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U. A. Liberman, ... , M. Modan, A. De Vries

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### Research Article

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# Metabolic and Calcium Kinetic Studies in Idiopathic Hypercalciuria

U. A. LIBERMAN, O. SPERLING, A. ATSMON, M. FRANK,  
M. MODAN, and A. DE VRIES

*From the Metabolic Unit, Department of Medicine D, Tel-Aviv University  
Medical School, Beilinson Hospital, Petah Tikva, Israel*

**ABSTRACT** Calcium balances and calcium kinetic studies using  $^{47}\text{Ca}$  were performed in nine male patients with idiopathic hypercalciuria and in three normal male subjects. A sharp reduction in calcium intake in eight patients with idiopathic hypercalciuria caused a decrease in urinary calcium excretion, the latter remaining elevated above that reported for normal subjects on a low calcium diet. The hypercalciuric patients had an enlarged miscible calcium pool size, an increased calcium turnover rate, increased bone formation and bone resorption rates, and an elevated true intestinal calcium absorption rate, the increase of the latter three parameters being proportional to the increase of the turnover rate. The fraction of the calcium turnover rate excreted in the urine was elevated whereas that constituted by the endogenous fecal calcium excretion was decreased. Arguments are presented for the concept that the primary abnormality in idiopathic hypercalciuria is neither renal calcium hyperexcretion nor intestinal calcium hyperabsorption, but a more fundamental disturbance in calcium metabolism of as yet unknown cause, leading to a high calcium turnover.

## INTRODUCTION

Since Flocks (1) first described in 1939 hypercalciuria without known cause in patients with renal calcium stones, several authors (2-8) have drawn attention to the frequency of this association. Albright (7) coined the name "idiopathic hypercalciuria" to describe a syndrome charac-

terized by a normal serum calcium, a low serum phosphorus, an increased urinary calcium excretion, and in most instances, a staphylococcal pyelonephritis, past or present, often complicated by kidney stones. Subsequently, the existence of the thus defined syndrome was questioned by several investigators who failed to confirm the presence of pyelonephritis (9, 10) and found significant hypophosphatemia in only a minority of the cases of idiopathic hypercalciuria (5, 10, 11). Moreover, the incidence of hypophosphatemia among normocalciuric renal stone patients was found to be similar to that among hypercalciuric renal stone patients (11). The name idiopathic hypercalciuria was retained, however, for a syndrome of unknown etiology characterized by an abnormally high renal excretion of calcium, normocalcemia, usually normophosphatemia, with or without renal stones and generally without radiological evidence of bone disease (8, 9, 12). Metabolic studies revealed that patients with idiopathic hypercalciuria generally have a low fecal calcium excretion indicating hyperabsorption of calcium from the intestine (8-10, 12-15) and are in slightly negative or normal calcium balance (10, 12, 14, 15).

In the present study further information was sought on calcium metabolism in patients with idiopathic hypercalciuria associated with renal calcium stones by measurement of calcium balance, examination of the influence of a low calcium diet on renal calcium excretion, and application of radiocalcium kinetic methods.

## METHODS

*Clinical data.* Nine adult patients with recurrent renal calcium stones and idiopathic hypercalciuria, and three

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healthy adult male subjects were studied. Their age is indicated in Table I. All patients had a urinary calcium excretion above 300 mg/day which is higher than the upper limit of normal according to the data given by Hodgkinson and Pyrah (2, 3) and Cottet (6) and according to our previous studies on a normal population in the southern part of Israel (16).

**Metabolic methods.** All studies were carried out in an air-conditioned metabolic ward having its own kitchen, a separate food supply, and medical personnel, including a trained dietitian. Before admission all patients were interviewed by the dietitian and their daily home calcium and phosphorus intake were calculated on the basis of a dietary record spanning several days. The diets given in the metabolic ward, specified according to calcium content—similar to home diet (A), moderately high (B), and low (C)—are listed in Table I. Three patients underwent two metabolic studies, each on different diets. Each individual's diet was constant during the whole course of each metabolic and radiokinetic study. Calcium and phosphorus balance studies were carried out on all subjects according to Reifenstein, Albright, and Wells (17). One duplicate of a day's food intake was analyzed for calcium and phosphorus at least once weekly. All food not consumed was pooled and analyzed at the end of the balance period. The metabolic balance period extending over 7–10 days was started after 3–5 days of adaptation to the metabolic ward routine. The procedure of collection of excreta and the methods for calcium and phosphorus determination in serum, urine, and feces were as described elsewhere (18).

