tamin D on calcium absorption or diminished increases in calcium absorption as vitamin D intake increases would provide a scientific rationale against excessive vitamin D supplementation and avoid pushing serum 25(OH)D concentrations to unnecessarily high levels.

None of the authors had any conflicts of interest with respect to the work presented.

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REFERENCES


Reply to J Huang et al

Dear Sir:

We thank Huang et al for their interest in our work and for their stimulating comments regarding the evidence of a vitamin D threshold on calcium absorption. The exploration or discovery of a threshold effect is statistically complex. Generally, there is no single approach that is sufficient (1). We presented several approaches to exploring the question of threshold, and nonlinearity in general. First (and most important), we visually examined and presented raw data via scatterplots and evaluated the nature of the relation via smoothing (loess) techniques to determine heuristically whether there was any evidence of a nonlinear effect. Second, linear, quadratic, and cubic spline models with a priori knots selected were fitted. The results from these models were not treated as sufficient to conclude a lack of a threshold, but rather they provided additional evidence that a nonlinear relation was not supported by the data at hand. Although the authors provide 2 references where polynomial parameterization and spline methods were not used, this clearly does not preclude the usefulness of this type of approach in exploring nonlinearity (2).

We state in the article that our data do not support a threshold effect, not that there is no threshold effect. There are factors in any study that hinder the detection of effects. Sample size is one such factor, and we acknowledge this. Small samples increase the probability of type II error and restrict the exploration of effects in certain subgroups of interest. Furthermore, as the authors point out, our range of vitamin D dose and concentration of 25-hydroxyvitamin D [25(OH)D] was limited to a specific range; thus, we cannot be certain whether a threshold effect may indeed exist on the edge or outside of this range. These kinds of limitations are shared across most studies of this type.

As we described in our methods, we examined piecewise linear models for calcium absorption, treating a 10-wk 25(OH)D concentration of 80 nmol/L as our a priori threshold and examining whether the relation between calcium absorption and 25(OH)D changes at this threshold. On the basis of the results of this exploration and the fact that the P values corresponding to the test for a change in slope at 80 nmol/L in both unadjusted and adjusted models were insignificant (P = 0.20 and 0.17, respectively), we strongly stand by our original reported model: 10-wk calcium absorption was observed to be a linear function of 10-wk 25(OH)D in our measured range of 25(OH)D.

As the authors correctly point out, the estimated linear relation between dose group and 10-wk calcium absorption was only marginally significant in the adjusted models (P = 0.03). However, we strongly disagree (on the basis of model residual and Q-Q plots, rather than relying solely on the scatterplot) that the data are nonnormal. We found no evidence of lack of fit; therefore, calcium absorption may be properly modeled with least-squares regression as presented.

We observed a unit increment of calcium absorption that shows a somewhat diminished absorption rate across dose, from 4.85% to 3.99% (P = 0.03). On the basis of model residual and Q-Q plots, rather than relying solely on the scatterplot) that the data are nonnormal. We found no evidence of lack of fit; therefore, calcium absorption may be properly modeled with least-squares regression as presented.

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strong correlation with 10-wk absorption, we used baseline calcium absorption as a covariate in all of our models for 10-wk calcium absorption. The reason to do this is exactly as the authors point out: we wanted to account for as much of the heterogeneity in outcome (10-wk calcium absorption) as possible, which means the inclusion of all informative predictors into the regression, because this will reduce the variance of the estimate for the effect of dose or vitamin D status.

A different question is whether there is a statistical interaction between vitamin D dose or 25(OH)D concentrations and baseline calcium absorption, meaning, is the effect of dose different for individuals with low baseline absorption values compared with those with high baseline values? We examined this as much as the data would allow by dividing the patients into baseline calcium absorption strata by quartiles, and we did not see a significant interaction in either analysis.

We stand by our original conclusions that our data fail to support a nonlinear or threshold effect with respect to calcium absorption in the range studied (40–130 nmol/L) with supplementation of 800–4000 IU vitamin D3/d.

Finally, it is important to understand the context of our study. Calcium absorption declines when there is insufficient 25(OH)D as substrate to generate sufficient calcitriol (<30 nmol/L). If subjects with severe deficiency had been included in our study, the response curve would undoubtedly be curvilinear with a decline in calcium absorption with concentrations <30 nmol/L (3). However, the hypothesis that there is a threshold at a higher serum 25(OH)D concentration (80 nmol/L) has now been shown from our study and others to be false (4–9). This finding is important for public policy in vitamin D recommendations. The statement by the authors about the harms of calcium absorption between vitamin D dose or 25(OH)D concentrations and baseline calcium absorption is odd because it should be the calcium absorbed that matters, whether or not it is accomplished through calcium intake or vitamin D intake.

Finally, we appreciate the authors pointing out the inconsistency between our reported overall mean for baseline calcium absorption and the group means by dose presented in Table 1. A corrected version of Table 1 appears in an erratum published in this issue of the Journal.

Neither of the authors reported a conflict of interest.

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REFERENCES


Dietary sodium and cardiovascular health strategies

Dear Sir:

We were very interested to read the recent article by Hendriksen et al (1) on the potential effect on health of salt reduction in processed foods and their prerequisites for the future decreases in cardiovascular disease and stroke if such reductions could be put in place. This would be the ideal situation of any country trying to deal with the current problems of salt and overall health (2). However, despite efforts around the world to decrease dietary salt and the recommendations for these reductions at an individual level, there does not appear to be much change in the incidence of overall cardiovascular disease (3). We think the problem is more at the level of human-motivated behavior and its possible physiologic regulation than with industry’s use of salt in processed foods. The ingestive behavior of humans with respect to salt, and of course water, is one very important aspect of what appears to have been overlooked in this report as well as in most studies involving salt intake. If humans are consuming far more sodium than appears to be needed, as indicated by Hendriksen et al (1), then could there be a physiologic reason for this?

The appropriate physiologic response to increased sodium intake would be an increase in plasma sodium concentrations, thus an increase in osmolality, which via osmoreceptors in the brain stimulates the release of the hormone vasopressin and thirst—that is, drinking. An increased fluid intake would lead temporarily to a decrease in osmolality (thus a decrease in vasopressin) and a temporary increase in blood volume and pressure, producing a temporary pressure diuresis and natriuresis. The same temporary pressure increase should reduce plasma concentrations of other hormones such as angiotensin and aldosterone. Urine excretion of sodium and water would therefore return volume and osmolality to within the normal range. This has been corroborated in humans and rats in studies in which high-salt diets decreased plasma renin activity, plasma angiotensin, and aldosterone (4, 5).

A decrease in plasma sodium concentrations is seen usually as a hypovolemia, a decrease in blood volume, and is associated with stimulation of the release into the blood of the regulatory hormone vasopressin and the enzyme renin. The latter stimulates the production of another regulatory hormone, angiotensin, which then stimulates the release of yet another regulatory hormone, aldosterone. To recover this loss of blood volume, both water and salt are needed and the normal physiologic mechanisms for this are thirst, ie, water intake, and salt appetite (6). Angiotensin, like increased osmolality, is a potent stimulus of thirst in all animals tested (6). Although there is good evidence in rodents that angiotensin and aldosterone actively stimulate sodium appetite (7), there is no clear evidence in humans that this is the case (8). However, it may be that the physiologic mechanisms of