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Serum 25- hydroxyvitamin D as a risk factor for bronchopulmonary dysplasia in preterm infants with respiratory distress syndrome

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Abstract
Background: Recent improvements in neonatal and obstetrical healthcare have increased preterm newborns' survival rates, particularly those who were born very low in weight (VLBW). However, main pulmonary difficulties for preterm newborns include respiratory morbidity, with its accompanying comorbidities, Broncho-pulmonary dysplasia (BPD) and respiratory distress syndrome (RDS). The aim of the work is to evaluate the role of 25-hydroxyvitamin D as an indicator for risk for bronchopulmonary dysplasia in preterm infants with RDS.
Methods: This prospective observational study was carried out on 50 preterm neonates with gestational ages lower than 32 weeks presented by respiratory distress. All new-borns were exposed to careful taking of history, physical examination and laboratory investigations (CBC, CRP, ABG, CXR and serum 25-hydroxyvitamin D (25OHD)). Prior to the start of vitamin D treatment, blood samples (0.5 ml) from all newborns were taken during their initial 24 hours of life. Vitamin D levels were then tested using an ELISA reader instrument (RT2100C, Germany) and kept at 0 to 4 degrees Celsius. Samples were delivered to the hospital laboratories for a vitamin D level analysis.
Results: There was a significant difference as regard to BPD and vit D, death/BPD with vit d level, BPD or Death relation to Vit D level, correlation of hospital stay and Vit D level, O2 supplementation duration, age, weight, length, head circumference and PH. And insignificant difference as regard to Vit D and chest x ray, vit D level and method of O2 supplementation, Gender, mode of delivery, maternal illness, Apgar 1, Apgar 2 and Downes, Ca, P, CRP, TLC, PLT, HB, PO2, PCO2, HCO3.
Conclusions: a significant association was existed between levels of vitamin D and BDP incidence and severity in these infants after birth. As well as correlation of hospital stay and Vit D.

Keywords: Bronchopulmonary dysplasia, serum 25- hydroxyvitamin d, respiratory distress syndrome, preterm infants

Introduction
Significant pulmonary issues for preterm newborns include respiratory morbidity with its accompanying consequences, respiratory distress syndrome (RDS), and broncho-pulmonary dysplasia (BPD) [1]. The most frequent and severe cause of respiratory failure (RF) in preterm newborns, RDS is inversely linked to the infant's gestational age.
RDS continues to be a serious, high-mortality condition in the extremely preterm newborn despite advancements in therapeutic methods [2].
The most frequent consequence in preterm newborns is BPD, a chronic pulmonary disease of pre-maturity. Babies born at or before 26 weeks of gestation are at the greatest risk. Approximately as 30% to 40% of newborns with very low birth weight (VLBW) are affected [3].
The extended requirement for supplementary oxygen or mechanical breathing over 36 weeks postmenstrual age is what characterizes the new BPD [3].
Infants with BPD frequently need readmission to the hospital and have an elevated frequency of ER or doctor visits for recurring infections, reactive airways diseases, and respiratory exacerbations. Former preterm babies are also more likely to have long-term lung abnormalities, have poor exercise tolerance, and need continuous respiratory drugs across childhood and adolescence [4].

A fat-soluble steroid known as vitamin D, it is well known for its traditional function in maintaining bone and calcium homeostasis [5]. Studies showed that vitamin D has a significant function in controlling the development and growth of the lungs. The link between acute respiratory problems in preterm babies and vitamin D insufficiency [2, 6]. Worldwide, newborns, pregnant women, and breastfeeding moms often need vitamin D. Preterm children, particularly those delivered before 32 weeks gestation, were thought to be at greater danger of deficiency in vitamin due to a shorter gestational period, insufficient reserves, and a lack of supplementation through the gut in the first few days after birth [7].

The purpose of this research is to assess 25-hydroxyvitamin D's potential to increase the risk of bronchopulmonary dysplasia in preterm babies with RDS.

