Vitamin D Supplementation and Status in Infants: A Prospective Cohort Observational Study

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ABSTRACT

Objective: Vitamin D status in infants depends on supplementation. We examined the vitamin D status in relation to supplementation dose and scheme in infants.

Patients and Methods: One hundred thirty-four infants age 6 months and 98 infants age 12 months (drop out 27%) were investigated. Vitamin D intake (diet, supplements), anthropometry, and 25-hydroxyvitamin D (25-OHD) serum concentration at the 6th and 12th months were assessed.

Results: Vitamin D intake of 1062 ± 694 IU at the 6th month was not different from that at the 12th month (937 ± 618 IU). Vitamin D intake expressed in international units per kilogram of body weight decreased from 141 ± 80 IU/kg at the 6th month to 93 ± 62 IU/kg at the 12th month ($P < 0.0001$), which was associated with a reduction in 25-OHD from 43 ± 20 ng/mL to 29 ± 12 ng/mL, respectively ($P < 0.0001$). In the subgroup of everyday supplemented infants (n = 43), vitamin D intake decreased from 143 ± 88 IU/kg at the 6th month to 118 ± 60 IU/kg at the 12th month ($P < 0.05$), which coincided with a reduction of 25-OHD from 40 ± 19 ng/mL to 32 ± 13 ng/mL ($P < 0.01$). In the subgroup with variable supplementation habits (n = 32), vitamin D intake decreased from 146 ± 79 IU/kg to 77 ± 56 IU/kg ($P < 0.001$), which was associated with a reduction of 25-OHD from 42 ± 21 ng/mL to 25 ± 8 ng/mL ($P < 0.0001$). 25-OHD concentration change between the 6th and the 12th months negatively correlated with the 25-OHD level assessed at the 6th month ($r = -0.82$; $P < 0.0001$).

Conclusions: Vitamin D supplementation of infants should consider their rapid body weight increment. We postulate vitamin D daily dose close to 100 IU/kg body weight as favorable for infants up to age 12 months.

Key Words: 25-hydroxyvitamin D, infants, supplementation, vitamin D

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Recent data suggest that vitamin D sufficiency in neonates and infants has long-lasting positive clinical implications in the later stages of life (1). As shown by Hyppönen et al (2) in a birth cohort of infants born in the mid-1960s who were regularly supplemented with a vitamin D dose of 2000 IU daily during the first year of life and were studied for the next 31 years, had a reduced risk for the development of type 1 diabetes by 80%. Moreover, the same cohort revealed that infants suspected of having rickets during the first year of life had a 3-fold increased risk for type 1 diabetes.

Epidemiologic studies, at least in adults, apart from the risk of osteomalacia and osteoporosis, have associated hypovitaminosis D with an increased risk of a number of cancers, autoimmune diseases (type 1 diabetes, multiple sclerosis, rheumatoid arthritis, and Crohn disease), heart disease, hypertension, metabolic syndrome, asthma, upper respiratory tract infections, muscle weakness, and falling (3–7). The pleiotropic action of vitamin D was already revealed on molecular, cellular, tissue, and organ levels. These observations modified the current knowledge about vitamin D metabolism and methods of diagnosis of vitamin D deficiency states (8).

The new evidence for beneficial role of proper vitamin D status has led the Committee on Nutrition and Section on Breastfeeding of the American Academy of Pediatrics to recommend a vitamin D daily intake of 400 IU for healthy infants, children, and adolescents beginning in the first few days of life (9). The same supplementation protocol for infants was recommended by a panel of Polish experts (10). The Canadian Pediatric Association recommended an 800-IU/day dose of vitamin D from all sources in the period from October to April in infants living between 40°N and 55°N (11).

Population studies in Poland (49°N to 54.5°N) (12,13), Europe (14), and the rest of world (15–17) showed disturbingly low serum levels of 25-hydroxyvitamin D (25-OHD), the marker of vitamin D status. A severe vitamin D deficiency state was revealed in 30% of the population (25-OHD serum concentration <10 ng/mL) and a vitamin D deficiency state in up to 80% of the population (25-OHD serum concentration <20 ng/mL), especially during the winter season (12–17). Keeping in mind the pleiotropic action of vitamin D, an alarmingly high prevalence of its deficiency should be considered as a serious public health problem and the proper vitamin D supplementation as an important element of early prophylactic nutritional interventions for a spectrum of disorders.

