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Clinical evaluation of levels of vitamin d in infants suffered from recurring wheezing from Bihar region

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Abstract
Being a tropical country, vitamin D deficiency was thought of uncommon in India, however, contrary to this belief recent studies have shown its prevalence to be as high as 50-90%. Previous studies from India used older definitions (<30 ng/mL) for defining vitamin D deficiency and insufficiency hence overestimated the association between vitamin D insufficiency/deficiency and wheeze. Recent Indian as well as international guidelines redefined the vitamin D deficiency as well as insufficiency as advocate using the same for ensuring uniformity. It was observed that lot of children visiting to emergency with recurrent wheeze did not have any underlying etiology except low vitamin D levels, on the other hand many children with even florid rickets doesn't have wheeze. Hence based on above findings the present study was planned for Clinical Evaluation of Levels of Vitamin D in Infants Suffered from Recurring Wheezing from Bihar Region.
The present study was planned in Department of Paediatrics, Darbhanga medical College and Hospital, Darbhanga, Bihar, India. The study was conducted from March 2019 to August 2019. The 30 infants of age up to 24 months were enrolled in the present study. The 15 cases were enrolled in Group A as study group having wheezing and remaining 15 cases were enrolled in Group B as control group patients. Two different cut off levels were used in the study to categorize 25(OH) D concentrations. The levels above 30 ng/ml (75 mmol/L) were accepted as sufficient, the levels under< 20 ng/ml (50 nmol/L) as vitamin D deficiency and under < 10 ng/ml as extreme deficient (25nmol/L).
The data generated from the present study concluded that no correlation between vitamin D levels and recurring puffed in infants was found but this may be due to the few numbers of patients that we studied with. The current findings not express important relationship among vitamin D level and recurring wheezing in the infants.

Keywords: vitamin D, infants, recurring wheezing, Bihar Region, etc

Introduction
Vitamin D deficiency can result from inadequate exposure to sunlight; malabsorption; accelerated catabolism from certain medications; and, in infants, the minimal amount of vitamin D found in breast milk. In children, vitamin D deficiency can result in rickets, which presents as bowing of the legs; in adults, it results in osteomalacia, which presents as a poorly mineralized skeletal matrix.
Vitamin D is important for calcium homeostasis and for optimal skeletal health. The major function of vitamin D is to increase the efficiency of calcium absorption from the small intestine. Heaney and colleagues demonstrated that maximum calcium absorption occurs at levels of 25-hydroxyvitamin D (25[OH] D) greater than 32 ng/mL [1].
Vitamin D also enhances the absorption of phosphorus from the distal small bowel. Adequate calcium and phosphorus absorption from the intestine is important for proper mineralization of the bone. The second major function of vitamin D is involvement in the maturation of osteoclasts, which resorb calcium from the bones.
The term vitamin D refers to either vitamin D2 or vitamin D3. Vitamin D3, also known as cholecalciferol, is either made in the skin or obtained in the diet from fatty fish. Vitamin D2, also known as ergocalciferol, is obtained from irradiated fungi, such as yeast. Vitamin D2 and vitamin D3 are used to supplement food products or are contained in multivitamins. (See Treatment and Medication.)
Past studies suggested that vitamin D3 may be more effective than vitamin D2 in establishing normal vitamin D stores. However, a study by Holick and colleagues demonstrated that vitamin D2 and vitamin D3 appear to be equipotent in raising 25(OH) D concentrations when they are given in daily doses of 1000 IU [2].
Vitamin D deficiency during pregnancy affects offspring. In a community-based study of 901 mother and offspring pairs, researchers found that maternal vitamin D deficiency (serum 25-hydroxyvitamin D < 50 nmol/L) at 18 weeks' pregnancy was associated with impaired lung development at age 6 in offspring, neurocognitive difficulties at age 10, increased risk of eating disorders in adolescence, and lower peak bone mass at age 20. Findings suggest that vitamin D plays an active role in fetal development, particularly the development of the brain, lungs, and bones.
The production of vitamin D3 in the skin involves a series of reactions initiating with 7-dehydrocholesterol. Upon exposure to ultraviolet B (UVB) radiation between the wavelengths of 290-315 nm, 7-dehydrocholesterol is converted to previtamin D3, which is then converted to vitamin D3 after a thermally induced isomerization reaction in the skin. From the skin, newly formed vitamin D3 enters the circulation by binding to vitamin D binding protein (DBP). In order to become active, vitamin D requires 2 sequential hydroxylations to form 1, 25-dihydroxyvitamin D (1, 25[OH] 2 D).
Vitamin D is initially hydroxylated in the 25 position by the hepatic microsomal and/or mitochondrial enzyme vitamin D

25-hydroxylase. The second hydroxylation occurs in the kidney and is performed by the P450 enzyme 25-hydroxyvitamin D-1 alpha-hydroxylase.

