PEDIATRIC PHARMACOTHERAPY

A Monthly Newsletter for Health Care Professionals from the University of Virginia Children's Hospital

Volume 15 Number 5 May 2009

Prevention and Management of Vitamin D Deficiency in Children: Part I: Vitamin D Requirements

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Vitamin D is obtained through two sources, dietary intake and endogenous production following exposure to ultraviolet sunlight.[1] Several demographic studies published within the last year have called attention to the increasing frequency of vitamin D deficiency in children.[2-5] There is a growing awareness that many infants, children, and adolescents are not achieving the recommended dietary intake.[6] In addition, concerns over the risks of melanoma have led many families to minimize their children's sun exposure. As a result, more children may require vitamin D supplementation to achieve desired serum levels of 25-hydroxyvitamin D (25(OH)D). The next two issues of *Pediatric Pharmacotherapy* will focus on vitamin D in children. This issue will provide an overview of recent studies of vitamin D status in the pediatric population and new guidelines for dietary intake. The June issue will describe methods for vitamin D supplementation.

Mechanism of Action

Vitamin D is a prohormone which is converted first in the liver to 25(OH)D, an inactive intermediate form, and then in the kidney to active 1,25-dihydroxyvitamin D [$1,25(OH)_2D$]. It is obtained through exogenous sources (vitamin D_2 or D_3) or through endogenous synthesis via absorption of ultraviolet B (UVB) radiation by the skin to produce vitamin D_3. Receptor sites for $1,25(OH)_2D$ are located throughout the body, in the skin, brain, stomach, pancreas, and gonadal tissues, as well as on activated T and B lymphocytes and macrophages.[1,7-11]

The active forms of vitamin D control enteral absorption of calcium and tubular reabsorption of calcium by the kidney, and regulate bone growth and remodeling through mobilization of calcium. Active $1,25(OH)_2D$ appears to have immunomodulating effects. It appears to increase insulin production in patients with type 1 diabetes and to stabilize inflammation in patients with multiple sclerosis or asthma. Its role in maintaining innate immunity may also be important in preventing cancer. Vitamin D may also increase myocardial contractility and help to maintain optimal cardiac function. As a result of these multiple functions, it has been suggested that vitamin D deficiency during infancy or childhood could have profound effects on long-term health.[1, 7-11]

Current Standards for Vitamin D Intake

It has traditionally been believed that normal dietary vitamin D intake will produce adequate serum 25(OH)D levels. The most recent guidelines from the Food and Nutrition Board of the Institute of Medicine, published in 1997, suggest a daily minimum vitamin D intake of 200 International Units (5 mcg) for infants, children, and adults up to 50 years of age to achieve serum 25(OH)D levels $\geq$ 20 ng/mL and prevent bone disease. The recommended daily intake increases to 400 International Units (10 mcg) for adults 51 to 70 years of age and 600 International Units (15 mcg) for adults over 71 years of age.[1,7-9]

In most clinical studies, vitamin D deficiency has been defined as a serum 25(OH)D level < 20 ng/mL. Levels between 20 and 30 ng/mL are indicative of vitamin D insufficiency. The target 25(OH)D goal of 20 ng/mL has recently come under criticism. Newer research has strongly suggested that serum 25(OH)D levels of 30 ng/mL or greater may be needed for optimal health benefits. It has been estimated that up to 1 billion people worldwide have vitamin D insufficiency or deficiency by these standards.[12]

Vitamin D Status in Infants and Children

Prevention of vitamin D deficiency may be most important during infancy, to produce optimal

bone formation and prevent rickets.[6,13,14] *In utero*, the primary source of vitamin D for the fetus is 25(OH)D from the mother. Active $1,25(OH)_2D$ does not cross the placenta. After birth, vitamin D goals may not be met with exclusive breastfeeding, since breastmilk provides only 20-70 International Units/L.[1,6,13,15]

Several studies have documented a relatively high incidence of vitamin D insufficiency or deficiency in infants and toddlers. In 2008, Gordon and colleagues evaluated a cross-sectional sample of 380 healthy infants and toddlers in an urban primary care clinic in Boston.[14] Forty-four of the 365 patients tested (12.1%) had serum 25(OH)D levels < 20 ng/mL, while 146 (40%) had levels less than 30 ng/mL. Three patients had radiographic evidence of rickets and another 13 had evidence of bone demineralization.

