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Original Article

Effect of combined maternal and infant vitamin D supplementation on vitamin D status of exclusively breastfed infants

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Abstract

Severe vitamin D deficiency in mothers and their breastfed infants is a significant health problem in the Middle East. Supplementation of the breastfed infant alone with the recommended dose of vitamin D may be insufficient in high-risk population. We investigated the effect of combined maternal and infant vitamin D supplementation on vitamin D status of the breastfed infant. We examined also the effect of supplementation on vitamin D antirachitic activity of breast milk in a subset of mothers. Healthy breastfeeding mothers ($n = 90$) were randomly assigned to 2000 IU daily (group 1) or 60 000 IU monthly (group 2) of vitamin D_2, and all their infants ($n = 92$) received 400 IU daily of vitamin D_2 for 3 months. Most infants had vitamin D deficiency – 25-hydroxyvitamin D [25(OH)D] $\leq$ 37.5 nmol L^{-1} – at study entry. Serum 25(OH)D concentrations at 3 months increased significantly from baseline in infants of mothers in group 1 (13.9 $\pm$ 8.6 vs. 49.6 $\pm$ 18.5 nmol L^{-1}, $P < 0.0001$) and group 2 (13.7 $\pm$ 12.1 vs. 44.6 $\pm$ 15.0 nmol L^{-1}, $P < 0.0001$). Maternal and infant serum 25(OH)D concentrations correlated positively at baseline ($r = 0.36$, $P = 0.01$) and 3 months ($r = 0.46$, $P = 0.002$). Milk antirachitic activity increased from undetectable (<20 IU L^{-1}) to a median of 50.9 IU L^{-1}. In conclusion, combined maternal and infant vitamin D supplementation was associated with a threefold increase in infants' serum 25(OH)D concentrations and a 64% reduction in the prevalence of vitamin D deficiency without causing hypervitaminosis D.

Keywords: vitamin D deficiency, 25-hydroxyvitamin D, breastfeeding women, breastfed infants.

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Introduction

Vitamin D deficiency rickets is very common in the Middle East (Molla *et al.* 2000; Al-Jurayyan *et al.* 2002; Najada *et al.* 2004; Hatun *et al.* 2005; Dawodu *et al.* 2006) and is reported increasingly among minority groups in Western countries (Kreiter *et al.* 2000; Wharton & Bishop 2003). Most of the cases of rickets occur in exclusively breastfed infants who lack sunshine exposure and are not supplemented with vitamin D (Kreiter *et al.* 2000; Molla *et al.* 2000; Wharton & Bishop 2003; Dawodu *et al.* 2006). Hence, it is recommended that exclusively breastfed infants receive daily 400 IU of vitamin D supplementation when sunshine exposure is low or maternal vitamin D status is judged to be inadequate (Holick 1998; Pettifor 2005). In previous studies we, and others, have shown that severe vitamin D deficiency in mothers and their breastfed infants is a significant health problem in the Middle East and parts of Asia because of sunshine deprivation and inadequate vitamin D intake (Atiq *et al.* 1998; Dawodu *et al.* 2003; Hatun *et al.* 2005). Many Middle Eastern and South Asian women maintain a very conservative style of dress that covers most of the body when outdoors, which limits sunlight exposure. In addition, vitamin D fortification of food is not mandatory in the United Arab Emirates (UAE) and in many other Middle Eastern countries, and the current dietary intake of vitamin D is relatively low (Saadi *et al.* 2006). In the UAE, 60–75% of infants are exclusively breastfed for 3–6 months (Department of Preventive Medicine 1992) and vitamin D supplementation is not routinely practiced (Dawodu *et al.* 2003). Direct vitamin D supplementation of the breastfed infant will address prevention of vitamin D deficiency in the infant but not in the mother.

