

## What does it mean to target specific serum 25-hydroxyvitamin D concentrations in children and adolescents?

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The task of determining dietary requirements for vitamin D intake is one of the key unresolved issues in vitamin- and mineral-related nutrition. The complexities of issues, including determining intake sources of vitamin D, seasonal changes in sun exposure at different latitudes, and population-related differences in the storage and metabolism of vitamin D, make the process of setting dietary guidelines difficult.

In determining dietary requirements, most have chosen to use the serum 25-hydroxyvitamin D [25(OH)D]<sup>1</sup> concentration as the primary biomarker of vitamin D, especially in healthy populations. This is despite the fact that the serum 25(OH)D concentration is not clearly a functional biomarker and is inconsistently related to identified health outcomes in otherwise healthy pediatric populations except at the extremes of usual population values (1, 2).

Nonetheless, there remains considerable interest in defining the relation between dietary vitamin D intake and serum 25(OH)D concentrations in children in whom relatively few such data exist (3). In infants, an intake of 400 IU/d will allow the vast majority if not nearly all infants who receive an appropriate diet to maintain a 25(OH)D concentration >30 nmol/L, which appears to be adequate to prevent rickets (3, 4), but comparable data in older children are minimal.

Two recent studies published in this issue of the Journal (5, 6) directly address this data limitation by using studies in young children and adolescents given vitamin D<sub>3</sub> supplements of 0, 400, or 800 IU/d (0, 10, or 20 μg/d). The populations studied in these reports were white children in Denmark and white adolescents in the United Kingdom who received 20 wk of wintertime supplementation in randomized, placebo-controlled, dose-response trials.

Results in children 4–8 y of age (5) showed that average total vitamin D daily intakes of 4.4 μg (175 IU) achieved a 50% population response of serum 25(OH)D concentration to >40 nmol/L and that total daily intakes of 19.5 μg (~800 IU/d) achieved a 97.5% response of serum 25(OH)D concentration to >50 nmol/L. In adolescents (6), a daily total intake of 6.6 μg (265 IU) met the 50% population response of serum 25(OH)D concentration to >40 nmol/L, and an intake >30 μg (1200 IU) would be needed to achieve a 97.5% response of serum 25(OH)D concentration to >50 nmol/L.

Of importance is that these conclusions were based on modeling responses of the individual subject data. In the provided data set, a daily intake of ~1000 IU/d (25 μg) led to a 25(OH)D value >50 nmol/L in nearly all of the adolescent study subjects (6). It is also important to note that the populations in these studies do not reflect fully a more racially diverse population or populations with greater sun exposure. Thus, caution should be used in interpreting these results on a global basis.

These results are very consistent with the Institute of Medicine's (IOM) 2011 report that establishes the Estimated Average Requirement at a daily vitamin D intake of 400 IU (10 μg). This intake would achieve the targeted adequate serum 25(OH)D concentration of 40 nmol/L in 50% of the population (3). The IOM's conclusion was based, however, on limited data, and it is important that the current (5, 6) studies support these results.

These results should lead to further discussion about the real meaning of values of serum 25(OH)D concentrations in children. Despite much fanfare, there are few data, either available to the IOM committee or available at the present time, that indicate a specific health benefit to achieving any given value of serum 25(OH)D, although there is reasonable support for the idea that values <30 nmol/L increase the risk of rickets in young children (3). It has been shown that serum 25(OH)D values of 40 nmol/L, consistent with the average values in the US population of children, lead to rates of calcium absorption consistent with those of children with values of 50–80 nmol/L (7). Although there continue to be numerous reports relating very low vitamin D status to a range of health problems, these have overwhelmingly been association studies. There have been only a few small controlled trials that evaluated these relations, and results have been conflicting in children, especially when only considering outcomes in children who are not clearly deficient in vitamin D intake or serum 25(OH)D values.

One important area of persistent confusion is the interpretation of the Recommended Dietary Allowance (RDA) for vitamin D. The IOM set the RDA as the intake associated with

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<sup>1</sup>Abbreviations used: IOM, Institute of Medicine; RDA, Recommended Dietary Allowance; 25(OH)D, 25-hydroxyvitamin D.