**Radiocalcium methods.** About 15  $\mu\text{C}$  of  $^{45}\text{Ca}$  (supplied as isotonic calcium chloride by the Radiochemical Centre, Amersham, England) was injected into the polyethylene tube of a previously prepared infusion of saline. The infusion was continued for 5–10 min after injection of  $^{45}\text{Ca}$ . Blood was drawn at frequent intervals during the 1st day and daily thereafter from the normal subjects and at daily intervals from six patients with idiopathic hypercalciuria. Radioactivity of plasma was measured on 3-ml samples, prepared from heparinized blood. Radioactivity of urinary calcium was measured either directly on 3-ml urine samples taken from the 24 hr collections, or on 50-ml samples of urine from which the calcium was precipitated as oxalate and redissolved in 3 ml of hot 70% perchloric acid. The content of  $^{45}\text{Ca}$  (stable calcium) of the samples used for measuring radioactivity was determined by flame spectrophotometry as described elsewhere (18) and the specific activity, expressed as per cent of the injected dose per gram of calcium, was calculated accordingly. The radioactivity of the pooled stools was determined either directly on 3 g of stool homogenate or on 3 g of ashed stool prepared from 50 g of homogenate dissolved in 3 ml of hot 0.5 N hydrochloric acid. Radioactivity was measured with a well-type scintillation counter (Baird-Atomic, Inc., Cambridge, Mass.) in conjunction with a single channel analyzer with a 2 inch NaI (thallium-activated) crystal. The voltage and sensitivity of the scaler was lowered until discrimination of  $^{45}\text{Ca}$  from  $^{45}\text{Sc}$  was complete. All the samples

measured were compared to standards of the respective injected doses.

**Handling of kinetic data.** Kinetic calculations were carried out according to a simplified method (19–21) based upon the assumption of an open one compartmental homogenous miscible calcium pool (21, 22). Calcium is removed from the pool via the plasma to the bone and is excreted in the urine and in the feces. It is further assumed that during the experimental period no labeled calcium is returned from the bone to the miscible calcium pool (21–24). According to this model the decrease in specific activity ( $R$ ) in plasma or in urine, after the tracer has become distributed homogeneously in the miscible pool, is described by a monoexponential curve  $R(t) = Ae^{-kt}$ , where  $A$  and  $k$  are experimental constants, and  $t$  is time in days. In most studies performed on human subjects a monoexponential decrease of plasma and urine specific activity was indeed found to occur between about 36 and 146 hr after intravenous injection of radiocalcium (19, 21–23). Accordingly in our study the parameters  $A$  and  $k$  were derived from the linear portion of the semilogarithmic urine specific activity curve obtained from 34 hr to 106, 130, or 154 hr after injection of the isotope. The miscible calcium pool ( $p$ ), the calcium turnover rate ( $v_T$ ), the urinary calcium excretion rate ( $v_u$ ), the endogenous fecal calcium excretion rate ( $v_f$ ), the bone formation rate ( $v_{+}$ ), the bone resorption rate ( $v_{-}$ ) and the absorbed fraction of the calcium intake ( $\alpha$ ) were calculated according to the equations of Aubert, Bronner, and Richelle (21) and Heaney and Whedon (19). The constants  $A$  and  $k$  were derived for each patient by the least mean square procedure using the CLSQ Fortran-coded Brookhaven computer program. For evaluation of the method of computation it was applied to the radiokinetic data from the normal reference standard of Heaney (25) and Heaney, Bauer, Bronner, Dymling, Lafferty, Nordin, and Rich (26). The results derived for exchangeable pool size and bone formation rate are comparable to those individually calculated by several investigators, as tabulated by Heaney (25).

## RESULTS

**Metabolic calcium balance data.** Table I presents the calcium balance data of the normal subjects and of the patients with idiopathic hypercalciuria. The ratio fecal calcium ( $v_f$ ) over calcium intake ( $v_i$ ) was lower in the hypercalciuric patients than in the normal subjects, the mean value for the former group being 0.52 and for the latter 0.75, the level of significance being  $P < 0.02$ . No significant difference was found in  $v_f/v_i$  between patients who received a high calcium intake and those obtaining their usual dietary calcium intake ( $P > 0.9$ ). The mean daily urinary calcium excretion during the balance periods was 0.437 g in the patients who received high calcium diets,

