EFFECT OF HIGH CALCIUM INTAKE ON STRONTIUM^{85} METABOLISM IN MAN *

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Studies carried out with tracer doses of radiostrontium (Sr^{85}) in man have revealed qualitative similarities but quantitative differences in metabolism of strontium and calcium (1–5). The principle of qualitative correlation between urinary excretion of calcium and of radiostrontium has been utilized in investigations of the removal of radiostrontium from man (6). It has been shown that elimination of radiostrontium could be considerably enhanced by inducing an increase of urinary calcium excretion, either by intravenous administration of calcium or by use of the combination of both agents (6). A study was then initiated to investigate the effect of *orally* administered calcium and of the duration of calcium supplementation on radiostrontium metabolism in man. It was hoped that prolonged oral administration of calcium would lead to a decrease in radiostrontium body burden by decreasing absorption of radiostrontium from the intestinal tract and by increasing its excretion via the kidney due to the concomitant increase of urinary calcium excretion during the phase of high calcium intake. Some of the data on the effect of high calcium intake on Sr^{85} metabolism in man has been preliminarily presented (7), and the results obtained in these and in additional studies are reported in this communication.

MATERIALS AND METHODS

Carrier-free Sr^{85}, a γ-emitter which has a half-life of 65 days, was administered as the chloride by the intravenous or oral route to 14 patients who were studied under controlled dietary conditions (8) on the Metabolic Research Ward.

All patients were in good physical condition; 11 were fully ambulatory and 3 were semiambulatory (Patients 6, 12, 13). The patients received no medication during the tracer studies except Patient 1 who received 50 mg of an estrogen analog [1] (9) during the entire course of the study.

The diet was a constant, analyzed low calcium diet which contained an average of 1,850 calories, 68 g protein, 265 g carbohydrate and 59 g fat, 150 mg calcium and 700 mg phosphorus per day. The fluid intake was kept constant during the entire study and the body weight was determined daily. In studies carried out in the high calcium phase, the calcium intake was raised by adding calcium gluconate tablets to the low calcium diet. All other constituents of the diet were kept constant. The Ca : P ratio was approximately 1 : 4 during low calcium intake and averaged 2 : 1 during high calcium intake.

All patients received tracer doses of Sr^{85} during low and high calcium intake; 3 received Sr^{85} intravenously, 3 received the tracer intravenously and orally at different times, and 8 received the tracer orally during the phase of low *and* high calcium intake. Sr^{85} studies carried out during low calcium intake preceded those performed during high calcium intake except in Patients 4 and 5 in whom the low calcium studies were performed 11 months after the high calcium intake had been discontinued. Table I lists the patients studied, the diagnoses, and duration of the radiostrontium studies carried out during low and high calcium intake. The amount of calcium added to the diet and the duration of calcium supplementation prior to the Sr^{85} studies performed during high calcium intake are also listed in this table. Calcium supplements were continued throughout the Sr^{85} studies during the high calcium phase. Tracer doses of Sr^{85} were given intravenously at different time intervals during high calcium intake to Patients 3 and 5, and orally to Patients 7 and 8 in order to investigate whether the duration of high calcium intake affected radiostrontium absorption and excretion.

The dose of Sr^{85} ranged from 0.2 to 0.4 μc per kg body weight. After intravenous injection or oral ingestion of a single dose of the radioisotope, samples of plasma were obtained for Sr^{85} analyses at 1, 4, 8 and 24 hours on the first day of each study. Subsequently, Sr^{85} plasma levels were determined daily for 6 days, and 3 times per week thereafter for as long as significant counts could be obtained with the equipment available. On the day of each tracer study, the 24-hour urine output was fractionated at time intervals at which plasma samples were

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[1] 3-Methoxy-16α-methyl-1,3,5,(10) estratriene-16β,17β-diol (Mytatrienediol).

