The Role of Calcium in Osteoporosis

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It is widely recognized that osteoporosis is common among Caucasian females in the United States, in the middle years and beyond. I understand it is common among oriental women as well. Estimates of prevalence vary, depending upon diagnostic criteria, but the cumulative risk of fractures related to reduced bone mass, and commonly attributed to osteoporosis, lies in the range of 30–50%, by the middle of the 9th decade of life. At the same time, it is also well recognized that calcium intake is relatively low among Caucasian females in the U.S. The HANES surveys, I & II, conducted by the U.S. Public Health Service from 1970 to 1980 (1, 2) have clearly documented that on any average day an American woman over age 50 is consuming less than 500mg of calcium from all sources, and less than one fourth of all U.S. women consume as much as the RDA on any typical day.

The question is: "Are these two facts related? Is the actual level of calcium intake sufficient to maintain health, or is it too low, and thus a part of the cause of osteoporosis?"

I propose to examine the state of this question, and in doing so I shall touch on the role of calcium under three headings: pathogenesis, prophylaxis, and treatment. These roles are separable in concept because, even if it should turn out that calcium intake played little or no role in pathogenesis, it might still be that calcium would be effective in a pharmacologic sense, as either prophylaxis or as treatment, just as it appears that fluoride may be useful in treatment, without our needing to invoke the notion of fluoride deficiency among the causes of osteoporosis.

Pathogenesis

When calcium intake is reduced in animals such as the domestic cat, severe osteoporosis develops in as little as three months. This lesion is, pathologically, osteoporosis; it is mediated by a parathyroid hormone; and it is, to a significant degree, reversible, upon restoration of calcium to the diet. But cats are not humans, nor humans cats, and it is not appropriate to use this evidence as proof of a role for calcium in the development of human osteoporosis. Nevertheless, what happens in animals does at least create a context of plausibility for a role of calcium deficiency in human osteoporosis.

Nutrition requirement. What, in fact, is the actual nutritional requirement for calcium in the human diet? The answer is that no one knows. Dr. Olson will examine the question of calcium requirement in detail. Here I shall touch on only a few isolated points related to the role of calcium in pathogenesis. The United States has set a level of 800 mg per day for the mature, non-pregnant, non-lactating, adult female, but the United Kingdom has a figure of 500 mg, and the World Health Organization a range of 400–500 mg. What these different figures tell us is only that the experts disagree. The numbers, which have ultimately been chosen, tend to be compromises, really acceptable to no one, too high for some, too low for others.

We get at the notion of a dietary requirement in a variety of different ways. One is to define the disease state that results from deficiency of a nutrient, and then find populations that are largely free of that disease, and see what kind of intake they habitually ingest. That approach is not suitable for calcium, precisely because there is major disagreement about whether osteoporosis is in any sense a calcium deficiency disorder. Those who say it is not, in effect, recognize essentially no calcium deficiency disorder short of severe malnutrition, and thus argue for very low requirements indeed. Those who suspect that there may be a relationship between calcium and osteoporosis ar-
gue for very high requirements, precisely because of the very ubiquity of osteoporosis in susceptible populations. The truth of the matter is that really good population data are not available. There is a rough inverse relationship between probable calcium intake and probable fracture risk in many populations across the world (3, 4), but the data are very soft indeed. Further, genetic differences in bone mass, even within Caucasians, and population differences in growth rate and in intakes of other nutrients which alter calcium requirement are probably more important in determining fracture resistance than are simple variations in calcium intake within the range encountered.

Hence the bulk of our information on nutritional requirements has come from traditional nutritional studies, conducted using the metabolic balance technique. Reported mean requirements ranged from below 200 mg to over 1,800 mg per day (5), and most of the lower estimates were obtained in young persons. There has never been a single study published on middle-aged or elderly women, which produced an estimate of mean requirements that was not above the current RDA. If these studies have any validity at all, they clearly indicate that the current RDA is set too low. I stress the word “if” because there are significant problems with the use of the balance technique to estimate calcium requirements.

The first of these problems is that the zero balance criterion for intake equal to the requirement turns out to be inadequate, for three reasons: 1) it fails to recognize, in studies performed in younger, though mature individuals, that bone mass is normally increasing between ages 20 and 35, and that such a normal increase requires a positive calcium balance, not equilibrium; thus, all the earlier studies—the ones on which the current RDA in the U.S. is based—turn out to rest on a false premise; 2) it fails to take into consideration non-excretory losses (sweat, dermis, hair, nails, sputum, etc.); and 3) it fails to provide a reserve to compensate for calcium losses which occur during illness, immobility, or any of the other generally catabolic episodes which commonly affect people throughout life.

