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Altered calcium metabolism in chronic renal failure

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Altered calcium metabolism in chronic renal failure. A compartmental analysis of ^{47}Ca tracer kinetic data and Ca balance measurements was employed to evaluate several indexes of Ca metabolism in patients with mild to severe renal insufficiency. Rates of Ca accretion and resorption and the size of the exchangeable Ca pools were measured. In addition, absolute measurements were made of total body Ca, P, Cl and Na by means of neutron activation analysis. Total body K was measured by whole-body counting. Total body levels of Ca, P, Na, Cl and K in patients with modest renal insufficiency did not differ from those of a normal contrast population. In patients with severe renal failure, however, there were a number of changes in Ca and P metabolism. The total body P/Ca and P/K ratios were increased above normal. Most of the patients with renal insufficiency had total body Ca levels within the normal range, when normalized for skeletal size and the age and sex of the patient. The levels of total body Ca were inversely related to the accretion rate of Ca into bone; that is, the patients with the greatest calcium deficit had the highest accretion rate. Alterations in compartment sizes and intercompartmental transfer rates were observed in severe renal failure. The increased size of an exchangeable Ca compartment together with the essentially normal levels of total body Ca suggest a translocation of skeletal Ca to soft tissue mediated by increased parathyroid hormone secretion. Further studies, including a measure of the size of the soft tissue and skeletal compartments, are required to substantiate this hypothesis.

Le modification du métabolisme du calcium dans l'insuffisance rénale chronique. Une analyse compartimentale des résultats de cinétiques du traceur ^{47}Ca et du bilan de calcium a été employée pour évaluer divers paramètres du métabolisme du calcium chez des malades atteints d'insuffisance rénale moyenne ou sévère. Les débits d'accrétion et de résorption et la taille des pools échangeables de calcium ont été déterminés. De surcroît les mesures des masses corporelles totales de Ca, P, Cl et Na ont été faites au moyen de l'activation neutronique. Le potassium total corporel a été mesuré par comptage corporel total. Les masses corporelles de Ca, P, Na, Cl et K des malades atteints d'insuffisance rénale modest ne sont pas différentes de celles d'une population normale. Chez les malades atteints d'insuffisance rénale sévère, cependant, il existe des modifications des métabolismes de Ca et P. Les rapports P/Ca et P/K de l'organisme entier sont augmentés par rapport aux valeurs normales. La plupart des malades atteints d'insuffisance rénale ont un Ca total dans l'éventail des valeurs normales quand les données sont corrigées par la masse du squelette l'âge et le sexe du malade. Le Ca total corporel est inversement corrélé au débit d'accrétion du Ca dans l'os; c'est-à-dire que les malades qui ont le déficit en calcium le plus grand ont aussi le débit d'accrétion le plus élevé. Des modifications de la taille des compartiments et des débits de transfert ont été observés dans l'insuffisance rénale sévère. L'augmentation de la taille d'un compartiment de Ca échangeable alors que le Ca total corporel est normal suggère une translocation du calcium squelettique vers les tissus mous sous l'influence d'une secrétion accrue d'hormone parathyroïdienne. Des travaux supplémentaires comprennant une mesure de la taille des compartiments tissulaires et squelettique sont nécessaires pour étayer cette hypothèse.

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Abnormalities of calcium (Ca) and phosphorus (P) metabolism in patients with renal insufficiency have been characterized in a number of studies [1–14]. Increased parathyroid hormone secretion [5], altered vitamin D metabolism, with concomitant malabsorption of Ca [6], and acidosis [7] have been indentified as important determinants of the altered Ca and P metabolism observed in patients with renal osteodystrophy.

The various methods used to determine the nature and degree of changes in Ca metabolism have significant limitations. For example, histological changes observed from bone biopsy specimens are not readily quantified and, further, provide information only on localized areas of bone. Photon absorptiometric techniques, while highly quantitative and precise, again provide information only on localized areas of the skeleton. Measurements made by radiographic technique can be applied to the entire skeleton, but these measurements lack the sensitivity required for quantifying levels of change associated with the development of pathological conditions.

Some of these difficulties are resolved by the use of total body neutron activation analysis (TBNAA),

which permits the direct *in vivo* measurement of total Ca and P content of the body to be made with a high degree of precision. Further, metabolic bone disease can also be evaluated in terms of bone turnover (i.e., bone mineral accretion and resorption) and by Ca absorption and endogenous excretion measurements. Ca tracer kinetic studies along with metabolic balance studies provide useful information on the internal compartmentalization and transfer of Ca in uremic patients. The simultaneous application of these techniques should provide a better understanding of Ca metabolism in renal failure.

