Urinary Calcium Excretion in Familial Hypocalciuric Hypercalcemia

PERSISTENCE OF RELATIVE HYPOCALCIURIA AFTER INDUCTION OF HYPOPARATHYROIDISM

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ABSTRACT Familial hypocalciuric hypercalcemia (FHH) is an autosomal dominant trait comprising hypercalcemia, hypophosphatemia, parathyroid hyperplasia, and unusually low renal clearance of calcium. We evaluated the role of parathyroid hormone in the relative hypocalciuria of FHH and characterized the renal transport of calcium in this disorder using three previously hypercalcemic FHH patients with surgical hypoparathyroidism and three controls with surgical hypoparathyroidism. Intravenous infusion of calcium chloride in two patients with FHH and in three controls increased serum calcium from a mean basal of 5.0 to a mean peak of 6.8 meq/liter in two FHH patients and from 4.2 to 5.7 in three control subjects. Urinary calcium in a third FHH patient was studied without calcium infusion during recovery from hypercalcemia of vitamin D intoxication. At all serum concentrations of calcium, calcium clearance was lower in FHH than in controls; at base-line serum calcium, the ratio of calcium clearance to inulin clearance (C_{Ca}/C_{IN}) in FHH subjects was 32% of that in controls and decreased to 19% during hypercalcemia. Calcium infusion increased the ratio of sodium clearance to inulin clearance in controls from a base line of 0.020 to 0.053 at peak concentrations of calcium in serum, but did not affect this parameter in FHH (0.017 at base-line serum calcium vs. 0.019 at peak).

When calcium infusion studies were performed (in two patients with FHH and one control) during administration of acetazolamide, a drug whose principal renal action causes inhibition of proximal transport of solute, C_{Ca}/C_{IN} in the patients with FHH was 29 and 7% of that of the control at base-line and peak serum calcium, respectively. In contrast, ethacrynic acid, a diuretic that acts in the ascending limb of the loop of Henle, increased C_{Ca}/C_{IN} more in the FHH patients than in the control subject; C_{Ca}/C_{IN} was 65% at base-line and 47% at peak serum calcium, compared with that of the control subject. The greater calciuric response to ethacrynic acid than to acetazolamide or calcium infusion alone in FHH indicates that a major renal locus of abnormal calcium transport in this disorder may be the ascending limb of the loop of Henle.

Decreased clearance of calcium in patients with FHH and hypoparathyroidism when compared with hypoparathyroid controls indicates that relative hypocalciuria in FHH is not dependent on hyperparathyroidism. Since the parathyroid glands in FHH are not appropriately suppressed by calcium, this implies that FHH represents a disorder of abnormal transport of, and/or response to, extracellular calcium in at least two organs, parathyroid gland and kidney.

INTRODUCTION

Familial hypocalciuric hypercalcemia (FHH)[1] or familial benign hypercalcemia is an autosomal disorder that resembles typical primary hyperparathyroidism (1, 2); patients with either disorder have hypercal-

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[1] *Abbreviations used in this paper:* FHH, familial hypocalciuric hypercalcemia; hPTH, human PTH; PTH, parathyroid hormone.

cemia and may have hypophosphatemia (3, 4). Although patients with FHH and patients with typical primary hyperparathyroidism exhibit similar elevation in serum concentration of total ultrafiltrable calcium and similar creatinine clearance (and thus similar filtrable loads of calcium) (3), patients with FHH have lower urinary excretion rates for calcium, indicating a lower renal clearance of calcium in FHH (3–5). Renal transport of magnesium also differs; in FHH, there is a normal or high serum concentration of magnesium (total and ultrafiltrable), reflecting a renal clearance of magnesium lower than that in typical primary hyperparathyroidism (3).

The pathogenesis of the low renal clearance of calcium and, in particular, the role of parathyroid hormone (PTH) in this process have not been elucidated. Although PTH decreases renal clearance of calcium and magnesium (6–9), indices of circulating PTH (plasma concentration of PTH fragments by immunoassay, urinary cyclic AMP [cAMP] excretion, and renal tubular maximum of phosphate transport corrected for glomerular filtration rate [T_mP/GFR]) are less abnormal in FHH than in typical primary hyperparathyroidism at any level of serum calcium (4, 10). Thus, factors other than merely the concentration of circulating PTH may determine the abnormal renal transport of divalent cations in FHH.

Attempts at total or subtotal parathyroidectomy in FHH occasionally have led to profound hypocalcemia (2) and a state resembling hypoparathyroidism (see below). In typical hypoparathyroidism, the absence of PTH effect on renal tubular calcium reabsorption leads to a high renal clearance of calcium (6, 8, 11). We compared the renal handling of calcium in a group with surgical hypoparathyroidism and FHH with that in a control group with surgical hypoparathyroidism. The low renal clearance of calcium characteristic of FHH persists even upon development of hypoparathyroidism. Moreover, our findings in this group with infusion of diuretics suggest that the loop of Henle is a possible locus for this abnormal calcium transport.

