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^{45}Ca KINETIC STUDY IN PATIENTS WITH THYROID DYSFUNCTION

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ABSTRACT

In order to elucidate the mechanism by which thyroid hormone influences the calcium metabolism, ^{45}Ca kinetic study and calcium, phosphorus and nitrogen balance study were carried out in 4 control subjects, 4 hyperthyroid patients, a hyperthyroid patient associated with hypoparathyroidism, 2 hypothyroid patients and 2 primary hyperparathyroid patients.

The conceptual model used to analize the kinetic data was that proposed by Heaney *et al.* and ^{45}Ca was counted by Lutwak's method, using a liquid scintillation spectrometer.

The sizes of miscible calcium pool, the turnover rates, the bone formation rates and the bone resorption rates were increased in hyperthyroid patients as much as in primary hyperparathyroid patients, while these were decreased in hypothyroid patients. Moreover, the bone resorption rates exceeded the bone formation rates in patients with hyperthyroidism as well as in patients with primary hyperparathyroidism.

Negative calcium, phosphorus and nitrogen balances were observed in hyperthyroid patients as well as in primary hyperparathyroid patients.

From these observations, it was suggested that the excessive destruction of bone is the primary event in the abnormal calcium metabolism in hyperthyroidism.

In 1891 von Recklinghausen[1] reported that necropsy of a 23-year old woman, with five years' history of thyrotoxicosis, revealed the severe bone involvement which had the characteristics of "puerperale Osteomalacie".

In 1929, Aub, Bauer, Heath and Ropes[2] demonstrated that urinary and fecal excretion of calcium and phosphorus is frequently increased in hyperthyroidism and lower than normal in myxedema. In addition, Golden and Abbott[3], in 1933, described roentgenographic evidence of skeletal demineralization in patients with thyrotoxicosis. Askanazy and Rutishauser[4] and, later, Follis[5] reported microscopic evidence of bone destruction in patients dying with hyperthyroidism. Also, hypercalcemia[6][7][8] and hyperphosphatemia[9] have been reported occasionally in hyperthyroidism. Thus, abnormal thyroid function was found to alter profoundly calcium metabolism.

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On the other hand, with the advent of tracer technic for measuring the skeletal accretion of calcium as outlined by Bauer *et al.*[10] in 1957, it has become possible to approximate the rate of bone formation. Thereafter, studies of the dynamics of calcium metabolism were spurred using ^{45}Ca[11)12)13)14)15)], ^{47}Ca[16)17)18)19)20)21)], ^{85}Sr[12)22)] and stable strontium[23)24)25)26)] as a tracer. Consequently a great progress has been made in better understanding of bone physiology. However, the reports in which the effects of thyroid hormone on calcium metabolism are investigated functionally are scanty[11)12)23)24)27)]. Therefore, the precise mechanism by which the thyroid hormone influences bone metabolism is not yet fully understood.

In order to elucidate this mechanism, the present study is undertaken with the aids of the conventional balance study and ^{45}Ca kinetic study in patients with thyroid disorders and, for purposes of comparison, in control subjects and primary hyperparathyroid patients. In this study, the conceptual model used to analize the kinetic data was that proposed by Heaney and Whedon[11] in 1958 and ^{45}Ca was measured by Lutwak's sensitive method[28], using a liquid scintillation spectrometer.

MATERIALS AND METHODS

In the present study, the diagnosis of thyroid disorders was made by the clinical features and the procedures which consist of the basal metabolic rate (BMR), ^{131}I-triiodothyronine resin sponge uptake (RSU) and ^{131}I thyroidal uptake. Parathyroid diseases were diagnosed by the abnormal levels of serum calcium, phosphorus and alkaline phosphatase activity. The diagnosis was confirmed surgically in patients with primary hyperparathyroidism.

^{45}Ca kinetics and calcium, phosphorus and nitrogen balance studies were performed in 13 subjects which consisted of 4 control subjects, 5 hyperthyroid, 2 hypothyroid and 2 primary hyperparathyroid patients and of which 7 were female and 6 were male subjects, ranging from 20 to 53 years old in their ages. All subjects were studied on a ward in the Nagoya university hospital and examined radiologically to detect the skeletal abnormality. Two adult male and two adult female subjects with normocalcemia, normophosphatemia, normophosphatasia and no detectable abnormality of bone were designated control subjects (Table 1). Five patients with hyperthyroidism, of which one was associated with hypoparathyroidism and under treatment with anti-thyroid drug, two patients with hypothyroidism and two patients with primary hyperparathyroidism were investigated. All subjects were ambulatory during studies except for one with primary hyperparathyroidism who was confined to bed because of femoral fracture and hypercalcemic crisis.

