Vitamin D requirements during lactation: high-dose maternal supplementation as therapy to prevent hypovitaminosis D for both the mother and the nursing infant\textsuperscript{1–4}

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ABSTRACT

Scientific data pertaining to vitamin D supplementation during lactation are scarce. The daily recommended intake for vitamin D during lactation has been arbitrarily set at 400 IU/d (10 \( \mu \)g/d). This recommendation is irrelevant with respect to maintaining the nutritional vitamin D status of mothers and nursing infants, especially among darkly pigmented individuals. Our objective was to examine the effect of high-dose maternal vitamin D\textsubscript{2} supplementation on the nutritional vitamin D status of mothers and nursing infants. Fully lactating women \((n = 18)\) were enrolled at 1 mo after birth to 1 of 2 treatment arms, ie, 1600 IU vitamin D\textsubscript{2} and 400 IU vitamin D\textsubscript{3} (prenatal vitamin) or 3600 IU vitamin D\textsubscript{2} and 400 IU vitamin D\textsubscript{3}, for a 3-mo study period. High-dose (1600 or 3600 IU/d) vitamin D\textsubscript{2} supplementation for a period of 3 mo safely increased circulating 25-hydroxyvitamin D [25(OH)D] concentrations for both groups. The antirachitic activity of milk from mothers receiving 2000 IU/d vitamin D increased by 34.2 IU/L, on average, whereas the activity in the 4000 IU/d group increased by 94.2 IU/L. Nursing infant circulating 25(OH)D concentrations reflected maternal intake and the amount contained in the milk. With unlimited sun exposure, an intake of 400 IU/d vitamin D would not sustain circulating 25(OH)D concentrations and thus would supply only limited amounts of vitamin D to nursing infants in breast milk. A maternal intake of 2000 IU/d vitamin D would elevate circulating 25(OH)D concentrations for both mothers and nursing infants, albeit with limited capacity, especially with respect to nursing infants. A maternal intake of 4000 IU/d could achieve substantial progress toward improving both maternal and neonatal nutritional vitamin D status. 

KEY WORDS Vitamin D, human milk, lactation, 25-hydroxyvitamin D

INTRODUCTION

Thirty-five years ago, nutritional rickets was thought to be disappearing (1). Many reports since then, however, indicated that this is not the case (2–5). Most cases reported in the past decade involved darkly pigmented infants who had been breast-fed exclusively. Hypovitaminosis D among breast-fed infants also is a severe problem in sunlight-rich environments such as the Middle East (6). This hypovitaminosis D occurs because sun exposure is extremely limited for both mothers and infants and dietary supplementation at the current daily recommended intake (DRI) of 400 IU is inconsequential.

In the past, human milk was thought to be an adequate source of antirachitic activity for neonates and growing infants. Even before the discovery of vitamin D, McCollum et al (7) and Park (8) stated that rickets was attributable to the lack of sunlight and a dietary factor X. They observed that factor X was found in “good breast milk” and cod liver oil and that, although rickets did develop among breast-fed children, it was rarely as severe as that among artificially fed infants. Those investigators did not know that the source of vitamin D in the mother’s milk was the mother’s exposure to the sun, which cutaneously generated large amounts of vitamin D. Early attempts to quantify the antirachitic potential in human milk were crude and yielded little information.

In the 1980s, the antirachitic activity of human milk was defined with sensitive assays to be 20–70 IU/L (9, 10). Furthermore, almost all of the activity was attributable to vitamin D and 25-hydroxyvitamin D [25(OH)D]. Those studies also demonstrated that dietary maternal vitamin D supplementation and ultraviolet light exposure increased the vitamin D content of human milk (11, 12). Specker et al (13) determined that the antirachitic content of human milk was lower among African American than white mothers. If a lactating mother has limited sun exposure and/or limited vitamin D intake (such as occurs with the current 400 IU DRI), then the vitamin D content of her milk is poor, especially if she has darker pigmentation.