METHODS

Subjects

We studied three patients with FHH, who had been referred to the National Institutes of Health (NIH) after having been rendered hypocalcemic by prior parathyroidectomy, and three control subjects with postsurgical hypoparathyroidism. Criteria for hypoparathyroidism were as follows: Serum calcium was <3.75 meq/liter in the absence of calcium and/or vitamin D supplementation on one or more occasions at least 6 mo after parathyroidectomy, urinary cAMP was not elevated during hypocalcemia, and plasma immunoreactive PTH was undetectable at a time of hypocalcemia. The three subjects with FHH were previously hypercalcemic members of typical FHH kindreds.

Subject 1. This 17-yr-old male had been hospitalized at 14 d of age with dehydration. The serum calcium was 10.5 meq/liter and the serum phosphorus 3.9 mg/100 ml. At neck exploration, three of four hyperplastic parathyroid glands were removed, but severe hypercalcemia recurred and 1 mo later the remaining hyperplastic gland was excised (12). Since that time, he has required calcium and vitamin D supplementation to maintain a serum calcium concentration > 4.0 meq/liter. Serum concentrations of calcium have been between 3.5 and 3.8 meq/liter at times of poor compliance. At least 11 other members of this patient's family had hypercalcemia; urinary calcium, evaluated in five hypercalcemic members, was <7 meq/d in all (family 0 in reference 2, family B in reference 13).

Subject 2. During an evaluation of paresthesiae in 1976, this 28-yr-old male had been found to have a serum concentration of calcium of 7.0 meq/liter and a serum phosphorus ranging between 1.7 and 2.1 mg/100 ml. He was otherwise asymptomatic. At neck exploration, 3¾ hyperplastic parathyroid glands were excised (total weight 1.6 g) but hypercalcemia persisted. At a subsequent exploration, the gland remnant was removed. Postoperatively, the serum calcium remained low, despite oral calcium supplements. During periods of poor compliance, the serum calcium has dropped as low as 3.6 meq/liter. Three other members of this subject's family (family N in reference 2) have had hypercalcemia without hypercalciuria.

Subject 3. This 7-yr-old female was hypercalcemic at birth (7 meq/liter), with a serum magnesium of 2.34 meq/liter, and a serum phosphorus of 3.4 mg/100 ml. Urine calcium was <1 meq/d. Radiographs showed subperiosteal resorption and diffuse undermineralization. At 2 wk of age, four hyperplastic parathyroid glands were excised. Since that time, she has required calcium and vitamin D. Without these medications the serum calcium concentration has been as low as 2.7 meq/liter. This subject and her family have been described in detail (13, 14). Urine calcium excretion in 13 of her hypercalcemic relatives was in the range characteristic of FHH (13).

Two of the three control subjects became hypoparathyroid after total thyroidectomy for nonmetastatic thyroid carcinoma (subjects 4 and 5). A third (subject 6), with primary hyperplasia, became hypoparathyroid after a second neck exploration 8 mo before study. His brother had primary hyperparathyroidism and Cushing's disease, which suggests that they have multiple endocrine neoplasia, Type I. None of the controls had had known episodes of vitamin D intoxication or urinary tract infections. None of the subjects was hypertensive, nor were they taking drugs (other than calciferol) known to alter renal handling of calcium.

Study protocol

The adult subjects were admitted to a metabolic ward and given a diet containing ~40 meq (800 mg) of calcium, 800–1,000 mg phosphorus, and 4–6 g sodium chloride/d. Dietary calcium was supplemented with calcium containing medications (Table I). Informed consent was obtained for all experimental procedures.

Serum and urinary electrolyte and phosphorus concentrations and serum calcium concentrations were determined in a Technicon-SMAC (Technicon Instruments Corp., Tarrytown, NY) in the Clinical Chemistry Laboratory of the Clinical Center, NIH. Serum and urinary magnesium and urinary calcium were analyzed by atomic absorption spectrophotometry (model 5000, Perkin-Elmer Corp., Instrument Div., Norwalk, CT). Normal ranges (2 SD) for serum com-

ponents were determined from 250 blood donors at the Clinical Center Blood Bank. cAMP in urine was measured by radioimmunoassay (10). PTH in plasma was analyzed with a radioimmunoassay specific for the midportion of the molecule, using purified human PTH (hPTH) as standard (15); the normal range was undetectable to 0.24 ng eq hPTH/ml. The detection limit was 0.10 ng eq hPTH/ml and PTH was detectable in plasma from 50% of normal subjects. Inulin concentration was determined in serum and urine by previously described methods (16).

Calcium, phosphorus, sodium, and creatinine were analyzed in specimens from 24-h urine collections. Calcium, phosphorus, magnesium, and electrolytes in serum and PTH in plasma were determined in samples obtained after overnight fast. cAMP was analyzed by radioimmunoassay in at least four sequential 12-h urine collections and adjusted for glomerular filtration rate as follows (17): $(U_{cAMP} \times S_{cr})/U_{cr}$, where U_{cAMP} is the urinary concentration of cAMP, and S_{cr} and U_{cr} are serum and urine concentrations of creatinine, respectively.

