Changes in Serum and Urinary Calcium during Treatment with Hydrochlorothiazide: Studies on Mechanisms

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ABSTRACT Studies were undertaken in man to evaluate the roles of volume depletion and of the parathyroid glands in mediating the changes in serum and urinary calcium which follow the administration of hydrochlorothiazide, 100 mg twice daily, for 4 days. 42 studies were carried out in 16 normal subjects, 9 patients with hyperparathyroidism, and 7 vitamin D–treated subjects with hypoparathyroidism. In six studies in normal subjects, daily sodium losses during thiazide administration were quantitatively replaced, and in six other studies the effect of equivalent sodium losses produced by furosemide was evaluated.

Although the magnitude of sodium losses was similar in three groups during therapy with thiazides, urinary calcium fell and urinary phosphorus increased significantly only in normal subjects and those with hyperparathyroidism; no change occurred in patients with hypoparathyroidism. With the replacement of the thiazide-induced sodium losses by NaCl in normals, urinary calcium did not change as urinary sodium increased 4- to 5-fold. Furosemide administration produced similar sodium losses while urinary calcium remained at or above control levels. After correction for changes in plasma protein concentration caused by thiazide-induced hemoconcentration, mean levels of serum calcium were significantly increased only in subjects with hyperparathyroidism and vitamin D–treated patients with hypoparathyroidism.

The results indicate that both depletion of extracellular fluid volume and the presence of the parathyroid glands are necessary for the decrease in urinary calcium in response to thiazide therapy. Both the reduction in urinary calcium and increase in urinary phosphate after the use of thiazides may be due, in part, to potentiation of the action of the parathyroid hormone on the nephron. The rise in serum calcium could be due to thiazide-induced release of calcium from bone into extracellular fluid, particularly in states where bone resorption may be augmented. i.e., vitamin D therapy or hyperparathyroidism.

INTRODUCTION

Diuretics of the benzothiadiazide (thiazide) group affect calcium metabolism by producing a fall in urinary calcium and, often, an increase in serum calcium concentration (1–8). The mechanisms whereby these drugs exert such actions are poorly understood. In a preliminary report, Suki, Hull, Rector, and Seldin (9) suggested that urinary calcium falls as a result of depletion of extracellular fluid volume (ECV)[1] secondary to the sodium losses produced by the diuretic. However, other preliminary observations suggested that the fall in urinary calcium was in some way dependent upon the presence of intact parathyroid glands (10, 11). Parfitt (10) concluded that the increase in serum calcium was not accounted for by the reduced urinary excretion of this ion. Moreover, Koppel, Massry, Shinaberger, Hartenbower, and Coburn (12) noted an increase in serum calcium in uremic patients with negligible uri-

This work was presented in part before the 8th European Congress of Calcified Tissue, Jerusalem, Israel, 1 April 1971.

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Received for publication 22 July 1971 and in revised form 18 November 1971.

[1] *Abbreviations used in this paper:* cyclic AMP, cyclic adenosine 3'5'-monophosphate; ECV, extracellular fluid volume; GFR, glomerular filtration rate; PTE, parathyroid extract.

nary excretion of calcium after the use of thiazide diuretics, indicating that the rise in serum calcium induced by thiazides is not due to the renal retention of calcium. Finally, experiments carried out in dogs have suggested that thiazide diuretics may directly produce parathyroid hyperplasia (13).

The present study was undertaken to evaluate in man the roles of ECV depletion and of the parathyroid glands in mediating the changes in urinary and serum calcium which follow the administration of hydrochlorothiazide.

METHODS

42 studies were carried out in 16 normal subjects, 9 patients with hyperparathyroidism, and 7 patients with hypoparathyroidism treated with vitamin D. The normal subjects were males, aged 24–65 yr and free of detectable cardiovascular, metabolic, hepatic, or renal abnormalities. The group with hyperparathyroidism consisted of one female and eight males, aged 28–65 yr. The diagnosis of hyperparathyroidism was made by the usual biochemical criteria (14) and was confirmed at surgery in six. The three unoperated patients exhibited hypercalcemia, hypophosphatemia, a low renal tubular reabsorption of phosphate, and responses to phosphate loading (15) and calcium infusion (16), which were consistent with the diagnosis of hyperparathyroidism. The patients with hypoparathyroidism included two females and five males, aged 26–65 yr. Hypoparathyroidism was idiopathic in two and resulted from surgery in 5 patients. In each, the diagnosis was established by the presence of hypocalcemia and hyperphosphatemia present for 6 months to several years before treatment with vitamin D. All had been receiving vitamin D_2, 50,000–100,000 IU/day, and supplemental calcium, 1–2 g/day, for periods ranging between 4 months and 8 yr. Patients with distinctly impaired renal function were not included in the study.