TABLE I  
Metabolic Calcium and Phosphorus Data

Patient	Age		Calcium					Phosphorus			
			Intake*	Urine	Fecal	Balance	Fecal/ intake	Intake	Urine	Fecal	Balance
			g/day								
<i>Normal subjects</i>											
E. M.	55	A	0.700	0.114	0.531	+0.055	0.76	0.484	0.300	0.272	-0.088
P. E.	51	B	1.152	0.232	0.767	+0.153	0.67	1.170	0.936	0.408	-0.174
S. M.	53	B	1.175	0.075	0.953	+0.147	0.81	1.144	0.707	0.464	-0.027
<i>Idiopathic hypercalciuria</i>											
L. M.	35	C‡	0.255	0.429	0.071	-0.245	0.28	0.526	0.672	0.110	-0.256
		A	0.763	0.673	0.261	-0.171	0.39	0.953	1.032	0.126	-0.206
S. Z.	28	C§	0.345	0.259	0.220	-0.134	0.64	0.745	0.474	0.227	+0.044
		A	0.930	0.360	0.540	+0.030	0.58	1.300	1.171	0.200	-0.071
B. M.	52	A	0.611	0.394	0.384	-0.167	0.63	1.002	0.754	0.282	-0.034
K. E.	40	A	0.906	0.553	0.491	-0.138	0.54	1.140	0.910	0.295	-0.065
R. D.	51	A	0.900	0.315	0.468	+0.117	0.52	1.221	0.874	0.321	+0.026
D. J.	43	A	0.782	0.377	0.500	-0.095	0.49	1.027	0.561	0.305	+0.161
		B	1.228	0.415	0.610	+0.203	0.63	1.421	0.715	0.436	+0.270
T. E.	49	B	1.259	0.584	0.370	+0.305	0.29	1.450	0.843	0.221	+0.386
K. M.	49	B	1.200	0.403	0.716	+0.081	0.59	1.430	1.026	0.324	+0.080
S. A.	56	B	1.200	0.332	0.739	+0.129	0.61	1.408	0.881	0.350	+0.177

\* A, diet containing an amount of calcium similar to mean daily calcium intake at home; B, moderately high calcium diet containing about 0.300-0.450 g of calcium/day in excess of usual home diet; C, low calcium diet.

‡ This low calcium and phosphorus diet was kept by the patient during the last year before hospitalization.

§ After 1 month of adaptation to this diet.

and 0.445 g in the patients who were maintained on a diet containing an amount of calcium equivalent to that in their home diet.

*Metabolic phosphorus balance data.* The phosphorus balance data (Table I) showed a parallelism with the calcium balance data only in some patients (D. J., T. E., K. M., S. A., and L. M.). Fecal phosphorus was found to be low relative to the phosphorus intake in the patients with idiopathic hypercalciuria. Edwards and Hodgkinson (11) observed in eight patients with renal stones, five of whom had idiopathic hypercalciuria, a linear relationship between phosphorus intake, below 2 g/day, and fecal phosphorus. The regression of fecal phosphorus upon phosphorus intake was given by these authors by an equation<sup>1</sup> that agrees well with that equation derived by Nordin and Smith<sup>2</sup> (11) in normal adult subjects. Applying these equations to the phosphorus intake of each subject in our study, we calculated the corre-

<sup>1</sup>  $y = 0.33x + 0.023$ ;  $y$  = fecal phosphorus (g/day),  $x$  = phosphorus intake (g/day).

<sup>2</sup>  $y = 0.31x + 0.098$ ;  $y$  = fecal phosphorus (g/day),  $x$  = phosphorus intake (g/day).

sponding fecal phosphorus. The fecal phosphorus excretion observed in each patient with idiopathic hypercalciuria was lower than the value calculated according to each of these formulae. The difference between the mean measured fecal phosphorus excretion and the means of each of the calculated values was highly significant according to a *t* test for paired values ( $P < 0.001$ ). There was no difference between the measured and calculated values for fecal excretion of phosphorus in the normal subjects (using equation<sup>1</sup>  $P > 0.10$ , equation<sup>2</sup>  $P > 0.80$ ).

Edwards and Hodgkinson (11) furthermore observed a direct linear relationship between net phosphorus absorption (intake minus fecal excretion) and daily urinary phosphorus excretion in their renal stone patients.<sup>3</sup> Applying this equation to the net absorption of phosphorus we calculated the corresponding urinary excretion of phosphorus in our patients. No significant difference was observed between the measured and calculated urinary phosphorus excretion in the patients with

<sup>3</sup>  $y = 0.86x + 0.180$ ;  $y$  = urine phosphorus (g/day),  $x$  = net phosphorus absorption (g/day).

TABLE II  
Daily Urinary Calcium and Phosphorus Excretion in Patients with Idiopathic Hypercalciuria on their Home Diet (Control Day), and during an Acute Reduction in their Calcium and Phosphorus Intake (1st-3rd Day)\*

Patients	Urinary calcium excretion				g/day	Urinary phosphorus excretion			
	Control day	1st day	2nd day	3rd day		Control day	1st day	2nd day	3rd day
L. M.	0.569	0.446	0.396	0.483	0.711	0.609	0.644	0.653	
S. Z.	0.414	0.234	0.206	0.180	0.863	0.867	0.709	0.655	
B. M.	0.385	0.196	0.243	0.254	0.802	0.717	0.541	0.468	
K. E.	0.599	0.367	0.400	0.344	1.154	0.955	0.971	0.719	
R. D.	0.377	0.312	0.256	0.291	0.991	0.699	0.616	0.631	
D. J.	0.426	0.267	0.254	0.265	0.694	0.620	0.372	0.421	
T. E.	0.385	0.277	0.266	0.318	1.083	0.729		0.721	
S. A.	0.491	0.293	0.232	0.262	1.454	1.149	0.669	0.762	

\* Reduced intake: calcium, 0.245-0.315 g/day; phosphorus, 678-868 g/day.

idiopathic hypercalciuria ( $P > 0.05$ ) and in the normal subjects ( $P > 0.80$ ).

