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Determinants of 25-Hydroxyvitamin D Concentrations in Infants and Toddlers

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Abstract

Background—Resurgence of rickets and recognition of excessive prevalence of hypovitaminosis D among all age groups in the western hemisphere have refocused attention on vitamin D nutrition.

Objective—To examine the prevalence of hypovitaminosis D [25-hydroxyvitamin D [25(OH)D] <30ng/mL] and characterize the determinants of 25(OH)D concentrations in 8- to 24-month-old healthy infants and toddlers living in Pittsburgh, Pennsylvania.

Methods—Serum 25(OH)D concentrations were measured and dietary intake of vitamin D, mode of feeding, summertime sun exposure characteristics, and skin color (sun-reactive skin type and melanin index) were assessed.

Results—A total of 111 healthy 8- to 24-month-old children (mean age [$\pm$ SD] 14.4 [$\pm$ 3.5] months; male, 51%; black, 67%) were studied. Serum 25(OH)D concentration was <30 ng/mL in 16% (n=18) of the children. Median (interquartile) 25(OH)D concentration was lower in children who were 13 months vs. <13 months of age [35 (31, 40.5) vs. 40 (35.8, 44.3) ng/mL, $p=0.013$]; with sun-reactive skin type IV and V vs. I, II, and III [36 (31, 41) vs. 44 (36.5, 48.5) ng/mL,

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Conflicts of Interest

Authors have no relevant financial relationships or conflicts of interest to disclose.

Author Contributions

All authors contributed to the conception, design, and critical revision of the manuscript. This project was HM's University of Pittsburgh School of Medicine Medical Student Scholarly Project. HM was responsible for study design, data acquisition and interpretation, and manuscript drafting and its revisions. KR served as a mentor, and was responsible for conception, planning, funding, and supervision of the study, and drafting of the manuscript and critical revisions of the manuscript. LW was responsible for data analysis, interpretation and manuscript drafting. FO was responsible for data acquisition. AN analyzed the vitamin D and calcium focused food frequency questionnaires and critically reviewed and revised the manuscript. SLG also served as a mentor and was responsible for study design, concept, funding, and drafting and critical revisions of the manuscript.

$p=0.001$]; and examined during fall/winter vs. spring/summer [35.5 (32.5, 38.5) vs. 39 (32.5, 44) ng/mL, $p=0.05$]. Age and skin type were significant independent predictors of 25(OH)D.

Conclusions—Concentrations of 25(OH)D tend to be lower in infants and toddlers during fall/winter, and in children who are older (≥13 months vs. <13 months of age) and have darker skin tone. Benefits of enhancement of 25(OH)D concentrations during fall/winter and in children with higher sun-reactive skin type need further exploration.

Keywords

infants; skin pigmentation; sun exposure toddlers; vitamin D

Introduction

Vitamin D is essential for calcium homeostasis and bone health.(1) However, through its non-calcemic actions it has been recognized to play a protective role against a wide variety of diseases including diabetes, psoriasis, cancer, infections, autoimmune and psychiatric disease.(2–12)

Resurgence of rickets and recognition of excessive prevalence of hypovitaminosis D among all age groups in the western hemisphere has refocused attention on vitamin D nutrition.(13–23) Vitamin D deficiency is a common nutrient deficiency in infants and children, second only to iron deficiency.(24) Risk factors for vitamin D deficiency in infants include exclusive breastfeeding without vitamin D supplementation and prematurity.(17, 23, 25–27) Also, dark skin tone, sunscreen use, clothing norms, and living in higher latitudes can compromise vitamin D photoproduction in the skin and cause hypovitaminosis D.(28) The majority of our vitamin D supply comes from casual sunlight exposure.(1) Our other sources are diet and supplements; however, very few foods are naturally rich in vitamin D.(5) In 2008, the American Academy of Pediatrics (AAP) recommended supplementation of 400 IU of vitamin D daily in all breastfed infants and infants and toddlers consuming less than 1 liter of vitamin D-fortified formula or milk per day.(29) One recent study suggests that most US infants are not consuming vitamin D in accordance to AAP guidelines.(5)