The studies were carried out in the Metabolic Unit of the Veterans Administration Hospital (Wadsworth). The subjects received constant diets which were adjusted individually to conform to their usual intake before the study to avoid variation from a preexisting steady state. The daily mineral content of the diets ranged between 600 and 1300 mg of calcium, 180 and 350 mg of magnesium, 400 and 2000 mg of phosphorus, and 60 and 250 mEq of sodium. Water was ingested ad lib. After 2 or 3 days of adjustment, each study with thiazide consisted of (*a*) a control period of 3–5 days, (*b*) a treatment period with 100 mg of hydrochlorothiazide given every 12 hr for either 3 days (6 studies) or 4 days (30 studies), and (*c*) a post-treatment period which usually lasted 4 days. The number of such studies carried out in normal subjects, patients with hyperparathyroidism, and those with hypoparathyroidism were 12, 11, and 7, respectively.

In order to evaluate the effects of a similar degree of depletion of ECV produced by another diuretic, six studies were carried out in normal subjects receiving 40 mg of furosemide twice daily in place of thiazide in the protocol described above.

In six additional studies in normal subjects, the thiazide-induced sodium losses were replaced quantitatively by oral administration of sodium chloride. The quantity of supplemental salt given on the 1st day was estimated from the magnitude of sodium diuresis observed on the 1st day of thiazide treatment in other studies. During the subsequent 3 days, the daily dose of sodium was adjusted to maintain the subjects in sodium balance as estimated from intake and urinary losses during the previous day and from fluctuations in body weight measured three times daily. At the end of thiazide treatment, sodium supplementation was discontinued.

24-hr urines were collected throughout, and blood samples were obtained twice each day, before breakfast at 8 a.m. and again at 4 p.m. In additional studies not listed above (two in patients with hyperparathyroidism and two in patients with hypoparathyroidism treated with vitamin D) only blood samples were collected. Body weight was measured each morning before breakfast and after the patient had voided. Glomerular filtration rate (GFR) was estimated from endogenous creatinine clearance. Creatinine, sodium, calcium, and phosphorus in plasma and urine, and total protein and water content of plasma were measured by methods previously reported from this laboratory (17, 18). The concentration of diffusible calcium in serum was measured in ultrafiltrates of serum prepared anaerobically (19) from eight patients with hyperparathyroidism before and on the 4th day of therapy with thiazides.

RESULTS

The effects of thiazide treatment, with and without supplemental sodium, and those of furosemide on creatinine clearance, urinary sodium, calcium, and phosphorus in all subjects are summarized in Table I. The results from a representative study in a normal subject are shown in Fig. 1. In subjects not receiving supplemental salt, the administration of hydrochlorothiazide produced the expected increase in sodium excretion,

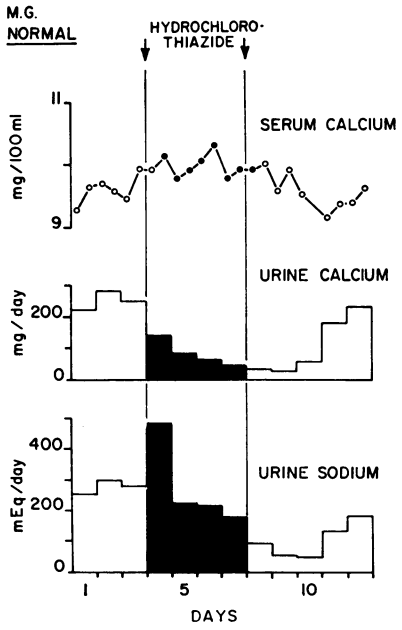

FIGURE 1 Representative study depicting the changes in serum calcium and urinary calcium and sodium in a normal subject receiving hydrochlorothiazide, 100 mg twice daily for 4 days.

with the peak sodium diuresis occurring on the 1st or 2nd day of treatment; urinary sodium then fell to or below control levels, and its excretion rate usually decreased further during the post-treatment period. The maximum cumulative sodium losses, calculated from the cumulative excretion of sodium in excess of the mean control level for each patient, were 261 ±28, 311 ±47, and 244 ±88 mEq/day (mean ±SE) in normal subjects, patients with hyperparathyroidism, and those with hypoparathyroidism, respectively ($P > 0.20$). All subjects lost weight and the percentage changes in body weight did not differ significantly among the three groups (Table II).