Methods

Patients. Thirteen patients with modest to severe renal insufficiency were studied. Brief clinical descriptions of each patient along with biochemical concentrations in the plasma are presented in Table 1. The patients were divided into two groups. Group I consisted of six patients with modest to mild renal insufficiency. Creatinine clearance (glomerular filtration rate, GFR) exceeded 10 ml/min in all patients. Although azotemic for a variable period of time (0.5 to 5 yr), group I patients were not hypocalcemic, hyperphosphatemic or acidotic. All patients in this group exhibited stable azotemia for at least four months prior to the study. Sodium bicarbonate and aluminum hydroxide gel were administered to patient 1 for six months prior to the study. Patient 4 received calcium carbonate (3.6 g/day) and aluminum hydroxide gel for two months prior to the study. Patients 2, 3, 5 and 6 had been treated with corticosteroids or immunosuppressives, or both, for variable periods of time before the study. Patients 3 and 5 had not received these medications for at least three months, while patients 2 and 6 had not been treated with steriods or immunosuppressives for a period of one year. Radiographic examination of the members of this group revealed mild demineralization and subperiosteal bone resorption. Patients 1 and 4 exhibited, in addition, modest vascular calcification.

Group II consisted of seven patients with severe renal failure. Creatinine clearance was less than 10 ml/min in all patients. Hypocalcemia and hyperphosphatemia were evident in all patients. Azotemia was of a longer duration in this group (three to eight years) and was stable for at least six months prior to the study. All patients in this group were prescribed aluminum hydroxide gels for many months prior to this study but the degree of adherence to this therapy was variable. In addition, patients 7, 10 and 11 received sodium bicarbonate and calcium carbonate (3.6 g/day) for six months to one year prior to the study. Patient 8 had been treated with corticosteroids and immunosuppressives for two years at the onset of the disease but had not received these medications for six years. Sketetal roentgenograms of patients in this group were characterized by only modest demineralization and subperiosteal resorption. Plasma alkaline phosphatase and total protein and albumin concentrations were within normal limits for patients in both groups.

Table 1. Clinical description of patients[a]

Patient No.	Age	Sex	Weight *kg*	Height *cm*	GFR *ml/min*	Plasma					Duration of azotemia *yr*	Diagnosis
						Cr *mg/100 ml*	Urea N *mg/100 ml*	Ca *mg/100 ml*	P *mg/100 ml*	HCO_3 *mEq/liter*		
Group I												
1	49	F	61.9	170.2	11	6.7	112	9.9	5.2	23	5	CP
2	46	M	109.4	177.5	20	5.5	74	9.5	5.0	20	2	CGN
3	50	M	93.4	172.7	60	2.0	30	9.9	3.4	30	0.5	CGN
4	60	F	51.4	160.5	12	4.6	44	9.5	5.3	25	0.5	ARF
5	63	M	87.5	171.2	33	3.1	25	9.8	2.9	28	1	NS
6	53	M	82.3	168.0	45	1.8	25	9.1	2.4	33	3	CGN
Mean					30	4.0	52	9.6	4.0	26	2	
Group II												
7	50	M	81.7	177.8	5	17.0	142	6.3	6.9	17	4	CRD
8	22	F	53.6	159.8	9	7.7	92	8.4	7.1	17	8	CGN
9	53	F	45.0	153.7	2	16.0	270	8.6	12.4	11	8	PRD
10	17	F	45.4	158.0	3	13.3	263	6.3	12.6	19	8	PRD
11	43	F	60.9	162.0	3	15.0	114	6.8	5.5	20	5	PRD
12	35	M	63.2	159.7	6	12.3	121	7.1	7.0	20	3	CRD
13	47	F	67.3	152.9	8	7.1	100	8.5	5.5	18	5	CRD
Mean					5	12.6	157	7.4	8.1	17	6	

[a] CP=chronic pyelonephritis; CGN=chronic glomerulonephritis; ARF=acute renal failure; NS=nephrotic syndrome; PRD=polycystic renal disease; CRD=chronic renal disease of unknown etiology.

Experimental design. All patients ingested a constant diet containing 500 mg of Ca and 800 mg of P for seven to ten days before and nine days after injection of ^{47}Ca. After seven to ten days of equilibration to a constant diet on a metabolic ward, ^{47}Ca (20 μCi; specific activity, 1.40 mCi/mg) was administered i.v. to each subject. The plasma activity was measured at 1 hr, 6 hr and, thereafter, every 24 hr for a period of nine days. The whole body concentration of ^{47}Ca was measured daily with the Brookhaven whole body counter. Stool and urine were collected over 24-hr periods and analyzed for stable and radiocalcium.