Studies among normal adults demonstrated that oral vitamin D intakes of up to 10 000 IU/d for a period of 5 mo are safe, with no evidence of toxicity (14, 15). We hypothesized that vitamin D intakes up to 10 times the DRI among lactating women not only would elevate maternal nutritional vitamin D status to safe healthy levels but also would supply the nursing infants, through milk transfer, with adequate vitamin D to prevent hypovitaminosis D. The hypothesis was investigated in this study.

METHODS

Subjects

Fully lactating mothers within 1 month after birth were eligible for inclusion in the study if they planned to continue full breastfeeding for the next 3 mo. The subjects were randomly divided

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into 2 groups. Exclusion criteria included preexisting type 1 or type 2 diabetes mellitus, hypertension, parathyroid disease, and uncontrolled thyroid disease.

Study design

This was a randomized controlled trial of lactating mothers. Each subject served as her own control; the vitamin D status at 1 mo was compared with values at 3 additional time points. Mothers were randomized to 1 of 2 vitamin D supplementation regimens. Groups 1 and 2 received 1600 and 3600 IU/d vitamin D2, respectively, in an oral suspension. Both groups received additional multivitamin capsules containing 400 IU vitamin D3 and were instructed to take them daily. Subjects also were instructed to limit sun exposure (for mother and infant). Furthermore, mothers were instructed to limit formula intake by the infant.

Blood, urine, and milk samples were obtained from the mothers at months 1, 2, 3, and 4 of lactation. Infant blood was collected at months 1 and 4 (beginning and end of the study). Maternal serum was monitored for total calcium, vitamin D2, vitamin D3, 25(OH)D2, and 25(OH)D3 concentrations. Infant serum was monitored for vitamin D2, vitamin D3, 25(OH)D2, 25(OH)D3, calcium, and phosphorus concentrations. Mother’s urine was monitored for vitamin D antirachitic activity values with reference data from biological activity assays (12).

Vitamin D2 was used as a specific tracking agent for maternal dosing because the contribution of vitamin D2 from other sources would be unlikely or minimal. By using vitamin D2 in this study, we could precisely define the increase in and/or transfer of vitamin D compounds from the mother to her infant without confounding factors such as dietary intake and sun exposure.

Laboratory measurements

Total blood calcium and urinary calcium and creatinine concentrations were determined in the General Clinical Research Center at the Medical University of South Carolina. Circulating and milk concentrations of vitamin D2, vitamin D3, 25(OH)D2, and 25(OH)D3 were determined with HPLC and radioimmunoassay techniques, as described previously (16–18).

Statistical methods

Groups 1 and 2 were compared at entrance into the study, for determination of potential differences with respect to sociodemographic and baseline clinical characteristics. The main variables of interest were maternal and infant 25(OH)D2, 25(OH)D3, and total circulating 25(OH)D concentrations and milk antirachitic activity with time (in months). Data were analyzed with SAS software (SAS Institute, Cary, NC), with Student’s t test, chi-square test, and one-way analysis of variance methods.

RESULTS

A convenience sample of 64 lactating women was enrolled, of whom 29 had stopped breast-feeding by the first visit. Thirty-five women came for the first visit; of those, 18 women (13 white women and 5 African American women), 9 in each group, continued breast-feeding and completed the 3-mo study period. There were 3 African American women in group 1 (2000 IU/d vitamin D) and 2 in group 2 (4000 IU/d vitamin D). The groups did not differ according to age, ethnicity profile, insurance status, number of pregnancies, pregnancy interval, infant sex, birth weight, or gestational age (Table 1).