*Effect of an acute reduction of calcium intake upon urinary calcium excretion.* In eight patients with idiopathic hypercalciuria who received their usual home diet, the daily calcium intake was acutely reduced to 0.245-0.315 g/day for 3 consecutive days. Urinary calcium, phosphorus, and creatinine were determined on 24-hr collections starting the day before the beginning of the test, and during the period of low calcium intake. The results are summarized in Table II. The daily urinary excretion of calcium and phosphorus decreased in all the patients examined, whereas the urinary creatinine was not altered significantly. The urinary calcium/creatinine ratio on the 3rd day of the low calcium diet was compared to the ratio obtained for the control day and an average decrease of 35.4%, range 11.4-65.2%, was observed. Nevertheless, seven of the eight patients continued to excrete in their urine above 0.250 g of calcium/day on the 3rd day of the test, and three of them excreted above 0.300 g/day (Table II). In five patients the daily calcium excretion exceeded their dietary calcium intake. The phosphorus/creatinine ratio on the 3rd day of the test was lower by an average of 34.7%, range 22.2-49.2%, than the ratio determined during the control day.

*Miscible calcium pool and turnover rate.* A statistical evaluation was carried out of the calcium kinetic data in our three normal subjects compared to the normal reference standard of

Heaney (25). The linear regression line of log urine specific activity by time for our normal subjects was compared with that derived from the log plasma and (or) urine calcium specific activity in the normals recorded by this author (25) (Fig. 1). The linear regression coefficients computed for these two normal groups were not significantly different ( $P > 0.5$ ) and the two groups were found to represent samples drawn from the same population in regard to calcium kinetics ( $P > 0.3$ ). It was concluded that there was no significant difference in the miscible calcium pools ( $p$ )

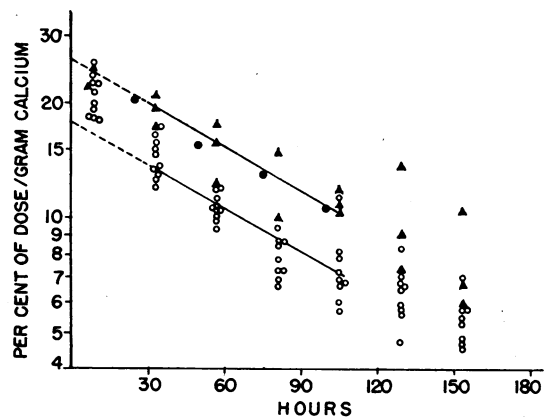


FIGURE 1 Semilogarithmic plot of urine specific activity in normal subjects (▲), and in patients with idiopathic hypercalciuria, (○) and the mean values of plasma and (or) urine specific activity in the normal reference standard of Heaney (25), (●). The linear regression lines from 33 to 105 hr after injection of  $^{45}\text{Ca}$  for normal subjects, upper solid line, and for patients with idiopathic hypercalciuria, lower solid line.

and the turnover rates ( $v_T$ ) between our normal subjects and the normals recorded by Heaney (25).

When comparing the linear regression coefficients computed for our normal subjects and our patients with idiopathic hypercalciuria we did not find them significantly different ( $P > 0.3$ ); however, the two groups were found to be samples drawn from different populations ( $P < 0.0001$ ) (Fig. 1). It was concluded that the miscible calcium pool size ( $p$ ) and the turnover rate ( $v_T$ ) of the patients with idiopathic hypercalciuria were significantly higher than those of the normal subjects (Table III). The miscible calcium pool size and the turnover rate of each subject, both normals and patients with idiopathic hypercalciuria, are

presented in Table III. In the three normal subjects and in the six patients with idiopathic hypercalciuria in whom regular plasma measurements were made (S. Z., R. D., D. J., T. E., K. M., and S. A.), the linear portion of the curve log plasma specific activity by time was found to be similar to that of the log urine specific activity by time (Fig. 2). Whereas in the normal subjects the slopes of the log urine and plasma specific activity by time continued unchanged up to the last urine and plasma sample obtained at 150–160 hr after injection of the tracer, in eight out of the nine patients with idiopathic hypercalciuria the slope changed and flattened at 100–125 hr after tracer injection. In the ninth patient (L. M.) the slope of the curve was still unchanged after 150 hr (Figs. 1 and 2).