Despite equivalent magnitudes of sodium diuresis and, presumably, a similar loss of ECV, the pattern of urinary excretion of calcium was distinctively different in the patients with hypoparathyroidism as compared to the patterns in normal subjects and in those with hyperparathyroidism. In the normals, thiazide therapy did not augment calcium excretion on the 1st or 2nd day of treatment despite the marked sodium diuresis. Mean calcium excretion fell progressively from a control level of 194 ±28 mg to 86 ±20 mg on the 4th day of thiazide therapy and remained below the control throughout the post-treatment period. The patients with hyperparathyroidism displayed qualitatively similar changes in urinary calcium; the mean excretion of calcium fell from a control level of 357 ±49 mg to 204 ±18 mg on return to control levels during the post-treatment period in all but one patient. Although the maximum absolute decrease in daily calcium excretion from the mean control value was greater in patients with hyperparathyroidism (217 ±42 mg/day) than in normals (97 ±14 mg/day), the per cent decrement from control levels was not different. In contrast, the mean urinary calcium excretion did not decrease in patients with hypoparathyroidism; the excretion rates were 347 ±76 mg/day during the control period and 406 ±106 mg/day on the 4th day of thiazide administration. Moreover, no significant change in urinary calcium excretion occurred during the post-treatment period.

The mean endogenous creatinine clearance rate decreased significantly on the 4th day of thiazide therapy in normals and on the 3rd day in those with hyperparathyroidism; the effect was variable in the patients with hypoparathyroidism. Alterations in filtered calcium, estimated as the product of creatinine clearance and 62% of total plasma calcium, did not account for either the reduction in urinary calcium in normals and those with hyperparathyroidism or for the difference between the calcium excretion observed in patients with hypoparathyroidism and in the other two groups of subjects (Fig. 2).

When thiazide-induced sodium losses were replaced by the oral supplementation of salt, creatinine clearances did not change consistently and sodium excretion remained 4–5 times above control levels throughout treatment. In contrast to the observations in normal subjects receiving thiazide diuretics alone, calcium excretion did not fall when sodium losses and depletion of ECV were prevented or modified by the oral replacement of salt. The mean calcium excretion rates were 162 ±31 mg/day during the control period and 147 ±35 mg/day on the 4th day of treatment. However, it should be noted that the rates of calcium excretion did not increase despite the very high excretion rates for sodium, and there was a clear dissociation between the renal handling of the two ions.

During treatment with furosemide, sodium excretion increased, and the mean maximum cumulative sodium loss for the period of furosemide treatment was 256 ±69 mEq/day, a value which is not significantly different from that occurring during thiazide treatment. Total urinary calcium also increased during the 4 days of treatment with furosemide, although the mean daily increments in urinary calcium excretion were not significantly above control values. When furosemide was discontinued, mean urinary sodium excretion fell significantly below the control value. Urinary calcium also decreased in each subject when furosemide was discontinued, but the change was not as marked as in the case of sodium. The mean percentage changes from control values for urinary calcium (− 17.2 ±11.7 and − 16.6 ±6.0% on the 1st and 2nd days after withdrawal of furosemide, respectively) differed significantly from the changes observed both during the 3rd and 4th days of thiazide treatment (− 48 ±8.4 and − 52.1 ±8.7%, respectively) and during the 1st and 2nd days after withdrawal of thiazides (− 59 ±6.2 and − 53

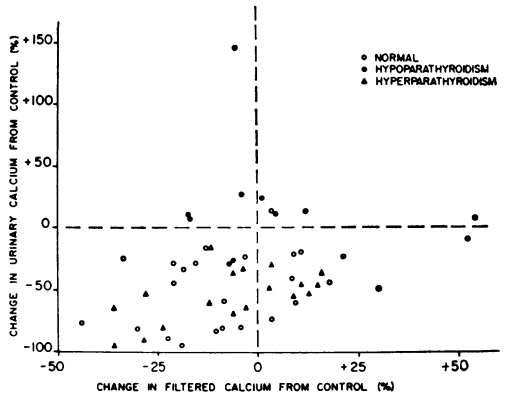

FIGURE 2 The relationship between the percentage change from control levels of urinary calcium and that of filtered calcium during treatment with hydrochlorothiazide. Each point represents data from an individual subject.

