Occurrence of Mixed-Type Hypercalciuria in Stone Formers

A.	Ariel	Sánchez
A.	Adriana	González
H.	Héctor	Sarano
H.	Hugo	Palou
J.J.	Juan J.	Premoli
A.	Alejandro	Dotta
M.C.	María C.	Vidal
R.C.	Rodolfo C.	Puche

Grupo Estudio Litiasis y Departamento de Ciencias Fisiológicas, Facultad de Medicina, Universidad Nacional de Rosario, Santa Fe, Argentina

Dr. A Sánchez, Urquiza 1358, 2000 Rosario, Santa Fe (Argentina)

Dear Sir,

We have recently begun to determine ionized serum calcium concentration in stone-forming patients with idiopathic hypercalciuria. We were surprised to find low fasting Ca^{++} in 5 of 9 patients classified as having absorptive hypercalciuria, according to a clinical protocol that included 24-hour urinary calcium following high-and low-calcium diets, an acute oral calcium load with measurement of the urinary calcium/creatinine ratio before and after the load [1] and serum parathyroid hormone (PTH).

Four of those patients plus 4 additional patients with tubular hypercalciuria and 9 control subjects were placed on 400 mg (10 mmol/day) of dietary calcium for 7 days. In the morning of the 8th day, in the fasting state and during mild water-induced diuresis (50–120 ml/h), total [2] and ionized serum calcium (Orion flow-through electrode), phosphate, sodium and creatinine were measured. The same determinations plus cyclic adenosine monophosphate (cAMP) and citrate were carried out in two 1-hour urine samples. For the calculation of the tubular reabsorption of calcium, ionized serum calcium was employed as an estimate of ultrafilterable calcium.

All subjects had normal blood pressure and normal PTH levels, measured with a commercial radioimmunoassay which recognizes the carboxyl terminus of the molecule. The results obtained are shown in table I.

Following dietary calcium restriction and a 12-hour fast, these patients with absorptive hypercalciuria could not maintain their serum calcium levels; the ensuing parathyroid stimulus increased the urinary excretion of cAMP and citrate and decreased the tubular reabsorption of phosphate. Such a stimulus, however, failed to increase calcemia and the tubular reabsorption of calcium. We are not aware of the existence of similar observations in the literature.

The information obtained demonstrates that some patients classified as having absorptive hypercalciuria show features (low serum calcium, elevated cAMP) one would expect to find in patients with tubular hypercalciuria. If one admits that stone formation is a multivariate phenomenon and that there may be more than one type of disturbance in the tubular handling of

calcium (a recognized common feature of hypercalciuria, [4–12], it can be concluded that clinicians in this field should expect an as yet undetermined proportion of stone formers with ‘mixed-type’ hypercalciuria. We hope this letter will induce other investigators to communicate similar findings.

Table I. Serum and urine data of normal and hypercalciuric subjects after 1 week calcium restriction (10 mmol/day), 12 -hour fast and during mild water-induced diuresis, (mean $\pm$ SE)

Normal	AH	TH
controls	(n = 4)	(n = 4)
(n=9)		

a p < 0.05: normal vs. AH; b p < 0.05: AH vs. TH; c p < 0.01: normal vs. AH; d p < 0.001: normal vs. AH; e p < 0.001: AH vs. TH.

AH = Absorptive hypercalciuria; TH = tubular hypercalciuria; CCr = creatinine clearance; TRCa = tubular reabsorption of calcium; TRP = tubular reabsorption of phosphorus; cAMP = cyclic adenosine monophosphate.

326

Sánchez/González/Sarano/Palou/Premoli/Dotta/Vidal/Puche

References

- Pak, C.Y.C.; Kaplan, H.; Bone, H.; Townsend, J.; Waters, O.: A simple test for the diagnosis of absorptive, resorptive and renal hypercalciurias. *New Engl. J. Med.* 292:497–500 (1975).
- Willis, J.B.: Determination of calcium and magnesium in urine by atomic absorption spectroscopy. *Analyt. Chem.* 33:556–559 (1961).
- Gilman, A.J.: A protein binding assay for adenosine 3' :5'-cyclic monophosphate. *Proc. natn. Acad. Sci. USA* 67:305–312 (1970).
- Broadus, A.E.; Dominguez, M.; Bartter, F.C.: Pathophysiological studies in idiopathic hypercalciuria: use of an oral calcium tolerance test to characterize distinctive hypercalciuric subgroups. *J. clin. Endocr. Metab.* 47:751–758 (1978).
- Coe, F.L.; Favus, M.J.; Crockett, T.; Strauss, A.L.; Porat, J.H.; Gantt, C.L.; Sherwood, L.M.: Effects of low-calcium diet on urine calcium excretion, parathyroid function and serum 1,25-(OH)₂D₃ levels in patients with idiopathic hypercalciuria and in normal subjects. *Am. J. Med.* 72:25–32 (1982).
- Muldowney, F.P.; Freaney, R.; Ryan, J.G.: The pathogenesis of idiopathic hypercalciuria: evidence for renal tubular calcium leak. *Q. J. Med.* 793:87–94 (1980).
- Pak, C.Y.C.; Galosy, R.A.: Fasting urinary calcium and adenosine 3'-5'-monophosphate: discriminant analysis for the identification of renal and absorptive hypercalciurias. *J. clin. Endocr. Metab.* 48:260–265 (1979).

Peacock, M.; Knowles, F.; Nordin, B.E.C.: Effect of calcium administration and deprivation on serum and urine calcium in stone-forming and control subjects. *Br. med. J.* 729–731 (1968).

Sutton, R.A.L.; Walker, V.R.: Responses to hydrochlorothiazide and acetazolamide in patients with calcium stones. *New Engl. J. Med.* 302:709–713 (1980).

Broadus, A.E.; Insogna, K.L.; Lang, R.; Mallette, L.E.; Oren, D.A.; Gertner, J.M.; Kliger, A.S.; Ellison, A.F.: A consideration of the hormonal basis and phosphate leak hypothesis of absorptive hypercalciuria. *J. clin. Endocr. Metab.* 55:161–169 (1984).

Ulmann, A.; Aubert, J.; Bordeau, A.; Cheynel, C.; Bader, C.: Effects of weight and glucose ingestion on urine calcium and phosphate excretion: implications for calcium urolithiasis. *J. clin. Endocr. Metab.* 54:1063–1068 (1982).

Mautalen, C.A.; Casco, C.; Massironi, C.; Repetto, L.: Estudios sobre la fisiopatología de la hipercalciuria idiopática. *Revta. ib.-am. Invest. clin.* 3:101–109 (1984).