

Low levels of vitamin D at one month of age and its association with bronchopulmonary dysplasia in premature newborns under 32 weeks and/or under 1500 g

Niveles bajos de vitamina D al mes de vida y su asociación con displasia broncopulmonar en recién nacidos prematuros menores de 32 semanas y/o menores de 1.500 g

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

Vitamin D deficiency is frequent in preterm newborns and has been related to respiratory pathology and bronchopulmonary dysplasia (BPD). However, evidence of its development is controversial. In Chile, there are no studies that analyze the relationship between vitamin D levels measured at one month of life and the diagnosis of bronchopulmonary dysplasia.

What does this study contribute to what is already known?

We present a retrospective data analysis of clinical records regarding 25-hydroxyvitamin D levels measured at one month of life in preterm newborns and its association with BPD. Most preterm newborns had VD deficiency; however, no association was observed between low VD levels with perinatal characteristics, respiratory support, hospital stay, and comorbidities evaluated, including BPD.

Abstract

Premature newborns (PTNBs) are at increased risk of vitamin D (VD) deficiency. VD is currently recognized for its multiple functions, including its role in lung maturation, and a reported association between VD deficiency and the development of bronchopulmonary dysplasia (BPD). **Objective:** To determine whether there is an association between low 25(OH)D levels measured at 1 month of age in PTNBs and BPD. **Patients and Method:** A retrospective study was conducted with data collected from clinical records of VLBW infants (< 1,500 grams) and/or < 32 weeks of gestational age. 25(OH)D levels at 1 month of age, perinatal characteristics, and postnatal outcomes were analyzed. Low 25(OH)D levels were defined as < 30 ng/ml, and a statistical association with BPD and other comor-

Keywords:

Bronchopulmonary Dysplasia; Prematurity; Vitamin D Deficiency; Vitamin D and Neonatal Outcome; 25-(OH)D

bidities was evaluated. **Results:** A total of 147 PTNBs were included in the analysis. The mean VD level was 22.0 ± 10.3 ng/ml. 85.0% (125/147) had low levels and 45.0% (66/147) developed BPD. No association was observed between low 25(OH)D levels and comorbidities, including BPD. The BPD group had a lower gestational age ($p < 0.0001$), birth weight ($p < 0.0001$), and greater need for any respiratory support ($p < 0.001$), along with a significant association with all comorbidities evaluated ($p < 0.001$). **Conclusions:** Most PTNBs had VD deficiency. No association was found between low VD levels and BPD.

Introduction

Vitamin D (VD) deficiency is a worldwide public health problem¹. In Chile, according to the National Health Survey 2016 – 2017, it is estimated that only 13% of women of childbearing age have sufficient levels of VD (≥ 30 ng/ml)^{2,3}.

In pregnancy, 25-hydroxyvitamin D [25-(OH)D] is critical for fetal development during cell proliferation, differentiation, and maturation stages, so its optimal concentrations can influence early organogenesis and subsequently affect health status⁴. 25-(OH)D freely crosses the placenta and levels in the newborn depend on the mother, corresponding to 50-70% of maternal levels^{5,6}.

25-(OH)D blood concentration is used as a biomarker reflecting the body status of VD levels because of its longer half-life than that of its metabolically active form [1,25-(OH)2D], being 15 to 20 days versus 10 to 20 hours, respectively. In addition, serum levels of 1,25-(OH)2D are variable within a single day^{5,7}. Despite advances in the development of sensitive and accurate tests, there is no consensus on their level for optimal health in pregnant women and newborns^{6, 8-12} and definitions for the general population are variable¹⁰. Furthermore, all these recommendations assume adequate intake and absorption of calcium and phosphate, which is not always the case⁹. Current literature¹⁰⁻¹² considers 3 ranges to establish VD status according to 25-(OH)D levels as follows: sufficiency ≥ 30 ng/ml, insufficiency between 20 - 29 ng/ml, and deficiency < 20 ng/ml.

Regarding VD deficiency, adverse maternal and fetal outcomes have been reported, with an emerging concern being its relationship with increased respiratory morbidity, including neonatal respiratory distress syndrome (NRDS)^{1,6,7}, bronchopulmonary dysplasia (BPD)¹³⁻¹⁵, and even recurrent wheezing and asthma^{5,6,16}.

