Journal of Population Therapeutics & Clinical Pharmacology

REVIEW ARTICLE
DOI: 10.53555/jptcp.v30i1.2466

THE ASSOCIATION BETWEEN VITAMIN D DEFICIENCY, INFLAMMATORY FACTORS, AND RESPIRATORY DISTRESS AMONG NEONATES: RETROSPECTIVE COHORT STUDY

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Abstract:

Background and Aim: Neonatal respiratory distress is a common complication among new-borns with fatal consequences if left untreated. Inflammation plays an important role in the pathophysiology of this condition as the neonate's immune system is not fully developed upon birth. Previously, it has been reported that vitamin D levels are attributed to inflammatory responses in adults and animal models. Hence, we aimed at evaluating the association between the vitamin D deficiency and inflammatory markers among neonates who suffer from respiratory distress after birth.

Methods and Materials: In this retrospective cohort study, we included neonatal cases with respiratory distress. The exclusion criteria were neonates with congenital syndromes and anomalies. Demographic characteristics and laboratory data (serum Vitamin D level, D-Dimer, C-reactive protein (CRP), Ferritin, and white blood cell count) was gathered. Patients were categorized into low or normal based on their serum vitamin D levels. We compared the association between vitamin D deficiency and inflammatory factors, using chi-square Fisher's exact, or t-test based on the dependent variable of interest. P-values lower than 0.05 were considered as statistically significant.

Results: We included 99 neonatal cases with respiratory distress (35 females and 64 males). 9 cases (9.18%) had low and 89 cases (90.82%) had normal vitamin D serum levels. There was a significant association between vitamin D deficiency and serum level of D-dimer (*p-value* < *0.001*). All of the neonates with low vitamin D levels (n=9, 100%) had abnormal D-dimer levels, whereas only 34 cases (38.20%) of those with normal vitamin D levels had abnormal D-dimer. however, we found no significant association between vitamin D deficiency and any significant decrease or increase in CRP level (*p-value = 0.34*), ferritin level (*p-value = 0.60*), and WBC level (*p-value = 0.24*).

Conclusion: Based on the findings of our study, there was a significant association between vitamin D deficiency and abnormal level of D-dimer, but no other significant association was found. Further studies are necessary with higher number of patients to evaluate the relationship between serum vitamin D levels and other inflammatory markers such as cytokines.

Keywords: Respiratory distress syndrome, Vitamin D deficiency, Neonate, Inflammatory factor.

Introduction

Respiratory distress syndrome is a common neonatal complication, primarily due to inadequate secretion of surfactant by the epithelial cells. This condition is more prevalent among premature neonates compared to term infants. Premature neonates also suffer from lower birth weight and higher incidence of respiratory distress which may result in increase of neonatal mortality [1-3]. Vitamin D is a fat-soluble steroid derivative with various and crucial physiological roles such as calcium absorption, bone maturation, phosphor absorption, calcification, body growth, and the function of immune system. Vitamin D plays an important role in bone metabolism and calcium storage. Many cells (brain, colon, prostate, breast and immune cells) have vitamin D receptors and respond to 1-25 dihydroxy vitamin D, which is the active form of vitamin D [4-6]. Several studies have shown that this vitamin plays a major role in the immune system's responses to infection. Low levels of vitamin D have been seen in asthmatic patients and it has been stated that the deficiency of this vitamin leads to a decrease in airway function. Hence, its deficiency has been shown to be associated with several complications in neonates and adults. Severe vitamin D deficiency during pregnancy has irreversible debilitating consequences like premature lung development and rickets [7-9].

Based on the current literature, vitamin D deficiency has been reported to increase the risk of neonatal and fetal growth retardation, incidence of fatal neonatal infections, and lower cognitive function and development. However, the role of inflammation and vitamin D deficiency among neonates has not been thoroughly studied [6, 10-12]. Several reports are available regarding the role of vitamin D supplementation and its inhibitory effect of inflammatory markers such as C-reactive protein, and immune cell counts. After activation, vitamin D improves the antimicrobial capacities of immune cells such as monocytes and macrophages, manages the matrix metalloproteinase expression, and function of neutrophils [13-15].

