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Review

Calcium Intake and Bone Mass: A Quantitative Review of the Evidence

Robert Graham Cumming

Department of Community Medicine, University of Sydney, Westmead Hospital, Westmead 2145, Australia

Summary. The relationship between calcium intake and bone mass remains controversial. In this paper, the published research on this association is reviewed using the quantitative technique of meta-analysis. Selection of studies was based on defined eligibility criteria, and information relating to study design was recorded. Study results were converted, where necessary, to similar outcome measures so that direct comparison among studies was possible. A total of 37 eligible papers, representing 49 separate studies or parts of studies, were identified in the literature. Calcium had a consistent prevention effect on the rate of bone loss in the 12 studies of calcium supplements in postmenopausal women. This effect was greatest in studies in which the baseline calcium was low, supporting the idea of a threshold beyond which the effect of calcium is reduced. Cross-sectional studies showed a small but consistent positive correlation between calcium intake and bone mass. This association was greater in studies of premenopausal women. Some caution is needed in interpreting the results of this meta-analysis because of the poor quality of many of the studies reviewed. Nevertheless, the consistency of findings suggests that women in their early postmenopausal years will benefit from a high calcium intake.

Key words: Calcium — Osteoporosis — Meta-analysis.

The nature of any relationship between calcium intake and osteoporosis is of great importance in public health. Decreased bone mass is associated with fractures of the hip, wrist, vertebrae, and other bones and these fractures are a cause of significant morbidity and cost [1]. Increased calcium intake should obviously be encouraged if it is likely to reduce the incidence of these fractures. However, despite public and commercial enthusiasm, much doubt remains in the research community regarding the calcium-osteoporosis association [2, 3].

Reviews of the literature on calcium and osteoporosis have resulted in conflicting conclusions [4–7]. The problem is that literature reviews can be very subjective in the studies they choose to review and in the way they interpret study findings. A new method of reviewing a body of literature, called meta-analysis [8, 9], has been developed recently and is being increasingly applied to public health problems [10]. In meta-analysis, the reviewer uses explicit criteria to select and review each study. Results of individual studies are combined into one or more quantitative conclusions. The meta-analytic approach also encourages searching for causes of different results in the literature that might be due to differences in study design. Public health examples of meta-analysis include a review of the association between alcohol and breast cancer [11] and another of tobacco smoking and stroke [12].

This paper applies meta-analytic techniques to a review of the literature on calcium intake and bone mass in adult women. The aim was to produce a single summary measure of the effect of calcium intake on bone mass for each of three different study types: intervention studies, in which subjects were given a calcium supplement, and longitudinal and cross-sectional observational studies. Possible explanations for discrepant findings were explored. This report concludes with a discussion of the implications of these results for future research and current public health action.

Methods

Procedures for the selection of papers to be included in this

review were designed to be as comprehensive as possible. The reference lists of all relevant papers and reviews known to the author were searched, as were the reference lists of all papers so identified. A manual search of Index Medicus sections "Calcium" and "Osteoporosis" for the period 1960 to June 1989 was also conducted, supplemented by a Medline computer search from 1966 onward using the key words "calcium," "osteoporosis," and "bone mass." From these sources, a list of potential papers was compiled and sent to several recognized experts in the field. They were asked to add any papers they thought should be included in a review of this topic.

A decision was made to include only published papers in this quantitative review. After reading a number of abstracts and other conference reports, it became clear that they contained inadequate detail for coding of study characteristics and computation of the required outcome measures.

This review is restricted to studies of adult human females. Only studies that used individuals as the unit of analysis were eligible for inclusion. The reported outcome had to be some measure of bone mass. Additional eligibility criteria were applied to intervention studies, i.e., those studies examining the effect on bone mass of a calcium supplement assigned by the investigators. A control group was needed which could not be given any active treatment. The intervention group could receive a calcium supplement only, not in combination with another factor like estrogen, exercise, or high-dose Vitamin D (Vitamin D supplements of 400 IU or less were not grounds for exclusion).

A form was developed to code important features and results of eligible studies. Among the study features recorded were year of publication, study type, sample size (of calcium and control groups only), mean age of subjects, mean baseline calcium intake, whether or not subjects were excluded if they had evidence of osteoporosis or were on medications that might effect bone metabolism, the type and dose of calcium supplement given in intervention studies, and the method used to measure dietary calcium in observational studies. The adequacy of controlling for confounding by menopausal age was also assessed. Most of the coding was done over a 1 month period by the author.