Despite published recommendations for vitamin D supplementation, vitamin D status in infants is still not fully recognized. It is unclear how far and to what extent the recommended dose of 400 IU/day covers the needs of the growing organism, expressed as the proposed adequate 25-OHD serum concentration (10). It is also

unclear, at least in Poland, how far the recommended vitamin D supplementation of infants is implemented by caregivers.

The aim of the study was to evaluate vitamin D intake from both supplementation and diet in Polish infants ages 6 and 12 months and assess the relation between vitamin D intake and the vitamin D status expressed by 25-OHD serum concentrations.

PATIENTS AND METHODS

Study Group

This was a prospective, cohort observational study. Four pediatric clinics located in Bialystok, Rzeszow, Warsaw, and Kielce from the central and the eastern parts of Poland participated in our study. The same standardized protocol was applied to all of the infants investigated. Recruitment rules were predefined in cooperating clinics. Every third infant admitted was selected for the study if the parents signed informed consent forms. The inclusion criteria were good general health, normal pregnancy, delivery on term (37–41 weeks of gestation), and birth weight >2500 g. The exclusion criteria were allergy, illness that required hospitalization, and low Apgar score at delivery (<7 points).

The study group consisted of 134 term-born white infants (69 boys) evaluated at age 6 months (183 ± 7 days, n = 134) and for a second time at age 12 months (365 ± 7 days, n = 98). In a subgroup of 36 infants who did not complete a study (dropout rate 27%), the anthropometric, dietary, supplementation, and vitamin D status characteristics were not significantly different at the sixth month from the rest of group that completed the study.

Medical and Dietary Investigations

Medical examination and anthropometric characteristics assessment were performed at both visits. A questionnaire was used to collect dietary data and vitamin D supplements. Vitamin D intake from diet was calculated basing on a 24-hour dietary recall using Dietetyk 2 (Food and Nutrition Institute, Warsaw, Poland, 2001). The vitamin D intake from supplements was assessed based on the dosage in 1 drop according to commercial information provided by pharmaceutical companies for their products. The supplementation scheme was analyzed according to predefined criteria: regular supplementation—supplement containing cholecalciferol given every day; occasional supplementation—supplement containing cholecalciferol given 3 times per week or less. Vitamin D intake from breast milk, because of the low amount of vitamin D (approximately 22 IU/L) and difficulties in assessing its daily intake, was omitted.

Laboratory Assessments

Fasting serum samples were collected between 8 and 10 AM and stored at −20°C up to 3 months. 25-OHD serum concentration was evaluated in the Department of Biochemistry and Experimental Medicine, Children's Memorial Health Institute, Warsaw, Poland. 25-OHD serum concentration was assayed using the radioreceptor method as described previously (18). Intraassay and interassay coefficient of variance values were 10% and 14%, respectively.

Statistical Analysis

The whole studied group was analyzed at 6 and 12 months of life. In addition, a subgroup of 82 infants with a complete spectrum of anthropometric, dietary, and biochemical data at both visits was selected from a whole group for additional analyses. The above-mentioned group was divided into 3 subgroups according to vitamin D supplementation scheme reported by caregivers:

1. Regular supplementation at both 6 and 12 months (n = 43). As reported by caregivers the vitamin D from supplements was given regularly, every day, for the whole period of the study.
2. Supplementation scheme changed between the 6th and the 12th month (n = 32). As reported by caregivers, the vitamin D intake from supplements changed during the period of the study; in 14 cases vitamin D supplementation was regularly given up to the 6th month of life and then vitamin D was given occasionally (3 times per week or less); in 7 cases the supplementation was occasional up to the 6th month and then vitamin D was given regularly; in 11 cases regular vitamin D supplementation after the 6th month was discontinued;
3. Occasional supplementation at both 6 and 12 months (n = 7). As reported by caregivers vitamin D supplementation was given occasionally for the whole period of the study (3 times per week or less).