TABLE I

Patients receiving tracer doses of Sr^{85} on low and high calcium diet *

Patient	Age	Sex	Diagnosis	Low calcium intake		High calcium intake			
				Sr^{85} study		Added calcium†		Sr^{85} study	
				route	*days*	*days*	*mg/day*	*route*	*days*
1	59	F	Multiple myeloma	i.v.	28	3	880	i.v.	27
2	45	F	Carcinoma of breast	i.v.	24	3	1,408	i.v.	27
3	71	M	Osteoarthritis	i.v.	15	20	1,408	i.v.	38
						54	672	i.v.	24
4	52	F	Carcinoma of breast	i.v.	18	146	1,408	i.v.	30
				oral‡	24	437	1,344	oral	14
5	66	F	Osteoporosis	i.v.	46	24	1,408	i.v.	20
				oral‡	23	196	1,408	i.v.	21
						247	1,344	oral	16
6	55	M	Osteoporosis	oral	26	14	1,408	oral	16
				i.v.	14	30	1,408	i.v.	16
7	74	F	Osteoporosis	oral	21	10	792	oral	12
						227	792	oral	12
8	50	M	Carcinoma of thyroid, hypoparathyroidism	oral	12	167	1,408	oral	15
						341	1,408	oral	24
						405	1,408	oral	18
						901	1,408	oral	16
9	59	F	Carcinoma of thyroid	oral	30	156	1,408	oral	24
10	62	F	Osteoporosis, rheumatoid arth.	oral	28	12	640	oral	20
11	77	F	Osteoporosis	oral	33	239	1,344	oral	25
12	70	F	Myxedema	oral	37	17	1,008	oral	23
13	68	M	Paget's disease of bone	oral	19	32	1,344	oral	22
14	63	F	Osteoporosis	oral	14	691	704	oral	22

* Low calcium diet = 159 mg calcium/day (average).

† Added to low calcium diet in the form of calcium gluconate tablets for number of days *before* the tracer study was performed during high calcium intake.

‡ Study on low calcium diet performed 11 months after discontinuation of high calcium intake.

obtained for Sr^{85} and calcium analyses. Each fractional urine collection was analyzed for Sr^{85}, calcium, and phosphorus. Subsequently, these analyses were determined daily on aliquots of 24-hour urine collections during the entire study. Each stool specimen was radioassayed separately.

The absorption of orally administered Sr^{85} was calculated from Sr^{86} stool analyses, and the unabsorbed fraction of the radioisotope and endogenous fecal Sr^{85} was determined: absorbed dose = administered dose (100 per cent) − unabsorbed dose; unabsorbed dose = total fecal Sr^{85} − endogenous fecal Sr^{85}. Endogenous fecal Sr^{85} was calculated either from fecal Sr^{85} excretions after intravenous administration of Sr^{85} to the same patient or by assuming that 15 per cent of the absorbed dose was excreted with the digestive juice, since 10 to 15 per cent of intravenously injected Sr^{85} was excreted in stool in 12 days (3).

Balances of nitrogen, calcium, and phosphorus were performed during each tracer study to determine the metabolic status of the patients and to correlate changes in calcium metabolism during high calcium intake with data obtained in Sr^{85} studies in this phase.

Metabolic balances were determined by analyzing aliquots of 6-day pools of urine and stool and aliquots of the diet. Urinary and fecal nitrogen were analyzed by the Kjeldahl method, phosphorus by the method of Fiske and Subbarow (8), urinary calcium by the method of Shohl and Pedley (9). Stool calcium and phosphorus were determined on ashed aliquots of 6-day collection pools. The technique of intravenous and oral administration of Sr^{85} and of Sr^{85} analyses of plasma, urine and stool have been described in previous communications (3, 6).

