Calcium Balance and Calcium Requirement in Spinal Osteoporosis

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The hypothesis that osteoporosis is a disorder of the protein matrix of bone has resulted in a lack of interest in calcium balance tests as a means of studying the pathogenesis and therapy of this disorder. It is true that the work of Albright and his associates, which was reviewed in their monograph published in 1948,[1] included many careful balance studies which demonstrated the effect of estrogens and androgens on calcium balance. It was implicit in their work, however, and explicitly stated by Moldawer[2] that feeding large doses of calcium *per se* would not produce the positive balance which could be induced by hormone therapy, and other investigators have been slow to challenge this assumption.

The protein matrix hypothesis has now been questioned, and it has been suggested that osteoporosis might be instead due to prolonged negative calcium balance.[3–7] If this were true, and in the absence of an absorption defect, calcium supplements alone should suffice to produce positive balance in patients with osteoporosis. There are a few reports in the literature which indicate that this is the case. Owen et al.[8] produced strongly positive calcium balance in six patients with spinal osteoporosis by feeding them calcium supplements, and Anderson[9] reported the same effect in three patients who were given calcium glycerophosphate. Whedon[10] observed that positive calcium balance could be produced by giving calcium supplements to patients with osteoporosis, and subsequently published balance data in support of this statement.[11] The observations reported in the present paper reinforce this view, which has also been confirmed by Harrison et al.[12]

PROCEDURE

Balance studies have been performed in seventeen cases (5 male and 12 female) of spinal osteoporosis without steatorrhea. Spinal osteoporosis was defined on the basis of vertebral biconcavity as decribed by Barnett and Nordin.[13]

All balance studies were performed in a metabolic ward. The patients were equilibrated on the balance diet for one week before collections were started, and for an additional week if the dietary intake was changed. The average balance period after equilibration was twelve days. Eleven balance studies were performed with the patient on a diet approximating as closely as possible the intake at home; ten after one week's administration of calcium glycerophosphate, and eight after calcium supplements had been given for six months or more.

The usual dose of calcium glycerophosphate was 6 gm. daily (1,140 mg. of calcium) but a few balance studies were carried out using twice this amount.

Analyses were performed on aliquots of homogenized feces and of acidified urine. Calcium was estimated in feces and urine by titration with Versene® after passage of the solutions through an ion exchange column to remove inorganic phosphate.

RESULTS

The relation between calcium intake and calcium output is shown in Table I and Figure 1. Although there is a high correlation between calcium intake and output, calcium balance becomes increasingly positive as the calcium intake rises. Five of eleven patients were in slightly negative calcium balance on intakes representing their own home diets; the remainder were in slightly positive balance. Nine of these eleven patients were given calcium glycerophosphate 6 gm. daily and seven went into strongly positive balance (more

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TABLE I
Calcium Intake and Calcium Balance in Twenty-nine Balance Studies in Seventeen Patients with Osteoporosis*

Patient	On Home Diet		On Calcium Supplements			
			After One Week		After One Year	
	Intake	Balance	Intake	Balance	Intake	Balance
C. C.	19.0	+2.1	37.9	+5.6	...	...
F. K.	...	...	...	...	34.2	+12.6
M. Y.	11.9	+1.4	32.0	+6.2	32.0	+19.9
S. J.	28.0	−2.2	...	...	68.0	+21.0
T. I.	14.0	+2.7	31.5	+7.9	...	...
M. G.	15.7	−3.2	27.0	+0.4	58.0	+13.2
A. M.	26.0	+2.9	59.0	+39.3	...	...
G. C.	14.4	−0.6	...	...	...	...
R. D.	11.8	−0.8	26.0	−1.3	...	...
C. O.	...	...	...	...	47.2	+34.6
M. M.	...	...	...	...	45.8	+11.8
G. S.	...	...	...	...	46.1	+9.5
S. M.	...	...	...	...	26.3	+4.4
E. S.	22.0	−3.4	46.0	+14.4	...	...
J. S.	18.0	+1.8	33.0	+6.0	...	...
T. M.	...	...	24.0	+7.6	...	...
J. G.	14.8	+1.3	37.0	+7.4	...	...
Mean	17.7	+2.0	35.3	+9.4	44.7	+15.9
Standard error	1.7	0.45	3.0	3.0	4.5	1.1

* All values in milligrams per kilograms per day.

than 5 mg. per kg. per day). Two patients (M. G. and R. D.) did not do so, but a strongly positive balance was subsequently induced in one (M. G.) using twice this amount of calcium; the other patient was not re-tested. The results of balance studies carried out after prolonged feeding of large doses of calcium were all strongly positive.

