Does the response of bone mass to calcium supplements depend on calcium absorption efficiency?

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Abstract

Objective: Calcium supplements can reduce bone resorption and slow bone loss after the menopause, but these effects may be limited by poor intestinal absorption. Since the increase in blood ionised calcium and decrease in serum parathyroid hormone after a calcium load are diminished in patients with poor calcium absorption, we aimed to see whether the response of bone mineral content (BMC) to calcium is related to initial calcium absorption.

Design: We retrospectively examined the changes in forearm BMC in 164 patients (139 women and 25 men) receiving calcium therapy alone for low bone density in a university hospital.

Methods: BMC was measured in a Molsgaard single energy absorptiometer and calcium absorption in a single blood sample 1 h after a dose of 5 μCi 45Ca in 20 mg calcium carrier. Results were analysed by simple and multiple regression analysis.

Results: Mean forearm BMC did not change significantly over the mean 43 (S.D., 33) months of treatment (1.023 (0.247) to 1.017 (0.246) g/cm). The annual percentage of change was positively related to both body weight ($r = 0.180; P = 0.020$) and radiocalcium absorption ($r = 0.185; P = 0.017$). Multiple linear regression confirmed that both variables contributed to the change in BMC ($P = 0.023$ and 0.019 respectively). The mean annual percentage of change in BMC on calcium therapy was not related to age, initial BMC, serum 1,25-dihydroxyvitamin D or fasting urinary calcium/creatinine ratio.

Conclusions: These results support our earlier studies which suggest that poor calcium absorption limits the response of bone to calcium supplements.

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Introduction

Calcium supplements have been shown to decrease bone resorption in both men and women (1–3), slow bone loss after the menopause (4–6) and perhaps reduce the risk of fracture (7, 8). The beneficial effect of calcium on bone mass does not appear to be as great as that of hormone replacement (4), and this may be due, in part, to the poor and variable absorption of calcium when compared with most other nutrients; true net calcium absorption from the diets of healthy adults is 7–46% (9). Furthermore, impaired calcium absorption occurs frequently in postmenopausal women with vertebral crush fractures (10) and, possibly, hip fracture (11). The possibility that calcium-absorptive status might influence the effect of calcium supplements on bone mass does not appear to have been investigated. We have reported that calcium supplements reduce bone resorption, as assessed by either urine hydroxyproline or pyridinoline cross-links excretion, in both men and women (1–3). We have also established that the rise in serum ionised calcium and falls in serum parathyroid hormone and fasting urine hydroxyproline in response to a calcium load in postmenopausal women are greater in those with more efficient calcium absorption (12, 13). We concluded that calcium supplements, at least in conventional doses, are likely to be ineffective in the prevention of bone loss in patients with low calcium absorption, and we have therefore mostly used calcium supplements as sole therapy in those with above-average calcium absorption efficiency (as measured by a radiocalcium absorption test). In this paper, we report that the response of forearm bone mass in these patients is a function of their hourly fractional rate of radiocalcium absorption.

Patients and methods

The series comprises 164 patients (139 women and 25 men), aged 26–86 years, attending our osteoporosis clinics who required treatment for osteoporosis.
Written informed consent was not obtained, as patients were being investigated for evidence of osteoporosis. They were treated with calcium supplements alone, either on the basis of radionuclide absorption above 0.55 of the dose per hour (13) (see below) (138 patients) or because of patient preference (in those with calcium absorption below 0.55 per hour) (26 patients). Patients taking treatment known to affect bone metabolism or with any disease known to affect bone or calcium metabolism (other than osteoporosis) were excluded. They are described in Table 1. Biochemical tests were performed according to a standard protocol. Patients fasted overnight, voided on waking, and attended the laboratory at approximately 0900 h, when they had a blood sample taken, immediately before providing a fasting urine sample. A drink of water containing 20 mg calcium carrier and 5 μCi 45Ca was then given, and another blood sample was taken after 1 h to measure serum radioactivity. The hourly fractional rate of calcium absorption was then calculated from the proportion of the dose circulating at 1 h (14). The mean value in normal premenopausal women is 0.75 (s.d., 0.24) of the dose per hour (14), in normal postmenopausal women 0.66 (0.28) per h (14) and in normal men 0.68 (0.20) per hour (Need et al., unpublished data). Calcium was measured in the urine sample by standard methods and divided by creatinine to give the fasting calcium/creatinine (Ca/Cr) ratio. Serum 1,25-dihydroxyvitamin D (1,25(OH)2D) (reference range 50–160 pmol/l) was measured by radioimmunoassay after high performance liquid chromatography (HPLC) (15) and serum 25 hydroxyvitamin D (25(OH)D) (reference range 40–160 nmol/l) by in-house radioimmunoassay.

