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Strontium absorption and excretion in normocalciuric subjects: relation to calcium metabolism

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The relationships of Sr intestinal absorption and renal excretion with biohumoral factors regulating Ca metabolism were studied in 47 normocalciuric subjects with Ca kidney stones. Sr concentrations were measured in serum and urine after an oral load of stable Sr (30.2 μmol/kg body wt). Enteral absorption of the ion (9.77 ± 0.438 mmol · L^{-1} · min, 240 min after Sr administration), expressed as the area under the plasma concentration–time curve (AUC), and renal clearance (CR_E) in these subjects during the test (2.80 ± 0.336 mL/min) were not different from values for 27 controls. CR_E was not correlated with AUCs. Plasma concentrations of parathyroid hormone (PTH) negatively correlated with AUCs (P <0.01) and correlated with CR_E after one outlier was excluded (P <0.05). Plasma concentrations of 1,25-dihydroxyvitamin D correlated positively with AUCs (P <0.01) when normalized to the plasma concentration of PTH. Multiple stepwise regression showed that PTH and phosphatemia were significantly related to AUC values at 240 min (P <0.01). These findings suggest that Sr absorption and excretion reflect the regulation of Ca metabolism, but some differences in renal handling of the two ions may exist.

Strontium is a bivalent ion, present in human fluids as a trace element and taking no part in the biological cycle *[1, 2]*. The transport of Sr ions through enteral and renal tubular cells is mediated by the same membrane carriers as used for calcium, and a highly significant correlation has been observed between Sr and Ca absorption *[2–6]*. Therefore, the oral administration of stable Sr is considered suitable for assessing Ca absorption and excretion in clinical practice *[1, 3, 7–10]*. According to the proposed tests, stable Sr is administered orally and ion concentrations are determined in serum 240 min after the oral load. Results of the absorption test at 240 min are the most representative of Sr bioavailability *[10]*, whereas those obtained during the first hour depend more on duodenal and jejunal absorption efficiency *[1, 9]*. Studies comparing Sr and Ca handling in humans showed that Sr ions are less absorbed in intestine than Ca, but are more quickly excreted in urine and in enteral lumen with digestive secretions *[4–6]*. These findings could be attributed to a lower cellular carrier affinity for Sr, which favors Ca transport to blood *[11, 12]*. Renal clearance represents 50–60% of the total body ion clearance *[13]*; its values show that Sr ions are extensively reabsorbed by the renal tubule *[1–6]*.

The biohumoral factors regulating Sr handling have not been extensively investigated, although they are generally assumed to be similar to those regulating Ca metabolism. The available data show that Sr absorption is increased by therapeutic administration of 1,25-dihydroxyvitamin D or renal activation of 25-hydroxyvitamin D-1α-hydroxylase *[14, 15]*. To investigate biohumoral factors regulating Sr handling, we analyzed the relationships of Sr absorption and renal clearance with the indices of Ca metabolism in a group of normocalciuric subjects with idiopathic Ca nephrolithiasis and normal kidney function. In these subjects, plasma and urine concentrations of Ca and phosphate were within the respective reference intervals, as were their secretions of calciotropic hormones *[16, 17]*.

Subjects and Methods

SUBJECTS

Forty-seven normocalciuric patients (29 men and 18 women, weights 69.7 ± 1.67 kg, ages 44 ± 2.0 years) with

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Ca-oxalate nephrolithiasis participated in the study. They were free of other diseases, and their 24-h Ca excretion was <7.5 mmol in the men or <6.25 mmol in the women and <0.1 mmol/kg of body weight for both sexes; their plasma Ca and creatinine concentrations were within the respective reference intervals. All patients consumed dairy products in their diet and took ~25 mmol of Ca per day. None took drugs. Four women were postmenopausal (ages 56–65 years). The Sr absorption test was also carried out in 27 age- and sex-matched healthy volunteers (ages 40 ± 2.1 years, 15 men and 12 women, 3 of whom were postmenopausal). None of the patients or controls had voiding difficulties.

