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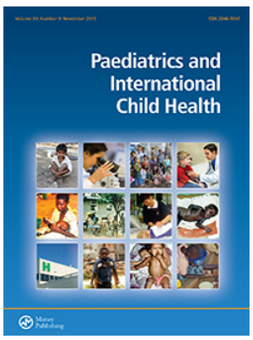

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Association of vitamin D deficiency with an increased risk of late-onset neonatal xepsis

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ABSTRACT

Background: Vitamin D deficiency in mothers and neonates is being recognised increasingly as a leading cause of many adverse health effects in the newborn infant, including sepsis.

Methods: A prospective observational study was conducted at a tertiary care Paediatric teaching hospital in northern India to assess vitamin D deficiency as a possible risk factor for late-onset sepsis (LOS) in term and late preterm neonates and also to examine the correlation between maternal and infant vitamin D levels during the neonatal period. Late-onset sepsis (LOS) was defined as the development of signs and symptoms of severe sepsis after 72 h of life and a positive sepsis screen. All term and late preterm neonates admitted with LOS between September 2015 and February 2016 who had not been previously admitted for >48 h and had not been prescribed antibiotics or vitamin D were included in the study. Matched controls were recruited from otherwise healthy neonates admitted with physiological hyperbilirubinaemia. Serum 25(OH) vitamin D was assessed in neonates in both groups and their mothers.

Results: A total of 421 neonates were admitted to the neonatal intensive care unit during the study period, 120 of whom satisfied the inclusion criteria, and 60 were recruited as cases. Sixty neonates were recruited as controls who were similar in gender, gestational age, age at admission and anthropometry. The study group had significantly lower mean (SD) vitamin D levels [15.37 ng/ml (10.0)] than the control group [21.37 ng/ml (9.53)] ($p = 0.001$). The odds ratio was 1.7 (95% CI 0.52–5.51) for LOS in vitamin D-deficient neonates. Mothers of septic neonates also had significantly lower mean (SD) vitamin D levels [17.87 (11.89)] than the mothers of non-septic neonates [23.65 ng/ml (9.55)] ($p = 0.004$). Maternal vitamin D levels strongly correlated to neonatal vitamin D levels in both groups.

Conclusion: Neonates with vitamin D deficiency are at greater risk of LOS than those with sufficient vitamin D levels.

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25(OH) vitamin D; neonatal sepsis; immunomodulation

Introduction

The biological actions of vitamin D extend well beyond its primary role in calcium-phosphate-bone metabolism, and it is increasingly recognised that vitamin D deficiency is associated with a wide range of pathological conditions [1]. 25(OH) vitamin D influences human immunity in several ways, including its effects on T-cell proliferation, immunoglobulin class switching, and cytokine release [2]. 1,25-dihydroxy vitamin D_3 stimulates the innate immune system to increase the production of antimicrobial peptides (AMP), such as cathelicidin, and its activated form LL-37, β2, and β3 defensins which have a broad spectrum of antimicrobial activities against bacteria, virus, and fungi [3].

Sepsis is a leading cause of neonatal morbidity and mortality worldwide, especially in low- and middle-income countries (LMIC) [4]. It is arbitrarily divided into early, late, and very late-onset based on the timing of appearance of clinical symptoms/signs. The known risk factors for community-acquired late-onset sepsis (LOS) include prematurity, low birthweight, lack of breastfeeding, and poor cord care [5].

The association of vitamin D deficiency and sepsis has been well documented in adults [6–8] and children [9,10]. In neonates, while the deficiency of vitamin D has been associated with an increased risk of early onset sepsis [11] and acute lower respiratory infection [12,13], it is not known whether this is true for LOS. Another important aspect of neonatal vitamin D status is its dependency on maternal vitamin D levels. Deficiency in mothers has been related to many adverse health outcomes in the newborn, including sepsis [14]. This assumes a greater importance in LMIC where vitamin D deficiency in mothers is very high [15].

This study was undertaken to assess the deficiency of vitamin D as a possible risk factor for LOS in term and

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late preterm neonates and to examine the correlation between maternal and infant vitamin D levels during the neonatal period.

