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Oral Calcium Tolerance Test and Serum Calcitonin in Calcium Stone Formers

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Summary. Ninety-seven male patients with idiopathic calcium urolithiasis and 17 normal male subjects were studied to evaluate the mechanism of idiopathic hypercalciuria with an oral calcium tolerance test, which has been useful in differentiating hypercalciuria. The changes in parathyroid function, such as parathormone and urinary cyclic AMP, and calcium after calcium load differed between absorptive hypercalciuria and renal hypercalciuria. We have confirmed that the change in serum calcitonin after calcium load was also different in these two hypercalciurias. The increase in serum calcium was sufficient to reduce parathyroid function but serum calcitonin was unchanged after calcium load in the control group, in patients with normocalciuria, and those with renal hypercalciuria. Although serum and urinary calcium were more elevated in absorptive hypercalciuria than in the other three groups, parathyroid function was not significantly reduced after loading in absorptive hypercalciuria. In this group only, the serum calcitonin was significantly elevated after calcium load. It is reasonable to suggest that, in this group, because parathyroid function is usually suppressed by intestinal hyperabsorption of calcium, parathyroid function may not be further suppressed by even calcium load. Possibly the significant stimulation of calcitonin may compensate for the lack of suppression of parathyroid function and maintain normal serum calcium levels in absorptive hypercalciuria. These results suggest that the change in serum calcitonin is also useful to differentiate abnormalities of calcium metabolism in patients with hypercalciuria.

Key words: Oral calcium tolerance test, Calcium, Parathyroid function, Calcitonin.

Introduction

The majority of stones in the upper urinary tract contain calcium; therefore, attention has been directed to the evaluation of calcium metabolism in urolithiasis. As urinary calcium excretion is raised in stone formers compared with controls [3] it is important to investigate the cause of this hypercalciuria for which the following mechanisms have been proposed:

1) A Primary increase in intestinal calcium absorption; absorptive hypercalciuria

2) A decrease in the renal tubular reabsorption of calcium; renal hypercalciuria, or

3) Normocalcaemic hyperparathyroidism; resorptive hypercalciuria [1, 8, 9].

Pak et al. [10] have described a simple oral calcium tolerance test which was useful in differentiating a large series of selected patients with well-documented metabolic abnormalities causing hypercalciuria. We have applied a modification of their method in the routine evaluation of a series of patients with calcium stones. The study was undertaken to ascertain the usefulness of the oral calcium tolerance test in classifying abnormalities of calcium metabolism in patients with calcium urolithiasis. Serum parathormone, cyclic AMP, calcitonin, serum ionised calcium, magnesium, sodium, uric acid and oxalate were also measured in order to identify differences between normal subjects, patients with normocalciuria, absorptive hypercalciuria and renal hypercalciuria.

Materials and Methods

Ninety-seven male patients aged 21 to 65 years with idiopathic calcium urolithiasis, and 17 healthy individuals aged 27 to 57 years without any history of renal stones or bone disease were studied. The stone formers were divided into two groups; a hypercalciuric group, consisting of 24 subjects who had an average 24 h urine calcium excretion greater than 280 mg, the upper limit (mean + 2 SD) obtained in the normal subjects, and a normocalciuric group consisting of the remaining 73 patients.

The hypercalciuric group was further divided into two sub-groups using criteria previously reported [5]. Absorptive hypercalciuria was confirmed in 20 patients, while a high fasting urinary calcium suggested renal hypercalciuria in four other patients. All were inpatients and had a creatinine clearance of more than 80 ml/min.

Oral Calcium Tolerance Test

Patients were maintained on a constant diet of known composition (daily content 200 mg of calcium, 100 mEq sodium, and 800 mg phosphorus) for 4 days. After an overnight fast from 9 p.m. (except for 300 ml of distilled water at 9 p.m.), a 2 h fasting urine sample was collected from 7 a.m. to 9 a.m. At 9 a.m. 1 g calcium was given orally with 300 ml of distilled water. Urine was collected in a 4 h pool from 9 a.m. to 1 p.m. To provide adequate urine flow, 300 ml of distilled water was given orally at 7 a.m. and 11 a.m. Venous blood was taken at 9 a.m. for calcium, ionised calcium, phosphate, magnesium, sodium, uric acid, creatinine, cyclic AMP, parathormone (PTH), and calcitonin. Urine volumes were measured, and a 10 ml specimen was frozen and stored for analysis of calcium, phosphate, magnesium, sodium, uric acid, creatinine, and oxalate.

