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Regulation of Parathyroid Hormone and Vitamin D in Essential Hypertension

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Patients with essential hypertension have been reported to have a higher serum concentration of parathyroid hormone (PTH) than normotensive individuals although this finding is not universal among studies. To further characterize the status of the calcium regulating hormones in essential hypertension, we measured the parathyroid gland response to acute EDTA-induced hypocalcemia and the renal response of $1,25(OH)_2$-vitamin D to dietary calcium deprivation in 16 hypertensive (H) and 15 normotensive (N) men. The average mean arterial blood pressure once all antihypertensive medications were discontinued was 108 ± 7 mm Hg for the hypertensive group and 89 ± 4 mm Hg for the normotensive group ($P < .01$). There were no group differences in baseline serum concentrations of ionized calcium, creatinine, intact PTH, and $1,25(OH)_2$-vitamin D, urinary calcium excretion, and creatinine clearance. After a 1-h infusion of EDTA at 12.5 mg/kg/h, the serum concentration of ionized calcium fell (H: 1.25 ± .03 to 1.17 ± .04 mmol/L, N: 1.26 ± .04 to 1.18 ± .04 mmol/L, P = NS) and PTH increased (H: 36 ± 9 to 91 ± 30 pg/mL, N: 40 ± 14 to 85 ± 28 pg/mL, P = NS). With an additional hour of EDTA at a dose of 25 mg/kg/h, serum ionized calcium concentration fell further (H: 1.01 ± .05 mmol/L, N: 1.03 ± .06 mmol/L, P = NS) and PTH increased to 150 ± 58 pg/mL in patients and 130 ± 32 pg/mL in controls ($P < .001$). The response suggested an increased maximal parathyroid gland secretory capacity in the hypertensive patients relative to the controls. There was no group difference in the serum concentration of $1,25(OH)_2$-vitamin D at baseline (H: 32 ± 6 pg/mL, N: 32 ± 8 pg/mL, $P < .90$) and following dietary calcium deprivation for three days (H 50 ± 12, N 48 ± 14 $P < 0.76$). The maximal stimulated PTH level was significantly higher in hypertensive than normotensive subjects in the absence of measured differences in serum ionized calcium concentration, serum $1,25(OH)_2$-vitamin D concentration, and creatinine clearance. These findings suggest an intrinsic alteration of PTH regulation in patients with essential hypertension, manifest as increased parathyroid gland secretory capacity. Am J Hypertens 1995;8:957–964

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Human essential hypertension has been associated with alterations of systemic calcium metabolism. Several links between calcium metabolism and blood pressure control have been hypothesized, such as common cellular transport systems or direct vascular actions of calcium and calcium-regulating hormones. When compared to normotensive controls, patients with essential hypertension have been reported to have decreased serum ionized calcium concentration,[1–5] hypercalciuria,[4–7] elevated serum parathyroid hormone

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(PTH) concentration,[6–10] low serum $1,25(OH)_2$-vitamin D concentration,[10] and decreased trochanteric bone mineral density.[11] However, other studies have reported no difference in these measurements between hypertensive and normotensive subjects.[12–14]

The detection of subtle differences in mineral metabolism between hypertensive and normotensive subjects may depend on the measurement conditions.[5] We reasoned that alterations in PTH and $1,25(OH)_2$-vitamin D metabolism would be magnified under stimulated conditions. In order to detect and characterize the nature of the blood pressure associated differences, we studied the regulatory response of PTH and $1,25(OH)_2$-vitamin D to the stimuli of acute hypocalcemia followed by a low calcium diet in hypertensive and normotensive men.

METHODS

Subjects Hypertensive and normotensive men between the ages of 18 and 70 years were recruited from an outpatient hypertension clinic population and from the general public. Women were not studied because of a previous finding that altered PTH metabolism in hypertensive subjects was dependent on gender.[10] Hypertensive subjects with possible secondary hypertension were excluded. Subjects were also excluded if they had disorders known to be associated with altered mineral metabolism, including primary hyperparathyroidism, calcium nephrolithiasis, alcohol abuse, untreated hyperthyroidism, and renal insufficiency. The protocol was approved by the Human Studies Committee of the Oregon Health Sciences University and all patients gave written informed consent.

