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ORIGINAL ARTICLE

Vitamin D levels and morbidity and mortality in very low birth weight preterm infants

Niveles de Vitamina D y morbimortalidad en el recién nacido prematuro de muy bajo peso al nacer

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

There is national information on vitamin D deficiency in critically ill patients and its negative effect on intensive care, and international information on vitamin D deficiency in premature infants and its relationship with different comorbidities.

What does this study contribute to what is already known?

We present data on vitamin D levels in preterm newborns and their association with morbidity. To our knowledge, this is the first study of this kind in this population in our country.

Abstract

Very low birth weight (VLBW) preterm newborns lack some nutrients such as vitamin D (VD), which is important in the function and development of different systems. **Objective:** To evaluate serum levels of 25-OH-VD in VLBW newborns and to describe the possible association between its deficit and frequent morbidities in this population. **Patients and Methods:** Cross-sectional study of VLBW newborns (< 1,500 g and/or < 32 weeks of gestational age). A single measurement of serum 25-OH-VD levels was performed in the first 72 hours of postnatal life (chemiluminescent immunoassay). Perinatal characteristics, treatments performed, and frequent comorbidities were analyzed. Deficiency of 25-OH-VD was defined as levels ≤ 20 ng/ml, determining a statistical association between this and various comorbidities at hospital discharge in the neonatal period. **Results:** 46 preterm newborns were evaluated. The mean serum level of 25-OH-VD was 19.7 ± 6.7 ng/ml. 52.2% (24/46) presented deficient levels, with lower values observed at lower gestational age ($p = 0.01$). There was an association between 25-OH-VD deficiency, the need for conventional mechanical ventilation ($p = 0.04$), and longer hospital stay ($p < 0.01$). There was an association with the presence of hemodynamically significant ductus arteriosus ($p < 0.01$). **Conclusions:** Deficiency of 25-OH-VD was frequent in VLBW newborns, with lower levels at lower gestational age. There was an association between 25-OH-VD deficiency, hospital stay, need for respiratory support, and patent ductus arteriosus.

Keywords:
Vitamin D;
25-OH-VD;
Newborn;
Patent Arteriosus Ductus;
Hospital Stay

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Introduction

Preterm newborns (PNB), especially those under 1500 grams, known as very low birth weight (VLBW) newborns[1], lack some nutrients that they normally obtain *in utero* in the last trimester of pregnancy[2]. Premature birth exposes them to a high risk of deficiency of minerals such as calcium and phosphorus, and micronutrients such as vitamin D (VD), considering that they get most of them in the last trimester of pregnancy[3].

Women during pregnancy frequently present low levels of 25-OH-VD, and even lower levels when measured in the umbilical cord[4].

VD is a fat-soluble vitamin that, when it is active, is involved in calcium homeostasis and the regulation of cell growth[5]. In mammals, VD is a cholesterol derivative, synthesized in the skin by the effect of UV-B radiation leading to the formation of cholecalciferol or vitamin D3[6]. This is the main source of VD in humans and can be obtained from the intake of some foods such as fish oils, liver, egg yolk, and fortified products[7], and Vitamin D2, or ergocalciferol, is obtained from ergosterol synthesized in plants with a much lower absorption than vitamin D3[8].

There are three biological forms of VD: the primary form; the 25- Hydroxy-Vitamin D in its hepatic hydroxylated form at carbon 25 (25-OH-VD), and the dihydroxylated form at the renal level 1α25 dihydroxy-cholecalciferol (1.25-OH2D)[9]. It should be noted that directly measured VD levels are highly variable, depending on the time of sun exposure, recent food intake, and also due to the short half-life of VD (about 24 hours)[9]. In parallel, the half-life of 1.25-OH2D is extremely short (a few hours), so its concentrations vary within a single day[9,10]. For this reason, serum levels of 25-OH-VD are the best representatives of VD deposits, with a half-life between 10 to 20 days[9]. Levels higher than 20 ng/ml are considered normal, and levels lower than or equal to 20 ng/ml are considered deficient[11,12].

