Prevalence of Vitamin D Deficiency Among Healthy Infants and Toddlers

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Objectives: To determine the prevalence of vitamin D deficiency and to examine whether 25-hydroxyvitamin D (25OHD) concentration varies as a function of skin pigmentation, season, sun exposure, breastfeeding, and vitamin D supplementation.

Design: Cross-sectional sample.

Setting: Urban primary care clinic.

Participants: Healthy infants and toddlers (N=380) who were seen for a routine health visit.

Outcome Measures: Primary outcomes were serum 25OHD and parathyroid hormone levels; secondary measures included data on sun exposure, nutrition, skin pigmentation, and parental health habits. Wrist and knee radiographs were obtained for vitamin D–deficient participants.

Results: The prevalence of vitamin D deficiency (≤20 ng/mL) was 12.1% (44 of 365 participants), and 146 participants (40.0%) had levels below an accepted optimal threshold (≤30 ng/mL). The prevalence did not vary between infants and toddlers or by skin pigmentation. There was an inverse correlation between serum 25OHD and parathyroid hormone levels (infants: r = −0.27, P < .001; toddlers: r = −0.20, P = .02). In multivariable models, breastfeeding without supplementation among infants and lower milk intake among toddlers were significant predictors of vitamin D deficiency. In vitamin D–deficient participants, 3 participants (7.5%) exhibited rachitic changes on radiographs, whereas 13 (32.5%) had evidence of demineralization.

Conclusions: Suboptimal vitamin D status is common among otherwise healthy young children. Predictors of vitamin D status vary in infants vs toddlers, information that is important to consider in the care of these young patients. One-third of vitamin D–deficient participants exhibited demineralization, highlighting the deleterious skeletal effects of this condition.


There has been concern raised about a resurgence of vitamin D deficiency and rickets among infants and children, with reports emerging in the United States from Alaska, Iowa, Nevada, California, North Carolina, Texas, and mother-infant pairs in Boston, among others. The prevalence of vitamin D deficiency in young children also appears to be high in other countries, including England, Greece, and Canada. One study from China found a 65.3% prevalence of vitamin D deficiency among 12- to 24-month-olds, but few cases (3.7%) of radiographic or clinical rickets were noted. Previous studies suggest risk factors to be dark skin pigmentation and breastfeeding without supplementation. To date, reports have focused primarily on young infants compared with toddlers.

Thus, there appears to be less information available regarding variables that predispose young children to vitamin D deficiency as they wean to fortified milk and solid foods.

For editorial comment see page 583

In 2004, another study reported a high prevalence of vitamin D deficiency among otherwise healthy teenagers who were seen for primary care. In the current study, we sought to determine the prevalence of vitamin D deficiency and radiographic rickets among young children seen at an urban primary care clinic. The primary objective was to test the hypothesis that vitamin D deficiency (25-hydroxyvitamin D [25OHD] level, ≤20 ng/mL) would convert to nanomoles per liter, multiply by...
We studied 380 primary care patients (age range, 8-24 months) who were seen for physical examinations between October 17, 2005, and June 15, 2007, at the Children’s Hospital Boston Primary Care Center and were undergoing a routine blood draw. The center is hospital based and provides well-child and acute care for 12,000 children annually, approximately 80% of whom live within the adjacent urban community. The population is primarily African American and Latino, and approximately 25% of parents are immigrants from diverse regions. The poverty rate for the communities served is 22% to 27%, compared with 20% for the city of Boston. Exclusion criteria included presence of a chronic disease and use of medications known to affect vitamin D metabolism during the previous 3 months. Parents or guardians provided written informed consent at study enrollment. The Committee on Clinical Investigation, Children’s Hospital Boston, approved the protocol.

CLINICAL AND ANTHROPOMETRIC DATA

Data were collected at the clinic visit, including age, sex, height, weight, nutritional intake, daily sun exposure, and pertinent findings (eg, genu varum) from the physical examination. Skin color and sensitivity were evaluated by a research assistant (L.S. or A.L.W.) using established methods. The skin pigmentation scale ranged from 1 (heavily pigmented, eg, black) to 4 (lightly pigmented, eg, white). The skin sensitivity scale ranged from 1 (burns easily) to 6 (never burns).