Various measures of effect were reported in the reviewed studies. In the intervention studies, one of the following two outcome measures was reported in most papers: the percentage of bone lost or the actual rate at which bone was lost (in grams per centimeter—cm^2 or cm^3) over the study period. All results were converted to the percentage of bone lost per year, and the difference between the percent lost in the calcium supplementation group and the percent lost in the control group was used as the measure of effect in this meta-analysis. For example, in the Riis et al. paper [13], the "percent difference per year" of 0.70 for the distal radius is the result of subtracting −3.86% (the annual bone loss in the control group) from −3.16% (the loss in the calcium group). The percent difference per year can be interpreted as the amount of bone loss prevented each year by calcium supplementation.

In observational studies (classified in this paper into cross-sectional and longitudinal studies) the most commonly reported measure of effect was Pearson's product-moment correlation coefficient (r). When this was not given, methods suggested by Glass et al. [8] were used to calculate correlation coefficients from information in the paper. These values may not be the same as would be calculated from the raw data but they do give an indication of the direction and approximate magnitude of any calcium-bone mass association. This approach was used to derive correlation coefficients for seven studies [14–20]. In Exton-Smith et al.'s paper [21], data given on each subject were used to directly calculate the correlation coefficient. In seven papers there were insufficient data to calculate this measure of effect [22–28]. In all these studies, associations were reported as not statistically significant at the 0.05 level and so a value of zero was assigned to the correlation coefficients.

For each study, results were recorded or derived for each bone site measured. Results adjusted for potential confounders were used in the few cases where these were reported. Within studies, effects were averaged to give a mean effect for each study. For the studies of postmenopausal women, summary measures of effect that averaged the mean effect for each study were calculated separately for intervention and longitudinal, and cross-sectional studies.

Several papers are included more than once in this review. In some of these, the same subjects were used for cross-sectional as well as longitudinal and/or intervention research [16, 22, 25, 26, 29]. By presenting results separately by study type, much of the problem caused by this nonindependence of results is avoided. Where possible, results are given separately for pre- and postmenopausal subjects. Finally, the results of Polley et al.'s [30] randomized trial are reported for both the intervention group given a calcium supplement and for the group that increased the calcium content of its diet.

Associations between the mean effects for individual studies and various study characteristics were assessed by calculation of Pearson correlation coefficients or by analysis of variance. Results weighted by sample size were also calculated.

Results

A total of 37 published papers on the relationship between calcium intake and bone mass that were eligible for inclusion in this review were found in the literature. From these papers, 49 separate studies or parts of studies were identified. Of these, seven were conducted among premenopausal women and six combined pre- and postmenopausal women. The remaining 36 studies were of postmenopausal women: 12 intervention studies, including nine randomized trials, eight longitudinal observational studies, and 16 cross-sectional studies. Studies were published between 1966 and 1989.

Selected features of these studies are shown in Tables 1 and 2 for intervention and observational studies, respectively. The median sample size in the intervention studies was 41 (range 22–110). The longitudinal studies ranged in size from just 14 subjects to 522 (median 61); the cross-sectional studies had between 17 and 912 subjects (median 88). Thus, many studies only had the statistical power to detect very large effects of calcium on bone mass.

Table 1 shows the mean percent difference per year (the difference between the annual percentage of bone lost in the group treated with calcium and the loss in the group on no treatment, a positive figure indicating a protective effect of calcium) for the 12 intervention studies in postmenopausal women. Several points emerge from this table.

Table 1. Selected characteristics and mean effects in intervention studies of the effect of calcium supplements on bone mass

Study	Randomized trial	Sample size (n)	Mean age (yr)	Calcium dose (mg)	Baseline calcium intake (mg)	Mean effect of calcium[a] (%)
Postmenopausal women						
[31]	No	29	81	750	450	4.27
[32]	No	54	52	1,000	792	0.00
[33]	Yes	41	66	1,000	—	0.85
[34]	No	42	50	800	—	1.69
[35]	Yes	36	60	800	—	4.35
[30]	Yes	92	57	1,000	716	0.82
[30]	Yes	110	57	Diet	692	0.12
[36]	Yes	42	57	1,040	548	1.01
[37]	Yes	22	59	Diet	737	−0.01
[13]	Yes	25	50	2,000	—	0.76
[38]	Yes	28	82	750	—	2.03
[39]	Yes	82	55	1,500	710	0.75
Premenopausal women						
[39]	Yes	35	42	1,500	652	0.02

[a] Percent difference per year: (percent bone lost per year in the group given calcium supplement minus percent bone lost per year in control group). The mean effect is the average of the "percent difference per year" for all bone sites measured in that study. A positive figure indicates a protective effect of calcium.