Clearances of inulin, creatinine, calcium, phosphorus, and sodium were calculated in the usual manner. No adjustment was made for ultrafiltrability of calcium in serum. Data were evaluated using the *t* test, two-way analysis of variance, and linear least-squares regression (18).

Clearance studies were performed after an overnight fast with the subjects recumbent except when voiding. To maintain urine flow, they drank 200 ml of distilled water at 0700 h and then every 30 min for the remainder of the study. Infusion of inulin (35 mg/kg body weight loading dose, followed by a sustaining infusion consisting of 0.07 mg/kg in 250 ml normal saline at 1.1 ml/min) was started at 0800 h. Between 0730 and 0830 h, 5 ml/kg of 0.15 M sodium chloride was given to expand extracellular fluid. Calcium chloride (100 meq elemental calcium/liter of 0.075 M sodium chloride) was infused at two rates: 75–100 μeq elemental calcium/kg·h and 100–160 μeq/kg·h. Urine from 20-min clearance periods was obtained before infusion of calcium (0830–0910 h) and during each rate of calcium infusion, after allowing 30 min for serum calcium to stabilize. Venous blood was obtained through an indwelling catheter without hemostasis (in an antecubital vein contralateral to the infusion catheter) at the midpoint of each urine collection period for determination of serum concentrations of calcium, sodium, and inulin.

The effects of diuretics were assessed with a modification of the calcium infusion protocol. Beginning at 0700 h, 200 ml of distilled water was ingested every 30 min and 5 ml/kg body weight of 0.15 M sodium chloride was given over a period of 1 h. Inulin was given as described above. At 0800 h, a loading dose of either ethacrynic acid (0.25 mg/kg) or acetazolamide (2.5 mg/kg) was given, followed by maintenance infusion (0.2 mg/kg h ethacrynic acid or 2.5 mg/kg h acetazolamide) for the remainder of the infusion. Urinary losses of sodium, potassium, and bicarbonate were estimated from urinary volume and rapid measurement of concentrations of urinary sodium and potassium (results obtained within 15 min) and were quantitatively replaced with intravenous solutions containing either 0.15 or 0.075 M sodium chloride and variable amounts of potassium chloride. Clearance periods were 15 min with a midpoint blood collection. Base-line collections were started after urinary volume varied <20% in two consecutive collections: This generally required 45–60 min. Calcium chloride was then infused at the two rates as described above and two 15-min clearance periods were obtained after allowing 30 min for serum calcium to stabilize.

RESULTS

Metabolic indices during steady state. With their usual calcium and vitamin D supplementation (Table I), FHH patients and controls were mildly hypocalcemic (Table II). Mean serum phosphorous was high in the three FHH patients and in two of three control subjects. Urinary excretion of phosphorus for the two groups was similar. The ratio of phosphorus clearance to creatinine clearance was similarly low in both groups. Taken together, these data indicate a high threshold for renal excretion of phosphorus in hypoparathyroid patients with FHH, in contrast to the low threshold in patients with FHH and hypercalcemia (10). At a time when serum calcium was low, immunoreactive PTH was below the lower limit of detectability and urinary cAMP was not elevated. Thus, by standard indices of circulating PTH (renal phosphate transport, plasma immunoreactive PTH, and urinary cAMP), patients with FHH were similar to the control subjects.

Table III shows means of serum and urinary calcium and magnesium, urinary sodium, and creatinine clearance obtained throughout the hospitalization. Subjects in both groups had similarly low to normal serum con-

TABLE I
Medications for Treatment of Hypoparathyroidism in Patients and Controls

Subject	Group	Age	Sex	Daily calciferol supplement	Daily calcium supplement*
		yr			
1	FHH	18	M	1.25 mg Ergocalciferol	34 g Calcium gluconate (3 g)
2	FHH	32	M	1.25 mg Ergocalciferol	10 g Calcium gluconate (0.9 g)
3	FHH	7	F	1.25 mg Ergocalciferol	11 g Calcium glubionate (0.7 g)
4	Control	38	F	0.25 mg Dihydrotachysterol	4 g Calcium gluconate (0.4 g)
5	Control	45	F	1.88 mg Ergocalciferol	9.6 g Calcium lactate (1.2 g)
6	Control	22	M	0.5 μg 1,25-Dihydroxycholecalciferol	30 g Calcium gluconate (2.7 g)

* Calcium as elemental calcium is given in parentheses.