All gave informed consent to the study, which was approved by San Raffaele's Hospital Ethical Committee.

EXPERIMENTAL PROTOCOL

A Sr oral load test was performed after overnight fasting. Sr was administered to patients at 30.2 μmol/kg body wt (2.65 mg/kg), in water solution [11.4 mmol/L (1 g/L)] as the chloride salt (obtained from BDH). Blood samples were drawn before and at 30, 60, and 240 min after Sr administration. Urine was also collected during the test.

Within-subject reproducibility of plasma Sr, including analytical and biological variability, had been previously calculated as the CV *[18]*:

$$CV(\%) = 100 \cdot \frac{\sqrt{\frac{1}{2n}\sum(x_i - y_i)^2}}{\frac{\sum(x_i + y_i)}{2n}} \quad (1)$$

where x_i and y_i are the values of the repeated measurements in the ith subject and n is the number of subjects. The CV for the area under the concentration–time curve (AUC)[5] was 20.6%, 20.0%, and 11.8%, respectively, after 30, 60, and 240 min in 15 subjects who submitted to the test twice. The CV of Sr urine excretion was calculated in 6 subjects and was 33.4%.

ASSAYS

Calcium, phosphate, creatinine, and sodium were measured in plasma and 24-h urine. Intact parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D in plasma were determined respectively by an IRMA and a radioreceptor assay (both from Nichols Institute). 1,25-Dihydroxyvitamin D was determined in 36 of 47 patients.

The Sr concentration was measured by atomic absorption spectrophotometry at 460.7 nm (Perkin-Elmer 4000) with use of an acetylene–air flame in 10-fold-diluted serum and 50-fold-diluted urine with 20 g/L lanthanum (BDH) and 100 mL/L hydrochloric acid as the diluent.

Bone mineral density (BMD) was assessed by dual-energy x-ray absorptiometry (Hologic QDR 1000) in 37 of the 47 stone formers (21 men and 16 women, 3 of whom were postmenopausal) at three femoral sites (neck, trochanter, Ward's triangle) and the L1–L4 lumbar spine vertebrae. The BMD values were expressed as the number of standard deviations from the mean of a Caucasian normal young population (*t*-score).

CALCULATIONS

Strontium absorption was calculated as the incremental (above baseline) serum AUC at 30, 60, and 240 min (AUC_{30}, AUC_{60}, AUC_{240}) determined by the trapezoid method and expressed as $mmol \cdot L^{-1} \cdot min$ *[14]*.

Renal excretion of Sr was quantified by assessing the fraction of administered Sr excreted in the urine (FE) and the Sr renal clearance (CR_E). FE was calculated as follows:

$$FE(\%) = (q_{E240}/D) \cdot 100 \quad (2)$$

where q_{E240} is the amount of Sr (above baseline) measured in the urine at the end of the test and D is the orally administered dose of Sr. Because the urinary excretion is the product of the renal clearance times the plasma concentration, CR_E was calculated as follows:

$$CR_E(mL/min) = q_{E240}/AUC_{240} \quad (3)$$

STATISTICAL ANALYSIS

Data are expressed in the text as mean ± SE. Statistical difference between the mean values were analyzed by Mann–Whitney's *U*-test. Simple linear correlations between variables were tested. Multiple stepwise regression was performed by assuming each of the AUC values as the dependent variable and age, Ca excretion, PTH, 1,25-dihydroxyvitamin D, CR_E, and plasma phosphate as independent variables. Multiple stepwise regression was also performed by assuming FE or CR_E as the dependent variable and age, Ca excretion, PTH, 1,25-dihydroxyvitamin D, AUC_{240}, and plasma phosphate as independent variables.

Results

All the patients showed reference interval values for PTH and electrolytes in plasma and urine (Table 1). BMD was measured in 37 of 47 stone formers, and 9 results indicated osteoporosis (*t*-score < -2.5, independent of measurement site).

