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# Defining Vitamin D Deficiency in Children: Beyond 25-OH Vitamin D Serum Concentrations

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**ABBREVIATIONS**

25(OH)D—25-OH vitamin D

CI—confidence interval

PTH—parathyroid hormone

IOM—Institute of Medicine

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It is generally accepted that of the circulating vitamin D metabolites, serum 25-OH vitamin D (25[OH]D) measurements best reflect clinical vitamin D status. In this issue of *Pediatrics*, Mansbach et al<sup>1</sup> address this issue, namely, what serum levels of 25(OH)D in infants and children should be used to define vitamin D sufficiency and deficiency states? Using the 2001–2006 National Health and Nutrition Examination Survey's cross-sectional surveys of 25(OH)D serum concentrations in a presumed healthy population of 4558 US children between ages 1 and 11 years, the authors estimate that 320 000 US children (95% confidence interval [CI]: 220 000–430 000) have 25(OH)D levels at <25 nmol/L, 6.3 million children (95% CI: 5.4–7.2 million) have levels at <50 nmol/L, and 24 million children (95% CI: 21–26 million) have levels at <75 nmol/L. Not unexpectedly, the lowest mean values were found in black children, nearly all of whom had levels of <75 nmol/L.

If one approximates the total population of US children between 1 and 11 years of age as 40 million,<sup>2</sup> the estimated prevalence of 25(OH)D levels of <75 nmol/L would be 60%, and the estimated prevalence with levels of <50 nmol/L would be 16%. Relatively few children (1%) would have serum levels of <27.5 nmol/L, the value used to define the level of deficiency in a 1997 Institute of Medicine (IOM) report.<sup>3</sup> However, if one uses a cut-off value of <50 nmol/L, as recently suggested by the American Academy of Pediatrics, then this article raises the issue that the numbers (6.4 million children) may be of more concern.<sup>4</sup> Vitamin D functions more like a hormone and has increasing importance for human health, including immunomodulatory and antiproliferative effects on disease. Although vitamin D has been associated with many disease outcomes, clinical trials have not shown that vitamin D is causally related to these diseases.

What is the significance of these “low” 25(OH)D levels in children who typically have no clinical features of vitamin D deficiency? Are there measurable functional outcomes of vitamin D “deficiency” associated with any serum 25(OH)D cut-off values that could be used to define clinically relevant sufficiency or deficiency states in children? Potential functional outcomes of “adequate” 25(OH)D levels in children include the absence of vitamin D deficiency rickets, maximal suppression of serum parathyroid hormone (PTH) concentrations, increased measures of bone mineralization (bone mineral density or bone mineral content), “optimal” calcium absorption (using stable isotopes of calcium), and decreased bone-fracture rates. Currently, data are not sufficient in children younger than 12 years to evaluate calcium-absorption or fracture rates as functional outcomes of any 25(OH)D level.<sup>5</sup>

The most studied functional outcome in children has been the occurrence of vitamin D deficiency rickets. A 1997 IOM report set the lower

limit of serum 25(OH)D for sufficiency as 27.5 nmol/L, largely on the basis of the absence of rickets (or any other overt signs of vitamin D deficiency) when levels were above this value in the People's Republic of China, and to a lesser extent in the United States and Norway.<sup>3</sup> However, studies on children from around the world have not supported an absolute threshold level of 25(OH)D for the occurrence of rickets.<sup>5</sup> Although most of these reports have been from developing countries, 2 studies from the United States have documented children with rickets with serum levels of >30 nmol/L.<sup>6,7</sup> In the most recent US report of 43 cases of nutritional rickets, the mean serum level of 25(OH)D was 52.2 ± 28.7 nmol/L (range: 11.7–137.3 nmol/L) at the time of diagnosis. Thus, a threshold level of 25(OH)D above which rickets does not occur cannot be defined for a general population.

In adolescents, there is evidence for an inverse relationship between serum 25(OH)D and serum PTH,<sup>8,9</sup> with a study in males suggesting maximal suppression levels of PTH with a 25(OH)D concentration of 60 to 80 nmol/L, as has been observed in adults.<sup>9</sup> However, this inverse relationship has not been consistently observed in infants and younger children to date.<sup>5</sup> A recent study found modest correlations of PTH and 25(OH)D levels in infants and young children,<sup>10</sup> but other reports have not confirmed this result.<sup>5,11,12</sup> More observational data are needed, and this would be a worthy objective

for another National Health and Nutrition Examination Survey of children.

In adolescents, baseline levels of circulating 25(OH)D are associated with higher measurements of bone mineralization (bone mineral density/bone mineral content).<sup>5</sup> However, in infants and young children there is little evidence to support any level of 25(OH)D that is associated with higher radiologic measures of bone mineral density or bone mineral content. In fact, the few randomized, controlled trials performed to date have found no consistent relationship.<sup>5,11</sup>

Perhaps we are naive in thinking that any single, absolute serum concentration of 25(OH)D can be identified that defines vitamin D sufficiency or deficiency in all individuals or populations of children. Many genetic, dietary, and environmental factors are involved in vitamin D, calcium, and bone metabolism. Environmental factors include skin pigmentation, sunshine exposure, sunscreen use, pollution, and season. Dietary factors include intake of dairy foods and the association of obesity with lower 25(OH)D levels. We have known for many years that genetic variations occur in the vitamin D receptors that interact with DNA in the cell nucleus to bring about gene transcription, and genetic polymorphisms occur that seem to be related to determinants of bone mass and osteoporosis in adults.<sup>13</sup> Another factor is the genetic variation in vitamin D-binding protein, which binds to and transports vitamin D to target tissues to maintain calcium homeostasis<sup>14</sup> and affects an

individual's response to variations in 25(OH)D intakes.<sup>15,16</sup> Furthermore, children have actively growing bones, and their needs for calcium and vitamin D differ from those of adults. The relative importance of serum PTH which interacts with both osteoclasts and osteoblasts during bone turnover and new bone formation has not been determined in children. What are normal PTH levels in normally growing active children, and are they the same in all genotypes? Is the 25(OH)D concentration that maximally suppresses the level of PTH the same as it is in adults? Is it the same for all children? This seems very unlikely. Our knowledge base makes the recommendation for vitamin D intakes and using 25(OH)D to define the sufficiency state problematic in children. The American Academy of Pediatrics recommendations for vitamin D intakes of 400 IU with a 25(OH)D threshold for vitamin D sufficiency of 50 nmol/L are largely based on studies in non-Hispanic white infants.<sup>4</sup> As noted in the article by Mansbach et al, as well as other reports, it is probable that appropriate vitamin D intakes and corresponding serum 25(OH)D levels to define deficiency are not the same across all ethnic groups. However, there is a long history of the safety of this dose in children, and this dose not only effectively prevents rickets but will also treat it.<sup>4</sup> Furthermore, 400 IU of vitamin D will maintain serum levels of 25(OH)D at >50 nmol/L in infants and children. The new IOM committee report on adequate intakes of vitamin D (expected to be published in the spring of 2010) is eagerly awaited.

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