Methods

This prospective observational study was conducted in the 20-bed extramural neonatal intensive care unit (NICU) of Chacha Nehru Bal Chikitsalaya, New Delhi, which is a tertiary-care paediatric teaching hospital. Late-onset sepsis (LOS) was defined as the development of signs and symptoms of severe sepsis after 72 h of life and a positive sepsis screen. All term (37–42 weeks of gestation) and late preterm (35–36^{+6} weeks of gestation) neonates (≤28 days of age) with LOS admitted between September 2015 and February 2016 were included after informed written consent had been given by their parents or guardians. Neonates with a history of previous hospitalisation for more than 48 h, who received antibiotics prior to admission and who had received vitamin D supplementation in any form were excluded. Neonates admitted during the same period with clinically significant physiological hyperbilirubinaemia (without sepsis) were enrolled as controls.

Detailed history were taken along with physical examination and blood culture, urine culture, chest radiograph and CSF (cerebrospinal fluid) examination was undertaken in all neonates with LOS. The sepsis screen included total leucocyte count (TLC), absolute neutrophil count (ANC), C-reactive protein (CRP), immature to the total neutrophil ratio (IT ratio) and micro ESR (erythrocyte sedimentation rate). A sepsis screen was considered positive when any two of five parameters were positive as per the Indian National Neonatology Forum (NNF) guidelines [16] Signs and symptoms of sepsis were taken as per the Integrated management of neonatal and childhood illness (IMNCI) guidelines [17]. This included: an inability to feed, convulsions, fast breathing (≥60 breaths/min), severe chest in-drawing, nasal flaring, grunting, bulging fontanelle, an axillary temperature of ≥37.5 °C (or feels hot to touch) or a temperature <35.5 °C (or feels cold to touch), lethargy, unconsciousness or movements which deviated from normal.

Vitamin D levels were considered 'deficient', 'insufficient', and 'optimum' when serum 25(OH) vitamin D levels were <20, <29 and 30–50 ng/mL, respectively, as per the U.S. Endocrine Society classification [18]. The following definitions were used: clinical sepsis, a neonate with signs, and symptoms of sepsis and a positive sepsis screen only; septicaemia, a neonate with signs and symptoms of sepsis, a positive sepsis screen and a positive blood culture (except coagulase-negative staphylococcus, for which two positive blood cultures were required); pneumonia, chest radiograph showing alveolar opacities assesses by a radiologist; urinary tract infection (UTI), growth of $>10^5$ CFUs/ml of an organism in urine obtained by urethral catheterisation or suprapubic aspiration; meningitis, in presence of suggestive CSF examination [16]. Neonates were treated as per the hospital protocol for management of neonatal sepsis and hyperbilirubinaemia. Mothers with vitamin D deficiency were referred to an adult physician for appropriate therapy. All the neonates were followed daily until discharge or death.

Statistical analysis

All the clinical and laboratory parameters were entered in a predesigned proforma. Data were managed on a Microsoft Excel spreadsheet and analysed using Statistical Product and Service Solutions Software (SPSS, version 22.0, Chicago, IL, U.S.A.). The baseline data were described as mean (SD). Student's *t*-test and the χ^2 test were used for continuous and categorical data, respectively, and Pearson's correlation coefficient was used to assess the correlation between maternal and neonatal vitamin D levels.

Ethics approval

The institute's ethics committee approved the study.

Results

A total of 421 neonates were admitted to the NICU in the study period, 120 of whom satisfied the inclusion criteria. Sixty neonates (45 who had been hospitalised more than 48 h before admission and 15 who received antibiotics before admission) were excluded and the remaining 60 were entered into the study. Sixty neonates with physiological hyperbilirubinaemia and without sepsis were enrolled as controls. The gestational age of the cases and controls were, respectively, 37.78 and 37.68 weeks. Most of them had been delivered vaginally, either at the hospital or at home to a multipara mother. The infants in the two groups were comparable in gender, feeding types, and anthropometry (Table 1) but those with sepsis had a significantly longer hospital stay than those admitted without sepsis.

The mean (SD) serum 25(OH) vitamin D level in the sepsis (case) group was 15.4 (10.0) (range 1.75–50.0) which was significantly lower than in controls [21.4 (9.5)] (range 3.7–35.1) ($p = 0.001$). Similarly, maternal vitamin D levels in the study group [mean (SD) 17.9 (11.9), range 4.8–70.6] was also significantly lower than in controls [mean (SD) 23.6 (9.5), range 7.2–40.2] ($p = 0.004$) (Table 2).

Almost two-thirds of septic neonates and half of the controls were vitamin D-deficient, and only 8% and 13% cases and controls, respectively, had sufficient vitamin D levels. The mothers of the neonates with sepsis also had similarly high rates of vitamin D deficiency and insufficiency (Table 3).