TABLE II

*Indices of PTH Activity during Periods of Mild Hypocalcemia**

Subject	Group	Serum calcium	Serum phosphorus	Urinary phosphorus	Phosphorus creatinine clearance ratio	PTH	Urinary cAMP
		meq/liter	*mg/100 ml*	*mg/24 h*		*ng eq/ml*	*nmol/100 ml glomerular filtrate*
1	FHH	4.2	4.6	558	0.05	<0.10	1.82
2	FHH	3.9	4.7	490	0.04	<0.10	2.45
3	FHH	3.5	6.5	322	0.09	<0.10	1.61
Mean		3.9	4.7‡	524‡	0.05‡	<0.10	1.96
4	Control	4.1	3.5	469	0.03	<0.10	1.86
5	Control	4.0	5.1	453	0.05	<0.10	ND
6	Control	4.1	4.7	388	0.04	<0.10	2.67
Mean		4.1	4.4	436	0.04	<0.10	2.27
Normal range		4.5–5.3	2.1–3.8	—	0.08–0.17§	<0.24‖	1.2–3.6¶

* Results obtained from fasting blood specimens and 24-h urine collections during a period of hypocalcemia. Data (except PTH radioimmunoassay) represent means of at least four determinations.
‡ Mean of two adult subjects (numbers 1 and 2) only.
§ Mean±2 SD determined in 10 normal volunteers.
‖ Normal values during hypocalcemia are >0.24 ng eq/ml.
¶ Mean±2 SD determined in 20 normal volunteers.

centrations of magnesium and similar urinary magnesium excretion. Despite higher calcium concentrations in serum during this period, adults with FHH and hypoparathyroidism each excreted less calcium in urine than any of the three controls (Table III).

Calcium transport by kidney at varying concentrations of calcium in serum. Calcium infusions were performed on the two hypoparathyroid FHH adults and three hypoparathyroid controls. Urinary calcium is expressed in Fig. 1 *A* per unit of time and in Fig. 1 *B* per unit of glomerular filtration rate. At all concentrations of calcium in serum, urinary calcium expressed in units of time (Fig. 1 *A*) or of glomerular filtration rate (Fig. 1 *B*) was higher in the three hypoparathyroid controls than in the FHH patients, and the absolute value of this difference increased at higher calcium concentrations in serum. Changes in glomerular filtration rate could not account for these differ-

TABLE III

*Serum and Urine Divalent Cations, Urinary Sodium, and Creatinine Clearances**

Subject	Group	Serum calcium	Serum magnesium	Urinary calcium		Urinary magnesium	Urinary sodium	Creatinine clearance
		meq/liter		*meq/d*	*meq/liter GF × 100*		*meq/d*	*ml/(min × 1.73 m²)*
1	FHH	4.8	1.55	5.5	3.5	6.2	118	99
2	FHH	4.2	1.39	1.7	1.1	5.4	167	107
3	FHH	3.5	1.30	1.6	1.8	5.0	80	111
Mean‡		4.5	1.47	3.6	2.3§	5.8	143	103
4	Control	4.2	1.53	11.4	7.5	6.7	86	98
5	Control	3.9	1.34	12.2	11.5	6.4	69	85
6	Control	4.1	1.57	8.2	6.0	5.4	142	107
Mean		4.1	1.48	10.6	8.3§	6.2	99	97
Normal range		4.4–5.3	1.4–2.1	—	—	—	—	97–140 (males) 85–125 (females)

GF, glomerular filtrate.
* Results of fasting serum and 24-h urine collections. Data are means of at least six determinations.
Data from subject 3 obtained during an admission 5 mo after recovery from vitamin D intoxication.
‡ Mean is average of two adult subjects (1 and 2) only.
§ Means differ $P < 0.025$.

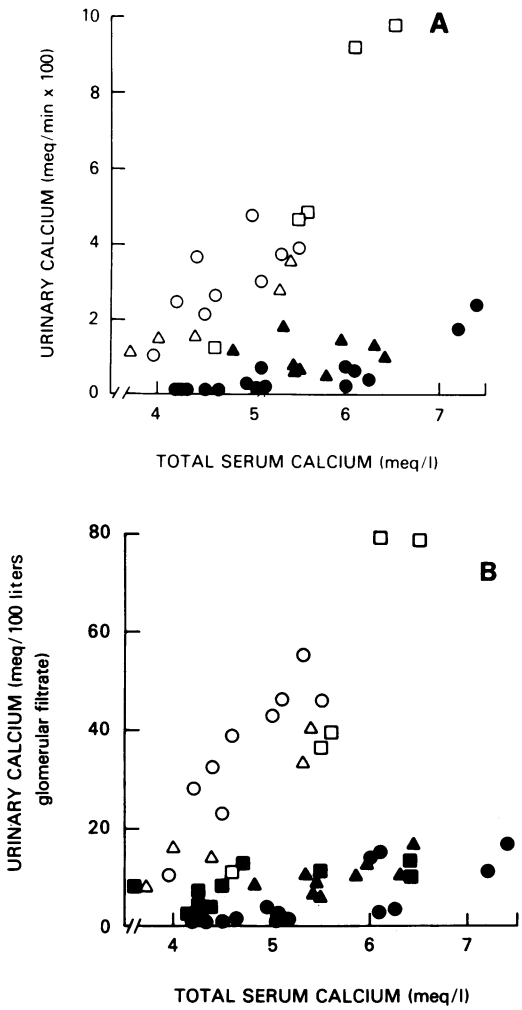

FIGURE 1 Effect of calcium load on urinary excretion of calcium in two FHH subjects (1, ▲; 2, ●) and three hypoparathyroid controls (4, ○; 5, △; 6, □) during infusion of calcium chloride. Calcium excretion is expressed as a function of time in *A* and glomerular filtration rate in *B*. Results from 12- and 24-h urine collections from subject 3 during an episode of vitamin D intoxication are plotted only in *B* (■) as a function of creatinine clearance. For each except subject 3, each point represents one 20-min clearance period. (Data from patient 3 were omitted from *A* because her age and small size result in data biased toward lower urinary calcium.)

