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Supplements: when will vitamin D have its day in the sun?

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Abstract

Most breast-fed and many formula-fed infants in the USA have an inadequate daily intake of vitamin D—below the amounts recommended by the American Academy of Pediatrics (AAP)—according to the results of a study by Perrine *et al.* The majority of infants might, therefore, need daily vitamin supplementation to meet the 2008 AAP recommendation.

Perrine and colleagues examined data from a longitudinal, questionnaire-based study of infant feeding practices, conducted between 2005 and 2007, to estimate the percentage of infants who either met the 2003 American Academy of Pediatrics (AAP) vitamin D intake recommendations or would have met the current 2008 AAP recommendations.¹ Daily vitamin D intake in infants is equivalent to the amount of vitamin D ingested (the AAP recommends minimal sun exposure for this age-group) both through supplements and milk; formula provides more vitamin D per unit volume than breast milk. The AAP-recommended daily intake of vitamin D was 200 IU in 2003, which was doubled to 400 IU daily in 2008.² Perrine *et al.*'s study took place while the 2003 recommendation was in effect. Overall, 44–58% of the infants met the 2003 recommendations, but only 11–25% of the infants would have met the 2008 recommendations (Table 1). The investigators used monthly questionnaires to collect information on both use of vitamin D supplements and the amount of formula and breast milk consumed daily.

Perrine and colleagues' article is particularly relevant given the abundance of literature supporting the health benefits of maintaining an optimal vitamin D status. Aside from its classic role in bone homeostasis, vitamin D has considerable effects on the immune and cardiovascular systems; a deficiency of this vitamin might, therefore, impair immunity and increase susceptibility to cardiovascular diseases and respiratory infections. Of particular interest to pediatric practitioners are the effects vitamin D has on immunity, including stimulation of defensin production (such as cathelicidin, which assists in the clearance of pathogens), as well as promotion of self-tolerance, which potentially reduces the risk of autoimmune disease.³ In addition, the ability of vitamin D to regulate cell growth and induce cell differentiation suggests that it might have natural anticancer properties.³

The results of several observational studies in pediatric populations suggest that vitamin D supplementation in early childhood might protect against numerous health problems, including the development of type 1 diabetes mellitus.⁴ In other studies, increased wheezing during a baby's early life showed an inverse relationship with low maternal vitamin D intake during pregnancy.⁵ An analysis of data from the National Health and Nutrition Examination

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Competing interests

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Survey showed that vitamin D deficiency (25-hydroxyvitamin D level <37.5 nmol/l) was associated with raised systolic blood pressure and HDL cholesterol levels in a cohort of individuals aged 1–21 years.⁶ However, large-scale epidemiologic studies are needed to confirm these relationships.

Adequacy of intake can be difficult to establish for any nutrient, as in many clinical settings the appropriate ingested amount to achieve desired health outcomes across the lifespan has not yet been defined. Conceptually, biomarkers of nutritional adequacy have been used for this purpose. These biomarkers can fall into several different categories (the examples given are all relevant to vitamin D status): markers of supply (serum 25-hydroxyvitamin D concentration), function (levels of parathyroid hormone and alkaline phosphatase), intermediate end points (outcomes that might be indirectly related to health benefits, such as improved calcium absorption and improved BMD), and disease risk or outcomes (rickets, decreased susceptibility to infection and autoimmune disease).⁷ Severe vitamin D deficiency causes hypocalcemia and hypophosphatemia. Parathyroid hormone and bone specific alkaline phosphatase levels increase in patients with vitamin D deficiency and are compensatory mechanisms for preservation of calcium and phosphate adequacy. Parathyroid hormone and bone-specific alkaline phosphatase secretion decreases with vitamin D repletion.