Patients and Methods

T At Tanta University Hospital's Neonatal Intensive Care Units (NICU), 50 preterm newborns with gestational ages fewer than (32 weeks) participated in this prospective observational research over a period of one year started at May 2021, presented by respiratory distress according to Downs' score and required O2 supplementation or assisted ventilation to determine if presence of serum 25 (OH) vit D on the initial day of life is an indicator of risk for BPD in preterm with RDS.

After receiving clearance from Tanta University's Ethical Committee, the research was carried out. All participants' parents provided signed, fully informed permission.

Full-term infants, infants without parental permission, children with significant congenital anomalies or chromosomal defects, and conditions in mothers who affect vitamin D levels, such as pregnancy-related diabetes, parathyroid diseases, problems with calcium metabolism, and renal diseases, were the criteria of exclusion.

Each and every newborn enrolled in the research underwent: taking of history (Gestational age at delivery, Prenatal history of any disease, Antenatal history of bleeding, Postnatal history, History of a sibling with prematurity, mode of delivery and instruments use), General physical examination, Laboratory investigations (Complete blood count (CBC), Arterial blood gases (ABG), C-reactive protein (CRP), Serum calcium and phosphorus, Chest X-ray (CXR), 25-hydroxyvitamin D (25OHD) serum concentrations in newborns within the first 24 hours: Before starting vitamin D treatment, blood samples (0.5 ml) were taken from all newborns during the first 24 hours of life. And kept at 0 to 4 degrees Celsius. In order to determine the amount of vitamin D, samples were submitted to the hospital's laboratories. Vitamin D levels in the blood were tested.

Employing an ELISA reader (RT2100C, Germany) and an enzyme-linked immunosorbent assay (ELISA). Before administering any vitamin D supplements, we figured that infants's-25OHD levels, measured on their initial day of birth, would be indicative of fetal vitamin D condition. According to institutional guidelines, vitamin D supplements for premature newborns were given at a level of 400 IU daily. The individuals in this research were divided into 3 groups: group 1 had a severe vitamin D deficit (25(OH) D <10 ng/mL). Deficit in group 2 (10–20 ng/mL). Deficiency in group 3 (20–30 ng/mL) [8].

Chest X-ray, clinical manifestations, and a blood gas analysis were used to diagnose the RDS. According to the NIH criteria [9], BPD was identified according to radiographic observations, the requirement and strategies for O2 treatment beyond 28 days of age, and other factors.

We made the decision to categorize O2 treatment as non-invasive (high flow nasal cannula, nasal prong, nasal CPAP, and non-invasive positive pressure ventilation) and invasive approaches (ventilator application).

Statistical analysis

With the aid of the IBM SPSS software program version 20.0, information was input into the computer and evaluated. (IBM Corp, Armonk, NY). Number and percentage were used to describe the qualitative results. The Shapiro-Wilk and the Kolmogorov-Smirnov tests were employed to confirm the normality of the distribution. The ranges of values (minimum and maximum), mean, standard deviation, median, and interquartile range (IQR) were used to characterize the quantitative information. For comparison between two investigated groups, normally distributed quantitative parameters were compared using student t-tests. F for the one-way ANOVA test for contrasting between more than two groups for quantitative parameters with a normally distributed distribution. To link two numerical variables with normally distributed distributions, use the Pearson coefficient. The acquired findings' significance was determined at the 5% level.

Results

After history taking and physical examination of 57 infants 5 were excluded for having major congenital anomaly /refusal of parental consent. 2 more cases were excluded for being transferred to another hospital. For the remaining 50 cases serum Vitamin D were measured and recorded and they were followed closely for developing of BPD.

Distribution of the studied instances based on obstetric data are showed in Table 1.

Table 1: Distribution of the studied instances based on obstetric data (n = 50)

		Patients (n = 50)
Sex	Male	30 (60%)
	Female	20 (40%)
Mode of delivery	CS	43 (86%)
	Vaginal	7 (14%)
Maternal illness	No	43 (86%)
	Hypertensive	7 (14%)
GA (weeks)	Min. – Max.	27.0 – 32.0
	Median (IQR)	29.0 (29.0 – 30.0)

IQR: Inter quartile range SD: Standard deviation

The distribution of instances according to anthropometrics measures and Descriptive analysis according to Apgar and Downs are showed in (Table 2).