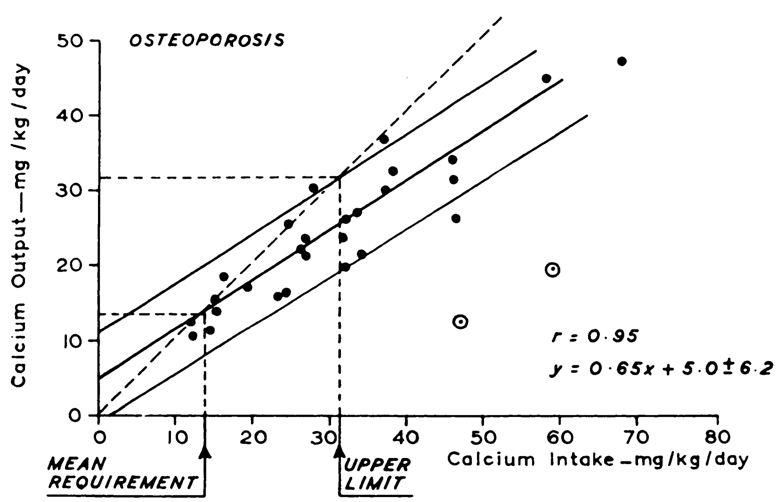

FIG. 1. The relationship between calcium intake and calcium output in twenty-nine calcium balance studies in seventeen patients with osteoporosis. (*Note:* circled points were not included in the calculation of the regression equation.)

TABLE II

Regression of Calcium Output on Calcium Intake and Theoretical Calcium Requirement in Normal Subjects, in Patients with Osteoporosis and in Patients with Steatorrhea.*

Subjects	No. of Subjects	No. of Balance Studies	Linear Regression of Output on Intake			Theoretical Calcium Requirement		
			r	Regression Equation	S.D.	Mean	S.E.	Upper Limit†
Normal........	39	92	0.97	y = 0.74x ± 2.4	1.05	9.3	0.45	17.6
Spinal and mixed osteoporosis...	17	29	0.91	y = 0.61x ± 6.1	3.0	15.5	1.9	31.0
Steatorrhea.....	22	28	0.87	y = 0.74x ± 4.9	4.3	18.9	2.2	52.0

* All values in milligrams per kilograms per day.
† Absolute intake which would protect 97.5 per cent of the population.

The regression of calcium output (y) on calcium intake (x) and the 95 per cent confidence limits are shown in Figure 1 and Table II. The regression is:

$$y = 0.61x \pm 6.1 \pm 1.0 \text{ mg. per kg. per day}$$

If calcium requirement is defined as the amount of calcium required for calcium balance, then the mean calcium requirement is the mean value at which calcium intake and output are equal. This corresponds to the point at which the mean regression line intercepts the 45 degree line as shown in Figure 1. Substituting x for y it can be calculated as follows:

$$x = 0.61x + 6.1$$

$$\therefore x = 15.5 \text{ mg. per kg. where x is the dietary calcium requirement}$$

The 95 per cent limits of this figure correspond to the values of x at which x and y are equal in the equations y = 0.61x + 6.1 − 6.0 and y = 61x + 6.1 + 6.0, i.e., the points at which the 45 degree line intercepts the upper and lower limit lines (Fig. 1). These values

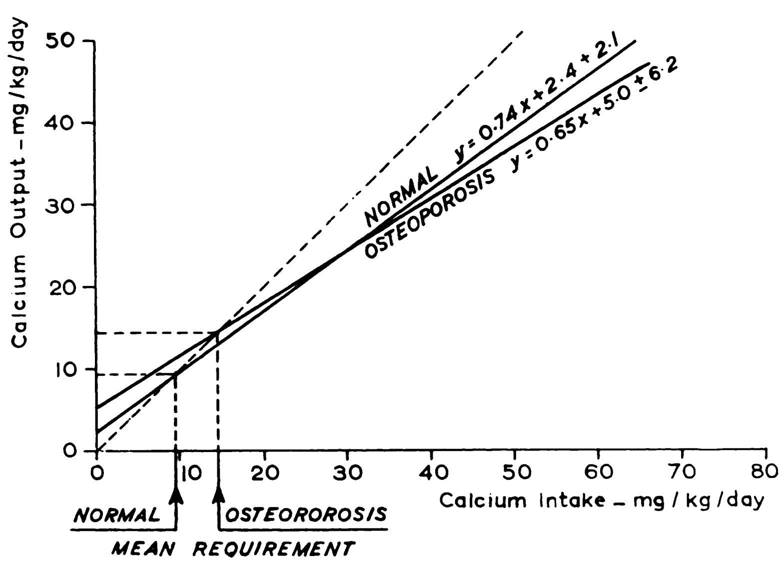

FIG. 2. The relationship between calcium intake and fecal calcium in twenty-nine balance studies in seventeen patients with osteoporosis. (*Note:* circled points were not included in the calculation of the regression equation.)