First, of the three differences less than 0.5%, two were in studies of increased dietary intake of calcium [30, 37]. Secondly, the three largest effects were in studies of women whose mean age was 60 years or over. The subjects in Lamke's study [35] (mean age 60 years) had all suffered a Colles' fracture and both Smith et al. [38] and Albanese et al. [31] studied women with an average age over 80 years living in nursing homes.

Finally, the six intervention studies that were conducted among samples of women with a mean age in their fifties and who were selected so that they had no evidence of bone disease were very consistent in their findings [13, 30, 32, 34, 36, 39]. The mean percent difference per year in these six studies ranged from 0 to 1.69% in favor of calcium, with an overall mean of 0.8%/year. Given a mean rate of bone loss in untreated women of, say, 2%/year in early menopause [5], this suggests that calcium supplements might prevent nearly half the bone loss that occurs in such women.

The only individual bone site at which bone loss was greater in the group given calcium tablets was the vertebrae: two of the three studies that examined the lumbar vertebrae found this [13, 32]. The other study of the vertebrae, that of Hansson and Roos [33], was conducted in a group of women with vertebral fractures. In the six studies in "healthy" early postmenopausal women the mean percent differences per year were as follows: distal radius 0.92% (n = 5 studies), shaft of radius 1.34% (n = 2), shaft of ulna 1.61% (n = 2), lumbar vertebrae −0.78% (n = 2), and metacarpals 0.57% (n = 3).

In contrast to the intervention studies, the eight longitudinal observational studies in postmenopausal women produced diverse results (Table 2). Two found an overall inverse relationship between calcium and bone mass, three reported no association at all, and the other three found weak positive correlations. The summary mean correlation coefficient for these eight studies was 0.02.

Among the 16 cross-sectional studies that comprised postmenopausal women, only one had a mean correlation coefficient for dietary calcium and bone mass that was negative (Table 2). Furthermore, only five of the 25 non-zero correlation coefficients for individual bone sites in these studies were negative. Nevertheless, correlation coefficients were uniformly low and the mean for all studies was 0.04. Mean correlation coefficients for particular bone sites were as follows: distal radius 0.02 (n = 6 studies), shaft of radius 0.03 (n = 10), femoral neck 0.03 (n = 2), lumbar vertebrae 0.07 (n = 3), metacarpals 0.04 (n = 3), and shaft of ulna 0.00 (n = 2).

There was a strong inverse relationship (r = −0.9) between baseline dietary calcium and percent difference per year in the seven intervention studies in which baseline calcium data were given. To assess whether this effect was simply a reflection of the mean age of study samples (age is related to both bone mass and dietary calcium), partial correlation coefficients controlling for age were calculated. The relationship remained strong, albeit somewhat reduced (r = −0.7).

No clear relationship was found between study

Table 2. Selected characteristics and mean effects in observational studies of the effects of calcium intake on bone mass

Study	Randomly selected sample	Sample size (n)	Mean age (yr)	Mean calcium intake (mg)	Mean effect of calcium (r)[a]
		Longitudinal studies			
Postmenopausal women					
[22]	No	44	5	712	0.20[b]
[14]	No	76	60	619	0.09[c]
[25]	No	16	71	1,308	0.00[d]
[26]	Yes	141	72	—	0.00[d]
[27]	No	103	50	910	0.00[d]
[16]	No	522	59	961	0.09[c]
[40]	No	61	64	872	−0.08
[29]	No	14	55	—	−0.17
Premenopausal women					
[40]	No	45	41	991	−0.07
		Cross-sectional studies			
Postmenopausal women					
[22]	No	80	52	712	0.00[b]
[23]	No	71	59	698	0.00[d]
[41]	No	59	61	430	0.01
[24]	No	77	60	—	0.00[d]
[21]	No	39	76	888	0.11[e]
[42]	No	67	55	683	−0.02
[43]	Yes	670	70	509	0.07
[25]	No	29	71	1,308	0.00[d]
[26]	Yes	263	72	—	0.00[d]
[16]	No	557	59	961	0.08
[28]	No	235	58	720	0.00[d]
[18]	Yes	324	67	742	0.03[c]
[29]	No	59	55	—	0.12
[44]	No	172	53	619	0.07
[20]	No	366	77	883	0.08[c]
[45]	Yes	912	64	545	0.05
Premenopausal women					
[23]	No	88	38	738	0.00[d]
[42]	No	17	43	683	0.18
[46]	No	60	29	871	0.24
[19]	Yes	86	29	1,052	0.39[c]
[44]	No	112	35	598	0.12
Mixture of pre- and postmenopausal women					
[47]	No	222	52	—	0.03
[48]	No	234	47	—	0.26
[15]	Yes	395	49	—	−0.03[c]
[25]	No	50	46	924	0.00[d]
[49]	Yes	28	57	—	0.07
[17]	No	225	56	904	0.12[c]