It has been established that VD is important in the function of a series of systems, such as adequate bone growth, the stimulation of insulin production, myocardial contractility, function modulation of activated B and T lymphocytes, and pulmonary growth and development, among others. Therefore, its deficit can negatively affect the well-being of neonates, leading to slow growth, possible metabolic bone disease, fractures, and infections[13,14]. The American Academy of Pediatrics (AAP) recommends VD supplementation in all newborns, especially preterm infants[12,15] because parenteral nutrition, breast milk, and milk formulas indicated in neonatal feeding do not contain the recommended intake, and oral supplementation is essential[16].

The objective of this study was to present local data on serum 25-OH-VD levels in VLBW infants and to describe the association with common morbidities affecting this group of patients.

Patients and Method

Cross-sectional study with prospective recruitment of VLBW infants (< 1,500 grams and/or < 32 weeks of gestational age), admitted to the Neonatology Service of the *Hospital Guillermo Grant Benavente* (HGGB) of Concepción, between May 1, 2019, and March 1, 2020. Newborns with major congenital malformations and/or chromosomopathies and those who died in immediate care were excluded.

In newborns who met the inclusion criteria, serum 25-OH-VD levels were measured with a single sample of 0.8 ml of blood collected within the first 72 hours of life and were simultaneously performed with the routine tests requested by the attending physician. The sample was processed in the central laboratory of the HGGB using a chemiluminescent immunoassay technique in a Cobas® analyzer (Roche). Levels higher than 20 ng/ml were considered normal, and levels lower than or equal to 20 ng/ml were considered deficient[11,12]. At the time of the examination, none of these preterm infants had previously received VD supplementation in parenteral and/or enteral nutrition, since vitamin supplementation occurred from 5 days of age in parenteral nutrition, and at 10 days of life by enteral route in all patients with milk intake greater than 100 ml/kg/day.

All the newborns in the study group were evaluated according to the protocol of the Neonatology Service of the HGGB as follows: echocardiography between 24 and 72 hours of postnatal life to detect hemodynamically significant patent ductus arteriosus (HS-PDA), transfontanelar ultrasound at 7, 14, and 30 days of postnatal life to detect lesions associated with prematurity, laboratory tests for metabolic bone disease (MBD) at 15, 30, 45, and 60 days, and serial fundus examination by indirect ophthalmoscopy from 4 weeks of chronological age for detection and follow-up of retinopathy of prematurity (ROP).

Of each patient, perinatal characteristics, treatments used, and associated pathologies were recorded, such as early or late onset sepsis defined by the presence of positive blood cultures, confirmed necrotizing enterocolitis (NEC) (Bell's stage II), intraventricular hemorrhage (IVH) according to Papile's classification[17], periventricular leukomalacia (PVL), MBD defined by alkaline phosphatase > 500 IU and plasma phosphate level < 4 mg/dl[15,18], bronchopulmonary dysplasia (BPD) according to Jobe and Bancalari's classification[19], and ROP according to stages and zones[20]. At

the discharge of each patient, all the variables previously described for the study were recorded.

The data were tabulated in Microsoft Excel. Parametric descriptive statistics were performed by calculating means and standard deviation and non-parametric statistics by calculating medians. For comparison of perinatal characteristics, Student's t-test was used for normally distributed variables and the Mann-Whitney U test when there was no normal distribution. The chi-square test was used for qualitative variables. To evaluate the statistical association between neonatal morbidities and the deficiency or normality of 25-OH-VD levels, the chi-square test, pairwise independence test of qualitative variables, and Yates correction for continuity as an indicator were applied. A $p < 0.05$ was considered significant. SPSS version 25.0 (IBM) statistical software was used for data analysis.

The study was approved by the Scientific Ethical Committee of the Concepción Health Service (CEC-SSC 20-07-27, dated 17.08.2020) and informed consent was requested from the parents of the neonates on admission as protocol.