Serum and urinary calcium were determined by OCPC colorimetric method, and serum ionised calcium anaerobically with Orion Biochemical ionised-calcium analyser, model SS-20. Serum phosphate was determined by Amador, phosphomolybdate method, and urinary phosphate by molybdenum blue method. Serum and urinary sodium were determined by ion-selective electrode method. Serum uric acid was determined by phosphotungstate method, and urinary uric acid by an enzymatic method (Uricase MEHA method). Serum and urinary creatinine were determined by Jaffe, alkaline picrate method. Serum and urinary magnesium were determined by atomic absorption spectrophotometry.

Urinary oxalate was determined by Snell and Snell's modified method [12]. Urinary and plasma cyclic AMP, serum parathormone and calcitonin were determined by radioimmunoassay [2]. Significance of the difference between the means in the two phases were obtained by Student's t test for paired data.

Results

The electrolyte data of the calcium loading test are summarised in Table 1. Fasting serum calcium and ionised calcium were similar in all groups and were significantly increased after the calcium load in every group. However, the loading serum calcium and ionised calcium in the controls and in the patients with normocalciuria were significantly lower than in those with absorptive hypercalciuria. In the control, normocalciuria and absorptive hypercalciuria groups, fasting urinary calcium was normal in most subjects, but in renal hypercalciuria, the individual values, as well as the mean value for fasting urinary calcium, were significantly increased. Eighteen of 20 patients with absorptive hypercalciuria had an exaggerated calciuric response. Patients with absorptive hypercalciuria had a mean value of 0.21 ± SE 0.06 calcium mg/mg creatinine, which was significantly higher than the control and those with normocalciuria ($p < 0.05$) (Figs. 1 and 2).

No significant difference was seen in the fasting serum phosphate in any group. Serum phosphate after calcium load was greatly increased in every group. The loading serum phosphate was lower in the normocalciuric group than in the other three groups, but the difference was not significant. No significant differences were seen in the urinary phosphate and serum magnesium in any group. The fasting urinary magnesium was highest in the absorptive hypercalciuric group, but the difference was not significant. Serum sodium and uric acid were similar in all groups, and were

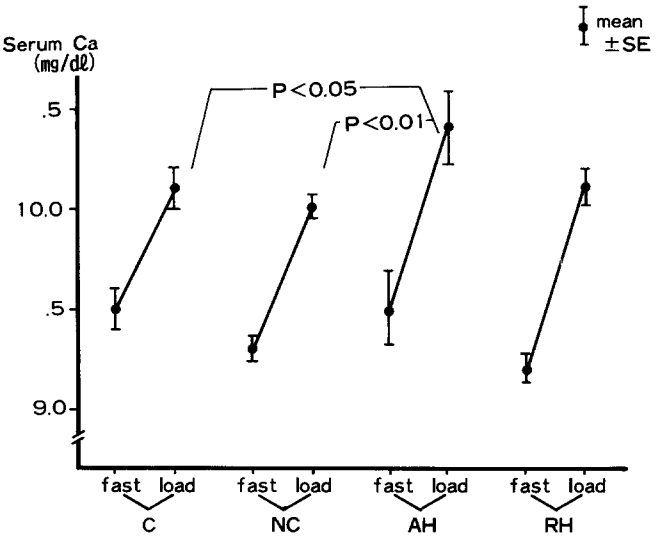

Fig. 1. Changes in serum calcium following calcium loading test (C = control, NC = normocalciuria, AH = Absorptive Hypercalciuria, RH = Renal Hypercalciuria)