[a] Average of correlation coefficients (r) for all bone sites measured in that study

[b] Values of only significant ($P < 0.05$) correlation coefficients were reported; nonsignificant correlation coefficients were assigned a value of zero

[c] Correlation coefficients were derived using methods of Glass et al. [8]

[d] Correlation coefficients assigned a value of zero because of insufficient information in paper for estimation

[e] Correlation coefficient calculated directly from data given in the paper

results and selected methodological features of studies. Characteristics examined, depending on type of study, included sample size, method of measurement of dietary calcium, and potential confounding by time since menopause. There was no consistent association in the intervention studies between dose and type of calcium supplement and size of effect.

Weighting study results by sample size had little effect on the conclusions of this meta-analysis. The weighted summary effect measures in postmenopausal women were 0.8%/year difference for the six intervention studies in early postmenopausal women and correlation coefficients of 0.06 for cross-sectional studies and 0.07 for the longitudinal studies.

Only seven studies in premenopausal women were found in the literature (see Tables 1 and 2). This limits interpretation but it is worth pointing out that the size of the correlation coefficients in the three cross-sectional studies in which they were given were all quite large compared with studies in postmenopausal women. Their summary mean correlation was 0.18. In the six cross-sectional studies in which only results for a combined pre- and postmenopausal sample were available, the summary mean correlation coefficient was 0.08.

Discussion

Contrary to the impression gained from reading recent reviews on the topic, the literature on calcium intake and bone mass is fairly consistent. Moreover, many discrepancies can be explained by differences in study design. Based on studies of the effect of calcium supplements in tablet form, it appears that a calcium supplement of around 1,000 mg/day in early postmenopausal women can prevent the loss of just under 1% of bone mass per year at all bone sites studied except the vertebrae.

The amount of bone loss prevented by calcium may not seem large but, taken over a period of say 10 years, it could have great impact on fracture incidence. Suppose the mean bone mass at a particular site is 1 g/cm at menopause and that bone is lost at a rate of 2%/year during early menopause. After 10 years, those not on supplements will have, on average, a bone mass of 0.8 g/cm, whereas in those taking calcium, the bone mass would be about 0.9. This difference of 0.1 g of bone/cm is enough to alter the risk of fractures [50, 51].

Calcium supplements proved most effective in studies in which the baseline calcium was low, the mean age of subjects was high, and/or the subjects had clinical evidence of osteoporosis. It has been suggested that the relationship between calcium intake and bone mass displays a threshold effect, so that beyond a certain intake additional calcium has no effect [5]. The findings of this review are consistent with this. There may also be a physiological basis for the reduced efficacy of calcium supplements observed among women in their early postmenopausal years compared with older women. Increased bone resorbtion immediately after menopause might result in the bioavailability of a large quantity of endogenous calcium. Calcium intake from diet or tablet supplements could have less importance during this period.

The results of cross-sectional studies of calcium intake and bone mass in postmenopausal women are also consistent. There was a very small positive correlation of less than 0.1 between current dietary calcium and bone mass. There are several possible reasons for this relationship being so weak compared with the results of the intervention studies. Poor measurement of variables lead to attenuation of measures of effect [52]. Bone mass is now measured with a high degree of reliability but dietary calcium is much more difficult to measure. Nelson et al. [53] have recently shown that at least 8 days of diet records are needed to achieve a reliability coefficient for calcium intake of over 0.9. In careful studies, the reliability coefficient for dietary calcium is about 0.6 [54, 55] but it has probably been lower in most bone mass studies, where inadequate attention has often been given to dietary measurement. In contrast, in intervention studies, calcium intake differs greatly between the two groups under study and so misclassification by calcium intake is unlikely.