TABLE III  
Calcium Kinetic Data

Patient	Exchangeable pool ( $p$ )	Turnover rate ( $v_T$ )	Bone formation rate ( $v_{0+}$ )	Bone resorption rate ( $v_{0-}$ )	Excretion rates		True intestinal absorption ( $\alpha$ )	
					Urinary ( $v_u$ )	Endogenous fecal ( $v_f$ )		
	g	g/day	g/day	g/day	g/day	g/day	% intake	
<i>Normal subjects</i>								
E. M.	4.020	0.755	0.522	0.467	0.114	0.119	41	
P. E.	5.400	0.957	0.585	0.432	0.232	0.140	45	
S. M.	3.640	0.696	0.499	0.352	0.075	0.122	27	
Mean*	3.827	0.830	0.535	0.417	0.140	0.127	38	
95% Confidence interval	Upper	4.790	1.020	0.671	0.596	0.389	0.160	67
	Lower	3.055	0.676	0.399	0.238	0.000	0.094	9
<i>Idiopathic hypercalciuria</i>								
L. M.	5.800	1.182	0.722	0.967	0.429	0.031	84	
S. Z.†	6.240	1.072	0.723	0.857	0.259	0.090	62	
	6.010	1.320	0.782	0.752	0.360	0.178	61	
B. M.	5.890	1.028	0.505	0.672	0.394	0.129	58	
K. E.	5.650	1.405	0.761	0.899	0.553	0.091	55	
R. D.	5.550	1.415	0.972	0.855	0.315	0.128	62	
D. J.	5.010	1.588	1.061	0.858	0.415	0.112	59	
T. E.	4.450	1.592	0.954	0.649	0.584	0.054	74	
K. M.	4.030	1.195	0.689	0.608	0.403	0.103	49	
S. A.	5.400	1.151	0.749	0.620	0.332	0.070	44	
Mean*	5.596	1.213	0.792	0.774	0.404	0.099	61	
95% Confidence interval	Upper	6.340	1.345	0.908	0.867	0.478	0.129	69
	Lower	4.940	1.095	0.676	0.681	0.330	0.069	52
Significance of difference								
Normal-idiopathic hypercalciuria ( $P$ )								
	<0.0001	<0.0001	<0.025	<0.001	<0.005	>0.2	<0.01	

\* The mean values of  $p$  and  $v_T$  were derived from the estimated linear regression line of log urine specific activity by time (33–105 hr after injection of the tracer) calculated from the pooled data of all subjects in each group. The mean values of the other calcium kinetic parameters are the arithmetic means.

† Patient S. Z. was studied twice, first on a low calcium diet, then on a calcium intake similar to his home diet.

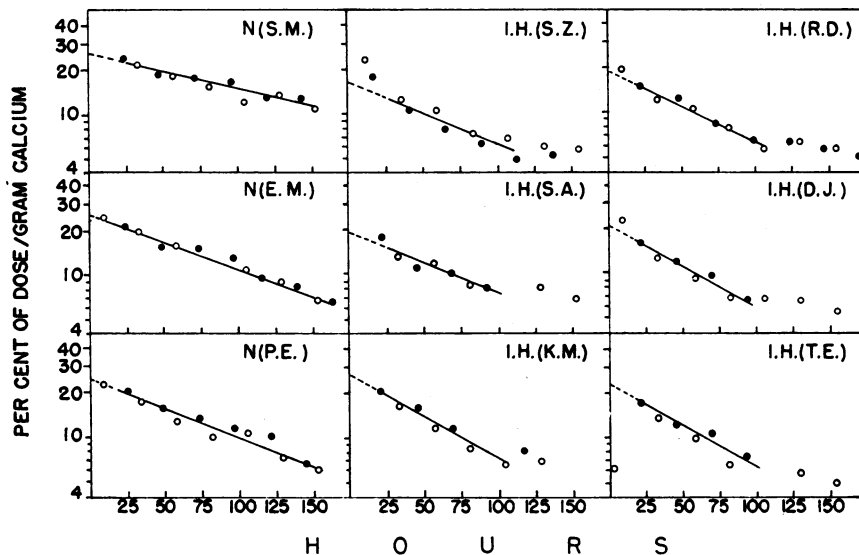


FIGURE 2 Semilogarithmic plot of plasma, (●), and urine (○) specific activity in normal subjects (N) and patients with idiopathic hypercalciuria (I. H.). Initials between parentheses.