BPD is a chronic lung disease resulting from aberrant pulmonary alveolar and vascular development affecting gas exchange¹⁷ and is caused by multiple factors acting on the immature airway¹⁸. It corresponds to the most prevalent long-term morbidity among extreme-

ly preterm newborns^{5,19}, with an incidence of 32% to 59% depending on the definition¹⁷ and is inversely proportional to gestational age²⁰.

It has been described that VD prevents inflammation and pulmonary fibrosis, reducing the incidence of BPD²¹. Also, low levels of 25-(OH)D could be associated with increased need and duration of ventilation support along with the development of BPD^{7,18}. Currently, the association between low levels of VD and BPD is controversial.

The objective of this study is to determine whether there is an association between low 25-(OH)D levels measured at 1 month of life and BPD in preterm newborns with birth weight $< 1,500$ g and/or < 32 weeks of gestational age.

Patients and Method

Retrospective observational study with data collection from clinical and laboratory records of very low birth weight newborns (VLBWNB), with a birth weight $< 1,500$ g and/or < 32 weeks of gestational age, hospitalized in the Neonatology Service of the *Hospital San Juan de Dios* (HSJD) in Santiago between 2020 and 2022. Clinical records with incomplete data, patients transferred from other centers, patients who died before one month of life, and those who did not require any type of ventilatory support and/or oxygen therapy were excluded.

Perinatal characteristics, treatments received, and pathologies associated with prematurity and related to the development of BPD were recorded. Among the morbidities, the following were included: NRDS requiring pulmonary surfactant, neonatal pneumonia, necrotizing enterocolitis (NEC) according to Bell's classification, hemodynamically significant patent ductus arteriosus (hsPDA) defined by its impact on cardiovascular function assessed by echocardiogram and therefore treated, clinical sepsis and/or confirmed with positive blood cultures, BPD diagnosed based on Jobe and Bancalari classification, i.e. patients who were still receiving supplemental oxygen ($FiO_2 > 21\%$) or mechanical ventilation at 36 weeks corrected gesta-

tional age or more. Maternal age was recorded, along with whether they had prenatal care based on their prenatal care card, and whether complete pulmonary maturation was achieved, defined as two or more doses of antenatal corticosteroid. The 25-(OH)D levels measured according to local protocol at 1 month of life were recorded, considering as sufficient levels ≥ 30 ng/mL, low levels < 30 ng/mL, insufficiency between 20–29 ng/mL, and deficiency as < 20 ng/mL^{15–17}.

Since it is an emerging field of research, no papers were found to establish a sample size calculation concordant with the methodology of this study.

The data were tabulated in a Microsoft Excel spreadsheet. Continuous variables were expressed as mean and standard deviation (SD) or median and interquartile range. The Shapiro-Wilk normality test was performed, the Student's t-test was used to calculate statistical differences for the parametric variables, and the Mann-Whitney test was used for the nonparametric ones. Categorical variables were expressed as frequency plus percentage, and Fisher and Chi-square tests were used to evaluate the association between the groups and the different qualitative variables. To analyze the relationship between BPD and VD levels and the independent variables, binary logistic regression was used. A $p < 0.05$ value with a 95% confidence interval was considered significant. STATA 16 statistical software was used for data analysis.

The study was approved by the Scientific Ethical Committee of the *Hospital San Juan de Dios* (research protocol review report N° 299 Version 1.0, July 25th, 2024). Waiver of informed consent was requested, and alphanumeric anonymization was performed; therefore, no sensitive data were recorded during the data recording procedure.

Results

There were 187 preterm deliveries of < 32 weeks and/or < 1500 g hospitalized in the Neonatal Intensive Care Unit of the HSJD between 2020 and 2022. A total of 206 clinical records were reviewed, excluding 59 patients: 12 with incomplete data on clinical records, 16 transferred from other hospitals, 21 died before one month of life, and 10 patients who did not require any ventilatory support and/or oxygen therapy. A total of 147 patients met the inclusion criteria, of whom 66 patients had BPD (Figure 1).

The median and SD of gestational age at birth were 29.2 ± 2.2 , weight was 1.297 ± 374 , and most newborns were male. APGAR score at 1'min was 5.5 ± 2.5 and at 5'min 8.1 ± 5.1 . Maternal age was 30.0 ± 6.3 , most of them had prenatal care, and 59.2% received complete pulmonary maturation therapy. A total of 74.2% had

NRDS, requiring surfactant in 48.3% of them, 33.3% had sepsis, and 13.0% had hsPDA. The median and SD of oxygen therapy days were 41.0 ± 41.0 , CPAP was 11.0 ± 13.5 , and IMV was 7.9 ± 22.0 . 45.0% of patients had a BPD diagnosis. Regarding the month of life 25-(OH)D levels, the median was 22.0 ± 10.3 ng/mL, only 15.0% (22/147) had sufficient VD levels (≥ 30 ng/mL) at month of life, while 85.0% (125/147) had low levels < 30 ng/mL (Table 1).