As respiratory distress is a severe condition affecting a considerable number of neonates globally, elucidating the relationship between the inflammatory markers and serum level of vitamin D can improve the understanding of this common complication and help lowering its incidence among this vulnerable population [10]. Thus, this study has been designed to evaluate the association between the vitamin D deficiency and inflammatory markers among neonates who suffer from respiratory distress after birth.

Methods and Materials

This study was a retrospective cohort study that included neonatal cases who were admitted to four educational hospitals in Tehran, Iran due to respiratory distress. The exclusion criteria were neonates with congenital syndromes and anomalies.

After a thorough clinical evaluation of the neonatal patient, cases with respiratory distress were included in our study. The data regarding neonatal sex, week of pregnancy termination, day of neonatal intensive care unit (NICU) admission, day of respiratory distress initiation, head circumference, weight, height, receiving inotrope, duration of hospitalization, cardiopulmonary resuscitation, type of delivery, neonatal and maternal COVID-19 test results, and outcome of treatment were gathered based on a standardized sheet prepared by the authors. Also, the laboratory

data included serum Vitamin D level, D-Dimer, C-reactive protein (CRP), Ferritin, and white blood cell count.

Statistical Analysis

Serum vitamin D was the independent variable of interest in our study. Patients were categorized into low or normal based on their serum vitamin D levels. Descriptive statistics was used to report sociodemographic and certain obstetric characteristics via mean, standard deviation, number, and percentage. To compare the association between certain continuous dependent variables among the two group with low and normal vitamin D, paired t-test was used. Also, to evaluate the association between vitamin D deficiency and inflammatory factors, chi-square or Fisher's exact tests were used. P-values lower than 0.05 were considered as statistically significant. STATA version 17 (StataCorp LLC), R (R Foundation for Statistical Computing, Vienna, Austria), and RStudio (RStudio, Inc., Boston, MA) were used for data cleaning, data analysis, and creating the figures.

Results

Overall, 99 neonatal cases with respiratory distress were included in our study, among which 35 (35.35%) were female and 64 (64.65%) were male. Only one mother and neonates were positive for COVID-19, hence, no further analysis was necessary. Also, 9 cases (9.18%) had low vitamin D serum level and 89 cases (90.82%) had normal vitamin D serum level. Only 5 cases (5.32%) received inotrope.

Table 1. The association between Vitamin D deficiency and various obstetric characteristic of the neonates

		Mean	SD	p-value
Pregnancy termination (week)	Low Vit D	34.88	1.90	0.65
	Normal Vit D	35.40	3.38	
Day of NICU Admission (day)	Low Vit D	0.39	0.46	0.31
	Normal Vit D	2.29	5.64	
Start Respiratory Distress (day)	Low Vit D	0.38	0.46	0.42
	Normal Vit D	1.70	4.92	
Head circumference	Low Vit D	33.66	2.82	0.92
	Normal Vit D	33.75	2.80	
Weight	Low Vit D	2537	626	0.52
	Normal Vit D	2690	694	
Height	Low Vit D	48.12	3.04	0.60
	Normal Vit D	48.93	4.33	
Duration of Hospitalization (day)	Low Vit D	7.55	5.05	0.36
	Normal Vit D	4.77	9.08	

The mean (±SD) week of pregnancy termination was 34.88 (±1.90) among neonates with vitamin D deficiencies and 35.40 (±3.38) among those with normal vitamin D serum level. No significant difference was observed among the two groups (*p-value = 0.65*). The mean day of respiratory distress initiation was 0.39 (±0.46), and 2.29 (±5.64) for those with deficient and normal vitamin D levels, respectively, with no significant difference among the two groups (*p-value = 0.31*). The duration of hospitalization was 7.55 days (±5.05), and 4.77 (±9.08) among those with deficient and normal vitamin D levels, respectively. No significant difference was observed among the two groups regarding the duration of hospitalization (*p-value = 0.36*). Further detail is available in Table 1 and Figure 1 and 2.