ences, because there was little change in inulin clearance throughout the infusion in either group. Mean inulin clearances in the FHH patients for the first two periods at base-line serum calcium concentrations were 107 ml/min, and they were 127 ml/min for the two periods at peak calcium concentration; in the control group clearances were 115 and 104 ml/min, respectively.

Subject 3 was not given the calcium infusion because of age. Urinary calciums obtained during recovery from an episode of vitamin D (dihydrotachysterol) intoxication associated with serum calcium concentrations as high as 7.1 meq/liter are shown in Fig. 1 *B*. The urinary calcium excretion rate at high serum calcium in this subject is significantly different from the rate in members of the hypoparathyroid control group and suggests that calcium transport by the kidney of subject 3 is similar to that in the two adults with FHH and hypoparathyroidism.

Relation of calcium clearance to sodium clearance. Base-line sodium clearance before the calcium infusion was similar in the two groups, but differed strikingly during hypercalcemia (Table IV and Fig. 2). In the control group there was a marked increase in sodium clearance with increased serum calcium, whereas in the FHH group there was little increase in sodium clearance in response to the calcium load (Fig. 2).

Infusion of diuretics. We further studied renal calcium transport, using acetazolamide and ethacrynic acid, two drugs that alter renal transport at different sites in the nephron. These studies were performed in the two adult patients with FHH (subjects 1 and 2) and in one control with hypoparathyroidism (subject 4). Base-line sodium excretion rate was affected similarly by acetazolamide in both groups. However, calcium clearance before and during calcium infusion remained lower in the patients with FHH (Table IV and Fig. 3 *A*). In fact, the absolute value of the difference in calcium clearances between groups was increased by the drug-induced inhibition of proximal sodium reabsorption.

Ethacrynic acid produced a greater natriuresis than acetazolamide (Table IV). Natriuresis for the control subject with hypoparathyroidism was, for unknown reasons, greater than for the two patients with FHH. Although the absolute value of the clearance of calcium was still higher in the control patient with hypoparathyroidism, infusion of ethacrynic acid markedly increased the ratio of calcium clearance to inulin clearance in the FHH patients (Table IV); it was increased six- and 23-fold in these two patients at base-line serum calcium and nine- and eightfold at peak serum calcium vs. fourfold in the control patient at both basal and peak serum calcium. In the region of overlap of sodium clearance (Fig. 3 *B*), the degree of calciuria during ethacrynic acid administration was similar for patients with FHH and for the control patient.

DISCUSSION

In our three patients with FHH, parathyroidectomy produced a state resembling chronic hypoparathyroidism. As in typical hypoparathyroidism, there was an increased renal threshold for phosphate excretion and a requirement for pharmacologic doses of calciferols

TABLE IV

Calcium and Sodium Clearance at Base Line and Peak Serum Calcium during Infusion of Calcium Chloride Alone or with Diuretics

Infusion	Group/patient		Serum calcium	Calcium excretion	Sodium excretion	C_{IN}	C_{Ca}/C_{IN}	C_{Na}/C_{IN}
			meq/liter	*meq/min*		*ml/min*		
$CaCl_2$	FHH							
	1*	Base line‡	5.1	0.011	0.22	117	0.018	0.014
		Peak‡	6.2	0.011	0.23	127	0.014	0.013
	2*	Base line‡	4.8	0.002	0.27	96	0.005	0.020
		Peak	6.7	0.018	0.43	127	0.022	0.025
	Control							
	4	Base line	4.2	0.017	0.40	94	0.043	0.031
		Peak	5.3	0.043	0.94	103	0.079	0.066
	5	Base line	3.7	0.015	0.20	132	0.030	0.011
		Peak	5.4	0.036	0.41	90	0.073	0.032
	6	Base line	4.8	0.013	0.30	118	0.022	0.018
		Peak	6.3	0.095	1.01	120	0.126	0.060
Acetazolamide plus $CaCl_2$	FHH							
	1*	Base line	4.4	0.015	1.33	117	0.028	0.079
		Peak	5.7	0.017	1.14	108	0.028	0.076
	2	Base line	4.5	0.0005	0.41	83	0.001	0.036
		Peak	6.1	0.003	0.67	97	0.005	0.049
	Control							
	4	Base line	4.3	0.017	0.47	78	0.050	0.042
		Peak	5.7	0.110	1.78	80	0.240	0.160
Ethacrynic acid plus $CaCl_2$	FHH							
	1	Base line	5.2	0.084	4.02	152	0.106	0.190
		Peak	6.0	0.083	3.32	108	0.130	0.220
	2	Base line	4.6	0.080	3.28	151	0.114	0.155
		Peak	5.7	0.106	3.78	125	0.150	0.218
	Control							
	4*	Base line	4.0	0.083	4.20	121	0.170	0.240
		Peak	5.4	0.198	6.37	118	0.310	0.394

* Mean of two infusions.