Rates of excretion ( $v_u$  and  $v_f$ ), bone formation ( $v_{o+}$ ), bone resorption ( $v_{o-}$ ) and true intestinal absorption ( $v_a$ ). The mean urinary calcium excretion rate ( $v_u$ ) in the patients with idiopathic hypercalciuria was significantly higher almost by a factor of 3 than that of the normal controls, whereas the endogenous fecal calcium excretion rates ( $v_f$ ) of both groups were in the same range (Table III). Our data for  $v_f$  are comparable to those of Heaney and Skillman (27),  $0.127 \pm 0.046$  g/day in 50 studies in a group of 31 subjects comprised of normals and patients with disorders of bone and calcium metabolism and of the parathyroid glands.

Since, as stated previously, the mean turnover rates and the mean excretion rates ( $v_u$  and  $v_f$ ) of our normal subjects were not statistically different from those of the normal reference standard of Heaney (25), the mean bone formation rates of the two groups were also in the same range. Furthermore, our  $v_{o+}$  data for normal subjects are comparable to other data on bone formation rates in normal subjects given in the literature (28-31). The bone formation rates ( $v_{o+}$ ) in eight patients with idiopathic hypercalciuria and the bone resorption rates ( $v_{o-}$ ) in all the nine patients were higher by a factor of 1.5-2 than those in the normal subjects (Table III), these differences being statistically significant.

True intestinal calcium absorption, expressed as per cent of intake ( $\alpha$ ), in the idiopathic hypercalciuric patients was higher by about a factor of 2 than in the normal subjects (Table III).

Assuming that during the balance and kinetic studies the patients are in a steady state, i.e. the amounts of calcium entering and leaving the miscible calcium pool are equal, it follows that  $v_u + v_f + v_{o+} = v_T = v_a + v_{o-}$ . Expressing  $v_u$ ,  $v_f$ ,  $v_{o+}$ ,  $v_{o-}$ , and  $v_a$  as fractions of  $v_T$  may indicate whether these parameters are changed in accordance with the increased  $v_T$  of our patients. The mean  $v_u/v_T \times 100$  in the normal subjects was  $16.6\% \pm 6.7$  and in the patients with idiopathic hypercalciuria  $31.3\% \pm 6.2$ . The mean  $v_f/v_T \times 100$  in the normals was  $16.0\% \pm 1.4$  and in the patients  $7.8\% \pm 3.5$ . The differences in these ratios between the normal subjects and the patients with idiopathic hypercalciuria are highly significant ( $P < 0.005$  for both ratios). On the other hand, the fractions of  $v_T$  made up by  $v_{o+}$ ,  $v_{o-}$ , and  $v_a$  are almost similar in both groups: in the normal subjects  $v_{o+}$   $67.3\% \pm 5.7$ ,  $v_{o-}$   $52.6\% \pm 8.6$ ,  $v_a$   $47.4\% \pm 8.6$ , and in the patients with idiopathic hypercalciuria,  $v_{o+}$   $60.9\% \pm 7.1$ ,  $v_{o-}$   $60.8\% \pm 12.7$ , and  $v_a$   $39.2\% \pm 12.7$ , the differences not being statistically significant ( $P > 0.1$ ,  $P > 0.3$ , and  $P > 0.3$ , respectively.)

## DISCUSSION

Henneman, Benedict, Forbes, and Dudley (8) were the first to draw attention to the low fecal calcium excretion in patients with idiopathic hypercalciuria. Other investigators confirmed this finding (9, 10, 12, 14, 15), which was interpreted as being due to intestinal hyperabsorption. Edwards and Hodgkinson (14) found a mean net intestinal absorption of calcium, i.e., calcium intake minus fecal calcium expressed as a fraction of calcium intake, of 32% in 11 renal stone patients with idiopathic hypercalciuria as compared to 25% in those with a normal daily excretion of calcium, the difference being significant. Our nine patients with idiopathic hypercalciuria also showed a markedly low fecal calcium with a significantly higher mean net intestinal absorption (48.5%) than the normal controls (25.5%). The hypercalciuric patients also showed an increased net intestinal absorption of phosphorus (76.4%), as compared to the normal subjects (56.1%).

The term mean net intestinal absorption of calcium, as defined above, does not take into account the endogenous fecal calcium, i.e., the calcium which is excreted into the gastrointestinal tract without being subsequently reabsorbed (20). The true intestinal absorption, derived by correction for the endogenous fecal calcium measured by radiokinetic methods and expressed as a fraction ( $\alpha$ ) of the calcium intake, was significantly elevated in seven of our nine patients with idiopathic hypercalciuria, the mean level being 61%, as compared to 38% in the normal controls. These results are in agreement with those of other workers (11, 27, 32-34).