RESULTS

Table II shows data on urinary and fecal Sr^{85} excretions and on Sr^{85} body retention of 6 patients after intravenous administration of the tracer during low and high calcium intake. Urinary Sr^{85} excretion was higher during high than low calcium intake except for Patient 3 (second study) and Patient 6. This increase ranged from 7.9 to 14.0 per cent. No appreciable change in fecal Sr^{85} was noted during low and high calcium intakes. Increased urinary Sr^{85} excretion was accompanied by an increase of calciuria and by a decrease of Sr^{85} body retention, which ranged from 5.7 to 16.5 per cent of the administered dose in Patients 1–5. Sr^{85} retention increased by 10.1 per cent in Patient 6, in whom urinary Sr^{85} and cal-

TABLE II

Sr^{85} metabolism in man on low and high calcium intake *

Patient	Age	Sex	Low calcium intake				High calcium intake					
			Excretion Sr^{85}			Sr^{85} retention	Added calcium†		Excretion Sr^{85}			Sr^{85} retention
			Ca	Urine	Stool				Ca	Urine	Stool	
			mg/day	*% dose*	*% dose*	*% dose*	*days*	*mg/day*	*mg/day*	*% dose*	*% dose*	*% dose*
1	59	F	97	47.9	14.4	37.7	3	880	224	60.3	14.8	24.9
2	45	F	87	44.5	19.0	36.5	3	1,408	127	52.4	16.8	30.8
3	74	M	37	17.2	18.2	64.6	20	1,408	67	28.1	20.1	51.8
							54	672	33	15.7	17.3	67.0
4	52	F	121	46.1	15.7	38.2	146	1,408	179	55.3	15.9	28.8
5	66	F	100	48.5	15.6	35.9	24	1,408	264	62.5	15.0	22.5
							196	1,408	281	68.5	12.1	19.4
6	55	M	29	17.4	16.3	66.3	30	1,408	13	10.6	13.0	76.4

* Intravenous administration of Sr^{85}; low calcium diet = 159 mg calcium/day (average). Sr^{85} excretion and retention are calculated for 12 days.

† Added to low calcium diet in the form of calcium gluconate tablets. The number of days indicates the duration of calcium supplementation *before* the tracer study was performed on high calcium intake.

cium excretion decreased during high calcium intake. A slight increase of Sr^{85} retention was also noted in the second study of Patient 3.

Table III shows data on intestinal absorption of orally administered tracer doses of Sr^{85} of 11 patients during low and high calcium intake. In 6 of these (Patients 4–7, 9, 10), Sr^{85} absorption was in approximately the same range during low calcium intake as in studies during which calcium intake was increased approximately 9 to 10-fold, while Sr^{85} absorption decreased in 4 patients during high calcium intake (Patients 11–14). An example of the variation of intestinal absorption of Sr^{85} is illustrated by studies of Patient 8. During low calcium intake Sr^{85} absorption was of magnitude similar to that after 167 and 901 days of high calcium intake, while it was appreciably lower after 341 days and slightly lower after 405 days of calcium supplementation. Sr^{85} absorption of 11 patients averaged 19.7 per cent of the dose during low calcium diet (SD 5.4) and 14.9 per cent during high calcium intake (SD 5.6). For Patients 7 and 8 only the first studies were used in these calculations. The average value of the

TABLE III

Sr^{85} metabolism in man on low and high calcium intake; oral administration of Sr^{85} *

Patient	Low calcium intake			High calcium intake				
	Sr^{85} absorption	Urinary excretion		Added calcium†		Sr^{85} absorption	Urinary excretion	
		Sr^{85}	Ca				Sr^{85}	Ca
	% dose	*% dose*	*mg/day*	*days*	*mg/day*	*% dose*	*% dose*	*mg/day*
4	13	6.9	133	437	1,344	15	6.4	258
5	23	14.9	113	23	1,344	22	11.4	223
6	27	2.1	16	14	1,408	21	2.2	10
7	20	2.2	17	10	792	20	3.1	46
				227	792	16	3.0	38
8	16	4.3	34	167	1,408	14	3.2	53
				341	1,408	8	3.7	61
				405	1,408	11	5.1	96
				901	1,408	19	7.8	105
9	22	11.0	160	156	1,408	19	10.2	264
10	20	5.6	48	12	640	17	5.2	49
11	25	4.0	33	239	1,344	10	6.0	97
12	25‡	12.4	185	17	1,008	13	6.4	210
13	10	2.7	79	32	1,344	5	1.5	60
14	16	6.7	77	691	704	8	5.6	112

* Sr^{85} excretion and retention are calculated for 12 days. Low calcium diet = 159 mg calcium/day (average). A single dose of Sr^{85} was given as the chloride at the beginning of each study.

