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ORIGINAL ARTICLE

Vitamin D deficiency/insufficiency on healthy infants receiving standard supplementation

Deficiencia e insuficiencia de vitamina D en lactantes sanos recibiendo suplementación estándar

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What do we know about the subject matter of this study?

Vitamin D deficiency can cause rickets and its supplementation is necessary during the first year of life, generally with 400 IU daily orally.

What does this study contribute to what is already known?

High frequency of vitamin D insufficiency and deficiency was observed in healthy infants with 400 UI daily supplementation, which questions the effectiveness of this measure, considering also how difficult it is to evaluate its adherence.

Abstract

Vitamin D (VD) is essential for calcium and phosphorus metabolism. Its deficiency can cause rickets. In Chile, newborns receive 400UI/day supplementation from the first day of age until the first year. **Objective:** To describe the VD plasma levels in healthy infants who received supplementation and secondarily to correlate this with seasonality and nutritional status. **Subjects and Method**: Cross-sectional study. Infants on exclusive or mixed breastfeeding, with monthly pediatric checkups receiving 400 UI VD supplementation were evaluated, measuring VD plasma levels at 6 months of age, weight, and length, and their nutritional status was classified according to the WHO growth references (weight/age and weight/length). The VD cut-off concentration values were ≤ 20 ng/ml, 21- 29 ng/ml, and ≥ 30 ng/ml considered as deficiency, insufficiency, and sufficiency, respectively. **Results:** 40 infants were studied, 40% had insufficient levels and 40% presented deficiency. Season and nutritional status were variables significantly related to lower VD values (Winter-Spring $p = 0.007$; at risk of malnutrition $p = 0.038$). **Conclusions:** The population who received supplementation presented a high frequency of VD deficiency and insufficiency which increases during winter and spring and in subjects at risk of malnutrition.

Keywords:
Vitamin D;
Infants;
Rickets;
Dietary Supplements

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Introduction

Vitamin D (VD) is essential for calcium and phosphorus metabolism, as well as for bone mineral accretion among other functions. 90% of total body VD is synthesized at the skin level after sun exposure, which is not recommended in infants due to their greater susceptibility to cumulative damage[1]. The remaining 10% is obtained from the diet, and the low concentration of VD in human milk (5-80 IU/l) is well known[2].

The cutaneous synthesis of VD is influenced by factors such as skin pigmentation, latitude, seasonality, environmental pollution, time of daytime exposure, type of clothing, and use of sunscreen[3].

Several studies have shown that hypovitaminosis D is frequent in the whole world population, especially in more extreme latitudes[4-5], which has also been described locally[6]. Worldwide, there is a VD deficiency in pregnancy of 54%[7]. About 50% of the Chilean population of childbearing age would have insufficient or deficient levels[6].

Children of mothers with VD deficiency are at higher risk of presenting insufficiency, as there is a correlation between umbilical cord levels and plasma levels in the newborn[7]. The cut-off levels to define deficiency and insufficiency are based on studies in adults[8] considering the mechanisms of calcium homeostasis in them since in children there is still no absolute consensus about the adequate levels[9-10].

VD supplementation during the first year of life is essential to prevent nutritional rickets, a consequence of extreme VD deficiency. Thus, in 2008, the American Academy of Pediatrics modified its recommendations by doubling the prophylactic doses of VD from 200 to 400 IU/day during the first 12 months of life[11], which proved to reach concentrations above 30 ng/ml in exclusively breastfed infants[12]. In the same year, Chile established as a national standard the daily oral VD administration of 400 IU from the first month of life until the age of one year for all infants. We are not aware of studies evaluating vitamin D status in children with supplementation children in our country.

The objective of this study was to describe the plasma concentration of vitamin D in a group of healthy infants who attend health check-ups at 6 months of age, receiving supplementation determined by national standards. Secondarily, to evaluate the association of the effect of season and nutritional status on plasma vitamin D concentration.

Subjects and Method

Cross-sectional study conducted at the *Clínica Santa María* in Santiago, Chile (latitude 33° S). Between January 2017 and January 2019, mothers of infants aged 3 or 4 months, attending monthly health check-ups, born full-term, healthy, exclusively breastfed, or mixed breastfed (with starting formula less than 200 ml/24 hours), and receiving supplementation with vitamins A, C, and D, 10 drops/day corresponding to 400 IU of VD2 (ergocalciferol) from the first month of life, were invited to participate. Exclusion criteria were history of chronic diseases or hospitalizations in the newborn period or later due to acute diseases, receiving VD in a presentation or dosage different from the standardized one, and children of vegan mothers or with anemia.

The following cut-off points were considered to establish the status of plasma VD concentrations: sufficiency ≥ 30 ng/ml, insufficiency between 20-29 ng/ml, and deficiency below 20 ng/ml[8].