LABORATORY MEASUREMENTS

One blood sample (15 mL) was obtained for each participant. Blood tests were performed in the hospital laboratory or sent to ARUP Laboratories (Salt Lake City, Utah). Serum 25OHD levels were determined at ARUP Laboratories using a chemiluminescent assay (LIAISON; DiaSorin Inc, Stillwater, Minnesota). Serum calcium, phosphorus, magnesium, and alkaline phosphatase levels were measured locally using an end point assay in a multichannel analyzer (Roche Diagnostics, Indianapolis, Indiana). Intact PTH was measured by a 2-site chemiluminescence immunoassay (Nichols Institute, San Clemente, California). Samples were analyzed in multiple assays. Interassay coefficients of variation were 5.4% to 7.0% for PTH, 8.6% to 10.0% for 25OHD, 0.7% for alkaline phosphatase, and 1.3% to 2.2% for the cations.

DEFINITIONS

The patients were divided into 3 diagnostic categories according to serum 25OHD levels, as rounded to the nearest integer: vitamin D deficiency (≤20 ng/mL), severe vitamin D deficiency (≤8 ng/mL), and suboptimal vitamin D status (≤30 ng/mL). The definition of vitamin D deficiency was based on growing consensus among experts that a 25OHD level of 20 ng/mL or less is the appropriate diagnostic threshold for deficiency. This threshold represents the low end of the reference range provided by the manufacturer of the assay. There is agreement among many skeletal health experts that 30 ng/mL represents an optimal level for 25OHD or a threshold of adequate concentration. This is supported by the fact that serum 25OHD level has been shown to be inversely correlated with PTH level at concentrations of 30 to 40 ng/mL. We decided a priori that a 5% prevalence of vitamin D deficiency would be clinically significant. The definition of severe vitamin D deficiency was based on the sensitivity of the 25OHD assay (7 ng/mL).

RADIOGRAPHIC EVALUATION

Participants found to have vitamin D deficiency underwent frontal bilateral wrist and knee computed radiography. Soft copies of radiographs were reviewed for rachitic changes on a single high-resolution monitor by 2 pediatric radiologists (P.K.K. and J.P.-R.), each working from a unique randomized list of participants. The interrater correlation coefficient was calculated for the Thacher R), each working from a unique randomized list of participants. The interrater correlation coefficient was calculated for the Thacher

STATISTICAL ANALYSIS

We used the Fisher exact test to compare the prevalence of vitamin D deficiency between infants and toddlers and to identify binary or polytomous variables associated with vitamin D deficiency among the patient group. To identify continuous variables associated with vitamin D deficiency, we used simple logistic regression with deficiency as the dichotomous dependent variable. To identify binary or polytomous variables associated with 25OHD level, we used the t test or 1-way analysis of variance (Fisher F test). To identify continuous variables associated with 25OHD level, we used simple linear regression.

We constructed a multiple logistic regression model for vitamin D deficiency and a multiple linear regression model for 25OHD concentration using all predictors of interest, whether or not the simple association was significant. We tested for con-
The prevalence of vitamin D deficiency (reported spending at least a half hour outdoors daily, but consumption of fortified milk. In addition, 290 (76.3%) reported vitamin use and 262 (68.9%) reported at least occasional mental assistance. Ninety-three (24.5%) reported multicommunity. A total of 254 (66.8%) reported receiving govern-

were Asian, and 10 (2.6%) were of another race or ethnicity. Of 380 infants, 377 (99.2%) were accompanied to the clinic visit by their mother (mean [SD] age, 28 [7] years). Of 380 infants, 377 (99.2%) were accompanied to the clinic visit by their mother (mean [SD] age, 28 [7] years).

Forty-six adults (12.1%) were white, 233 (61.3%) were African American, 110 (28.9%) were Latino, 18 (4.7%) had hypophosphatemia, and 4 (1.1%) had normophosphatemia. Elevated PTH levels were seen in 5 (1.4%)

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had levels below an accepted optimal threshold (Table 1). Cation concentrations were within the refer-

Among hypothesized predictors of 25OHD level, we found a marked effect for breastfeeding without supplementation in infants (Figure). In toddlers, 25OHD level increased 2.9 ng/mL per cup per day of milk consumption (95% confidence interval [CI], 1.4-4.4; P < .001) (Figure). In infants, sunny season was paradoxically associated with a lower 25OHD level (mean [SE], 31.1 [1.1] ng/mL from April to September vs 37.8 [1.1] ng/mL from October to March; P < .001).

VARIABLES ASSOCIATED WITH DEFICIENCY OR 25OHD LEVEL

For infants and toddlers, there was a modest, but signifi-
cant, inverse correlation between serum 25OHD and PTH levels (infants: r = −0.27, P < .001; toddlers: r = −0.20, P = .02). There were no significant differences in hormone levels or the strength of the correlation between the variables in infants vs toddlers.