Table 1. Demographic and clinical characteristics.

Characteristics	Cases, *n* (%)	Controls, *n* (%)	*p*-value
Gestation			0.31
Term	45 (75)	39 (65)	
Late preterm	15 (25)	21 (35)	
Age (weeks)	37.78 (1.7)	37.68 (1.8)	0.75
Place of delivery			0.19
Home	23 (38.3)	31 (51.7)	
Hospital	37 (61.7)	29 (48.3)	
Mode of delivery			0.55
Vaginal	52 (86.7)	55 (91.7)	
Age (weeks)	8 (13.3)	5 (8.3)	
Primipara mother	14 (23.3)	24 (40)	0.05
Male	35 (58.3)	42 (70)	0.18
Feeding			0.33
Exclusive breastfeeding	43 (71.7)	37 (61.7)	
Mixed (formula + breastmilk)	17 (28.3)	23 (38.3)	
Age at admission, days, mean (SD)	15.5 (6.4)	13.48 (6.7)	0.09
Weight at admission, *g*, mean (SD)	2625.12 (486.2)	2495.58 (490.1)	0.14
Length (cm) mean (SD)	49.97 (2.6)	49.16 (3.9)	0.18
Head circumference, cm, mean (SD)	33.35 (1.5)	32.7417 (1.5)	0.28
Mean duration of hospital stay, days, mean (SD)	10.7 (8.1)	3.30 (0.8)	**<0.001**

Note: *p*-values in bold are statistically significant.

Table 2. Neonatal and maternal 25(OH) vitamin D levels.

	Cases	Controls	
	n = 60	*n* = 60	
25(OH)D (ng/ml)	Mean (SD)	Mean (SD)	*p*-value
Newborns	15.4 (10.0)	21.4 (9.5)	**0.001**
Mothers	17.9 (11.9)	23.6 (9.5)	**0.004**

Note: *p*-values in bold are statistically significant.

Table 3. Vitamin D status in the infants and mothers.

25(OH) vitamin D	Deficient, *n* (%)	Insufficient, *n* (%)	Sufficient, *n* (%)
Infant			
Cases	38 (63.3)	17 (28.3)	5 (8.3)
Controls	30 (50.0)	22 (36.7)	8 (13.3)
Age, wks, mean (SD)	37.78 (1.7)	37.68 (1.8)	0.75
Mother			
Cases	42 (70.0)	13 (21.7)	5 (8.3)
Controls	23 (38.3)	22 (36.7)	15 (25.0)

Fifty-five neonates with sepsis had a 25(OH) vitamin D level <30 ng/ml (deficient or insufficient) compared with 52 in the control group, odds ratio (OR) 1.7 (CI 0.52–5.51) for LOS in vitamin D-deficient neonates. There was also a strong correlation between maternal and neonatal vitamin D levels (Pearson correlation R = 0.896, $p = 0.01$).

Pneumonia was the most common diagnosis in neonates with sepsis (51.7%), followed by clinical sepsis (31.7%) (Table 4). Of the 60 neonates, 57 (95%) were discharged and three (5%) died. The three who died all had culture-positive sepsis with pneumonia, and all had very low vitamin D levels: 6.5, 3.0, and 10.7 ng/mL, respectively. They all had multi-organ failure and required mechanical ventilation and inotropes. Methicillin-sensitive *Staphylococcus aureus* was cultured in two neonates, and one had *Streptococci pneumoniae* which was sensitive to ceftriaxone.

Table 4. Clinical classification of sepsis in the cases (*n* = 60).

	n (%)
Clinical sepsis	19 (31.7)
Septicaemia	12 (20.0)
Urinary tract infection	5 (8.3)
Pneumonia	31 (51.7)
Meningitis	6 (10.0)

Discussion

This prospective observational study analysed vitamin D status in 60 term and late preterm neonates with sepsis and compared it with 60 matched controls of non-septic neonates: the septic neonates had significantly lower mean levels of serum vitamin D. The mothers of the septic neonates also had lower vitamin D levels than mothers of the controls. There was also a positive correlation between maternal and neonatal vitamin D levels.