Patients with treated hypertension were withdrawn from antihypertensive medications under close supervision and were untreated for at least 2 months at the onset of the protocol. Study subjects were asked to refrain from using vitamin or mineral supplements, including calcium carbonate. After all blood pressure medications and dietary supplements were stopped, patients and controls were seen on at least 3 separate days for measurement of blood pressure in the supine, seated, and standing positions using a Hawksley random-zero sphygmomanometer. In order to qualify for the study, hypertensive subjects were required to have a mean arterial pressure (MAP) $\geq$ 105 mm Hg in any position on three separate measurements. Normotensive subjects were required to have an MAP $<$ 105 mm Hg in all positions at each visit. Baseline measurements were performed, including serum concentrations of calcium, phosphorus, magnesium, intact PTH, $1,25(OH)_2$-vitamin D, and 25 (OH)-vitamin D, and 24-h urinary excretion of calcium, sodium, phosphorus, magnesium, creatinine, and potassium.

EDTA Infusion Test Subjects were admitted to the Clinical Research Center (CRC) after an overnight fast for a modified EDTA-infusion test.[15–17] Beginning at 8 AM, subjects received an infusion of 5% dextrose at 250 mL/h for 1 h. At 9 AM, Na-EDTA was infused at a dose of 12.5 mg/kg/h for the first hour and 25 mg/kg/h for the second hour. EDTA was dissolved in 5% dextrose with 20 mL of 0.5% lidocaine added and was infused at a rate of 250 mL/h. An infusion of 5% dextrose was resumed for 1 h after the EDTA infusion. Blood specimens were obtained at baseline and every 15 min during and for 1 h following the EDTA infusion for measurement of total calcium, ionized Ca, and intact PTH. The clinical status of the subjects was carefully monitored throughout the infusion for signs of hypocalcemia.

Calcium Deprivation Test Following the EDTA infusion, subjects were instructed by a dietician to consume a diet containing $<$400 mg calcium/day for 3 days by avoiding dairy products, eggs, seafoods, and certain vegetables. Subjects returned to the CRC daily for fasting measurements of total calcium, ionized Ca, and $1,25(OH)_2$-vitamin D_3.

Measurements Ionized calcium was measured on fresh, anerobically collected, iced whole blood specimens using a calcium electrode (Lablyte 820 Analyzer, Beckman Instruments, Brea, CA). Serum and urine concentrations of total calcium, phosphorus, magnesium and creatinine were measured with an automated analyzer. Serum intact PTH was measured with a two-site immunoradiometric assay (Nichols Institute, San Juan Capistrano, CA). Serum $1,25(OH)_2$-vitamin D_3 was measured with a radioreceptor assay using calf thymus receptor[18] and 25(OH)-vitamin D was measured with a specific binding assay (Incstar, Stillwater, MN).

Analysis Data were analyzed by analysis of variance using a multiple nested model to test specific hypotheses. Repeated measures of variables of interest were fitted to a polynomial model and nested within blood pressure group and protocol phase; this allowed for comparing the rate of change of response between blood pressure groups within a given phase. The model was used to test for overall and phase-specific group effects and for time effects. A $P < .05$ was considered significant. Results are reported as mean $\pm$ 1 standard deviation.

RESULTS

Baseline characteristics of the 16 hypertensive patients and 15 normotensive control subjects who com-

