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More Evidence on Low Vitamin D Levels Fuels Push to Revise Recommended Intake

Mike Mitka

A RECENT SPATE OF PUBLISHED studies adds to the drumbeat of those researchers who argue that vitamin D deficiency and insufficiency are tied to poor health outcomes for a variety of conditions in a large proportion of the US population. But the nature of these studies, mainly retrospective analyses, makes it difficult for regulatory bodies or specialty societies to develop specific recommendations for raising the established levels for minimum vitamin D intake. These circumstances have left some physicians reluctant to aggressively diagnose and treat their patients for vitamin D insufficiency.

More rigorous studies could clarify recent findings associating vitamin D insufficiency with such health problems as osteoporosis and bone fracture, muscle weakness, cancer, autoimmune disease, diabetes, schizophrenia, depression, lung dysfunction, kidney disease, and cardiovascular disease.

"We know vitamin D can prevent rickets in children, but there are all these other health outcomes thought to be affected by vitamin D," said Michal L. Melamed, MD, MHS, an assistant professor of medicine and epidemiology at Albert Einstein College of Medicine, Bronx, NY. "We need randomized clinical trials to see if supplementing vitamin D has an effect on the non-traditional outcomes."

HIGH PREVALENCE

Such trials may be needed sooner rather than later, if recent studies revealing a high prevalence of vitamin D insufficiency in children are any indication.

Melamed and colleagues analyzed levels of 25-dihydroxyvitamin D (25[OH]D), the serum marker for vitamin D, in 9757 children and young adults (aged 1-21 years) who partici-



Research continues to show links between low vitamin D levels and poor health outcomes.

ated in the National Health and Nutrition Examination Survey (NHANES) 2001-2004, and found 9% had vitamin D deficiency (25[OH]D less than 15 ng/mL) and 61% had vitamin D insufficiency (25[OH]D of 15-29 ng/mL). They also found that vitamin D deficiency was associated with elevated parathyroid hormone levels, higher systolic blood pressure, lower serum calcium, and lower high-density lipoprotein cholesterol levels compared with vitamin D sufficiency (Kumar J et al. *Pediatrics*. 2009;124[3]:e362-e370).

Melamed's article accompanied another appearing in the same issue of *Pediatrics* that found low vitamin D levels were strongly associated with

overweight status and abdominal obesity in 3577 fasting nonpregnant adolescents (aged 12-19 years) participating in NHANES 2001-2004. This study also found that vitamin D levels were inversely associated with systolic blood pressure and plasma glucose concentrations (Reis JP et al. *Pediatrics*. 2009;124[3]:e371-e379).

Jonathan M. Mansbach, MD, an assistant professor of pediatrics at Harvard Medical School in Boston, and colleagues also used the same NHANES data but looked at children aged 1 to 11 years. The mean serum 25(OH)D level in this group was 28.0 ng/mL. The researchers also found that children aged 6 to 11 years had lower mean levels of serum 25(OH)D compared with younger children, and that levels were lower in girls than in boys. Further, levels were lower in non-Hispanic black and Mexican-American children than in non-Hispanic white children (Mansbach JM et al. *Pediatrics*. 2009;124[5]:1404-1410).

Mansbach, who came to study vitamin D levels because of its link with respiratory tract illnesses, said it may be time to increase recommended intake levels of the vitamin. "Vitamin D used to be all about rickets, and whatever the level you needed to prevent rickets was the acceptable level," he said. "But as other risk factors have arisen, the recommended level should also be on the rise."

Striking a note of caution about dramatically changing minimum intake levels for vitamin D is Frank R. Greer, MD, a professor of pediatrics at the University of Wisconsin in Madison.

Greer, who wrote a commentary accompanying Mansbach's paper, said



in an e-mail exchange that vitamin D advocates should not overstate what the science shows. “Most of the evidence is epidemiologic evidence, in which ‘low’ 25(OH)D levels have been associated with various disease processes—this is not the same as cause and effect,” said Greer. “There would have to be randomized controlled trials with increasing amounts of vitamin D to demonstrate functional outcomes such as prevention of cardiovascular disease, diabetes, cancer, et cetera.”

