

Multiorgan Damage a Concern

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One expert suggested that the alarm may be unwarranted because the recent studies raise more questions than they answer. Everyone agreed that no one really knows how to define adequate vitamin D levels in children and adolescents, and that much more study is needed.

A report by a committee of the Institute of Medicine on what constitutes adequate intakes of vitamin D is expected to be released in the spring of 2010 and is "eagerly awaited," said Dr. Frank Greer, professor of pediatrics at the University of Wisconsin, Madison, and a coauthor of the AAP's 2008 guidelines on vitamin D intake.

What inflamed concerns about pediatric vitamin D levels? Studies such as one published online in *Pediatrics* last month (doi:10.1542/peds.2009-0051). Nine percent of U.S. children and adolescents (representing 7.6 million people) have 25-hydroxyvitamin D (25[OH]D) deficiency and 61% (50.8 million children and adolescents) have insufficient 25(OH)D levels in serum tests, according to a study by Dr. Juhi Kumar and associates. Only 4% were taking daily vitamin D supplementation (400 IU).

The investigators calculated prevalence using data on 9,757 children and adolescents from the 2001-2004 National Health and Nutrition Examination Survey (NHANES), defining 25(OH)D deficiency as a serum level below 15 ng/mL and insufficiency as 15-29 ng/mL.

Evidence is mounting that bone health may not be the only issue related to vitamin D levels. After adjustment for confounding variables, analyses of data on 6,275 of the NHANES participants found that deficiency in 25(OH)D was associated with more than a threefold increased risk for elevated parathyroid hormone levels, a more than doubled risk for higher systolic blood pressure, and reduced levels of serum calcium and HDL cholesterol, compared with children and adolescents whose 25(OH)D levels were at least 30 ng/mL, said Dr. Kumar of Albert Einstein College of Medicine, New York.

A separate analysis of data on 3,528

adolescents from NHANES 2001-2004 found that low serum 25(OH)D levels (less than 15 ng/mL) were associated with roughly a doubling in risk for hypertension and fasting hyperglycemia and nearly a quadrupled risk for metabolic syndrome, compared with adolescents with levels above 26 ng/mL, reported Jared P. Reis, Ph.D., of the National Heart, Lung, and Blood Institute, and his associates. The study was published online in *Pediatrics* last month (doi:10.1542/peds.2009-0213).

"These are staggering numbers" that are supported by smaller studies in the literature, said Dr. Catherine M. Gordon, director of the bone health program at Children's Hospital, Boston. "We may eventually be at the point of saying that we need to universally screen vitamin D levels, just like we screen for lead levels in children," she said in an interview, but "I don't think we're quite there from a cost-effectiveness standpoint. I do think that children should be universally supplemented, but that's a controversial point."

If physicians or their assistants intensified attention to childhood growth and nutritional habits, "perhaps we can catch obesity earlier, perhaps we can catch undernutrition earlier," and flag low vitamin D levels earlier, Dr. Bhatia suggested.

It's hard to drink enough milk to get the recommended 400 IU of vitamin D daily, and "most children are not real excited about eating mackerel or sardines" to get vitamin D, noted Dr. Gordon, who specializes in pediatric endocrinology and in adolescent medicine. "That pushes us to supplement."

She recommended annual screening of vitamin D levels in children and adolescents at risk for vitamin D deficiency, including those who are obese, those who have problems that lead to malabsorption of vitamin D (such as cystic fibrosis or inflammatory bowel disease), and those who are taking medications that may increase vitamin D metabolism, such as anticonvulsants.

Dr. Greer, a neonatologist, also might screen African American infants who

were exclusively breastfed and children whose families practice *purdah*, an Arabic cultural tradition of covering up before going outside.

There's a growing consensus that 25(OH)D levels of 20 ng/mL or lower constitute vitamin D deficiency in children and adults because higher levels are sufficient for skeletal health, Dr. Gordon said. "I'm a believer in trying to keep all of our levels above 30 ng/mL" because the extraskeletal benefits of vitamin D (on the immune system, cell proliferation, and more) are conferred at these higher levels. Levels of 21-30 ng/mL, then, might be considered insufficient. Patients in risk groups may need 800-2,000 IU/day of vitamin D to maintain good serum levels, she noted.

"The problem is, there are not any good guidelines on what a normal level

should be," Dr. Greer said. "In the wintertime, everybody in the United States has pretty low levels, but they go up in the summertime, and most of us don't get rickets."