TABLE I

Changes in Creatinine Clearance and Urinary Sodium, Calcium, and Phosphate in Normal

Group (No.)		Control (mean ±SE)	Drug treatment (days) 1	2
			% change from control	
Thiazide Normal (12)	C_{Cr} (*ml/min*)	143 ±9.1	+5.7 ±2.3*	−5.9 ±3.0
	$U_{Na}V$ (*mEq/day*)	163 ±13	+149 ±16‡	+35 ±12‡
	$U_{Ca}V$ (*mg/day*)	194 ±28	−11.1 ±10.0	−43 ±8.8‡
	U_PV (*mg/day*)	1115 ±78	+8.8 ±4.8	+18.1 ±5.1‡
Thiazide Hyperparathyroidism (10)	C_{Cr}	110 ±11.3	+18.5 ±6.2‡	−6.5 ±3.8
	$U_{Na}V$	133 ±18	+183 ±41‡	+89 ±28‡
	$U_{Ca}V$	357 ±49	−3.3 ±11.3	−42.2 ±7.0‡
	U_PV	1166 ±169	+24.8 ±6.8‡	+26.2 ±22.1
Thiazide Hypoparathyroidism (7)	C_{Cr}	88 ±8.1	+5.8 ±12.6	+0.4 ±5.4
	$U_{Na}V$	149 ±12	+77 ±23‡	+40 ±13‡
	$U_{Ca}V$	347 ±76	−9.5 ±8.8	−5.1 ±8.0
	U_PV	874 ±121	−3.2 ±8.6	+7.3 ±10.8
Thiazide + NaCl Normal (6)	C_{Cr}	125 ±15.6	6.3 ±5.0	4.0 ±5.8
	$U_{Na}V$	131 ±12	+297 ±23‡	+302 ±30‡
	$U_{Ca}V$	162 ±31	+16.3 ±3.4‡	−13.1 ±6.7
	U_PV	977 ±68	+28.4 ±7.5‡	+21.4 ±7.0*
Furosemide Normal (6)	C_{Cr}	131 ±19	−3.1 ±2.9	−3.5 ±4.5
	$U_{Na}V$	170 ±21	+65 ±6‡	+45 ±25
	$U_{Ca}V$	172 ±31	+28.3 ±11.4	+42 ±39.8
	U_PV	1116 ±116	−7.1 ±2.6	+9.2 ±5.0

Abbreviations: C_{Cr} = endogenous creatinine clearance, $U_{Na}V$ = urinary sodium, $U_{Ca}V$ = urinary calcium, and U_PV = urinary phosphate. Each value represents mean ±SE.

* Values showing significant change from control: $P < 0.05$.

‡ Values showing significant change from control: $P < 0.01$.

±8.7%), when cumulative sodium losses produced by the two drugs were similar.

During treatment with thiazides alone, the urinary excretion of phosphate increased by as much as 352 ±77 and 206 ±61 mg/day in normal subjects and in patients with hyperparathyroidism, respectively. In contrast, mean urinary phosphate failed to change significantly in the patients with hypoparathyroidism. In the normal subjects receiving thiazides with replacement of sodium losses, phosphate excretion also increased, particularly on the 1st day of treatment.

The changes in serum calcium levels for all groups of patients are summarized in Table III, and the mean calcium levels in individual patients before, during and after therapy with hydrochlorothiazide are shown in Fig. 3. For each individual patient, these data represent the means of six to nine values during the control period, five values during the last 2½ days of treatment, and four to six values obtained 3–5 days after treatment was discontinued. The mean increases in serum calcium levels were 0.59 ±0.087 mg/day in normal subjects, 0.66 ±0.130 in those with hyperparathyroidism, and 0.63 ±0.111 in patients with hypoparathyroidism. When the drug was discontinued, serum calcium usually returned to or below the control levels. The concentration of plasma proteins increased during treatment with thiazides as a result of hemoconcentration, and the increased protein concentration should result in more protein-bound calcium. To adjust for changes in total plasma calcium resulting merely from alterations in protein-bound calcium, the total calcium levels were "corrected" for the change in plasma proteins according to a formula described by Parfitt (10),

$$\text{"Corrected" calcium} = \text{measured calcium} / \left(0.60 + \frac{\text{total protein}}{18.5}\right)$$

