Metabolic balance studies of mineral supplementation in osteoporosis

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SUMMARY
1. We studied the effect of mineral supplementation and its duration in osteoporosis by analysing the calcium and phosphorus balances of 49 treated osteoporotic patients whose median length of calcium treatment was 19 weeks with a range of 8 days to over 4 years. Forty-four studies satisfied statistical criteria of reproducibility and included 35 women (10 also receiving oestrogen replacement therapy) and nine men.

2. Mean calcium balance was positive in women taking calcium supplements alone, \( +1.9 \pm 2.5 \text{ mmol daily} \) \((P<0.002)\), and was significantly more positive \((P<0.05)\) in women also taking oestrogens, \( +4.2 \pm 2.1 \text{ mmol daily} \). Calcium balance was not significantly positive in men.

3. Calcium balance correlated negatively with duration of supplementation, but, significantly, only when duration of supplementation was expressed logarithmically \((r=-0.401, P<0.01)\) giving the regression equation \( y=4.2-1.6 \log x \), where \( y = \) calcium balance in mol/day and \( x = \) duration of supplementation in weeks. Theoretical net calcium retention, without allowance for dermal loss, could be calculated by integration.

4. Mean phosphorus balance was significantly positive in both groups of women and in the whole population. Although its correlation with duration of supplementation did not reach statistical significance \((P<0.1)\), the ratio of the regression slopes for calcium and phosphorus, 1.5:1, corresponded to their molar ratio in bone.

5. These statistics are, we believe, the first to describe an exponential decline in calcium balance during mineral treatment of osteoporosis, but they firmly suggest that such treatment, with or without oestrogen therapy, conveys temporary benefit.

Key words: calcium, metabolic balance, metabolism, osteoporosis, phosphorus.

INTRODUCTION
The original notion of osteoporosis as a calcium deficiency disease [1–4] has long been a rationale for calcium treatment. Many metabolic balance studies of calcium treatment have recorded positive calcium balance [3–11], sometimes over prolonged periods. Simultaneous phosphate retention was not demonstrated [6, 8, 11] however, and calcium is now thought to act by temporarily inhibiting bone resorption [12–16]. Although a decline in calcium balance with time should therefore be expected, no statistical regression has yet been described.

In post-menopausal osteoporosis the benefit of hormone replacement therapy is clearer [15, 16]. Opinions differ, however, over the age limits for treatment [14] and whether combined therapy with calcium conveys an additional benefit. It therefore seemed valuable to extend previous studies [11] by comparing the balance performance of all our osteoporotic men and women who had been taking calcium supplements for known periods of time, with and without additional oestrogen replacement, and assessing its relationship to the length of therapy.

PATIENTS AND METHODS
Forty-nine osteoporotic patients, who had been studied on metabolic balance, fulfilled the following additional criteria: all had spinal crush fractures due to idiopathic or post-menopausal disease; all had been taking calcium supplements for periods that could be precisely recorded, and claimed full compliance; none had previously undergone a metabolic balance study. Supplements contained 20.0–26.7 mmol of calcium daily, almost exclusively in the form of microcrystalline hydroxyapatite compound (Ossopan), which also provides extra phosphorus. Dur-
tion of supplementation varied from 8 days to 232 weeks. Most patients were additionally receiving a small vitamin D supplement providing 800–1600 i.u. daily. Patient selection was blind with respect to balance data.

All patients were studied on a metabolic ward. Diets were constructed to match domestic intake and mineral supplements were given with meals. After an initial 5-day run-up, using cuprous thiocyanate as an internal faecal marker [17], two 4-day collections were made using carmine as an external faecal marker. Calcium and copper were measured by atomic absorption spectrophotometry, and phosphorus was determined by an autoanalyser method.

The possible errors in human balance studies are well known, and standards of reproducibility have usually been arbitrary [10, 11]. To develop statistical criteria each two calcium balance periods were first compared, showing a mean difference of 2.1 ± 2.3 mmol daily; five patients showed a difference outside this mean plus two sds (range 2.5–2.8 sd) and on these grounds their results were omitted as probably being spurious. Re-calculation of the remaining 44 gave a mean difference of 1.4 ± 1.2 mmol/day for calcium and 1.8 ± 1.7 mmol/day for phosphorus. Subtraction of the first period from the second to confirm temporary equilibration showed a negligible mean change in calcium balance of +0.1 ± 1.6 mmol/day. Equilibration was equally complete in those who had taken supplements for the shortest times. All further results were therefore expressed as the mean of each two periods. The 44 patients comprised nine men (aged 59 ± 10 years), 10 women (aged 61 ± 4 years) also taking a form of oestrogen equivalent to at least 10 μg daily of ethinyloestadiol and 25 women not taking oestrogens (aged 64 ± 8 years). Data were collected from the metabolic ward over a total period of 10 years, usually from studies investigating subsequent additional modes of treatment [11].