Upon entering the cell, the 1, 25(OH) 2 D hormone binds to the vitamin D receptor (VDR). The bound vitamin D receptor then forms a heterodimer with the retinoic acid X receptor (RXR). This heterodimer then goes to the nucleus to bind deoxyribonucleic acid (DNA) and increases transcription of vitamin D–related genes.

Inadequate circulating 25(OH) D is associated with elevated parathyroid hormone (PTH); this condition is called secondary hyperparathyroidism. The rise in PTH may result in increased mobilization of calcium from the bone, which leads to decreased mineralization of the bone. Of note, prolonged exposure to the sun does not cause vitamin D toxicity. This is because after prolonged UVB radiation exposure, the vitamin D made in the skin is further degraded to the inactive vitamin D metabolites tachysterol and lumisterol.

As strongly suggested by genetic, molecular, cellular, and animal studies, extraskeletal effects related to vitamin D signaling include roles in cell proliferation, immune and muscle function, skin differentiation, and reproduction, with vitamin D having vascular and metabolic actions as well. Observational studies have pointed to a relationship between poor vitamin D status and almost all diseases connected to these extraskeletal influences. However, while randomized, controlled trials and Mendelian randomization studies have indicated that vitamin D supplementation can lower the incidence of some disorders, only mixed conclusions on the matter have been reached globally [3].

The treatment of vitamin D insufficiency can decrease the risk of hip and nonvertebral fractures. A meta-analysis by Boonen *et al* of postmenopausal women and of men aged 50 years or older reporting a risk of hip fracture found that oral vitamin D supplementation reduced the risk of hip fractures by 18% when vitamin D and calcium were taken together. Most of the trials that demonstrated the antifracture efficacy of vitamin D used approximately 800 IU of vitamin D3. The minimum 25(OH) D level at which antifracture efficacy was observed was 30 ng/ml (74 nmol/L), suggesting a threshold for optimal levels of 25(OH) D for fracture protection.

Results from another meta-analysis, evaluating the efficacy of oral vitamin D supplementation in the prevention of hip and other nonvertebral bone fractures in individuals aged 65 years or older, indicated that vitamin D offers dose-dependent fracture protection [38]. The analysis, by Bischoff-Ferrari *et al*, took into account 12 double-blind, randomized, controlled trials (RCTs) for nonvertebral fractures (n = 42,279) and 8 RCTs for hip fractures (n = 40,886), comparing the results obtained from the use of oral vitamin D (with or without calcium) with those derived from the administration of calcium alone and from placebo use.

In this study, doses of more than 400 IU/day were found to reduce fractures by at least 20% in individuals aged 65 years or older [4]. In contrast to the Boonen study, the investigators maintained that these effects were independent of calcium supplementation. Vitamin D insufficiency contributes to osteoporosis by decreasing intestinal calcium absorption. Treatment of vitamin D deficiency has been shown to improve bone mineral density. An analysis of the Third National Health and Nutrition Examination Survey (NHANES III) demonstrated a positive correlation between circulating 25(OH) D levels and bone mineral density [5].

Vitamin D supplementation has been associated with a reduction in falls and improved muscle strength in the elderly. A meta-analysis demonstrated that vitamin D supplementation resulted in a reduction in falls of about 22% in ambulatory and institutionalized elderly subjects, as compared with controls [43, 44]. Another meta-analysis examining muscle strength associated with vitamin D supplementation found significant improvement in reduced postural sway, timed up-and-go test results, and lower extremity strength in a pooled analysis of 13 studies [6].

Epidemiologic data suggest that vitamin D deficiency places adults at risk for developing cancer [; these apparently include breast, colon, and prostate cancer. Several studies using cultured cancer cells in mice models have also supported the notion that vitamin D prevents the growth of cancers [7]. Larger, randomized clinical trials are underway in humans to establish the role of vitamin D in the prevention of cancers.

Vitamin D insufficiency may increase the risk for type I and type II diabetes mellitus. In NHANES III, lower vitamin D status was associated with higher fasting glucose and 2-hour glucose after an oral glucose tolerance test [8]. Furthermore, vitamin D supplementation in adults has been associated with improved insulin sensitivity in several small, case-control studies [9].