TABLE 1. BASELINE CHARACTERISTICS OF HYPERTENSIVE PATIENTS AND NORMOTENSIVE CONTROL SUBJECTS

	Hypertensive Patients (n = 16)	Normotensive Controls (n = 15)	P
Supine blood pressure (mm Hg)			
Systolic	146 ± 10	120 ± 8	<.01
Diastolic	89 ± 7	74 ± 4	<.01
Mean arterial pressure	108 ± 7	89 ± 4	<.01
Age (years)	52.8 ± 8.1	48.8 ± 14.1	.36
Body weight (kg)	96.1 ± 15.6	85.7 ± 12.7	.05
Body mass index (kg/m^2)	30.3 ± 4.0	27.0 ± 3.7	.025
Serum measurements			
Ionized calcium (mmol/L)	1.25 ± 0.03	1.26 ± 0.04	.62
Total calcium (mg/dL)	9.2 ± 0.4	9.4 ± 0.3	.13
Phosphorus (mg/dL)	2.9 ± 0.4	3.0 ± 0.4	.51
Magnesium (mg/dL)	2.1 ± 0.2	2.0 ± 0.2	.56
Creatinine (mg/dL)	1.1 ± 0.1	1.1 ± 0.1	.34
Intact PTH (pg/mL)	36 ± 9	39 ± 14	.46
1,25(OH)$_2$-vitamin D (pg/mL)	32 ± 6	32 ± 8	.90
25(OH)-vitamin D (ng/mL)	14 ± 3	12 ± 4	.41
Urine measurements			
Calcium (mg/24 h)	208 ± 128	164 ± 77	.26
Magnesium (mg/24 h)	135 ± 50	121 ± 39	.39
Phosphorus (mg/24 h)	1170 ± 388	1055 ± 346	.39
Creatinine (mg/24 h)	1806 ± 438	1698 ± 373	.47
Sodium (mmol/24 h)	186 ± 50	167 ± 58	.32
Potassium (mmol/24 h)	80 ± 17	71 ± 19	.16
Creatinine clearance (mL/min/1.73 m^2)	154 ± 21	150 ± 11	.76

Values are mean ± SD.

pleted the study are shown in Table 1. Blood pressure was significantly higher in patients than controls by design. Although all patients met the specified blood pressure criteria, the degree of blood pressure elevation was mild, as indicated by an average, untreated baseline blood pressure of 146 ± 10/ 89 ± 7 mm Hg. There was no significant difference in the average age of the two groups. Body weight and body mass index were greater in the hypertensive patients than the normotensive controls. There were no significant group differences in the serum concentrations of minerals, mineral-regulating hormones, and creatinine, in the urinary excretion of sodium, calcium and other minerals, or in creatinine clearance. Baseline dietary intake was similar in patients and controls with respect to calcium, phosphorus, magnesium, and sodium (Table 2). However, dietary intake of calories, cholesterol, and potassium were significantly higher in the hypertensive than in the normotensive group.

On the day of the EDTA infusion, the baseline concentrations of serum ionized calcium and PTH were also similar in hypertensive and normotensive subjects. Infusion of EDTA caused an immediate fall in the serum ionized calcium concentration (Figure 1, $P < .001$). Serum ionized calcium fell further during the second hour of the EDTA infusion when the higher

TABLE 2. BASELINE DAILY DIETARY INTAKE FOR HYPERTENSIVE PATIENTS AND NORMOTENSIVE CONTROL SUBJECTS

	Hypertensive Patients (n = 16)	Normotensive Controls (n = 15)	P
Total calories (kcal)	2763 ± 507	2377 ± 547	.051
Carbohydrate (g)	315 ± 111	284 ± 59	.352
Protein (g)	107 ± 20	92 ± 25	.076
Total fat (g)	115 ± 20	93 ± 35	.040
Cholesterol (mg)	356 ± 92	232 ± 86	.001
Minerals and electrolytes			
Calcium (mg)	937 ± 233	1019 ± 348	.444
Phosphorus (mg)	1628 ± 284	1481 ± 400	.245
Magnesium (mg)	402 ± 105	366 ± 78	.294
Sodium (mmol)	159 ± 46	142 ± 41	.287
Potassium (mmol)	99 ± 14	85 ± 17	.020
Vitamins			
Vitamin A (μg*)	1254 ± 491	1230 ± 577	.900
Vitamin C (mg)	144 ± 72	123 ± 81	.448
Vitamin D (μg)	7.9 ± 4.6	5.6 ± 1.8	.089
Thiamine (mg)	2.0 ± 0.5	1.8 ± 0.4	.249
Other			
Zinc (mg)	15 ± 4	12 ± 4	.112
Ethanol (g)	12 ± 13	11 ± 14	.788

Values are mean ± SD.