Results

83 preterm infants met the inclusion criteria, of which 46 were evaluated and completed the study. The remaining group, due to different reasons such as lack of reagent in the laboratory or not presenting medical indication for the test, did not enter the follow-up (figure 1).

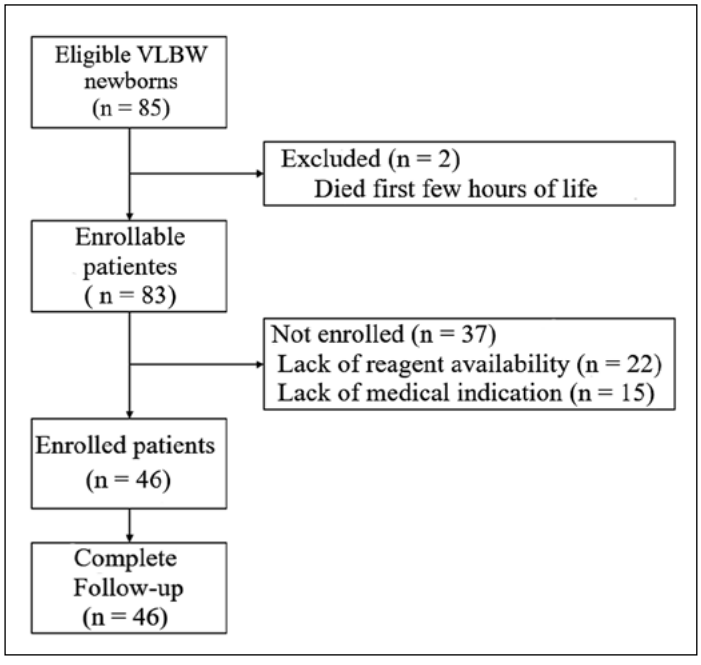

Figure 1. Study flow chart.

In the total group of preterm infants, the mean and standard deviation (SD) of 25-OH-VD levels was 19.7 ± 6.7 ng/ml. Of the 46 VLBW infants evaluated, 52.2% (24/46) had deficient levels, with a mean ± SD of 14.4 ± 3.3 ng/ml, (range 8.1-19.2), and 47.8% (22/46) had normal levels with 25.4 ± 4.5 ng/ml (range 20.1-40.6).

The mean ± SD of gestational age and birth weight of the total group was 29.6 ± 2.1 weeks and 1282 ± 352 grams, respectively, and 17.4% of them presented a weight below 1000 grams. There was no gender predominance. 87% of the mothers received antenatal corticosteroids and 37% received antibiotics before delivery. Of the neonates evaluated, 67% were delivered via cesarean section, and the APGAR score showed a median of 9 at 5 minutes after birth.

Table 1 shows the perinatal characteristics of the newborns with deficient and normal 25-OH-VD levels. The group with deficient levels had lower gestational age ($p = 0.01$) compared with the preterm group with normal levels. There was no association between deficit and nutritional status at birth. No differences were observed between the two groups with respect to gender, type of delivery, and antenatal corticosteroid administration, among others (table 1).

Table 2 describes some of the treatments provided during hospitalization. Preterm infants with 25-OH-VD deficiency had a greater need for respiratory support by CPAP ($p = 0.02$) and invasive ventilation ($p = 0.04$) compared with preterm NBs with normal levels. The duration of hospitalization was longer in the group of preterm infants with deficient levels ($p < 0.01$) (table 3). At lower gestational age, 25-OH-VD levels in the first 72 hours of postnatal life were lower (figure 2).

Table 3 describes the most frequent comorbidities of VLBW infants and their relationship with 25-OH-VD deficiency. A significant association was observed between deficient levels and hemodynamically significant patent ductus arteriosus, which required pharmacological treatment ($p < 0.01$). No association was observed between low levels and MBD, development of early and/or late onset sepsis confirmed by positive blood cultures, confirmed NEC, IVH, white matter lesion, ROP, and BPD. There was also no association between deficient 25-OH-VD levels and mortality ($p = 0.1$) (table 3).