Table 2: Descriptive analysis of the studied instances based on anthropometric measurement and Apgar and Downs (n = 50)

		Min.-Max.	Median (IQR)
Anthropometric measurement	Weight (gm)	895.0-1850.0	1260.0 (1195.0-1400.0)
	Length (cm)	36.70-42.10	38.50(38.10-39.70)
	Head circumference (cm)	25.70-29.50	27.50 (27.0-28.0)
Apgar and Downs	Apgar 1	1.0-9.0	6.50 (6.0-8.0)
	Apgar 2	1.0-9.0	8.0 (6.0-9.0)
Downes		4.0-8.0	6.0 (5.0-7.0)

SD: Standard deviation, IQR: Inter quartile range.

Distribution of the studied cases according to 25 OH vitamin D and chest x-ray are showed in (Figure 1).

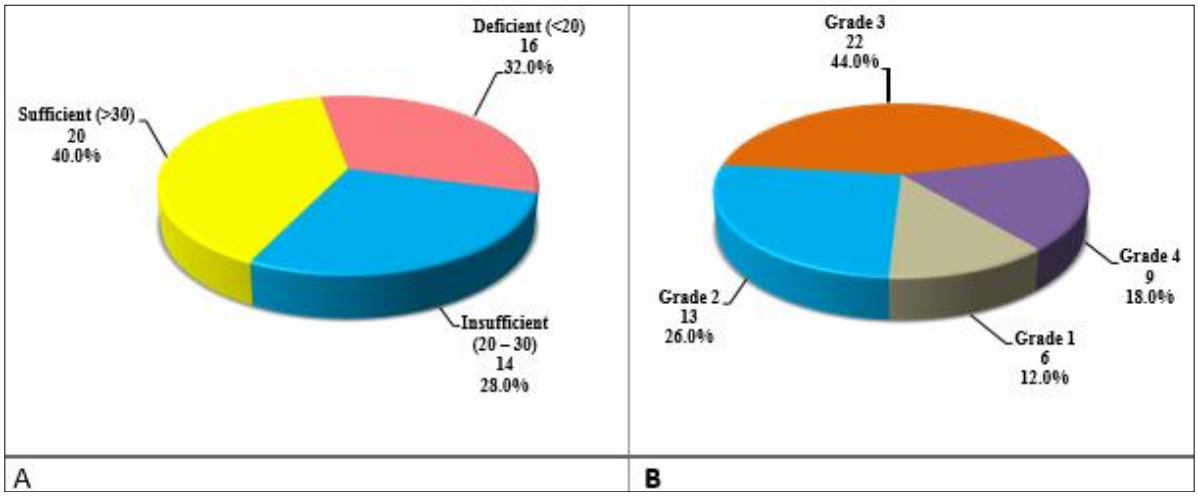

Fig 1: Distribution of the studied instances based on 25 OH vitamin D and chest x- ray

Descriptive analysis of the studied instances based on Ca, PO4 and CRP, CBC, ABG, O2 supplementation (days) and hospital (days) are showed in (Table 3).

Table 3: Descriptive analysis of the studied instances based on Ca, PO4 and CRP, CBC, ABG, O2 supplementation (days) and hospital (days)