There is another measurement problem in postmenopausal women. Current calcium intake in these women is likely to have any effect on current bone mass through a combination of two mechanisms: a direct effect on the current rate of bone loss and an indirect effect on peak bone mass, mediated via the imperfect association between past and current calcium intake. The multiple associations involved make it questionable whether cross-sectional studies are of value in this age group.

Another factor that might cause correlation coefficients to be spuriously low is the way in which subjects were selected. All but seven cross-sectional studies of calcium intake and bone mass have been conducted on volunteer samples of women with no evidence of bone disorders. The range of values of both bone mass and dietary calcium is likely to be restricted in these women, thus decreasing any association [56].

The inconsistent findings of the longitudinal observational studies are not easily explained. Bias due to selection of volunteers, poor measurement of dietary calcium, and lack of control for confounding could all contribute to the diverse results. At a minimum, all future longitudinal studies should control for baseline bone mass. It is a proxy for confounding by variables like postmenopausal age and body mass. Furthermore, the rate of bone loss (the outcome of interest in these studies) may be directly influenced by the absolute amount of bone present [16].

Perhaps the major problem in all studies of bone mass and calcium intake in postmenopausal women is that any effect of calcium is likely to be difficult to identify because of the much greater effect of estrogen deficiency. All studies of determinants of bone mass in postmenopausal women should control for

confounding by menopausal age. Supporting this are the results of studies in premenopausal women, in which the correlations between dietary calcium and bone mass were greater than in postmenopausal women.

Several studies were excluded from this review. In particular, only published papers were considered and so there is a potential for publication bias. This is a bias away from the null hypothesis caused by differential publication of studies that report an effect compared with studies that find no effect. However, in an area as controversial as that of calcium and osteoporosis, nearly all studies of any merit would be published and so the likelihood of this bias is small. Recently, it has even been suggested that the validity of a meta-analysis is improved by the exclusion of unpublished studies because such studies are likely to be of poor quality [57].

The exclusion of the often cited paper by Matkovic et al. [58] requires some comment. This study was conducted in two areas of Yugoslavia with differing calcium intakes. Unfortunately, dietary calcium was only measured in a subsample of the subjects whose bone mass was assessed and so the comparison in this paper was between bone mass in a region with high average calcium intake and a region with low average intake. Ecological studies, of which this is an example, are particularly prone to bias due to confounding [52].

Three other important papers, all supporting a positive association between calcium and bone mass, did not meet the inclusion criteria for this meta-analysis. In a prospective study, Holbrook et al. [59] recently demonstrated a protective effect of dietary calcium on the incidence of hip fractures. Riggs et al. [60] reported that calcium supplements decreased the risk of vertebral fractures. However, the calcium was given with large doses of Vitamin D in many cases. Finally, Nordin et al. [61] found that calcium supplements slowed the rate of bone loss in the metacarpals. Unfortunately, the published report provided inadequate detail for calculating the percent difference per year measure required for this review.

In view of the consistent findings in this paper, why is there so much controversy in relation to calcium and osteoporosis? One reason is the lack of epidemiologic and statistical expertise among many researchers and reviewers in the field of osteoporosis research. Many researchers seem to look only at the P value in interpreting their findings, ignoring the size of any effect. For example, correlation coefficients averaging 0.12 ($P > 0.05$) in one study of 59 subjects were deemed to be evidence against a calcium effect [29], whereas a derived correlation coefficient of around 0.05 ($P < 0.05$) in a study of 912 subjects was seen by the authors as supporting calcium [45]. There is also disagreement among authors about what constitutes an important calcium effect. Thus, in two of the best studies to date, the findings for the distal radius were almost the same: 0.66 [13] versus 0.82 [30] % difference per year in favor of calcium. Nevertheless, the authors drew opposite conclusions.

Even in the intervention studies, many recognized principles of research design were absent. Sample sizes were generally inadequate to detect important differences, blinding of investigators was rarely reported, all analyses violated the "intention to treat" principle, and there appeared to be a belief that randomization, even in very small studies, was adequate to deal with confounding. In comparison with the large, well-designed studies of risk factors for cardiovascular disease, research into the epidemiology and prevention of osteoporosis remains primitive.

In summary, in the published literature up to October 1989, there is a consistent positive effect of calcium supplements in tablet form in postmenopausal women at all bone sites except the vertebrae. This supports the recommendation of a high calcium intake for these women, particularly in the early postmenopausal years. Cross-sectional studies suggest that calcium has an important effect in premenopausal women. However, there is a need for well-designed studies to be conducted in this group of women before public health action is taken to increase their calcium intake.

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