REVISTA ESPAÑOLA DE FISIOLOGIA, 35, 311-316, 1979

Different Types of Hypercalciuria in Patients with Renal Lithiasis and Evidence of the Calcium Renal Waste

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(Received on September 7, 1978)

B. PINTO and F. J. RUIZ-MARCELLAN. *Different Types of Hypercalciuria in Patients with Renal Lithiasis and Evidence of the Calcium Renal Waste.* Rev. esp. Fisiol, 35, 311-316. 1979.

A study of normal subjects and patients with hypercalciuria and recurrent renal stones has identified three main types of hypercalciuria: complex, absorptive and renal. Complex hypercalciuria is a combination of absorption, renal leak and resorption factors. Absorption and renal leak were examined by means of a ^{45}Ca test. Resorption is defined as an increase of the urinary calcium : creatinine ratio while the subjects are being maintained on an intake of 400 mg of calcium per 24 h.

The presence of hypercalciuria in patients who form renal stones is an old observation (6); however, reports vary as to its prevalence (7, 9, 10). In studying 420 stoneforming patients, we found hypercalciuria present in 43.3 % (16).

The definition of hypercalciuria appears to depend partly on the population investigated (16). In patients from Catalonia, in northeastern Spain, a 250 mg/24 hr urinary calcium excretion was the upper limit of normal when their intake of calcium was 900 to 1,000 mg/24 hr (16).

For many years primary hypercalciuria had been classified as either absorptive or resorptive, depending on whether its origin was from intestine or bone (11, 12). PAK (14) has described a third type, one of renal origin. However, the findings of PEACOCK and NORDIN (15) do not appear to support the presence of renal leak as a cause for primary hypercalciuria.

This present report outlines evidence of the presence of different types of hypercalciuria (absorptive, renal and complex) and emphasizes the existence of renal leak as a cause of hypercalciuria in some formers of renal stones.

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Materials and Methods

This study of hypercalciuria and its classification into different types involved two phases: 1) a study to select normal controls and to detect hypercalciuria in recurrent stone-formers, and 2) an attempt to classify hypercalciuria into different types.

Phase 1. The participants selected as a result of the first phase were 25 normal subjects without hypercalciuria and 59 patients who recurrently formed oxalate-phosphate stones. To determine that the controls and patients were appropriate subjects, examinations were performed on blood and 24-hr urine samples for concentrations of calcium, magnesium, phosphate, uric acid, and creatinine. Twenty-four-hour urinary oxalate values were determined. Phosphate, uric acid, and creatinine clearances were measured. Titratable acid, pH and ammonia were determined from 2-hr urine samples.

Blood samples were drawn in the morning after the subjects had fasted for 8 hr. All subjects received a diet containing 900 to 1,000 mg of calcium per 24 hr throughout this phase. The presence of hypercalciuria was confirmed with three separated 24-hr determinations. All of the hypercalciuric patients in this study were free of other defects, such as hyperoxaluria, hyperuricosuria or hypercalcemia. Patients possessing any sign of hyperparathyroidism (besides hypercalciuria) were excluded from this study.

Phase 2. In this 12-day study of hypercalciuria, the normal subjects and hypercalciuric patients were maintained on a diet containing 400 mg of calcium/24 hr. On the 5th day, after the subjects had fasted for 10 hr, 4-hr urine samples were collected; calcium, magnesium, and creatinine were measured; and calcium:magnesium, and calcium:creatinine ratios were performed. Also on the 5th day, 250 mg of calcium chloride containing 25 μCi of ^{45}Ca was orally administered to each subject. At 1, 2 and 3 hr after receiving the radioactive dose, the participants drank 200 ml of distilled water. Urine was collected during the 4 hr after ^{45}Ca administration. Blood plasma (heparinized) was also obtained on the 4th hr. In these 4 hr blood and urine samples, creatinine was determined as well as the calcium and creatinine clearances. Twenty-four-hour urine collections were then continued for 7 additional days. Radioactivity was counted on all blood and urine samples. Additionally, parathyroid hormone (PTH) concentrations were measured in all subjects.