To assess nutritional status, the data used was obtained in the health check-up by the pediatricians participating in the study, using a mechanical scale for weight (SECA® 725 1021009) and a stadiometer for length (SECA® 416 1721009). The nutritional classification was performed according to World Health Organization guidelines[13].

The participating mothers were asked to provide informed consent, previously approved by the Ethics Committee of *Clínica Santa María*.

Monthly clinical follow-up was performed from 3 to 6 months of age to ensure adherence to supplementation, and to assess feeding, nutritional, and health status. Educational material was provided to promote the continuation of breastfeeding and the correct introduction of complementary feeding. The pediatrician in charge, as well as the mother, completed a specially designed questionnaire, both for the first evaluation and for the monthly check-up.

VD levels were evaluated at 6 months of life. To measure 25(OH)D levels, the enzyme-linked fluorescence assay (ELFA) technique was used (VIDA 3®, Bio Merieux, France)[14]. The measurement of VD was financed by funds from the 2017 Research Tender of the Academic Direction of *Clínica Santa María*. Those infants who presented low concentrations at 6 months were prescribed treatment with oral cholecalciferol at a dose of 1000 IU daily.

Sample size

Based on local literature[15-16], we estimated the frequency of VD insufficiency and deficiency in the group of healthy infants. Considering 95% of confidence level and 5% error, the sample size obtained was 55 infants. During the study, it was considered that the results were categorical in demonstrating a high frequency of deficiency and a low response to supplementation, therefore, together with the Ethics Committee, it was decided to suspend the study and start the analysis with 40 patients enrolled after 6 months.

For the comparison of the proportion of infants with VD less than 30 ng/ml, the power was calculated at 6.8%, obtaining a value of 100%. This shows that, although the previously calculated sample size was not achieved, the sample size obtained was sufficient to estimate this proportion.

Statistical methods

A descriptive analysis was performed for all the variables recorded. Summary measures were calculated for quantitative variables and absolute and percentage frequency distribution for the qualitative ones. The normality of quantitative variables was evaluated using the Shapiro-Wilk test. To evaluate the effect of the different variables (season, nutritional status, and type of lactation) on VD values, a linear regression analysis was performed, with the variable VD response and the predictor variables.

Results

43 patients participated in the study, 3 were excluded before 6 months (see flow chart), and 57.5% were males. The mean maternal age was 33.3 +/- 4.5 years.

At 6 months, 40% of the infants presented deficiency and another 40% VD insufficiency. (Table 1). Samples were collected during all seasons of the year, and were slightly lower in winter and spring, showing no significant difference.

The nutritional status of the children was mostly eutrophic (72.5%). 95% were exclusively breastfed and only 2 infants received mixed breastfeeding (< 200 ml formula per day).

Relationship of vitamin D concentration to the seasons of the year

When analyzing the total VD measurements according to the season of the year, it was observed that the median decreased from summer to winter (Figure 1). Mixed-effects multilevel linear regression analysis showed that the variables significantly related to lower VD values were the winter-spring period and nutritional status of risk of malnutrition. VD values decreased on average 8.29 units when the measurement was performed in the winter-spring period compared with the summer-autumn period. Regarding nutritional status, in infants at risk of malnutrition, vitamin D values would be lower by 9.28 units on average, compared with eutrophic infants. Vitamin D values in overweight or obese infants would not be significantly different from eutrophic infants (Table 2).

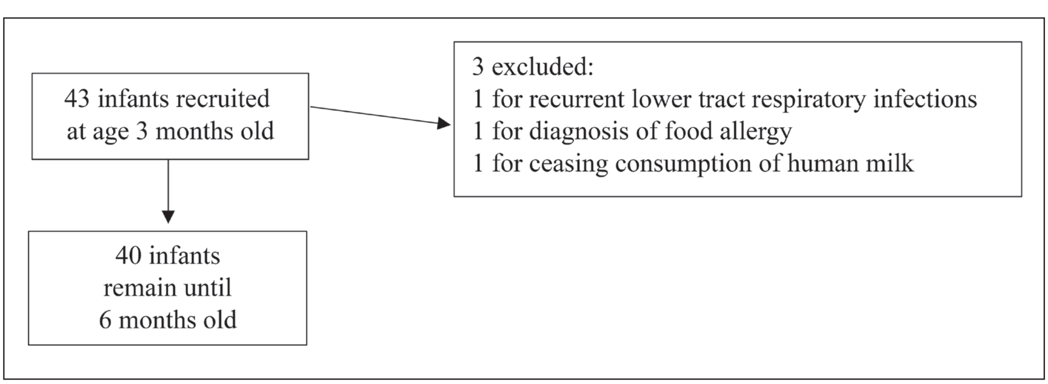
Discussion

There is a high frequency of VD deficiency and insufficiency in our study population.

