.

Introduction

Nephrolithiasis is one of the most frequent diseases of the urinary tract [1]. The pathogenesis of urinary stone formation seems to be multifactorial and is not fully clarified. The most important metabolic factors involved in renal lithogenesis are disturbances of the calcium-phosphate (Ca-P) metabolism [1, 2]. This fact explains the numerous reports on the role of Ca-P related hormones in the pathogenesis of nephrolithiasis [3, 4, 5, 6] and the role of PTH in bone metabolism in patients with active and non-active renal stone disease [7, 8, 9].

The present study aimed to answer the following question: do patients with active nephrolithiasis differ from those with non-active renal stone disease and healthy subjects with respect to PTH secretion and markers of bone turnover?

Material and methods

Two groups of patients with nephrolithiasis were examined. The first group consisted of 19 patients with active nephrolithiasis (8 females and 11 males, aged 42.9±2.2 years, mean±SEM), while the second group comprised 14 patients with non-active nephrolithiasis (7 females and 7 males, aged

VSP, Utrecht
Akadémiai Kiadó, Budapest

39.6±2.9 years). Active nephrolithiasis was diagnosed according to Smith's criteria [10]. The control group comprised 17 healthy persons (8 females and 9 males, aged 36.0±3.4 years). All investigations were done in patients receiving for 7 days a low-calcium (10 mmol), low-purine (100 mg) and low-protein (40 g) diet. On days 5 and 6 of the above-mentioned dietary regimen, urine was collected for the estimation of calcium, phosphate, magnesium, oxalic acid and creatinine (results of these parameters were calculated per 10 mmol of excreted creatinine). On day 7 blood samples were taken from fasting subjects for the estimation of alkaline phosphatase and its thermolabile bone fraction activity, plasma calcium, inorganic phosphates, PTH and osteocalcin. Then all subjects received an i.v. infusion of calcium gluconate during 4 hours (15 mg Ca/kg b.w. dissolved in 500 ml of 0.9% saline). After completion of the infusion blood samples were withdrawn again for the estimation of the above-mentioned parameters.

Serum and urine calcium concentrations were estimated by flame photometry [11]. Urinary magnesium was assessed colorimetrically, using the POCh kit (Gliwice – Poland). Total and the thermolabile fraction of alkaline phosphatase activity were estimated according to King and Armstrong [12], and urinary oxalic acid by a titration method [13]. Serum PTH and osteocalcin concentrations were estimated by radioimmunoassay [14]. All the other parameters were assessed by routine methods [12]. Results obtained in this study were evaluated statistically performing analysis of variance and the post-hoc Bonferoni and Student's *t*-tests.

Results

Urinary excretion of calcium and oxalate was significantly higher in patients with active nephrolithiasis than in controls. Calciuria was also significantly higher in active than non-active nephrolithiasis (Table 1). In contrast, urinary magnesium and phosphorus excretion was of the same magnitude in all examined groups.

Patients with active nephrolithiasis did not differ from those with non-active disease and from healthy subjects with respect to plasma calcium level both before and after i.v. calcium infusion (Table 2). In contrast, plasma inorganic phosphate level was significantly lower both in active and non-active stone formers than in controls.

Patients with both active and non-active nephrolithiasis showed significantly higher baseline plasma PTH levels than healthy subjects. Infusion of i.v. calcium was followed by a significant decline of plasma PTH level in all examined groups (Table 3). Serum osteocalcin concentrations were significantly higher in both groups of patients with nephrolithiasis than in control subjects.

Total activity of alkaline phosphatase was of similar magnitude in all examined groups. However, activity of its bone fraction was significantly higher in both groups of patients with nephrolithiasis than in controls. Finally,

Table 1

Urinary excretion of calcium (Ca), phosphate (P), magnesium (Mg) and oxalate, calculated per 10 mmol of creatinine in healthy subjects and in patients with active and non-active nephrolithiasis (means±SEM)

	Urinary excretion			
	Ca (mmol/10 mmol creatinine)	P (mmol/10 mmol creatinine)	Mg (mmol/10 mmol creatinine)	Oxalate (μmol/10 mmol creatinine)
Healthy subjects	2.11±0.17	15.9±0.81	1.74±0.18	181±16.5
Active nephrolithiasis	$^{***\ *}$ 4.59±0.40	18.2±1.45	1.77±0.16	** 301±42.2
Non-active nephrolithiasis	$^{+}$ 3.19±0.30	19.0±1.52	1.68±0.18	219±47.7