Procedures. Radioactivity in blood plasma samples was counted by placing 1 ml of plasma in vials containing 10 ml of solubilizer liquid counting phase combining system for liquid counting of radioactive samples (PCS). Urine samples of 0.5 ml were counted in a mixture of 2,5-diphenyl oxazole (PPO), 1.4-bis-(2-5-phenyloxazolyl) benzene (POPOP), toluene, and ethanol in a ratio of 0.2:0.02:60:40. Sample quenching was corrected by using an internal standard. Oxalate in urine was determined by gas chromatography (3). Calcium and magnesium were measured by atomic absorption procedure (18). Uric acid was quantified with uricase (8). Creatinine was determined by the TAUSSKY method (17) and phosphate by the FISKE and SUBBAROW procedure (5). Urinary ammonia was measured by the Berthelot reaction (2), and plasma parathormone levels were determined radioimmunologically (1).

Reagents. ^{45}Ca as calcium chloride with a specific activity of 150 μCi per ml, PPO, POPOP; and PCS (sheet KP/ld, 11/1/71) were purchased from Amersham Radiochemical Centre (England). Bovine parathormone and its antibody at a 1/500 titer was bought from Inolex, Chicago

(U.S.A.). The remaining reagents were of the highest purity commercially available.

Apparatus. Spectrophotometric readings were performed with a U.V.-visible (Hitachi-Perkin Elmer, model 139) spectrophotometer. Radioactivity was counted in a liquid scintillation counter (Nuclear Chicago, model Isocap-300). Cation determinations were performed with a Perkin Elmer atomic absorption spectrophotometer (model 360). Gas chromatography was performed with a 3850 A Hewlett-Packard gas chromatograph apparatus connected to a model 18850 A terminal. Samples were centrifuged in a Sorvall refrigerated unit (model RC-2B).

Validity of Radiocalcium Clearance. The validity of the radioisotope-labeled-calcium clearance procedure, performed as described in Phase 2, was investigated. After a 10 hr fast the subjects intravenously received 240 ml of saline containing 25 μCi ^{45}Ca at the rate of 1 ml/min. At 30, 90, 150 and 210 min, blood samples were taken. Urine was collected at 1, 2, 3 and 4 hr. Radioactivity in the samples was counted as described in the Procedures section. This experiment was performed in five normal subjects and also in two patients with absorptive and three with excretive or renal hypercalciuria.

Results

Validity of Clearance Procedure. Good correlation was found between the clearances of ^{45}Ca that had been infused at a constant rate and excretion of the ^{45}Ca that had been orally administered ($r = 0.98$) (table I).

Normal Subjects. The normal subjects (12 men and 13 women) ranged in age from 23 to 52 years (mean, 44.36 ± 15.70). The urinary calcium of the 25 normal subjects varied from 96 to 241 mg/24 hr.

Table I. *Validity of the radiocalcium clearance test.*

The radiocalcium clearances were performed on five controls and five hypercalciuric patients as described in Methods.

ml/minute/1.73 m²	
Constant ^{45}Ca infusion	4-h oral dose
Control	
0.31 ± 0.10	0.28
0.76 ± 0.19	0.98
0.72 ± 0.09	0.87
0.66 ± 0.21	0.85
0.83 ± 0.08	0.81
Absorptive hypercalciuria	
0.21 ± 0.04	0.10
0.48 ± 0.12	0.59
Renal or excretive hypercalciuria	
3.01 ± 0.13	2.87
2.15 ± 0.20	2.08
1.56 ± 0.11	1.37

When the subjects were maintained on a 400 mg/24 hr calcium intake, the urinary calcium:creatinine ratio ranged from 0.04 to 0.12.

The percentage of urinary radioactivity excreted during the 7 days of urine collections after the oral dose of ^{45}Ca varied from 1.38 to 4.98 per cent. The radiocalcium clearance varied from 0.28 to 0.98 ml/min 1.73 m². Parathyroid hormone concentrations varied from 0.09 to 0.80 ng/ml (table II). There was no correlation between calciuria and the urinary calcium: creatinine ratio ($r = 0.53$), the 7-day urinary excretion of ^{45}Ca ($r = 0.12$), of the radiocalcium clearance ($r = 0.23$).

