No Severe Hypercalcemia with Daily Vitamin D₃ Supplementation of up to 30 µg during the First Year of Life

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Keywords

Hypercalcemia · Ionized calcium · Vitamin D · 25-Hydroxyvitamin D · Parathyroid hormone · Infancy · Calcium and phosphate metabolism

Abstract

Background: Vitamin D supplementation is widely recommended for infants, but the optimal dose remains unclear. High intake may result in hypercalcemia. **Methods:** We evaluated the incidence of hypercalcemia during the first year of life in a cohort of 987 healthy children who received 10 or 30 µg of vitamin D₃ supplementation daily. Ionized calcium (Ca-ion) was analyzed at 6 and 12 months, and serum 25-hydroxyvitamin D (25-OHD) and parathyroid hormone (PTH) concentration at 12 months. Severe hypercalcemia was defined as Ca-ion exceeding the reference limit (1.16–1.39 mmol/L) by 10%. **Results:** No severe hypercalcemia occurred. Mild hypercalcemia (1.40–1.52 mmol/L) was present at 6 months in 28% and at 12 months in 2% of infants. At 12 months, 25-OHD ranged between 23 and 241 nmol/L (median 97), and PTH was between undetectable and 104 pg/mL (median 24) and was below the reference range (11.5–78.4

pg/mL) in 11%. 25-OHD and Ca-ion correlated positively ($r = 0.149$), and 25-OHD was slightly higher in the 12 infants with mild hypercalcemia (median 97 vs. 110 nmol/L, $p = 0.046$). **Conclusions:** Vitamin D₃ supplementation of 10 or 30 µg did not cause severe hypercalcemia. Mild hypercalcemia was more prevalent at 6 months than at 12 months, and was associated weakly with 25-OHD at 12 months.

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Introduction

The association between vitamin D deficiency and rickets is well established [1]. However, sufficient serum 25-hydroxyvitamin D (25-OHD) concentration is still under debate: both 50 nmol/L [2] and 75 nmol/L [3] have been regarded as thresholds. Dietary intake of vitamin D is usually not sufficient in breastfed infants, and vitamin D supplementation is widely recommended across the globe [2–4]. Despite the recommendations, vitamin D deficiency is still common in infancy [5–8].

According to the Endocrine Society, 25-OHD concentrations ≤ 250 nmol/L are safe for children [9], whereas

concentrations >375 nmol/L are excessive [2]. The Institute of Medicine stated that 25-OHD concentrations >125 nmol/L might indicate excess intake, and the daily tolerable upper intake level of vitamin D from all sources is defined as 25 µg for infants under 6 months and as 38 µg for infants from 7 to 12 months [2]. Vitamin D toxicity is defined as 25-OHD >250 nmol/L with concurrent hypercalcemia, hypercalciuria, and suppressed parathyroid hormone (PTH) concentration [10].

Vitamin D toxicity is mostly caused by excess intake of oral supplements or excessive fortification of dairy products [11–15]. Published data are mostly based on single patient reports or small case series with remarkably high vitamin D doses. In infants, severe hypercalcemia has been reported after exposure to large oral vitamin D doses of up to 15,000 µg [16, 17]. Single cases of mild asymptomatic hypercalcemia have been described in children who received 1,400–4,000 IU vitamin D and had 25-OHD levels between 197 and 255 nmol/L [18]. On the other hand, mild hypercalcemia and hypercalciuria are not uncommon in healthy infants even without the presence of high 25-OHD concentrations [19]. Overall, data on hypervitaminosis D in infants are scarce.

We examined the incidence of hypercalcemia in a cohort of 987 infants receiving either the recommended (10 µg) or a 3-fold (30 µg) dose of daily supplemental vitamin D₃ during the first year of life.