Discussion

Most preterm infants younger than 32 weeks gestational age presented deficient levels of 25-OH-VD in the first 72 hours after birth; the lower the gestational age, the lower the 25-OH-VD levels. This relationship

was demonstrated by Monangi et al. [20], who in a population similar to ours found 64% of neonates with a deficit in the first 48 hours after birth. Likewise, Dawodu et al.[21], who evaluated preterm newborns between 26 and 34 weeks of gestational age, found 44% of neonates with severe 25-OH-VD deficiency (< 5 ng/ml) before supplementation.

Bearing in mind that the preterm infants presents 25-OH-VD deficiency from birth, it is important to consider the factors that determine these levels. There is the passive transplacental transfer of 25-OH-VD to the fetus, with neonatal levels between 50% and 70% of maternal levels[22]. Maternal deficiency can be produced by various factors, among which suboptimal intake, intestinal malabsorption, increased catabolism due to some drugs, or secondary to decreased production, as occurs especially in the black race[22].

Decreased maternal sun exposure, for whatever reason, is one of the main factors that lead to low levels of 25-OH-VD in both the mother and the newborn[22]. Considering that the levels in pregnant women are highly relevant for the infant, the possibility of maternal supplementation has been evaluated. A systematic review showed a decrease in the risk of low-birth-weight infants and a possible reduction in fetal and neonatal mortality when supplementing pregnant women with up to 2,000 IU/day[23]. The association between newborns with birth weights below the 10th percentile for gestational age (small for gestational age) and 25-OH-VD deficiency has been established in the literature[24], however, our study did not demonstrate this association.

Another factor influencing neonatal 25-OH-VD

Table 1. Perinatal characteristics of 46 VLBW infants, according to normal or deficient levels of vitamin D

	VLBW infant with deficient levels of Vit D ≤ 20 ng/ml	VLBW infant with normal levels of Vit D > 20 ng/ml	p
nº (%)	24 (52.2)	22 (47.8)	
X ± SD Gestational age, wks [rango]	28.9 ± 2.3 [23-34]	30.4 ± 1.5 [28-34]	0.01
X ± SD Birth wight, g [rango]	1.195 ± 315 [425-1.940]	1.379 ± 344 [795-2185]	0.15
Female gender, nº (%)	12 (50)	10 (45.4)	0.76
AGA, nº (%)	13 (54.1)	9 (40.9)	0.38
SGA, nº (%)	9 (37.5)	11 (50)	0.4
LGA, nº (%)	2 (8.3)	2 (9.1)	0.93
APGAR 5 min, median [range]	8 [1-9]	9 [3-9]	0.14
Vaginal delivery, nº (%)	10 (41.6)	5 (22.7)	0.17
Antenatal corticosteroids, nº (%)	21 (87.5)	19 (86.3)	0.91
Antenatal antibiotics, nº (%)	9 (37.5)	8 (36.3)	0.94
PROM > 18 hours, nº (%)	7 (29.1)	3 (13.6)	0.21

VLBW infants = very low birth wight newborns; AGA = adequate for gestational age; SGA = small for gestational age; LGA = large for gestational age; PROM = premature rupture of membranes.

Table 2. Treatments during hospitalization in 46 VLBW infants, according to normal or deficient levels of vitamin D

	VLBW infants with deficient levels of Vit D ≤ 20 ng/ml	VLBW infants with normal levels of Vit D > 20 ng/ml	p
nº (%)	24 (52.2)	22 (47.8)	
Days to full enteral feeding, median, [range]	11 [5-55]	9 [5-22]	0.08
Preterm with surfactant, nº (%)	12 (50)	6 (27.3)	0.12
Preterm with CPAP, nº (%)	23 (95.8)	14 (63.6)	0.02
Preterm with NIPPV, nº (%)	9 (37.5)	8 (36.4)	0.94
Preterm with, CMV nº (%)	11 (45.8)	3 (13.6)	0.04

VLBW infants = very low birth wight newborns; CPAP = Continuous positive airway pressure; NIPPV = nasal intermittent positive pressure ventilation; CMV = conventional mechanical ventilation.

levels is the type of postnatal feeding administered. Breast milk contains between 12-60 IU/l versus most formulas containing 400 IU/l[25]. For this reason, supplementation is necessary, especially in those neonates exclusively breastfed[25]. The American Academy of Pediatrics recommends that newborns fed with exclusive or mixed breastfeeding should be supplemented with 400 IU/day, indicated from the first days of postnatal life, an indication that would have no adverse effects and would prevent rickets[7]. There is still no clarity about the most adequate dose to avoid deleterious extra-skeletal effects[7].