Various investigators (10-12, 14) have discussed the hypothesis that intestinal hyperabsorption of calcium is the primary cause of idiopathic hypercalciuria, the urinary hyperexcretion of calcium being a secondary and compensatory phenomenon. However, most observations indicate that this hypothesis does not hold for the majority of patients with idiopathic hypercalciuria. Patients with idiopathic hypercalciuria give no history of excessive vitamin D intake (14) and no evidence was obtained for hypersensitivity to vitamin D (8, 12, 14).

Secondly, if intestinal overabsorption of calcium would be primary, calcium balances would be expected to be positive or zero. In only a few patients

with idiopathic hypercalciuria zero calcium balances were found (10, 14), but in most patients a slightly negative calcium balance was observed (10, 12, 14, 15). Four of our patients were in a slightly negative calcium balance while receiving a diet adjusted to their usual calcium intake.

Thirdly, although in several studies on idiopathic hypercalciuric patients (2, 3, 5, 8, 10, 13-15, 35) a sudden reduction in calcium intake was followed by a decrease in urinary calcium excretion, the latter remained considerably higher than that of normal controls under similar dietary conditions (2, 3, 5, 8, 10, 13-15), and was in some patients in excess of their daily intake. Our observations are in accord with these findings. In contrast, in a patient with hypercalciuria due to sarcoidosis, a condition in which intestinal calcium hyperabsorption is well established (15, 36, 37), the response to a low calcium diet was similar to that of normals (14). It was also observed that patients with idiopathic hypercalciuria excreted during fasting 2-3 times more calcium in their urine than fasting normal controls. Moreover, the calcium excretion remained elevated during the oral administration of EDTA (ethylenediaminetetraacetic acid), despite the fact that the fecal excretion of calcium exceeded the dietary intake (14).

Fourthly, in the present study the four patients who received a high calcium diet absorbed more calcium than patients on their usual home diet though the mean urinary calcium excretion was similar in both groups. Our observations and those cited suggest that at least in the majority of patients with idiopathic hypercalciuria increased intestinal calcium absorption is not the primary disturbance.

Jackson and Dancaster (15) were the first to suggest that patients with idiopathic hypercalciuria have a primary renal calcium loss, intestinal hyperabsorption being secondary. Patients with idiopathic hypercalciuria have an increased renal calcium clearance, but no evidence of an increased filtered load of calcium has been found (38), indicating that the tubular reabsorption of calcium is reduced. It has been suggested that the hypercalciuria might be caused by an increase in the plasma nonionized filterable calcium, since this fraction is poorly reabsorbed by the renal tubule (39). However, no increase in plasma nonionized



filterable calcium, such as calcium citrate, was found (40).

Additional disturbances in tubular function have been looked for in idiopathic hypercalciuria. In many studies either no disturbances were found (12, 38, 40–42) or only slight impairment in some tubular functions were observed which are similar to those present in hypercalciuria due to other causes (12, 42). It was suggested therefore that excess calcium excretion is responsible for the disturbed tubular function occasionally found in such patients (12, 42). The administration of alkali to patients with idiopathic hypercalciuria causes a reduction of urinary calcium (12, 38), an effect similar to that in patients with renal tubular acidosis. However, no obvious systematic acidosis was reported in patients with idiopathic hypercalciuria (12, 38) nor was it found in ours, and a similar response to alkali has been found in normal subjects (38) and in patients with hypercalciuria due to primary hyperparathyroidism, Paget's disease of bone, or sarcoidosis (12). Patients with idiopathic hypercalciuria responded normally to intravenous administration of parathyroid hormone, to oral administration of sodium phosphate (9, 12), and to sodium deprivation (38). Thus, no clear evidence of a general tubular malfunction has been found in patients with idiopathic hypercalciuria (11, 12, 38). Brodwall and Leake proposed that the hypercalciuria could be secondary to a reduction in tubular citric acid reabsorption (43). An increased urinary citric acid excretion was indeed found by Hodgkinson in idiopathic hypercalciuric patients, but the increase was no greater than that in other conditions associated with hypercalciuria (40).

A more general disturbance of calcium metabolism in idiopathic hypercalciuria is suggested by the results of the calcium kinetic data obtained in the present study. The semilogarithmic curves of the urinary calcium specific activity by time obtained in the group of hypercalciuric patients were found to differ significantly from those in the group of normal subjects, the curves being parallel, but in the former group having a lower urinary specific activity. The question might be raised whether this difference in the specific activity of the urine indeed reflects a real difference in calcium pool size and turnover rates. Since patients with idiopathic hypercalciuria excrete more calcium in

their urine than do normal subjects, it is to be expected that the former excrete more  $^{47}\text{Ca}$  in their urine than the latter during the first 24 hr after injection of the isotope. Upon reaching kinetic equilibrium, less radioactive calcium will have been retained by the hypercalciuric patients and consequently the specific activities of their urine and plasma will be lower than those in the normal subjects. To obviate the possible influence of this difference in the handling of the injected isotope on the location of the curves, we expressed the specific activity of calcium excreted in the urine as per cent of the dose retained after 24 hr. We again found that the monoexponential portion of the urine specific activity curve of the patients with idiopathic hypercalciuria was parallel but not identical with the curve of the normal subjects.