The median for the group with sufficient VD levels was 40ng/mL, being statistically significant ($p < 0.0001$) compared to the median for the group with low VD levels, which was 17.8ng/mL. Regarding perinatal outcomes, there was no significant difference in the median between groups according to month of life VD levels in terms of gestational age, birth weight, sex, and APGAR score at 1' and 5' minutes. In the group with sufficient VD levels, maternal age was higher ($p = 0.0104$) compared to the group with low levels.

There were no differences between the groups regarding prenatal care and pulmonary maturation. In relation to respiratory support, there were no differences between the groups according to VD levels in median days of IMV, days of CPAP, and days of oxygen therapy. Regarding medical comorbidities, in the group with sufficient VD levels, 68.2% had NRDS and 50.0% required surfactant compared to the group with low VD levels, in which 75.2% had NRDS and 48.0% required surfactant, with no statistically significant differences. There was a trend in relation to preterm newborns with hsPDA, where 15.2% had low VD levels, while there were no cases in the group with sufficient VD levels ($p = 0.0500$). No differences were found between the two groups in terms of clinical and/or confirmed sepsis. In the group with sufficient VD levels, 54.5% developed BPD compared to 43.2% in the group with low VD levels; this variable was not significant. There were no differences in the median hospital stay according to VD levels (Table 2). Of the sample studied, 6 patients had NEC, all with low VD levels at one month of life, and 5 patients had neonatal pneumonia, of which only 2 had sufficient VD levels.

Table 3 summarizes the characteristics of the BPD and non-BPD groups. Regarding the mean and SD of month-of-life vitamin D levels, there was no significant difference between the two groups. In the BPD group, both gestational age ($p < 0.0001$) and birth weight ($p < 0.0001$) were significantly lower than the non-BPD group, with no differences in sex, APGAR score at 1' and 5' minutes, maternal age, prenatal care, and lung maturation. The group that developed BPD had a greater need for all types of respiratory support, with more days of IMV ($p = 0.0006$), CPAP