In the context of the revised AAP guidelines for vitamin D intake and recent Institute of Medicine (IOM) dietary reference intake report for vitamin D (30), we examined the prevalence of hypovitaminosis D [25-hydroxyvitamin D [25(OH)D] <30ng/mL] and characterized the determinants of 25(OH)D concentrations in 8- to 24-month-old healthy infants and toddlers. We also explored the prevailing norms regarding vitamin D nutrition among physicians and parents.

Materials and Methods

Participants

We studied 111 healthy 8- to 24- month-old infants and toddlers residing in and around Pittsburgh, PA (latitude 40.4° N). Subjects were recruited between September, 2011 and June, 2012 when presenting to the Primary Care Center of Children's Hospital of Pittsburgh of UPMC (University of Pittsburgh Medical Center) for routine blood draws. Children with

conditions that could affect vitamin D metabolism or absorption were excluded. The study was open to subjects of all races and ethnicities, and racial-categorization was specified by the parents.

Study Design

Cross-sectional assessments of 25(OH)D concentration, anthropometric data, and degree of skin melanin, as well as parent reported sun-reactive skin type, dietary intake of vitamin D, and sunlight exposure were completed in the enrolled children. Parental written informed consent was obtained prior to study participation. The protocol was approved by the University of Pittsburgh Institutional Review Board.

Study Measurements

Vitamin D and Calcium Intake—We assessed participants' dietary intake of vitamin D and calcium using a short calcium- and vitamin D-focused food frequency questionnaire. The questionnaire assessed the consumption of multivitamins, cod liver oil, calcium and vitamin D supplements; average daily intake of breast milk, infant and toddler formula, cow's milk, other dairy foods, vitamin D-fortified orange juice, and jarred baby food; weekly intake of breakfast bars and cereal; and monthly intake of fish and dried mushrooms. The questionnaire was analyzed using the Food Processor SQL, version 10.4.0 (2008), ESHA Research, Salem, OR, to quantify the reported daily dietary intake of vitamin D (IU) and calcium (mg).

Sunlight exposure—We ascertained the following summertime sunlight exposure behaviors of the participants using a questionnaire: (i) duration of daily sun exposure (< or 2 hours), (ii) parts of body typically exposed to sunlight (face, hands, arms, legs), (iii) sunscreen use (frequency, brand, sun protection factor [SPF]), and (iv) history of travel to sunny location.

Skin color data—We measured participants' melanin index from the forehead, back of the hand, and upper inner arm with a hand-held dermatospectrophotometer (DSM II Colormeter, Cortex Technology, Hadsund, Denmark) and assessed their parent-reported Fitzpatrick sun-reactive skin type.(31, 32) Light-skinned individuals were characterized as skin type I (easy burn and no tan), II (easy burn and slight tan), or III (burn and then tan) and dark-skinned individuals were classified as skin type IV (no burn and good tan) or V (never burn and markedly tan).

25-hydroxyvitamin D—We measured the serum 25(OH)D concentrations at the UPMC Clinical Chemistry laboratory using a liquid chromatography – tandem mass spectrometry (LC-MS/MS) system from Waters Corporation, (Milford, MA, USA). LC-MS/MS assay quantifies the contributions of 25(OH)D₂ and 25(OH)D₃ to estimate the total 25(OH)D. The methodology is equally specific in distinguishing both 25(OH)D₂ and 25(OH)D₃ and is calibrated using reagents from ChromSystems (Gräfelfing, Germany). The assay is checked with controls (UTAK Laboratories, Inc., Valencia, CA, USA) and National Institutes of Standards and Technology (NIST) standard reference material 972 (NIST, Gaithersburg, MD, USA).