	Min.-Max.	Mean ± SD.	Median (IQR)
Ca (mg/dl)	6.20 – 25.0	8.11 ± 2.52	7.90 (7.40 – 8.30)
PO4 (mg/dl)	4.50 – 8.10	6.06 ± 0.88	6.10 (5.20 – 6.70)
CRP	25.0 – 74.0	46.56 ± 11.16	45.0 (40.0 – 55.0)
CBC			
TLC (x103/ul)	10.0 – 33.0	22.24 ± 6.03	23.0 (18.0 – 27.0)
PLT (x103/ul)	160.0 – 320.0	248.2 ± 48.26	250.0 (210.0-300.0)
HB (g/dl)	12.90 – 15.50	14.19 ± 0.68	14.30 (13.80-14.70)
ABG			
PH	7.12 – 7.33	7.24 ± 0.05	7.24 (7.20 – 7.28)
PO2	45.0 – 66.0	56.42 ± 5.45	57.0 (53.0 – 60.0)
PCO2	55.0 – 73.0	66.18 ± 3.42	66.0 (65.0 – 69.0)
HCO3	16.0 – 26.0	21.16 ± 2.56	21.50 (19.0 – 23.0)
O2 supplementation (days)			
	12.0 – 45.0	23.86 ± 8.68	22.0(16.0 – 30.0)
Hospital (days)	12.0 – 50.0	27.18 ± 8.47	25.50 (20.0 – 34.0)

IQR: Inter quartile range SD: Standard deviation

Distribution of the studied instances based on O2 supplementation, BPD and death are showed in (Table 4).

Table 4: Distribution of the studied instances based on O2 supplementation, BPD, and death

O2 supplementation		No (%)
Nasal Cannula		4 (8%)
CPAP		16 (32%)
MV		30 (60%)
BPD	No	32 (64%)
	Yes	18 (36%)
	Mild	6 (12%)
	Moderate	9 (18%)
	Severe	3 (6%)
Death	Alive	46 (92%)
	With BPD	17 (37%)
	Without BPD	29 (58%)
	Died	4 (8%)
	BPD or Death	21 (42%)

There was statistically significant difference as regard to BPD and vit D, death/BPD combination with vit d level, BPD or Death relation to Vit D level p value <0.005. No substantial variation was existed regarding to gender, mode of delivery, maternal illness and hypertensive (Table 5**)**.

Table 5: Relation between 25 OH vitamin D and different variables

	N	25 OH vitamin D (ng/ml)		Test of Sig.	p
		Min. – Max.	Median		
Chest x-ray					
Grade 1	6	26.90 – 40.0	33.0	F=1.215	0.315
Grade 2	13	15.0 – 46.0	26.0		
Grade 3	22	14.0 – 43.10	26.85		
Grade 4	9	15.0 – 36.20	22.0		

O2 supplementation					
Nasal Cannula	4	23.90-40.0	37.50	F=2.662	0.080
CPAP	16	17.0-43.0	28.10		
M.V	30	14.0-46.0	23.25		
BPD					
No	32	16.0-46.0	31.0	t=2.423*	0.034*
YES	18	14.0-37.30	20.25		
BPD					
No	32	16.0-46.0	31.0	F=9.046*	0.004*
Mild	6	16.50-32.40	23.75		
Moderate	9	14.0-35.0	16.0		
Severe	3	14.40-37.30	16.0		
Death					
Alive	46	14.0-46.0	26.95	t=0.031	0.975
Died	4	16.0-37.30	29.10		
Death BPD combination					
Survival with BPD	17	14.0-35.0	18.0	F=6.120*	0.004*
Survival without BPD	29	17.0-46.0	33.0		
Death	4	16.0-37.30	29.10		
BPD or Death					
No	29	17.0-46.0	33.0	t=3.251*	0.002*
Yes	21	14.0-37.30	22.0		
Gender	Male 30	14.40-42.0	26.50	t=0.221	0.826
	Female 20	14.0-46.0	27.05		
Mode of delivery	CS 43	14.0-46.0	27.0	t=0.234	0.816
	Vaginal 7	16.0-42.0	18.0		
Maternalillness	No 43	15.0-46.0	27.0	t=0.474	0.638
	Hypertensive 7	14.0-40.20	25.0		

There was significant difference as regard to correlation of hospital stay and Vit D level, O2 supplementation duration, GA, weight, length, head circumference $p \leq 0.05$, PH p=0.008 and no substantial variation was existed as regard to Ca, P, CRP, CBC, PCO2, PO2, HCO3, APGAR 1, APGAR 2, Downes **(**Table 6**)**.