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a serum 25(OH)D concentration of 50 nmol/L. However, despite claims to the contrary, it is not the correct interpretation of the RDA that this is the value that 97.5% of individuals should achieve (8). This confusion was explained in detail by the National Academies of Medicine in a recent online explanation (9). To bring nearly all of the population to concentrations >50 nmol/L would require vitamin D intakes that are well above those consistent with the Estimated Average Requirement and the RDA as determined by the IOM (3).

So where does this leave us in relation to vitamin D? First, neither the data presented this month in the *Journal* nor any other data currently existing provide any substantial evidence that the Dietary Reference Intakes for vitamin D in the United States published in 2011 (3) are in need of urgent revision. The results of the pending omega-3 and vitamin D trial in the United States [VITAL (Vitamin D and Omega-3 trial)] in adults should be awaited and reviewed to consider this issue in adults and any implications it might have for pediatric populations (10). In children, there is a compelling need for similar large multicenter, properly controlled vitamin D supplementation trials with meaningful biological endpoints, both in healthy children and those with chronic illnesses.

For individual families and health care providers, the most important challenge pending such trials is to meaningfully evaluate population intakes of vitamin D and ensure that the recommended daily intakes for children (400–600 IU) are met. This means evaluating how we fund the provision of vitamin D supplements to children in the first 2–3 y of life who are at the highest risk of clinical dietary vitamin D deficiency and how we approach fortification strategies for vitamin D targeted at high-risk groups.

Vitamin D is critical for the health of children, and an adequate intake should be ensured. However, there is no evidence that high-dose intakes are commonly a cure for most non-bone-related disease processes. Nor may it be substituted in disease-prevention strategies for children that include a healthy overall diet, exercise, and vaccinations. Focusing our health discussion on children on

these topics is more important than focusing on any single nutrient such as vitamin D or a specific relation between dietary intake and serum 25(OH)D status.

The author is a member of the scientific advisory board of The Milk Professor Education Program (MilkPEP).

## REFERENCES

1. LeBlanc E, Chou R, Zakher B, Daeges M, Pappas M. Screening for vitamin D deficiency: systematic review for the U.S. Preventive Services Task Force Recommendation. Rockville (MD): Agency for Healthcare Research and Quality; 2014. Evidence Syntheses No.: 119.
2. Manson JE, Bassuk SS. Vitamin D research and clinical practice: at a crossroads. *JAMA* 2015;313:1311–2.
3. Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for calcium and vitamin D. Washington (DC): National Academies Press; 2011.
4. Abrams SA, Hawthorne KM, Rogers SP, Hicks PD, Carpenter TO. Effects of ethnicity and vitamin D supplementation on vitamin D status and changes in bone mineral content in infants. *BMC Pediatr* 2012;16:12:6.
5. Mortensen C, Damsgaard CT, Hauger H, Ritz C, Lanham-New SA, Smith TJ, Hennessy Á, Dowling K, Cashman KD, Kiely M, et al. Estimation of the dietary requirement for vitamin D in white children aged 4–8 y: a randomized, controlled, dose-response trial. *Am J Clin Nutr* 2016;104:1310–7.
6. Smith TJ, Tripkovic L, Damsgaard CT, Mølgaard C, Ritz C, Wilson-Barnes SL, Dowling KG, Hennessy Á, Cashman KD, Kiely M, et al. Estimation of the dietary requirement for vitamin D in adolescents aged 14–18 y: a dose-response, double-blind, randomized placebo-controlled trial. *Am J Clin Nutr* 2016;104:1301–9.
7. Abrams SA, Hawthorne KM, Chen Z. Supplementation with 1000 IU vitamin D/d leads to parathyroid hormone suppression, but not increased fractional calcium absorption, in 4–8-y-old children: a double-blind randomized controlled trial. *Am J Clin Nutr* 2013;97:217–23.
8. Heaney R, Garland C, Baggerly C, French C, Gorham E. Letter to Veugelers, P.J. and Ekwaru, J.P.: a statistical error in the estimation of the Recommended Dietary Allowance for vitamin D. *Nutrients* 2014;6: 4472–5.
9. National Academies of Sciences. Engineering, medicine. [cited 2016 Sep 18]. Available from: <http://www.nationalacademies.org/hmd/Global/News%20Announcements/How-the-RDA-for-Vitamin-D-Was-Determined>.
10. Pradhan AD, Manson JE. Update on the Vitamin D and Omega-3 trial (VITAL). *J Steroid Biochem Mol Biol* 2016;155(Pt B):252–6.