The compartmental model of radiocalcium kinetics (Fig. 1); the experimental details of the measurement of ^{47}Ca in plasma, urine and feces; and the use of a digital computer program to analyze the kinetic data have been previously described [15]. The Berman simulation analysis and modeling (SAAM) program (modified for the CDC-6600 computer) was used to adjust the parameters of the above mathematical model to the data [15]. The program obtains, by an iterative system, the best coefficients for a given set of differential equations describing the model. This set of coefficients is then used to determine the desired parameters of the system, the sizes of the compartments and the transfer rates between them. The flow rates are then calculated from the product of the transfer rate and compartment size. The parameter values with their

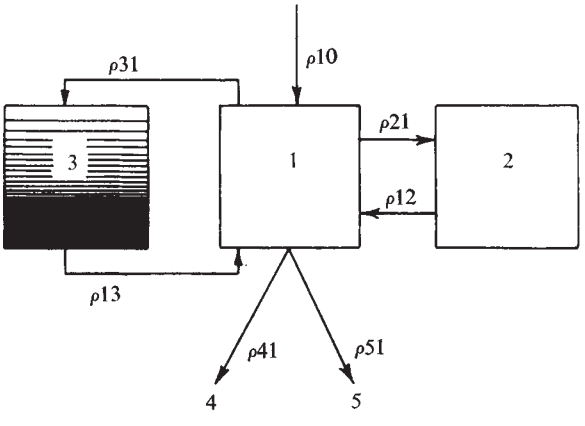

Fig. 1. *The compartmental model of radiocalcium kinetics.* Compartments are designated as follows: Compartment 1 represents the pool of Ca in isotopic equilibrium within one hour after injection. Compartment 2 represents the physiologic pool of Ca in isotopic equilibrium within three days. Compartment 3 is assumed to represent very slowly exchanging calcified tissue. The transfer constants are designated as follows: $\rho 10$ = Ca intake; $\rho 21$ = rate of transfer of Ca to compartment 2; $\rho 13$ = rate of resorption and slow exchange from bone and extraosseous calcification to blood; $\rho 31$ = the rate of accretion into bone and extraosseous calcification; $\rho 41$ = urinary Ca excretion rate; $\rho 51$ = the endogenous fecal Ca excretion rate.

computational errors provide an objective quantitative comparison of the fit of the ^{47}Ca data.

The radiocalcium kinetic data obtained for patients with renal insufficiency were compared to a previously reported normal population [16] utilizing the National Institutes of Health (NIH)-SAAM program analysis [15]. Total body Ca (TB_{Ca}) and total body potassium (TB_K) in these normal subjects were estimated from height and weight [17].

Total body levels of Ca, Na, Cl and P were measured by *in vivo* neutron activation analysis [18]. In addition, absolute levels of total body K (^{40}K) were measured by whole body counting. Total body levels of these elements were measured in the patients with renal failure and in a contrast normal population. This latter group consisted of normal volunteers without evidence of renal, bone, metabolic or cardiovascular disease.

In order to calculate the relative deficit in TB_{Ca} in individual patients from the absolute measurement of TB_{Ca}, it is necessary to normalize the data for each patient with a correction based on sex, age and skeletal size. The variation in Ca content of an individual is large because of variation in the size of the individual as well as in the degree of mineralization. Thus, in addition to the need for an accurate method of measuring the calcified tissue mass, a standard reference is needed against which the measurement may be compared.

To normalize the absolute TB_{Ca} measurement, the following algorithm was used to calculate the "normal" (i.e., predicted) TB_{Ca} in a subject based on his weight (lean body mass), height, sex and age [17, 18]:

$$TB_{Ca_E} = \alpha H \sqrt{K} \quad \text{where} \quad TB_{Ca_E} = \text{Predicted normal total body Ca } (g).$$

H = the height (m); K = the total body potassium (g); $\alpha m = 54.4$ for males; $\alpha f = 57.0$ for females.

The measured TB_{Ca}, expressed in terms of the predicted normal calcium (TB_{Ca_E}), is referred to as the calcium ratio. The relative deficit for an individual patient is then 1 − Ca ratio. In the normal subjects, the Ca ratio is 1.0 ± 0.1 (2SD).

Ca balance studies were performed on the metabolic research ward of the Brookhaven National Laboratory Hospital. The methods followed were essentially those outlined by Reifenstein, Albright and Wells [19]. Diet and feces were ashed in a muffle furnace before Ca analysis. Pooled nine-day lots of stool were analyzed and average daily fecal Ca excretion calculated. Urine and serum were analyzed directly. Fecal and dietary Ca was determined by atomic absorption spectrometry [20]; urine and plasma Ca and P, urea nitrogen (urea N), creatinine (Cr) and

bicarbonate (HCO_3) concentrations were measured by standard methods utilizing an autoanalyzer.

Results

Body composition in renal insufficiency. The values of TB_{Ca}, TB_P, TB_{Cl}, TB_K and TB_{Na} obtained in the groups of renal failure patients and the mean values noted in 14 normal patients are listed in Table 2. The ratio of TB_{Ca} to lean body mass (TB_K) in group I and group II did not differ significantly from that found in the normal subjects.

The TB_{Ca}/TB_{Ca_E} ratio in patients with renal failure was variable. In five of six patients in group I, the Ca ratio was within normal limits (0.9 to 1.1). The TB_{Ca}/TB_{Ca_E} ratio was decreased in three patients in group II, but was within normal limits or increased in four other patients in the group. Three of these latter patients had polycystic renal disease.