Dietary intakes of vitamin D up to 10 times the DRI for lactating women for a period of 3 mo resulted in no adverse events associated with vitamin D. Serum calcium concentrations all remained in the normal range, and no observation of hypercalcemia was noted (data not shown). This is not surprising, because circulating vitamin D and 25(OH)D concentrations never exceeded normal levels (Figures 1 and 2). There was a significant interaction of vitamin D concentrations with time in both groups. Although subjects in group 1 (who received 1600 IU/d vitamin D2 and 400 IU/d vitamin D3) did not exhibit increases in circulating concentrations of vitamin D3 from baseline to 3 mo (from 1.0 ± 0.4 to 1.2 ± 1.2 ng/mL; mean ± SEM; P > 0.7), they did exhibit increases in circulating vitamin D2 concentrations (from <0.5 to 2.2 ± 0.7 ng/mL; P < 0.01). In this group, circulating 25(OH)D concentrations actually decreased during this time period (from 27.2 ± 3.2 to 18.7 ± 1.7 ng/mL; P < 0.02), whereas circulating 25(OH)D2 concentrations increased (from 0.4 ± 0.1 to 17.4 ± 1.0 ng/mL; P < 0.0001). The total circulating 25(OH)D concentrations in this patient group increased from 27.6 ± 3.3 to 36.1 ± 2.3 ng/mL (P < 0.05).

Compared with group 1, higher concentrations of total circulating 25(OH)D were observed for subjects in group 2 (who received 3600 IU/d vitamin D2 and 400 IU/d vitamin D3). In group 2, circulating vitamin D2 concentrations increased slightly (from 0.9 ± 0.4 to 2.8 ± 1.0 ng/mL; P < 0.06), whereas circulating vitamin D3 concentrations increased from 0.6 ± 0.1 to 6.6 ± 2.4 ng/mL (P < 0.04) (Figure 2). As for group 1, circulating 25(OH)D3 concentrations decreased (from 32.0 ± 2.5 to 18.9 ± 3.0 ng/mL; P < 0.0007), whereas 25(OH)D2 concentrations increased (from 1.8 ± 1.0 to 25.0 ± 2.5 ng/mL; P < 0.0001). Total circulating 25(OH)D concentrations increased from 32.9 ± 2.4 to 44.5 ± 3.9 ng/mL (P < 0.04).

Comparisons between groups 1 and 2 revealed no significant differences at baseline for any of the vitamin D indices for mothers and infants. Although 25(OH)D3 concentrations did not differ between the groups during the study period, there were significant differences between the 2 groups with respect to 25(OH)2D concentrations (P < 0.01), with higher concentrations in the 4000 IU group.

The changes in milk antirachitic activity observed during the study period are presented in Figure 3. Subjects who received a total of 2000 IU/d vitamin D for 3 mo exhibited increases in milk activity from 35.5 ± 3.5 to 69.7 ± 3.0 IU/L (P < 0.0001), whereas the increase observed in the 4000 IU/d group was from 40.4 ± 3.7 to 134.6 ± 48.3 IU/L (P < 0.0001). This elevation was attributable to increases in milk concentrations of both vitamin D2 and 25(OH)D2 (data not shown).

The increases in circulating 25(OH)D2, 25(OH)D3, and total 25(OH)D concentrations for the infants at baseline and after 3 mo of nursing from mothers receiving 2000 or 4000 IU/d vitamin D are presented in Figures 4 and 5. As with the mothers, there was a significant interaction of vitamin D concentrations with time for both infant groups. Infants of mothers ingesting 2000 IU/d exhibited increases in circulating 25(OH)D2 and 25(OH)D3 concentrations, from 7.9 ± 1.1 to 21.9 ± 4.7 ng/mL (P < 0.02) and from <0.5 to 6.0 ± 1.0 ng/mL (P < 0.0007),
respectively. Total circulating 25(OH)D concentrations increased from 7.9 ± 1.1 to 27.8 ± 3.9 ng/mL (P < 0.02).

Infants of mothers receiving 4000 IU/d exhibited increases in circulating 25(OH)D₃ and 25(OH)D₂ concentrations from 12.7 ± 3.4 to 18.8 ± 4.1 ng/mL (P < 0.2, NS) and from 0.8 ± 0.4 to 12.0 ± 1.4 ng/mL (P < 0.0001), respectively. Total circulating 25(OH)D concentrations increased from 13.4 ± 3.3 to 30.8 ± 5.0 ng/mL (P < 0.01). Compared with infants in the 2000 IU group, infants in the 4000 IU group exhibited higher 25(OH)D₂ concentrations at the end of the study period (P < 0.003).