We have recently shown that supplementation of vitamin D deficient breastfeeding women in the UAE with 2000 IU once daily or 60 000 IU once monthly of vitamin D_2 is moderately effective in improving their vitamin D status, without inducing toxicity (Saadi *et al.* 2007). The rationale for studying daily vs. monthly supplementation was that monthly dosing could improve compliance as our clinical experience indicates a low compliance with daily vitamin D supplement usage among women in the UAE (Dawodu *et al.* 1997). As part of that study, we investigated the effect of combining maternal supplementation and supplementation of her exclusively breastfed infant with recommended daily 400 IU of vitamin D, on the vitamin D status of the infants. The rationale for this combined approach was that maternal supplementation alone with 2000 IU day^{-1} of vitamin D_2 did not fully optimize breast milk vitamin D content and the vitamin D status of exclusively breastfed infants in a recent US study (Hollis & Wagner 2004). In addition, baseline vitamin D status of un-supplemented exclusively breastfed infants in the UAE population (Dawodu *et al.* 2003) is half the level of the US study (Hollis & Wagner 2004), making it ethically difficult not to supplement all infants. We tested the hypothesis that, combining the recommended infant supplementation with high-dose maternal supplementation (2000 IU once daily or 60 000 IU once monthly) of vitamin D_2, could optimize vitamin D status and prevent vitamin D deficiency in infants without causing hypervitaminosis D in a population with high prevalence of severe vitamin D deficiency among breastfeeding women and their infants. We examined also the effect of high-dose vitamin D supplementation on milk vitamin D content in a subset of breastfeeding women. We studied vitamin D_2 rather than the more potent vitamin D_3 because the former is the only high-dose calciferol available in the UAE.

Methods

Subjects

The subjects were 90 healthy breastfeeding mothers (76 Arabs and 14 South Asians) and 92 infants (two mothers had twins). The mothers were recruited during the period of September 2005–February 2006 at the time of their first post-natal visit to the Maternal and Child Health Clinic in Al Ain (latitude 24°N and longitude 55°E) in the UAE for participation in a study of high-dose maternal vitamin D supplementation (Saadi *et al.* 2007). The Maternal and Child Health Clinic promotes and supports exclusive breastfeeding for the first 6 months of life. Education

and clinical demonstration are provided by a lactation consultant and lactation nurse to all mothers attending the clinic. The women delivered at term and agreed to continue exclusive breastfeeding for the next 3 months. In addition, mothers were contacted by phone twice weekly by the lactation nurse to encourage continuing exclusive breastfeeding. None of the participants had a history of diseases known to affect vitamin D status. The study was approved by the Ethics Committee of the Al Ain Medical District and the mothers received both oral and written information and gave informed consent.

Study design

The details of the design and the biochemical investigations in the high-dose maternal vitamin D supplementation study have been described in our previous publication (Saadi *et al.* 2007). Briefly, the breastfeeding women were randomly allocated to either oral 2000 IU once daily or 60 000 IU once monthly of vitamin D_2 in an open (not blinded) randomized parallel group clinical trial. Vitamin D_2 was used in the study because it was the only high-dose vitamin D supplement available in the UAE at the time. The 2000 IU vitamin D_2 capsule was provided in a tamper resistant container of 90 capsules for the study period. Pill count at each visit was used to monitor compliance. The 60 000 IU D_2 tablet was ingested under direct observation at each monthly clinic visit. All women received oral supplementation of 600 mg day^{-1} of elemental calcium. Breastfed infants of mothers in either group of the supplementation strategy were given 400 IU of vitamin D_2 for 3 months. Vitamin D_2 solution was purchased from Schwarz Pharma, Inc. (Milwaukee, WI, USA) and 6 mL (8000 IU mL^{-1}) were provided in a brown dropper bottle to each participating mother. Mothers were instructed to administer 2 drops day^{-1} (400 IU) during the study period. The bottles were marked at approximately three equal parts and mothers were requested to bring the bottles with them at each follow-up visit to monitor compliance. Infant feeding status was assessed by maternal reporting. Maternal data collected included age, parity, weight, educational status (1 to 5, with 1 as illiterate and 5 as college level) and outdoor sunlight exposure per day during the 6 weeks preceding the baseline visit. Infant's age and weight were recorded. Blood samples were collected from the mothers at entry and at monthly visits just before the administration of the next monthly vitamin D_2 dose and after 3 months of vitamin D supplementation, and from the infants at entry and after 3 months of vitamin D supplementation. The serum was separated and frozen at –80° centigrade until analysed. Breast milk samples were obtained from a subset of 12 mothers at baseline and eight mothers after 3 months of vitamin D supplementation. The major end points of the study were the change from baseline in serum 25-hydroxyvitamin D [25(OH)D] concentrations of infants and the proportion of infants without vitamin D deficiency at the end of the study.