TB_{Ca}, whether expressed in absolute terms or relative to lean body mass (TB_K), did not correlate with GFR or the plasma HCO_3 or plasma Ca concentrations.

TB_P expressed in terms of calcified tissue mass (TB_{Ca}) or lean body mass (TB_K) is significantly higher in patients with renal insufficiency than in normal subjects. The P/Ca ratio was increased in eight of ten patients with GFR less than 20 ml/min. The relationship between the total body P/Ca ratio, plasma P and GFR is depicted in Fig. 2. All patients with plasma P in excess of 6 mg/100 ml had increased P/Ca ratios.

The total body Na/K ratio was significantly increased in group II patients above mean values observed in the normal subjects. No significant differences in body composition with regards to K or Cl were noted among subjects in group I, group II and normal subjects.

Radiocalcium kinetics in renal insufficiency. The values of the transfer rates and compartment sizes and the error in the computer-derived values for the model system are listed in Table 3. The computer-derived fit of the model to the experimental data obtained in renal insufficiency is as good as that previously observed in normal control subjects indicating that the model represents the kinetic data for individuals with renal failure very well [15]. In Table 4, the mean kinetic data relative to TB_{Ca} in the two groups of patients are compared to the mean of data from normal subjects previously reported [15, 16].

In patients with modest renal insufficiency, (group I), the following indexes of Ca metabolism as esti-

Table 2. Body composition in renal insufficiency[a]

Patient No.	TB_{Ca} g	TB_K g	TB_{Cl} g	TB_{Na} g	TB_P g	Ca/K	Na/K	Na/Cl	P/Ca	P/K	$\frac{TBCa}{TBCa_E}$
Group I											
1	840	89.7	69.6	73.8	529	9.36	0.82	1.06	0.63	5.90	0.914
2	1134	147.9	99.1	98.2	660	7.67	0.66	0.99	0.58	4.46	1.014
3	1086	127.8	75.2	92.2	566	8.50	0.72	1.23	0.52	4.43	1.054
4	512	65.0	54.5	56.8	281	7.88	0.87	1.04	0.55	4.32	0.619
5	1182	97.4	76.7	94.4	517	12.14	0.96	1.23	0.44	5.31	1.178
6	1061	119.6	72.4	77.5	438	8.87	0.65	1.07	0.41	3.66	1.077
Mean	969	107.9	74.6	82.2	498	9.07	0.78	1.10	0.52	4.68	0.976
SEM	103	12.1	5.9	6.4	53	0.66	0.05	0.04	0.03	0.33	0.079
Group II											
7	1259	120.1	105.0	90.4	594	10.48	0.75	0.86	0.47	4.95	1.120
8	708	81.0	78.9	70.0	431	8.74	0.86	0.89	0.61	5.32	0.881
9	733	59.4	71.9	69.6	670	12.34	1.17	0.97	0.91	11.28	1.009
10	729	72.1	49.0	57.5	529	10.11	0.71	1.05	0.73	7.34	0.924
11	817	66.0	57.2	63.0	392	12.38	0.95	1.10	0.48	5.94	0.961
12	791	105.4	55.7	61.1	444	7.5	0.58	1.10	0.56	4.21	0.885
13	622	74.3	69.6	63.2	696	8.36	0.85	0.91	1.12	9.37	0.828
Mean	808	82.6	69.6	67.8	537	9.99	0.84[b]	0.98	0.70[c]	6.92[c]	0.944
SEM	79	8.3	7.1	4.1	46	0.72	0.07	0.04	0.09	0.98	0.036
Normal mean	1015	117.9	75.2	78.9	472	8.84	0.69	1.05	0.47	4.11	1.000
SEM	53	8.8	3.2	3.9	29	0.28	0.02	0.02	0.02	0.21	0.010
$N=14$											

[a] TB_{Ca} = total body calcium; TB_K = total body potassium; TB_{Cl} = total body chloride; TB_{Na} = total body sodium; TB_P = total body phosphorus; Ca/K = ratio of TB_{Ca}/TB_K; Na/K, ratio of TB_{Na}/TB_K; Na/Cl = ratio of TB_{Na}/TB_{Cl}; P/Ca = ratio of TB_P/TB_{Ca}; P/K = ratio of TB_P/TB_K; TB_{Ca}/TB_{Ca_E} = ratio of measured TB_{Ca} to estimated TB_{Ca}.
[b] Value is significantly greater than normal, $P<0.05$ as determined by covariance analysis.
[c] Values are significantly greater than normal, $P<0.01$ as determined by covariance analysis.