RESULTS

CLINICAL CHARACTERISTICS

The final sample included 380 subjects (Table 1). Bio-

chemical measurements were available for 365 (Table 2). Among toddlers, mean intake of milk exceeded that of juice (Table 1). Cation concentrations were within the reference range for 354 infants and toddlers; 1 participant (0.2%) had hypocalcemia, 1 (1.4%) had hypercalcemia, 1 (0.2%)

had hypophosphatemia, and 4 (1.1%) had hypermagne-

sia. Elevated PTH levels were seen in 5 (1.4%).

DESCRIPTIVE CHARACTERISTICS OF CAREGIVERS

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Variables potentially associated with vitamin D deficiency were examined one at a time by Fisher exact test or simple logistic regression (Table 3). The prevalence of deficiency did not vary by sex, season, time spent outdoors, sunscreen use, sun sensitivity, or skin pigmentation. Breastfeeding without supplementation was strongly associated with vitamin D deficiency among infants, with a more than 10-fold increase in risk relative to infants who were exclusively bottle-fed (Table 3). Among toddlers, milk consumption significantly decreased odds of deficiency (odds ratio [OR], 0.51; 95% CI, 0.34-0.76; \( P < .001 \)), whereas juice consumption had the opposite effect (OR, 1.31; 95% CI, 1.02-1.69; \( P = .03 \)). There was no significant simple association between body mass index (calculated as weight in kilograms divided by height in meters squared) and vitamin D deficiency in either infants (OR, 0.84 per kg/m²; 95% CI, 0.62-1.13; \( P = .25 \)) or toddlers (OR, 1.05 per kg/m²; 95% CI, 0.77-1.42; \( P = .76 \)). In the toddler group, there was no significant association between fortified cereal intake and vitamin D deficiency (OR, 1.27 per cup per day; 95% CI, 0.62-2.60; \( P = .51 \)).

### Table 2. Laboratory Findings

<table>
<thead>
<tr>
<th>Level</th>
<th>Mean (SD)</th>
<th>Range</th>
<th>Infants ( a )</th>
<th>Toddlers ( a )</th>
<th>Infant Mean (SD) – Toddler Mean (SD)</th>
<th>( P ) Value ( b )</th>
</tr>
</thead>
<tbody>
<tr>
<td>25OHD, ng/mL</td>
<td>34.3 (12.3)</td>
<td>[7-72]</td>
<td>35.2 (15.2)</td>
<td>[7-96]</td>
<td>-0.8 (1.5)</td>
<td>.59</td>
</tr>
<tr>
<td>PTH, pg/mL</td>
<td>30.3 (37.0)</td>
<td>[5-508]</td>
<td>29.6 (30.9)</td>
<td>[4-334]</td>
<td>0.7 (3.8)</td>
<td>.85</td>
</tr>
<tr>
<td>Alkaline phosphatase, U/L</td>
<td>313 (270)</td>
<td>[106-2987]</td>
<td>352 (446)</td>
<td>[100-4293]</td>
<td>-39 (38)</td>
<td>.37</td>
</tr>
<tr>
<td>Calcium, mg/dL</td>
<td>10.51 (0.43)</td>
<td>[7.0-11.9]</td>
<td>10.39 (0.36)</td>
<td>[9.6-11.3]</td>
<td>0.12 (0.04)</td>
<td>.005</td>
</tr>
<tr>
<td>Magnesium, mEq/L</td>
<td>1.95 (0.16)</td>
<td>[1.5-2.5]</td>
<td>1.88 (0.16)</td>
<td>[1.6-2.2]</td>
<td>0.15 (0.05)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Phosphorus, mg/dL</td>
<td>5.87 (0.51)</td>
<td>[3.7-7.0]</td>
<td>5.69 (0.70)</td>
<td>[2.5-7.2]</td>
<td>0.18 (0.06)</td>
<td>.01</td>
</tr>
</tbody>
</table>

Abbreviations: 25OHD, 25-hydroxyvitamin D; PTH, parathyroid hormone. SI conversion factors: To convert alkaline phosphatase to microkatal per liter, multiply by 0.0167; calcium to millimoles per liter, multiply by 0.25; magnesium to millimoles per liter, multiply by 0.50; 25OHD to nanomoles per liter, multiply by 2.496; PTH to nanograms per liter, multiply by 0.1053; and phosphorus to millimoles per liter, multiply by 0.323.

\( a \) Sample size varied between 238 and 242 for infants and 125 and 127 for toddlers.

\( b \) \( P \) value for equal distribution in infants and toddlers by \( t \) test (not assuming equal variance); confirmed by Wilcoxon rank sum test.