Statistical evaluation was based on Student’s t-test, linear regression and the correlation coefficient, r.

RESULTS

Overall balance

Details of overall mean calcium and phosphorus balances are given in Table 1. Calcium and phosphorus balances were significantly positive in a molar ratio of 1.3:1. Calcium balance correlated positively with net absorption (diet minus faeces; r = 0.755, P < 0.001) but not with calcium intake over this narrow range (r = −0.097) nor with urinary calcium (r = −0.168).

Calcium and phosphorus balances in the three subsets are shown in Table 2. The duration of mineral supplementation was similar in each group. The median duration of oestrogen replacement was greater (38 weeks), but the difference was not significant (P > 0.1). With respect to calcium balance, women taking oestrogens performed better than women receiving supplements alone. Women taking mineral alone were also in significant positive calcium (and phosphorus) balance, but men were not; there was, however, no significant difference between these two groups.

Relation to duration of supplementation

Analysis of all calcium balances relative to absolute duration of supplementation showed no significant correlation (r = −0.304). When duration of supplementation was expressed logarithmically, however, either as log or as ln, the correlation was highly significant (r = −0.401 and −0.382 respectively, P < 0.01), although individual values varied widely (see Fig. 1). The exponential regression was given by the equation:

\[ y = 4.2 - 1.6 \log x \]

Table 1. Details of calcium and phosphorus balances in 44 osteoporotic patients receiving mineral supplements for a log mean period of 19 weeks (range 8 days to 232 weeks)

<table>
<thead>
<tr>
<th>Intake (mmol/day)</th>
<th>Calcium</th>
<th>Phosphorus</th>
</tr>
</thead>
<tbody>
<tr>
<td>51.9 ± 6.0</td>
<td>55.4 ± 10.9</td>
<td></td>
</tr>
<tr>
<td>Urinary loss (mmol/day)</td>
<td>4.9 ± 2.1</td>
<td>24.4 ± 6.9</td>
</tr>
<tr>
<td>Faecal loss (mmol/day)</td>
<td>44.7 ± 6.4</td>
<td>29.3 ± 7.6</td>
</tr>
<tr>
<td>Balance (mmol/day)</td>
<td>+2.3 ± 2.6†</td>
<td>+1.8 ± 3.0*</td>
</tr>
</tbody>
</table>

Table 2. Calcium and phosphorus balances in three groups of osteoporotic patients receiving mineral supplements

<table>
<thead>
<tr>
<th>Group</th>
<th>Subjects</th>
<th>Mean (log) duration of supplementation (weeks)</th>
<th>Balance (mmol/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Women taking oestrogens (n = 10)</td>
<td>15</td>
<td>+4.2 ± 2.1**</td>
</tr>
<tr>
<td>2</td>
<td>Women not taking oestrogens (n = 25)</td>
<td>19</td>
<td>+1.9 ± 2.3***†</td>
</tr>
<tr>
<td>3</td>
<td>Men (n = 9)</td>
<td>24</td>
<td>+1.0 ± 2.6††</td>
</tr>
<tr>
<td>4</td>
<td>All</td>
<td>19</td>
<td>+2.3 ± 2.6***</td>
</tr>
</tbody>
</table>
Fig. 1. Relationship between calcium balance, without allowance for dermal calcium loss, and duration of mineral supplementation (illustrated on a log scale) in 44 osteoporotic patients divided into three groups: 25 women taking calcium supplements alone (●), 10 women additionally receiving oestrogen therapy (○) and nine men (□). The semi-logarithmic linear regression is shown for women taking calcium alone \( r = 0.411, P < 0.05 \) and \( y = 4.2 - 1.8 \log x \). The stippled area represents 95% confidence limits for the population as a whole, for whom \( r = -0.401, P < 0.01 \) and \( y = 4.2 - 1.6 \log x \).

or

\[
y = 4.2 - 0.65 \ln x
\]

where \( y \) = calcium balance in mmol/day and \( x \) = duration of supplementation in weeks. The 95% confidence limits of this regression (Fig. 1) suggested a minimum duration of positive balance of 104 weeks. Integration of the areas below these confidence limits over 2 years, without allowance for dermal loss, gave values for net calcium retention of 0.68 and 2.07 mol (27 and 83 g).