The normality of the distribution of analyzed data was controlled by Kolmogorow-Smirnow and Shapiro-Wilk tests. For the evaluation of differences between the consecutive study groups, the nonparametric Kruskal-Wallis ANOVA rank test and Mann-Whitney *U* test were performed. Among studied subgroups, a Wilcoxon matched-pairs test was performed to evaluate the differences for outcomes assessed at 6 and 12 months. The Spearman rank test was performed to assess relations between selected parameters. The results are presented as mean ± standard standard deviation and were regarded to be significant at $P < 0.05$.

Ethics

Ethical approval was obtained for the study from the ethics committee of the Children's Memorial Health Institute. Parents gave their written informed consent before the study.

RESULTS

Neonatal Characteristics

A total of 134 healthy infants were included in the study, of which 69 (51.5%) were boys. Among the studied group, 50 infants (37.3%) were born in the summer season (May–October) and 84 infants (62.7%) were born in the winter season (November–April). All infants were born at term (Hbd 40 weeks ±1.1) and had a first-minute Apgar score of 10.0 ± 0.3 (8–10), birth weight was 3484 ± 432 g (2510 g–4600 g), birth body length was 55.8 ± 2.5 cm (50–65 cm), and birth head circumference was 34.3 ± 1.7 cm (31–38 cm).

Anthropometric Characteristics at Ages 6 and 12 Months

Table 1 provides anthropometric and Table 2 dietary characteristics of 134 infants evaluated at the age of 6 months and the remaining 98 infants at the age of 12 months who completed our study (dropout rate 27%).

As expected in growing infants, a significant increase in body weight and body length of 2060 ± 632 g and of 7.7 ± 2.3 cm was observed between 6 and 12 months of life ($P < 0.0001$). The head, arm, and chest circumferences also increased, but not body mass index and Cole index, indicating proportional growth rate. When skinfold thicknesses were analyzed, arm and subscapula

TABLE 1. Anthropometric characteristics

Variable	6th month, n = 134	12th month, n = 98	P
Body weight, g	8064 ± 917 (6400–12,800)	10,209 ± 1454 (8200–18,000)	<0.0001
Body length, cm	68.7 ± 2.8 (63.2–77.0)	76.5 ± 2.5 (70.0–84.0)	<0.0001
BMI, kg/m^2	17.1 ± 1.6 (12.4–22.8)	17.2 ± 1.6 (12.1–22.3)	NS
Cole index	1.01 ± 0.09 (0.74–1.32)	1.02 ± 0.10 (0.83–1.48)	NS
Head circumference, cm	43.6 ± 1.3 (40.5–47.5)	46.7 ± 1.3 (43.4–51.0)	<0.0001
Chest circumference, cm	44.7 ± 2.1 (41.5–53.0)	47.5 ± 2.2 (43.0–59.0)	<0.0001
Arm circumference, cm	14.9 ± 1.3 (11.0–19.0)	15.9 ± 1.4 (11.0–22.0)	<0.0001
Skinfold thickness, mm			
Arm	9.8 ± 2.6 (4.0–20.0)	9.8 ± 3.2 (5.4–22.0)	NS
Abdomen	8.4 ± 2.6 (4.7–19.0)	7.0 ± 2.9 (3.4–18.0)	<0.001
Subscapula	7.3 ± 1.6 (4.0–14.5)	7.4 ± 1.6 (5.0–13.0)	NS
No. teeth	0.7 ± 1.1 (0–7)	6.3 ± 1.9 (2–12)	<0.0001

BMI = body mass index; NS = not significant.

skinfolds were not different; however, in 12-month-old infants the abdomen skinfold thickness was reduced by 1.3 ± 2.2 mm, compared with the values observed at the age of 6 months ($P < 0.001$) (Table 1).

Dietary Characteristics and Vitamin D Status at Ages 6 and 12 Months

As shown in Table 2, the prevalence of infants fully breast-fed at the age of 6 months was 3.7%, but breast-feeding as a part of the diet at both 6 and 12 months was reported in 65.0% and in 43.9% of infants, respectively. Every third and more than half of the infants investigated at 6 and 12 months were fully formula fed, respectively. When the vitamin D supplementation scheme was analyzed, the prevalence of infants with reported regular pharmaceutical supplementation decreased from 82.1% at the 6th month to 60.2% at the 12th month. The prevalence of infants who were occasionally supplemented or were not supplemented at the age of 12 months was higher than that observed in the 6th month. Supplementation scheme changes observed between the 6th and the 12th month coincided with a modification of a vitamin D daily dose. As indicated in Table 2, 91.8% of infants investigated at the age of 6 months and 86.7% at the 12th month were supplemented with vitamin D doses that were higher than 400 IU.