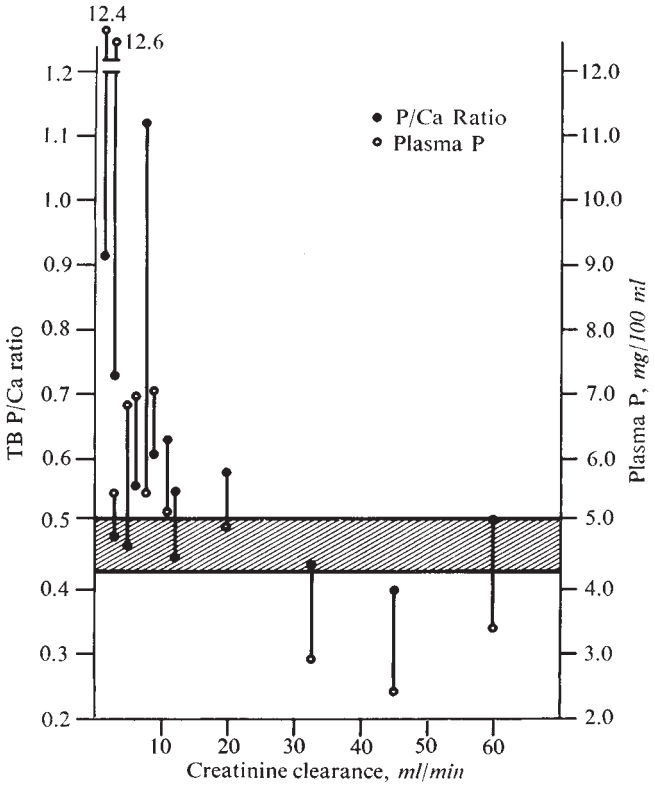

Fig. 2. *The total body P/Ca ratio in relation to glomerular filtration rate and plasma P concentration. Open circles* depict plasma P concentration; *closed circles* depict the total body P/Ca ratio. The *cross-hatched area* depicts the normal limits of the TB P/Ca ratio with 95% confidence.

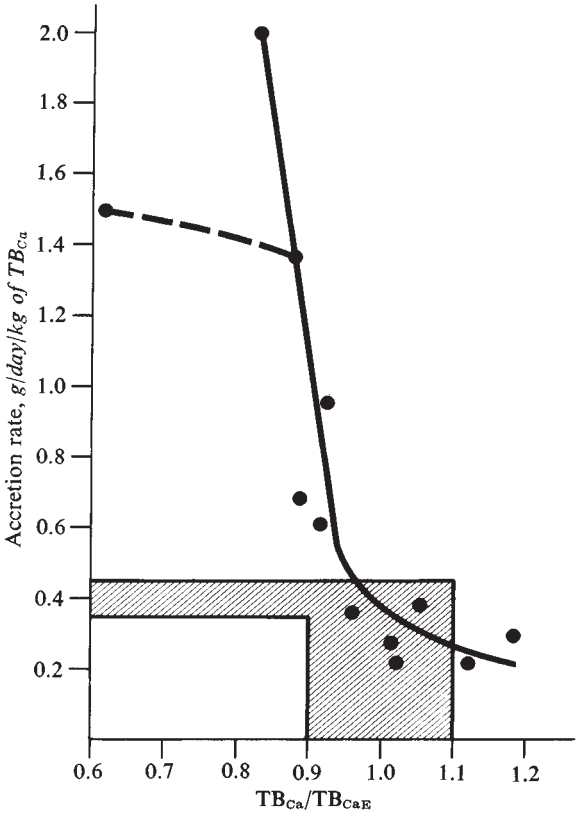

Fig. 3. *The relationship between accretion rate and the ratio of the observed to estimated total body calcium* (TB_{Ca}/TB_{CaE}). Accretion rate is corrected to 1000 g of TB_{Ca}. The normal limits of accretion rate and TB_{Ca}/TB_{CaE} are depicted by *cross-hatched area* with 95% confidence. The *line* is drawn by visual approximation.

mated by compartmental analysis are *not* significantly different from the normal mean values: compartment 1, compartment 2, the rates of exchange, accretion and resorption rate. Patients with severe renal failure (group II) were characterized by a marked increase in exchange rate (ρ12, 21) and a significant increase in the size of compartment 2. In both groups of renal patients, the accretion rate and compartment 2 were inversely related to the TB_{Ca}/TB_{Ca_E} ratio (Figs. 3 and 4). Further, a linear relationship was noted between the size of compartment 1 and the plasma Ca concentration. This relationship is significant ($r=0.763$, $P<0.01$) only if patient 13 is excluded from the patient population (Fig. 5). Endogenous fecal Ca excretion was not significantly different from normal values in both groups of patients. Urinary Ca excretion was significantly decreased below normal values and strikingly correlated with GFR in both groups of patients.

Calcium balance in renal insufficiency. The data obtained from Ca balance studies on each patient are shown in Table 5. In group I (patients with a GFR of more than 10 ml/min), the total fecal Ca excretion exceeded Ca intake in only one individual (patient 2), thus producing a negative Ca balance. In group II (patients with a GFR less than 10 ml/min), the total fecal excretion exceeded Ca intake in three of seven patients, thus producing a negative Ca balance. Positive Ca balance (>100 mg/day) was observed in three patients with a GFR less than 5 ml/min and polycystic renal disease.

