LETTERS TO THE EDITOR

SOME QUESTIONS ABOUT "EPIDEMIOLOGIC ASSOCIATION BETWEEN DIETARY CALCIUM INTAKE AND BLOOD PRESSURE: A META-ANALYSIS OF PUBLISHED DATA"

The meta-analysis of studies of calcium and hypertension by Cappuccio et al. (1) in a recent issue of the Journal concluded, "...our analysis is consistent with an inverse association between dietary calcium intake and blood pressure" (p. 943). This closely resembles the conclusion of several similar analyses. However, like the others, Cappuccio et al. were concerned about the heterogeneity of the published studies and considered it "premature" to recommend increasing calcium intake at the present state of knowledge. The small effects found in the studies suggest that there is only a small proportion of the population with a calcium-sensitive vascular response, and the prudent question is whether one should treat the whole population to benefit a small minority. Cappuccio et al. thought not, concluding, "the presumed benefits, if any, are insufficient to outweigh the possible hazards of exposing entire populations...to increasing amounts of dietary or supplemental calcium..." (p. 943).

I wondered what possible hazards the authors might have envisioned, particularly in view of two recent consensus statements, on calcium intake (2) and on osteoporosis (3), both of which recommended increasing calcium intake and found no significant hazard associated therewith.

In support of hazard from increased intake, Cappuccio et al. cited five articles: Kaplan and Meese (4) and Rose and Day (5) to the effect that a calcium load could do more harm than good; Coe et al. (6) to the effect that increasing calcium intake could increase the risk of kidney stone disease; and Wilkinson (7) and Nicar and Pak (8) to the effect that calcium supplements have greater bioavailability than food calcium (thereby further increasing the risk of stones). Since these conclusions appeared to be at variance with a large literature that points in exactly opposite directions, I reviewed all the references concerned. It turns out that none supports the position of Cappuccio et al. about possible harm, and it is difficult to see how four of the five could have been construed in that direction.

Kaplan and Meese (4) found the evidence for a calcium effect on blood pressure unpersuasive, as did Cappuccio et al., but they presented no data with respect to harm. In addition, Rose and Day (5) made an eloquent plea in the opposite direction, i.e., that in order to help the minority with an uncommon response to an environmental variable, it was necessary (and probably appropriate) to treat the whole population. Coe et al. (6) mentioned the dangers of low (not high) calcium intake in patients with stone disease; they did not list diet calcium as a significant risk factor for stones, nor did they recommend reduction of calcium intake in treatment. Wilkinson (7), writing in 1976 about absorption of dietary calcium, makes no mention of calcium supplements. More to the point, more recent work has shown supplements to be no more absorbable than food calcium, and often substantially less.

Only the paper by Nicar et al. (8) might be construed as support for the point about higher absorbability. This paper reported apparently higher absorption from calcium citrate than from calcium carbonate (although not from food calcium). It turns out, however, that the measure of absorption employed was based on incremental urinary calcium excretion, ignoring the fact that citrate increases urinary calcium loss. Hence a urinary test cannot be used to compare bioavailability of a citrate salt with another calcium source. Moreover, direct isotope-based tests of absorption of calcium citrate show no detectable superiority over other sources (9).

Finally, Cappuccio et al. seemingly have ignored other recent work pertinent to their conclusion, such as that of Curhan et al. (10) who showed, in ~200,000 person-years of experience, an inverse relation between calcium intake and stone risk.

Cappuccio et al. aside, the decision about calcium and hypertension ought not be made in a vacuum. Given the existing consensus that increasing the calcium intake of the population will confer a net benefit with respect to bone health, one should have thought that any additional benefit with respect to hypertension, however small, would have to be counted as a plus.

REFERENCES


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THE AUTHORS REPLY

We appreciate Dr. Heaney's comments (1) on our paper on the epidemiologic association between calcium and
blood pressure (2), although his statement of our conclusions is incomplete. We clearly say "... that it is premature to make recommendations ... to increase their dietary calcium intake above the Recommended Dietary Allowance. ..." This is in agreement with the conclusions of the NIH Consensus Conference on optimal calcium intake (3), which state, "A recommendation for increased calcium intake for prevention of hypertension is not warranted at this time" (p. 1944).

Our analysis of observational studies shows a small negative association between dietary calcium and blood pressure in the presence of a likely publication bias suggesting that the effect may be overestimated. We agree that the decision about calcium and hypertension ought not be made in a vacuum and we do not do so. There is a large body of evidence from randomized controlled trials (4–7) indicating that large calcium supplements (median 1,000 mg per day) do not exert a consistent beneficial effect on blood pressure and that the results of such trials are also compatible with small increases in blood pressure. Therefore, a recommendation to increase the Recommended Dietary Allowance for dietary calcium or to use calcium supplements to lower blood pressure or to prevent hypertension appears unjustified based on the available evidence. This does not detract from the potential benefits of an adequate calcium intake for the prevention of bone demineralization and osteoporosis.

We refer to Rose and Day (8) to introduce the concept of the population approach. Rose (9) differentiates between "removing or reducing some unnatural exposure in order to restore a state of biological normality" and "adding some other unnatural factor in the hope of conferring protection." Calcium supplements belong in the latter category, for which "there can be no prior presumption of safety, and hence the required evidence of benefit and (particularly) safety must be more stringent. This effectively rules out this type of measure except where the offered benefit is rather large..." (9).

Dr. Heaney points to a large prospective study (10), suggesting that high calcium intake may be protective for kidney stones. This is an observational study in which a cause-effect relation cannot be proven. Furthermore, the lack of measurement of salt intake, which is associated with both calcium intake and kidney stones (11), may have acted, at least in part, as a potential confounder; and the possibility of selection bias to explain, for instance, the unusual inverse rather than positive relation between age and kidney stone incidence (11, 12) cannot be excluded.

Finally, Coe et al. (13) discuss the danger of low calcium intake in idiopathic hypercalciuria, a separate clinical entity. Calcium supplements do increase urinary calcium excretion, as consistently shown in randomized controlled trials (4–7); and people with high blood pressure do have a greater prevalence of kidney stones (14).

The potential harm from population-based policies of mass calcium supplementation in non-calcium-depleted populations is unknown. We agree with Rose (9) that until there is compelling evidence of benefit and safety, we should refrain from recommending populations with adequate calcium intake to further increase their intake for either the prevention or treatment of hypertension.

REFERENCES


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RE: "SELECTION BIAS IN CASE-REFERENT STUDIES"

The importance of recognizing selection bias in case-referent studies is emphasized by Dr. Pearce in his review (1) of my Workbook of Epidemiology (2). As suggested by Dr. Pearce, bias may be introduced in the identification of