Dietary intake of calcium, phosphorus and nitrogen was kept constant and

balance studies were carried out following the techniques of Albright, Reifenstein and Wells[29]. Each study was preceded by a period for equilibration of at least five days on this regimen.

Stools, diets and refusals were homogenized and weighed. Suitable aliquots were ashed in a muffle furnace at 560°C overnight. The ash was dissolved in hydrochloric acid.

The following analytical methods were used:
calcium—Clark-Collip's method[30]
dietary and fecal phosphorus—Taussky-Shorr's method[31]
serum and urinary phosphorus—Fiske-Subbarow's method[32]
nitrogen—micro-Kjeldahl's method[33]
serum alkaline phosphatase—King-Armstrong's method[34]

After equilibrium period ^{45}Ca, 5 to 10 μc, was injected intravenously at 8 A.M. on the first day of the balance study. Serum samples for ^{45}Ca specific activity were drawn at 2 hr, 6 hr, and 12 hr after the injection of ^{45}Ca and from the second day they were drawn twice daily for 4 days and later once daily until the ninth day of study. Urines were collected in 24-hr aliquots and stools were collected for nine days, using Carmine marker for demarcation of stools.

Samples were prepared for counting by the method of Lutwak[28] and counting was done in a liquid scintillation spectrometer.

Every sample was counted for periods sufficiently long to make the probable error less than 1 per cent.

As seen in Fig. 1, following the injection of ^{45}Ca the serum specific activity of the isotope was plotted as fraction dose administered/gm calcium semilogarithmically against time for nine days. After a period of one day required for mixing in the extracellular fluid and exchangeable bone, the specific activity declined as a straight line function (k) of accretion and excretion until five days, when a break in the slope occured (slope k). Following the break, the serum specific activity again declined exponentially to define slope k'. Slope k was determined by the method of least squares, and slope k' was drawn arbitrarily. This was also the case with the other subjects.

Bone formation rates, and miscible calcium pool were calculated by the method described by Heaney and Whedon[11] in 1958.

Terminology used in the ^{45}Ca tracer studies was as follows:

E = total amount of calcium in miscible pool, expressed in g.

X_0 = specific activity of miscible pool calcium at time 0.

K_u = fractional rate of loss of miscible pool isotope by urinary excretion.

$f_{u\infty} = f_{u_{t_2-t_1}}/(e^{kt_1} - e^{kt_2})$ where t_1 is the time just after completion of mixing and t_2 is one just prior to the breake of curves and $f_{u_{t_2-t_1}}$ is the fraction of the administered dose excreted in the urine during the interval, t_1 to t_2.

K_s = fractional rate of loss of miscible pool isotope by fecal excretion.

$f_{s\infty} = f_{s_{t_2-t_1}}/(e^{kt_1} - e^{kt_2})$.

K = fractional rate of loss of miscible isotope from pool by all routes.

BFR = calcium entering bone expressed in gm/day.

Miscible calcium pool size (E) and bone formation rate (BFR) were calculated by the method described in detail by Heaney and Whedon, and bone resorption rate (BRR) was calculated by the method described by Aubert *et al.*[35] The following formulae were used:

$E = \text{Dose}/X_0$.

$\text{BFR} = \text{EK}(1 - f_{u\infty} - f_{s\infty})$.

BRR = BFR − calcium balance.

RESULTS

1) Serum calcium, phosphorus and alkaline phosphatase levels. As seen in Table 1 the serum calcium level was increased in two primary hyperparathyroid patients (14.4 and 12 8 mg/dl, respectively) and decreased in a hyperthyroid patient associated with hypoparathyroidism (8.0 mg/dl). In the other subjects it was normal, namely its range was as follows: 9.2 to 10.4 mg/dl in control subjects, 9.5 to 10.3 mg/dl in four hyperthyroid patients and 9.8 to 10.0 mg/dl in two hypothyroid patiets.