‡ Mean of serum calcium concentrations and clearances for two to three clearance periods at base-line calcium (before calcium chloride infusion) or peak calcium (during infusion of calcium chloride at maximal rate).

and calcium. Moreover, at a time of hypocalcemia, circulating PTH activity was not increased, as evidenced by undetectable immunoreactive PTH, as well as a lack of a compensatory rise in urinary cAMP excretion. These parameters were similar to those of a control group with surgical hypoparathyroidism. If in FHH, renal tubular reabsorption of calcium showed dependency on circulating PTH similar to that for other parameters, such as calcium concentration in serum and renal tubular reabsorption of phosphate, the three FHH patients with hypoparathyroidism should have exhibited the high renal clearance of calcium usually seen in hypoparathyroidism. This was not the case, however, as renal clearance of calcium in subjects with FHH and hypoparathyroidism remained low when examined at steady-state levels of calcium in serum (Table III) or during calcium infusion (Fig. 1).

The patients with FHH and hypoparathyroidism in this study had previously been more severely affected than most patients presenting with FHH. In two patients (Nos. 1 and 3), the disorder presented with severe hypercalcemia in infancy and the other presented with one of the highest serum calcium concentrations we have documented in an adult with FHH (2). Thus, it is possible that these patients are not representative

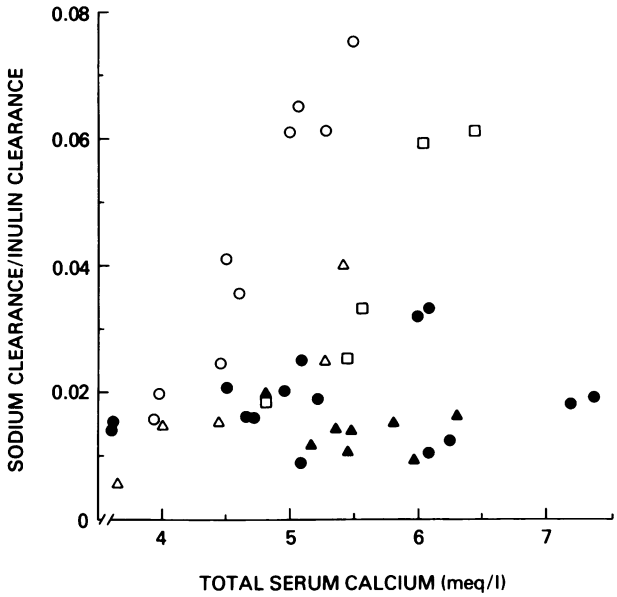

FIGURE 2 Sodium-to-inulin clearance ratio as a function of total serum calcium during infusion of calcium chloride in two subjects with FHH (1, ▲; 2, ●) and three controls with hypoparathyroidism (4, ○; 5, △; 6, □). Each point represents one clearance period for one subject. In the control subjects with hypoparathyroidism, there was a significant correlation ($y = 0.55 + 0.094x$, $r = 0.69$, $P < 0.01$), but not in subjects with FHH ($y = 0.13 + 0.0036x$, $r = 0.08$, $P > 0.05$). The slopes for the two regressions are significantly different ($P < 0.01$).