The balance technique, as commonly employed, is inadequate for another reason also, and that is that changes in calcium intake reflexly alter bone remodeling, with high intakes suppressing, and low intakes increasing the activation of new remodeling sites. Because of the relatively long time between activation of a remodeling site and the completion of remodeling at that same site, manipulation of calcium intake evokes transient changes in calcium balance related to the sequencing of remodeling, changes which are in no way reflective of the new skeletal equilibrium state. Normally the time required for bone to come into a new equilibrium after calcium intake has been altered can extend to many months, and the problem becomes even worse in middle-aged and elderly individuals, because the time-to-equilibrium may extend to as much as 1–2 years. There has been only one study published to date in which balance was measured after more than two years on a manipulated calcium intake (6), and whereas the results would suggest that positive calcium balance is maintained under such circumstances, the number of patients thus studied is so small that only the most limited of conclusions can be drawn.

An alternative is to study patients, insofar as possible, on diets which are as close to their own natural, self-selected intakes as can be managed. We at Creighton have done exactly that in a cohort of nearly 200 perimenopausal women, looking at the relationship between absorbed intake and calcium balance (7). It is clear from these studies, both that there is a highly significant positive relationship between balance and intake, particularly absorbed intake, and that at low levels of absorption the women concerned are all in negative balance, while at higher levels, they are in a more positive balance. This relationship constitutes the strongest evidence available to date that the calcium intake of normal American women is a limiting factor in determining bone health.

There are many reasons why absorbed intake may be low, with low ingested intake being only one of them. It is important, therefore, to look at the question of effective calcium intake. Here we must be concerned with the state of vitamin D metabolism, including the amount of solar exposure of the individual, and the ability of the vitamin D-hormonal system to produce appropriate amounts of calcitriol and the other possibly important D-metabolites. It must be said that there remain many unanswered questions in this general area. It is important also to recognize that there are nutrient-nutrient interactions which,
in effect, raise or lower the requirement for calcium. High intakes of protein and sodium lead to excess urinary excretion of calcium and thus effectively raise the calcium requirement. High intakes of fiber decrease calcium absorption with the same effect. Similarly many drugs which are ubiquitous in our environment, such as alcohol and caffeine, particularly when consumed at more than modest levels, increase calcium losses, and can thus be thought of as reducing effective calcium intake. It may well be that low per capita protein and sodium intakes in Third World populations are the principal reason for their seemingly better adaptation to low calcium intakes.

We have reported elsewhere that the relationship between intake and balance varies with estrogen status (8), and that the mean intake required to maintain zero balance is approximately 1.0 g/day in the estrogen-replete woman and 1.5 g/day in the estrogen-deprived. Given the dispersion of our data, the corresponding RDA's would be closer to 1.4 g/day for the estrogen-replete population and 1.8−2.0 g/day the estrogen-deprived. These studies constitute essentially the only data in existence which bear usefully on requirements and allowances in the population at risk. No population data have been accumulated in persons ingesting chronic intake levels in these ranges, and hence it is not possible to say what bone status at such intakes might be. This remains an important area for future investigation.

There has been a persistent argument in the literature of this field for many years, perhaps most eloquently expressed by Hegsted et al. (9), which goes something as follows: “Most people in the world build (presumably) adequate skeletons on calcium intake levels far lower than suggested in any of the First World RDA’s. Therefore it is absurd to propose that the intake should be even higher than the current RDA’s.” But this argument is not persuasive because, while it may be that calcium intakes are adequate to build a skeleton when growth forces are dominant and other nutrients are limiting, they may not be adequate either to hold on to that skeleton in later life, or to build enough of it to last throughout life, given the fact of the seemingly ubiquitous loss of bone with advancing age.

This argument naturally leads to a question as to what influence different levels of calcium intake might have on bone mass. This is a harder question to answer than one might at first think, simply because of the unavailability, until recently, of suitable technology for measurement of bone mass. Most techniques for use in the filed have relied extensively on the metacarpal. While this bone does vary with bone mass in other regions of the body, still it is only relatively weakly correlated with them. Thus, both negative and positive data bearing on the role of calcium in the genesis of osteoporosis can be derived from such studies, and neither set is persuasive for advocates of the other point of view. I shall sample data from both sides of this controversy.