In women also taking oestrogens the negative correlation between calcium balance and log duration of supplementation was higher \( (r = -0.587) \), although with the smaller number this failed to reach statistical significance \( (0.1 > P > 0.05) \). The correlation was significant among women taking calcium alone \( (r = -0.411, P < 0.05, \text{ see Fig. 1}) \). It was not significant in men \( (r = -0.252) \).

The equivalent regression for phosphorus was statistically insignificant \( (r = -0.258, 0.1 > P > 0.05) \), the equation being:

\[
y = 3.3 - 0.44 \ln x
\]

Nevertheless the ratio between the two regression slopes of 1.5:1 was equivalent to the molar ratio for calcium and phosphorus in bone. Separate correlations in females taking and not taking oestrogens also failed to reach statistical significance \( (r = -0.514 \text{ and } r = -0.276, \text{ respectively}) \).

DISCUSSION

This retrospective cross-sectional study suggests that a positive effect of supplements on mineral balance in established osteoporosis is temporary and follows a mathematical progression of exponential decay. These findings, although perhaps not unexpected, have not to our knowledge previously been documented. They may help in the long-standing debate over the value of calcium supplements [12–14].

Over the whole study period, with a median duration of 19 weeks, calcium and phosphorus balances, in a ratio appropriate to bone mineral, were significantly positive among the population as a whole and separately in two groups of women taking either minerals alone or oestrogens as well. Notwithstanding the limits both in numbers and in balance precision, results also distinguished statistically a superior additional effect of oestrogen replacement in a group of women whose mean age was over 60 years (see [14]). The lack of significant difference between men and women taking calcium alone may mean that the number of men was too small to show a significant positive calcium balance on their own, but the possibility cannot be excluded that calcium supplements had no effect in this sex.

Radioisotopic estimates of calcium loss through skin in the absence of sweating differ widely and their accuracy is unknown. While application of lower estimates [18] did not affect the statistical significance of present results, much greater daily dermal losses [19] would plainly affect our evidence. While we doubt the physiological importance of calcium loss in insensible perspiration, this issue cannot be resolved here; however, it should not affect the significant negative exponential regression of calcium balance with time.

The molar ratio of calcium to phosphorus in bone is 1.5 (less than the 1.67 for hydroxyapatite) [20]. Although it was perhaps fortuitous to derive an identical ratio between the present regression slopes for calcium and phosphorus, this qualitative relationship helps to corroborate declining mineral retention, regardless of whether the regression for phosphorus reached statistical significance as well. It is widely accepted that calcium supplements do not prevent ultimate bone mineral loss [12, 15, 16]; this too is predicted by present regression statistics. Although balances were not significantly related to the duration of oestrogen therapy, our study was not suited to investigating this matter: oestrogen therapy had usually been started much earlier and the numbers of subjects were small.

Although we could not validate long-term compliance we presume that any such lack would only lessen the statistical significance of our results. Nevertheless their wide variance clearly indicated that individual response is unpredictable. Adverse side-effects were not seen: mean net intestinal calcium absorption from intakes of just over 2 g daily was only 14% and urinary calcium excretion was low enough to suggest little risk of urinary stone complications; indeed none was observed over follow-up periods of over 10 years.
Present data are the obverse of those of Malm [21],
who noted the relative lack of adaptation to low-calcium diets among osteoporotic patients. Heaney et al. [22] noted a positive correlation between calcium balance and long-term dietary intake in pre- and post-menopausal females, although the correlation was not statistically significant. This might suggest that should calcium supplements be started, they should never be stopped.

In the current absence of other drugs licensed for the treatment of osteoporosis, the present results may perhaps strengthen the rationale for calcium treatment whether or not it is combined with oestrogen therapy for established osteoporosis in post-menopausal females, even over the age of 60 years (see [14]). However, a protective effect of calcium supplementation against further fracture remains unproven.

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REFERENCES