25-Hydroxyvitamin D and calcium absorption

Dear Sir:

Aloia et al (1), in a secondary analysis of data accumulated for another purpose, reported that intestinal calcium absorption efficiency is related to serum calcitriol, but not to serum 25-hydroxyvitamin D [25(OH)D], as my colleagues and I had reported some years ago (2–4). They reject the notion that the relation of 25(OH)D to absorption can usefully define vitamin D status. I thank them for giving me the opportunity to clarify the role of 25(OH)D in calcium absorption.

First of all, there is need to set forth the facts that must be incorporated into and explained by an operational model.

1) 25(OH)D, whether given as such, or produced through cholecalciferol administration, unquestionably increases calcium absorption efficiency under certain conditions. This has been established with different interventional designs by a variety of investigative groups for at least the last 35 y (2–7) and has been shown to be true even in anephric patients (5). But this is not to propose that 25(OH)D is in any sense a "regulator" of calcium absorption as Nordin (8) suggested might be my position.

2) Calcitriol is, in fact, the principal regulator of calcium absorption efficiency. About this there should be no dispute. This regulation extends across the full range of possible absorptive response.

3) Unlike calcitriol, 25(OH)D produces an absorptive effect only at the lower end of the vitamin D status continuum. This is shown by the fact that outdoor summer workers do not hyperabsorb calcium, despite high serum concentrations of 25(OH)D (9). Furthermore, despite high vitamin D status, their calcium absorption efficiency is capable of being down-regulated to passive absorptive values by high calcium intakes.

4) Finally, calcitriol, while necessary, is not sufficient. Calcitriol, despite widespread assumptions to the contrary, does not exhibit an appreciable calcium absorptive effect in patients with end-stage renal disease (7, 10). Moreover, as Nordin (8) noted, calcium absorption efficiency is defective in nutritional vitamin D deficiency. This is despite the fact that serum calcitriol concentrations are generally normal and sometimes even high in this condition.

To explain this seeming paradox, as some have attempted to do, by proposing that the intestinal requirement for calcitriol is higher than normal in vitamin D deficiency is to beg the question. What is it that these individuals are lacking? The most obvious answer to that question is not calcitriol but 25(OH)D. And, in fact, supplying that molecule normalizes absorption.

I cannot definitively say why Aloia et al (1) failed to find an effect of 25(OH)D in their observational study; nor can I say why it is that the absorptive apparatus appears to need both molecules. Nevertheless taking this dual need as fact, it is possible to propose a satisfactory model that integrates all 4 of the above points. In this model, 25(OH)D does not elevate calcium absorption in its own right but is permissive rather than directly causal. The actual regulatory stimulus for absorption is precisely calcitriol, as I believe we all agree. Renal production of calcitriol is regulated in the usual way mainly by parathyroid hormone. But actual mucosal response to calcitriol is dependent on serum 25(OH)D. Thus, when vitamin D status [expressed as serum 25(OH)D] is suboptimal, intestinal responsiveness to calcitriol is blunted [but improves as vitamin D status improves (2)]. And when vitamin D is replete, ie, with high 25(OH)D concentrations, hyperabsorption is prevented by classical endocrine down-regulation of calcitriol synthesis.

In other words, vitamin D—as cholecalciferol or as 25(OH)D—does not so much cause active calcium absorption, as it permits the body to regulate absorption via calcitriol. In terms of clinical investigation, only those individuals who experience a blunted response to calcitriol (because of "low" vitamin D status) will show an absorptive response to elevation of serum 25(OH)D. Not finding a relation between 25(OH)D and calcium absorption in an association study (eg, reference 1) cannot negate the mass of evidence from interventional studies (eg, references 2–7). [Incidentally, the point at which further elevation of serum 25(OH)D concentration produces no further enabling of absorptive regulation (~30–32 ng/mL) is, I submit, the best available estimate of the lower end of the range of vitamin D adequacy for an absorption endpoint.]

Can one characterize those individuals whose calcium absorption improves with a rise in 25(OH)D? I suggest that they are individuals with vitamin D status at the low end of the continuum who have a mild degree of calcium hunger, ie, whose systems are attempting to retain calcium. For whatever reason (low net intake, excessive loss, net bone accretion), they are unable to meet fully the endogenous need for calcium. An example would be the bisphosphonate-treated patients in the report by Kendler et al (6), a situation known to lower serum calcium and elevate parathyroid hormone. Conversely, those who show no response despite comparably low concentrations of 25(OH)D are those with efficient renal control of calcitriol, those with high calcium intakes, or those with primary bone loss (as in the perimenopause).

Mechanistically, it would be highly desirable to understand the molecular basis for the demonstrable effect of 25(OH)D under these circumstances. Nevertheless, lacking that understanding, it is necessary to recognize the fact of the 25(OH)D effect. In the practical order, that means ensuring a 25(OH)D concentration of at least 30 ng/mL.

The author had no conflicts of interest to declare.

Robert P Heaney
REFERENCES


LETTERS TO THE EDITOR