Table 2. The association between Vitamin D deficiency and level of inflammatory factors, outcome, and type of delivery

		Low Vit D	Normal Vit D	*p-value*
D-dimer	*Abnormal*	9 (100%)	34 (38.20%)	***< 0.001****
	Normal	0	55 (61.80%)	
CRP	*Abnormal*	0	8 (8.99%)	*0.34*
	Normal	9 (100%)	81 (91.01%)	
Ferritin	*Abnormal*	1 (11.11%)	16 (17.98%)	*0.60*
	Normal	8 (88.89%)	73 (82.02%)	
WBC	*Abnormal*	0	12 (13.48%)	*0.24*
	Normal	9 (100%)	77 (86.52%)	
Outcome	*Complete Remission*	5 (55.56%)	29 (32.58%)	*0.35*
	Partial Remission	4 (44.44%)	57 (64.04%)	
	Death	0	3 (3.37%)	
Type of Delivery	*C-section*	9 (100%)	82 (92.13%)	*0.38*
	Natural	0	7 (7.87%)	
Respiratory Distress Syndrome	*No*	0	45 (50.56%)	***0.004****
	Yes	9 (100%)	44 (49.44%)	

There was a significant association between vitamin D deficiency and serum level of D-dimer (*p-value < 0.001*). All of the neonates with low vitamin D levels (n=9, 100%) had abnormal D-dimer levels, whereas only 34 cases (38.20%) of those with normal vitamin D levels had abnormal D-dimer. Also, there was no significant association between vitamin D deficiency and any significant decrease or increase in CRP level (*p-value = 0.34*), ferritin level (*p-value = 0.60*), and WBC level (*p-value = 0.24*). Among those with vitamin D deficiency, 5 cases (55.56%) had complete remission and 4 cases (44.44%) had partial remission. It should be added that only 3 cases (3.37%) died who had normal vitamin D levels. Also, all of the cases with vitamin D deficiency were delivered via C-section, however, no significant association was found (*p-value = 0.38*). Table 2 summarizes further details regarding the association of vitamin D deficiency and neonatal and obstetric outcomes.