Laboratory tests

Serum 25(OH)D concentrations were determined by radioimmunoassay (DiaSorin; Stillwater, MN, USA). The intrassay and interassay CVs were 8.3% and 3.2% respectively. As an internal quality control measure two reference controls provided by DiaSorin, low normal range and high-normal range, were assayed as unknowns in the same manner as patient samples. An aliquot from a full breast expression that is well mixed was kept frozen until transported on ice to Dr Hollis' research laboratory in South Carolina for estimation of milk vitamin D antirachitic activity (ARA). The measurement of milk vitamin D ARA was preformed as previously described (Hollis 1983).

Statistical analyses

We compared the effect of combining the two regimens of maternal high-dose vitamin D supplementation with recommended vitamin D supplementation for breastfed infants on the serum 25(OH)D concentration of infants after 3 months of supplementation. We examined also the efficacy of the combined maternal and infant vitamin D supplementation in preventing vitamin D deficiency in infants based on data from mother–infant pairs. For this study, vitamin D deficiency in an infant was defined as serum 25(OH)D

concentration ≤ 37.5 nmol L^{-1} based on recent physiologic studies and reports in infants and adults (Thomas *et al.* 1998; Gessner *et al.* 2003). Baseline milk vitamin D ARA was compared with post-supplementation ARA values. The data were analysed with SPSS statistical software (version 15; SPSS Inc, Chicago, IL, USA). The methods included paired *t*-test, chi-square test, Pearson's correlation coefficient, and two-way analysis of variance ANOVA (without interaction) to test the effect of vitamin D regimen as well as (loss to) follow-up on the various baseline and follow-up parameters. Paired binomial observations were analysed using McNemar test. *P*-values < 0.05 were considered significant.

Results

Baseline data

Of the 90 breastfeeding women, 45 were randomized to 2000 IU once daily (group 1) and 45 to 60 000 IU once monthly (group 2) groups. The baseline characteristics of the mothers and infants are summarized in Table 1. Forty-six per cent of breastfeeding women reported multivitamin intake and 27% reported supplemental calcium intake during pregnancy. Forty-four mothers (22 in group 1 and 22 in group 2), and 46 infants (22 in group 1 and 24 in group 2) completed the study. There were two pairs of twins in group 2. Reasons for not completing the study included pregnancy (one subject), diarrhoea in the breastfed infant (one subject), loss of exclusive breastfeeding status (one subject), leaving the country (three subjects) and no particular reason was given in the rest of subjects. There were no significant differences noted in the baseline characteristics between mothers (and infants) that completed the study and those who dropped out (Table 1). Similarly, there were no significant differences between daily and intermittent supplementation regimen groups except for a slightly higher mean serum 25(OH)D concentration in mothers in daily compared with monthly regimen group (27.3 ± 10.4 vs. 23.2 ± 10.7 nmol L^{-1}). Maternal and infant serum 25(OH)D concentrations correlated positively ($r = 0.36$, $P = 0.01$). Of the 92 infants, 87 (95%) were vitamin D deficient and the highest

Table 1. Baseline characteristics of mothers and infants by type of maternal vitamin D supplementation regimen and follow-up status