*** $p<0.001$, ** $p<0.01$ – significance of the difference between respective values obtained in healthy subjects and patients with active nephrolithiasis;
* $p<0.001$ – significance of the difference between patients with active and non-active nephrolithiasis;
$^{+}$ $p<0.05$ – significance of the difference between healthy subjects and patients with non-active nephrolithiasis

Table 2

Plasma levels of calcium (Ca) and inorganic phosphate (P) before (0′) and after (240′) i.v. calcium infusion in healthy subjects and patients with active and non-active nephrolithiasis (means±SEM)

	Ca (mmol/l)		P (mmol/l)	
	0′	240′	0′	240′
Healthy subjects	2.48±0.02	$^{+++}$ 3.04±0.05	1.21±0.03	$^{+++}$ 1.42±0.04
Active nephrolithiasis	2.49±0.02	$^{+++}$ 3.06±0.05	** 1.08±0.03	$^{*\ +++}$ 1.29±0.05
Non-active nephrolithiasis	2.50±0.02	$^{+++}$ 3.18±0.05	$^{+}$ 1.07±0.05	$^{+++}$ 1.36±0.06

** $p<0.01$, * $p<0.05$ – significance of the difference between respective values obtained in healthy subjects and patients with active nephrolithiasis;
$^{+}$ $p<0.05$ – significance of the difference between healthy subjects and patients with non-active nephrolithiasis;
$^{+++}$ $p<0.001$ – significance of the difference between results obtained at time points 0′ and 240′

Table 3
Plasma levels of PTH and osteocalcin and activity of alkaline phosphatase (A.P.) and its bone fraction (B.F.) before (0′) and after (240′) i.v. calcium infusion in healthy subjects and patients with active and non-active nephrolithiasis (means±SEM)

	PTH (ng/ml)		Osteocalcin (ng/ml)		A.P. (nmol/l/s)	
	0′	240′	0′	240′	Total	B.F.
Healthy subjects	0.43±0.05	+++ 0.24±0.03	12.6±2.04	13.2±2.28	708±52	278±24
Active nephrolithiasis	*** 0.74±0.06	*** +++ 0.47±0.04	*** 44.4±6.24	*** 42.6±5.88	838±46	*** 452±30
Non-active nephrolithiasis	** 0.63±0.06	** +++ 0.41±0.04	+ 27.5±5.41	*** 38.1±4.82	713±55	+ 362±26

*** $p<0.001$ – significance of the difference between respective values obtained in healthy subjects and patients with active nephrolithiasis;
+ $p<0.05$ – significance of the difference between patients with active and non-active nephrolithiasis;
*** $p<0.001$, ** $p<0.01$, + $p<0.05$ – significance of the difference between healthy subjects and patients with non-active nephrolithiasis;
+++ $p<0.001$ – significance of the difference between results obtained at time points 0′ and 240′

a significantly higher activity of the bone fraction of alkaline phosphatase was found in patients with active than in those with non-active nephrolithiasis (Table 3).

In all examined groups there were no significant correlations between plasma PTH and osteocalcin concentration, between PTH and activity of alkaline phosphatase as well as between PTH and urinary calcium secretion.

Discussion

As shown in this study, patients with both active and non-active renal stone disease showed marked abnormalities in the Ca-P metabolism (elevated plasma levels of PTH and osteocalcin, elevated bone fraction of alkaline phosphatase, elevated calciuria) and higher excretion of oxalic acid as compared with controls. In addition, abnormalities of parameters related to Ca-P metabolism and oxaluria were more marked in patients with active than in those with non-active nephrolithiasis. These results seem to indicate that Smith's diagnostic criteria for active renal stone disease are only of relative value, since similar metabolic abnormalities were present in both groups of renal stone formers.

The question arises: what is the reason of the metabolic abnormalities found in patients with nephrolithiasis? As increased urinary excretion of calcium was found in both groups of patients with nephrolithiasis, it seems likely that primary defect in renal calcium conservation is the *primum movens* of stone formation. In turn, elevated calcium loss in urine could be the triggering mechanism for elevated PTH secretion. PTH by stimulating osteoclasts, and secondarily osteoblasts, can contribute to bone calcium mobilization and in-

creased urinary calcium excretion [15, 16]. Although results obtained in this and other studies [2, 7, 8, 9] seem to confirm the above suggested chain of biological events, they do not answer the question, whether abnormalities in renal Ca-P handling in patients with nephrolithiasis are consequences of an intrinsic renal defect or a secondary product of primarily extrarenal metabolic abnormalities. As calciuria and oxaluria were not significantly related to either plasma PTH level or osteoblast activity related parameters, participation of factors other than PTH in the pathogenesis of nephrolithiasis seems to be likely. This statement seems to be supported by results reported in many studies [3, 4, 8, 9, 17, 18].