TABLE 1. Subjects

Subjects	Age (years)	Sex	Height (cm)	Weight (kg)	Serum Ca (mg/dl)	Serum P (mg/dl)	Serum ALP (K.A.u.)	BMR (%)	RSU (%)	Diagnosis
C. I.	26	F	153	44	9.5	3.5	6.4			Control subject
T. H.	53	F	151	68	10.4	3.6	4.0			Control subject
M. H.	40	M	165	51	9.4	3.2	6.0			Control subject
K. T.	46	M	162	63	9.2	3.5	5.8			Control subject
M. K.	37	F	145	40	10.3	3.0	5.6	+47.6	41.6	Hyperthyroidism
K. A.	49	F	149	39	9.9	4.4	11.8	+36.1	67.7	Hyperthyroidism
M. S.	42	M	163	51	9.8	3.3	11.3	+40.1	48.1	Hyperthyroidism
Y. K.	53	M	157	48	9.5	3.6	10.2	+42.0	42.7	Hyperthyroidism
K. M.	24	M	169	57	8.0	4.4	40.0	+14.7	37.9	Hyperthyroidism associated with hypoparathyroidism and under treatment with antithyroid drug
A. N.	38	F	136	41	10.0	3.5	5.3	−17.0	21.8	Hypothyroidism
S. A.	38	M	148	48	9.8	4.6	7.8	−36.0	21.1	Hypothyroidism
S. Y.	20	F	150	27	14.4	1.9	28.5			Primary hyperparathyroidism complicated with femoral fracture and hypercalcemic crisis
M. T.	24	F	150	46	12.8	2.1	8.6			Primary hyperparathyroidism

The serum phosphorus level was decreased in two primary hyperparathyroid patients (1.9 and 2.1 mg/dl, respectively). In the other subjects, it was normal as follows: it ranged from 3.2 to 3.6 mg/dl in control subjects, from 3.0 to 4.4 mg/dl in five hyperthyroid patients and from 3.5 to 4.6 mg/dl in two hypothyroid patients.

The serum alkaline phosphatase activity was increased in four of five hyperthyroid patients (range 10.2 to 40.0 K.A.u.) and in one of two primary hyperparathyroid patients (28.5 K.A.u.). In the other subjects, it was normal, ranging as follows: from 4.0 to 6.4 K.A.u. in control subjects and from 5.3 to 7.8 K.A.u. in two hypothyroid patients.

2) ^{45}Ca kinetic studies Table 2 summarizes ^{45}Ca kinetic data. The miscible calcium pool sizes in four control subjects ranged from 2949 to 5399 (average 4147) mg Ca. In four hyperthyroid patients, these were increased definitely,

TABLE 2. Calcium Kinetic Data

Subjects	E		K ± SE	BFR		BRR		Standard B.W. for Japanese people (kg)
	mg	mg/kg		mg/day	mg/kg/day	mg/day	mg/kg/day	
Control subjects								
C. I.	2949	58.6	0.217±0.015	412	8.2	482	9.6	50.3
T. H.	4144	80.9	0.172±0.008	472	9.2	467	9.1	51.2
M. H.	5399	90.7	0.205±0.041	383	6.4	345	5.8	59.5
K. T.	4096	71.2	0.173±0.009	504	8.7	462	8.0	57.5
Mean	4147	75.4	0.192	443	8.1	439	8.1	
±SE	500	12.5	0.011	28	0.6	37	0.8	
Hyperthyroid patients								
M. K.	5233	112.5	0.327±0.015	1398	30.0	1557	33.5	46.5
K. A.	5848	117.0	0.482±0.053	2554	51.0	2669	53.4	50.0
M. S.	5571	95.8	0.294±0.019	1677	28.8	1781	30.6	58.1
Y. K.	7302	136.8	0.419±0.010	2620	49.1	2711	50.8	53.4
Mean	5988	115.5	0.381	2062	39.7	2179	42.1	
±SE	456	8.4	0.043	309	6.0	298	5.8	
Hyperthyroid patient associated with hypoparathyroidism								
K. M.	8928	147.0	0.458±0.014	4038	66.8	3589	59.1	60.4
Hypothyroid patients								
A. N.	2407	57.7	0.105±0.018	135	3.2	153	3.7	41.7
S. A.	2937	62.2	0.121±0.013	236	5.0	261	5.5	47.2
Primary hyperparathyroid patients								
S. Y.	6939	142.2	0.394±0.015	2693	55.2	3093	63.4	48.8
M. T.	4755	97.4	0.368±0.013	1499	30.7	1647	33.8	48.8