Discussion

Total body levels of Ca, Na, K, P and Cl in patients with modest renal insufficiency were not significantly different from those of persons in the contrast population. This would indicate that in the early stages of renal disease no significant abnormalities of body composition develop with regard to these elements. However, patients with severe renal failure exhibited an increased total body P/Ca ratio, as well as an increased P/K ratio (i.e., phosphorus normalized to the lean body mass). This increased P was noted particularly in patients with plasma P in excess of 6.0 mg/100 ml and a GFR less than 20 ml/min (Fig.

2). This finding confirms a previous observation that phosphate retention occurs in patients when the GFR decreases below 20 ml/min [25]. Recent studies have also reported an increased P content of uremic bone [26, 27].

It was observed that in most patients with renal insufficiency, the total body Ca, when normalized for skeletal size, sex and age of the individual (TB_{Ca}/TB_{Ca_E}) was generally within ±10% (2 SD) of the mean of the normal contrast population. The patients with the significantly low Ca ratio all had a high accretion rate of Ca into bone ($\rho 31$). In fact, a significant inverse relationship was observed between the Ca ratio (TB_{Ca}/TB_{Ca_E}) and the accretion rate in patients with renal failure (see Fig. 3). Thus, when the Ca ratio was less than 0.95, the accretion rate increased to 1.4 to 2.0 g/day/kg of TB_{Ca}. When the Ca ratio was greater than 0.95 (i.e., essentially normal), the accretion rate was normal or below the normal range. Thus, in what appears to

Table 3. Radiocalcium kinetics in renal insufficiency[a]

Patient No.	Compartment, *g*			Urine $\rho 41$ *g/day*	Stool $\rho 51$ *g/day*	Accretion $\rho 31$ *g/day*	Exchange $\rho 12, 21$ *g/day*
	1	2	1 and 2				
Group I							
1	2.13 ±0.23 (11%)	2.34 ±0.52 (22%)	4.47 ±0.73 (16%)	0.0130 ±0.0009 (7%)	0.115 ±0.101 (11%)	0.514 ±0.013 (2%)	1.27 ±0.25 (20%)
2	2.72 ±0.31 (11%)	2.17 ±0.47 (22%)	4.89 ±0.80 (16%)	0.0113 ±0.0012 (10%)	0.089 ±0.010 (11%)	0.246 ±0.011 (4%)	1.47 ±0.21 (14%)
3	1.99 ±0.28 (14%)	2.19 ±0.41 (19%)	4.19 ±0.45 (11%)	0.0471 ±0.0033 (7%)	0.089 ±0.009 (11%)	0.401 ±0.011 (3%)	4.78 ±1.74 (36%)
4	1.49 ±0.09 (6%)	2.21 ±0.16 (7%)	3.70 ±0.22 (6%)	0.0201 ±0.0007 (3%)	0.088 ±0.004 (5%)	0.762 ±0.005 (1%)	2.38 ±0.27 (11%)
5	3.67 ±0.37 (10%)	2.61 ±0.44 (16%)	6.28 ±0.75 (12%)	0.035 ±0.003 (7%)	0.093 ±0.008 (8%)	0.361 ±0.010 (3%)	2.28 ±0.71 (31%)
6	2.17 ±0.21 (10%)	3.21 ±0.51 (16%)	5.38 ±0.71 (13%)	0.133 ±0.009 (7%)	0.042 ±0.004 (10%)	0.475 ±0.012 (3%)	2.19 ±0.29 (14%)
Group II							
7	1.83 ±0.32 (17%)	2.23 ±0.52 (23%)	4.06 ±0.68 (17%)	0.0118 ±0.0014 (12%)	0.067 ±0.009 (14%)	0.274 ±0.010 (4%)	4.40 ±1.73 (39%)
8	1.94 ±0.18 (9%)	3.16 ±0.50 (16%)	5.09 ±0.64 (12%)	0.0024 ±0.0001 (5%)	0.114 ±0.011 (10%)	0.963 ±0.011 (1.2%)	1.44 ±0.20 (14%)
9	1.67 ±0.19 (12%)	1.58 ±0.27 (17%)	3.25 ±0.39 (12%)	0.0210 ±0.0016 (8%)	0.077 ±0.007 (9%)	0.199 ±0.008 (4%)	2.52 ±0.87 (34%)
10	1.00 ±0.12 (12%)	2.69 ±0.29 (11%)	3.69 ±0.34 (9%)	0.0151 ±0.0006 (4%)	0.049 ±0.004 (8%)	0.696 ±0.004 (0.6%)	2.40 ±0.36 (15%)
11	1.48 ±0.16 (11%)	2.01 ±0.26 (13%)	3.49 ±0.31 (9%)	0.009 ±0.0005 (6%)	0.103 ±0.008 (8%)	0.297 ±0.009 (3%)	3.40 ±0.82 (24%)
12	1.35 ±0.09 (6%)	2.17 ±0.15 (7%)	3.52 ±0.18 (5%)	0.0089 ±0.0002 (2%)	0.079 ±0.004 (5%)	0.542 ±0.004 (0.7%)	2.44 ±0.33 (14%)
13	3.60 ±0.31 (8%)	3.40 ±0.48 (14%)	7.00 ±0.70 (10%)	0.0317 ±0.001 (4%)	0.136 ±0.013 (9%)	1.63 ±0.014 (0.8%)	1.81 ±0.36 (20%)

[a] See legend to Fig. 1 for definition of terms. The computer-calculated errors of the various indexes; also shown as percent errors.