**Expressed as μg of retinoid equivalent.*

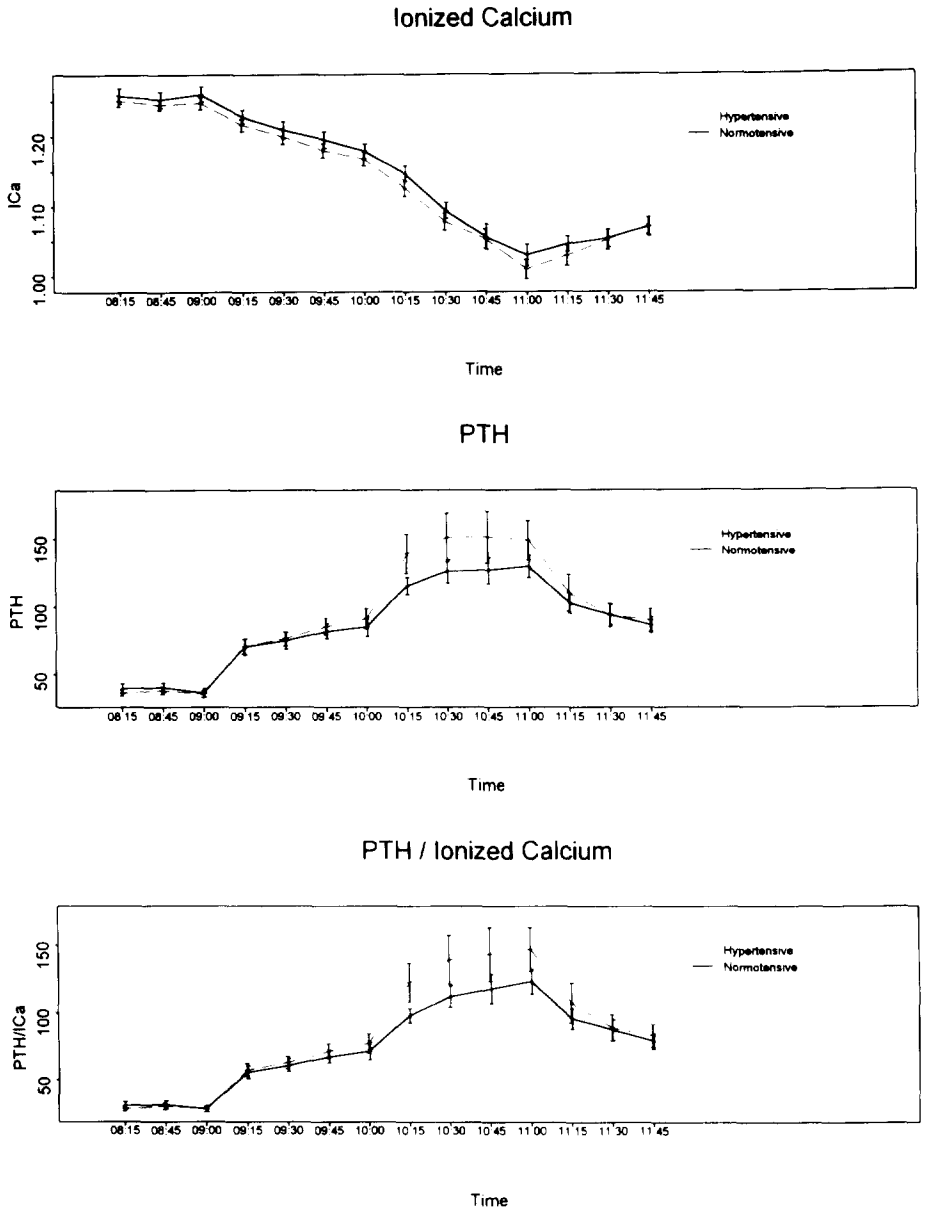

FIGURE 1. *Time course of changes in serum ionized calcium concentration, intact PTH concentration, and the ratio of PTH/calcium before, during and after EDTA infusion for hypertensive (dashed lines) and normotensive (solid lines) subjects.*

dose was administered. The time course and magnitude of the fall in serum ionized calcium were similar in the hypertensive and normotensive subjects (P = .42). Serum PTH concentration rose in a dose dependent manner in concert with the fall in ionized calcium. However, the serum PTH concentration rose to a significantly higher level in the hypertensive patients than the normotensive controls during the second hour of the EDTA infusion ($P < .001$). The decline in PTH after cessation of the EDTA infusion was similar between the groups (P = .22). The ratio of PTH to ionized calcium also reached a higher value in patients than controls during the second hour of the infusion ($P < .001$). The relationship between serum ionized calcium and PTH concentration indicated an increased secretory maximum for PTH for the patients as compared to the controls (Figure 2).