Statistical Analysis

Descriptive statistics are presented as medians with interquartile ranges for continuous variables and frequencies with percentages for categorical variables. Mann-Whitney U or Kruskal-Wallis tests were used to compare 25(OH)D levels between comparison groups; Chi-Square or Fisher's Exact test were used to test the association between two categorical variables; and Pearson r was used for testing the correlation between two continuous variables. Multivariable linear regression was performed to examine the independent association between the significant independent variables (age group, subjective skin type, and season of enrollment) with the 25(OH)D concentrations using the stepwise selection method. Participants enrolled during April through September and October through March were classified as being studied during spring/summer and fall/winter, respectively. P value 0.05 was considered statistically significant. All analyses were performed with SPSS 20.

Results

Demographic Data (Table 1)

We studied 111 children with cross-sectional measurements of 25(OH)D concentrations. Studied participants' characteristics are shown in table 1.

Dietary Data

Mode of feeding (breast vs. infant formula), median daily intake of milk/milk products and breakfast cereal, daily dietary intake of vitamin D and calcium, and proportion of children meeting the current dietary AAP and IOM guidelines for these nutrients are shown in table 2. Reported intake of vitamin D-fortified orange juice was not thought to be accurate and thus the data were removed from dietary vitamin D and calcium analysis. Six infants were exclusively breastfed, and only one of them was receiving vitamin D supplementation. The reported daily intake of vitamin D was higher than the AAP recommended amount (400 IU/day) in 62% of the subjects. Of those not meeting the AAP guidelines for vitamin D intake (n=41), only 10% (n=4) were receiving vitamin D supplements. Overall vitamin D supplementation rates were low; the difference in the rates of supplementation between African American (AA) vs. non-African American subjects was not statistically significant. Parental reasons for not providing vitamin D supplements in children not meeting the AAP guidelines for vitamin D intake (n=37) were: (i) did not receive a recommendation from a health care provider, (ii) did not know that it was useful, (iii) thought milk/formula provided enough vitamin D, (iv) child disliked supplement, and (v) forgot to give supplement.

Sunlight Exposure and Sunscreen Use (Table 2)

There was no significant difference in time spent in the sun between AA and non-AA subjects. Non-AA subjects were significantly more likely to use sunscreen than AA subjects ($p<0.001$). Non-AA subjects were also significantly more likely to travel to a sunny location ($p=0.015$).

Skin Color Assessment

Melanin index at the forehead, upper inner arm, and dorsum of hand were positively associated with each other, respectively ($r=0.93, 0.9, 0.92$; $p<0.001$). Melanin index was also positively associated with the sun-reactive skin type (light-skinned vs. dark-skinned, $p=0.001$).

Vitamin D Status

Participants' vitamin D statuses were classified as follows: vitamin D-deficient [25(OH)D <20 ng/mL] – 3 (3%); insufficient [25(OH)D 20 to <30 ng/mL] – 15 (14%); and sufficient [25(OH)D ≥ 30 ng/mL] – 93 (84%).

Predictors of 25-hydroxyvitamin D concentrations (Table 3)

Median 25(OH)D concentration was lower in subjects ≥ 13 vs. <13 months [35 (31, 40.5) vs. 40 (35.8, 44.3) ng/mL, $p=0.013$]; enrolled in the fall/winter vs. spring/summer [35.5 (32.5, 38.5) vs. 39 (32.5, 44) ng/mL, $p=0.05$]; and with dark skin vs. light skin (skin type IV–V vs. I–III) [36 (31, 41) vs. 44 (36.5, 48.5) ng/mL, $p=0.001$] (figure 1). There was no significant difference in 25(OH)D concentration in males vs. females, AA vs. non-AA, or in relation to mode of feeding (breast vs. infant formula), sun exposure ($<$ vs. ≥ 2 hours per day), or sunscreen use. Serum 25(OH)D concentration was not significantly associated with daily calcium or vitamin D intake, cups of milk/milk equivalent per day, cups of breakfast cereal per day, or skin melanin index. On univariate analysis, age group, season, and sun-reactive skin type (subjective skin pigmentation) were significantly associated with 25(OH)D concentration. In a multivariable regression model, age group (β -coefficient [95% CI]; -4 [$-7, -0.8$], $p=0.014$) and skin type (-7 [$-11, -3$], $p=0.001$) were independent predictors of 25(OH)D concentration.