Definition of Types of Hypercalciuria in Patients. While the patients were receiving a diet containing 900-1,000 mg calcium per day, if their urinary calcium excretion was greater than 250 mg/24 hr, they were considered to have hypercalciuria (10).

Absorptive hypercalciuria was defined

as the urinary excretion during the 7-day collection period of more than 5 % of the radioactivity from the oral dose of ^{45}Ca.

Resorptive hypercalciuria was defined as an increase of the urinary calcium creatinine ratio of greater than 0.12, when the subjects were maintained on the diet containing 400 mg calcium/day for at least 5 days. This definition was derived from a similar one established by NORDIN *et al.* (13).

An increase in the radiocalcium clearance of greater than 1 ml/min/1.73 m^2 was considered to be excretive, or renal leak, hypercalciuria.

The foregoing definitions and limitations were derived from the study of the group of normal subjects.

All of the patients had normal values of serum magnesium, phosphate and calcium and of urinary phosphate and oxalate and creatinine clearances.

Absorptive hypercalciuria. The patients with absorptive hypercalciuria comprised 10 patients (five men and five women), whose ages ranged from 21 to 52 years (mean, 42.71 ± 17.90). Their mean 24 hr urinary calcium values were increased. The length of time that they had formed renal stones ranged from 2 to 25 years (mean, 9.5 ± 7.78). The mean number of stones formed was 14.9 ± 9.76, and the mean of the urinary calcium:creatinine ratio was normal. The percentage of radioactivity excreted 7 days after the oral dose was increased. The mean values of the radiocalcium clearance were within the normal range. Parathyroid hormone levels were normal (table II).

Renal or Excretive hypercalciuria. This group comprised six patients (one woman and five men). Their ages ranged from 30 to 52 years mean 44.16 ± 12.72. The main finding was an increase of the radiocalcium clearance (range 1.37 to 2.87 ml/min/1.73 m^2. Other findings were hypercalciuria varying from 290 to 366 mg/24 hr. The duration of their disease ranged from 2 to 18 years (mean, 7 ± 6). The number of stones formed varied from 5 to 70 (mean 17.5 ± 23.7). The urinary calcium: creatinine ratio was normal. The mean

Table II. *Results of the Calciuria Study.*
Mean values of the different groups of subjects.

Type of subjects	N	Urinary calcium mg/24 h	Urinary calcium/ Creatinine ratio	7-day excretion of urinay ^{45}Ca %	Radiocalcium clearance ml/min/1.73 m^2	PTH ng/ml
Control	25	171.7±48.7	0.085±0.02	3.46±0.82	0.75±0.17	0.46±0.24
Absorptive hypercalciuria	10	310.3±36.8	0.083±0.02	15.55±10.25*	0.67±0.21	0.42±0.25
Renal or excretive hypercalciuria	6	317.3±23.5	0.093±0.01	2.23±0.73	1.88±0.52*	0.22±0.11
Complex hypercalciuria						
a) Absorptive plus renal	10	307.4±33.1	0.10±0.02	11.75±6.52	1.44±0.18	0.41±0.24
b) Resorptive plus absorptive	10	302.1±41.3	0.20±0.08	18.20±14.56	0.78±0.19	0.34±0.22
c) Resorptive plus renal	8	305.3±29.1	0.26±0.08	2.99±0.95	1.99±0.60	0.40±0.13
d) Resorptive plus absorptive and renal	15	303.5±54.4	0.24±0.12	17.52±13.81	1.54±0.55	0.41±0.18

* $p < 0.0001$.

value of radioactivity excreted in the urine during 7 days were within the normal range (table II). Parathyroid hormone levels were normal.

Complex or Mixed hypercalciuria. Forty-two of the patients studied had a complex, or mixed, form of hypercalciuria, which can be subgrouped into four distinct subgroups.