TABLE 2. Feeding, supplementation scheme, and vitamin D dosage

Variable	6th month, n = 134	12th month, n = 98
Feeding type, n		
Fully breast-fed	5 (3.7%)	0 (0%)
Breast-feeding and formula	87 (65.0%)	43 (43.9%)
Fully formula fed	42 (31.3%)	55 (56.1%)
Vitamin D supplementation, n		
Regular	110 (82.1%)	59 (60.2%)
Occasional	19 (14.2%)	23 (23.5%)
Not given	5 (3.7%)	16 (16.3%)
Vitamin D supplementation, n		
Below 400 IU/d	2 (1.5%)	8 (8.2%)
400 IU/d	9 (6.7%)	5 (5.1%)
400–800 IU/d	53 (39.6%)	29 (29.6%)
800–2000 IU/d	48 (35.8%)	38 (38.8%)
2000–4000 IU/d	17 (12.7%)	2 (2.0%)

Table 3 presents the vitamin D intake and status assessed at 6 and 12 months of life. As indicated, lack of significant differences was noted neither for an estimated daily vitamin D intake from diet only or from supplementation only nor for the total vitamin D intake. When total vitamin D intake per kilogram body weight was analyzed, however, the amounts of international units per kilogram were significantly lower at the 12th month compared with that at the 6th month of life, which coincided with a significant decrease in serum levels of 25-OHD ($P < 0.0001$) (Table 3). As shown in Figure 1, 25-OHD serum concentrations <30 ng/mL were observed in 26.1% and in 59.6% of infants investigated at the age of 6 and 12 months, respectively. At the 12th month of age, the prevalence of infants showing 25-OHD levels below 20 ng/mL increased 3-fold compared with that noted at the 6th month (Fig. 1).

Specifically, at the 6th month of life, 3 infants had 25-OHD levels below 10 ng/mL (4.2 ± 3.1 ng/mL), which surprisingly coincided with mean vitamin D doses of 803 ± 464.6 IU/day (98.6 ± 58.4 IU/kg/day), all regularly supplemented. Furthermore, 5 infants at the age of 6 months revealed 25-OHD levels between 10.0 and 19.9 ng/mL (16.4 ± 0.8 ng/mL), with a mean vitamin D daily dose of 552 ± 59.4 IU (72.4 ± 1.9 IU/kg), 3 infants regularly and 2 infants occasionally supplemented. At the 12th month, 3 infants (2 regularly supplemented and 1 not supplemented) had 25-OHD levels <10 ng/mL (8.0 ± 1.2 ng/mL), which coincided with vitamin D doses of 404 ± 304.1 IU (40.1 ± 28.2 IU/kg).

TABLE 3. Vitamin D status and intake

Variable	6th month, n = 134	12th month, n = 98	P
25-hydroxyvitamin D	42.9 ± 20.2	28.6 ± 11.9	<0.0001
Vitamin D			
From diet, IU	174.5 ± 230.3	204.8 ± 182.4	NS
From supplements, IU	1016.2 ± 633.9	957.4 ± 517.9	NS
Total intake, IU	1061.8 ± 694.4	936.6 ± 618.2	NS
Total intake, IU/kg	141.3 ± 79.9	93.4 ± 61.7	<0.0001

NS = not significant.