Materials and Methods

Study Cohort

This randomized, controlled, double-blind vitamin D₃ intervention study comprised 987 healthy term (37–42 weeks of gestation) infants (495 boys, 492 girls) born at Kättilöopisto Maternity Hospital, Helsinki, Finland. Recruitment and the 2-year follow-up occurred between January 2013 and June 2016. The mothers were of Caucasian origin (>90% ethnic Finns) without regular medication, and pregnancies were uneventful and singleton. Infants with a small or large weight for gestational age (SD score <−2 or >+2), seizures, or need for early antibiotic treatment, nasal continuous positive airway pressure >24 h, extended phototherapy >72 h, nasogastric tube >24 h, or intravenous glucose infusion were excluded.

Infants were randomized to receive 5 drops of vitamin D₃ supplementation of either 10 or 30 µg per day from age 2 weeks to 2 years. The study preparation contained vitamin D₃ dissolved in medium-chain triglyceride oil (DeviSol Drops D₃[®]; Orion Pharmaceuticals, Espoo, Finland). Simultaneous use of other vitamin D supplements was not allowed.

Parents gave written informed consent before entering the study. The Research Ethics Committee of the Hospital District of Helsinki and Uusimaa approved the trial (ID 107/13/03/2012), and the study protocol was registered in ClinicalTrials.com (NCT01723852).

Data Collection and Safety Monitoring

Data for the present study were obtained during the first 12 months and were analyzed blinded without knowing to which intervention group the participants belonged. We included in this study those 762 of the 987 infants who met the inclusion criteria and had complete data available on ionized calcium (Ca-ion), 25-OHD, and PTH concentrations from the 6- and 12-month visits.

Baseline demographics were collected from the hospital birth records, and maternal use of vitamin D supplements during pregnancy was requested retrospectively with questionnaires. Anthropometric measurements at 6 and 12 months were collected during study visits and compared with Finnish references [20]. Families prospectively reported the daily intake of vitamin D₃ supplementation with vitamin D diaries. Compliance to vitamin D₃ supplementation was calculated as the percentage of days when the supplement was administered during the follow-up period. Compliance was considered good if the child received >80% of the planned doses.

An umbilical cord blood sample at birth, a capillary blood sample at 6 months, and a venous blood sample at 12 months were obtained. Ca-ion (reference range for pH-adjusted Ca-ion 1.16–1.39 mmol/L) served as a safety measurement at 6 and 12 months. The predefined safe upper limit was set at 1.53 mmol/L (i.e., a value that exceeds the upper reference limit by ≥10%). Higher Ca-ion concentrations were regarded as indicative of severe hypercalcemia and values between 1.40 and 1.52 mmol/L were indicative of mild hypercalcemia. In the case of severe hypercalcemia, an external safety monitor was to be informed, and predefined safety operations and follow-ups were to be initiated, including repeated samples for Ca-ion and Ca, 25-OHD, and PTH, and the interruption of vitamin D supplementation. In the case of suspected vitamin D excess, in line with good clinical practice, the external monitor was to be informed. A study nurse or a pediatrician was available at any time during the study, and families were encouraged to contact the study group if symptoms potentially indicative of hypercalcemia, such as suspected prolonged abdominal pain, vomiting, fatigue, or failure to thrive, were observed.

Laboratory Analyses

Umbilical cord blood 25-OHD, serum 25-OHD, and intact PTH were measured at the Pediatric Research Center, University of Helsinki, Helsinki, Finland, with a fully automated IDS-iSYS analyzer (IDS Ltd., Boldon, UK) with chemiluminescence detection. The intra- and interassay coefficients of variation for 25-OHD were <5 and <7%, respectively, and those for PTH <6 and <6%. The quality and accuracy of 25-OHD analyses were ensured by adhering to the Vitamin D External Quality Assessment (DE-QAS, Charing Cross Hospital, London, UK): in 2014 and 2015, 25-OHD concentrations were on average 10% higher compared with the National Institute of Standards and Technology (NIST) standards. PTH concentrations below the detection limit (4.5 pg/mL) were coded as 4.4 pg/mL (IDS-iSYS iPTH reference range 11.5–78.4 pg/mL). Ca-ion concentrations, adjusted to pH 7.40, were analyzed at the Central Laboratory of Helsinki University Hospital (HUSLAB) by a blood gas analyzer ABL 90 FLEX or ABL 835 FLEX.