Subjects, Patients with Hyperparathyroidism and Those with Hypoparathyroidism

Drug treatment (days)		Post-treatment (days)			
3	4	1	2	3	4
% change from control		*% change from control*			
−10.0 ±5.0	−15.1 ±5.3‡	−13.3 ±4.4‡	−13.1 ±5.0‡	−8.2 ±3.2*	−14.2 ±6.3
−4 ±6	−31 ±5‡	−63 ±6‡	−72 ±7‡	−74 ±8‡	−51 ±15‡
−49 ±8.3‡	−52 ±8.5‡	−59 ±6.2‡	−53 ±8.7‡	−53 ±7.0‡	−21 ±7.7*
+29.7 ±5.5‡	+19.3 ±6.1‡	+12.7 ±6.1	+1.3 ±6.8	−11.3 ±4.3*	−16.5 ±6.8
−15.3 ±4.4‡	−11.1 ±6.3	−3.2 ±8.4	−6.6 ±5.2	+0.4 ±4.1	+8.9 ±4.8
+23 ±21	−10 ±15	−30 ±16	−52 ±10‡	−59 ±8‡	−45 ±24
−56.1 ±7.6‡	−46.3 ±7.3‡	−57.9 ±7.7‡	−50.2 ±8.7‡	−39.0 ±10.9‡	+9.4 ±23.6
+16.6 ±10.2	+23.8 ±22.1	+7.6 ±4.9	−1.6 ±4.9	−17.1 ±9.5	−37.5 ±12.9*
+0.4 ±9.1	+2.7 ±12.6	−1.9 ±6.1	+2.3 ±9.3	+7.0 ±9.7	+1.8 ±10.2
+26 ±17	+5 ±18	−36 ±14	−34 ±19	−30 ±23	−12 ±32
−1.8 ±8.3	+20 ±32	+11.6 ±24	−5.3 ±7.3	+4.5 ±11.8	−5.0 ±17.1
+13.0 ±11.6	+21.8 ±13.6	+22 ±13.3	+9.2 ±14.2	−7.6 ±16.1	−3.6 ±13.2
−1.4 ±4.0	−1.4 ±2.0	−1.0 ±2.2	+0.7 ±5.2	−2.0 ±5.8	−3.2 ±4.9
+301 ±48‡	+282 ±42‡	+78 ±24‡	−18 ±14	−26 ±15	−10 ±22
+2.3 ±11.5	−3.9 ±15.0	−27.4 ±10.0*	−17.0 ±7.6	+6.0 ±13.1	+6.8 ±13.5
+16.8 ±8.1	+10.6 ±5.6	+6.4 ±5.5	−1.8 ±5.3	+2.9 ±7.1	−3.1 ±11.7
−11.0 ±5.5	−4.2 ±7.0	−15.4 ±5.2*	−10.0 ±4.5	−2.9 ±2.7	−3.6 ±8.3
+7 ±9	+15 ±20	−69 ±17‡	−48 ±10‡	−40 ±12‡	−31 ±16
+21.1 ±20.4	+53.1 ±39.9	−17.2 ±11.7	−16.6 ±6.0*	−12.0 ±6.7	−9.1 ±16.5
+11.1 ±8.8	+6.8 ±5.2	−8.6 ±9.6	−2.0 ±6.3	−0.2 ±9.5	−11 ±4.7

where it is assumed that plasma calcium is 60% diffusible and that the protein-bound fraction changes in proportion to the changes in the concentration of total protein. With such adjustments, the mean increases in "corrected" calcium levels with thiazide therapy were 0.19 ±0.099, 0.48 ±0.066, and 0.40 ±0.134 mg/100 ml in the normal subjects, and patients with hyper- and hypoparathyroidism, respectively. Moreover, in the patients with hyperparathyroidism where ultrafiltrable calcium levels were actually measured, these increased by 0.27 ±0.092 mg/100 ml ($P < 0.025$), a value which is approximately 60% of the "corrected" change in total calcium concentration.

DISCUSSION

Although previous studies have shown that the administration of hydrochlorothiazide to normal subjects and those with hyperparathyroidism causes a decrease in urinary calcium, the mechanisms(s) responsible for this phenomenon remains unclear. Urinary calcium represents the difference between the quantity filtered at the glomeruli and that reabsorbed by the tubules. A decrease in the filtered load of calcium or an increase in the renal tubular reabsorption can produce a fall in urinary calcium. The results of other work (1, 3, 8) and of the present study show that the decrease in urinary calcium observed in normal subjects and in patients with hyperparathyroidism cannot be accounted for by a reduction in filtered calcium (Fig. 2).