Characteristic	Subjects completing study		Subjects lost to follow-up		Total	
	Daily regimen	Monthly regimen	Daily regimen	Monthly regimen	Daily regimen	Monthly regimen
Mothers (*n*)	22	22	23	23	45	45
Age (year)*	28.1 ± 4.7	27.6 ± 6.5	30.3 ± 6.1	32.1 ± 6.2	29.2 ± 5.5	29.9 ± 6.7
Weight (kg)*	74.5 ± 11.7	71.3 ± 11.7	70.8 ± 11.5	68.7 ± 19.9	72.6 ± 11.6	70.1 ± 16.1
Parity†	3.0	2.0	3.0	3.0	3.0	2.5
Education†	5.0	4.0	4.0	4.5	4.5	5.0
Sunlight exposure (h day^{-1})*	0.3 ± 0.5	0.3 ± 0.6	0.5 ± 1.1	0.4 ± 0.7	0.4 ± 0.8	0.4 ± 0.6
Serum 25(OH)D (nmol L^{-1})*	29.2 ± 10.2	22.3 ± 10.0	27.3 ± 10.4	23.2 ± 10.7	27.3 ± 10.4	23.2 ± 10.7
Vitamin D deficient (%)‡	86 [19]	91 [20]	91 [21]	83 [19]	89 [40]	87 [39]
Infants (*n*)	22	24	23	23	45	47
Age (days)*	19.1 ± 25.4	20.6 ± 22.9	18.6 ± 19.9	24.2 ± 28.5	18.9 ± 22.5	22.4 ± 25.6
Weight (kg)*	3.7 ± 0.86	3.6 ± 0.86	3.8 ± 1.1	4.0 ± 1.5	3.7 ± 1.0	3.8 ± 1.2
Serum 25(OH)D (nmol L^{-1})*	13.9 ± 8.6	13.7 ± 12.1	12.4 ± 5.3	16.2 ± 9.6	13.1 ± 7.1	15.0 ± 10.9
Vitamin D deficient (%)‡	96 [21]	92 [22]	100 [23]	91 [21]	98 [44]	92 [43]

25(OH)D, 25-hydroxyvitamin D; Educational status (1–5), illiterate, primary, secondary, high school and college; *Mean ± SD; †Median. ‡*n* in brackets.

Table 2. Follow-up results of mother-infant pairs by type of maternal vitamin D supplementation regimen

Variable	Daily regimen	Monthly regimen	Total
Mothers (*n*)	22	22	44
Follow-up 25(OH)D (nmol L^{-1})*	41.7 ± 14.0	35.8 ± 9.9	38.7 ± 12.3
Increment in 25(OH)D (nmol L^{-1})*	12.5 ± 14.2	13.5 ± 10.6	13.0 ± 12.4
Vitamin D deficient (%)†	36 [8]	50 [11]	43 [19]
Infants (*n*)	22	24	46
Follow-up 25(OH)D (nmol L^{-1})*	49.6 ± 18.5	44.6 ± 15.0	47.0 ± 16.8
Increment in 25 (OH)D (nmol L^{-1})*	35.7 ± 20.2	30.9 ± 22.1	33.2 ± 21.1
Vitamin D deficient (%)†	23 [5]	38 [9]	30 [14]

25(OH)D, 25-hydroxyvitamin D; *Mean ± SD; †*n* in brackets.

serum 25(OH)D concentration was 54.5 nmol L^{-1}. Vitamin D ARA was undetectable (<20 IU/L) in the milk of the 12 mothers who donated milk.