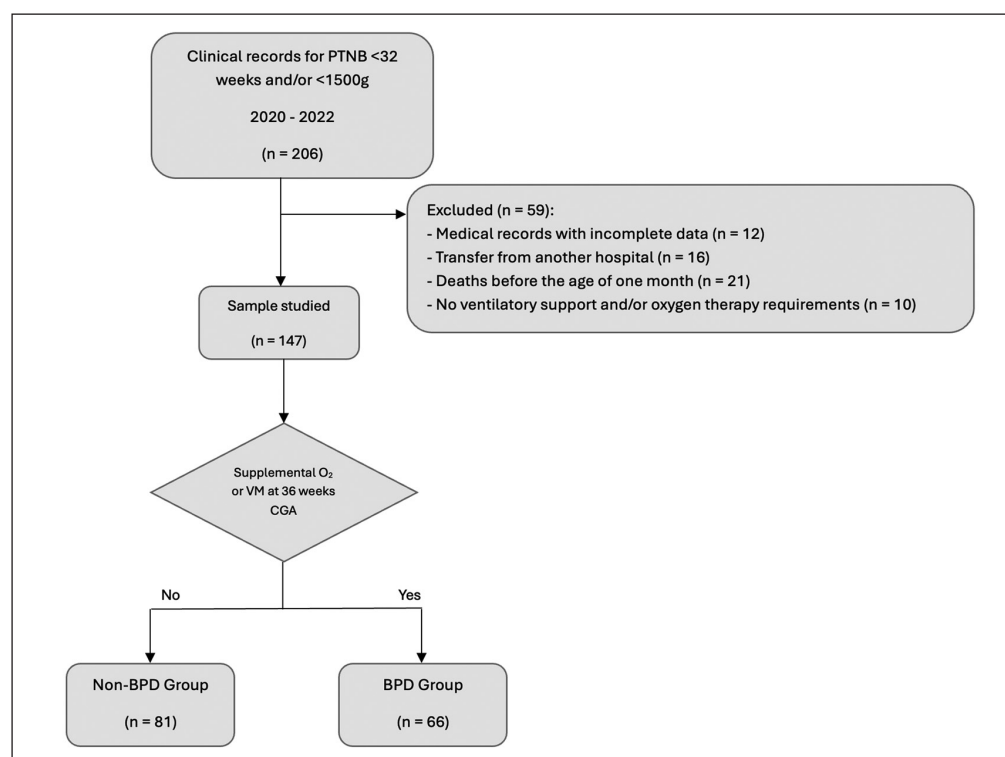


Figure 1. Flowchart of the study. Abbreviations: PTNB, premature newborn; O₂, oxygen; MV, mechanical ventilation; CGA, corrected gestational age; BPD, bronchopulmonary dysplasia.

Table 1. General description of the sample of 147 premature infants < 32 weeks gestational age and/or < 1500g

Variables	n = 147
25-(OH)D Levels ng/mL	22.0 ± 10.3
Sufficiency ≥ 30 ng/mL	42 ± 10.0
Insufficiency 20 - 29 ng/mL	24.5 ± 2.8
Deficiency < 20 ng/mL	15.2 ± 3.2
Age (weeks)	29.2 ± 2.2
Weight (grams)	1297 ± 374
Male sex (%)	91 (61.9%)
APGAR score 1'min	5.5 ± 2.5
APGAR score 5'min	8.1 ± 5.1
Maternal age (years)	30.0 ± 6.3
Prenatal care (%)	132 (90.0%)
Pulmonary maturation therapy (%)	87 (59.2%)
IMV Days	7.9 ± 22.0
CPAP Days	11.0 ± 13.5
Oxygen therapy days	41.0 ± 41.0
Days of hospitalization	69.0 ± 30.3
NRDS (%)	109 (74.2%)
Surfactant (%)	71 (48.3%)
hsPDA (%)	19 (13.0%)
Clinical and/or proven sepsis (%)	49 (33.3%)
BPD (%)	66 (45.0%)
Deceased	3 (2.0%)

Data are expressed as mean ± standard deviation or n (%). Number of patients according to 25-(OH)D levels: sufficiency n = 22; insufficiency n = 46; deficiency n = 79. Abbreviations: IMV, invasive mechanical ventilation; NRDS, neonatal respiratory distress syndrome; hsPDA, hemodynamically significant patent ductus arteriosus; BPD, bronchopulmonary dysplasia.

($p < 0.0001$), and oxygen therapy ($p < 0.0001$), in addition to a longer hospital stay ($p < 0.0001$) versus the non-BPD group. In the BPD group, 71.2% developed NRDS requiring surfactant ($p < 0.0001$) versus 29.6% in the non-BPD group. An association was also observed between the BPD group and the presence of hsPDA ($p = 0.0014$) and clinical and/or confirmed sepsis ($p = 0.0001$).

Finally, vitamin D levels were analyzed by range of sufficiency, insufficiency, and deficiency for the BPD and non-BPD group (Table 4). 53.7% of the sample had VD levels in the deficiency range, and 31.3% had VD levels in the insufficiency range at 1 month of life. No association was found between BPD and low VD levels ($< 30\text{ng/mL}$) at 1 month of life.

Discussion

VD deficiency is frequently observed in pregnant and lactating women. In pregnancy, VD deficiency has been reported between 47 and 83% in white and black women, respectively⁴. Several studies have evaluated cord blood VD levels, showing a high prevalence of deficiency among newborns, ranging from 28% in Poland to more than 80% in Germany and Thailand⁶. In preterm newborns, deficiency is described in 70% with a range between 33 to 80%²². These figures agree with our results, where most of them had deficient VD levels, and globally, 85% had low VD levels. Re-

Table 2. Characteristics of 147 premature infants according to low and sufficient levels of 25-(OH)D measured at one month of age