Following the two hour period of EDTA-induced hypocalcemia, the serum concentration of $1,25(OH)_2$-vitamin D had not changed from baseline (P = .76, Figure 3). Over the next three days while the subjects consumed a low calcium diet, the $1,25(OH)_2$-vitamin D concentration rose significantly above baseline ($P <$ .001). However, there were no differences in $1,25(OH)_2$-vitamin D concentrations between the hypertensive and normotensive subjects under baseline or stimulated conditions (P = .82). Also, the serum concentration of 1,25(OH)-vitamin D was not different in the two groups throughout the study (P = .24, Table 1, Figure 3). The serum concentrations of ionized and total calcium fell comparably in the two groups while on the low calcium diet ($P < .01$ for the hypertensive group and $P < .05$ for the normotensive group).

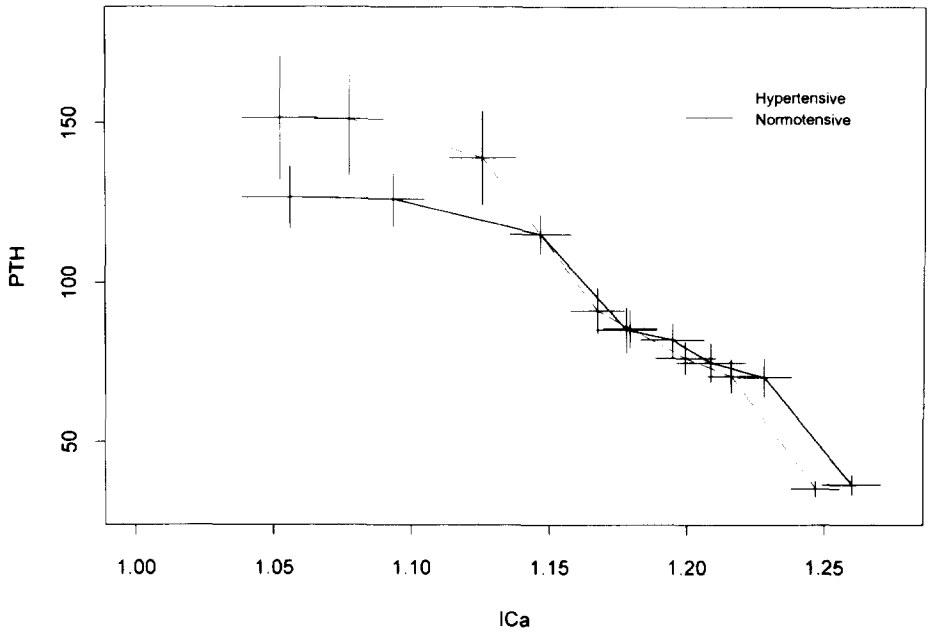

FIGURE 2. *Relationship between intact PTH and serum ionized calcium with induction of EDTA-induced hypocalcemia. Responses shown for hypertensive (dashed line) and normotensive (solid line) subjects.*

DISCUSSION

An association between calcium metabolism and blood pressure regulation has been observed in a number of studies. Several hypotheses have been proposed regarding a possible causal link between calcium metabolism and blood pressure regulation. For example, the cellular basis for altered calcium metabolism may also underlie the elevated blood pressure.[19] Alternatively, systemic alterations in mineral metabolism may contribute to hypertension.[20] Along these lines, both PTH and $1,25(OH)_2$-vitamin D have been shown to induce acute and chronic changes in blood pressure of experimental animals.[21–23]

PTH- and $1,25(OH)_2$-vitamin D-specific receptors have been demonstrated in vascular tissue.[24,25] Fur-