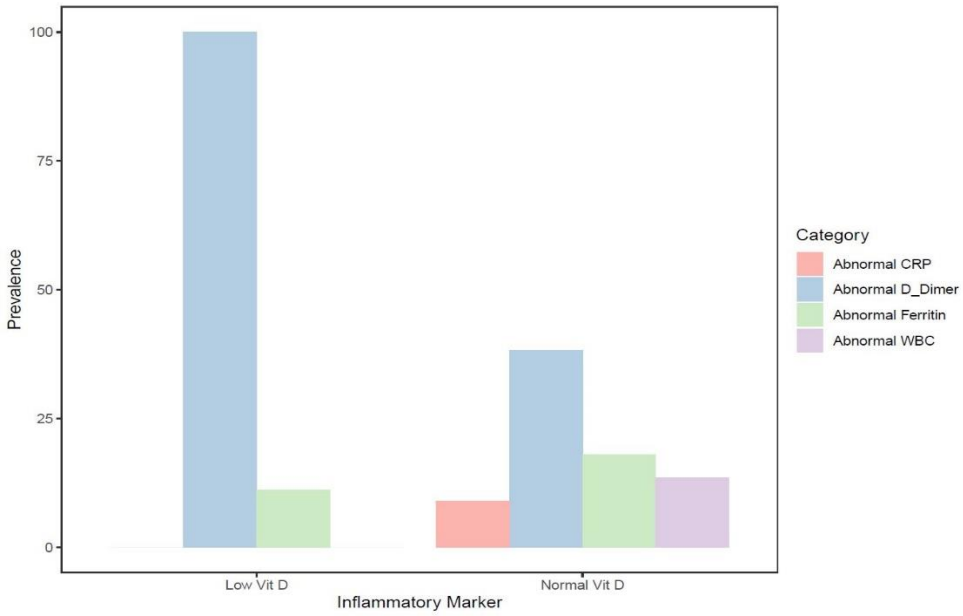

Figure 1. The bar-plot of inflammatory markers and Vitamin D level

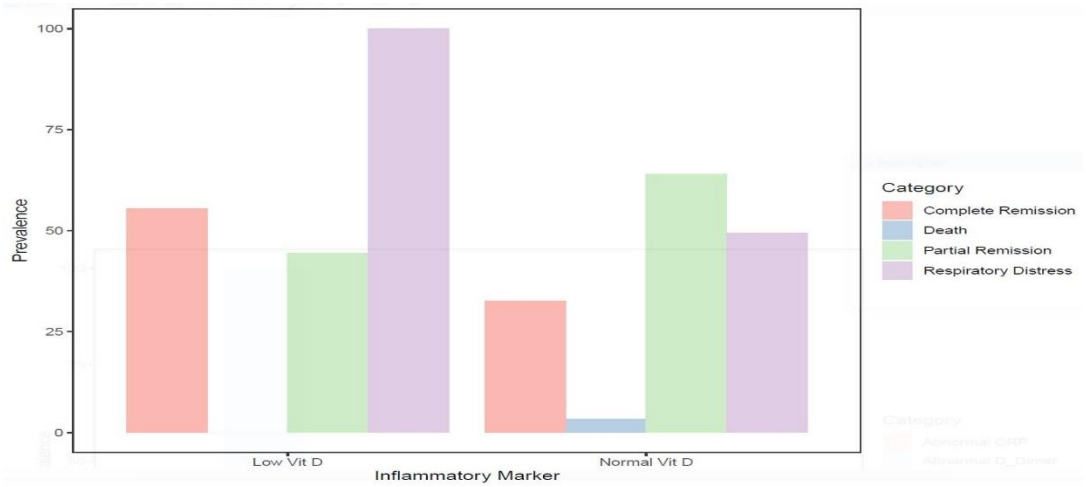

Figure 2. The bar-plot of patient outcome and Vitamin D level

Discussion

The effect of vitamin D on lung development and maturation, and lung disease early in life, is an emerging area of research. Although there are some animal and research data suggesting that vitamin D deficiency is a risk factor for respiratory distress, in fact, clinical studies in this area are still scarce. One study reported that low serum vitamin D at birth was an independent risk factor for respiratory distress. In addition, another study reported higher serum vitamin D levels in preterm infants have been shown to prevent respiratory distress [4, 16, 17]. Based on a recent meta-analysis study, vitamin D levels were significantly lower in children with respiratory distress compared to those with normal respiratory function, suggesting the crucial role of vitamin D deficiency on neonatal respiratory function [6, 10, 13].

The precise role of vitamin D, in the development of dyspnoea is still not fully understood. Vitamin D is a steroid hormone that regulates neonatal lung development and binds to the corresponding receptors, leading to the synthesis of phosphatidylglycerol and phosphatidylcholine. Vitamin D improves the secretion of surfactant by induction of type II alveolar epithelial cells. Vitamin D inadequacy adversely affects maturation of the respiratory system [6, 14, 18]. Vitamin D deficiency leads to downregulation of airway proliferative protein expression, leading to inflammatory responses, small airway spasms, and decreased alveolar surface tension, which may result in alveolar collapse. Vitamin D deficiency can induce oxidative stress, stimulating the body to produce large amounts of oxygen free radicals, causing lipid peroxidation damage to the airways and alveoli [6, 12, 14, 18-21].