Bone mineral content (BMC) was measured in the Molsgaard bone mineral analyser (Copenhagen, Denmark) by single-photon absorptiometry. Scanning was started at an interosseous space of 8 mm, six scans being performed proximal to this point at 4 mm intervals. The γ-source was radioactive iodine [125I], and the arm was immersed in a water bath. With this method, tissue fat causes less attenuation of the photon beam than does water, and so produces a negative absorbance. The integral of this negative deflection above the baseline is added to the measured BMC by computer software supplied with the instrument to give BMC corrected for fat (16). The normal range in premenopausal women is 0.943–1.535 g/cm (17); in men 25–50 years old, 1.305–2.205 g/cm (Need et al., unpublished data). All patients were then prescribed calcium supplements. These were given either as 1.0 g/day calcium as calcium lactogluconate (Sandocal; Sandoz, Basle, Switzerland) (41 patients), 1.0 g/day calcium as calcium carbonate (Calsup; 3M Pharmaceuticals, Sydney, Australia) (29 patients) or 1.2 g/day calcium as calcium carbonate (Caltrate; Whitehall Laboratories, Sydney, Australia) (94 patients). Patients were advised to take the supplement in the evening, but were allowed to split the dose between morning and evening if they found this more acceptable.

BMC was remeasured after calcium therapy had commenced (median interval 30 months, range 6–138 months), and the average annual percentage of change in BMC calculated. Potential determinants of the rate of change in forearm BMC during calcium therapy were tested by simple and multiple linear regression. Differences between groups were analysed by one-way analysis of variance with Minitab (State College, PA, USA), Version 12. A P value of <0.05 was considered significant.

We collected our data from subjects seen in our out-patient osteoporosis clinics and in accordance with a standard protocol. Data were pooled for analysis for the purpose of this study. No financial support was required. The patients were not charged for either consultation, densitometry or biochemical measurements.

**Results**

The sex distribution and menopausal status of the patients in this series are shown in Table 1. Twenty-five were men and 139 were women, 12 of whom were premenopausal. Their median age was 62 (range 26–86) years, and the median treatment period was 30 months (range 5–138). Mean weight

| Table 1 Demographic and measured variables in 164 clinic patients (mean (s.d.)).* |
|------------------|------------------|------------------|------------------|------------------|
|                  | All              | Men              | Pre-menopausal   | Postmenopausal   | P     |
| n                | 164              | 25               | 12               | 127              |       |
| Age (years)      | 61 (11)          | 55 (11)          | 44 (11)          | 64 (9)           | <0.001|
| Weight (kg)      | 69 (13)          | 74 (11)          | 68 (12)          | 68 (13)          | 0.108 |
| 45Ca absorption (fraction/h) | 0.80 (0.28) | 0.84 (0.30) | 0.89 (0.48) | 0.79 (0.26) | 0.357 |
| Serum 1,25(OH)2D pmol/l | 121 (39)[16] | 121 (31)[5] | 136 (43)[2] | 120 (36)[10] | 0.444 |
| Urinary Ca/Cr    | 0.24 (0.15)     | 0.24 (0.11)     | 0.21 (0.14)     | 0.24 (0.16)     | 0.772 |
| Forearm BMC (g/cm) | 1.022 (0.247) | 1.421 (0.202) | 1.053 (0.101) | 0.941 (0.179) | <0.001|

* Determined by one-way analysis of variance between men, pre- and post menopausal women.

[ ] Number of missing cases.

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was 69 (S.D. 13) kg, and mean hourly fractional rate of calcium absorption was 0.80 (0.28) per hour. Initial BMC was below the young normal range in 67 (45%) of the women and 8 (32%) of the men. Mean serum 25(OH)D was 59 (24) nmol/l. Seven patients had values below 20 nmol/l, eight had values of 20–30 nmol/l and 17 had values of 30–40 nmol/l.

Univariate correlation coefficients for selected variables are shown in Table 2. The initial forearm BMC was related inversely to age ($P < 0.001$) and positively to body weight ($P < 0.001$). Radiocalcium absorption was positively related to serum 1,25(OH)$_2$D ($P = 0.003$), but not to serum 25(OH)D, age, weight, BMC or Ca/Cr.