Follow-up data

All mothers who were assigned daily vitamin D took more than two-thirds of the prescribed capsules. All infants received more than two-thirds of the prescribed vitamin D_2 drops. Serum 25(OH)D concentrations, the primary endpoint of the study, were the main biochemical data available in mother–infant pairs. Serum 25(OH)D concentrations increased significantly from baseline in the daily and monthly supplementation groups in both the mothers and their infants (Table 2). Compared with the baseline values, the mean increments in maternal (and infant) serum 25(OH)D concentrations at 3 months in the daily and monthly regimens were significant ($P < 0.0001$). The increments did not differ between the daily and monthly groups for both mothers ($P = 0.8$) and infants ($P = 0.4$; Table 2). Maternal and infant serum 25(OH)D concentrations correlated positively at 3 months ($r = 0.46$, $P = 0.002$). The highest serum 25(OH)D concentrations achieved after combined vitamin D supplementation was 83.4 nmol L^{-1} in one infant. Of the 46 infants, 14 (30%) were vitamin D deficient at 3 months compared with 43 (94%) at baseline ($P < 0.0001$, by McNemar test). Milk vitamin D ARA increased from undetectable (<20 IU L^{-1}) at baseline to a median of 50.9 IU L^{-1} (range 0–62.5) after 3 months of supplementation. Among the eight mothers who donated milk, the only one who had undetectable milk vitamin D ARA at 3 months was the only one who had very low serum 25(OH)D concentration (≤37.5 nmol L^{-1}) at the end of the study.

Discussion

Exclusively breastfeeding mothers and infants in this study had low baseline nutritional vitamin D status. This is probably a reflection of maternal and infant sunshine deprivation and inadequate vitamin D intake as discussed in previous other reports (Dawodu *et al.* 1998, 2003; Saadi *et al.* 2006, 2007). The data from this study confirm that vitamin D deficiency in mothers and their exclusively breastfed infants is a major public health issue in the UAE that warrants urgent preventive intervention.

We found that combined high-dose maternal vitamin D_2 supplementation (2000 IU once daily or 60 000 IU once monthly) and 400 IU once daily of vitamin D_2 supplementation for exclusively breastfed infants was associated with a significant improvement in vitamin D status of vitamin D deficient infants. In infants of mothers on the daily or monthly regimen, the mean serum 25(OH)D concentrations increased by threefold from baseline values and the serum 25(OH)D concentration correlated positively with maternal vitamin D status. There was a 64% reduction in the prevalence of vitamin D deficiency from 94% at baseline to 30% ($P < 0.0001$) after 3 months of combined maternal and infant vitamin D supplementation without causing hypervitaminosis D. These results support the hypothesis of the study. To our

knowledge, a supplementation strategy that may result in such a significant reduction in the prevalence of vitamin D deficiency among exclusively breastfed infants in a high-risk population has not been reported. We also demonstrated a modest increase in vitamin D content of milk from a small subset of the mothers evaluated. It is not possible to determine whether the increase in serum 25(OH)D concentrations of the breastfed infants in this study was due to the modest increase in vitamin D intake from mother's milk or from direct infant's vitamin D supplementation as there was no control group with infant supplementation alone.