**Figure.** Nutritional factors associated with serum levels of 25-hydroxyvitamin D (25OHD) in 247 infants at their 9-month visit to a primary care clinic (A) and 133 toddlers at their 18-month visit (B). Bars indicate mean and standard error of the mean. D Suppl indicates vitamin D supplementation. To convert 25OHD to nanomoles per liter, multiply by 2.496.

### INDEPENDENT PREDICTORS OF DEFICIENCY OR 25OHD LEVEL

Multiple logistic regression models, evaluating predictors of vitamin D deficiency with adjustment for other predictors, are summarized in Table 4. Among infants, breastfeeding without supplementation markedly increased the odds of vitamin D deficiency compared with infants who were exclusively bottle-fed. Among toddlers, milk consumption significantly decreased odds of deficiency, whereas body mass index showed an opposite, marginally significant effect. In the adjusted analysis, juice consumption showed no effect on vitamin D deficiency in toddlers.

These results were corroborated by multiple linear regression models for 25OHD level. Breastfeeding without supplementation in infants was associated with a significantly lower level of 25OHD (mean [SD], 16.7 [3.4] ng/mL vs 36.3 [9.9] ng/mL in infants who were exclusively bottle-fed; \( P < .001 \)). In toddlers, milk consumption (3.1-ng/mL increase in 25OHD level per cup of milk...
per day; 95% CI, 1.5-4.8; \( P < .001 \) and body mass index (~2.7-ng/mL decrease in 25OHD level per kilogram per meters squared; 95% confidence interval, ~4.5 to ~0.8; \( P = .005 \)) were significantly associated with 25OHD level.

In infants, sunny season was paradoxically associated with lower 25OHD levels (mean [SD], 31.6[1.1] ng/mL from April to September vs 37.8[1.1] ng/mL from October to March; \( P < .001 \)).

**RADIOGRAPHIC ASSESSMENTS**

Of the 44 participants who had vitamin D deficiency, 40 (90.9%) returned to undergo bilateral wrist and knee radiography. Using the Thacher system,27 3 (7.5%; 0.8% of the total sample) exhibited rachitic changes. One child had visible genu varum on physical examination and a total knee-wrist score of 2. Comparing results from the 2 radiologists, the interrater correlation coefficient for the total knee-wrist score was 0.69. Using the demineralization scale, 13 of 40 (32.5%; 3.5% of the total sample) had evidence of demineralization (range of scores, 1-3 on a 5-point scale). All participants with rachitic changes also exhibited demineralization. The interrater correlation coefficient for this second assessment scale was 0.42.

**COMMENT**

We found a relatively high prevalence of vitamin D deficiency among otherwise healthy infants and toddlers in a convenience sample from an urban clinic. A striking 40% had serum 25OHD levels below a threshold that is becoming increasingly accepted as ideal for bone health and protection conferred against malignancy, infection, and other forms of disease.\(^{22-24}\) Among children found to be vitamin D deficient, a few exhibited rachitic changes radiographically, but one-third had evidence of demineralization. Only 1 child had signs of rickets on physical examination. Thus, these infants and toddlers had a subclinical deficiency that could make detection of this issue particularly problematic in routine clinical practice, as a child's vitamin D status is not typically evaluated as part of routine care. Among infants, breastfeeding with-
Interestingly, strong significant trends were seen despite the fact that exclusive breastfeeding was strikingly low among study participants. The current recommendation of the American Academy of Pediatrics and the Institute of Medicine is to provide 200 IU of vitamin D daily to most infants, children, and adolescents, although some have questioned whether this dosage recommendation is adequate. In this study, only 2% of breastfed infants were receiving vitamin D supplementation. All Massachusetts Medicaid-based insurance plans cover multivitamins containing 200 IU of vitamin D, although supplemental vitamins are not available through the Special Supplemental Nutrition Program for Women, Infants, and Children. Thus, lack of supplementation may have been related to barriers to access or lack of awareness. Furthermore, the fact that some infants were vitamin D deficient despite reported supplementation raises questions about the current dosage recommendation and overall compliance. These issues will need to be addressed in future studies that include a larger subset of breastfed infants and more rigorous measures of compliance. Nonetheless, these findings endorse recommendations for health care providers and parents to ensure that breastfed infants receive daily vitamin D supplementation for the duration of breastfeeding.