The renal tubular reabsorption of calcium is closely related to that of sodium (17, 18, 20, 21), and it is likely that certain events promoting sodium transport in the nephron can also augment the reabsorption of calcium. Also, enhanced tubular reabsorption of calcium follows increased action of parathyroid hormone (22, 23). Epstein reported that subjects receiving a diet low in sodium display a fall in their urinary calcium (24). Further, Suki and coworkers suggested in a

TABLE II

Effect of Hydrochlorothiazide and Furosemide on Body Weight

Study Group (No.)	Body weight		Per cent change in weight
	Control	Maximum change	
	kg		%
Thiazide Normal (11)	85.2 ±3.91	−2.3 ±0.27	−2.67 ±0.26
Thiazide Hyperparathyroid (10)	73.6 ±4.92	−1.9 ±0.19	−2.56 ±0.35
Thiazide Hypoparathyroid (7)	64.9 ±3.73	−1.4 ±0.13	−2.13 ±0.18
Furosemide Normal (6)	84.7 ±5.23	−1.9 ±0.24	−2.28 ±0.27

All data are expressed as mean ±SE.

preliminary report that the thiazide-induced saliuresis and consequent reduction in ECV cause enhanced reabsorption of sodium as well as calcium in a part of the nephron not directly affected by the diuretic (9). Certain results from the present study are consistent with such a postulate. First, in normals and patients with hyperparathyroidism, the thiazide-induced sodium losses and reduction in body weight, with a presumed decrease in ECV, were temporally associated with a fall in urinary calcium. In addition, urinary calcium remained low during the first 2 to 3 days of the posttreatment period while urinary sodium was very low. Moreover, the replacement of sodium losses with supplemental salt abolished the effect of thiazides on urinary calcium. However, patients with hypoparathyroidism and equivalent losses of sodium and body weight and, presumably, similar depletion of ECV, did not show a decrease in urinary calcium. Also, after cessation of treatment with either hydrochlorothiazide or furosemide, a greater reduction in urinary calcium was noted in the thiazide-treated group despite similar cumulative losses of sodium. These observations suggest that factors other than or in addition to ECV depletion may be operative. Such factors include a direct action of thiazides on calcium reabsorption, thiazide-induced potentiation of parathyroid hormone action on the nephron, or direct stimulation of the parathyroid glands by the drug.

It is possible that thiazide diuretics directly increase the tubular reabsorption of calcium, but such an action seems unlikely. The mean urinary calcium did not decrease on the 1st day of thiazide treatment in the

TABLE III

Changes in Serum Protein and Calcium Concentrations before, during

Study Group (No.)	Serum protein			Serum calcium
	Control	Treatment	Post-treatment	Control
		g/100 ml		*mg/100 ml*
Thiazide Normal (11)	7.21 ±0.22	7.96 ±0.27	7.36 ±0.19	9.48 ±0.095
Thiazide Hyperparathyroid (13)	7.30 ±0.26	7.66 ±0.35	7.14 ±0.32	11.23 ±0.231
Thiazide Hypoparathyroid (10)	7.18 ±0.34	7.61 ±0.38	7.03 ±0.29	9.06 ±0.157
Thiazide + NaCl replacement Normal (6)	7.24 ±0.18	7.22 ±0.08	7.18 ±0.24	10.00 ±0.098
Furosemide Normal (6)	7.43 ±0.11	7.78 ±0.17	7.23 ±0.14	9.38 ±0.129

All data are mean ±SE. "Corrected" serum calcium is derived in a manner described in the text.
* Differs significantly from zero: $P < 0.01$.
‡ Differs significantly from zero: $P < 0.05$.

present study. Further, acute studies in man (25, 26) and dogs (27, 28) show that urinary calcium rises shortly after the administration of thiazides (28), although the increase in calcium excretion relative to that of sodium is small when compared to other diuretics such as furosemide, ethacrynic acid, and mercurial compounds (25, 26, 28). This dissociation between urinary calcium and sodium with thiazides could be related to direct inhibition of sodium reabsorption at a site in the distal convoluted tubule where the transport of calcium and sodium are not closely associated or may be negatively related (29).