The AAP recommendation to consume at least 400 IU/day of vitamin D is based largely on studies of non-Hispanic white infants and may not be optimal for other races, he added. "Nobody has looked at large numbers of African American infants" and vitamin D.

Meanwhile, the "inflammatory" reports about vitamin D deficiency appearing in the medical literature "are driving people at the NIH Office of Dietary Supplements crazy," Dr. Greer said.

The study investigators and physicians who were mentioned in this story reported having no potential conflicts of interest related to these topics. ■

Vitamin D Tests Lack Standardization

Just as there is no consensus about adequate levels of vitamin D, the tests of serum vitamin D levels lack standardization, too.

"There has been a lot of controversy and debate behind the scenes" on whether to test for serum 25(OH)D using chemiluminescent technology or liquid chromatography/mass spectrometry technology, Ravinder J. Singh, Ph.D., said in an interview.

Smaller hospital laboratories tend to favor the former, while most of the larger reference laboratories have adopted the latter, which is considered the preferred method, said Dr. Singh, codirector of the endocrine lab at the Mayo Clinic, Rochester, Minn.

Most of the clinical analytes used in the tests lack standardization or "harmonization" from one U.S. geographical region to the next, he added. In rare situations, clinicians will get discrepant results, but in general, clinicians should believe the results of either test, he said.

"Because we are not fully standardized, it's good to have caution, but it's not like every number we are giv-

ing them is garbage, either," Dr. Singh said.

There's also a need for standard reference material to ensure accuracy in 25(OH)D testing, he added. The National Institute of Standards and Technology created vials of vitamin D metabolites that labs can compare with results of their test methods for quality control, but there's no mandate that these be used.

"There is a need for laboratories and the manufacturers of the tests to work together to standardize the testing so that clinicians can rely upon the results," Dr. Singh said.

The need has greatly increased with the rising attention to vitamin D. Not long ago, Dr. Singh's reference lab used to process 50 serum samples per day for vitamin D levels. Today, "we may be doing 5,000 a day," he said.

Dr. Singh will be one of three experts in an audioconference on vitamin D testing this month, sponsored by the AACC (American Association for Clinical Chemistry). For information, visit www.aacc.org.

—Sherry Boschert

Growth Hormone Shows Benefit in Children With Crohn's

BY HEIDI SPLETE

CHICAGO — Children with Crohn's disease who received growth hormone in addition to corticosteroids showed significant improvements in symptoms after 12 weeks, based on data from 20 children aged 7-18 years with active Crohn's disease.

Previous studies have shown that growth hormone may reduce symptoms in adults with Crohn's disease and may improve growth in children, but the effect of growth hormone on intestinal inflammation in children with Crohn's is not well known, said Dr. Lee Denson of Cincinnati Children's Hospital Medical Center.

To assess the impact of growth hormone on symptoms in children with Crohn's, Dr. Denson and colleagues randomized 10 children with active disease to receive corticosteroids alone, or to receive 0.075 mg/kg per day of growth hormone (somatropin) in addition to corticosteroids.

After 12 weeks, 65% of the children who received growth hormone showed clinical remission of their Crohn's, compared with 20% of the children who did not receive growth hormone, a statistically significant difference. Growth hormone is not currently approved by the Food and Drug Administration to treat Crohn's disease, Dr. Denson reported at the annual Digestive Disease Week.

Endoscopic disease activity (measured using the Crohn's Disease Endoscopic Index of Severity) was lower in the growth hormone group. The difference between the groups was not significant. But 70% of the children in the growth hormone group achieved inactive mucosal disease at 12 weeks, compared with 50% of the children who didn't take growth hormone.

Microarray analyses of colon biopsies showed increases in some cellular components involved in neurophysiological function, cell signaling, and solute transport in children who took growth hormone that

were not seen in biopsies from children who didn't take growth hormone, but the implications of these differences aren't fully understood.

In addition, 61% of the children who received growth hormone maintained their clinical response through 64 weeks, and differences in their predicted adult height after 48 weeks compared with baseline indicated catch-up growth.

"In the longer phase of the study, we found that most children who received growth hormone had a catch-up [in growth] and got back to where they would have been without the illness," said Dr. Denson said. The growth hormone was well tolerated, and the results indicate the need for a larger multicenter study to assess the overall benefit of using growth hormone to treat Crohn's disease symptoms in children.

Dr. Denson has received grant and research support from Abbott Laboratories and Genentech Inc. This study was sponsored in part by Genentech. ■