Statistical Analysis

All available anthropometric measurements and laboratory results for the first 12 months were included. The normality of the

Table 1. Baseline characteristics of mothers and infants

	Total (<i>n</i> = 762)	Boys (<i>n</i> = 368)	Girls (<i>n</i> = 394)	<i>p</i> value ¹
Mothers				
Duration of gestation, days	281 (8)	281 (8)	282 (7)	0.024 ²
Age of mother, years	32 (4)	32 (4)	32 (4)	0.567
Supplemental vitamin D ₃ , µg/day ⁵	15.8 (16.7)	16.2 (16.6)	15.3 (16.8)	0.281 ²
Infants				
Birth weight, kg	3.53 (0.39)	3.58 (0.39)	3.49 (0.39)	0.001
Birth weight, SD score	−0.3 (0.8)	−0.3 (0.8)	−0.2 (0.8)	0.285
Birth length, cm	50.3 (1.7)	50.7 (1.7)	50.1 (1.7)	<0.001
Birth length, SD score	−0.2 (0.9)	−0.3 (0.9)	−0.1 (0.9)	0.036
Birth head circumference, cm	35.2 (1.4)	35.4 (1.4)	35.0 (1.3)	<0.001
Cord blood 25-OHD, nmol/L ^{4, 6}	90 (26)	92 (27)	88 (24)	0.01
Distribution of birth seasons, %				0.605 ³
Winter	18	18	18	
Spring	43	41	46	
Summer	21	22	20	
Autumn	18	19	17	

Values are given as means (±SD) unless otherwise indicated. 25-OHD, 25-hydroxyvitamin D. ¹ Independent samples *t* test unless otherwise indicated. ² Mann-Whitney U test. ³ χ^2 test. ⁴ Tested after logarithmic transformation. ⁵ Data available for 357 boys and 381 girls. ⁶ Data available for 362 boys and 384 girls.

Table 2. Infants' characteristics at 6 and 12 months

	Boys (<i>n</i> = 368)	Girls (<i>n</i> = 394)	<i>p</i> value ¹
6 months			
Decimal age, years	0.5 (0.02)	0.5 (0.02)	0.862
Length, cm	68.4 (2.0)	66.7 (1.9)	<0.001
Length, SD score	−0.5 (1.0)	−0.4 (1.0)	0.470
Weight, kg	8.3 (0.9)	7.6 (0.8)	<0.001
Length-adjusted weights, %	3.3 (9.4)	1.5 (9.1)	0.008
Compliance during 0–6 months, %	89 (13)	88 (13)	0.396 ²
Compliance exceeding 80%, %	85	85	0.985 ³
Breastfed, % ⁴	77	82	0.071 ³
12 months			
Decimal age, years	1.0 (0.03)	1.0 (0.03)	0.778
Length, cm	76.2 (2.4)	74.5 (2.3)	<0.001
Length, SD score	−0.5 (1.0)	−0.6 (1.0)	0.413
Weight, kg	10.2 (1.1)	9.4 (1.0)	<0.001
Length-adjusted weights, %	2.0 (8.5)	0.2 (8.3)	0.004
Compliance during 0–12 months, % ⁵	89 (12)	89 (11)	0.506 ²
Compliance exceeding 80%, % ⁵	85	85	0.909 ³
Breastfed, % ⁴	39	42	0.324 ³

Values are given as means (±SD) unless otherwise indicated. ¹ Independent samples *t* test if not indicated otherwise. ² Mann-Whitney U test. ³ χ^2 test. ⁴ Data available for 359 boys and 388 girls. ⁵ Data available for 347 boys and 361 girls

variables was visually inspected, and a logarithmic transformation was applied for skewed variables (PTH and umbilical cord blood 25-OHD). Anthropometric measurements and laboratory values are presented as means (±SD) or medians (interquartile ranges).