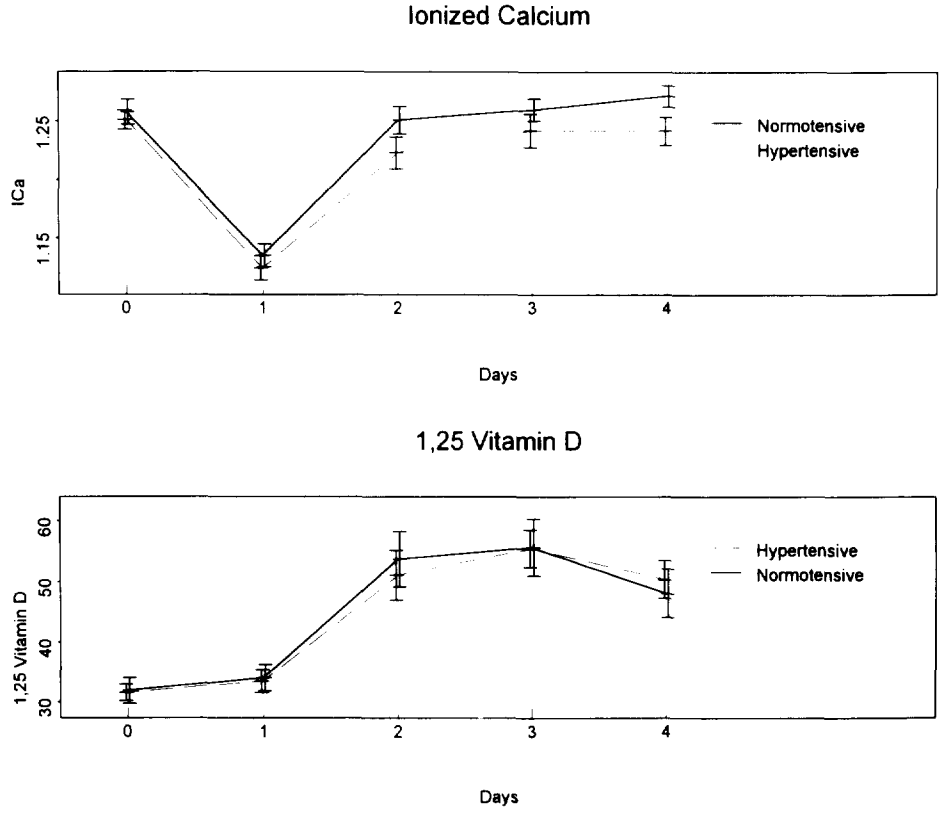

FIGURE 3. *Ionized calcium and $1,25(OH)_2$-vitamin D concentrations at baseline, after EDTA infusion, and during calcium deprivation for hypertensive (dashed line) and normotensive (solid line) subjects.*

thermore, variations in PTH and 1,25(OH)$_2$-vitamin D levels have been linked to blood pressure regulation in humans. Thus, a full understanding of systemic mineral metabolism in essential hypertension may be relevant to the vascular changes that are the proximate cause of the high blood pressure. These considerations may also be relevant to the finding that oral calcium supplementation has been reported to lower blood pressure in human and experimental hypertension.[26,27]

The detection of differences in calcium metabolism between hypertensive and normotensive subjects depends on patient characteristics including renin status, sex, age and diet.[3,5,9,10] Recently, we reported that differences in urinary calcium excretion were detectable only when subjects consumed standardized diets.[5] In that study, hypertensive subjects consuming a controlled diet had higher urinary calcium excretion, lower serum ionized calcium concentration and no difference in PTH concentration as compared to normotensive subjects. We hypothesized that presumed blood pressure associated differences in serum PTH concentration or parathyroid activity would be unmasked by acute hypocalcemia induced by a controlled infusion of Na-EDTA. Similarly, differences in serum 1,25(OH)$_2$-vitamin D concentration should be brought out by several days of dietary calcium deprivation.