Table 4. Comparison of radiocalcium kinetics in renal insufficiency with normal patients[a]

	Compartment, *g/kg of* TB_{Ca}			Transfer rates, *g/day/kg of* TB_{Ca}			
	1	2	1 and 2	Urine $\rho 41$	Stool $\rho 51$	Accretion $\rho 31$	Exchange $\rho 12, 21$
Group I							
Mean	2.48	2.72	5.21	0.0443	0.106	0.575	2.67
SEM	0.19	0.36	0.46	0.0141	0.022	0.190	0.62
Group II							
Mean	2.45	3.26	5.70	0.0194	0.119	0.925	3.10
SEM	0.58	0.51	1.03	0.0007	0.020	0.322	0.25
Normal mean[b]	2.86	2.14	5.00	0.150	0.134	0.405	1.72
SEM	0.13	0.17	0.22	0.001	0.002	0.024	0.36
$N=23$							
Group I *vs.* group II[c]	*NS*	*NS*	*NS*	*NS*	*NS*	*NS*	*NS*
Group I *vs.* normal[c]	*NS*	*NS*	*NS*	0.001	*NS*	*NS*	*NS*
Group II *vs.* normal[c]	*NS*	0.025	*NS*	0.001	*NS*	*NS*	0.001

[a] See legend to Fig. 1 for definition of terms.
[b] Normal values are corrected to TB_{Ca} of 1000 g based on height and weights reported by Heaney et al [16] and Cohn et al [15].
[c] *P* value for each of the groups as determined by Student's *t* test.

Table 5. Calcium balance in renal insufficiency (mg/day)[a]

Patient No.	Intake	Total fecal	Endo fecal	Net fecal	Absorption	Urine	Accretion rate	Resorption rate	Ca balance
Group I									
1	567	519	115	404	163	16	514	482	32
2	478	489	89	400	78	16	246	273	−27
3	483	407	89	318	165	51	401	376	25
4	538	394	88	306	232	22	762	640	122
5	497	386	93	293	204	35	361	285	76
6	573	411	42	369	204	133	475	446	29
Mean	522	434	86.0	348	174	45.5	460	417	43
SEM	17	23	9.7	20	22	18.3	72	56	16
Group II									
7	567	416	67	349	218	23	274	146	128
8	479	575	114	461	18	3	963	1062	−99
9	516	412	77	335	181	27	199	122	77
10	507	378	49	329	178	15	696	582	114
11	486	300	103	197	289	12	297	123	174
12	573	641	79	562	11	3	542	613	−71
13	480	638	136	502	0	31	1630	1819	−189
Mean	515	480	89.3	390	142	16.3	657	745	19
SEM	15	51	11.3	47	39	4.2	191	250	17

[a] Intake=intake of Ca in diet; total fecal=total fecal Ca excretion; endo fecal=endogenous fecal Ca excretion into the gastrointestinal (GI) tract; net fecal=total fecal−endogenous fecal Ca excretion; absorption=net absorption of Ca across the GI tract; urine=urinary Ca excretion; accretion rate=bone formation rate or transfer of Ca from compartment 1 to compartment 3 ($\rho 31$); resorption rate=bone resorption rate ($\rho 13$); Ca balance=Ca intake−total fecal excretion and urinary Ca excretion.