At the time of this study, no data were available in Chile that reflected the nutritional status of VD in healthy supplemented infants. Recently, Pacheco et al[17] reported no deficiency and only 6.8% of insufficiency in 6-month-old infants seen in a public health center in Santiago (Latitude 33ºS) in a randomized clinical trial designed to compare standard supplementation vs. single dose, however, in this study, it was not established in which season of the year the measurements were made and it presented 55% frequency of exclusive breastfeeding.

On the other hand, the international prevalence of VD deficiency and insufficiency in healthy supplemented infants is variable as it depends on multiple factors including geographical, racial, and nutritional ones ranging from about 9.8 to 9.5% in Kayseri, Turkey[18] (latitude 38ºN), 12 to 40% in Boston, USA[19] (latitude 42ºN), and 41 to 44% in Taiwan[20] (latitude 23ºN).

The main weakness of our study is the small number of patients studied in addition to the difficulty in determining adherence to the supplement which has previously been reported as low in local and foreign



Patient flowchart

studies[21-22]. In our study, the mothers were asked about the supplement administration, attended monthly check-ups, answered surveys, and received regular education from the age of 3 months, in addition to accepting to puncture their healthy children to know the plasma concentrations of this vitamin, so it could be inferred that they were motivated to receive it.

On the other hand, the population studied corresponds to users of the private health system, generally with greater access to medical check-ups, and better nutrition and socioeconomic level than most of the national population. This situation should be a warning and challenge us to design a next study that includes the public health system and different areas of the Metropolitan Region. We should also consider in new studies those infants who received neither breast milk nor milk formulas, but modified cow's milk not fortified with VD, which is widely used in Chile.

Another aspect to investigate in the future is the VD maternal concentrations and its supplementation during pregnancy since, considering that the half-life of this supplement would be 3 weeks, the moment of transfer to the fetus would be short[23].

Despite all the above, this study establishes a precedent for evaluating alternatives to the currently used supplementation dose (e.g., considering higher daily doses or the use of weekly or monthly loads), the type of supplementation (ergocalciferol vs. cholecalciferol), and monitoring adherence.

As in other studies carried out in older children and adults, this study presents the same seasonal variation of VD concentrations, which clearly increased in the summer-autumn period[24]. Therefore, it can be extrapolated that sun exposure would have an impact on younger infants even when the recommendations are not to expose them to the sun.

In our study, no significant differences in VD concentrations were observed between eutrophic infants and those classified as overweight or obese, widely described at older ages[16], but there were lower concentrations in those at risk of malnutrition versus the eutrophic ones.

In conclusion, more studies are needed on the nutritional status of vitamin D in infants receiving supplementation with daily doses of 400 IU, even more so after the prolonged period of confinement we are experiencing at the time of writing this article.

Table 1. Distribution of variables of interest at 6 months old

Variable	Average and SD	Range
Vitamin D (ng/ml)	23.6 ± 9.5	8.10-54.80
	n	%
Vitamin D (ng/ml)		
Deficient (< 20)	16	40
Insufficient (20 a 29)	16	40
Sufficient (≥ 30)	8	20
Nutritional Status		
Malnutrition	0	00.0
Risk of malnutrition	5	12.5
Eutrophic	29	72.5
Overweight	5	12.5
Obesity	1	2.5
Receives Breastfeeding	38	95

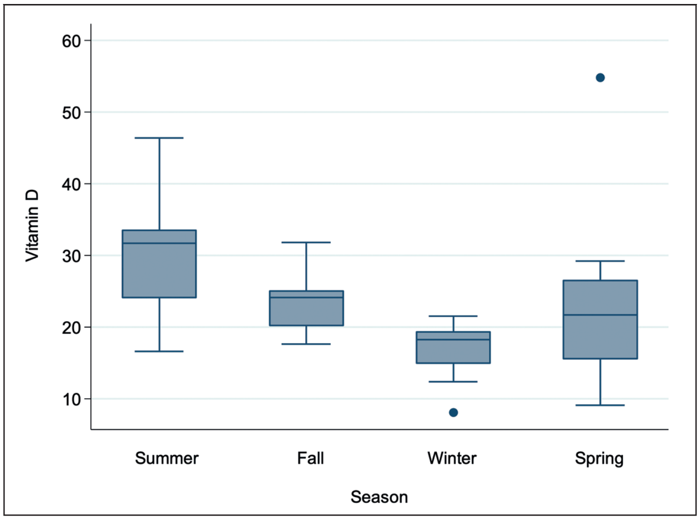


Figure 1. Variation in Vitamin D plasma levels (ng/ml) during seasons throughout the year.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Table 2. Multiple linear regression for prediction of Vitamin D levels

Variable		Coefficient	CI 95%	P-value
Season	Winter-Spring	-8.29	(-14.18; -2.41)	0.007
Nutritional Status	Risk of malnutrition	-9.28	(-18.02; -0.53)	0.038
	Overweight-Obesity	-1.34	(-9.28; 6.61)	0.735

*Reference categories: summer-autumn seasons and eutrophic nutritional status.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author. to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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