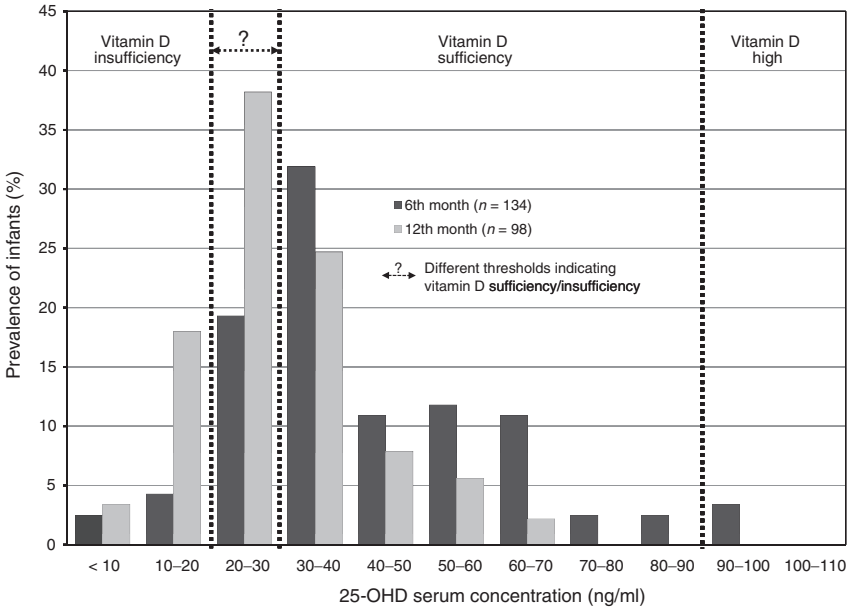

FIGURE 1. Prevalence of infants in relation to 25-OHD serum concentration assessed at 6 and 12 months of age. 25-OHD serum concentration of 30 ng/mL or higher indicates vitamin D sufficiency according to Canadian Paediatric Society recommendations (11). 25-OHD serum concentration of 20 ng/mL or higher indicates vitamin D sufficiency according to recent Polish recommendations (10).

Furthermore, 17 infants at the age of 12 months (8 regularly supplemented, 7 occasionally, and 2 not supplemented) revealed 25-OHD levels between 10.0 and 19.9 ng/mL (17 ± 2.5 ng/mL); with a mean vitamin D dose of 770 ± 59.4 IU (78.2 ± 51.3 IU/kg). Nonetheless, at both 6 and 12 months, anthropometric parameters of described infants, irrespective of the severity of vitamin D insufficiency/deficiency, were normal.

Finally, there were no differences between winter- versus summer-born infants for vitamin D intake or for 25-OHD serum concentrations at both study points.

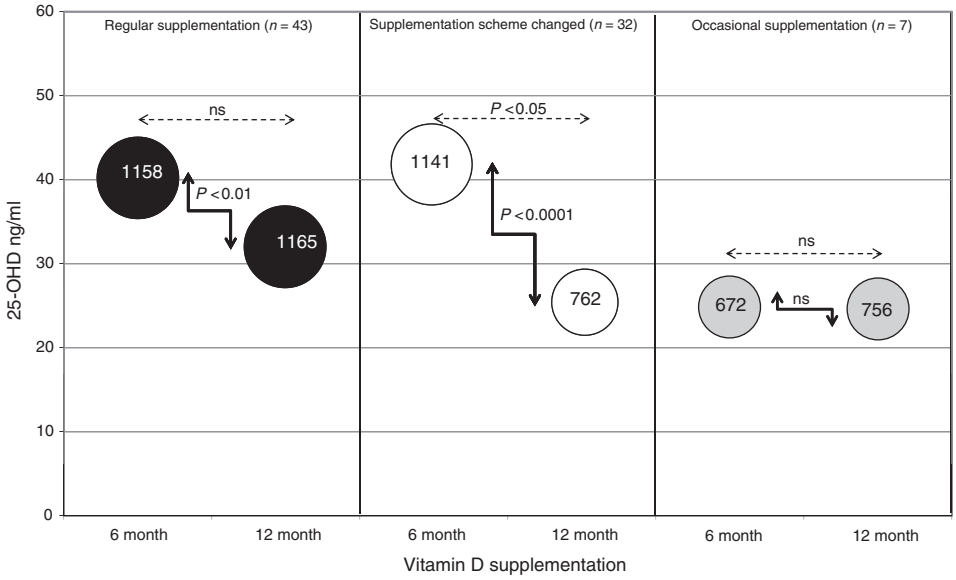

FIGURE 2. 25-OHD serum concentration at 6 and 12 months of age in relation to supplementation scheme and vitamin D total intake expressed in international units. The dotted arrows show the significance of vitamin D dosage change between the 6th and the 12th month within each group, as expressed in international units. The solid arrows show the significance of 25-OHD concentration change between the 6th and the 12th month within each group. The size of the circles reflect the magnitude of vitamin D dosage in international units.