† Added to low calcium diet in the form of calcium gluconate tablets for number of days *before* the tracer study was performed on high calcium diet.

‡ Calculated from the 22-day stool excretion because of delayed peristalsis in a patient with myxedema.

TABLE IV

Calcium and phosphorus balances of patients receiving tracer doses of Sr^{85} intravenously during low and high calcium intake

Patient	Calcium intake	High calcium intake*	Study	Calcium				Phosphorus			
				Intake	Urine	Stool	Bal.	Intake	Urine	Stool	Bal.
		days	*days*	*mg/day*			*mg/day*	*mg/day*			*mg/day*
1	Low		46	160	78	155	− 73	668	466	227	− 25
	High†	3	6	1,048	227	1,146	−325	688	381	393	− 86
2	Low		36	146	81	139	− 74	587	466	163	− 42
	High†	3	18	1,546	163	1,345	+ 38	598	275	251	+ 72
	Low		12	138	39	148	− 49	712	512	238	− 38
3	High†	20	42	1,566	91	922	+553	704	278	226	+200
	High†	54	24	837	32	740	+ 65	721	320	360	+ 41
4	Low		18	179	128	197	−146	796	667	258	−129
	High†	146	14	1,611	236	1,329	+ 46	819	616	383	−180
	Low		30	154	114	119	− 79	673	529	164	− 20
5	High†	24	42	1,565	277	1,126	+162	659	375	193	+ 91
	High†	196	30	1,571	302	1,268	+ 1	634	377	265	− 8
6	Low		18	172	38	164	− 30	833	726	157	− 50
	High†	30	12	1,584	13	837	+734	885	410	192	+283

* Number of days of high calcium intake *before* Sr^{85} study started during high calcium intake.
† Calcium gluconate tablets added to low calcium diet.

paired difference was 4.8 per cent (SD 5.2, SE of the mean, 1.56). The differences were significant at the 2 per cent level.

Urinary radiostrontium excretion of these 11 patients was variable during high calcium intake; it remained approximately in the same range as during low calcium intake in 7 patients (4, 6, 7, 9, 10, 14 and in the first two studies of Patient 8),

TABLE V

Calcium and phosphorus balances of patients receiving tracer doses of Sr^{85} orally during low and high calcium intake

Patient	Calcium intake	High calcium intake*	Study	Calcium				Phosphorus			
				Intake	Urine	Stool	Bal.	Intake	Urine	Stool	Bal.
		days	*days*	*mg/day*			*mg/day*	*mg/day*			*mg/day*
4	High†	437	10	1,552	270	1,075	+207	848	573	236	+ 39
	Low‡		20	244	154	228	−138	842	667	218	− 43
5	High†	247	42	1,496	224	1,152	+120	681	442	224	+ 15
	Low‡		24	190	116	130	− 56	655	508	167	− 20
6	Low		18	178	18	181	− 21	828	530	211	+ 87
	High†	14	18	1,585	17	1,208	+360	839	370	313	+156
	Low		42	119	17	113	− 11	540	354	121	+ 65
7	High†	10	52	908	32	504	+372	539	182	174	+183
	High†	227	24	908	28	358	+522	517	290	155	+ 72
	Low		15	189	23	202	− 36	707	375	280	+ 52
	High†	167	20	1,566	50	1,440	+ 76	702	311	345	+ 46
8	High†	341	24	1,564	62	1,389	+113	702	290	335	+ 77
	High†	405	18	1,579	86	1,335	+158	704	324	329	+ 51
	High†	932	16	1,527	105	1,288	+134	698	384	309	+ 5
9	Low		36	160	179	190	−209	673	597	164	− 88
	High†	156	24	1,577	230	1,332	+ 15	689	495	250	− 56
10	Low		30	191	44	206	− 59	667	444	196	+ 27
	High†	12	24	851	51	673	+127	699	407	291	+ 1
11	Low		98	119	33	106	− 20	528	361	134	+ 33
	High†	239	42	1,483	97	1,281	+105	519	266	225	+ 28
12	Low		24	157	185	180	−208	680	423	211	+ 46
	High†	17	64	1,186	210	745	+231	691	207	278	+206
13	Low		24	170	75	228	−133	677	457	193	+ 27
	High†	32	36	1,501	61	1,433	+ 7	624	376	259	− 11
14	Low		48	177	92	172	− 87	842	553	252	+ 37
	High†	691	22	830	116	757	− 43	650	398	283	− 31