In the current study, no baseline differences in the serum concentrations of ionized calcium, PTH and 1,25(OH)$_2$-vitamin D and urinary excretion of calcium were found, although this could be due to lack of controlled diets.[5] However, a controlled and comparable degree of EDTA-induced hypocalcemia resulted in a significantly larger PTH response in the hypertensive patients that the normotensive controls (Figures 1 and 2). This finding is consistent with several published studies showing that the serum concentration of PTH, as measured by intact, N-terminal, and C-terminal assays systems, is higher in hypertensive patients than in normotensive control subjects.[6–10] In these studies, the blood PTH concentration, although higher in hypertensive than in normotensive subjects, was still in the normal range. Of particular note, Grobbee found a continuous relationship between blood pressure and PTH in a population studied under free-living conditions.[8] Also, normotensive offspring of hypertensive parents have been reported to have higher PTH concentration than offspring of normotensive parents.[28]

In our study, the level of blood pressure was only mildly elevated in the patient group. The mild degree of blood pressure elevation in our sample could lead to an underestimate of altered calcium metabolism associated with hypertension. The hypertensive patients were heavier than the normotensive control subjects (Table 1). While serum PTH has been reported to be elevated in obese subjects,[29] other studies do not support this relationship.[30–32] Therefore, we believe that the difference in body weight is an unlikely explanation for our observations. We found no differences between the hypertensive and normotensive groups in other factors known to influence PTH secretion, such as serum ionized calcium concentration, 1,25(OH)$_2$-vitamin D concentration, and renal function as estimated by the serum creatinine concentration and creatinine clearance (Table 1). Therefore, our results suggest an intrinsic alteration of PTH regulation in hypertensive subjects. Because we did not attempt to suppress PTH secretion with a calcium load, the complete relationship between serum ionized calcium concentration and PTH concentration was not defined. However, it would appear that the maximum secretory capacity of PTH is increased in hypertensive subjects.[33] This interpretation suggests underlying parathyroid hyperplasia in human hypertensive subjects as has been described in the spontaneously hypertensive rat[34] and in renal transplant patients who have undergone parathyroidectomy for hypercalcemia.[16] Our results could also be explained by end-organ resistance to PTH in essential hypertension.[35]

In contrast to PTH, the serum concentration of 1,25(OH)$_2$-vitamin D was not different in the two groups of subjects under basal and stimulated conditions. This result agrees with a previous report from our group,[10] but contrasts with Resnick's finding that 1,25(OH)$_2$-vitamin D was elevated in patients with low-renin hypertension.[9] Whether the 1,25(OH)$_2$-vitamin D concentrations are appropriate in the face of altered PTH regulation is a matter of conjecture and should be addressed in future studies. However, our data does not support the presence of readily apparent differences in 1,25(OH)$_2$-vitamin D regulation between hypertensive and normotensive subjects. No group differences were found in serum ionized calcium concentration and urinary calcium excretion under free-living conditions (ie, subjects not on fixed, metabolic diets). This study was not designed to detect differences in these variables, but rather to test for differences in PTH and 1,25(OH)$_2$-vitamin D responsiveness. However, it is noteworthy that the serum concentration of ionized calcium was consistently, if not significantly, lower in hypertensive than normotensive subjects throughout the study (Figures 1 and 3).

If there is a mechanistic link between the regulation of blood pressure and calcium metabolism, then it would appear that we are measuring indirect markers rather than actual mediators of the relationship. Our current findings should be incorporated with the body of evidence that urinary calcium excretion is

increased in patients with high blood pressure[4–7] and that hypertensive individuals are more likely than normotensive subjects to be consuming low calcium diets.[36] Although speculative, this constellation of findings could be explained by the presence of a cellular defect in calcium transport in at least a subset of individuals with elevated blood pressure. Abnormal cell calcium transport could affect vascular responsiveness, resulting in elevated blood pressure, and epithelial calcium transport, resulting in impaired intestinal absorption and renal reabsorption of calcium. The appropriate systemic response would be chronic stimulation of the parathyroid glands and the development of increased secretory capacity for PTH as observed in this study. As noted, partial PTH resistance in hypertension could result in similar findings.[35] Additional studies in humans and experimental animals will be needed to identify more precisely the nature of the putative cell calcium defect that links alterations in calcium metabolism to elevated arterial blood pressure.

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