Vitamin D influences the innate immune system through several distinct mechanisms. Immune cells express vitamin D receptors that bind vitamin D and, upon pathogen recognition, activate downstream pathways leading to the production of antimicrobial peptides. Immune cells can produce vitamin D locally depending on vitamin D availability [2, 5, 22, 23]. In cell lines, vitamin D inhibits the production of the inflammatory cytokine IL-6, a stimulator of CRP production in the liver. Additionally, vitamin D downregulates the MMP production in experimental studies. However, there are no data specific to MMP-8, D-dimer, and vitamin D. Hence, this is the first study to evaluate the association between vitamin D deficiency and D-dimer among neonates with respiratory distress [1, 3, 24-26].

Previous cross-sectional studies have shown that vitamin D status is inversely related to CRP levels in asymptomatic, elderly, obese adults and children with lupus [27-29]. The results of this study are consistent with previous studies. However, previous randomized controlled trials evaluating the effectiveness of vitamin D supplementation in reducing CRP have shown conflicting results.

Recently, a meta-analysis of 10 studies involving 924 people found that vitamin D supplementation significantly decreased circulating levels of CRP in adults. Another study found that vitamin D supplementation during pregnancy resulted in a significant decrease in maternal serum CRP levels [30-32]. If the inverse relationship between vitamin D and CRP in neonates with low vitamin D levels in this study is causal, then the results suggest that vitamin D supplementation protects against an excessive inflammatory response in the foetus. Further interventional studies should confirm the potential protective effect of adequate vitamin D on the fetal inflammatory response [33, 34].

While some studies in adults have inversely correlated vitamin D with inflammatory mediators, studies among neonates are sparse. However, most studies have been conducted on vitamin D deficient populations or on specific patient groups. Interestingly, in a study of asymptomatic adults, the inverse relationship between 25(OH)D and CRP was reversed in subjects with high vitamin D levels. Similarly, no inverse correlation was observed between 25(OH)D and CRP in neonates with 25(OH)D above her 50 nmol/l. One recent study shows that 25(OH)D is positively associated with the inflammatory biomarkers MMP-8 and hs-CRP[15, 19, 35-38]. In contrast to previous studies, this cohort study lacked vitamin D deficiency, as 99% of subjects had 25(OH)D concentrations above 50 nmol/L. Therefore, the results of these studies primarily represent vitamin D-sufficient populations. Previously, higher vitamin D levels had both anti- and pro-inflammatory effects, suggesting that the association between 25(OH)D and inflammation might be U-shaped. However, such studies did not include neonates with vitamin D deficiency, so they were unable to confirm a possible U-shaped association. It may suggest that it allows the immune system to respond more efficiently [6, 11, 14, 27, 39-41].

As vitamin D deficiency is a global health problem among women and especially pregnant women, it has been postulated that screening for vitamin D deficiency among neonates with mothers at high risk of vitamin D deficiency is beneficial as vitamin D deficiency is associated with other types of deficiency such as calcium deficiency. However, as screening imposes financial and work-force burden on healthcare systems, such suggestion should be investigated more rigorously [42, 43].

To the best of our knowledge, our study is the first study to report the association between vitamin D deficiency and inflammatory markers among neonates with respiratory distress. More importantly, our study had no missing cases. However, our study was faced with certain limitations. The number of cases with vitamin D deficiencies was approximately low. Also, maternal vitamin D deficiency may have affected the neonates and we had no data in this regard. To mitigate these limitations, further studies should be conducted with higher sample sizes and including the vitamin D profile of the mother during pregnancy or at the time of pregnancy termination. Also, we did not measure the erythrocyte sedimentation rate (ESR) among the cases, which is an important inflammatory marker.

Conclusion

Based on the findings of our study, there was a significant association between vitamin D deficiency and abnormal level of D-dimer, but no other significant association was found. Further studies are necessary with higher number of patients and maternal vitamin D serum levels to evaluate the relationship between serum vitamin D levels and other inflammatory markers such as cytokines, and erythrocyte sedimentation rate (ESR).

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