Variables	Vit D < 30 ng/mL (n = 125)	Vit D ≥ 30 ng/mL (n = 22)	p-value
Vitamin D (ng/mL)	17.8 (14.8 – 23.0)	40.4 (33.4 – 46.9)	< 0.0001*
Age (weeks)	30.0 (28.0 – 31.0)	30.0 (28.0 – 30.0)	0.5512*
Weight (grams)	1.310.0 (1.015.0 – 1.535.0)	1.305.0 (882.0 – 1.620.0)	0.5815*
Male sex (%)	63.2	54.5	0.4408 [‡]
APGAR score 1'min	6.0 (3.0 – 8.0)	7.5 (5.0 – 8.0)	0.0679*
APGAR score 5'min	8.0 (7.0 – 9.0)	9.0 (8.0 – 9.0)	0.1987*
Maternal age (years)	29.0 (26.0 – 34.0)	34.0 (30.0 – 38.0)	0.0104*
Prenatal care (%)	90.4	86.4	0.5641 [‡]
Pulmonary maturation therapy (%)	59.2	59.1	0.9923 [‡]
IMV Days	1.0 (0.0 – 4.0)	1.0 (0.0 – 7.0)	0.8653*
CPAP Days	5.0 (1.0 – 13.0)	7.0 (1.0 – 30.0)	0.7457*
Oxygen therapy days	31.0 (4.0 – 62.0)	45.5 (2.0 – 80.0)	0.5142*
Días hospitalización	62.0 (45.0 – 85.0)	66.0 (56.0 – 87.0)	0.2429*
NRDS (%)	75.2	68.2	0.4881 [‡]
Surfactant (%)	48.0	50.0	0.8626 [‡]
hsPDA (%)	15.2	0	0.0500 [‡]
Clinical and/or proven sepsis (%)	31.2	45.5	0.1909 [‡]
BDP (%)	43.2	54.5	0.3238 [‡]

Data are expressed as median (p25–p75) or n (%). *Mann-Whitney test, [‡]Test of proportions. Abbreviations: IMV, invasive mechanical ventilation; NRDS, neonatal respiratory distress syndrome; hsPDA, hemodynamically significant patent ductus arteriosus; BPD, bronchopulmonary dysplasia.

Table 3. Characteristics of 147 premature infants <32 weeks of gestational age according to BPD and non-BPD groups

Variables	Non-BPD Group (n = 81)	BPD Group (n = 66)	p-value
Vitamin D (ng/mL)	21.3 ± 9.3	22.9 ± 11.4	0.3314*
Age (weeks)	30.2 ± 1.6	28.0 ± 2.2	< 0.0001*
Weight (grams)	1416.4 ± 325.2	1150.0 ± 379.5	< 0.0001*
Male sex (%; IC 95%)	56.8 (45.3 – 67.7)	68.2 (55.5 – 79.1)	0.1572 [‡]
APGAR score 1'min	5.9 ± 2.4	5.2 ± 2.5	0.0782*
APGAR score 5'min	8.7 ± 6.7	7.3 ± 1.7	0.0749*
Maternal age (years)	30.2 ± 5.9	29.8 ± 6.8	0.7448*
Prenatal care (%; IC 95%)	92.6 (84.5 – 97.2)	86.4 (75.6 – 93.5)	0.2146 [‡]
Pulmonary maturation therapy (%; IC 95%)	58.0 (46.5 – 68.9)	60.6 (47.8 – 72.4)	0.7514 [‡]
IMV Days	1.8 ± 4.6	15.3 ± 30.5	0.0006*
CPAP Days	5.3 ± 8.9	17.5 ± 15.1	< 0.0001*
Oxygen therapy days	16.5 ± 24.4	70.7 ± 36.6	< 0.0001*
Days of hospitalization	54.5 ± 20.2	86.8 ± 31.2	< 0.0001*
SDRN (%) IC 95%	58.0 (46.5 – 68.9)	93.9 (85.2 – 98.3)	< 0.0001 [‡]
Surfactante (%) IC 95%	29.6 (19.9 – 40.8)	71.2 (58.7 – 81.6)	< 0.0001 [‡]
hsPDA(%)	4.9 (1.3 – 12.1)	22.7 (13.3 – 34.6)	0.0014 [‡]
Clinical and/or proven sepsis (%)	19.8 (11.7 – 30.0)	50.0 (37.4 – 62.5)	0.0001 [‡]

Data are expressed as mean ± standard deviation or n (%). *Student t test, [‡]Test of proportions. Abbreviations: IMV, invasive mechanical ventilation; NRDS, neonatal respiratory distress syndrome; hsPDA, hemodynamically significant patent ductus arteriosus; BPD, bronchopulmonary dysplasia.