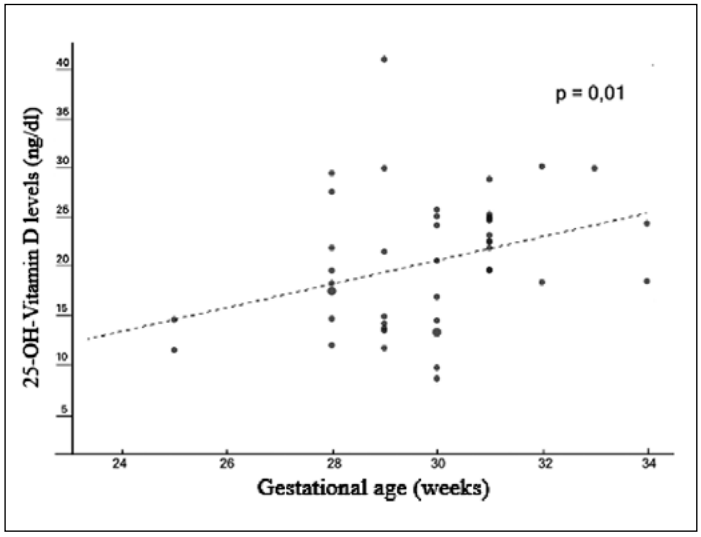

Figure 2. 25-OH-Vitamin D levels in the first 72 hours of postnatal life according to gestational age. Pearson linear correlation, r = 0,37.

It has been established that VD would act in different systems through diverse mechanisms, therefore, its potential role in diverse neonatal morbidities has been studied but with inconclusive results. Regarding the respiratory system, animal models have shown that the VD receptor would have a role in perinatal lung development, both in differentiation and maturation since embryogenesis[26]. Our study found no differences in the development of BPD, a finding similar to that described by Joung et al.[27], who observed no increase in the incidence of BPD with low levels of 25-OH-VD in the umbilical cord in neonates younger than 29 weeks gestational age at birth. However, Çetinkaya et al.[28] reported that preterm infants less than 32 weeks gestational age at birth with deficient levels required more respiratory support, invasive and/or noninvasive ventilation, and also showed a higher prevalence of hs-PDA in relation to 25-OH-VD deficit or insufficiency, in agreement with what was found in our study.

In this clinical trial, we did not observe an association in the incidence of early and/or late onset sepsis with 25-OH-VD deficiency at birth. A study in a similar population of preterm infants reported that newborns whose mothers had lower levels of VD were at higher risk of early onset sepsis[29]. Also, the study by Dhandai et al.[30] found a higher incidence of late onset sepsis in term and near-term newborns who had lower VD levels at hospital admission. The higher incidence of sepsis reported in those studies could be related to the role of 1.25-OH2D which would promote lymphocyte differentiation from Th1 to Th2 and inhibit the proliferation of activated B cells[31]. It has been shown

Table 3. Normal or deficient levels of 25-OH-Vitamin D and its association with different neonatal comorbidities