Garn, reviewing data obtained from the Ten-State Nutrition Survey, found only unimpressive differences in bone mass between individuals ingesting the lowest and the highest 15 percentiles of calcium intakes (10). By contrast, the data of Matkovic and co-workers from Yugoslavia (11) show a much larger difference in the metacarpal cortical area, for essentially all ages from 25 on, in groups whose average calcium intakes differed by approximately a factor of two. Anderson and co-workers at the University of North Carolina have found intake-related differences in cortical bone mass, but not in trabecular (12). The reasons for the discrepancy among these various studies are not at all clear, and it is thus of considerable relevance to look at such fracture data as are available. A very dramatic decrease in hip fracture risk was found in women from the high calcium region of the Yugoslav study. It is also of interest that, while there was protection against hip fractures, the Yugoslav investigators found no difference between the two intake groups for risk of wrist fracture. (We have no fracture data for the subjects of the Ten-State Nutrition Survey.)

This difference in protection for two different fractures highlights the probable importance of separating osteoporosis into distinct fracture syndromes. Nordin et al. (13), Meunier et al. (14), and most recently, Riggs et al. (15) have called attention to the fact that there are probably at least two distinct fracture syndromes, one of which is characterized predominantly by wrist and spine fractures, and the other by extremity and hip (particularly femoral neck) fractures. I am not certain that this rough classification is the best we can do, and I cite this heterogeneity because,
if it turns out that calcium has a role to play in pathogenesis of this disorder, it is unlikely that this role would be the same for what may be distinct fracture syndromes, just as it would no longer be reasonable to propose that iron deficiency plays the same role in all types of anemia.

The Yugoslav data (11) highlight another aspect of this question which may prove to be even more important. This was the finding that peak bone mass (at about age 35 in both sexes) was substantially higher in the high calcium intake region than in the lower intake group. By contrast, the rate of loss with age, though not directly inferable from this type of cross-sectional data, appeared to be essentially the same in both groups, irrespective of the calcium intake level. But starting with less bone means that the subject ends up with less bone, and one notes, most clearly for the males, that individuals from the high intake region had, at age 75, as much bone as 35 year olds from the low calcium intake region. This is a matter of considerable importance, because all studies that have looked at the relationship between bone mass and fracture have clearly indicated that there is an inverse relationship between bone mass and fracture risk, and the data of Conrad Johnston and his co-workers (16) indicate that the best predictor of future bone mass is past bone mass. Thus, one of the most important questions confronting the field of osteoporosis research is to determine prospectively what may be the relationship between calcium intake in early adult life and the level of bone mass achieved at age 35. If calcium intake is, in any important sense, limiting, then it may be that the ground for osteoporosis is laid well before the postmenopausal bone loss begins, and that the best prophylaxis would be employed many years prior to the time of fracture risk. This is an important question because it is now answerable with modern techniques, and because its answer have far reaching implications for public policy.

There remains an extremely important, unanswered question which has not, in any sense, been addressed by any of the studies alluded to in the foregoing. It must be borne in mind that, in the normal human adult, calcium absorption from a typical human diet is relatively inefficient, generally ranging from 20 to 30% of the ingested load. It is also well known that the organism possesses many physiologic mechanisms for substantially increasing absorption efficiency. The question, then, is simply this: “If calcium intakes are, as some maintain, too low to meet physiologic need for optimum bone structure, then why does not the organism adapt by increasing the efficiency of calcium absorption?” It has to be said, in all honesty, that no one knows the answer to that question. But not knowing the answer is not equivalent to concluding that calcium intake is unimportant.

At the same time it must also be recognized that calcium absorption efficiency, in normal individuals, never drops to zero. Even in the total absence of endogenous production of calcitriol, absorption averages about 15% of the ingested load (17). Simple calculation suffices to indicate that 15% absorption of a 2,000 mg calcium intake will result in absorption of about 300 mg of calcium, whereas even 50% absorption for a 400 mg intake will produce only 200 mg. This simple, but often overlooked fact, is the basis for the distinction which I made at the outset, namely that calcium may have a role to play in prophylaxis or treatment, even if it turns out not to have a role in pathogenesis.

**Propylaxis**

I have already alluded to the apparent protection against hip fracture provided by high calcium intakes in the Yugoslav study (11). This study is one of only a small handful in the medical literature which have even looked at the relationship between calcium intake and either age-related bone loss or osteoporotic fractures. In this connection, therefore, it is instructive to shift briefly to the dental literature. Wical and Swoope (18) noted greater alveolar ridge resorption following full jaw extraction and the fitting of a dental plate, in patients with low habitual calcium intakes. Because no such study is ever adequately controlled, the senior investigator subsequently performed a double-blind, placebo-controlled study of the effect of calcium supplements on jaw bone loss following tooth extraction (19). Even as long as one year after extraction, there was a substantial reduction of the amount of alveolar ridge bone loss in those given a calcium supplement.