Table 4. Description according to vitamin D levels by Non-DBP and DBP group

25-(OH)D ng/mL levels	Non-BPD Group (n = 81) N (%)	BPD Group (n = 66) N (%)	p-value
Sufficiency ≥ 30 ng/mL	10 (12.4)	12 (18.2)	0,614 χ^2
Insufficiency 20 - 29 ng/mL	26 (32.1)	20 (30.3)	
Deficiency < 20 ng/mL	45 (55.6)	34 (51.2)	

Data are expressed in n (%). χ^2 Chi-square test. Abbreviations: BPD, bronchopulmonary dysplasia.

garding the nutritional regimen according to the local protocol, enteral stimulation is initiated at 24 - 48 hours of life, starting parenteral nutrition (PN) from the first day of life, and the supply of vitamins and trace elements from the 4th day of life through the PN. Breast milk (BM) is fortified when reaching an enteral volume of 80 - 100cc/kg/day and, when PN is suspended, 800 IU of VD (400 IU based on ACD vitamins and 400 IU of vitamin D) is administered via oral mucosa. BM fortification started at 2% and increased every 2 days up to 6% according to tolerance. The total feeding volume is 150cc/kg/day. Feeding can be BM or preterm formula.

Regarding the different regimens of VD intake in preterm newborns, Yang et al. observed no differences between the high-dose (800-1000 IU/day) and low-dose (400 IU/day) groups in calcium, phosphate, and 25-(OH)D concentrations and BPD. However, length, head circumference, and IgA and IgG levels were significantly increased in the high-dose group²³. A recently published study observed that VD deficiency in preterm newborns is associated with longer duration of PN and lower BM intake, affecting calcium and PTH levels²⁴.

There were high levels of sepsis among preterm newborns (Table 1), although unrelated to VD levels (Table 2). In different studies with measurement of 25-(OH)D from cord blood and in the first 72h of life, no relationship was found between VD deficiency and sepsis^{1,18,25}; however, in the work of Kim et al, a higher frequency of sepsis was observed in premature newborns with severe deficiency (< 10ng/mL)¹⁸. Systemic inflammation induced by sepsis, either early or late, affects normal pulmonary and vascular development, being a risk factor for BPD²⁶, which is observed in our results, being more frequent in the BPD group (Table 3).

PTNB have a higher risk of VD deficiency, since transplacental transfer of 25-(OH)D is mainly in the third trimester of gestation^{5,22}. Several maternal risk factors contribute to low maternal-fetal 25-(OH)D concentrations, causing neonatal insufficiency⁶, with

risk of affecting anthropometric parameters, bone health, immune system, neurological development, and even increasing the risk of asthma and type 1 diabetes, being still an emerging field of research^{5,6}. In this context, Motlagh et al. measured maternal and preterm 25-(OH)D levels in the first 72 hours of life, observing a high rate of VD insufficiency and deficiency in the mother (44%) and preterm newborns (49%), raising the possible long-term public health impact of preventing VD deficiency⁴, especially in the critical period of development²⁷, recommending to screening for VD disorders in pregnant women to prevent complications⁴. A randomized study (n = 2500) sought to determine the effectiveness of a prenatal screening program to optimize 25-(OH)D levels and prevent pregnancy complications, decreasing preeclampsia, gestational diabetes mellitus, and preterm delivery by 60%, 50%, and 40%, respectively, in the screened pregnant group²⁸, concluding that prenatal VD screening and treatment is an effective approach to detect women with deficiency, improve 25(OH)D levels, and decrease adverse pregnancy outcomes^{4,28}.

The biological effects of the metabolically active form of VD, 1,25-(OH)₂D, are mediated by the VD receptor (VDR), with over 3000 genes reported to have VDR, many of which are involved in lung development by regulating the pseudoglandular and saccular stages, where the proximal and distal airways are formed, respectively⁷. Experimental studies have shown that VD plays a role in lung morphogenesis and surfactant production, as VDR is also present in type II pneumocytes^{7,21,29}. VD has antifibrotic, antioxidant, and anti-inflammatory actions, aids in lung development and maturation, and plays an essential role in surfactant production, alveolar structure, and function²¹. In animal models, VD deficiency during lung development was associated with inhibition of fibroblast and pneumocyte II proliferation, and reduced surfactant and antioxidant production. Prenatal VD deficiency has been associated with impaired lung anatomical development, including irregular cartilage, increased smooth muscle mass, and impaired lung function²².