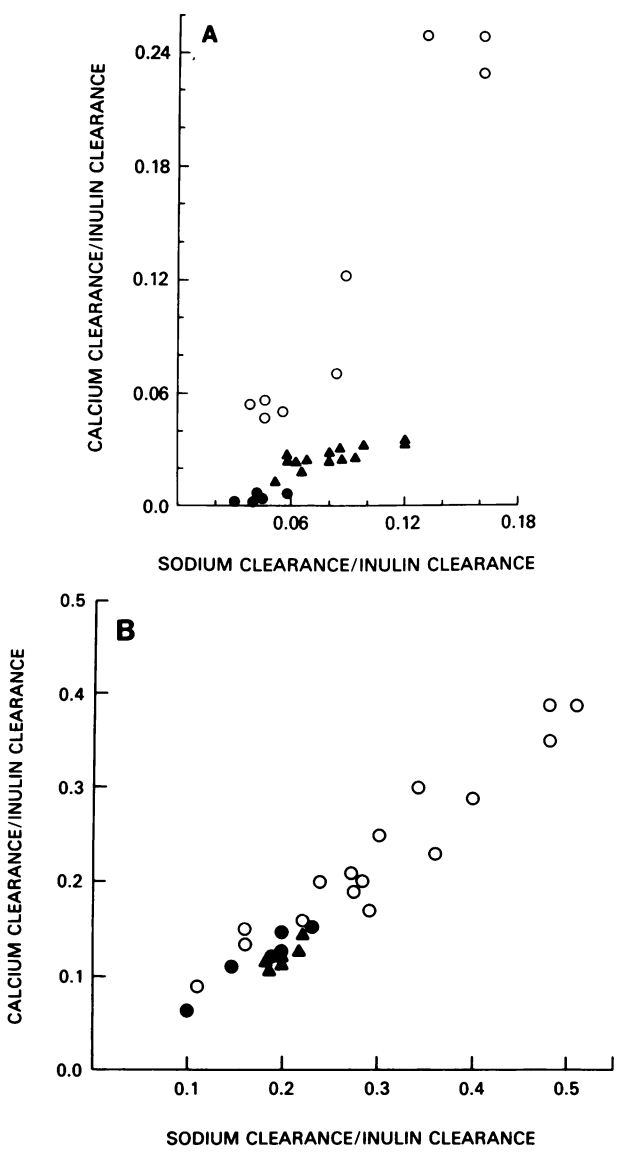

FIGURE 3 Effect of acetazolamide (*A*) or ethacrynic acid (*B*) administration during calcium chloride infusion on calcium clearance as a function of sodium clearance (with both clearances corrected for inulin clearance). Each point represents one clearance period. Studies were performed in two patients with FHH (1, ▲; 2, ●) and on two occasions in one control with hypoparathyroidism (4, ○).

of the genre and that the disorders we have identified are unique to them. However, since detailed evaluation of family members shows that these patients come from families with otherwise characteristic features of FHH, it is more likely that these patients showed a more severe form of the same disorder.

Although the low renal clearance of calcium in FHH is not dependent on hyperparathyroidism, our findings do not exclude the possibility that the low calcium clearance in FHH represents an exaggerated anticalciuric response to PTH (19). There is evidence that small amounts of PTH may circulate in patients with surgical hypoparathyroidism (20). If the low renal clearance of calcium in FHH does not represent an exaggerated anticalciuric response to PTH, other extra or intracellular factors must account for this feature. Among the factors that may affect renal calcium clearance are phosphate loading or depletion (21, 22), acid-base status (23), urinary sodium excretion (7), vitamin D related sterols (24) and serum concentration of calcium. Urinary phosphorus excretion and serum phosphorus concentration were comparable in the two groups, with the exception of subject 4 with persistently normal serum phosphorus and normal renal handling of phosphorus, despite other evidence of hypoparathyroidism (Table II). Although it is possible that this difference in phosphate excretion or balance may have caused calciuria (directly, or indirectly as a manifestation of renal tubular disease), her urinary calcium was consistently in the range of the other two controls. There was no evidence for a difference between groups in hydrogen ion metabolism; serum concentrations of chloride and bicarbonate in both groups were similar (data not shown). Although vitamin D related sterols

in some studies increase renal tubular reabsorption of calcium, this effect has not been found consistently and even opposite effects have been found (24). In this study, all subjects were taking pharmacologic doses of vitamin D. Circulating levels of calciferols were not measured, but it is not likely that the FHH patients had higher circulating levels of active vitamin D metabolites, since oral calcium requirements were similar in both groups.

From the data in Fig. 1, it appears that for any serum concentration of calcium or filtered load of calcium, tubular reabsorption of calcium is greater with FHH than in the controls. Infusion of diuretics which inhibit calcium transport in specific regions of the nephron provide an opportunity to localize sites of increased calcium reabsorption. Infusion of calcium together with acetazolamide increased the calcium clearance in the control patient, but produced virtually no change in the patients with FHH (Table IV). This suggests that the load of calcium delivered to the distal nephron as a result of calcium infusion and inhibition of proximal tubular reabsorption by acetazolamide exceeded the capacity of the distal segment to reabsorb calcium in the control but not in the patients with FHH (25, 26). This also suggests that the principal site of enhanced renal tubular reabsorption of calcium in FHH is not in the proximal tubule.

Ethacrynic acid, which inhibits sodium and calcium transport primarily in the thick ascending limb of the loop of Henle (26, 27), increased calcium clearance in the patients with FHH and in the control patient (Table IV). Although calcium clearance remained higher in the control than in the FHH patients after ethacrynic acid, the diuretic had a much greater effect on calcium clearance in the FHH subjects, so that the discrepancy between the two groups was proportionately less (Table IV). Sodium clearance after ethacrynic acid infusion was also greater in the control than in the patients with FHH, but, in those clearance periods where sodium clearance in the FHH patients was similar to that of the control, calcium clearance was also equivalent (Fig. 3 *B*). This is in striking contrast to the results obtained with infusion of calcium alone or calcium and acetazolamide (Fig. 3 *A*); at similar sodium clearances, calcium clearance was considerably lower in the FHH patients. These results suggest that the site of supranormal calcium reabsorption in FHH is the thick ascending limb of the loop of Henle. The greater natriuretic response of the control patient to ethacrynic acid raises the possibility that in FHH other ions such as sodium also are reabsorbed more avidly at this site. An alternative interpretation of these findings is that a site of avid calcium reabsorption distal to the loop of Henle in FHH is saturated by the large amount of calcium delivered to it as a consequence of the effect of ethacrynic acid. According to this interpretation, the fact that the calciuria in the patients with FHH did not achieve that of the controls reflects the persistence of some calcium (and perhaps sodium) reabsorption at that site.