Unlike some earlier studies, the prevalence of vitamin D deficiency in this group of patients was not correlated with age or skin pigmentation. There was an inverse correlation between serum 25(OH)D and parathyroid hormone levels ($p<0.001$ for infants, $p<0.02$ for toddlers), indicative of increasing secondary hyperparathyroidism. Multivariate analysis revealed that breastfeeding without vitamin D supplementation and a lower milk intake in toddlers were significant predictors of vitamin D deficiency. The authors concluded that their study added evidence for the increasing prevalence of vitamin D deficiency in infants and young children and suggests the need for routine supplementation.[14]

In addition to studies conducted in infants, there has been considerable interest in the vitamin D status of older children and adolescents during the past decade. Saintonge and colleagues examined the rates of vitamin D deficiency in the adolescent participants (ages 12 to 19 years) in the Third National Health and Nutrition Examination Survey (NHANES III), which included data collected between 1988 and 1994.[2] Using a serum 25(OH)D level < 20 ng/mL as the criterion, 14% of the 2,955 teens had vitamin D deficiency. Using a higher cut-off of 30 ng/mL, the number rose to 48%. Black adolescents had 20 times the risk of vitamin D deficiency compared to non-Hispanic white adolescents. Females had more than double the risk compared to males. An inverse relationship was found between patient weight and 25(OH)D levels, suggesting that being overweight increased the risk for vitamin D deficiency.

Additional information from the NHANES project has recently been published, with data collected between 2001 and 2004. Ginde and colleagues reported a significant decline in 25(OH)D levels from the 1988-1994 (NHANES III) collection period to the 2001-2004 period.[3] Among the 12 to 19 year old age group, the mean serum 25(OH)D level declined from approximately 32 ng/mL in the NHANES III survey to 24 ng/mL in the NHANES 2001-2004 survey. The decline persisted across all ethnic and gender subgroups, but was most pronounced in black males. Only 23% of 4,224 adolescents had serum 25(OH)D levels greater than the currently recommended 30 ng/mL target. The authors of both papers call for further study of the growing numbers of children and adolescents with vitamin D deficiency and the impact of this condition on bone growth and mineralization during puberty, as well as overall health status.

New Recommendations

An extensive review on vitamin D deficiency in children, with new recommendations for supplementation, was published in the August 2008 issue of *Pediatrics* by Misra and colleagues on behalf of the Drug and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society.[16] This paper provides an excellent resource for pediatric health care providers on topics ranging from biomarkers of vitamin D deficiency to dietary sources and dosing of vitamin D products.

Based on a review of the literature, the group recommended that serum 25(OH)D levels be maintained at least above 20 ng/mL and that daily supplementation with 400 International Units (10 mcg) of vitamin D be initiated within days of birth for all breastfed infants and in formula-fed infants and children who do not ingest at least 1 L of vitamin D-fortified milk each day. Premature infants, dark-skinned children, and children who live at higher latitudes may require larger doses of vitamin D, up to 800 International Units (20 mcg) per day. Supplementation for vitamin D insufficient or deficient children should be dosed according to the chart below:

Patient Age	Dose (International Units/day)
< 1 month	1,000
1-12 months	1,000 to 5,000
> 12 months	> 5,000

In addition to their recommendations, the authors also highlighted the need for additional studies to determine if higher levels of 25(OH)D (> 32 ng/mL) should be considered, as well as to

determine the appropriate balance of the benefits and risks of sunlight exposure.[16]

In November 2008, the American Academy of Pediatrics (AAP) released a guidance paper on the prevention of rickets and vitamin D deficiency in infants, children, and adolescents.[6] This new report replaces their 2003 statement which recommended a daily intake of 200 International Units. As in the Lawson Wilkins Society article, the 2008 AAP statement recommends that the daily vitamin D intake for all pediatric patients be increased to 400 International Units (10 mcg), with a goal 25(OH)D level of at least 20 ng/mL. The AAP statement also recommends that breastfed infants receive a vitamin D supplement at a dose of 400 International Units/day beginning shortly after birth and continuing until they are weaned and consuming at least 1 L of vitamin D-fortified formula or milk per day.