The 'immune functions' of vitamin D has been under extensive research in recent years [19]. Adequate concentration of vitamin D was found to stimulate genetic expression of antimicrobial peptides (AMP), especially cathelicidin in human monocyte, neutrophil and other cell lines [20]. *In-vitro* studies have found LL-37, the activated form of cathelicidin, to be active against various pathogens, including *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa* [21], the principal pathogens involved in LOS. Cord blood vitamin D deficiency, by its effects on TLR (Toll-like receptor)-induced antimicrobial production can alter *in vitro* monocyte responses as well [22]. Therefore, vitamin D and its deficiency are expected to play a role in the pathogenesis of LOS. In a review of the role of vitamin D in neonatal immune function [23], it was concluded that the mechanism by which vitamin D influences human immunity is complex; it enhances innate immunity while down-regulating the acquired immune response. The role of vitamin D in neonatal immunomodulation requires further research.

In a study in Turkey [24], neonates with early onset sepsis (EOS) were found to have significantly lower serum 25(OH) vitamin D levels than healthy controls. In multivariate analysis, a cord blood 25(OH) vitamin D <30 ng/mL was associated with an increased risk of EOS (OR 5.6, 95% CI 1.3–23.5). Another study from Turkey [8] documented significantly lower 25(OH) vitamin D levels in neonates with EOS and their mothers than in healthy controls. A positive correlation between neonatal and maternal vitamin D status was demonstrated. Similarly, neonatal and maternal vitamin D deficiency was associated with increased risk of acute lower respiratory tract infection (ALRTI) in term neonates [9,10]. There is a

scarcity of literature on the role of vitamin D deficiency in LOS. This study demonstrated an OR of 1.7 for LOS in vitamin D-deficient neonates, putting them at a much greater risk than those with sufficient vitamin D.

There was a very high prevalence of vitamin D deficiency both in the neonates and in their mothers, irrespective of whether they were septic. Only 8.3% of the cases and 13.3% of the controls (10.8% of the total participants) were vitamin D-sufficient. Similar high rates of vitamin D deficiency have been observed across the globe including in high-income countries. A study from the U.S.A. reported vitamin D deficiency and insufficiency in 38.9% and 29.8% of the 165 cord blood samples collected from healthy newborns [25]. A study of Polish newborns reported a 25(OH) vitamin D level of <20 ng/mL in 41 healthy neonates of mothers receiving a mean (SD) vitamin D supplementation of 420 IU/day (80) during pregnancy [26]. A study from northern India [27] reported hypovitaminosis D in 95.7% of cord blood samples which were strongly correlated with a very high prevalence of maternal vitamin D deficiency (84%), as in this study. The foetus and the newborn are dependent on the mother for 25(OH) vitamin D [28] and vitamin D supplementation during pregnancy has been seen to increase 25(OH) vitamin D levels in the neonate [29]. Although the most appropriate timing and dosage of vitamin D during pregnancy to ensure foetal and neonatal wellbeing are still unknown, it is imperative that, in addition to proper nutrition and sunlight exposure, screening for vitamin D deficiency and early supplementation should be implemented to help decrease neonatal morbidity.

Our study had some limitations. The sample size was small and so outcome parameters (e.g. survival, duration of hospital stays, need for inotropes/mechanical ventilation, etc.) between vitamin D-deficient and -sufficient neonates could not assessed. As sepsis may suppress vitamin D levels, it would be helpful to have estimated vitamin D levels after recovery. In addition, other known risk factors of LOS were not studied and so multivariate regression analysis could not be performed to see whether vitamin D deficiency was an independent risk factor for LOS. The vitamin D status of the neonates was also not stratified according to the season of birth, which is known to influence the serum 25(OH) vitamin D levels [24].

Some important aspects should be considered when assessing 25(OH) vitamin D levels with respect to neonatal sepsis. First, an inverse correlation was observed between 25(OH) vitamin D levels and CRP in vitamin D deficient neonates [30]. Therefore, an elevated CRP in a vitamin D deficient newborn may reflect only a heightened inflammatory state and not necessarily be an indicator of sepsis. On the other hand, 25(OH) vitamin D levels were found to be increased in neonates similar to other acute phase reactants [31]. Thus, actual levels of 25(OH) vitamin D in septic neonates maybe much lower when assessed during inflammation.

The prevalence of vitamin D deficiency in mothers and their neonates is very high, predisposing both to a number of morbidities including LOS in the infants. Further research is required to elucidate the role of vitamin D supplementation in pregnancy and to neonates, for prevention of such adverse outcomes.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Rajeshwari Dhandai completed her DNB in Pediatrics. Her area of interest is Neonatology.

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