Analysis of sodium clearance as a function of serum calcium reveals a much greater natriuretic response to calcium infusion in the control than the FHH group (Fig. 2). There are several possible mechanisms by which hypercalcemia could cause natriuresis in hypoparathyroidism. Calcium infusion could directly stimulate natriuretic factors. One such factor is calcitonin; in high doses, salmon calcitonin is natriuretic in man (28). At present, there is no evidence that increased endogenous calcitonin produces this effect. Furthermore, there is no information at present suggesting deficient calcitonin secretion in FHH. Calcium could also act directly on the kidney. Calcium from the renal tubular lumen could interfere with sodium reabsorption, or calcium from the antelumenal (plasma) surface of the tubule could inhibit sodium reabsorption. An abnormality in either of these mechanisms may explain the differences between FHH and controls. According to the first mechanism, in FHH most of the increment in filtered calcium would be reabsorbed from the lumenal fluid proximal to sites at which it would otherwise interfere with sodium transport. According to the second mechanism, renal cells in FHH would be insensitive to the normal effects of antelumenal calcium concentration on sodium transport. Our data are consistent with either of the latter two mechanisms. Moreover, the finding that impairment of urinary concentrating ability is less than in similarly hypercalcemic patients with typical hyperparathyroidism (29) is also consistent with either mechanism.

All three patients with FHH and hypoparathyroidism (as well as the three controls with hypoparathyroidism) showed low-to-normal serum magnesium concentrations. This contrasts with the findings in patients with FHH and hypercalcemia, where serum concentrations of magnesium are usually above the normal mean, with decreased renal clearance of magnesium (3). Although formal clearance studies were not performed for magnesium, the lower steady-state serum concentration of magnesium and similar steady-state urinary excretion of magnesium when compared with controls suggest that resolution of the low magnesium clearance in FHH may have resulted from the lowering of PTH. Thus, unlike the excessive tubular reabsorption of calcium, which is partly if not totally independent of PTH, the decreased renal clearance of magnesium appears to be dependent on PTH. This suggests a tentative mechanism for the difference in renal magnesium handling between FHH and typical

primary hyperparathyroidism. Magnesium clearance in these disorders is affected by two opposing factors; PTH, which decreases, and hypercalcemia (or hypercalciuria), which increases magnesium clearance. In typical primary hyperparathyroidism, these effects usually balance each other; rarely, the effect of hypercalcemia predominates, leading to increased magnesium clearance and hypomagnesemia (30). In FHH, the low magnesium clearance reflects a predominant effect of PTH as a result of impaired magnesuric response to hypercalcemia or less calciuria.

In comparison with that in typical primary hyperparathyroidism, the kidney in FHH exhibits differences in transport of calcium, magnesium, sodium, and free water (29), and in the cAMP response to PTH (31). However, a genetic defect confined to the kidney may not account for all features in FHH. If a renal defect were the sole cause of chronic hypercalcemia in FHH, the parathyroid glands should be suppressed (unless the renal defect in FHH results in a parathyroid-directed stimulus of unknown variety). Current evidence suggests that the parathyroid glands in FHH are not suppressed and may be hyperactive. In some reports, parathyroid glands have been described as histopathologically normal (1, 4, 32), although a recent detailed histologic analysis of surgical specimens showed that at least 13 of 18 patients with FHH exhibited parathyroid hyperplasia (33). Furthermore, severely symptomatic primary hyperparathyroidism has been documented in neonatal members of three FHH kindreds (13).

Both the parathyroids and the renal tubules manifest an abnormality of calcium metabolism in FHH; parathyroid gland growth and PTH secretion are not regulated by calcium in a normal fashion (13, 33), and the renal tubules, via a process that is independent of hyperparathyroidism, reabsorb an excessive fraction of filtered calcium. A single genetic trait must explain the abnormalities in both organs. Little is known about the mechanism whereby cells respond to changes in the concentration of extracellular calcium ion. There is indirect evidence that changes in calcium concentration outside the parathyroid cell produce parallel changes in cytosolic calcium which in turn affect hormone secretion (34). These effects of calcium may be mediated by intracellular binding proteins such as calmodulin (35). FHH could represent an abnormality in the function of an intracellular calcium binding protein or in transport of calcium to or from cytosol, or in regulation of these processes by unidentified extracellular factors. Since FHH may be the first recognized example of a multiorgan derangement in calcium metabolism, studies of this syndrome may help elucidate basic mechanisms of cell regulation by calcium.

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