TABLE III

Relationship Between Dietary Calcium and Fecal and Urinary Calcium in Normal Subjects, in Patients with Osteoporosis and in Steatorrhea*

Subjects	Linear Regression of Fecal Calcium on Intake			Linear Regression of Urinary Calcium on Intake			
	r	Regression Equations	S.D.	r	p		S.D.
Normal..........	0.94	y = 0.67x ± 0.44	1.6	+0.34	<0.01	y = 0.56x + 2.1	1.0
Osteoporosis......	0.91	y = 0.66x ± 1.1	3.0	−0.036	>0.05	...	...
Steatorrhea.......	0.86	y = 0.71x ± 3.5	4.4	+0.31	>0.05	...	...

* All values in milligrams per kilograms per day.

are 0 and +31.0 mg. per kg. per day, respectively (Table II).

The relation between calcium intake and fecal calcium and the 95 per cent limits are shown in Figure 2 and Table III. The regression equation is:

$$y = 0.66x + 1.1 \pm 6.0 \text{ mg. per kg. per day}$$

There was no correlation between dietary calcium and urinary calcium, as shown in Figure 3 and Table III.

COMMENTS

The calcium balance data in these patients with osteoporosis differ in two respects from the results obtained in normal subjects as collected from the literature and analysed by Nordin[4,14] and by other workers.[15–18] In the first place, the calculated mean requirement is significantly greater than that of normal subjects (15.5 ± 1.7* as compared with 9.3 ± 0.5 mg.* per kg. per day) (Table II). Secondly, the regression of output on intake is less steep than in normal subjects so that the negative balance in those on low calcium diets and the positive balance in those on high calcium diets are both greater than normal (Fig. 4). These abnormalities depend upon both fecal and urinary calcium. Although the slope of the regression of fecal calcium on calcium intake in the patients with osteoporosis does not differ from that in normal subjects (Table III), the fecal calcium of the former is 0.6 mg. per kg. higher at all intake levels and

* Standard error of mean.

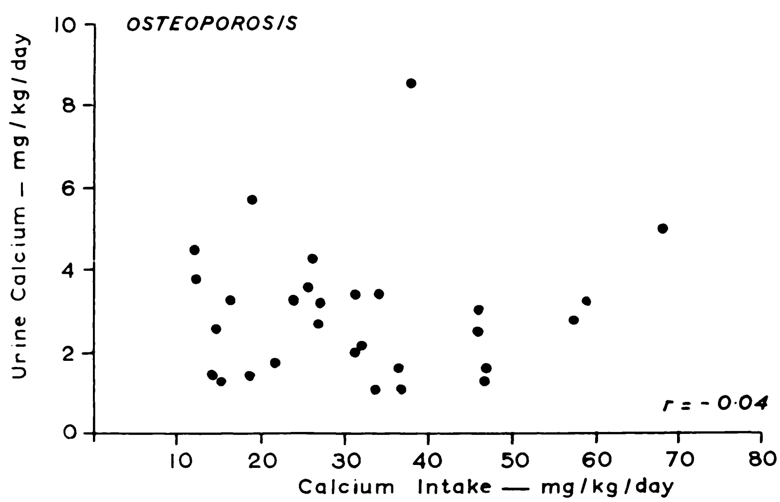

FIG. 3. The relationship between calcium intake and urinary calcium in twenty-nine balance studies in seventeen patients with osteoporosis.

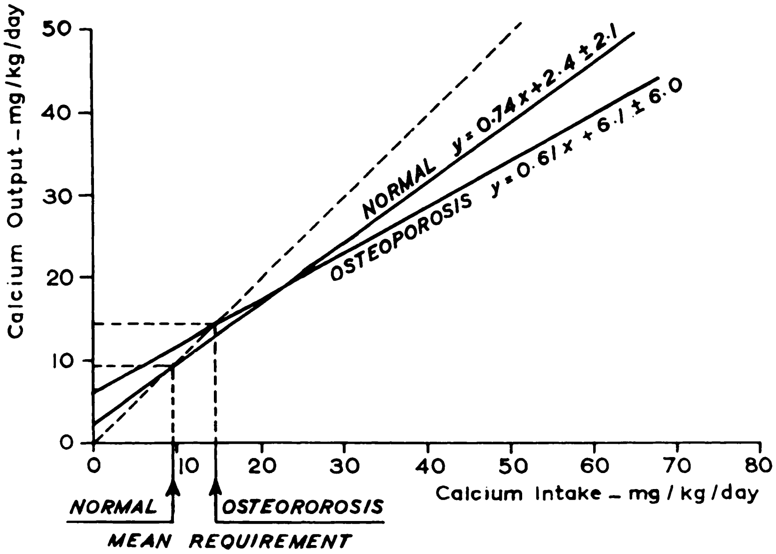

Fig. 4. The regression of calcium output on calcium intake in normal subjects and patients with osteoporosis indicating the difference in mean requirement of the two groups.