ranging from 5233 to 7302 (average 5988) mg Ca, while in two hypothyroid patients these were small, 2407 and 2937 mg Ca, respectively. Two hyperparathyroid patients had increased miscible calcium pool sizes which were 6939 and 4755 mg Ca, respectively. Although there were some overlaps of the ranges of the miscible calcium pool sizes among control subjects and either hyperthyroid patients or hyperparathyroid patients, these were separated clearly when corrected by the standard body weight, matched for age, sex and height, a measurement which is likely to more closely correlates with skeletal mass than actual body weight[36)37)]. Namely, the ranges of the corrected miscible calcium pool sizes were 58.6 to 90.7 (average 75.4) mg Ca/kg in control subjects, 95.8 to 136.8 (average 115.5) mg Ca/kg in four hyperthyroid patients and 142.2 and 97.4 mg Ca/kg in two primary hyperparathyroid patients, respectively.

Turnover rates varied from 0.172 to 0.217 (average 0.192) in control aubjects. These were increased in four hyperthyroid patients ranging from 0.294 to 0.482 (average 0.381) and two hyperparathyroid patients, being 0.394 and 0.368, respectively, while these were decreased in two hypothyroid patients, being 0.105 and 0.121, respectively. Figs. 1-4 illustrate the curves of slope k and slope k' in representative cases of each group; control, hyperthyroid, hypothyroid and primary hyperparathyroid group. In these figures it would be seen that the curves of slope k in a hyperthyroid patient and a primary hyperparathyroid patient decline more rapidly than the curve in a control subject, while the curve of slope k in a hypothyroid patient declines more slowly than that in a control subject.

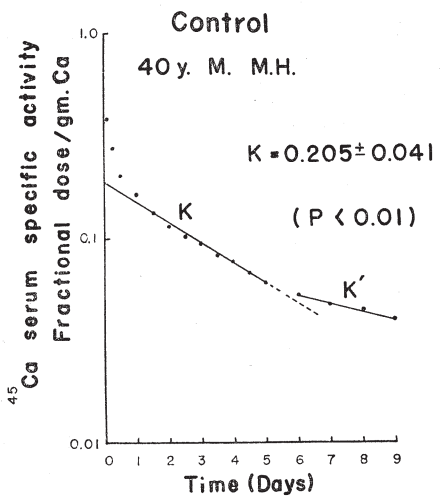

FIG. 1. ^{45}Ca serum specific activity curve in a forty years old male control subject.

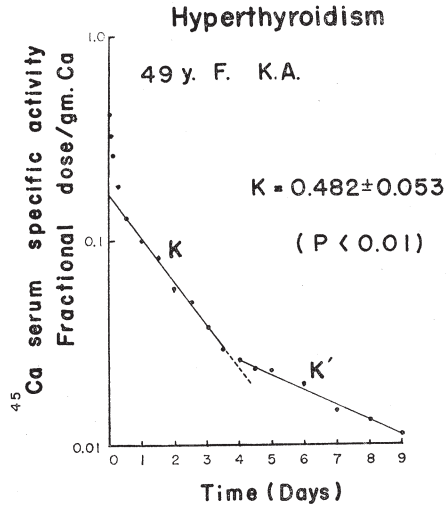

FIG. 2. ^{45}Ca serum specific activity curve in a fifty-two years old female patient with hyperthyroidism.

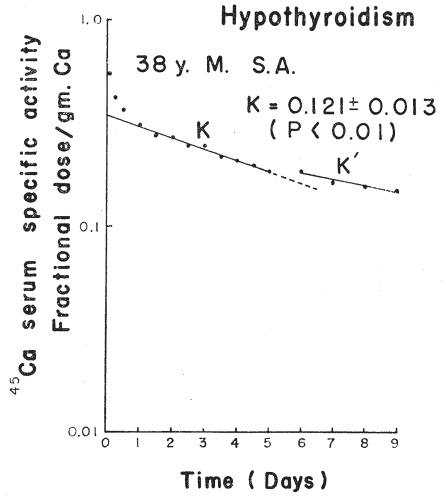

FIG. 3. ^{45}Ca serum specific activity curve in a thirty-eight years old male patient with hypothyroidism.