The same type of protection, but in this case against age-related cortical bone loss, was evident
in a study done in our laboratory a number of years ago, in which age-related bone loss in the metacarpal was suppressed as a result of calcium supplementation (20). Nordin et al. (21) and Albanese et al. (22) have independently shown similar, partial protection against age-related cortical bone loss in calcium-supplemented patients. Of interest in connection with possible differences in relationships between calcium intake and different fracture syndromes is the fact that while we saw protection at the metacarpal, we were not able, in our study, to see a protective effect on bone loss at the distal radius. (Recall that the Yugoslav data also showed no protection of high calcium intake for wrist fracture.)

I must hasten to add, however, that the problem which besets the use of manipulated intakes to determine nutritional requirements also plagues intervention studies such as these. Any agency, such as a calcium supplement, which suppresses bone remodeling, can be expected to reduce age-related bone loss, or obliterate it entirely for a time, or even temporarily lead to an increase in bone mass. And unless such supplementation is followed for a period longer than one to two years, one cannot safely conclude that the effect will be sustained, or what the subsequent rate of loss will be.

Treatment

Calcium has been fairly widely used in the therapy of established osteoporosis for probably the better part of thirty years, and perhaps the strongest statement which can be made about such therapy is that its effects have not been dramatic. Part of the problem may lie in the fact that, once the damage is done, there is always superimposed an element of disuse on whatever may have been the original pathogenesis, and this disuse only aggravates the generally downward trend in bone mass. Perhaps in part for this same reason most therapies have not produced the dramatic results which one would hope for.

Only fairly recently have even moderately sophisticated techniques been used to look at possible beneficial effects of calcium and other therapies. Perhaps the best such data come from a recent publication from the Mayo Clinic (23) in which untreated patients were compared with patients treated with either calcium alone, or calcium plus vitamin D. Unfortunately this study was not randomized, the duration of follow-up was different for the two groups, and the amount of vitamin D employed bordered on the pharmacologic, at least in those patients in which it was used. Hence for all these reasons the results cannot be considered conclusive. Nevertheless, the fracture rate was reduced from over 800 new vertebral compression events per 1,000 patient years to approximately half that level. This suppression in fracture frequency is quite impressive, and would be more than adequate to justify the use of calcium, either alone or as an adjunct to other therapy. This kind of study very much needs to be repeated, so as to establish once and for all its ultimate validity.

At the same time it must also be said that there is an a priori reasonableness about the use of calcium in the therapy of a disorder characterized by deficiency of mineralized tissue. Calcium supplements, as is well demonstrated, can suppress bone remodeling, and thus slow, to some extent, the continuing loss of bone which otherwise is the lot of all patients with osteoporosis. Further, it is unreasonable to expect that any other therapy will be very effective in arresting or reversing the disorder if calcium intake is in any significant sense limiting. Thus it seems inescapable that calcium will increasingly be used as an adjuvant to most therapeutic regimens, which will be employed either experimentally or clinically in the foreseeable future.

In this connection, it is probably important to emphasize the essential safety of calcium supplements. Intakes up to at least 2.5 g of elemental calcium per day, even in younger individuals who have more efficient absorption, are clearly without clinical complications, and they are even more innocuous in the elderly, in whom absorption efficiency is, for one reason or another, generally lower than in the young.

Conclusion

In summary, it seems likely that calcium does have a role to play in this disorder, but the exact nature and importance of that role remain uncertain. If calcium is involved in pathogenesis, it seems likely that it will be more important for one fracture syndrome than another (probably, for example the type involving cortical bone loss). It is likely that low calcium intake is only one of
several interacting risk factors, more important in some individuals than in others, and aggravated or minimized by other factors, such as vitamin D status, physical exercise, and intakes of protein, sodium, caffeine, and fiber. In any event it seems that high calcium intakes can be a practical and effective means of combating some of the bone catabolic effects of other nutrients or drug excesses, or of unfavorable lifestyle factors in First World populations. Finally it seems highly likely that calcium, by itself, can ameliorate some of the progression of osteoporosis, and at very least is probably an essential adjuvant in most present and future therapeutic regimens.

REFERENCES

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