Daily supplementation is also recommended for older children and adolescents who do not consume at least 400 International Units of vitamin D with their usual diet. The AAP guidelines were based on studies documenting the safety of vitamin D at this higher dose as well as new evidence suggesting a possible role for vitamin D in preventing cancer, cardiovascular disease, and diabetes.[6]

Patients at Increased Risk

Vitamin D deficiency is common in children with malabsorption syndromes such as cystic fibrosis and chronic illnesses such as kidney disease, asthma, and type I diabetes mellitus. It is also seen in children who take medications known to interfere with vitamin D absorption or metabolism, including cholestyramine, colestipol, phenobarbital, and phenytoin.[1,4-6]

In the March 2009 issue of *Pediatrics*, Ali and colleagues compared serum 25(OH)D levels in children with chronic kidney disease from 1987 to 1996 and again between 2005 and 2006.[4] The purpose of the study was to evaluate the impact of implementing routine vitamin D supplementation in these patients. The yearly mean serum 25(OH)D level during the first decade studied ranged from 11.6 to 30.2 ng/mL, with a prevalence of vitamin D deficiency (defined as a level < 15 ng/mL) ranging from 20 to 75%. During the second assessment period (2005-2006), the mean serum 25(OH)D level was 21.8 ng/mL and the prevalence of vitamin D deficiency was 39%. As in the larger epidemiologic studies, black and Hispanic children had lower 25(OH)D levels on average than non-Hispanic white children. The authors concluded that routine vitamin D supplementation was useful, but that inadequate dosing and non-adherence may be limiting the benefits of treatment.

Brehm and colleagues evaluated the prevalence of vitamin D insufficiency and deficiency in children with asthma in Costa Rica.[17] In the sample of 616 children between 7 and 11 years of age, 21 (3.4%) had vitamin D deficiency, defined as a serum 25(OH)D level < 20 ng/mL. An additional 152 children (24.6%) had levels between 20 and 30 ng/mL, indicating vitamin D insufficiency. Using bivariate analyses, the authors found that serum 25(OH)D levels were inversely associated with total serum IgE levels and peripheral eosinophil count. The association remained significant after adjustment for age, sex, body mass index, and parental education level. There was also a significant relationship between increased 25(OH)D levels and reductions in levels of IgE to dust mite. Although the authors acknowledge that the cross-sectional design of the study precludes establishing a causal relationship between low vitamin D levels and increasing asthma morbidity, they suggest that their findings might serve as a baseline for further research into the relationship between vitamin D status and asthma severity in children.

A deficiency of vitamin D may be particularly detrimental in children with diabetes, where it plays a role in controlling insulin production. In a cross-sectional analysis of 128 children with type 1 diabetes published in the January 2009 issue of *The Journal of Pediatrics*, Svoren and colleagues found that 15% had serum 25(OH)D levels $\leq$ 20 ng/mL.[5] Sixty-one percent had levels < 30 ng/mL. Patients with vitamin D deficiency were significantly older, had a longer duration of diabetes, and lower HgA1c levels ($p<0.05$).

Treatment with vitamin D supplementation can make a significant improvement in these high-risk pediatric populations. Arpadi and colleagues studied vitamin D supplementation in children with HIV infection, where rates of vitamin D deficiency may be as high as 90%.[18] They conducted a randomized, double-blind study of 57 children (ages 6-16 years), who received vitamin D (100,000 International Units every 2 months with calcium 1 gram/day) or placebo. Treatment resulted in significantly higher 25(OH)D levels. At the end of 1 year, only 7% of the vitamin D-treated patients had 25(OH)D levels < 20 ng/mL, compared to 50% of the children in the placebo group.

Summary

Over the past two years, a wide range of papers have been published on the role of vitamin D in maintaining overall good health. At the same time, a growing number of studies have documented an increase in the frequency of vitamin D deficiency in children throughout the world. Based on these findings, several professional organizations have published recommendations for increasing the daily vitamin D intake in infants, children, and adolescents to 400 International Units/day. As a result, many more children are likely to need vitamin D supplementation. The next issue of *Pediatric Pharmacotherapy* will provide information on supplement selection, dosing, and monitoring.