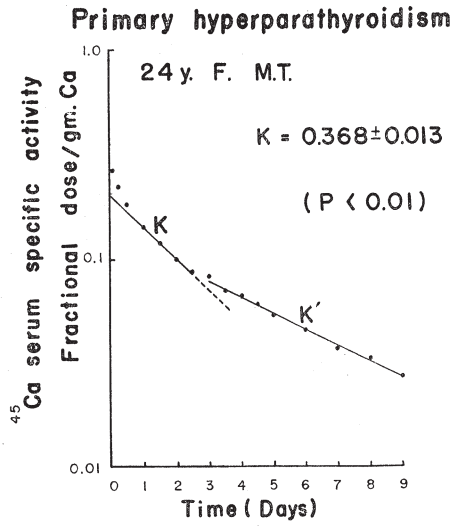

FIG. 4. ^{45}Ca serum specific activity curve in a twenty-four years old female patient with primary hyperparathyroidism.

Bone formation rates ranged from 6.4 to 9.2 (average 8.1) mg Ca/kg/day in control subjects and these were increased in four hyperthyroid patients varying from 28.8 to 51.0 (average 39.7) mg Ca/kg/day and in two hyperparathyroid patients these were 55.2 and 30.7 mg Ca/kg/day, respectively, while the rates decreased in hypothyroid patients, being 3.2 and 5.0 mg Ca/kg/day, respectively.

Bone resorption rates varied from 5.8 to 9.6 (average 8.1) mg Ca/kg/day in control subjects. These were markedly increased in four hyperthyroid patients, ranging from 30.6 to 53.4 (average 42.1) mg Ca/kg/day and in two primary hyperparathyroid patients, being 63.4 and 33.8 mg Ca/kg/day, respectively, while the rates were decreased in two hypothyroid patients, 3.7 and 5.5 mg Ca/kg/day, respectively. A patient with hyperthyroidism, K.M., who was also associated with hypoparathyroidism and under treatment with anti-thyroid drug had similar results to those in other hyperthyroid patients as follows: miscible calcium pool was 8928 mg Ca (147.0 mg Ca/kg), turnover rate 0.458, bone formation rate 66.8 mg Ca/kg/day, bone resorption rate 59.1 mg Ca/kg/day. But in all hyperthyroid patients except for K.M. and primary hyperparathyroid patients bone resorption rates exceeded bone formation rates.

3) *Balance studies* The results are shown in Table 3. In three of five hyperthyroid patients as well as two primary hyperparathyroid patients urinary excretion of calcium was more than 172 mg Ca/day, the maximal value observed

TABLE 3. Balance Data

Subjects	Calcium (mg/day)				Phosphorus (mg/day)				Nitrogen (g/day)				Theoretical phosphorus balance (mg/day)
	Intake	Urine	Feces	Balance	Intake	Urine	Feces	Balance	Intake	Urine	Feces	Balance	
Control subjects													
C. I.	500	141	429	− 70	698	541	352	−195	8.0	6.6	1.7	−0.3	− 51
T. H.	509	172	332	+ 5	795	618	229	− 52	8.7	8.3	1.2	−0.8	− 52
M. H.	444	65	341	+ 38	780	235	462	+ 83	7.2	4.5	2.4	+0.3	+ 37
K. T.	432	139	251	+ 42	868	473	301	+ 94	9.3	7.3	1.7	+0.3	+ 39
Mean	471	129	338	+ 4	785	467	336	− 18	8.3	6.7	1.8	−0.1	− 7
Hyperthyroid patients													
M. K.	220	235	144	−159	491	565	226	−300	4.6	5.2	1.2	−1.8	−193
K. A.	476	242	349	−115	925	600	380	− 55	8.3	7.1	1.8	−0.6	− 92
M. S.	501	131	474	−104	973	785	445	−257	9.8	8.3	2.5	−1.0	−110
Y. K.	500	264	327	− 91	963	811	204	− 52	9.4	10.0	1.2	−1.8	−163
Mean	424	218	324	−117	838	690	314	−166	8.0	7.7	1.7	−1.3	−140
Hyperthyroid patient associated with hypoparathyroidism													
K. M.	762	68	245	+449	927	530	298	+ 99	10.1	7.5	2.0	+0.6	+242
Hypothyroid patients													
A. N.	465	40	443	− 18	674	276	526	−128	6.0	5.6	0.9	−0.5	− 42
S. A.	397	47	375	− 25	587	296	322	− 31	5.9	4.3	1.3	+0.3	+ 8
Primary hyperparathyroid patients													
S. Y.	1	299	102	−400	65	432	77	−444	2.4	2.3	0.7	−0.6	−220
M. T.	238	281	105	−148	675	637	211	−173	6.9	5.9	1.6	−0.6	−107