Joergensen *et al* determined that vitamin D deficiency in type 1 diabetes may predict all causes of mortality but not development of microvascular complications [10]. The contribution of vitamin D deficiency to mortality must be mediated by nonvascular mechanisms. A study by Li *et al* indicated that vitamin D deficiency (serum 25-hydroxyvitamin D < 12 ng/mL) is related to an increased stroke risk in adults, with an association also found between higher vitamin D levels and a reduced stroke risk. The study, on adults aged 20 years or older, found that evidence for the relationship between high serum 25-hydroxyvitamin D levels and decreased stroke risk was particularly strong among females below age 50 years [11].

Low levels of vitamin D have also been linked to increased cardiovascular disease (CVD) biomarkers in older adults. In an observational study of 957 hypertensive older adults, vitamin D deficiency (< 25 nmol/L) was associated with higher levels of biomarkers linked with CVD and conditions such as multiple sclerosis and rheumatoid arthritis [12, 14]. Individuals deficient in vitamin D had significantly higher levels of the inflammatory biomarkers interleukin-6 (IL-6) and C-reactive protein (CRP), and higher IL-6: IL-10 and CRP: IL-10 ratios compared with subjects who had serum vitamin D levels > 75 nmol/L [12, 13].

A meta-analysis evaluated the effect of vitamin D supplementation (using a mean supplementation dosage of about 500 IU daily) on all-cause mortality in 18 randomized controlled trials and found a 7% relative risk reduction for death [15]. Severe vitamin D deficiency (25(OH) D < 10 ng/mL) has been associated with increased in-hospital mortality in patients admitted for acute coronary syndrome. [16].

A Cochrane Review of 50 randomized, controlled trials that included more than 94,000 individuals, primarily elderly women, found that vitamin D3 supplementation decreased mortality. Other forms of vitamin D, including vitamin D2, calcitriol, and alpha-calcidiol, did not reduce mortality [17].

A study by Manson *et al* to evaluate the efficacy of vitamin D supplementation and omega-3 fatty acids in lowering the

risk of invasive cancer and cardiovascular disease found no such reduction associated with the administration of vitamin D. The report, which included 25,871 participants (males aged 50 years or older and females aged 55 years or older) and had a median follow-up period of 5.3 years, determined that compared with a placebo group, there was no decrease in the incidence of breast, prostate, or colorectal cancer, or in myocardial infarction, stroke, or cardiovascular-related death, among subjects who consumed 2000 IU per day in supplementary vitamin D [18].

A wheeze is a continuous, coarse, whistling sound produced in the respiratory airways during breathing. For wheezes to occur, some part of the respiratory tree must be narrowed or obstructed (for example narrowing of the lower respiratory tract in an asthmatic attack), or airflow velocity within the respiratory tree must be heightened. Wheezing is commonly experienced by persons with a lung disease; the most common cause of recurrent wheezing is asthma attacks, though it can also be a symptom of lung cancer, congestive heart failure, and certain types of heart diseases.

The differential diagnosis of wheezing is wide, and the reason for wheezing in a given patient is determined by considering the characteristics of the wheezes and the historical and clinical findings made by the examining physician.

Wheezes occupy different portions of the respiratory cycle depending on the site of airway obstruction and its nature. The fraction of the respiratory cycle during which a wheeze is produced roughly corresponds to the degree of airway obstruction. Bronchiolar disease usually causes wheezing that occurs in the expiratory phase of respiration. As a rule, extrathoracic airway obstruction produce inspiratory sounds. Intrathoracic major airway obstruction produces inspiratory as well as expiratory sounds. Distal airway obstruction predominantly produces expiratory sounds [19].

The presence of expiratory phase wheezing signifies that the patient's peak expiratory flow rate is less than 50% of normal. Wheezing heard in the inspiratory phase, on the other hand, is often a sign of a stiff stenosis, usually caused by tumors, foreign bodies or scarring. This is especially true if the wheeze is monotonal, occurs throughout the inspiratory phase (i.e. is "holoinspiratory"), and is heard more proximally, in the trachea. Inspiratory wheezing also occurs in hypersensitivity pneumonitis. Wheezes heard at the end of both expiratory and inspiratory phases usually signify the periodic opening of deflated alveoli, as occurs in some diseases that lead to collapse of parts of the lungs.

The location of the wheeze can also be an important clue to the diagnosis. Diffuse processes that affect most parts of the lungs are more likely to produce wheezing that may be heard throughout the chest via a stethoscope. Localized processes, such as the occlusion of a portion of the respiratory tree, are more likely to produce wheezing at that location, hence the sound will be loudest and radiate outwardly. The pitch of a wheeze does not reliably predict the degree of narrowing in the affected airway [20].