An independent samples *t* test or a Mann-Whitney U test was used to assess differences between girls and boys. Differences between categorical variables were analyzed with a Pearson χ^2 test. A bivariate correlation was performed either with Pearson's or Spear-

Fig. 1. Flow chart of recruitment and follow-up with the numbers of excluded and discontinued subjects, and the numbers of blood samples analyzed at 6 and 12 months. 25-OHD, 25-hydroxyvitamin D; Ca-ion, ionized calcium; PTH, parathyroid hormone.

man's correlation. A multivariate linear regression analysis was used to evaluate factors associating with Ca-ion at 12 months. Changes in Ca-ion concentrations over time were examined with repeated measures ANCOVA. A p value <0.05 was considered significant. Statistical analyses were performed using IBM SPSS version 22 for Windows.

Results

Baseline characteristics are presented in Table 1. These did not differ between girls and boys except for the duration of gestation and anthropometry. Table 2 summarizes anthropometry at 6 and 12 months. Girls were leaner compared with boys at both ages. Data on breastfeeding were available for 98% of the infants; 79% of infants were breastfed at 6 months and 41% at 12 months; others were formula-fed. Solid foods or infant cereals were introduced on average at 4.5 months.

At 6 months 92% ($n = 888$) and at 12 months 89% ($n = 861$) of the recruited participants attended the follow-up visit (Fig. 1). The loss from follow-up was similar for both sexes ($p = 0.139$ and $p = 0.112$). Ca-ion, 25-OHD,

and PTH concentrations from 6- and 12-month visits were available for 762 infants. Data on compliance were missing from 1 infant at 6 months and from 54 infants at 12 months. The mean compliance for vitamin D₃ supplementation during the 12 months was 89%, and good compliance ($>80\%$) was observed in 85% ($n = 603$) of the participants.

None of the children had severe hypercalcemia (Ca-ion ≥ 1.53 mmol/L) at either of the follow-up visits. Mild hypercalcemia (1.40–1.52 mmol/L) was present at 6 months in 28% ($n = 213$) of infants and at 12 months in 2% ($n = 12$) of infants (Table 3). No clinical signs of hypercalcemia were reported. Ca-ion concentrations at both time points were higher in girls compared with boys (Table 3.)

Serum 25-OHD and PTH were measured at 12 months (Table 3). Median 25-OHD concentration was 97 nmol/L. In 18% of the infants, the 25-OHD concentration exceeded 125 nmol/L. PTH was suppressed (<11.5 pg/mL) in 11% ($n = 87$) of the 762 infants.

Median 25-OHD at 12 months was slightly higher in the 12 infants with mild hypercalcemia (97 vs. 110 nmol/L, $p = 0.046$). Median PTH, however, was significantly low-

Table 3. Plasma concentrations of Ca-ion at 6 and 12 months, and 25-OHD and PTH at 12 months

	Total (<i>n</i> = 762)	Boys (<i>n</i> = 368)	Girls (<i>n</i> = 394)	<i>p</i> value ¹
6 months				
Ca-ion, mmol/L	1.37 (1.35–1.40)	1.37 (1.34–1.40)	1.38 (1.35–1.40)	0.006
1.16–1.39, %	72	74	70	0.267 ²
>1.40, %	28	26	30	
12 months				
Ca-ion, mmol/L	1.33 (1.31–1.35)	1.33 (1.31–1.35)	1.34 (1.31–1.36)	0.001
1.16–1.39, %	98	99	97	0.027 ²
>1.40, %	2	1	3	
25-OHD, nmol/L	97 (77–117)	94 (77–117)	99 (78–117)	0.168
<50, %	1	1	1	0.818 ²
50–75, %	20	20	20	
75–125, %	61	60	63	
>125, %	18	19	16	
PTH, pg/mL ³	24 (16–33)	23 (16–31)	24 (16–35)	0.270

Values are given as medians (IQR) unless otherwise indicated. Ca-ion, ionized calcium; 25-OHD, 25-hydroxyvitamin D; PTH, parathyroid hormone. ¹ Independent samples *t* test if not indicated otherwise. ² χ^2 test. ³ Tested after logarithmic transformation.

er in those with mild hypercalcemia compared with those with normocalcemia (13 vs. 24 pg/mL, $p = 0.001$). 25-OHD and PTH correlated ($r = -0.277$, $p < 0.001$), but despite these findings the mildly elevated Ca-ion concentrations were not associated with especially high 25-OHD or low PTH concentrations (Fig. 2). In infants with mild hypercalcemia ($n = 12$), PTH ranged between 4.4 and 27 pg/mL and was below the reference range in 4 infants, while their 25-OHD ranged between 73 and 176 nmol/L.