The current study is strengthened by the fact that radiographic assessments, another biomarker of vitamin D status, were obtained in a subset of patients, in addition to biochemical measurements. Previous studies have commonly been case series of infants with known rickets. Demineralization was detected radiographically in one third of our vitamin D–deficient participants. Although most deficiencies were subclinical, radiographic data suggest that many children exhibited deleterious effects. One group has advocated that physicians obtain a 25OHD measurement and wrist radiographs as a screening measure for high-risk children, with consideration given to the possibility of multiple risk factors being present in a given child. Examples include a breastfed infant with a low
serum 25OHD level who lives at a high latitude or an overweight African American toddler from the same northern city. Another approach would be to obtain radiographs for those with evidence of longstanding vitamin D deficiency (eg, low 25OHD level with secondary hyperparathyroidism and/or physical manifestations of rickets). The child in this study with both physical and radiographic evidence of rickets exhibited this biochemical profile, including an undetectable serum 25OHD level and a markedly elevated PTH level. Because rickets can cause significant morbidity, radiographic evaluation, in addition to biochemical screening, would be an appropriate consideration in the most at-risk child.

Among the toddlers studied, there was a significant inverse relationship noted between body mass index and 25OHD level in multivariable models. This association was noted in our previous study of adolescents\textsuperscript{35-37} and in previous studies of adults.\textsuperscript{35-37} In simple logistic regression models, only juice and milk consumption were significant predictors of vitamin D deficiency, suggesting that confounding existed between body mass index and juice consumption. One study has suggested that vitamin D deficiency in adults who are obese is caused by decreased bioavailability, because of deposition of this fat-soluble vitamin in adipose tissue.\textsuperscript{35} The current data suggest that an elevated body mass index is a risk factor for vitamin D deficiency. Although there is no consensus regarding the appropriateness of routine vitamin D screening for overweight patients, daily vitamin D supplementation, as for all children, would be warranted. Higher supplementation doses may be needed in this circumstance, but longitudinal studies examining the relationship between specific doses of vitamin D supplementation and both vitamin D levels and other health outcomes are needed to answer that question.

These findings must be considered in light of acknowledged limitations. The study was cross-sectional; therefore, causality cannot be inferred. The study sample was enriched with subgroups known to be at higher risk for vitamin D deficiency, including African American and Latino children. Interestingly, however, we did not see the expected association of vitamin D deficiency with dark skin pigmentation. The strikingly low prevalence of breastfed infants in the sample also limits the generalizability of these results. Nonetheless, we observed a strong, significant association between breastfeeding and vitamin D deficiency, especially in the absence of vitamin D supplementation, that deserves attention. The fact that we used an urban convenience sample may also limit the generalizability of these findings. We obtained information on weekly outdoor activities, but this measure may have provided only indirect information about sun exposure, and we found no association between this variable and 25OHD level. We also did not ask parents about clothing and swaddling practices, information that would have been especially informative because we noted an unexpected significant trend of low 25OHD levels during sunny months. Although we asked whether parents and their children were receiving vitamin D supplementation, more specific information on the actual quantity of vitamin D received and compliance would assist in determining whether noncompliance affected our results. Finally, information on nutrition and health habits for children and caretakers was obtained by self-report, which has inherent limitations.

In summary, these data add to accumulating evidence that vitamin D deficiency, a preventable health problem, is common among infants and toddlers, across ethnicity and season. A relationship was noted between the risk of vitamin D deficiency and lack of supplementation among breastfed infants and among toddlers with a higher body mass index. Among toddlers, there was a protective effect seen between milk consumption and lower risk of deficiency. These data underscore the fact that all breastfed infants should receive vitamin D supplementation for the duration of breastfeeding. However, further studies are needed to determine whether a 200 IU daily dose will provide adequate supplementation. Given the potential benefits of vitamin D on bone\textsuperscript{38} and other tissues,\textsuperscript{2,5,44} and growing data supporting its immunomodulatory and antiproliferative effects,\textsuperscript{39-44} the current findings support recommendations advocating for vitamin D supplementation for all young children.\textsuperscript{26-30,44} These findings also raise the important question of whether some children, such as those with established risk factors for vitamin D deficiency, should receive periodic measurements of 25OHD levels.

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Author Contributions: Dr Gordon had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Gordon, Kleinman, and Cox. Acquisition of data: Gordon, Sinclair, Williams, Kleinman, Perez-Rossello, and Cox. Analysis and interpretation of data: Gordon, Feldman, Sinclair, Kleinman, and Perez-Rossello. Drafting of the manuscript: Gordon, Feldman, Williams, and Kleinman. Critical revision of the manuscript for important intellectual content: Gordon, Feldman, Sinclair, Williams, Kleinman, Perez-Rossello, and Cox. Statistical analysis: Feldman. Obtained funding: Gordon. Administrative, technical, or material support: Sinclair, Williams, and Cox. Study supervision: Gordon and Cox.

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