RECOMMENDATIONS RECONSIDERED

Even though results from such rigorous studies may be years away, there has been some movement on minimum acceptable levels of vitamin D intake. Last year, Greer helped the American Academy of Pediatrics (AAP) revise its guidelines to recommend increasing the daily intake of vitamin D from 200 IU per day to 400 IU per day for all infants, children, and adolescents beginning in the first few days of life. In making the change, the guidelines’ authors said that new evidence supported a potential role for vitamin D in maintaining innate immunity and preventing diseases such as diabetes and cancer (Wagner CL et al. *Pediatrics*. 2008;122[5]:1142-1152).

Greer added that the AAP will not be making any additional recommendations regarding vitamin D intake until after publication of an Institute of Medicine (IOM) report scheduled for release in May 2010. Advocates of vitamin D are eagerly awaiting the IOM report, which is expected to emphasize the need for more intake of the vitamin and may encourage its further use as a food additive. Currently the IOM recommends supplemental vitamin D intake at 200 IU per day from birth to age 50 years, 400 IU per day for those aged 51 to 70 years, and 600 IU per day for adults aged 71 years or older.

But even if the IOM changes its recommendations, which are currently designed to provide adequate levels for bone health, Greer does not

expect levels to exceed 400 IU per day for children. “Personally, I will be surprised if [the IOM] recommends any more than 400 IU,” Greer said. If it does, he added, the AAP would need to reconsider its own position.

The IOM report, sponsored by the US Department of Health and Human Services, the US Department of Agriculture, and Health Canada, will be the work of a committee assigned to assess current relevant data and update, as appropriate, the dietary reference intakes for vitamin D and calcium. The committee will look beyond vitamin D and bone health to consider chronic and non-chronic disease indicators.

Michael F. Holick, MD, PhD, professor of medicine, physiology, and biophysics at Boston University School of Medicine, is a great believer in the benefits of vitamin D who hopes the IOM reconsiders not only the daily minimum intake level but also the recommended upper limits, which are designed to prevent such adverse effects as nausea, vomiting, and even heart rhythm abnormalities. Current upper limits are 1000 IU per day for infants up to 1 year and 2000 IU per day for those aged 1 year or older.

“What really is needed is for the IOM not only to come out with new recommendations to substantially increase vitamin D intake for children and adults, but to markedly increase the upper limits,” Holick said. “That is why food manufacturers are reluctant to fortify their food; they worry about vitamin D toxicity.” The IOM did say in its activity description that the study would “give priority to examining whether a critical adverse effect can be selected that will allow for the determination of a so-called benchmark intake (<http://www.iom.edu/Activities/Nutrition/DRIVitDCalcium.aspx>).”

Holick thinks the risks of reaching toxic levels of consumption are overstated. He would raise the upper limit to 5000 IU per day for children and suggested that an adult could

receive up to 10 000 IU of vitamin D per day without any adverse effects. Indeed, Holick and colleagues are successfully treating patients deficient in vitamin D with such megadoses. In a small study, they successfully treated 84% of patients with vitamin D deficiency by giving them 50 000 IU of ergocalciferol weekly for 8 weeks and then 50 000 IU every other week for up to 6 years (Pietras SM et al. *Arch Intern Med*. 2009; 169[19]:1806-1807).

MORE FINDINGS

And while some await the IOM report and others argue for increasing daily intake of vitamin D, the research continues.

Besides her work on vitamin D insufficiency in children, Melamed has also recently published work finding an association between vitamin D insufficiency and progression of kidney disease in blacks. Blacks, whose dark skin pigment makes it difficult to obtain vitamin D through sunlight exposure (the easiest way to get the vitamin), have end-stage renal disease at disproportionately high rates compared with whites. Using Medicare claims files linked with NHANES (1988-1994), Melamed and colleagues examined 25(OH)D levels in 13 328 individuals. The researchers found that 34% of non-Hispanic blacks had 25(OH)D levels less than 15 ng/mL compared with 5% of non-Hispanic whites (Melamed ML et al. *J Am Soc Nephrol*. 2009;20[12]:2631-2639).

As researchers continue to find associations between vitamin D deficiency and adverse outcomes, are physicians getting the message? Melamed thought so, while Holick offered a qualified “yes.”

“What happens is the patient hears about this in the news and brings it to her physician’s attention,” Holick said. “The physician is then reluctant to do the test, but when he does, he finds the patient is vitamin D deficient—and then he gets religion.” □