Table 6: Correlation between 25 OH vitamin D (ng/ml) with hospital (days), o2 supplementation and demographic data, different lab and Apgar and Downes.

25 OH vitamin D (ng/ml)		
	r	**p**
Hospital (days)	-0.413	0.003*
o2 supplementation (days)	-0.354	0.012*
GA (weeks)	0.310	0.028*
Weight (gm)	0.325	0.025*
Length (cm)	0.311	0.028*
Head circumference (cm)	0.356	0.011*
Ca (mg/dl)	0.115	0.426
PH (mg/dl)	-0.031	0.831
CRP	0.098	0.497
TLC (x103/ul)	0.183	0.203
PLT (x103/ul)	0.138	0.341
HB (g/dl)	-0.117	0.419
PH	0.372	0.008*
PO2	0.191	0.183
PCO2	0.189	0.189
HCO3	0.106	0.465
Apgar 1	0.082	0.571
Apgar 2	-0.058	0.688
Downes	0.122	0.400

r: Pearson coefficient *: Statistically significant at $p \leq 0.05$

no substantial variation was existed regarding to gender, mode of delivery, maternal illness and hypertensive

There was not statistically significant as regards to gender, Mode of delivery, and maternal illness.

Discussion

The multi-organ system that makes up the body of a human depends on vitamin D, which also has a significant effect on children's and newborns' health. By preserving the constant equilibrium of minerals in the body, controlling both phosphorus and calcium metabolism, and being essential for the growth, differentiation, and immune control of a variety of tissue cells, supplementation of vitamin D can help prevent the occurrence of numerous illnesses in newborns. It also plays a role in preterm infants' neonatal respiratory, infectious, and immune systems [10].

In preterm neonates as well as throughout pregnancy, hypovitaminosis D is a common condition. Studies is also being done on the connection between BPD and vitamin D insufficiency in preterm newborns, although there is still a lack of clinical proof and differing perspectives [11].

According to studies, the high prevalence of catastrophic growth restriction and BPD is strongly connected to histological evidence of inadequate placental vascular perfusion, albeit the mechanism behind this relationship is unclear [11].

Regarding gender, no statistically substantial variation was found in the current investigation. Similar to this, investigations like those done by Jafari *et al.* [12] on 113 preterm newborns to investigate the relationship among vitamin D Insufficiency and respiratory consequences in preterm infants have not shown a correlation between neonatal sex and levels of vitamin D. The results of the current research are consistent with those of Jafari *et al.* [12] and Kim *et al.* [10] studies in that there was no statistically substantial variation between maternal sickness and delivery method.

The results of the current investigation, which compared the APGAR and DOWNS scores, revealed no statistically substantial variations. This conclusion is consistent with a study by Elfarargy *et al*. [13] on 100 preterm newborns who were given MV and had RD. APGAR and DOWNS scores and vitamin D levels were investigated as potential adjuvant treatments in controlling and prevention of BPD in newborns, but no correlation was identified.

The results of the present investigation supported those of Elfarargy *et al*. [13] and shown that hospital stays were statistically significantly longer when vitamin D levels were decreased. Onwuneme *et al*. [14] did research on 94 preterm newborns in opposition to these results. To evaluate the relationship between preterm baby outcomes and serum 25OHD levels. They discovered no connection between vitamin D status and length of hospital stays.

The current investigation shown that the longer the period of oxygen taking supplements, the lesser the level of vitamin D, with a statistically substantial variation detected, p value equal to 0.012. This conclusion concurred with that of Kazzi *et al*. [15]. There were 89 VLBWI (≤1250 g). African Americans in the research group. The group with fewer units of vitamin D had higher RSS (P=0.012) on the initial day of life and longer durations of oxygen use, mechanical ventilation, and non-invasive oxygen utilization, which is in agreement with Haiyan Ge *et al*. [16] who discovered that the greater the levels of vitamin D, the lesser the oxygen support period required for premature infants with BPD. They divided the RSS scores into three categories: mild (1.0-3.9), moderate (4.0-6.9), and severe (7.0-10.0).