Low basal levels of urinary calcium could not be responsible for the failure of thiazides to cause a fall in calcium excretion in patients with hypoparathyroidism since the control rates of calcium excretion in these subjects were similar to or exceeded those of normals and the subjects with hyperparathyroidism. It is unlikely that treatment with large doses of vitamin D_2 prevented a fall in urinary calcium in response to thiazide diuretic. Parfitt (10) reported a decrease in urinary calcium in a patient with idiopathic osteoporosis receiving vitamin D_2, and we have observed a reduction in urinary calcium after thiazide administration in two normal subjects receiving vitamin D_2, 50,000 IU/day (unpublished data). It appears, therefore, that parathyroid hormone must be present before thiazides cause a fall in urinary calcium. There is evidence that parathyroid hormone exerts renal action through activation of an adenyl cyclase system with the release of cyclic AMP (30–32). Thiazides can inhibit phosphodiesterase (33, 34), an enzyme which accelerates degradation of cyclic AMP. Therefore, in the presence of parathyroid hormone, thiazides might lead to increased renal concentrations of cyclic AMP and potentiate the action of the hormone. Such an augmentation of hormone action is suggested by our observations in two vitamin D–treated patients with hypoparathyroidism who received two standardized infusions of parathyroid extract (PTE), first as a control and later on the 4th day of therapy with thiazides; in these two patients, the diuretic-induced sodium losses were not replaced. Urinary calcium fell by 17 and 43% with infusion of PTE alone and by 57 and 69% during the administration of PTE with thiazides in the two patients, respectively (unpublished observations). The increase in urinary phosphate in normals and in those with hyperparathyroidism and the absence of phosphaturia in patients with hypoparathyroidism with thiazide administration are also consistent with hydrochlorothiazide potentiating the action of parathyroid hormone. Eknoyan, Suki, and Martinez-Maldonado (28) observed brisk phosphaturia after the

and after Therapy with Hydrochlorothiazide or Furosemide

Serum calcium		Δ Serum calcium		Δ "Corrected" serum calcium	
Treatment	Post-treatment	Control to treatment	Treatment to post-treatment	Control to treatment	Treatment to post-treatment
mg/100 ml		*mg/100 ml*		*mg/100 ml*	
10.05 ±0.089	9.51 ±0.113	+0.59 ±0.087*	−0.56 ±0.110*	0.19 ±0.099	−0.22 ±0.107
11.89 ±0.184	11.15 ±0.260	+0.66 ±0.130*	−0.74 ±0.150*	0.48 ±0.066*	−0.42 ±0.132*
9.68 ±0.223	9.09 ±0.138	+0.63 ±0.111*	−0.57 ±0.191‡	0.40 ±0.134‡	−0.32 ±0.162
10.00 ±0.032	9.98 ±0.119	0.00 ±0.115	−0.02 ±0.142	0.01 ±0.109	0.01 ±0.096
9.38 ±0.128	9.22 ±0.163	+0.01 ±0.099	−0.16 ±0.144	−0.17 ±0.094	+0.14 ±0.168

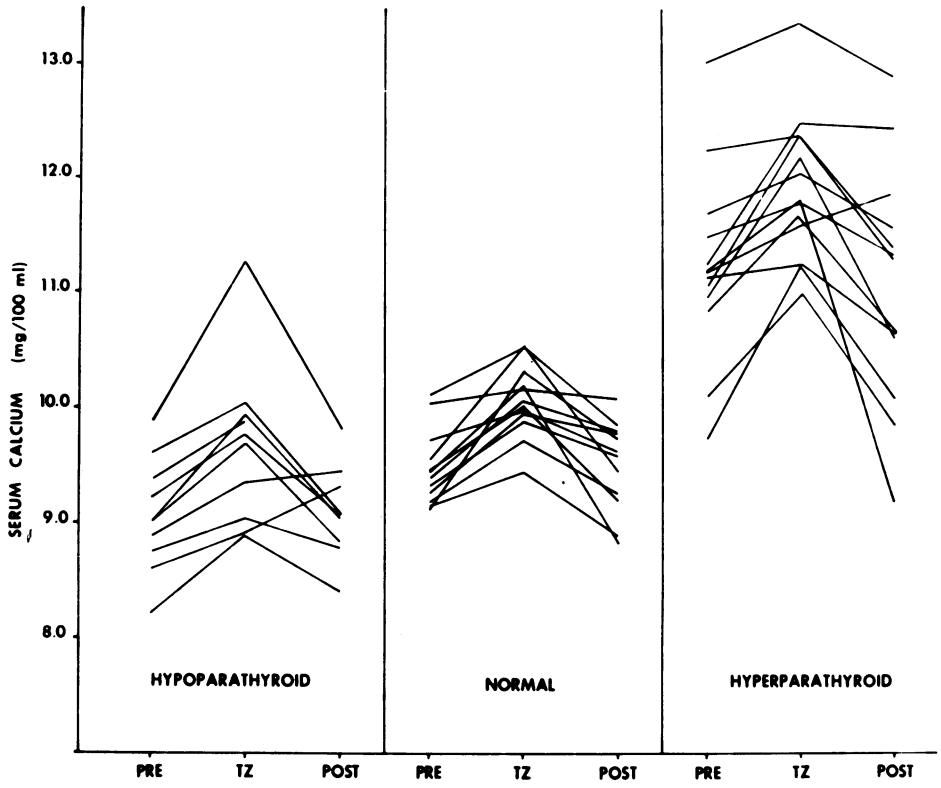

FIGURE 3 The levels of total serum calcium during the control period (PRE), hydrochlorothiazide administration (TZ), and the post-treatment period (Post) in normals and patients with hypoparathyroidism and hyperparathyroidism. Each line represents a single subject and connects the mean value of four to nine determinations made during each period.