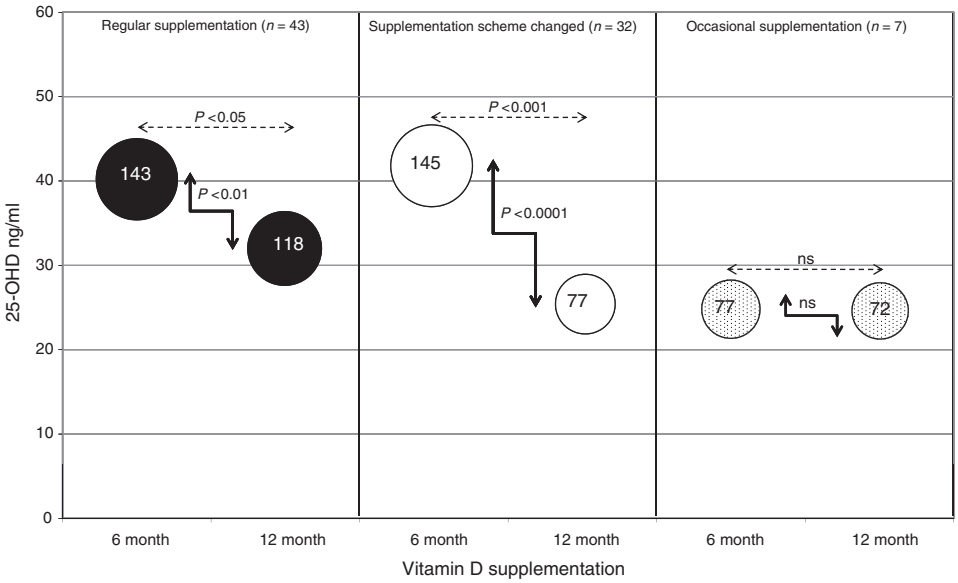

FIGURE 3. 25-OHD serum concentration at 6 and 12 months of age in relation to supplementation scheme and vitamin D total intake expressed in international units per kilogram body weight. The dotted arrows show the significance of vitamin D dosage change between the 6th and the 12th month within each group, as expressed in international units per kilogram body weight. The solid arrows show the significance of 25-OHD concentration change between the 6th and the 12th month within each group. The size of the circles reflect the magnitude of vitamin D dosage in international units per kilogram.

Supplementation Scheme and Vitamin D Status at Ages 6 and 12 Months

Figure 2 presents 25-OHD serum concentrations at 6 and 12 months of age in healthy infants in relation to supplementation scheme and vitamin D total intake. As shown, in the group of infants (n = 43) regularly supplemented with vitamin D in doses of 1158 ± 730 IU at the 6th month and of 1165 ± 568 IU at the 12th month (not significant; ns), the 25-OHD serum concentrations decreased from the value of 40.2 ± 18.8 ng/mL to 32.0 ± 12.7 ng/mL ($P < 0.01$). In the group of infants (n = 32) with reported changes in the supplementation scheme, the daily vitamin D intake decreased between the 6th and the 12th month of life from 1141 ± 622 IU to 762 ± 564 IU ($P < 0.05$), which coincided with a significant decrease in 25-OHD level from 41.8 ± 20.7 ng/mL to 25.4 ± 8.5 ng/mL ($P < 0.0001$). Although vitamin D intake in infants (n = 7) occasionally supplemented trended to increase with age, 25-OHD concentrations reached a plateau at levels close to 25 ng/mL.

Figure 3 shows 25-OHD serum concentrations in relation to vitamin D dose calculated per kilogram body weight. As indicated, a significant decrease of vitamin D dose expressed in IU/kg was observed between the 6th and the 12th month in both regularly supplemented infants and in those with reported changes in supplementation regime, but not in the occasionally supplemented group. In regularly supplemented infants (n = 43), the vitamin D dose related to body weight decreased from 143.4 ± 88.4 IU/kg to 118.0 ± 60.4 IU/kg ($P < 0.05$). An almost 2-fold decrease in international units per kilogram body weight was noted in the group that changed vitamin D administration habits (145.7 ± 79.1 IU/kg vs 77.3 ± 56.2 IU/kg; $P < 0.001$). The reduction of vitamin D for kilogram body weight in both groups coincided with a significant decrease in 25-OHD levels, as shown in Figure 3.