The efficacy of maternal supplementation alone in the prevention of vitamin D deficiency in breastfed infants in high-risk population is not known. There were two previous smaller sample-sized studies (Ala-Houhala *et al.* 1986; Hollis & Wagner 2004) on improving vitamin D status of breastfed infants through high-dose maternal vitamin D supplementation alone. In a study of 17 breastfeeding women in Finland, maternal supplementation with 2000 IU of vitamin D_3 once daily for 15 weeks increased mean serum 25(OH)D concentrations of the infant from baseline value of 21.3 nmol L^{-1} to 63.0 nmol L^{-1} after supplementation, and was equivalent to supplementing the infant with 400 IU of vitamin D once daily (Ala-Houhala *et al.* 1986). In another study of 18 breastfeeding women in the USA, the authors found that maternal supplementation with 2000 IU of vitamin D_2 once daily for 3 months increased the infants' mean serum 25(OH)D concentration from a baseline of 19.8 ± 2.8 nmol L^{-1} to 69.5 ± 9.8 nmol L^{-1}, while 4000 IU once daily increased the infants' mean serum 25(OH)D concentration from 33.5 ± 8.3 nmol L^{-1} to 77.0 ± 12.5 nmol L^{-1} (Hollis & Wagner 2004). In the latter study, maternal supplementation with 2000 IU once daily increased the mean milk vitamin D ARA by 34 IU L^{-1} while 4000 IU once daily increased the mean milk ARA by 94 IU L^{-1}; and there was a direct relationship between the increments in milk vitamin D ARA and serum 25(OH)D concentration in the infant (Hollis & Wagner 2004). The mean serum 25(OH)D concentration of infants in this population with high prevalence of vitamin D deficiency was lower than that of the US study (47.0 ± 16.8 vs. 69.5 ± 9.8 nmol L^{-1}) despite infant supplementation. The data from this study highlight the importance of taking into consideration the baseline vitamin D status of the population in designing clinical trials aiming at prevention of vitamin D deficiency in breastfed infants. Additionally, the results of baseline vitamin D status of infants in this study and other data on effect of maternal vitamin D supplementation on milk vitamin D content (Hollis & Wagner 2004; Wagner *et al.* 2006) may be valuable in designing a clinical trial to investigate the efficacy of maternal supplementation alone in the prevention of vitamin D deficiency in mothers and their breastfed infants in high-risk population. It has been argued that if such a strategy is successful in ensuring vitamin D sufficiency for mother and her breastfed infant, it could provide important health benefits beyond bone health for both mothers and infants (Hollis & Wagner 2004; Dawodu & Wagner 2007). It would be more appropriate to use vitamin D_3 in future studies because vitamin D_3 is more effective than vitamin D_2 that was used in this study (Armas *et al.* 2004).

The limitations of our study include a lack of control group of infants on vitamin D supplementation alone and a small number of human milk samples for evaluation of vitamin D ARA. We also had two pairs of twins in one group of infants and their results are unlikely to be independent. Additionally, the dropout rates for mothers (and infants) were very high. This is unlikely to have affected our results since the baseline characteristics of the dropout subjects were not significantly different from those who completed the study. Our study did not evaluate seasonal changes in serum 25(OH)D concentrations. Our previous studies, however, show no significant seasonal variation in 25(OH)D concentrations between September and February in the UAE, where there is abundant sunshine year-round (Saadi *et al.* 2006). Finally, we did not measure serum or urine calcium in infants to assess vitamin D toxicity. The latter was extremely unlikely, however, given that the highest serum 25(OH)D concentration achieved was far below the toxic range.

In summary, we demonstrated that high-dose maternal vitamin D_2 supplementation combined with the recommended dose of vitamin D supplementation for exclusively breastfed infants, at least in a

population with high prevalence of vitamin D deficiency, may be effective in improving vitamin D status and achieving significant reduction in the prevalence of vitamin D deficiency without inducing hypervitaminosis D. This study provides also important preliminary baseline data as well as the first data on the effect of high-dose maternal vitamin D supplementation on the vitamin D ARA of the milk of vitamin D deficient lactating mothers.

Key messages

- Severe vitamin D deficiency is a significant health problem in exclusively breastfeeding mothers and their infants in Middle Eastern countries and the optimal strategy to prevent vitamin D deficiency in mother–infant dyad is unclear.
- This report focuses on the effect of combining recommended infant vitamin D supplementation and a high-dose maternal supplementation on the vitamin D status of exclusively breastfed infants in a population with high prevalence of mother–infant vitamin D deficiency.
- High-dose maternal vitamin D supplementation combined with the currently recommended infant supplementation was associated with a 64% reduction in the prevalence of vitamin D deficiency among exclusively breastfed infants.
- High-dose maternal vitamin D supplementation was associated with a significant increase in the milk vitamin D content without causing hypervitaminosis D.
- Trials of maternal supplementation alone to prevent vitamin D deficiency in exclusively breastfeeding mothers and their infants are indicated.

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Conflicts of interest

None declared.

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