in control subjects, while two hypothyroid patients excreted daily 40 mg and 47 mg of calcium in urine, respectively.

Fecal excretion of calcium was low in two hyperparathyroid patients, the values being 102 and 105 mg Ca/day, respectively. It ranged from 144 to 474 (average 324) mg Ca/day in four hyperthyroid patients and 443 and 375 mg Ca/day in two hypothyroid patients, respectively. These values did not differ significantly from the values in control subjects (range 251 to 429 mg Ca/day).

All hyperthyroid patients except for K.M. and two hyperparathyroid patients showed negative calcium balances ranging from -91 to -400 mg Ca/day, negative phosphorus balances ranging from -52 to -444 mgP/day and nitrogen balances ranging from -0.6 to -1.8 g N/day. The patient, K.M., was only one who had positive balances of calcium, phosphorus and nitrogen in hyperthyroid patients probably because of the special circumstances mentioned above.

A primary hyperparathyroid patient, S.Y., showed hypercalciuria despite of distinctly low intake of calcium, phosphorus and nitrogen due to frequent vomiting caused by hypercalcemic crisis.

Theoretical phosphorus balance paralleled closely to phosphorus balance actually measured.

DISCUSSION

In the present study the serum calcium and phosphorus concentrations were normal in all hyperthyroid patients and hypothyroid patients except for a patient, K.M., who had hypocalcemia owing to accompanying hypoparathyroidism. Despite of normocalcemia, urinary excretion of calcium tended to be increased in hyperthyroidism and decreased in hypothyroidism. Calcium and phosphorus balances were negative in all hyperthyroid patients except for K.M.

Hypercalcemia[6)7)8)] and hyperphosphatemia[9)] have been occasionally reported in thyrotoxicosis.

Furthermore, earlier reports[1)3)4)5)] have demonstrated the increased bone destruction anatomically or radiologically in patients with hyperthyroidism.

These findings suggest that the abnormal thyroid function profoundly alters calcium metabolism.

However, the precise mechanism by which thyroid hormone influences calcium metabolism can not be elucidated by the analysis of serum calcium and phosphorus or the conventional balance studies. Balance studies give only net changes in total body calcium and do not indicate whether changes in calcium balance results from alterations of rates of calcium movement into or out of bone.

Therefore, in order to elucidate this mechanism, ^{45}Ca kinetic studies were

carried out, combined with the conventional balance studies in the present investigation.

^{45}Ca was measured by Lutwak's sensitive method[28] which permits to trace serum specific activity sufficiently long to estimate the bone formation rate accurately from its curve.

The present study revealed that the sizes of miscible calcium pool, the turnover rates of calcium were increased in hyperthyroid patients as much as in primary hyperparathyroid patients, while these were decreased in hypothyroid patients.

Serum alkaline phosphatase activity was elevated in four of five hyperthyroid patients and one of two primary hyperparathyroid patients in the present series. This finding may be explained by the present observation that the bone formation rates were increased in hyperthyroid patients as well as in primary hyperparathyroid patients.

Aub *et al.*[2] demonstrated that the urinary and fecal excretion of calcium and phosphorus is frequently increased in hyperthyroidism and lower than normal in myxedema. From these observations they suggested that the thyroid hormone has a direct catabolic effect on the calcium deposits in the bones.

Krane *et al.*[27] carried out ^{45}Ca kinetic study and the conventional balance study in patients with thyroid diseases and demonstrated that the sizes of compartment and turnover rates of calcium were increased in hyperthyroidism and decreased in hypothyroidism. Furthermore, they suggested that bone formation and bone destruction may be increased in hyperthyroidism.