The profile of mean plasma Sr concentration during the test is shown in Fig. 1: The values were greatest 240 min after the oral Sr load. The values of Sr absorption and renal excretion (Table 2) were not different from the control values. No significant differences were found between the men's and women's values: AUC_{240} was 10.56 ± 0.644 $mmol \cdot L^{-1} \cdot min$ in women and 9.29 ± 0.578 in men; CR_E was 2.7 ± 0.34 mL/min and 2.9 ± 0.48, respectively.

Neither AUCs, FE, nor CR_E correlated with Ca or

[5] Nonstandard abbreviations: AUC, area under the plasma Sr concentration–time curve; CR_E, **Sr renal clearance; FE, fractional urine excretion of the administered Sr; BMD, bone mineral density; PTH, parathyroid hormone.**

Table 1. Divalent ion metabolism indices in 47 normocalciuric stone formers.

	Ref. value	Mean ± SE measured in stone formers
Plasma		
Calcium, mmol/L	2.1–2.6	2.37 ± 0.011
Phosphate, mmol/L	0.8–1.55	1.13 ± 0.027
Parathyroid hormone, ng/L	10–65	33.6 ± 2.07
1,25-Dihydroxyvitamin D, ng/L[a]	25–70	47.8 ± 3.01
Urine		
Creatinine clearance, mL/min	70–140	91 ± 4.4
Calcium, mmol/24 h	M, 2–7.5 F, 1.8–6.25	
	Both sexes, <0.1 mmol/kg bw[c]	4.41 ± 0.168
Phosphate, mmol/24 h	10–35	26.28 ± 1.123
Sodium, mmol/24 h		151 ± 10.7
BMD[b] *t*-score		
L1–L4 lumbar spine		−1.18 ± 0.171
Upper total femur		−1.37 ± 0.133

[a] 1,25-Dihydroxyvitamin D was measured in 36 patients.
[b] Measured in 37 patients, normal when *t*-score was >−1.
[c] Body weight (bw) was 69.7 ± 1.67 kg.

phosphate excretions, Ca or phosphate plasma concentrations, and lumbar or femoral BMD.

Table 3 reports the results of the correlation analysis between the indices of Sr absorption, renal excretion, and calciotropic hormones. Sr FE positively correlated with AUC_{240}, but not with AUC_{30} and AUC_{60}. Sr CR_E showed no relation with absorption values. Plasma concentrations of PTH correlated negatively with AUC_{30} (Fig. 2; upper panel), AUC_{60}, and AUC_{240}, the correlation strength decreasing at 240 min. PTH values also correlated negatively

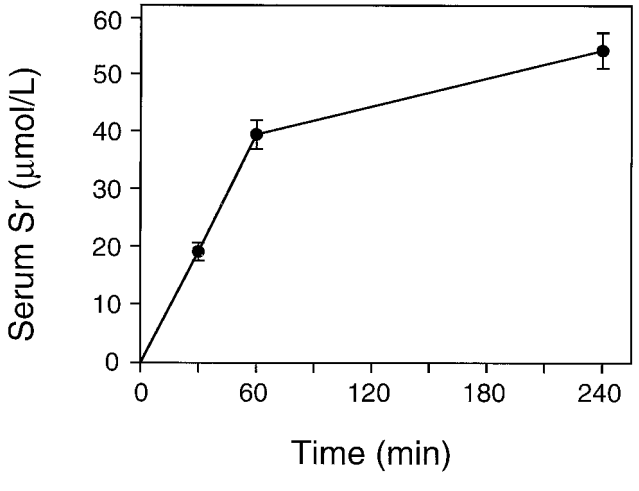

Fig. 1. Sr concentrations in serum measured 30, 60, and 240 min after an oral load of 30.2 μmol/kg body wt (2.65 mg/kg body wt; see *Methods*).

Table 2. Results of Sr oral load test.