Patients 42 to 51 (five men and five women; age range, 24 to 52 years, mean 43.7) may be considered as having mixed absorptive and renal defects. In these patients the most significant finding was the increase in excretion of the urinary radioactivity during the 7 days after the oral dose of ^{45}Ca (range 8.33 to 30.90). The mean of the radiocalcium clearances was increased (range, 1.10 to 1.74 ml/min/1.73 m^2).

The hypercalciuria in patients 52 to 61 (four men and six women; age range, 20 to 54 years; mean, 42.1) was a resorptive and absorptive form. The mean urinary calcium:creatinine ratio was increased (range, 0.13 to 0.40). The mean of the 7-day urinary ^{45}Ca excretion was also increased (range, 5.51 to 53.36 %).

Patients 62 to 69 (five men and three women; age range 26 to 51 years; mean, 43.1) were affected by resorption plus renal defects. In this subgroup the mean urinary calcium:creatinine ratio was elevated (range, 0.16 to 0.40). The radiocalcium clearance was markedly increased.

Patients 70 to 84 (nine men and six women; age range, 22 to 55 years; mean, 42.9) were affected by resorption, absorption, and excretion defects (table II).

The PTH values of the patients with complex hypercalciuria were normal.

Discussion

This study was designed in an attempt to clarify some of the diverse findings and opinions of the investigators in the field of renal lithiasis, and specially to answer some of the questions related to the origin of hypercalciuria.

The results show that although absorptive and renal or excretive hypercalciuria appears to be two separate causal factors in the hypercalciuria associated with renal lithiasis, the resorptive or bone origin of hypercalciuria could not be identified as the sole factor in this disorder. However, the bone involvement, shown by the increase of the urinary calcium:creatinine ratio, seems to occur in primary hypercalciuria of renal lithiasis when associated with the other types.

Renal involvement appears to be a mechanism of hypercalciuria in some stone formers. The exact mechanism of the calcium renal leak is still unknown, but the presence of renal hypercalciuria contradicts the findings of PEACOCK and NORDIN (15) and confirms previous suggestions indicating renal involvement (4). Although PEACOCK and NORDIN did not find any differences between the normal and hypercalciuric subjects, their conclusions were based on the experiments performed on 11 stone formers. Of these 11, only 8 were hypercalciuric, according to the standards of these investigators. Furthermore, one of the normal subjects was hypercalciuric. These experiments were performed by intravenously administering a calcium solution at the rate of 200 mg per hr. During these experiments the urinary flow was at least 3 ml per min. No indications of the volume expansion were given.

Although several tests have been described in the literature to investigate intestinal absorption of calcium, the procedure described in the present report has the advantage of having investigated the intestinal, bone and renal factors in one test. Although the urinary calcium:creatinine ratio appears to be a good test to investigate the state of bone, the ratio approach had no advantage when used to define the intestinal absorption by examin-

ing the relationship between the urinary 24 hr and fasting calcium:creatinine ratio (11). The absence of radioactive calcium diminished the sensitivity of the test.

The greater number of patients with complex hypercalciuria, as compared with those having the absorptive or renal form suggests two possibilities: either the simple types transform into the complex type, or simply the complex type of hypercalciuria is more prevalent as such. We suggest that the first possibility is the case, because of the large numbers of patients possessing absorptive plus excretive, resorptive plus absorptive and resorptive plus excretive hypercalciuria. However, to establish this possibility further investigation is needed.

Acknowledgement

We are indebted to Dr. F. SOLÉ-BALCELLS, head of this Division, for his help and patronage.

Resumen

Del estudio de individuos normales y litiásicos recidivantes, con hipercalciuria, se identificaron tres tipos fundamentales de hipercalciuria: absortiva, renal y mixta.

La hipercalciuria mixta es una mezcla de los factores absortivo, renal y resortivo. La absorción y la pérdida renal de calcio fueron investigados con Ca^{45}. La resorción viene definida por el aumento del cociente cálcico: creatinina urinario, mientras que los individuos fueron mantenidos en una ingesta de 400 mg de calcio y día.

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