Fraser[23] and Eisenberg[24] also studied the calcium kinetics in patients with thyroid disorders using stable strontium as a tracer and obtained similar results demonstrated by Krane *et al.* Moreover, they found that the bone formation rate was increased in hyperthyroidism and decreased in hypothyroidism.

These reports mentioned above are compatible with the results obtained in the present study. However, the increased bone formation rate by itself does not explain the skeletal involvement and hypercalcemia encountered occasionally in hyperthyroid patients. Also, it seems to be in conflict with negative calcium balances observed usually in hyperthyroid patients.

In the present study the author calculated the bone resorption rate which has never been observed by earlier investigators in patients with thyroid diseases.

This observation gave the results that the bone resorption rate was increased in hyperthyroid patients as much as in primary hyperparathyroid patients, while the rate was decreased in hypothyroid patients. Furthermore, the bone resorption rate exceeded the bone formation rate in all hyperthyroid and primary hyperparathyroid patients except for one, K.M., who was under treatment with the anti-thyroid drug in the present study.

These results indicate that in hyperthyroidism as well as in primary hyper-

parathyroidism both bone destruction and bone formation are proceeding at an increased rate and that bone destruction exceeds bone formation.

Moreover, from these observations, kinetically the calcium metabolism in hyperthyroidism seems to be quite similar to that in primary hyperparathyroidism.

Using quantitative microradiographic and histologic methods, Adams *et al.*[33] also demonstrated that bone resorption was increased and bone formation was normal or increased in hyperthyroidism. Their findings are compatible with the present result that the bone formation rate as well as the bone resorption rate are significantly increased in hyperthyroid patients.

The effects of thyroid hormone on calcium metabolism are probably not mediated by parathyroid hormone.

Cope and Donaldson recorded details of a patient with thyrotoxicosis which was treated surgically and in whom tetany developed post-operatively owing to hypoparathyroidism. The tetany disappeared when the thyrotoxicosis recurred, but reappeared when anti-thyroid drugs were given[39]. These facts may show that thyroid hormone has an action which raises the level of serum calcium in the absence of the parathyroid glands. Thus, in order to explain hypercalcemia in thyrotoxicosis, parathyroid hormone does not appear to be a necessary factor.

The most probable explanation of altered calcium metabolism in hyperthyroidism may be that the metabolic activity of the osteoclast is stimulated by thyroid hormone. This results in excessive destruction of bone in hyperthyroidism. The weakened bones respond with an increase in the osteoblastic activity in hyperthyroid patients. If calcium and phosphorus mobilized from bone to the extracellular fluid by this mechanism are far greater than those excreted in urine and feces, hypercalcemia and hyperphosphatemia might appear in thyrotoxic patients. The similarity of calcium kinetics in hyperthyroidism to that in primary hyperparathyroidism may also be explained by the same mechanism, increased osteoclastic activity, consisting in both diseases. However, hypercalcemia is not constant finding in hyperthyroidism, while it is the rule in primary hyperparathyroidism. This discrepancy may result from the difference between the extraosseous sites on which each hormone acts, as suggested from the present results that fecal excretion of calcium was decreased in primary hyperparathyroidism while it was normal in hyperthyroidism.

SUMMARY AND CONCLUSION

1) ^{45}Ca kinetic studies and calcium, phosphorus and nitrogen balance studies were carried out in 13 subjects which consisted of 4 control subjects, 4 thyrotoxic patients, a thyrotoxic patient associated with hypoparathyroidism, 2 hypothyroid

patients and 2 primary hyperparathyroid patients.

2) The sizes of miscible calcium pool, turnover rates and bone formation rates were increased in patients with hyperthyroidism and primary hyperparathyroidism while these were decreased in hypothyroid patiens. Bone resorption rates exceeded bone formation rates in 4 thyrotoxic patients and 2 primary hyperparathyroid patients.

3) Negative calcium and phosphorus balances were found in 4 hyperthyroid patients and 2 primary hyperparathyroid patients.

4) From the present study it was suggested that the excessive destruction of bone is the primary event in the abnormal calcium metabolism in hyperthyroidism. It was also discussed that the similarity of calcium kinetics in hyperthyroidism to that in primary hyperparathyroidism may be explained by the same mechanism, the increased osteoclastic activity, consisting in both diseases.

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