* Number of days of high calcium intake *before* Sr^{85} study started during high calcium intake.
† Calcium gluconate tablets added to low calcium diet.
‡ Study on low calcium diet performed 11 months after discontinuation of high calcium intake.

was slightly higher in Patient 11 and the last two studies of Patient 8, and was slightly lower in Patients 12 and 13. Urinary calcium excretion of most patients increased in the high calcium phase. In 3 semiambulatory patients, 6, 12 and 13, the calciuria did not change or even decrease in this phase.

Table IV shows data of calcium and phosphorus balances of 6 patients who received Sr^{85} intravenously during low and high calcium intake. In the latter phase, calcium intake was approximately ten times higher than during low calcium intake except in Patient 1 in whom the calcium intake was increased by a factor of 6.5. Urinary calcium excretion of 4 of 6 patients increased during high calcium intake and the stool calcium of most patients increased considerably during this phase. The calcium balances of Patients 3 and 6 improved markedly and were + 554 and + 734 mg per day, those of Patients 2, 4 and 5 improved by 112, 192 and 241 mg per day. The calcium balance of Patient 1 did not improve but became markedly negative. However, the duration of this latter study was only 6 days.

Table V lists the calcium and phosphorus balances of 11 patients who received Sr^{85} orally during low and high calcium intake. The high calcium intake was approximately ten times as high as the low calcium intake except in Patients 7, 10, and 14 in whom the calcium intake was raised by factors of 7.6, 4.5, and 4.6, respectively. The calciuria of Patients 9 and 12 was relatively high during low calcium intake. During high calcium intake, the urinary calcium excretion of Patients 4, 5, 9 and 11 increased. A gradual rise of the calciuria from 23 to 105 mg was noted in Patient 8 in 901 days of calcium supplementation. The calciuria of the remaining 6 patients either did not change or increased slightly during high calcium intake. Fecal calcium increased considerably in all patients during high calcium intake. The improvement of the calcium balance ranged from 44 mg per day in Patient 4 to 533 mg per day in Patient 7 during calcium supplementation.

DISCUSSION

The use of orally administered calcium supplements for the purpose of decreasing absorption of radiostrontium presupposes that increased calcium intake may lead to increased intestinal absorption and increased body stores of calcium, so that fewer sites may be available for radiostrontium uptake. Also, increased calciuria during high calcium intake may be accompanied by increased radiostrontium excretion, thereby leading to decreased Sr^{85} body burden.

Data obtained in the present studies revealed no appreciable difference in Sr^{85} absorption during low and high calcium intake in 7 of 11 patients, while Sr^{85} absorption decreased appreciably in 5 of 15 studies during high calcium intake (Patients 11–14 and Patient 5, Study 2). However, the average of the paired difference during the two phases of calcium intake was significant at the 2 per cent level despite the high value of the standard deviations which were due to the fact that Sr^{85} absorption was determined by difference between fecal Sr^{85} excretion (corrected for endogenous Sr^{85}) and Sr^{85} intake. Spontaneous fluctuations of Sr^{85} absorption may, in part, account for decreased radiostrontium absorption during high calcium intake as shown by the data of Patient 8.