acute infusion of chlorothiazide in parathyroidectomized dogs. Such a discrepancy between their results and the present observations in man could be due to differences between species, the duration of hypoparathyroidism, different levels of serum calcium, the route of administration and dosage of the diuretic, or the duration of observation.

The possibility that short-term administration of thiazide diuretics exerts an effect on urinary calcium by stimulating the secretion of parathyroid hormone seems unlikely. Coe, Canterbury, and Reiss (35) report a reduction in plasma immunoreactive parathyroid hormone after the administration of thiazides and, in a preliminary study in six patients evaluated in our facility, no consistent change in plasma parathyroid hormone levels was observed (11).

The present data suggest that both depletion of ECV and the presence of intact parathyroid glands are necessary before treatment with thiazides can cause a fall in urinary calcium. However, it can be argued that ECV depletion is primarily responsible for the decrease in urinary calcium and that the absence of such a response in patients with hypoparathyroidism may be due to an altered reaction to ECV depletion, per se, in such subjects. The present observations do not exclude this possibility.

A rise in the level of serum calcium has been described in normal subjects receiving thiazides (3, 36), and thiazides can cause overt hypercalcemia in patients with hyperparathyroidism (10, 37–40). It has been suggested that the use of thiazides may be of value in the diagnosis of primary hyperparathyroidism (39, 40). In the present study, an increase in levels of total serum calcium was observed in normals, and in patients with hyper- and hypoparathyroidism during treatment with thiazides; moreover, hypercalcemia became evident in the two normocalcemic patients subsequently shown to have hyperparathyroidism. Overt hypercalcemia did not occur otherwise, except in one patient with hypoparathyroidism treated with vitamin D (Fig. 3). Hypercalcemia has been reported during thiazide treatment in a patient receiving vitamin D (10), and therapy with thiazides aggravated hypercalcemia in two patients with malignant disease (39). These observations sug-

gest that thiazides may induce hypercalcemia in patients with conditions associated with enhanced rates of bone resorption.

Several factors may be responsible for the increase in levels of plasma calcium. Hemoconcentration of plasma proteins probably accounts in part for the augmented serum calcium levels. However, after adjustment for changes in plasma protein, the "corrected" serum calcium levels were still significantly increased during thiazide therapy in patients with hyper- and hypoparathyroidism, while in normals, the "corrected" values were not significantly greater than controls. Also, plasma calcium did not change in the normal subjects when thiazide-induced sodium losses were replaced and hemoconcentration was prevented. The reduction in urinary calcium during thiazide treatment does not seem to be the primary factor contributing to the elevation of plasma calcium. Thus, serum calcium increased in patients with hypoparathyroidism while urinary calcium did not change, and previous data (12) have shown an increase in serum calcium in response to thiazide treatment in uremic patients with little or no urinary output. In addition, Parfitt (10) found no correlation between the change in serum calcium and the quantitative decrease in urinary calcium excretion.

It is possible that thiazides produce an increase in plasma calcium by enhancing the release of this ion from bone into the extracellular fluid. This augmented release might be achieved by a direct action on bone, by potentiation of the action of parathyroid hormone, or by enhancing bone resorption caused by other factors, e.g., vitamin D or malignant diseases.

Finally, the elevation in plasma calcium concentration could be produced by increased gastrointestinal absorption of calcium. In this regard, the available data are contradictory: observations of enhanced calcium absorption have been described (8) and others have reported either unchanged or decreased absorption (2, 5, 41, 42).

ACKNOWLEDGMENTS

Technical assistance was provided by Robert Adachi, John Lee, Mrs. Sonia Soghomomian, and Mrs. Miriam Bick, with secretarial aid by Miss Catherine Weckesser. The assistance of the nursing and dietetic staff of the Metabolic Balance Unit is gratefully acknowledged.

This work was supported by U. S. Public Health Service Grants TIAM 5383 and RR05468, and by a grant from the Southern California Kidney Foundation.

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