THE ROLE OF DIETARY CALCIUM IN THE PREVENTION OF POSTMENOPAUSAL OSTEOPOROSIS

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Summary

Recent controlled clinical trials of the effect of dietary calcium supplementation in postmenopausal women have uniformly supported the conclusion that increasing calcium intake can slow bone loss at appendicular and axial skeletal sites. Supplementation may be more effective in those with a low calcium intake or when combined with an exercise regimen in those with low bone mass. Calcium has its effect by reducing bone resorption. The effect of dietary calcium on bone is presumably due to the absorbed fraction which is influenced negatively by other dietary factors such as dietary fibre and positively by the circulating concentration of the active form of vitamin D, calcitriol. To improve the efficacy of calcium supplements it will be necessary to optimise absorption. Nevertheless in the light of these recent trials it would be reasonable to increase the Australian recommended dietary intake for postmenopausal women to 1500 mg calcium per day.

I. INTRODUCTION

Until recently there has been considerable doubt about whether there is any effect of dietary calcium supplementals on the skeletal system. Several reviews suggested that the evidence pointed to no effect (Kanis and Passmore 1989; Evans 1990), although other reviews have taken a more optimistic view of the evidence (Nordin and Heaney 1990; Cumming 1990). In the last few years several studies have demonstrated a clear effect of dietary calcium supplementals on maintenance of bone mass in postmenopausal women. This evidence will be reviewed together with studies of factors which may impact on the effectiveness of dietary calcium supplementals in preventing bone loss. The review will not consider the role of calcium in the development of peak bone mass now considered to occur around the age of twenty except to say that the evidence for a substantial effect is to date rather weak (Johnston et al. 1992). Furthermore the benefits of intervention in teenage years to prevent a fracture sixty years later would have to be substantial. This is because the major impact of osteoporosis is in the seventies and eighties and is due to postmenopausal loss of bone. Therefore it is sensible to concentrate efforts on maintenance of skeletal strength on the postmenopausal period of life.

II. RECENT CONTROLLED STUDIES OF THE EFFECTS OF CALCIUM SUPPLEMENTS ON BONE MASS

Many studies of the effects of dietary calcium supplements have been carried out. Many of these studies have been flawed because the studies have not been placebo controlled. This

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means that the control group is likely to increase their calcium intake through the study. Another problem with many previous studies is that the sample size selected to study the effects of calcium has been too small when the errors in the methods of measuring bone density andcalcium intake are considered in relation to the size of the changes in bone mass that could be reasonably be expected. Thus for procedural reasons many previous negative studies are invalid. The effects of dietary calcium supplementals has been studied in four recently published studies all of which meet the criteria of being randomised, controlled double blind studies.

In a recent study (Prince et al. 1991) we selected women who were at increased risk of bone loss by virtue of the fact that they had a low bone mass. The women selected for the study had a mean age of 54 years and had a bone mass at least one SD below the premenopausal mean, they were all less than 10 years postmenopausal. Their mean baseline calcium intake was 800 mg per day. Both calcium supplemented and control groups were encouraged to participate in an exercise regimen. Over the two years of the study the subjects who had their diet supplemented with one gram of calcium as calcium lactate-gluconate did not loose any significant amount of bone at the ultradistal forearm site which consists of 60% trabecular bone, the control group lost at the rate of 2.4% per year. The effects were less marked at the more cortical site in the forearm. The effectiveness of the calcium supplement was greater the further away the women were from the menopause.

In a study of postmenopausal women selected because their calcium intake was less than 400 mg per day and because they were more than five years postmenopausal Dawson-Hughes and colleagues (Dawson-Hughes et al. 1990) showed that calcium supplementation with 500 mg of calcium citrate malate stopped bone loss at the radius, femoral neck and spine whereas in the control group bone loss continued at all sites at the rate of 2.11 to 2.85% per two years. No effect of calcium supplementation was found in women less than five years postmenopausal perhaps because of a small sample size. No effect of calcium supplementation was found in women with intakes of calcium greater than 600 mg per day perhaps because the rate of bone loss in the placebo group was low.

A study of unselected perimenopausal women, 28% of whom were premenopausal, (Elders et al. 1991) showed that supplementation with one or two grams of calcium lactate-gluconate slowed vertebral bone loss from 3.5% per two years in the control group to 1.3% to 1.7% in the two treatment groups. The treatment was more effective in slowing bone loss in the first year of the study at the vertebral site but was ineffective in slowing loss at the metacarpal site. The base line calcium intakes in the three groups were 1150 mg per day.

In a four year study of unselected pre and postmenopausal women (Smith et al. 1989)) bone mass loss was significantly reduced at the radius and humerus in the postmenopausal group supplemented with 1.5 g of calcium carbonate. The rates of bone loss fell significantly from 2.24% to 2.61% per year at the various sites in the placebo group to 0.92% to 1.54% in calcium group. The base line calcium intake was 707 mg per day.