### DISCUSSION

Rickets was nearly eradicated in the United States with vitamin D fortification of milk in the 1930s (1). However, recent reports showing a resurgence of rickets in infancy focused renewed attention on the vitamin D status of infants and their mothers (2–5). The reported cases occurred almost exclusively among African American infants who were breastfed (2, 3). Why has this been the case? There are 2 major reasons for this affliction. The first is sun paranoia, which is constantly reinforced by

![Image of graph](https://example.com/image.png)

**FIGURE 1.** Circulating vitamin D concentrations (mean ± SEM) over time among lactating mothers receiving 1600 IU/d vitamin D₂ and 400 IU/d vitamin D₃ (n = 9).
the medical profession and the media. We are told to avoid the sun totally or to wear sunscreen. In fact, the American Academy of Pediatrics (19) recommends that newborn infants receive no sun exposure during the first 6 mo of life. By following these recommendations, we disrupt an important endocrine pathway that has evolved over millions of years, ie, the solar-driven production of vitamin D3 in our skin. This lack of solar exposure is especially acute among darkly pigmented individuals, because

FIGURE 2. Circulating vitamin D concentrations (mean ± SEM) over time among lactating mothers receiving 3600 IU/d vitamin D2 and 400 IU/d vitamin D3 (n = 9).

FIGURE 3. Milk antirachitic activity (mean ± SEM) over time among lactating mothers receiving 2000 or 4000 IU/d vitamin D (n = 18). Whole-milk samples were evaluated for vitamin D antirachitic activity through measurement of vitamin D2, vitamin D3, 25(OH)D2, and 25(OH)D3 concentrations in the milk; values were converted to biological activity with reference data from biological activity assays.
they require many times the exposure to generate vitamin D₃ in the epidermis (20).

The second reason for hypovitaminosis D among breastfed infants is the inadequate DRI value for vitamin D among lactating women. In fact, the DRI of 200–400 IU/d, which was arbitrarily set, is inadequate for the adult population in general (21). The DRI for vitamin D clearly needs to be revised. For example, white individuals exposed (total body) to 10–15 min of peak sunlight in the summer endogenously produce and release into the circulation ~20 000 IU of vitamin D₃ (22, 23). It is ironic that the 1989 US Nutrition Guidelines state that 2000 IU/d vitamin D may be harmful (24). This guideline is in error and is based on

**FIGURE 4.** Circulating 25(OH)D concentrations (mean ± SEM) over time among nursing infants of mothers receiving 1600 IU/d vitamin D₂ and 400 IU/d vitamin D₃ (n = 9).

**FIGURE 5.** Circulating 25(OH)D concentrations (mean ± SEM) over time among nursing infants of mothers receiving 3600 IU/d vitamin D₂ and 400 IU/d vitamin D₃ (n = 8).
mothers received 4000 IU/d vitamin D for a period of 3 mo, and noted that the DRI of 400 IU/d vitamin D for adults. It is important to note that, while the intake of 400 IU/d vitamin D elevates maternal 25(OH)D concentrations, but does not elevate the nutritional status of mothers or nursing infants. This is indicated by the occurrence of hypovitaminosis D and rickets among breastfed infants (2–4). Maternal intake of 2000 IU/d vitamin D elevates maternal 25(OH)D concentrations, but the amount passed on to nursing infants through the milk is still inadequate to elevate the infants’ circulating 25(OH)D concentrations satisfactorily. Maternal intake of 4000 IU/d increases maternal circulating concentrations to a degree that enough vitamin D enters the milk to produce significant effects on the infants’ circulating 25(OH)D concentrations. We conclude that the current DRI of 400 IU/d vitamin D for lactating mothers is irrelevant to the vitamin D nutritional status of mothers and nursing infants. Maternal vitamin D intakes of ≥4000 IU/d appear to be safe and to provide sufficient vitamin D to ensure adequate nutritional vitamin D status for both mothers and nursing infants. Additional detailed studies will be required to determine the optimal vitamin D supplementation regimen for lactating women.

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