References

1. National Institutes of Health Office of Dietary Supplements. Dietary supplement fact sheet: vitamin D. Available at: http://ods.od.nih.gov/factsheets/vitamind.asp (accessed 5/3/09).
2. Saintonge S, Bang H, Gerber JM. Implications of a new definition of vitamin D deficiency in a multiracial US adolescent population: the National Health and Nutrition Examination Survey III. Pediatrics 2009;123:797-803.
3. Ginde AA, Liu MC, Camargo CA. Demographic differences and trends of vitamin D insufficiency in the US population, 1988-2004. Arch Intern Med 2009;169:626-32.
4. Ali FN, Arguelles LM, Langman CB, et al. Vitamin D deficiency in children with chronic kidney disease: uncovering an epidemic. Pediatrics 2009;123:791-6.
5. Svoren BM, Volkening LK, Wood JR. Significant vitamin D deficiency in youth with Type 1 diabetes mellitus. J Pediatr 2009;154:132-4.
6. Wagner CL, Greer FR, American Academy of Pediatrics Section on Breastfeeding, American Academy of Pediatrics Committee on Nutrition. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. Pediatrics 2008;122:1142-52.
7. Institute of Medicine, Food and Nutrition Board. Dietary reference intakes: calcium, phosphorus, magnesium vitamin D, and fluoride. Washington DC: National Academy Press, 1997.
8. Vitamin D. *Drug Facts and Comparisons*. Efacts [online]. 2009. Available from Wolters Kluwer Health, Inc. (accessed 5/1//09).
9. Drisdol® prescribing information. Sanofi-Aventis US, LLC. March 2007. Available at www.products.sanofi-aventis.us/drisdol/drisdol.pdfb (accessed 5/1/09).
10. Huh SY, Gordon GM. Vitamin D deficiency in children and adolescents: epidemiology, impact and treatment. Rev Endocr Metab Disord 2008;9:161-79.
11. Prentice A, Goldberg GR, Schoenmakers I. Vitamin D across the lifecycle: physiology and biomarkers. Am J Clin Nutr 2008;88 (suppl):500S-506S.
12. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266-81.
13. Greer FR. 25-hydroxyvitamin D: functional outcomes in infants and young children. Am J Clin Nutr 2008;88(suppl):529S-533S.
14. Gordon CM, Feldman HA, Sinclair L, et al. Prevalence of vitamin D deficiency among healthy infants and toddlers. Arch Pediatr Adolesc Med 2008;162:505-12.
15. Hollis BW, Wagner CL. Assessment of dietary vitamin D requirements during pregnancy and lactation. Am J Clin Nutr 2004;79:717-26.
16. Misra M, Pacaud D, Petryk A, et al. Vitamin D deficiency in children and its management: review of current knowledge and recommendations. Pediatrics 2008;122:398-417.
17. Brehm JM, Celedon JC, Soto-Quiros ME, et al. Serum vitamin D levels and markers of severity of childhood asthma in Costa Rica. Am J Respir Crit Care Med 2009;179:765-71.
18. Arpadi SM, McMahon D, Abrams EJ, et al. Effect of bimonthly supplementation with oral cholecalciferol on serum 25-hyroxyvitamin D concentrations in HIV-infected children and adolescents. Pediatrics 2009;123:e121-e126.

The author and editors would like to thank Dr. Alan D. Rogol for reviewing this article prior to publication.

Formulary Update

The Pharmacy and Therapeutics Committee did not meet during April. Their next meeting will be held on 5/22/09.

New CD of Printable Pediatric Medication Instructions Available

The American College of Clinical Pharmacy (ACCP) has recently announced the release of the 5th edition of the *Pediatric Medication Education Text (PMET5)*. This resource provides single-page written medication instructions (in both English and Spanish) for parents and caregivers of young children. Written by Marcia L. Buck, Pharm.D. and Anne E. Hendrick, Pharm.D., PMET has been a leading source for pediatric-specific medication instructions for the past decade. The 5th edition, with 55 new drug monographs, is on CD-ROM to allow for easy desk-top printing. PMET5 is available throughout the UVA Children's Hospital. For more information or to purchase the CD-ROM, visit the ACCP website at www.accp.com/bookstore/th_05pmet.aspx

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