By 2008, the 2003 AAP recommendation of 200 IU of vitamin D as a daily dose for infants was recognized to be inadequate to prevent vitamin D deficiency. The 2008 recommendation (400 IU of vitamin D daily) stemmed primarily from clinical experience and from a small number of studies that focused largely on the prevention of rickets. Decades of clinical experience suggests that a daily supplementation dose of 400 IU vitamin D daily is the minimum intake that seems to prevent most cases of rickets.²

Functional biomarkers, such as levels of alkaline phosphatase and parathyroid hormone, have been studied in adults. The finding that a 25-hydroxyvitamin D serum concentration of ≥ 80 nmol/l results in a plateau in serum parathyroid hormone levels led to the adoption of 80 nmol/l as the optimal serum 25-hydroxyvitamin D level in adults.⁸ However, these data have yet to be replicated in infants and children. The vitamin D intake that would lead to desirable immunologic outcomes, such as prevention of autoimmune disease, infections and cancer, has also not yet been well-defined in either adults or children.

The safety of administering any dose of vitamin D supplementation is of particular concern when considering appropriate dosing in children, especially infants. Vitamin D toxicity is associated with hypercalcemia and hypercalciuria, and potentially nephrocalcinosis and hyperphosphatemia. However, both parents and health-care practitioners should be reassured that a daily dose of 400 IU vitamin D is safe in infants, as many decades of experience support this recommendation. Moreover, although data obtained in children are scarce, the results of some studies confirm that doses of up to 1,000 IU vitamin D per day are also safe in this young population.⁹

The work of Perrine *et al.* illustrates the gap that exists between the latest scientific knowledge and the acceptance and incorporation of such knowledge into daily clinical practice. However, the study has several limitations; for example, Perrine and colleagues only considered the actual implementation of the AAP recommendation, as reported by parents, as the study's end point. The study did not account for the efficacy of communication and reinforcement of this recommendation to parents by health-care providers, and did not examine the reasons why parents might have chosen not to follow the recommendation (such as difficulty of administration, personal belief or safety concerns). Moreover, the study was conducted when only the 2003 AAP recommendation was in effect

and, therefore, the researchers could not determine whether any difference in behavior had occurred after the new dose recommendation was made public.

A complementary study¹⁰ examined two factors that influenced adherence to the 2003 AAP recommendations: pediatricians' recommendations to parents and parental acceptance of the recommendation. Only 36.4% of pediatricians recommended vitamin D supplementation for breast-fed infants. Those that did not recommend supplementation agreed with the statement that "the recommendation is not evidence-based".¹⁰ Moreover, only 44.6% of the parents to whom vitamin D supplementation was recommended by their pediatrician actually followed the recommendation. According to the investigators, those parents who did not follow their pediatrician's advice were influenced by their belief that breast milk contained all of the required levels of nutrients, and the fact that giving vitamins to infants was inconvenient. However, the pediatricians' recommendation (if given) did influence many parents to administer the supplement.

The findings of these two studies^{1,10} underscore that in this era of evidence-based medicine, both health-care providers and the public expect the results of high-quality research to be the basis for recommendations published by official organizations before widely accepting these recommendations into their daily practice. In reality, clinical practice often lags behind the scientific advances that drive any type of health recommendation. The study by Perrine *et al.* highlights this point. However, while awaiting the results of ongoing longitudinal studies the clinical community occasionally has to accept recommendations based on less rigorous studies that nonetheless show established short-term and potential long-term benefit. Vitamin D recommendations might need to be reinforced by national campaigns geared toward both health-care providers and the public. Both groups need to be made aware of the safety and potential benefits of vitamin D supplementation and the fact that without supplementation, infants might be at risk of deficiency of this important nutrient and, potentially, associated long-term health problems, such as type 1 diabetes mellitus or cancer in later life. We hope that, with the collection of critically needed longitudinal health outcomes data, pediatric recommendations for supplementation will soon become more widely accepted, and vitamin D will eventually earn its 'day in the sun'.

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Table 1

Proportion of infants receiving the AAP-recommended daily intake of vitamin D

AAP recommendation	All groups (min–max, %)	Breast milk (min–max, %)	Mixed (min–max, %)	Formula (min–max, %)
2003 (200 IU daily)	43.6–57.9	9.4–12.6	29.3–35.3	81.3–98.2
2008 (400 IU daily)	11.4–25.0	5.3–12.6	8.5–14.4	19.9–37.4

Abbreviation: AAP; American Academy of Pediatrics.