Participants with good compliance did not have higher Ca-ion concentrations than those with <80% compliance at 6 months (median 1.37 vs. 1.38 mmol/L, $p = 0.956$) or at 12 months (median 1.33 mmol/L vs. 1.33 mmol/L, $p = 0.807$). 25-OHD concentrations (median 98 nmol/L vs. 90 nmol/L, $p = 0.049$) and PTH concentrations at 12 months (median 24 vs. 20 pg/mL, $p = 0.036$) were higher in those with higher compliance. Breastfeeding or use of formula milk did not affect the incidence of mild hypercalcemia at 6 or 12 months ($p = 0.669$ and $p = 0.089$).

Ca-ion at 12 months correlated weakly with 25-OHD ($r = 0.149$, $p < 0.001$) and inversely with PTH ($r = -0.237$, $p < 0.001$). The most important determinant of Ca-ion at 12 months was Ca-ion at 6 months (Table 4), explaining 7% of the variation. Other modifying variables were PTH, age, sex, and 25-OHD. Growth parameters or adherence to supplementation did not affect Ca-ion concentration at 12 months. In the repeated measures ANCOVA using PTH and age as covariates, Ca-ion decreased significant-

Fig. 2. Correlation between parathyroid hormone (PTH) and serum 25-hydroxyvitamin D (S-25-OHD) at 12 months. Blue circles indicate values for infants with ionized calcium (Ca-ion) concentrations within the reference range (1.16–1.39 mmol/L), and red symbols indicate values for infants with mildly elevated Ca-ion concentrations (1.40–1.52 mmol/L). PTH concentrations below the detection limit (<4.5 pg/mL; $n = 20$) are marked as 4.4.

Table 4. Multivariate regression analysis of predictors for Ca-ion concentration at 12 months ($n = 707$)

	Adjusted B	95% CI	<i>p</i> value
Ca-ion at 6 months	0.214	0.157; 0.271	<0.001
PTH at 12 months	-0.001	-0.001; -0.0004	<0.001
Age	-0.144	-0.222; -0.065	<0.001
Sex	0.007	0.003; 0.012	0.002
25-OHD at 12 months	0.0001	0.000009; 0.0002	0.029
Length at 12 months	-0.002	-0.004; 0.0004	0.101
Length-adjusted weights at 12 months	-0.00004	-0.0003; 0.0002	0.785
Compliance during 0–12 months	0.00006	-0.0001; 0.0003	0.557

Data are given as regression coefficients (B) and 95% CI. Ca-ion, ionized calcium; 25-OHD, 25-hydroxyvitamin D; PTH, parathyroid hormone. Adjusted $R^2 = 0.160$ and $p < 0.001$ for the model.

ly with time ($p < 0.001$), and the decrease was more pronounced in boys than in girls ($p = 0.001$). Growth, adherence, or 25-OHD at 12 months did not affect the temporal change in Ca-ion concentrations from age 6 to 12 months.

Discussion

Despite the wide use of vitamin D supplements among infants, the available safety data are limited. This study evaluated the safety of daily supplemental doses of 10 and 30 μg in an ethnically homogenous cohort of healthy infants during the first year of life. Data were obtained as a part of the Vitamin D₃ Intervention in Infants (VIDI) trial. None of the study participants, half of whom received 30 μg of vitamin D₃ daily for 12 months, developed severe hypercalcemia, defined here with very strict criteria as values exceeding the upper reference limit by $\geq 10\%$ (Ca-ion > 1.53 mmol/L). We found asymptomatic mild hypercalcemia, defined as Ca-ion values exceeding the upper reference limit by $< 10\%$, in 28% of infants at 6 months and in 2% at 12 months. These results are in line with the findings from our previous short-term vitamin D₃ intervention in infants [21], which confirmed the safety of 3 months' use of vitamin D₃ supplementation of up to 40 μg .