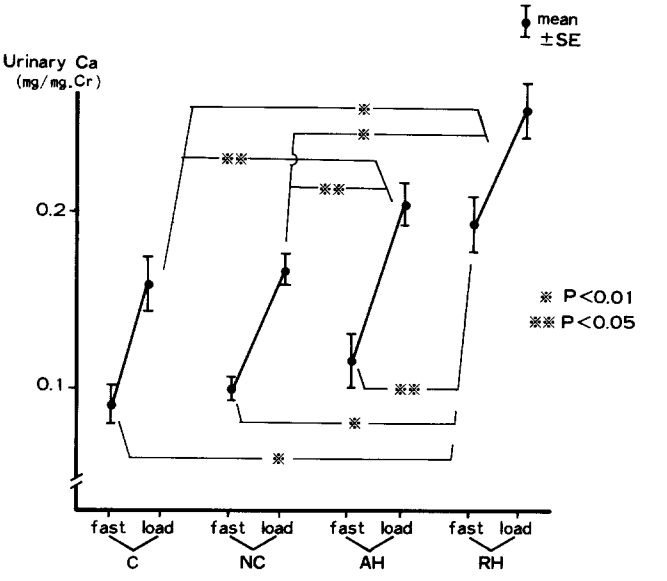

Fig. 2. Changes in urinary calcium following calcium loading test (C = control, NC = normocalciuria, AH = Absorptive hypercalciuria, RH = Renal Hypercalciuria)

unchanged after calcium load. The fasting urinary sodium was lower in hypercalciuric patients than in the control and normocalciuric patients, but the difference was not significant. Urinary sodium was significantly increased after loading. Urinary uric acid was significantly decreased after loading (control $p < 0.05$, normocalciuria and absorptive hypercalciuria $p < 0.001$). Urinary oxalate, which was normal in every group, was decreased after calcium loading, but the difference was not significant.

The endocrinological data are given in Table 2. Basal parathyroid function, as determined by measurements of both serum parathormone and urinary cyclic AMP, was nor-

Table 1. Changes in serum and urinary calcium concentration during calcium loading test

		Control	Calcium urolithiasis			*p*-value					
			N	AH	RH						
		(n = 17)	(n = 73)	(n = 20)	(n = 4)	C:N	C:AH	C:RH	N:AH	N:RH	AH:RH
Serum Ca	fast	9.5 ± 0.4[a]	9.3 ± 0.4[a]	9.5 ± 0.4[a]	9.2 ± 0.6[b]	ns	ns	ns	ns	ns	ns
(mg/dl)	load	10.1 ± 0.5[a]	10.0 ± 0.5[a]	10.4 ± 0.4[a]	10.1 ± 0.9[b]	ns	$p < 0.05$	ns	$p < 0.01$	ns	ns
Serum Ca^{++}	fast	4.7 ± 0.1[a]	4.8 ± 0.2[a]	4.7 ± 0.2[a]	4.6 ± 0.3[b]	ns	ns	ns	ns	ns	ns
(mg/dl)	load	4.9 ± 0.2[a]	5.0 ± 0.3[a]	5.2 ± 0.2[a]	4.8 ± 0.3[b]	ns	$p < 0.05$	ns	$p < 0.05$	ns	ns
Urinary Ca	fast	9.0 ± 5.2[a]	10.1 ± 5.4[a]	11.8 ± 7.0[a]	19.5 ± 3.3[b]	ns	ns	$p < 0.01$	ns	$p < 0.01$	$p < 0.05$
(mg/mg · Cr x 100)	load	15.9 ± 6.7[a]	16.7 ± 7.2[a]	20.5 ± 6.0[a]	26.1 ± 3.8[b]	ns	$p < 0.05$	$p < 0.01$	$p < 0.05$	$p < 0.01$	ns

[a] $p < 0.001$ [b] $p < 0.01$ [c] $p < 0.05$ (mean ± SD)
ns: not significant; C: Control; N: Normocalciuria; AH: Absorptive Hypercalciuria; RH: Renal Hypercalciuria