Urinary Sr^{85} excretion of patients who received the tracer orally did not increase during calcium supplementation in general, and in some instances actually decreased due to decreased Sr^{85} absorption (Patients 12, 13). The relatively short period of high calcium intake, for example, in Patient 6 and in the first study of Patient 7, is apparently not the reason for lack of this increase, since similar negative results were obtained in Patients 4, 7, and 8 after prolonged calcium supplementation of 437, 227, and 341 days, respectively. Urinary excretion of calcium and radiostrontium may remain in the same range or may, in rare instances, even decrease during high calcium intake in certain pathophysiological conditions, for instance, due to changes in the state of mobilization and repair of disuse osteoporosis (Patient 6). Increase of urinary calcium excretion during high calcium intake was accompanied by a somewhat higher urinary Sr^{85} excretion after intravenous Sr^{85} administration.

It was hoped that the absorption of orally administered radiostrontium in man would greatly decrease during high calcium intake, as shown in studies in experimental animals by Kidman, Tutt and Vaughan (10), Copp, Axelrod and Hamilton (11), MacDonald, Spain, Ezmirlian and Rounds

(12), and Wasserman, Comar and Papadopoulou (13). Whether the effect of high calcium intake in rats is due to species differences or to the very high dietary calcium intake (13), as compared with that used in the present study in man, is not certain.

The results obtained in man are in agreement with studies carried out in mature rats (14–16). Varying calcium intake levels used in studies of Sr^{90} bone retention in mature rats (14) have revealed an inverse relationship between dietary calcium intake and bone retention of Sr^{90} and Ca^{45}, but the concentration of Sr^{90} decreased less than that of Ca^{45} when the diet was supplemented with calcium. In other experiments (15), increased calcium intake had no effect in decreasing the concentration of Sr^{90} in bone, while that of Ca^{45} decreased approximately 50 per cent; these investigators pointed out that factors other than calcium, such as the level of phosphate and carbonate in the diet, may influence Sr^{90} uptake by bone. The radiostrontium body burden could be reduced in immature rats by increased dietary calcium intake, whether the phosphorus intake was low or high, while similar results could be obtained in mature rats only when dietary calcium *and* phosphorus intake were raised simultaneously (16). Copp and co-workers have demonstrated that urinary and fecal radiostrontium excretions could be increased in rats receiving a phosphorus-deficient diet (11). Cramer and Copp (17) later showed that urinary excretion of radiocalcium of both young and old rats may remain high on phosphorus-deficient diets regardless of the level of calcium intake, and that radiostrontium excretion of young rats increased during low phosphorus intake. MacDonald and co-workers have shown that the Sr^{90} body burden of rats could be reduced by increasing dietary calcium and the body burden could be further decreased by increasing the phosphorus content (12).

SUMMARY

1. The effect of high calcium intake of varying duration was studied on radiostrontium (Sr^{85}) metabolism in 14 patients under controlled dietary conditions. The calcium intake of 10 patients was approximately 10 times as high during high as during low calcium intake.

2. Tracer doses of Sr^{85} were given orally or intravenously in separate studies during low and high calcium intake to the same subject.

3. The intestinal absorption of orally administered tracer doses of Sr^{85} was of similar magnitude during low and high calcium intake in 7 of 11 patients and was lower in 4 patients during high than during low calcium intake.

4. The addition of calcium to the diet resulted in increased urinary excretion of calcium in most patients. This increase was accompanied by a somewhat higher excretion of radiostrontium after intravenous doses of Sr^{85} in 4 of 6 patients, while in general, no increase of urinary Sr^{85} excretion occurred when Sr^{85} was given orally.

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