We observed a marked decrease in the prevalence of mild hypercalcemia from 6 to 12 months. Higher Ca-ion concentrations were associated with female sex and younger age at the time of study visit. The decrease in the Ca-ion concentration with time supports our previous hypothesis [21] that the 25-OHD concentration, and thus the risk of mild hypercalcemia, will decrease as the vita-

min D₃ dose, in relation to child's weight, decreases. Compared with boys, the higher prevalence of mildly elevated Ca-ion values in girls is probably related to smaller body size. These findings also raise the question of whether vitamin D₃ dose should be adjusted during early childhood in relation to the child's weight, in line with most medications during childhood.

We used very strict criteria to define mild and severe hypercalcemia. Reference ranges for Ca-ion in early infancy vary between laboratories, and it is uncertain whether the mildly elevated values ($< 10\%$ above the upper reference range) represent true hypercalcemia or rather false reference values. Suppressed PTH may be a better marker of an excessive intake of vitamin D. Unfortunately, we were not able to measure PTH at 6 months due to a limited sample volume, but at 12 months an inverse correlation between Ca-ion and PTH was observed. Only 4 of the 762 infants (0.5%) had both mild hypercalcemia and subnormal PTH concurrently at 12 months, while most of the infants had normal PTH, suggesting that these mildly elevated Ca-ion concentrations were not clinically relevant. Hypercalciuria has been regarded as a good marker of hypervitaminosis D. In our previous vitamin D intervention in infants [21], hypercalciuria, defined as urine calcium/creatinine ratio > 2.2 mmol/mmol, was present in 39% of all infants regardless of their vitamin D dose (25-OHD concentration), and occurred simultaneously with normal plasma calcium concentrations. Since urine calcium excretion was considered as an inaccurate marker, we focused the safety follow-up in the current study on Ca-ion concentrations.

Finland has a long history of vitamin D supplementation [22]. The recommended dose for children under 2 years of age is 10 μg , starting at 2 weeks of age. Recom-

mendations are well adopted, and 86% of Finnish children aged 1 year receive regular supplementation [23]. Therefore, it was not a surprise that the mean compliance in the present study was 89%. A further strength of this unique study is the large number of healthy infants with homogenous background.

As the study is ongoing, our data analysis was performed without knowing to which intervention group each child belonged. However, we know that half of the infants received a D₃ supplemental dose of 30 µg per day, and with this dose none of the infants developed severe hypercalcemia. Instead of using the exact daily intake, we investigated the association of serum 25-OHD with Ca-ion. 25-OHD concentration was slightly higher in infants with mild hypercalcemia than in those with normocalcemia. Vitamin D status can be regarded as an even better marker than the reported intake as responses to vitamin D supplementation may be individual [24, 25]. Unfortunately, we lack data on 25-OHD and PTH concentrations at 6 months, when mild hypercalcemia was more prevalent. Furthermore, no 1,25-OH₂D levels were measured. On the other hand, our study reliably shows that clinically significant hypercalcemia is not a relevant risk in infants when using vitamin D₃ supplementation of up to 30 µg per day.

In summary, we conclude that daily supplementation of either 10 or 30 µg of vitamin D₃ did not cause severe

hypercalcemia in healthy infants born full-term and with normal weight. Mild hypercalcemia was common at 6 months but it decreased with age; it was very rare at 12 months and was associated with low PTH concentration in only a few children. Furthermore, the mildly elevated concentrations were not associated with excessively high 25-OHD values. These observations confirm the safety of the supplemental doses used and suggest that mildly increased Ca-ion values may reflect inappropriate reference values rather than significantly altered calcium balance.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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