Discussion

In the present study, 16% of infants and toddlers had hypovitaminosis D. We found the risk of hypovitaminosis D was higher among toddlers, children with higher parent-reported sun-reactive skin type, and in those examined during fall/winter. Although only a few children were breastfed, the majority of them were not receiving the AAP recommended vitamin D supplementation.

The incidence of hypovitaminosis D in our cohort was significantly less than the incidences reported in several other recent studies of infants and young children. (14–18, 20, 21, 23, 26, 33) One reason for this could be the small proportion of our sample that was <12 months of age (7%), the age until which breastfeeding is recommended and thus an age group especially susceptible to vitamin D deficiency if not receiving supplementation. In our sample, children ≥ 13 months of age had lower 25(OH)D levels than infants <13 months of age, perhaps due to switching from supplemented infant formulas to table foods and independent feeding, as is expected around 1 year of age. (34)

Our finding that season of recruitment was significantly associated with 25(OH)D, with higher levels occurring during the spring/summer months, is in concordance with data from

previous studies.(15, 16, 21, 23, 33) Higher levels during the spring/summer correlate with a greater opportunity for sun exposure during these months. Children with a higher reported sun-reactive type had significantly lower 25(OH)D than children with a lower sun-reactive skin type, as melanin acts as a natural barrier to vitamin D synthesis in the skin.(15, 21, 35). Sun-reactive skin type is a surrogate measure of skin melanin content and dark-skinned individuals have higher sun-reactive skin type (Type IV or V) and light-skinned individuals have lower sun-reactive skin type (I or II or III). Contrary to our finding, a similar study in Boston by Gordon *et al.* examining the prevalence of hypovitaminosis D in infants and toddlers did not find any association between vitamin D status and skin pigmentation assessed by sun-reactive pigmentary response, though a different assessment tool was used. (17) Decreased sun exposure and sunscreen use are both established risk factors for vitamin D deficiency.(26, 36) However, these factors were not predictors of 25(OH)D concentration in our study or the study conducted by Gordon *et al.*(17) This may be due to the relatively small proportion of non-AA subjects in this study, as seasonal variation and sun exposure have greater effects on those with less skin pigmentation.(37)

This study is unique in that we examined skin color in two different ways: subjectively with the Fitzpatrick sun-reactive skin type and objectively by measuring melanin index with DSM II dermatospectrophotometer. Sun-reactive skin type was strongly correlated with melanization index at all three anatomic sites. Despite its correlation with subjective skin type, melanin index was not associated with 25(OH)D. Validity of either of these 2 measures in the context of vitamin D research need further exploration.

Though study subjects who consumed more dietary vitamin D and calcium were more likely to have sufficient serum 25(OH)D concentrations, the association was not statistically significant (figure 2). This could be due to the fact that the number of subjects with hypovitaminosis D was small, and thus there may have been inadequate power to show a difference between the two groups. Additionally, it has been shown before that a positive relationship between dietary vitamin D and 25(OH)D was only seen in white subjects during the winter months.(37) Thus, lack of association between dietary vitamin D and 25(OH)D concentration could be explained by the potential dominance of causal sunlight exposure in the determination of vitamin D status. In addition, mode of feeding in infants (breast vs. infant formula) was not associated with 25(OH)D concentration, but given the small number of breastfeeding infants in the study, this finding is difficult to interpret. Neither the amount of milk/alternate milk products nor fortified breakfast cereal consumed per day was associated with 25(OH)D concentration. This differs from several studies describing a strong relationship between milk intake and 25(OH)D concentration.(17, 21, 23, 38)