Table 2. Endocrinological changes during calcium loading test

		Control	Calcium urolithiasis			*p*-value					
			N	AH	RH						
		(n = 17)	(n = 73)	(n = 20)	(n = 4)	C:N	C:AH	C:RH	N:AH	N:RH	AH:RH
Urinary cAMP	fast	3.90 ± 0.92[c]	4.17 ± 1.58[c]	3.08 ± 1.33[c]	5.01 ± 2.65[c]	ns	ns	ns	ns	ns	$p < 0.05$
(μmoles/g · Cr)	load	2.95 ± 1.47[c]	3.12 ± 2.17[c]	2.62 ± 1.77[c]	2.77 ± 2.06[c]	ns	ns	ns	ns	ns	ns
Plasma cAMP	fast	20.2 ± 4.9	21.5 ± 3.4	20.3 ± 6.9	22.7 ± 7.0	ns	ns	ns	ns	ns	ns
(pmole/ml)	load	22.0 ± 2.3	22.5 ± 3.7	22.2 ± 7.9	23.3 ± 3.8	ns	ns	ns	ns	ns	ns
Serum PTH	fast	157 ± 62[a]	197 ± 137[a]	154 ± 76	227 ± 108[c]	ns	ns	ns	ns	ns	ns
(pg/ml)	load	101 ± 70[a]	138 ± 77[a]	123 ± 88	108 ± 57[c]	ns	ns	ns	ns	ns	ns
%TRP	fast	90.6 ± 5.6[c]	88.8 ± 3.7[c]	91.2 ± 4.7	85.6 ± 1.3[c]	ns	ns	ns	ns	ns	$p < 0.05$
(%)	load	93.5 ± 3.6[c]	92.0 ± 5.2[c]	93.7 ± 2.7	90.5 ± 2.2[c]	ns	ns	ns	ns	ns	ns
Serum Calcitonin	fast	66.4 ± 40.1	70.2 ± 23.7	72.9 ± 24.7[c]	58.8 ± 30.6	ns	ns	ns	ns	ns	ns
(pg/ml)	load	69.4 ± 42.0	72.8 ± 33.3	95.8 ± 20.8[c]	65.4 ± 27.7	ns	$p < 0.05$	ns	$p < 0.01$	ns	$p < 0.05$

[a] $p < 0.001$ [b] $p < 0.01$ [c] $p < 0.05$ (mean ± SD)
ns: not significant; C: Control; N: Normocalciuria; AH: Absorptive Hypercalciuria; RH: Renal Hypercalciuria

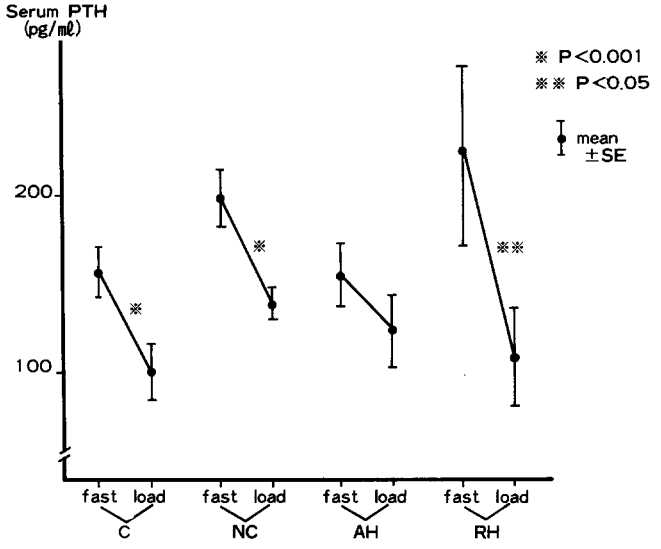

Fig. 3. Changes in serum PTH following calcium loading test (*C* = control, *NC* = normocalciuria, *AH* = Absorptive Hypercalciuria, *RH* = Renal Hypercalciuria)

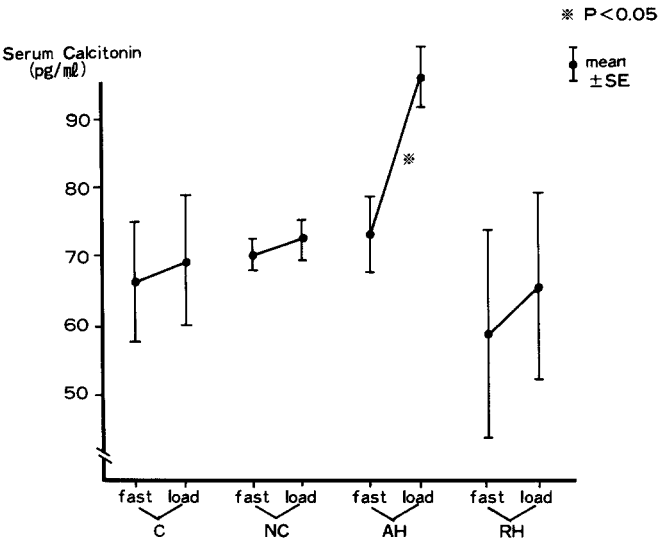

Fig. 5. Changes in serum calcitonin following calcium loading test (*C* = control, *NC* = normocalciuria, *AH* = Absorptive Hypercalciuria, *RH* = Renal Hypercalciuria)