In recent years, VD and the occurrence of lung disease have become a hot topic. It has been reported that VD prevents lung inflammation and fibrosis, thus reducing the incidence of BPD²¹, and that low VD levels could increase the risk of BPD, with the deficiency being associated with greater need for and longer duration of MV, along with the development of BPD^{7,18}. A randomized study in extreme preterm newborns evaluated early VD supplementation (800 IU/day) in the first 48 hours of life, which showed a significant reduction in BPD incidence and a decrease in levels of inflammatory markers such as CRP, IL-6, and TNF- α suggesting that early initiation of VD may prevent inflammation and improve outcomes in preterm newborns^{29,30}.

In 2015, Çetinkaya et al. (Turkey) published the first study, which proposed a possible association between maternal/neonatal 25-(OH)D levels and the development of BPD, which included 132 preterm newborns $\leq$ 32 weeks with NRDS. 31% developed BPD, all with VD levels at admission $< 10\text{ng/ml}$, being significantly lower than PTNB without BPD¹³. In 2021, Lu et al (China) measured 25-(OH)D levels in 286 preterm newborns < 37 weeks and $< 1,500\text{g}$, at birth and 6 months after reaching 40 weeks corrected age, to investigate the relationship between 25-(OH)D level at birth, BPD, and long-term lung function. PTNB with BPD had lower levels at birth than those in the non-BPD group, suggesting that the 25-(OH)D value at birth plays a role in long-term lung function impairment¹⁴. Park HW et al. (Korea) performed a systematic review and meta-analysis to evaluate the relationship between VD levels at birth and BPD, including 8 papers with a total of 909 PTNB, finding that both deficiency and low levels of VD at birth were associated with BPD²².

In contrast to the above studies, Joung et al. (USA) measured umbilical cord 25-(OH)D levels in 44 PTNB < 29 weeks and at 36 weeks of corrected age, finding that neither VD levels at birth nor at 36 weeks were associated with the development of BPD¹⁹. In Chile, in 2023, Vera and Bancalari published a paper that included PTNB < 32 weeks in which 25-(OH)VD was measured in the first 72 h of life, which showed no association between low levels and development of BPD²⁵.

The current evidence regarding the association between VD deficiency and BPD is still unclear. To date, the different studies include mostly the Middle Eastern population, with different values to define deficiency and low levels of VD, in addition to exploring the relationship between VD levels at birth with later development of BPD^{7,15,22}, being extremely limited the literature that includes VD levels measured later and relationship with BPD^{14,19}. Only two papers previously

mentioned were found, in which postnatal levels were measured to evaluate the association with BPD, with contradictory results^{14,19}.

To the best of our knowledge, this is the first work in Chile that studies the relationship between VD levels measured at one month of life and diagnosis of BPD. Our results in relation to the characteristics of the BPD group are consistent with those described in the literature regarding its association with greater need and longer duration of respiratory support, inversely proportional development to gestational age and birth weight, longer hospital stay, and association with NRDS and surfactant requirement, without finding an association between low VD levels at one month of life and BPD and other medical variables described. However, it was observed that PTNB with low levels had a higher frequency of hspDA, similar to what has been described in other studies^{13,25}, and all PTNB with NEC had low VD levels at one month of life. In this context, a possible association has been described for the increased expression of Toll-like receptors 2 and 4 in preterm newborns with NEC, which would be modulated by adequate levels of VD²⁵.

This is a preliminary study with several limitations. Since it is a retrospective data analysis from clinical records, it may contain errors, it has a small study population, and is limited to a single center. 25-(OH)D levels were evaluated in supplemented preterm newborns, with no maternal levels record, history of prenatal supplementation, nor cord blood VD levels, or before initiation of supplementation. The measurement method of VD is also not available, since they were processed in an external laboratory. At this point, it is important to consider that there are several methods to measure 25-(OH)D levels with different yields, especially at low VD concentrations, the gold standard being liquid chromatography coupled with tandem mass spectrometry¹⁵.

Conclusions

Most PTNB had VD deficiency at one month of life. There was no association between low VD levels and perinatal characteristics, respiratory support, hospital stay, and comorbidities evaluated, including BPD. The BPD group had lower gestational age, birth weight, and a higher need and longer duration of any respiratory support, along with a significant association with all comorbidities described.

For the moment, more multicenter and prospective studies are needed to demonstrate the relationship between VD levels assessed at different times and their association with respiratory evolution and BPD.

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: This study was approved by the respective Research Ethics Committee. The authors state that the information has been obtained anonymously from previous data.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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