Conclusions

1. Patients with nephrolithiasis are characterized by elevated plasma levels of PTH and osteocalcin, elevated activity of the bone isozyme of alkaline phosphatase, lower phosphataemia and increased urinary excretion of calcium and oxalic acid.

2. These metabolic abnormalities are more marked in patients with active than with non-active renal stone disease.

3. Smith's criteria of active nephrolithiasis seem to be of limited pathogenetic and diagnostic value.

References

1. Smith, L. H.: The pathophysiology and medical treatment of urolithiasis. *Semin. Nephrol., 10,* 31 (1990).
2. Kiersztejn, M., Kuczera, M., Kokot, F.: Selected biochemical parameters in patients with active nephrolithiasis. *Acta Med. Pol., 27,* 77 (1986).
3. Filipponi, P., Mannarelli, C., Gubbiotti, G., Blass, A., Moretti, I., Tini, S., Giuseppetti, N., Ballanti, S., Morucci, P.: The effects of calcitonin on idiopathic nephrolithiasis. Evidence of bone involvement in fasting hypercalciuria. *J. Endocrinol. Invest., 11,* 509 (1988).
4. Kuczera, M., Kiersztejn, M., Kokot, F.: Endokrine Veränderungen bei Kranken mit aktiver Nierensteinkrankheit. *Nieren- u. Hochdruckkrank., 22,* 13 (1993).
5. Buckhardt, P., Jaeger, P.: Secondary hyperparathyroidism in idiopathic renal hypercalciuria: Fact or theory? *J. Clin. Endocrinol. Metab., 53,* 550 (1981).
6. Halabe, A., Sutton, R. A. L.: Primary hyperparathyroidism and idiopathic hypercalciuria. *Mineral Electrolyte Metab., 13,* 278 (1987).
7. Barkin, J., Wilson, D. R., Manuel, M. A., Bayley, A., Murray, T., Harrison, J.: Bone mineral content in idiopathic calcium nephrolithiasis. *Mineral Electrolyte Metab., 11,* 19 (1985).
8. Bataille, P., Achard, J. M., Fournier, A., Boudailliez, B., Westeel, P. F., El Esper, N., Bergor, C., Jans, I., Lalau, J. D., Petit, J., Henon, G., Laval-Jeantet, M. A., Bouillon, R., Sebert, J. L.: Diet, vitamin D and vertebral mineral density in hypercalciuric calcium stone formers. *Kidney Int., 39,* 1193 (1991).
9. Sutton, R. A. L., Waler, V. L.: Bone resorption and hypercalciuria in calcium stone formers. *Metabolism, 35,* 485 (1986).
10. Smith, L. H.: Calcium containing renal stones. *Kidney Int., 13,* 383 (1978).
11. Homolka, J.: Biochemical Diagnosis. PZWL, Warszawa 1961.

12. Kokot, F.: Methods of Laboratory Tests in Clinical Medicine. PZWL, Warszawa 1969.
13. Dick, M.: Simplified urinary oxalate method. *Proc. Ass. Clin. Biochem.*, 180 (1967).
14. Kokot, F., Stupnicki, R.: Radioimmunological and Radiocompetitive Methods in Clinical Medicine. PZWL, Warszawa 1985.
15. Parfitt, A. M.: Bone and plasma calcium homeostasis. *Bone, 8,* S1 (1987).
16. Epstein, S.: Serum and urinary markers of bone remodeling: Assessment of bone turnover. *Endocrinol. Rev., 9,* 437 (1988).
17. Menon, M.: Calcium oxalate lithiasis. In: Rajfer, J. (ed.): Urologic Endocrinology. W. B. Saunders Company, Philadelphia 1986.
18. Kuczera, M., Kiersztejn, M., Kokot, F., Klin, M.: Secretion of sex hormones and gonadotropins in male patients with active nephrolithiasis. *Endokrynol. Pol., 44,* 539 (1993).