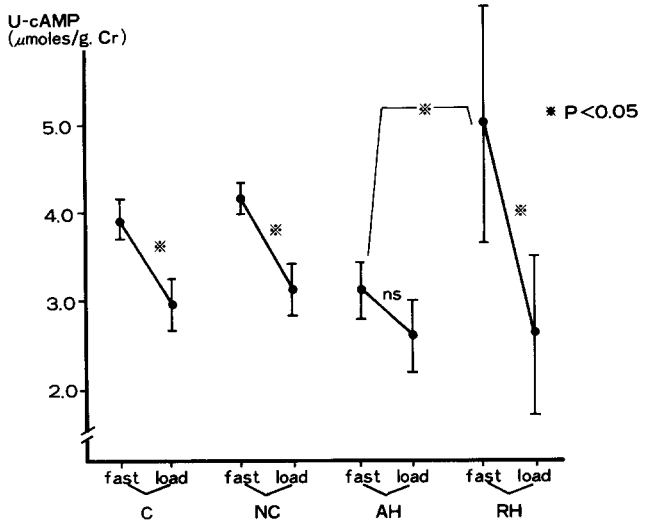

Fig. 4. Changes in urinary-cAMP following calcium loading test (*C* = control, *NC* = normocalciuria, *AH* = Adsorptive Hypercalciuria, *RH* = Renal Hypercalciuria)

mal in the control, normocalciuric, and absorptive hypercalciuric groups, but at the upper limit of normal in renal hypercalciuria. Both parameters were lowest in absorptive hypercalciuria, but the differences were not significant. Urinary cyclic AMP and serum parathormone declined significantly in controls and in normocalciuria and renal hypercalciuria following calcium loading, but especially so in renal hypercalciuria. However, these parameters were not significantly decreased in absorptive hypercalciuria after calcium loading. No significant difference was seen in plasma fasting and loading cyclic AMP in any group. Nephrogenus cyclic AMP was shown as minus in a few cases, and is not shown in the table (Figs. 3 and 4). The fasting tubular reabsorption of phosphate (% TRP) in the stone formers with absorptive hypercalciuria was significantly lower than in those with renal hypercalciuria. The % TRP was significantly elevated after loading in controls and in normocalciuria and renal hypercalciuria, but was not significantly elevated in absorptive hypercalciuria. The fasting serum calcitonin was slightly higher in absorptive hypercalciuria than in the other three groups. Following a calcium load serum calcitonin was significantly elevated in only absorptive hypercalciuria ($P < 0.05$) (Fig. 5).

Discussion

The usefulness of the oral calcium tolerance test in the differential diagnosis of hypercalciuria has been confirmed in many studies [4, 7, 11] but little work has been done on serum calcitonin metabolism in calcium stone formers. In this study all subjects were male because the pathogenesis of urolithiasis may be slightly different from that in females. Pak's original calcium restricted diet was 400 mg per day. However, Japanese adult men normally take 400–600 mg of calcium so all subjects were instructed to take a diet containing less calcium. The calcium load resulted in a significant rise in serum and urinary calcium, and serum ionised calcium in every group. The increase in serum calcium was sufficient to reduce parathyroid function, but serum calcitonin was unchanged after calcium loading in controls and in patients with normocalciuria and renal hypercalciuria. Although the serum and urinary calcium showed a greater increase after calcium loading in absorptive hypercalciuria than in the other three groups, indicating a greater avidity for gut calcium absorption in these patients, serum parathormone was not significantly reduced, whereas serum calcitonin was sig-

nificantly elevated in this group of patients. These findings would suggest that parathyroid function is maximally suppressed in patients with absorptive hypercalciuria. Perhaps stimulation of calcitonin in response to calcium loading may compensate for the lack of parathyroid suppression in patients with absorptive hypercalciuria so as to maintain serum calcium concentrations within the normal range. We have described elsewhere that the injection of calcitonin decreases the hypercalciuria of patients with malignant hypercalcaemia and primary hyperparathyroidism, and in some calcium stone formers [6]. These results suggest that calcitonin might be a hormone concerned with the pathogenesis of hypercalciuria associated with calcium urolithiasis, but there are few reports.

The measurement of serum calcitonin and parathormone in response to a calcium load may assist in the differential diagnosis of hypercalciuria.

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