As opposed to Fort *et al*. [17], who carried out research to establish the ideal dosage of vitamin D administration for achieving biochemical sufficient vitamin D in babies with severely low GA. 100 preterm newborns were included in the research population and were randomly assigned to either placebo (n = 36) or 200 IU of vitamin D. (n = 34). 800 IU/d (n = 30), and they discovered no connection between levels of vitamin D and the demand for supplemental oxygen.

The current investigation found no correlation between the mortality rate and vitamin D (4 deaths out of 50 patients with vitamin D varying between 16:37 ng/ml) with no statistically substantial variation identified, p value = 0.975. This conclusion concurred with Fort *et al*. [17], Onwuneme *et al*. [14], and Jafari *et al*. [12] who showed no link between vitamin D levels and infant death rates.

According to the present research, 18 preterms had BPD development compared to 29 preterms without BPD. This result was in accordance with Çetinkaya *et al*. [18] that vitamin D insufficiency enhanced the probability of BPD incidence with a statistically substantial variation detected, p value = 0.001. They measured the 25OHD concentrations at the time of being admitted to the intensive care unit for a cohort of 100 preterm babies (≤32 weeks), and they found that vitamin D levels were substantially reduced in patients with BPD.

The current research also agreed with Mao *et al*.'s [19] case-controlled work on 60 preterm newborns, which examined the hypothesis that vitamin D and inflammatory cytokines could be indicators of risk for BPD in infants. At 24 hours following delivery, they found that preterm newborns in the BPD group had substantially decreased vitamin D levels than those in the non-BPD group. Contrary to these results, Joung *et al*. [20] examined the relationship of 25(OH) D levels at birth and at 36 weeks' corrected GA with BPD in preterm children delivered before 29 full weeks of gestation. They studied 44 preterm infants. They stated that neither the cord blood nor the corrected age 25(OH) D levels at 36 weeks were linked to the development of BPD in this group of severely preterm children.

Out of 17 BPD, 6 were mild, 9 were intermediate, and 3 were severe, and the current research demonstrated a correlation between vitamin d insufficiency and BPD severity, with p value = 0.004, which is in agreement with the findings of Kazzi *et al*. [15] who discovered a correlation between the severity of BPD in VLBW babies and their level of vitamin D insufficiency. Additionally, Haiyan Ge *et al*. [16] observed that the severity of BPD was connected with blood vitamin D levels at birth, which were substantially reduced in the BPD group than the non-BPD group.

As opposed to Mao *et al*. [19], who discovered that the level of vitamin D of preterm newborns in the BPD group was considerably lower than that of the non-BPD group at 24 hours after delivery, there was no correlation between vitamin D insufficiency and the severity of BPD. and this result is consistent with Fort *et al*. [17] who noted that supplementing with vitamin D did not enhance BPD. We showed that among preterm babies with RDS, low s-25OHD levels (defined as ≤ 20 ng/ml) during the first 24 h of life were linked to a greater chance of moderate severity of BPD and a greater probability for frequent requests for supplemental oxygen upon release home. The cause of the increased risk of respiratory morbidities in preterm newborns with vitamin D insufficiency is yet unknown. Numerous animal and laboratory research have provided us with insight into the potential function of vitamin D in lung development.as devastating lung programming and development may be hampered and elevated post-natal danger of respiratory morbidity due to fatal exposure to "deficient" amounts of vitamin D throughout crucial stages of lung development.

Limitations include a limited sample size, the study's single institution, and the possibility that results might differ based on factors including race, dietary status, and sun exposure.

Conclusions

There is a strong correlation between the occurrence and severity of BDP in these newborns and vitamin D deficiency. Our findings imply that vitamin D exposure in preterm newborns with RDS may be an indicator of risk for BPD. In order to maximize an infant's levels of vitamin D at birth and minimize respiratory morbidities, it's crucial to maintain an appropriate maternal vitamin D level throughout pregnancy.

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Conflict of Interest

Nil

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