Forearm BMC did not change significantly over the mean 43 (33) months of treatment, the initial value being 1.023 (0.245) g/cm and the final value 1.017 (0.246) g/cm. The annual percentage change in forearm BMC was related positively to body weight ($P = 0.020$) and radiocalcium absorption ($P = 0.017$) (Fig. 1) but was not significantly related to age, initial forearm BMC, serum 1,25(OH)$_2$D or fasting urinary Ca/Cr (Table 2). The trends were the same in those with calcium absorption below 0.55 per hour but did not reach statistical significance.

When the annual percentage rate of change in BMC was regressed simultaneously on age, initial BMC, Ca/Cr, weight and radiocalcium absorption, only weight ($P = 0.023$) and radiocalcium absorption ($P = 0.019$) were significant determinants of the change in BMC; age, Ca/Cr and initial BMC remained insignificant (Table 3).

The interquartile values for change in BMC against body weight and radiocalcium absorption are shown in Table 4. There was a step-wise decrease in BMC change as radiocalcium absorption diminished, but when the relationship with weight was examined, a poor BMC response appeared to be restricted to those with the lowest body weight. Patients in the lowest quartile for both radiocalcium absorption and weight had a change of $-1.54 (1.89)$% per annum during 53 months of observation, while those in the highest quartile for weight and radiocalcium absorption had a change of $+0.53 (2.73)$% per annum during 41 months of observation. The difference between these two rates was significant ($P = 0.040$).

### Table 2
Univariate correlations between age, weight, initial BMC, radiocalcium absorption, fasting urinary calcium/creatinine (Ca/Cr) ratio and annual rate of change in BMC (%BMC/year) in 164 patients.

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Wt</th>
<th>BMC</th>
<th>$^{45}$Ca absorption</th>
<th>1,25(OH)$_2$D</th>
<th>Ca/Cr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wt</td>
<td>$-0.196^*$</td>
<td></td>
<td></td>
<td>0.105</td>
<td>0.016</td>
<td>0.059</td>
</tr>
<tr>
<td>BMC</td>
<td>$-0.438^{***}$</td>
<td>0.307^{***}</td>
<td></td>
<td>0.031</td>
<td>$-0.109$</td>
<td>0.0052</td>
</tr>
<tr>
<td>$^{45}$Ca absorption</td>
<td>0.016</td>
<td>$-0.034$</td>
<td>0.019</td>
<td>0.241^{**}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,25(OH)$_2$D</td>
<td>0.016</td>
<td>$-0.034$</td>
<td>0.019</td>
<td>0.241^{**}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ca/Cr</td>
<td>0.059</td>
<td>$-0.052$</td>
<td>0.018</td>
<td>0.094</td>
<td>0.180^{*}</td>
<td></td>
</tr>
<tr>
<td>%BMC/year</td>
<td>0.011</td>
<td>0.001</td>
<td>0.185^{*}</td>
<td>$-0.087$</td>
<td>$-0.087$</td>
<td></td>
</tr>
</tbody>
</table>

Significance of correlation coefficient (Pearson): *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

### Table 3
Multiple regression of percentage of annual change in BMC (%BMC/year) on body weight and radiocalcium absorption.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Coefficient</th>
<th>Standard deviation</th>
<th>$T$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>$-2.9249$</td>
<td>0.91750</td>
<td>$-3.19$</td>
<td>0.002</td>
</tr>
<tr>
<td>Weight</td>
<td>0.02691</td>
<td>0.01168</td>
<td>2.30</td>
<td>0.023</td>
</tr>
<tr>
<td>$^{45}$Ca absorption</td>
<td>1.29000</td>
<td>0.54250</td>
<td>2.38</td>
<td>0.019</td>
</tr>
</tbody>
</table>

$r = 0.25; P < 0.001$.
The regression equation is \(\%\text{BMC/y} = -2.92 + 0.0269 \times \text{Wt} + 1.29^{45}\text{Ca absorption} \times \text{f/h} \times \text{Student's t-test}.$

### Table 4
Percentage of annual change in forearm BMC for each quartile of (a) body weight and (b) radiocalcium absorption.