	VLBW infants with deficient levels of Vit D ≤ 20 ng/ml	VLBW infants with normal levels of Vit D > 20 ng/ml	p*
nº (%)	24 (52.2)	22 (47.8)	
EOS and/or LOS, nº (%)	3 (12.5)	2 (9.1)	0.39
NEC, nº (%)	5 (20.8)	1 (4.5)	0.23
IVH, nº (%)	9 (37.5)	2 (9.1)	0.06
PVL, nº (%)	4 (16.6)	0	0.13
hs-PDA, nº (%)	16 (66.7)	3 (13.6)	< 0.01
BPD, nº (%)	5 (20.8)	1 (4.5)	0.23
ROP, nº (%)	2 (8.3)	1 (4.5)	0.61
MBD, nº (%)	4 (16.6)	0	0.13
Hospitalization □ 50 days, nº (%)	14 (58.3)	3 (13.6)	< 0.01
Death, nº (%)	2 (8.3)	0	0.51

*Pearson's chi-square test, test of independence between pairs of qualitative variables. Indicator: Yates Continuity Correction. EOA = early onset sepsis; LOS = Late onset sepsis; NEC = necrotizing enterocolitis; IVH = intraventricular hemorrhage; PVL = Periventricular leukomalacia; hs-PDA = hemodynamically significant patent ductus arteriosus; BPD = bronchopulmonary dysplasia; ROP = retinopathy of prematurity; MBD = Neonatal metabolic bone disease.

that low levels of VD are associated with less differentiation of Th1 to Th2 lymphocytes and plasmacytoid dendritic cells, putting these children at a higher risk of viral and bacterial infections and various inflammatory processes[31].

In this study, we found no association between ROP and 25-OH-VD deficiency, similar to that described by Shah et al.[32]. Some research on the role of VD in diabetic retinopathy and the development of abnormal neovascularization showed that VD receptor agonists could regulate ocular angiogenesis by modulating vascular endothelial growth factor expression[33].

Regarding 25-OH-VD levels and the development of NEC, the reported results are contradictory. Our study found no association between low levels and the development of NEC, as observed by Kim et al.[34] in a similar population of preterm infants. However, Yang et al[35] found significantly lower levels in neonates who developed NEC vs. those who did not. The possible association would be due to the increased expression of Toll-like receptors 2 and 4 (TLR2 and TLR4) in patients with NEC. These receptors would be modulated by maintaining of adequate VD levels, as has been studied in murine animal models, where a reduction in the expression of TLR2 and TLR4 was observed, with the consequent decrease in structural damage and preservation of the intestinal barrier function[36].

White matter lesion or PVL was not associated with 25-OH-VD deficiency in this study. It has been mentioned that, in adult patients, the deficit would favor a higher risk of white matter damage, with possible cerebral microangiopathy and lacunar stroke[37]. The association between low levels and increased incidence of PVL has not been reported in neonatal studies. Preterm infants with deficit also did not have a higher incidence of IVH in our study, in contrast to the findings of Boskabadi et al.[38].

The close relationship between 25-OH-VD levels and adequate bone mineralization is known, however, in this clinical work, we did not observe a higher incidence of MBD in those newborns with VD deficit, unlike what was published by Chhina et al.[39] in preterm infants younger than 32 weeks of gestational age in India.

To the best of our knowledge, this would be the first study in Chile that has evaluated 25-OH-VD levels in preterm infants. In our country, it was reported that patients under 15 years of age, admitted to the Pediatric Intensive Care Unit, presented a high incidence of 25-OH-25-OH-VD deficiency associated with an unfavorable clinical outcome[40].

Among the limitations of this clinical trial are the small size of the population evaluated and the fact that the study was carried out in a single center, the results could vary in preterm infants from other geographical latitudes, with mothers of different races, with different nutritional states, and different degrees of sunlight exposure. The lower gestational age observed in the group of newborns with deficient levels could explain both the higher incidence of deficit and some associated variables, which could be objectified through multivariate analysis, something that this study lacks because of its limited sample size and because it is primarily descriptive.

In conclusion, 25-OH-VD deficiency was frequent in VLBW infants, with lower serum levels at lower gestational age. We observed an association between the deficit in the first 72 hours after birth, hospital stay, need for respiratory support, and the presence of hs-PDA. No association was found between low serum VD levels and other common neonatal morbidities. Further multicenter, prospective studies are needed to evaluate the effect of VD deficit at birth and its relationship with neonatal outcomes.

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.

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.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

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