Relation Between 25-OHD Concentration Change and Vitamin D Dosage, Supplementation Scheme, and Anthropometrics

The 25-OHD serum concentration change between the 6th and the 12th month, when analyzed in the whole group, did not correlate with changes in body weight ($r = -0.11$) and body length ($r = -0.06$) of the infants. The 25-OHD serum concentration change between the 6th and the 12th months correlated with changes in the vitamin D dosage expressed both in international units ($r = 0.26$; $P < 0.05$) and in international units per kilogram body weight ($r = 0.29$; $P < 0.01$).

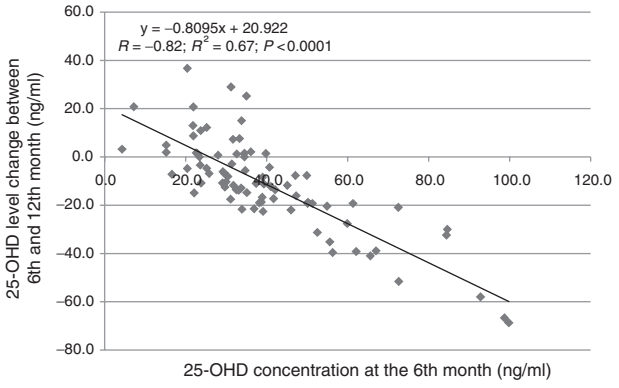

FIGURE 4. Relation between 25-OHD serum concentration change observed between the 6th and the 12th month and the 25-OHD serum concentration assessed at the 6th month.

When relationships were investigated within each studied subgroup, it appeared that the 25-OHD serum concentration change between the 6th and the 12th month did not correlate with body length changes or weight changes or with vitamin D dose changes (both in international units and international units per kilogram).

Finally, strong and negative correlation was noted between the 25-OHD serum concentration change observed between the 6 and 12 month and the 25-OHD serum concentration assessed at the 6th month ($r = -0.82$; $P < 0.0001$) (Fig. 4).

DISCUSSION

Using the data from the prospective cohort observational study we showed that Polish infants at the ages of 6 and 12 months, in general, were exposed to vitamin D doses that were markedly higher than the recommended daily intake of 400 IU. As expected, the major source of such doses were pharmaceutical supplements that, together with a diet, resulted in vitamin D daily intake close to 1000 IU at both the 6th and the 12th month of life. The skin synthesis from sun exposure, although an important natural source of vitamin D, was considered in only a small way the result of recommended avoidance of direct sun exposure for infants and use of sunscreens, umbrellas, stroller canopies, or sun-shield tents to protect infants while outside. Bearing in mind the safety issue it must be emphasized that adverse events in our study were not recorded and that the anthropometric data showed physiological values at the 6th and 12th months of life. The second finding is that, despite a relatively comparable vitamin D dosage in international units, the vitamin D status characterized by 25-OHD serum concentrations decreased significantly in our infants as a whole group from the optimal levels (42.9 ng/mL) at the 6th month to the suboptimal (28.6 ng/mL) at the 12th month. Third, the observed 25-OHD concentration decrease at least in part was related to reduced vitamin D intake when controlled for body weight. Therefore, vitamin D status in our study was linked to vitamin D supplementation; the vitamin D dose was expressed in international units per kilogram body weight.

When the supplementation scheme at both 6 and 12 months was analyzed, vitamin D dosage expressed in international units per kilogram (and in international units) decreased almost 2-fold in infants, with reported changes in the supplementation scheme that was associated with a significant reduction in serum 25-OHD concentration. In 25 cases in that group, as reported by caregivers, the vitamin D supplementation was discontinued or was occasional after the 6th month of life, resulting in a significant depletion of vitamin D status. Contrasting results were obtained in regularly versus occasionally supplemented groups. It appeared that vitamin D given occasionally in dosages close to 75 IU/kg body weight resulted in 25-OHD serum concentration close to 25.0 ng/mL at both the 6th and the 12th month. In regularly supplemented infants, vitamin D was given in daily doses that were at both study points almost 3-fold higher than the recommended 400 IU. Interestingly, at the 12th month the vitamin D dose in international units was even slightly increased, but when calculated per kilogram body weight it was in fact significantly lower, which again coincided with a significant reduction in 25-OHD serum concentration. Based on results assessed in regularly supplemented infants but also in the other 2 groups, we are now much closer to estimating the adequate vitamin D dose and expected 25-OHD concentration; with the vitamin D dose should consider the body weight of the supplemented infant.