A special type of wheeze is stridor. Stridor — the word is from the Latin, strīdor — is a harsh, high-pitched, vibrating sound that is heard in respiratory tract obstruction. Stridor heard solely in the inspiratory phase of respiration usually indicates an upper respiratory tract obstruction, "as with aspiration of a foreign body (such as the fabled pediatric peanut)." Stridor in the inspiratory phase is usually heard with obstruction in the upper airways, such as the trachea, epiglottis, or larynx; because a block here means that no air may reach either lung, this condition is a medical emergency. Biphasic stridor (occurring during both the inspiratory and expiratory phases) indicates narrowing at the level of the glottis or subglottis, the point between the upper and lower airways.

Being a tropical country, vitamin D deficiency was thought of uncommon in India, however, contrary to this belief recent studies have shown its prevalence to be as high as 50-90%. Previous studies from India used older definitions (<30 ng/mL) for defining vitamin D deficiency and insufficiency hence overestimated the association between vitamin D insufficiency/deficiency and wheeze. Recent Indian as well as international guidelines redefined the vitamin D deficiency as well as insufficiency as advocate using the same for ensuring uniformity. It was observed that lot of children visiting to emergency with recurrent wheeze did not have any underlying etiology except low vitamin D levels, on the other hand many children with even florid rickets doesn't have wheeze. Hence based on above findings the present study was planned for Clinical Evaluation of Levels of Vitamin D in Infants Suffered from Recurring Wheezing from Bihar Region.

Methodology

The present study was planned in Department of Paediatrics, Darbhanga medical College and Hospital, Darbhanga, Bihar, India. The study was conducted from March 2019 to August 2019. The 30 infants of age up to 24 months were enrolled in the present study. The 15 cases were enrolled in Group A as study group having wheezing and remaining 15 cases were enrolled in Group B as control group patients. Two different cut off levels were used in the study to categorize 25(OH) D concentrations. The levels above 30 ng/ml (75 mmol/L) were accepted as sufficient, the levels under< 20 ng/ml (50 nmol/L) as vitamin D deficiency and under < 10 ng/ml as extreme deficient (25nmol/L).

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Following was the inclusion and exclusion criteria for the present study.

Inclusion Criteria: Cases having wheezing.

Exclusion Criteria: Cases with history of congenital heart disease, chronic lung disease, and immunodeficiency.

Results & Discussion

About one in every three children have at least one episode of wheezing prior to their third birthday and cumulative prevalence of wheeze is around 50% at six years of age. Recurrent wheeze is defined as three or more episodes of parentally reported wheeze in the past 12 months of life [21]. Its occurrence is quite common and is reported in 6.2% of the Indian children [22]. Although there are many risk factors responsible for the development of recurrent wheezing, recently, vitamin D has gained significant interest. Studies reported that low vitamin D levels even in cord blood may be responsible for many childhood diseases [23]. Consequently, more studies reported the association of low serum vitamin D levels and severe asthma in children [24]. Although there are many risk factors including infections and allergy, for the development of recurrent wheezing [25]; recently, vitamin D emerged as significant risk factor owing

to its immunomodulatory propertie [26].

Table 1: Basic Details

Groups	Group A	Group B
Group of	Wheezing Cases	Control Cases
Age	7 – 18 months	8 – 16 months
Sex		
Males	7	10
Females	8	5
Total Cases	15	15

Table 2: Comparison of Serum 25 (OH) D levels

Groups	Group A	Group B
Group of	Wheezing Cases	Control Cases
Vitamin D level (ng/ml)		
< 10 ng/ml	5	1
11 – 20 ng/ml	4	4
21 – 30 ng/ml	3	7
> 31 ng/ml	2	3
Total Cases	15	15

In pediatric and adult populations, several trials have failed to show a significant benefit of vitamin D supplementation on respiratory outcomes, including asthma or upper respiratory infections [27]. In addition, in a study of extremely preterm infants, vitamin D did not affect duration of respiratory support [28]. However, multiple observational studies have shown an association between respiratory disease and low vitamin D levels [29]. In term infants, differences in cord 25(OH) D levels were associated with meaningful differences in the risk of lower respiratory tract infection with respiratory syncytial virus [30]. A recent individual patient data meta-analysis found that supplementation decreases respiratory infections, particularly in vitamin D–deficient patients or those receiving daily dosing [31, 32]. However, results of studies in other populations should not be extrapolated to preterm infants who may be in a critical developmental window with regard to the effects of vitamin D on the pulmonary and immune systems.

