No vitamin D threshold for calcium absorption: why does this matter?1–3

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It has long been known that 1,25-dihydroxyvitamin D stimulates calcium absorption and that there is a correlation between serum 25-hydroxyvitamin D [25(OH)D]4 and calcium absorption at low serum concentrations when transcellular processes are more important (1). Calcium absorption has been used as one of several measures to determine vitamin D intake requirements or sufficiency (2). Previoulsy, it was suggested that there was a threshold for maximal calcium absorption at a serum 25(OH)D concentration of 80 nmol/L (32 ng/mL), with a steep increase starting from 28 nmol/L (3). The basis for this threshold was data from a study that used a single-isotope method that showed no difference in fractional calcium absorption (FCA) from 75 to 125 nmol/L (3). Other suggested threshold values (29, 50, and 85 nmol/L) for maximal calcium absorption were from studies that did not directly measure calcium absorption (3). The need to clarify the calcium absorption threshold was pointed out by the Institute of Medicine committee to determine the vitamin D and calcium requirements in its 2011 report, because at the time there were no published randomized controlled trials (RCTs) to indicate whether a threshold even existed above 25(OH)D concentrations considered to be deficient (2). Since that time, 3 RCTs have been published, including the study published in this issue of the Journal (4).

In the study by Aloia et al (4), the FCA response to multiple doses of supplemental vitamin D3 was measured for the first time by using the more precise dual-isotope method (4). This trial, which reported a baseline 25(OH)D concentration of 63 nmol/L, found no threshold for calcium absorption at the various doses of vitamin D supplementation. Specifically, after 8 wk, the researchers found increases of 3.9%, 5.0%, and 6.7% in FCA in response to 800, 2000, and 4000 IU vitamin D3/d, respectively, by using a 300-mg Ca load. The placebo group without any supplementation decreased FCA by 2.6%. There are at least 2 reasons why these findings are important. First, whereas some available evidence seemed to have suggested that there was no serum 25(OH)D threshold for FCA (5, 6), only a dose-response study can definitively prove this. Second, the decrease in the placebo group is not surprising given that typical dietary vitamin D intake is low in this group of women (2, 5) who tend to take a small amount of supplements before entering a trial (2). The decrease in FCA underscores the need for adequate vitamin D in maintaining calcium absorption.

Additional information is available from 2 other recent double-blind controlled studies that used vitamin D3 supplementation in postmenopausal women with adequate calcium intake (5, 7). In the Gallagher et al (7) study, multiple doses of vitamin D3 were used from 400 to 4800 IU/d, and findings showed that there was a 6% increase in FCA by using the single-isotope method and a low calcium carrier load (100 mg). These findings are consistent with the Aloia et al study, which showed a 6.7% increase in FCA when women were supplemented with 4000 IU/d and given a 300-mg Ca load (4). In our laboratory (5), we used a similar dual stable-isotope method with a 300-mg carrier Ca load and a similar baseline serum 25(OH)D concentration in postmenopausal women. In this study, vitamin D3 intake increased from 400 to 2500 IU/d, and there was a 3.7% increase in FCA. The slightly greater increase in FCA of 5% in the Aloia et al study using nearly identical methods may be explained by an absence of any vitamin D supplementation in the control group (4). In addition, an earlier study (6) administered a large dose of vitamin D2 (50,000 IU/d) to postmenopausal women for 15 d. This study used dual stable isotopes and found a 3% increase in FCA compared with baseline. The effect of vitamin D2 supplementation on FCA has not been found in studies that used smaller daily doses of vitamin D2 (ie, 1000 IU/d) (8, 9), possibly because of its shorter half-life compared with vitamin D3. Overall, there is an increase in calcium absorption with higher vitamin D3 intakes in adults and no threshold. This appears to differ in children. In a study with multiple doses of vitamin D3 of up to 4000 IU/d given to children by using a single stable-isotope method and a low calcium carrier load (150 mg), none of the vitamin D3 doses or serum 25(OH)D concentrations influenced FCA (10). It is possible that the higher baseline 25(OH)D concentration of 70 nmol/L attenuated the response to vitamin D.

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4 Abbreviations used: FCA, fractional calcium absorption; RCT, randomized controlled trial; 25(OH)D, 25-hydroxyvitamin D.

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D intake in the children, but serum 25(OH)D increased significantly in the higher-dose groups (10). The relations between serum 25(OH)D or 1,25-dihydroxyvitamin D and FCA are not strong in any of the RCT studies (4, 5, 7, 10). Other vitamin D metabolites or genetic factors that may further explain how vitamin D influences calcium absorption were not studied in these RCTs.

The outcomes of the Aloia et al (4) study combined with evidence from other recent studies argue against increasing vitamin D requirements above the current Recommended Dietary Allowance of 600–800 IU/d to increase calcium absorption in average healthy individuals. Indeed, if the intake of calcium is at 1000 mg/d, a 3.7–6.7% increase in absorption with 2000–4000 IU/d would provide an additional 37–67 mg Ca/d, which is similar to that found in 0.25 cup of milk or 1 ounce of almonds. Thus, taking high doses of vitamin D is an efficient way to maintain calcium balance. Nevertheless, the interplay of habitual low calcium intake in some individuals and the effects of vitamin D intake is not clear. In addition, higher doses of vitamin D might be justified in the future if the large trials currently being conducted show that there are nonskeletal health benefits.

Where does this leave us at the moment? There are 2 implications. The Dietary Reference Intake should not rely on calcium absorption as a measure of vitamin D sufficiency to determine adequate intake. It is important to consume the recommended intakes of vitamin D and calcium to avoid low net calcium absorption and to maintain bone health.

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REFERENCES