	Stone formers	Controls
n	47	27
AUC_{30}, mmol · L^{-1} · min	0.33 ± 0.025	0.32 ± 0.041
AUC_{60}, mmol · L^{-1} · min	1.25 ± 0.073	0.98 ± 0.069
AUC_{240}, mmol · L^{-1} · min	9.77 ± 0.438	8.00 ± 0.460
FE, % of administered Sr	1.3 ± 0.14	1.5 ± 0.61
CR_E, mL/min	2.80 ± 0.336	3.15 ± 1.381

Results in controls and stone formers were not statistically different.

with Sr FE. The negative correlation between PTH and CR_E became significant when one outlier with very high clearance was excluded ($r = -0.346$, $P < 0.05$, n = 46; Fig. 2, lower panel). Plasma concentrations of 1,25-dihydroxyvitamin D, measured in 36 patients, had no relation with Sr AUCs and excretion; when normalized to the concentration of plasma PTH (picograms of 1,25-dihydroxyvitamin D per picogram of PTH), however, they correlated positively with AUC_{30} ($r = 0.425$, $P < 0.01$) and AUC_{60} ($r = 0.388$, $P < 0.05$).

Multiple stepwise regression showed that PTH was the only analyte significantly related to AUC_{30}, AUC_{60}, CR_E, and FE, whereas PTH and plasma phosphate were significantly related to AUC_{240} (cumulative $r^2 = 0.274$, $P < 0.01$).

Discussion

Strontium absorption and excretion were measured in a group of normocalciuric subjects with Ca kidney stones by an oral load of stable Sr. The Ca metabolism of these subjects was comparable with that of normal subjects *[16, 17]*. Accordingly, the values of Sr absorption and renal excretion obtained in our population were similar to those found or previously reported in healthy subjects *[1, 3, 7–11]*. We saw no clear influence of gender on Sr absorption; a lower body water content could sustain the slightly higher values of women in comparison with those in men.

We measured 4-h Sr excretion after an oral load to estimate the renal Sr clearance *[1–3]*. Renal clearance represents 50–60% of total body Sr clearance *[1–6, 13, 19]*; the other part of ion clearance is predominantly carried out by bone and digestive secretions, which become

Table 3. Correlation between Sr absorption or excretion indices and calciotropic hormones.

	AUC_{30}	AUC_{60}	AUC_{240}	FE	CR_E
FE	0.198	0.272	0.321[a]		0.788[b]
CR_E	−0.182	−0.164	−0.168	0.788[b]	
PTH	−0.426[b]	−0.419[b]	−0.357[a]	−0.447[b]	−0.328[a,c]
1,25-$(OH)_2$D	−0.028	−0.096	−0.218	−0.197	−0.171

[a] $P < 0.05$; [b] $P < 0.01$.
[c] n = 46: the significant correlation coefficient between CR_E and parathyroid hormone was obtained after exclusion of an outlier, as shown in Fig. 2 (lower panel); when this patient was not excluded, the correlation was not significant (n = 47, $r = -0.225$).
1,25-$(OH)_2$D, 1,25-dihydroxyvitamin D.