Wheezing is quite prevalent in pre-school children and consequently, many children develop asthma [34]. Insufficiency/ deficiency of vitamin D is widespread in all parts of the world [14]. 25(OH) D is the major stable and circulating form of vitamin D with a half-life of 2-3 weeks and its level is the best available indicators of vitamin D status [33]. Many cut-offs have been chosen to define insufficiency/deficiency of vitamin D but most of the guidelines meet consensus at a level of < 20 ng/mL, to label as insufficient, this cut-off was chosen in concordance to international standards. Vitamin D has an important role in the lung development and regulation of innate and adaptive immunity. A significant association exists between the number of vitamin D receptors genes and the respiratory syncytial virus bronchiolitis [35]. Conversely, serum 25(OH) D levels are inversely related to respiratory viral infections in children [36]. So, there is enough evidence to conclude that vitamin D plays an important role in respiratory diseases like asthma and wheeze in children.

Vitamin D insufficiency has been implicated in a number of immune related illnesses including multiple sclerosis, type 1 diabetes, and cancer [37], as well as respiratory diseases such as asthma [38]. In developing countries there is an association between the risk of ALRI and both rickets and subclinical vitamin D deficiency in children [39]. The same association has not been demonstrated elsewhere, but vitamin D deficiency has been linked to ALRI severity in Canada and the Middle East [40]. This variability could be secondary to differences in study population and design. Additionally, serum 25 hydroxy vitamin D is likely influenced by acute illness and medical intervention, perhaps making it a less reliable measure of pre-illness vitamin D status [41].

The results of the present study suggest that apart from young infants (<6 kg), 400 IU/d would be inadequate to achieve a level of intake above 80 IU/kg/day, and that a more appropriate vitamin D dose might be better estimated according to weight. In fact, in their position statement, the Canadian Pediatric Society has suggested that infants and young children may need a vitamin D intake up to 2.5 mcg/kg/d (100 IU/kg/d) in order to optimize their serum 25(OH) D levels. [42]. Furthermore, a study correlating vitamin D intake and serum levels suggested that vitamin D supplementation in infants should consider their rapid body weight increment [43]. Finally, the 2011 Institute of Medicine recommendations for vitamin D intake consider benefits for bone health only but do suggest different dosing based on age. In addition to recommended daily intakes of 400 and 600 IU for children under and over 1 year of age, the IOM provides an upper limit for vitamin D intake based on 6 different pediatric age ranges [44].

Clinically, serum calcifediol [25(OH) D] is used as a marker of vitamin D level [45]. In various populations calcifediol levels in cord blood are strongly correlated with maternal levels during pregnancy [46], with maternal calcifediol as the source of the fetal vitamin D pool [47]. Vitamin D deficiency in pregnant women and infants is common worldwide, including both developed and developing countries, ranging from 45 to 90% in pregnant women and 61–94% in infants. [48]. Based on growing epidemiological evidence, vitamin D deficiency has been linked to an increased risk of respiratory infections and asthma [49]. However, it is still unclear if and to what extent antenatal or early postnatal vitamin D deficiency would affect the development of wheeze or asthma later in life. Previous reviews on vitamin D supplementation during pregnancy have given conflicting messages [50].

Several researches have established a relationship among pregnant women with inferior vitamin D ingestion and an advanced jeopardy of wheeze in offspring. In a recent research, superior maternal circulating25 (OH) absorptions in pregnancy were separately connected with inferiorperil of lower respiratory infections in progeny in the first year of life but no relationship was found with breathless at 1year or 4 year, or asthma at age 4-6 years [51]. The authors have no knowledge about the maternal vitamin D levels but suggest that vitamin D levels of the infants hospitalized for serious infections and recurrent wheezing should be followed carefully. Recent studies have shown a potential physiologic function of vitamin D inadaptable usual in born and adaptive immunity [52].

Vitamin D metabolites contribute to defense at epithelial surfaces by stimulating production of antimicrobial peptides such as defensins and cathelicidin [53]. Janssen *et al*. recently showed significant associations of a number of innate immunity genes (including the VDR) with the severity of Respiratory Syncytial Virus (RSV) bronchiolitis [54]. Roth *et al*. found the association between two VDR gene polymorphisms and ALR Iinjuvenile children [55]. Jartti *et*

al. establish that serum 25(OH) D levels were reversely connected with RSV, Rhinovirus and multiple viral cause, by contrast no association was found with other viral infections [56]. Taken together, these studies point out the important role of vitamin D in the relation between respiratory viruses and their link to recurring wheezing.

Conclusion

The data generated from the present study concluded that no correlation between vitamin D levels and recurring puffed in infants was found but this may be due to the few numbers of patients that we studied with. The current findings not express important relationship among vitamin D level and recurring wheezing in the infants.

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