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Mean weight (kg)</th>
<th>$\Delta$BMC % p.a.</th>
<th>Mean $^{45}$Ca absorption (fx/h)</th>
<th>$\Delta$BMC % p.a.</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>54.9</td>
<td>$-0.92$ (2.0)</td>
<td>0.51</td>
<td>$-0.51$ (1.9)</td>
</tr>
<tr>
<td>II</td>
<td>64.4</td>
<td>0.30 (1.9)</td>
<td>0.68</td>
<td>0.09 (1.9)</td>
</tr>
<tr>
<td>III</td>
<td>71.2</td>
<td>0.29 (2.1)</td>
<td>0.85</td>
<td>$-0.03$ (1.7)</td>
</tr>
<tr>
<td>IV</td>
<td>85.9</td>
<td>0.13 (1.9)</td>
<td>1.18</td>
<td>0.35 (2.6)</td>
</tr>
</tbody>
</table>

$P = 0.019$ * Determined by one-way analysis of variance.

p.a., per annum; fx/h, fraction/h.
Discussion

The new observation in this paper is that change in BMC during calcium therapy for low bone density is related to calcium-absorptive status. This appeared to apply across the range of calcium absorption efficiencies measured in the whole set (Fig. 1) and in spite of the fact that patients were selected on the basis that their fractional radiocalcium absorption was in the desirable range (above 0.55 per hour). We have shown that when hourly fractional calcium absorption is above 0.55 there is a reduction in urine hydroxyproline excretion, indicative of a reduction in bone resorption. Calcium supplements of 1 g appear to have no effect on bone resorption markers in women with calcium absorption below 0.55 per hour (13). Patients with calcium absorption above 0.55 per hour had a greater rise in serum ionised calcium and a greater calcium absorption below 0.55 per hour (12). In our cohort, bone mass was stabilised by calcium supplements, with no significant change in BMC (−0.03 (S.D., 2.0)% per annum). The expected rate of bone loss in subjects of this age, if left untreated, is more than 1% per annum (17). In this study, we have used fat-corrected forearm bone mass, which has a precision of 1% (16), to measure the effect of calcium therapy on the skeleton. In our hands, this measurement site discriminates between fracture and non-fracture patients (18). In other studies, the forearm bone mass has been shown to predict fracture (19, 20). It also shows responsiveness to a variety of treatments for osteoporosis (21). Another index of calcium efficacy is, of course, its fracture prevention (7, 8), but this cannot be assessed in a study of the current size. Most studies of calcium therapy for osteoporosis extend over 2 years (4, 5), but in this study we have followed patients treated in our osteoporosis clinics, for a mean of 3.5 years. This indicates that the response is durable.

In interpreting the results of this study, it should be realised that we have not measured habitual calcium intake in our subjects and that calcium supplementation will presumably have less effect in those with higher intakes (22). The trends shown in this paper may therefore have been greater if we had selected patients with low calcium intake. However, our fasting test of calcium absorption is not influenced much by diet, and we could find no relationship between calcium intake and radiocalcium absorption in 72 premenopausal women (23). Moreover, three different commercial forms of calcium supplement were used in this study, but there is evidence that all these forms of calcium have comparable absorption (24, 25). Other limitations of the study include its retrospective character, diversity of subject groups and form of calcium, and the fact that BMC was measured at only one site. The results need to be confirmed in a prospective study.

Mean serum 25(OH)D in our cohort was 59 (24) nmol/l, and 32 patients had values below the laboratory reference range. However, radiocalcium absorption was not related to serum 25(OH)D, although it was positively related to serum 1,25(OH)2D as expected (10). 1,25(OH)2D is the physiologically active form of the vitamin and has greater affinity for the vitamin D receptor than 25(OH)D. The change in BMC was unrelated to serum 1,25(OH)2D, indicating that the effective modulator of calcium action on bone in our study was calcium absorption, and not vitamin D status. Other factors obviously must affect calcium absorption. While serum 25(OH)D status does influence bone turnover and bone loss, it is not related to calcium absorption in our patients, and we suspect there is another mechanism for its actions on bone.

We have confirmed that body weight is a determinant of bone loss. However, the increase in bone loss seems to be confined to those in the lowest quartile of weight, just as, in two studies, an increase in hip fracture risk seems to be confined to that group (26, 27). It has been speculated that greater bone loss in lighter subjects is due to lower mechanical stress, lower circulating residual oestrogen levels or lack of anabolic hormones, such as insulin (28). None of these arguments are wholly convincing, especially not the first, when forearm BMC is used as the indicator. Thus, the cause of the relationship between BMC and body weight remains to be clarified. Calcium is cheap and appears to be effective in preventing ongoing bone loss, but poor calcium absorption is common in ageing men and women, especially those with osteoporosis, and this may limit its beneficial effect. These results support our earlier studies which suggest that impaired calcium absorption efficiency limits the response of bone to calcium supplements.

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