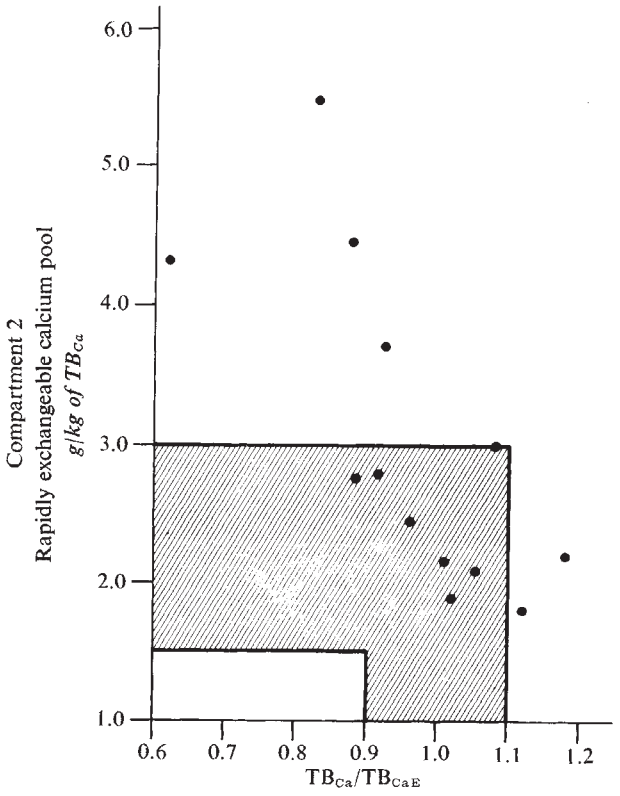

Fig. 4. *The relationship between the compartment 2 and the TB_{Ca}/TB_{Ca_E} ratio.* The *cross-hatched area* depicts the normal limits of both of these variables with 95% confidence. Excluding patient 4, the relationship between these variables is highly significant ($r=0.72$, $P<0.01$, $y=-7.58\times+10.37$).

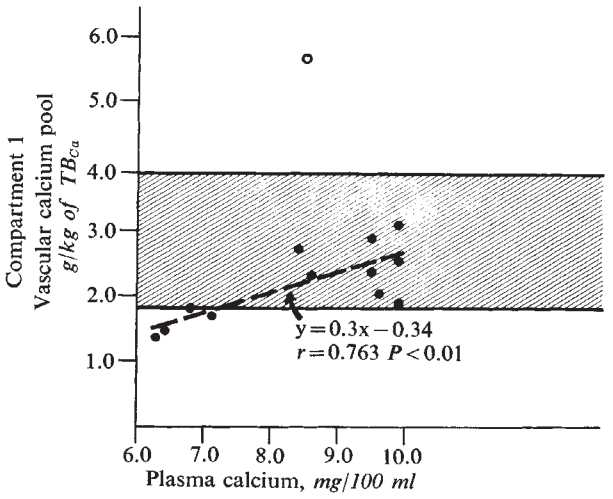

Fig. 5. *The relationship between plasma Ca concentration and compartment 1.* The *open circle* represents patient 13 who is excluded from the calculation of the regression line. The *cross-hatched area* depicts the normal limits of compartment 1 with 95% confidence.

be a homeostatic relationship, the accretion rate of Ca into bone increased when the total body Ca fell below the predicted normal value.

A similar relationship exists between the Ca ratio and the size of compartment 2 (see Fig. 4). As the total body Ca deficit increases, the size of the exchangeable Ca, compartment 2, also increases. (However, since the exact physical analog of compartment 2 has not been identified, it is difficult to draw any conclusions from these data *vis-a-vis* the increased Ca deposition in the soft tissue.)

The Ca balance was variable, and tended to be slightly positive in most patients in the short-term study. While the balance data are in contrast to the negative Ca balance data reported by a number of investigators, they are consistent with the normal values for total body Ca as measured here by TBNAA. It must be noted, however, that Ca absorption, and hence Ca balance, is a function of a number of poorly defined factors such as the dietary intake, type and duration of the disease and previous therapeutic regimens, all of which may influence the results. In addition, technical errors, such as incomplete stool collection (since no markers were used in the present study) could lead to relatively large cumulative error with this sensitive technique.

The present study illustrates how short-term balance studies and the new technique of TBNAA complement each other and provide new and useful data. The balance data obtained over a period of a few weeks provide a sensitive differential measure of the direction and rate of change of total body Ca at that point in time. The measurement of TB_{Ca} by neutron activation, on the other hand, provides a direct and accurate integral measure; i.e., the sum of all previous changes in Ca balance.

Finally, several interesting observations were made from a study of the compartmental analysis of the Ca kinetic data. In early stages of renal failure, prior to the development of severe metabolic acidosis, the distribution and metabolism of Ca in the patient does not differ significantly from that of individuals in the normal contrast population. No significant changes appear in the values for compartment sizes and intercompartmental transfer constants for group I patients. However, as renal disease progresses into severe renal failure with attendant systemic acidosis, compartment 2 increases in size, and the intercompartmental flux (ρ12, 21) also increases as compared to the normal value.

The size of compartment 1 in the renal patients did not differ significantly from that of members of the contrast population. Interestingly, a linear relation-

ship was observed between the size of compartment 1 and the concentration of plasma Ca (see Fig. 5).

Thus, it appears that the factors which depress plasma Ca in renal patients also alter the distribution of Ca between compartments 1 and 2. Since the increased exchangeable Ca and the increased soft tissue Ca observed in uremia are reduced to normal following subtotal parathyroidectomy [13], it is tempting to speculate that the increased parathyroid hormone secretion in patients with renal insufficiency has a role in the observed altered Ca distribution. One possible explanation for the marked increase in the exchangeable Ca, compartment 2, concomitant with an essentially normal total-body Ca, is the translocation of skeletal Ca to soft tissue, mediated by the increased parathyroid hormone secretion. Quite clearly, further studies are required to substantiate this hypothesis, namely, a quantitative measure of both soft tissue and osseous Ca, as well as a measure of the level of circulating parathyroid hormone.

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