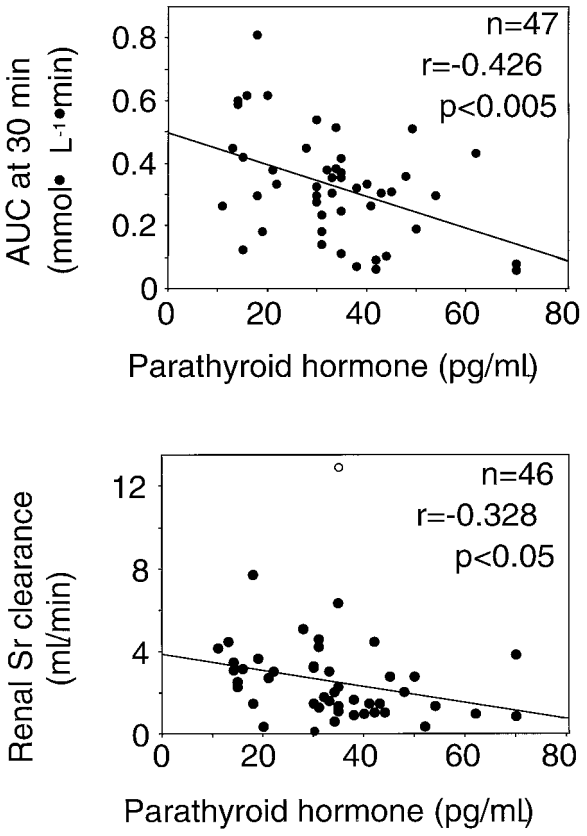

Fig. 2. Correlation of the plasma concentrations of PTH with Sr absorption at 30 min (*top*) and urine Sr clearance (*bottom*).

When a patient with abnormally high values of Sr clearance (○) was omitted, the correlation between plasma concentrations of PTH and Sr clearance became significant, yielding the regression line shown in the *lower panel*.

relevant later in the period of patient observation *[1–6, 13]*. Our findings did not show any correlation between renal Sr clearance and enteral absorption. Because Ca excretion is decreased by PTH activity on distal tubular cells, a negative correlation between renal Sr clearance and PTH plasma concentrations was expected, as for Ca. Conversely, renal Sr clearance and PTH plasma concentrations correlated weakly in our patients ($r = -0.328$), but only when one subject with a very high clearance value was excluded from the analysis. Difficulty in finding a strong correlation could be attributed to an imprecise estimate of Sr clearance, given the relative short period of urine collection (4 h). In addition, some differences in Ca and Sr tubular handling cannot be excluded. These ions could be reabsorbed by different mechanisms or handled differently by the same carriers. Because of the different carrier affinity, PTH stimulates Ca transport more than it does Sr; therefore, PTH could increase tubular discrimination between the ions *[5, 6]*, and its effect on Sr reabsorption could be too small to reveal a strong correlation.

PTH was the variable most significantly linked to enteral Sr absorption. The negative correlation between these two provides evidence of the interplay between parathyroid secretion and Ca absorption: Hormone secretion is inhibited in the subjects with high Ca and Sr absorption and stimulated when enteral ion absorption is low *[17]*. The relation is more evident in the early phases of absorption processes, when excretion, bone deposition, and other metabolic factors scarcely influence the plasma values of bivalent ions *[2, 4–6, 13]*.

Stepwise regression indicated that plasma phosphate variations significantly affect the last phases of Sr absorption during the test—in agreement with our knowledge that plasma phosphate negatively influences 1,25-dihydroxyvitamin D synthesis and consequently the enteral transport of Ca and Sr *[14, 15, 20]*.

Although 1,25-dihydroxyvitamin D is well known to increase Sr and Ca absorption *[14, 15, 17]*, its plasma concentrations do not correlate with either enteral absorption or urine excretion of Sr. Our results are similar to those previously observed, which showed a lack of correlation between 1,25-dihydroxyvitamin D and Ca absorption as assessed by radiocalcium in normal subjects *[21, 22]*. These findings suggest that plasma concentrations of 1,25-dihydroxyvitamin D may be insufficient indices of the hormone biological activity, given the complex interrelationships with the other variables *[20–23]*. When these interrelationships are taken into account by normalizing 1,25-dihydroxyvitamin D plasma values to PTH concentrations, their cooperative role in enhancing absorption of bivalent ions emerges *[23]*. The normalization to PTH was previously proposed as an index of 1,25-dihydroxyvitamin D production *[24]*.

In conclusion, this study of a normocalciuric population suggests that Sr absorption reflects the hormonal regulation of Ca absorption. Some differences in renal handling of the two ions are suggested by the weak correlation of renal Sr clearance with PTH and by the lack of relationship with Sr absorption and Ca excretion.

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