this contributes about 1.0 mg. per kg. to their higher theoretical calcium requirement. However, this difference is not statistically significant (Table III) and, therefore, it is impossible to say whether it is real or whether the series simply includes a few patients with defective absorption, possibly due to mild vitamin D deficiency.[5,6] Further work is clearly required to elucidate this point.

The difference in urinary calcium contributes rather more to the higher theoretical requirement of those with osteoporosis. We have already reported that there is no correlation between dietary and urinary calcium in osteoporosis, even with the patients on very low calcium diets.[14] In this series, the mean urinary calcium was 3.3 mg. per kg. per day and was uninfluenced by calcium intake as shown in Figure 3 and Table III. The "fixity" of the urinary calcium, therefore, accentuates the negative calcium balance at low intakes and so increases the theoretical requirement, but it also increases the positive calcium balance at high levels of intake and accounts for the difference between the regression slopes of calcium output on intake in normal and osteoporotic subjects. This difference does not appear to be due to excessive absorption at high intake levels as reported by Harrison et al.,[12] but they used a different calcium supplement.

These data support the concept that osteoporosis could be due to prolonged negative calcium balance caused by failure of adaptation to a relatively inadequate intake. This failure appears to be mainly a failure in the regulation of urinary calcium.

The mean values obtained in twenty-eight balance studies on twenty-two patients with steatorrhea[19] are also shown for purposes of comparison in Tables II and III. In patients with steatorrhea, the slope of the regression of output on intake is a little steeper than in normal subjects and calcium output is higher at all levels of intake than in normal and osteoporotic subjects due to a significantly higher fecal calcium. These data are compatible with the concept that the osteoporosis of steatorrhea is at least in part due to malabsorption of calcium.

About half the patients with osteoporosis were in positive calcium balance when taking diets representing their home intakes. This may signify that the home intake was not correctly assessed, or was not reproduced with sufficient precision to reveal small negative balance. Alternatively, it may be that the "active phase" of the disease (if such exists) was already over when these patients were seen and that they were at that time in balance on their home intakes. Again it has been suggested that conventional calcium balances fail to take into account loss of calcium through skin[20] which may amount to as much as 150 mg. per day under "comfortable conditions."[21] If this were true of these patients, they would all have been in negative calcium balance on their home diets.

The latter explanation is perhaps supported by clinical observations with calcium therapy.[14] We have found that a positive balance of as much as 6 mg. per kg. is generally required to relieve backache, but that even prolonged positive balance at this level produces little or no improvement as seen on roentgenograms. This rather suggests that the true positive balance may not be as great as the balance data indicate.

It is perhaps surprising, even when this insensible loss of calcium is taken into account, that calcium supplements have not yet produced any convincing changes on the spinal roentgenograms apart from some possible hardening of the end plates.[14] However, relief of backache is the rule and a deterioration as seen on the spinal roentgenograms has only been observed in two of fifty-three patients who have been treated with calcium supplements for six months or longer. This suggests that bone resorption is reduced, if not stopped, and it seems likely that roentgenologic assessment is not sufficiently sensitive to detect the storage of mineral which is taking place.

SUMMARY

Twenty-nine metabolic balance studies have been performed on seventeen patients with spinal and mixed osteoporosis. The patients went into strongly sustained positive balance when given calcium supplements. The mean calcium requirement of these patients with osteoporosis was significantly higher than that of normal subjects. This was largely due to their inability to vary their urine calcium with variations in their dietary intake.

The results are compatible with the concept that osteoporosis is due to prolonged negative calcium balance occurring in subjects with a higher than normal calcium requirement or unable to adapt to an inadequate intake.

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ERRATUM

Since there are some errors in the article entitled "Calcium Balance and Calcium Requirement in Spinal Osteoporosis" by B. E. C. Nordin, M.D. (*Am. J. Clin. Nutrition*, 10: 384, 1962), Dr. Nordin will supply anyone interested with a corrected reprint.