III. FACTORS INFLUENCING THE EFFICACY OF DIETARY CALCIUM SUPPLEMENTATION ON BONE MASS

It can be concluded that when these recent studies are added to previous clinical trials fulfilling the usual criteria for acceptability and having sufficient power to show an effect (Recker et al. 1977; Lamke et al. 1978; Smith et al. 1981; Riis et al. 1987; Polley et al. 1987) there is substantial evidence that calcium supplementation is effective in reducing bone loss at most skeletal sites including the lumbar spine. In this regard one study has been incorrectly quoted as showing no effect of calcium supplementation on bone mass (Riis et al. 1987). In fact there was a statistically significant slowing of bone loss in at the distal forearm site. At the lumbar spine the bone loss observed was small when compared to the measurement error of the bone densitometer used, so that it is not clear as to whether there was any significant bone loss

There are however large differences in the absorbability of calcium in various foods, for example spinach calcium is much less available than bone meal calcium (Heaney et al. 1990). The reasons for these differences are unclear and probably do not relate to the fact that the spinach calcium is calcium oxalate. Lactose has been shown in some studies to increase calcium absorption (Cochet et al. 1983) but not others (Greenwald et al. 1963). However studies which have compared the absorption of milk calcium with other calcium salts have not shown any difference in calcium absorption between the various preparations (Sheikh et al. 1987; Heaney et al. 1990).

Dietary fibre has been shown to have significant effects on calcium absorption (Reinhold et al. 1976) probably related to the uronic acid content of the fibre (James et al. 1978). This has recently been re-examined in elderly people where the addition of wheat bran induced a 20% reduction in retention of dietary calcium (Knox et al. 1991). This is potentially a very significant effect. Phytic acid is another food constituent that may impair calcium absorption. Lastly pathological situations such as pancreatic malabsorption may impair calcium absorption by the formation of calcium soaps.

(a) Calcitriol

We have shown (Prince et al. 1991) that the effect of calcium supplementation on bone mass was strongly dependent on the circulating concentration of calcitriol (1,25 dihydroxycholecalciferol) (Fig). This hormone is a major regulator of the active absorption of dietary calcium in the intestine. In a previous study it has been shown that increasing calcitriol levels from 22.5 pmol/l to 210 pmol/l in chronic renal failure patients increased the percent absorption of a 300 mg calcium meal from 14% to 58% (Sheik et al. 1988). The importance of the circulating level of calcitriol in improving the bone response to calcium supplementation may thus be that higher levels of calcitriol increase calcium absorption. Because active absorption is less important with the high load of calcium we used in the study it is also possible that high calcitriol levels are a marker for calcium deficiency due either to gut resistance to calcium absorption or increased urine calcium loss. Whatever the mechanism of the relationship there is evidence that administration of exogenous calcitriol will stop postmenopausal bone loss (Gallagher and Goldgar 1990) and fracture (Tilyard et al. 1992).

An alternative is to increase endogenous calcitriol production by the kidneys. The most obvious way would be to decrease dietary phosphorus absorption. Decreasing dietary phosphorus intake or absorption has been shown to increase calcitriol levels in normal subjects with normal renal function (Portale et al. 1986; Villa et al. 1991) It is therefore of great interest to note that various calcium salts have been shown to be effective phosphorus binders in particular calcium acetate (Sheikh et al. 1989: Schiller et al. 1989). In this regard our recent study showed that the calcium supplement used significantly reduced 24 hour urine phosphorus as well as increasing urine calcium (Prince et al. 1991), thus it was probably acting to reduce phosphorus absorption which may have reduced the suppressive effect of calcium on calcitriol levels.

VI. EFFECTIVENESS OF CALCIUM SUPPLEMENTATION IN PREVENTING FRACTURE

Critics of calcium supplementation have in general claimed that increased dietary calcium has no or little effect on skeletal mass (Evans 1990). This is clearly no longer tenable. The next question to be answered is whether the effect is large enough to have a significant effect on the prevention of fracture. This question has been addressed in a randomised study of hip fracture in which elderly subjects had their diet supplemented with calcium and vitamin D. A preliminary report showed a significant reduction in hip fracture in the supplemented group (Meunier et al.

in either the placebo or calcium supplemented group compared with baseline. Note that the trials that have been performed in general show a slowing of the rate of bone loss with calcium supplements rather than cessation of this loss.

In view of the fact that calcium supplementation is not uniformly effective in completely preventing bone loss attention must be directed to improving the efficacy of this approach. In the studies reviewed above, two (Dawson-Hughes et al. 1990; Prince et al. 1991) examined factors associated with an increase in efficacy. Firstly both found that increasing years since the menopause increased the effectiveness. There is rapid bone loss early on in menopause due to increased bone resorption as a result of the loss of the direct oestrogen effect on bone. This does not seem to be as well reversed by calcium supplementation as the later continuing bone loss. Secondly the Dawson-Hughes study showed more benefit for those with calcium intakes below 400 mg per day. We could not find this effect in our study (Prince et al. 1991) but the mean calcium intake was 800 mg per day so that we had few subjects on such low calcium intake. Thirdly our study was of subjects who already had low bone mass. This group is at high future risk of fracture (Hui et al. 1989) which is why they were selected for study. Thus it is possible that these subjects are also the ones who are more susceptible to the effects of calcium supplementation.