Another possible explanation of the difference between the respective specific activity curves is the assumption that patients with idiopathic hypercalciuria preferentially excrete in their urine some form of complexed calcium salt which does not exchange or exchanges only slowly with ionized calcium. Consequently, during the period of examination the complexed calcium would not reach equilibrium with the ionized  $^{47}\text{Ca}$  injected. Though it was claimed that such a complexed nonexchangeable calcium exists in normal urine (44), other investigators failed to substantiate this (45). Furthermore, as this presumed complexed nonexchangeable calcium is thought to be preferentially excreted in the urine, it would constitute only a small part of the calcium pool. Accordingly, the plasma specific activity curves of patients with idiopathic hypercalciuria should differ from their urine specific activity curves, whereas they should be similar to the plasma specific activity curves of normal subjects. However, in six of our patients with idiopathic hypercalciuria whose plasma specific activity was measured, the curve of log plasma specific activity by time was similar to the curve of log urine specific activity by time and different from the urine and plasma specific activity curves of the normal subjects. These results are in accordance with the observations recently published by Anderson, Lee, and Tomlinson (46) who also found a significant difference between the plasma specific activity curves of normal subjects and patients with idiopathic hypercalciuria. It seems to us, therefore, that the nonidentity of

the specific activity curves of the urine in patients with idiopathic hypercalciuria and in normal subjects reflects an actual difference between their miscible calcium pool sizes and turnover rates, the pool being enlarged and the calcium turnover rate increased in the former.

The increased turnover rate is only partially due to the increased urinary excretion rate of calcium, since eight out of our nine patients also had an increased bone formation rate ( $v_{o+}$ ). It must be kept in mind that the term bone formation rate is defined as the rate of calcium loss from the pool by routes other than urinary and fecal excretion. This term, therefore, includes both true bone formation and slow exchange processes.

In eight out of our nine patients with idiopathic hypercalciuria the monoexponential decrease of log urine specific activity by time continued until 100–125 hr after injection of the  $^{47}\text{Ca}$ , after which the curve assumed a new slope. In the six patients for whom adequate data are available, the decrease in plasma specific activity showed similar behavior. In our normal subjects no change in the slopes of urine and plasma specific activity curves was obtained till 153 hr. According to the literature (21, 22) the period preceding deflection, period  $\theta$  according to Heaney and Whedon (19), ranges in normal subjects from 150 to 250 hr. Two interpretations of this phenomenon of change in slope have been offered. Heaney and Whedon (19) attributed the change in the slope to the return of the isotope to the miscible pool due to resorption of labeled bone, whereas Aubert and Milhaud (47) ascribed it to a slow exchange process. It may be pertinent that all our nine patients with idiopathic hypercalciuria had an increased  $v_{o-}$ . Whether in our patients with idiopathic hypercalciuria the increased  $v_{o+}$  is due to a true increase in bone formation and the shorter period  $\theta$  reflects their increased  $v_{o-}$ , or whether both the increased  $v_{o+}$  and the shorter period  $\theta$  values reflect an increased slow exchange process, can not be resolved by present methods.

A further point of interest is the finding that patients with idiopathic hypercalciuria excrete a larger fraction of their calcium turnover in the urine ( $v_u/v_T$ ) than do normal subjects, and that the former excrete a smaller fraction of their turnover in the feces ( $v_f/v_T$ ), though their mean  $v_f$  is similar to that in the normal subjects. On

the other hand, in respect to the relative contribution of the total calcium excretion rate ( $v_u + v_f$ ) and the other kinetic parameters to the calcium turnover, the hypercalciuric patients do not differ from the normal subjects, the increases in ( $v_u + v_f$ ),  $v_{o+}$ ,  $v_a$ , and  $v_{o-}$  being proportional to the increase in  $v_T$ .

Increased miscible calcium pool, turnover rate, and bone formation rate have been found in calcium kinetic studies in patients with primary hyperparathyroidism (48, 49), Paget's disease of bone (31, 49), and active acromegaly (49), but none of our patients showed any clinical or laboratory findings compatible with these diseases. It seems to us that the primary disturbance in idiopathic hypercalciuria is neither intestinal hyperabsorption nor urinary hyperexcretion of calcium, but both these, and the increase in  $p$ ,  $v_T$ ,  $v_{o+}$ , and  $v_{o-}$  may reflect a more fundamental disturbance in calcium metabolism leading to a high calcium turnover, possibly due to some as yet unknown hormonal imbalance.

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