The majority of our subjects, approximately two thirds, met the AAP specified threshold level of dietary intake of vitamin D (400 IU/day). However, among subjects who failed to meet that threshold, only 10% were receiving vitamin D supplements. Parental reasons for not providing vitamin D supplementation were: not receiving a recommendation from their pediatric provider; child's dislike of the supplement, or the assumption that their child's diet was adequate. Interestingly, cost was not cited as a prohibitive factor. Several studies have discussed the inadequacy of both physicians in prescribing, and parents in administering supplements and this study reaffirms this information.(5, 14) One contributing factor to the

small percentage of children receiving vitamin D supplementation may be lack of knowledge of the roles of vitamin D and indications for supplementation among caregivers. In a focus-group study of school teachers, office workers, and elderly in Australia, general knowledge regarding the roles of vitamin D, the issues surrounding vitamin D deficiency, and the behaviors that contribute to vitamin D status was very poor.(39) Public health and targeted educational strategies for improving parents' understanding of vitamin D, its roles in health, and indications for supplementation would be helpful to encourage supplementation when appropriate. Research exploring successful techniques for improving adherence to vitamin D supplementation is also needed. One study demonstrated no significant difference in vitamin D supplementation with parental implementation intentions, but did suggest the possibility of reminder techniques such as providing handouts or refrigerator magnets to encourage adherence.(40)

We acknowledge that our study has several limitations including small sample size and a small proportion of children who were breastfed or younger in age (<12 months old). The skewed nature of subject age is relevant because recommended feeding practices shift significantly at 1 year of age, when cow's milk is introduced and breastfeeding and/or supplemented infant formula are weaned. The generalizability of this study may be limited by the fact that the vast majority of subjects were urban, African American children. However, both of these characteristics are established risk factors for vitamin D deficiency. Lastly, self-report of nutrition/health habits has inherent limitations. The short vitamin D food frequency questionnaire was modified from a previously validated questionnaire designed for pre-adolescents to include infant formulas and foods typically consumed by infants and toddlers. (41)

The compellation of roles of vitamin D beyond bone health continues to expand. Inadequate vitamin D nutrition in childhood has been indicated not only in acute disease but in the development of chronic disease in the future, making pediatric vitamin D status even more relevant.(4) Notably, 25(OH)D concentrations necessary for non-calcemic benefits of vitamin D remain unknown, and may be even higher than that required for endocrine function, the value upon which the current IOM-recommended dietary allowances are based. (2, 3, 30) Current recommendations for vitamin D supplementation may not be adequate for those at increased risk of hypovitaminosis D (i.e. those with increased skin pigmentation or residents of higher latitudes during fall/winter).

Conclusions

In conclusion, hypovitaminosis D was not uncommon in the urban Pittsburgh infant and toddler population. Toddlers appear to be at a greater risk for hypovitaminosis D than infants, possibly due to the switch from vitamin D-fortified formula to table foods. Season and darker skin color (indicated by higher sun-reactive skin type) were significant predictors of 25(OH)D concentration in infants and toddlers. Benefits of enhancement of 25(OH)D concentrations during fall/winter and in infants with higher sun-reactive skin type need further exploration.

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Figure 1. Distribution of 25(OH)D concentrations in infants vs. toddlers (shown in upper panel) and light- vs. dark-skinned subjects (shown in lower panel).

Figure 2.
Dietary vitamin D intake in relation to 25(OH)D concentration.