IV. MECHANISM OF ACTION OF DIETARY CALCIUM SUPPLEMENTATION ON BONE MASS

Studies of the physiological effect of calcium on bone clearly show a reduction in the urine hydroxyproline creatinine ratio, a measure of bone resorption, with increased calcium intake (Elders et al. 1991; Prince et al. 1991). It is likely that this reduction in bone resorption is mediated in part by a fall in parathyroid hormone as a result of a rise in plasma calcium consequent on the absorption of a calcium load. Although neither a rise in plasma calcium nor a fall in PTH was observed in either study that examined these issues (Elders et al. 1991; Prince et al. 1991), in both studies blood sampling was performed 12 hr after the administration of the calcium. When blood samples are obtained sooner after the administration of calcium then the appropriate rise in calcium and fall in PTH has been observed (Horowitz et al. 1987; Kent et al. 1991). Another possibility is that the rise in plasma calcium may have stimulated endogenous calcitonin production (Dick and Prince 1991) which would be expected to directly suppress osteoclast activity, the bone cell responsible for bone resorption. Further work needs to be done on the timing of administration of the calcium supplements in view of evidence for a nocturnal increase in bone resorption (Eastell et al. 1992)

V. FACTORS INFLUENCING INTESTINAL CALCIUM ABSORPTION

If indeed the effectiveness of calcium supplementation on preventing bone loss is dependent on the fraction that is absorbed then attention needs to be paid to factors influencing this. The absorbability of calcium does not seem to be particularly dependent on the solubility of the calcium salt in water (Sheik et al. 1987; Heaney et al. 1990). Thus despite solubility in water varying from 0.0056 g/dl for calcium carbonate to 43.6 g/dl for calcium acetate fractional absorption was about 33% (Sheikh et al. 1987). Gastric acidity has been said to be important in increasing the solubility of calcium and there is certainly evidence that achlorhydria impairs calcium absorption from the less soluble calcium carbonate than the more soluble calcium citrate (Recker 1985). However when the preparations are taken with a meal the differences in absorption are abolished (Bo-Lin et al. 1984; Recker 1985).

1991). It is not possible in this trial to separate out effects due to calcium from effects due to vitamin D. Conducting a study in postmenopausal women would be difficult because of the relatively low fracture rate. We have however modelled the effect of a 50% reduction in the rate of bone loss using a formula relating bone mass and age to hip fracture rates (Melton et al. 1988) If this reduction in bone loss occurs from the age of 50 the predicted lifetime risk of fracture falls from 17.2% to 6.6%. The importance of preventing further bone loss even in elderly subjects who have lost enough bone to develop fractures has recently been underlined by controlled clinical trials of diphosphonates which show a reduction in fracture in rates in patients who have already sustained vertebral fractures and who already have a low bone mass (Storm et al. 1990; Watts et al. 1990). In these studies the agent used had only a small effect on preventing or slightly increasing bone mass. Thus small effects on bone mass may have significant anti-fracture effects.

VII. CONCLUSIONS

As a result of these recent studies the question is raised as to what the recommended intake of calcium should be. Of the papers considered above, all of which were carried out in developed countries such as our own, in three the average basal calcium intake was 700 to 1000 mg per day which was then supplemented by at least 1000 mg suggesting that the recommended intake to slow bone loss is in the order of 1500 to 2000 mg per day. The Dawson-Hughes study showed no benefit of calcium supplementation in the subjects with dietary intake above 400 mg per day but the placebo group was loosing little bone anyway. The recommendation of 1500 mg is consistent with balance study data in postmenopausal women which suggest that to achieve calcium balance a dietary calcium intake of 1500 mg per day is required (Heaney et al. 1989) data recently confirmed by another balance study (Hasling et al. 1992). This level is significantly above that currently recommended for Australian postmenopausal women which is 1000 mg per day. The Elders study could not find any significant difference between bone loss in the group receiving 2000 mg of calcium and those receiving 3000 mg in their perimenopausal subjects. In an uncontrolled, unrandomised study of perimenopausal women Nilas et al could not find any difference in the rate of bone loss between subjects ingesting 1000 or 2000 mg per day (Nilas et al. 1984). This question has not been studied in older women. What is required is a properly controlled trial with sufficient power to study the effect of dietary intakes of calcium between 1000 and 2000 mg to determine whether there is a threshold for calcium intake. A study of this sort would have to control for other factors that impinge on bone mass such exercise.

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Instead of ↑ Ca^{2+} supplementation, reduce in phytate ?

Influence of high intake of Ca^{2+} on other micronutrient ?
eg Mn^{2+}
Mg^{2+}