The problem of vitamin D dosage in relation to infant weight was pointed out as an important issue in the Canadian position statement paper, and our findings remain in good concordance with this paper (11). Our results showed that to maintain the infant's vitamin D status within the optimal range, the supplementation dose close to 100 IU of D_3 per kilogram of body weight should be considered favorable. Unfortunately, the infants' optimal range for 25-OHD serum concentrations is at present not well established. Kovacs (19), Hollis and Wagner (20), and Holick (21) suggested that the desired 25-OHD level in infants should be >30 ng/mL, as it is in adults. The question remains whether the 25-OHD level of 30 ng/mL is an important goal to achieve during infancy. Despite the paucity of infant data, available papers indicate that the 25-OHD concentration close to 20 ng/mL (50 nmol/L) coincided with signs of bone demineralization (22), mild rickets (23), and increased risk for acute lower respiratory tract infection (23). Furthermore, the risk for respiratory tract infections in infancy was negatively associated with the 25-OHD level in umbilical cord blood, and was markedly lower for infants starting their life with a cord blood 25-OHD concentration of 30 ng/mL or higher (24). On the contrary, regular vitamin D supplementation of infants (2000 IU/day; likely to result in a 25-OHD concentration of 30 ng/mL or higher) markedly decreased the risk for type 1 diabetes later in life (2). Available evidence indicates that prevention of both nonskeletal and skeletal manifestations of hypovitaminosis D seems effective with 25-OHD levels >30 ng/mL rather than ≤20 ng/mL. Nonetheless, it should be emphasized that the optimal 25-OHD serum concentration in infancy and young childhood is still an issue of debate, and 25-OHD thresholds of >20 or >30 ng/mL have caused controversy in the literature. Nevertheless, if we assume that 25-OHD serum concentration in infancy should be similar to that recommended by Kovacs, Hollis and Wagner, and Holick (>30 ng/mL), then our data show indirectly the vitamin D dosage adequate for maintaining infants' vitamin D status within the proposed optimal range (19–21). Furthermore, Cannell et al (25) proposed a vitamin D daily dose close to 90 IU/kg as suitable for healthy children, which is in agreement with our findings.

Another interesting finding is the inverse relation between 25-OHD concentration assessed at the 6th month and the change in its concentration at the 12th month. Mawer et al (26), Lukaszkiewicz et al (27), and Leidig-Bruckner et al (28) showed that 25-OHD concentration at follow-up was inversely related to its concentration at baseline. According to Hollis et al (29), the relation between circulating cholecalciferol and 25-OHD is not linear but saturable and controlled, with Vmax achieved when circulating 25-OHD exceeded 40 ng/mL (100 nmol/L). It can be therefore speculated that in subjects showing proper vitamin D status, the hepatic 25-hydroxylation activity of CYP2R1 (25-hydroxylase) may be decreased when compared to that in the state of vitamin D deficiency. Results obtained in infants with the highest 25-OHD concentrations at the 6th month of life that showed the highest 25-OHD concentration decrease at the 12th month of life may reflect, at least in part, the proposed existence of feedback control, probably at the hepatic hydroxylation level.

Vitamin D supplementation in infants should take into account their rapid growth and weight increment as well as the necessity to adjust vitamin D dose in relation to kilogram of body weight. Based on the 25-OHD serum concentrations assayed in our study conditions, we postulate that in infants up to age 12 months the vitamin D dose close to 100 IU/kg should be considered favorable. Nevertheless, keeping in mind the ongoing debate on the desirable 25-OHD serum concentration in infancy and young childhood, caution is still advised when trying to incorporate our proposal without safety considerations.

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