Table 1

Study subject characteristics

Characteristic	All participants (n=111) Median (25 th %ile, 75 th %ile) or n (%)
Age (months)	13 (12, 17)
<i>Infants</i> (<13 months)	50 (45)
<i>Toddlers</i> (13 months)	61 (55)
Height (cm)	76.5 (73.7, 80)
Weight (kg)	10.3 (9.6, 11.5)
Gender	
<i>Male</i>	56 (51)
<i>Female</i>	55 (49)
Race	
<i>African American</i>	74 (67)
<i>Non-African American^a</i>	37 (33)
Season of enrollment	
<i>Spring/Summer</i> (April-Sept.) ^b	77 (69)
<i>Fall/Winter</i> (Oct.-March)	34 (31)
Subjective skin type (Fitzpatrick)	
<i>Light-skinned</i> (I–III)	21 (20)
<i>Dark-skinned</i> (IV–V)	86 (80)
Melanization index	62.7 (52.2, 70.8)
25(OH)D (ng/mL)	37 (33, 42)

^a 13 Caucasian, 2 Asian American, 22 children reported as being more than one race

^b Excludes June and July when no recruitment occurred

Table 2

Dietary and sun behavior practices

Characteristic	All participants (n=111) Median (25 th %ile, 75 th %ile) or n (%)
Feeding method	
<i>Breast, no vitamin D supplement</i>	5 (4.5)
<i>Breast, vitamin D supplement</i>	1 (0.9)
<i>Infant formula and breast</i>	1 (0.9)
<i>Infant formula only</i>	28 (25)
<i>Milk and alternate milk product*</i>	109 (98.2)
<i>Fortified cereal</i>	76 (68.5)
<i>Milk and alternate milk product* intake (cups/day)</i>	3 (2, 5)
<i>Fortified cereal intake (cups/day)</i>	0.9 (0.6, 2)
<i>Dietary calcium (mg/day)</i>	1412.1 (1015.6, 1863.7)
<i>Dietary vitamin D (IU/day)</i>	487.8 (322.7, 686.8)
<i>Subjects meeting AAP recommendation for dietary vitamin D intake (400IU/day)^a</i>	68(62.4)
<i>Infants meeting IOM AI for calcium intake (260mg/day)^b</i>	48 (98)
<i>Toddlers meeting IOM estimated average requirement for calcium (500mg/day)^c</i>	57 (95)
<i>Toddlers meeting IOM RDA for calcium intake (700 mg/day)^c</i>	55 (91.7)
Vitamin D supplementation	
<i>Yes</i>	6 (5)
<i>No</i>	105 (95)
Sun exposure	
<i>2 hours/day</i>	58 (55)
<i>>2 hours/day</i>	48 (45)
Uses sunscreen	
<i>Yes</i>	36 (32)
<i>No</i>	75 (68)

* Cow's milk, soy milk, Lactaid®, chocolate milk, Ensure®, PediaSure®, Carnation® Instant Breakfast, toddler formula

^a N= 109 subjects,

^b N=49 infants,

^c N= 60 toddlers

Table 3

Predictors of 25(OH) Vitamin D levels

Univariate Analysis <i>Variable</i>	P value
Age group (<13 months vs. 13 months)	0.013 *
Male vs. Female	0.293
African American vs. Non-African American	0.575
Breastfed vs. non-breastfed	0.707
Vitamin D intake (IU/day)	0.792
Season of recruitment (Spring/Summer vs. Fall/Winter)	0.050 *
Sunscreen use vs. no sunscreen use	0.666
Hours in sun (2 hours vs. >2 hours per day)	0.333
Sun-reactive skin type (I–III vs. IV–V)	0.001 *
Melanization Index	
Divided at median	0.706
Divided into tertiles	0.729
Analyzed as a continuous variable	0.367
Multivariate Analysis <i>Variable</i>	β-coefficient [95% CI]
Age group (<13 months vs. 13 months)	−4 [−7, −0.8], p=0.014 *
Sun-reactive skin type (I–III vs. IV–V)	−7 [−11, −3], p=0.001 *
Season of recruitment (Spring/Summer vs. Fall/Winter)	−3 [−1, 0.9], p=0.141

* P value 0.05 was considered statistically significant