

RESEARCH PAPER

Vitamin D Status in Children with Recurrent Wheeze

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Abstract

Background: it has been shown that low serum 25-hydroxyvitamin D concentration was associated with a higher risk of upper and lower respiratory infections in children

Aim to evaluate vitamin D concentration and selected biochemical markers in infants and children with recurrent wheeze.

Methods: a case-control study has been carried out to measure serum vitamin Concentration; on 33 patients with recurrent wheeze, their ages ranged from 4-60 months; over the period from the 1st of March 2014 to the end of June 2014.

Forty-two age and sex matched healthy children were selected as control group. List of investigation was measured by spectrophotometer as serum calcium, phosphorus, alkaline phosphatase and 25-OH vitamin.

Result: Frequency of breast feeding in the first two years of life was low in wheezy children and significantly shorter duration of breast feeding less than 4 months in wheezy children than control group, P value 0.01. Vitamin D concentration was significantly low in children with recurrent wheeze than the control group; (21.69 ng/ml, 39.36 ng/ml) respectively with p-value 0.000. The severity of vitamin D deficiency was significant in children with recurrent wheeze, severe deficiency of vitamin D ≤ 5 ng/ml recorded in 4(100%), p-value of 0.001. while mean serum calcium, phosphorus and alkaline phosphatase shows no significant difference.

There is no significant relation observed between mean Vitamin D concentration and selected variables of infants and children with wheeze (P value > 0.05)

Conclusion: vitamin D supplementation may be considered in infants and children with recurrent wheeze.

Key words: vitamin D, recurrent wheeze, children

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Introduction

There are many studies highlighting associations between childhood asthma and vitamin D deficiency. The hypothesis is that vitamin D could have a central role in these

pathological situations and that it may represent a novel preventive and/or therapeutic strategy.¹ Meta-analysis data of published clinical trials concluded that vitamin D supplementation decreased the risk of asthma exacerbations in those with 25OHD levels less than 10ng/ml. The evidence suggests that there is a protective effect of higher vitamin D level primary prevention of asthma and its exacerbations.² Almost all cells in the body possess vitamin D receptors, including cells of the immune system. This has fueled more research and hypotheses that vitamin D may be integral to immune system regulatory

functions. Vitamin D deficiency can affect Th1 and Th2 cytokines, which may also contribute to the development of atopy.³ Vitamin D, can modulate the innate and adaptive immune responses; 1, 25-Dihydroxyvitamin D stimulates innate (macrophage) immunity by enhancing bacterial killing but it also modulates adaptive (lymphocyte) immunity to minimize inflammation and autoimmune disease.⁴ During a bacterial infection, macrophages acquire the capacity to convert circulating 25 vitamin D into 1, 25 OH vitamin D, which is a direct inducer of the expression of genes encoding for antimicrobial peptides and cathelicidin in antimicrobial peptide in particular. This peptide is central in host defense against respiratory tract pathogens.⁵ Deficiency in vitamin D is associated with increased autoimmunity as well as an increased susceptibility to infection. Many studies in adults and children found a higher prevalence of vitamin D deficiency in asthmatics than in the normal population; in addition, low vitamin D levels are associated with increasing severity of asthma and impaired pulmonary function. Patients with vitamin D deficiency have shown to have increased airway hyper-responsiveness and increased corticosteroid requirements.⁶

Subjects and Methods

A Case-control study has been carried out to measure serum level of vitamin D; 33 infants and children with recurrent wheeze (more than 3 attacks)^{7,8} who were admitted to Basra Maternity and Children Hospital and Basra teaching Hospital or those who visit pediatric emergency room, their ages ranged from 4-60 months; over the period from the 1st of March to the end of June 2014 were included. Forty-two infants and children visiting AL-Razi

primary health care center for routine checkup and vaccination were age and sex matched as control group.

Exclusion criteria including history of:

1. Congenital heart diseases, chronic lung disease, immunodeficiency, neurologic or metabolic disease.
2. Prematurity with or without admission to neonatal care unit
3. Vitamin D supplements for the last 3 weeks.⁹
4. Steroids treatment for previous one month.¹⁰

Especial Questionnaire was designed for the purpose of the study. An informed consent was obtained from the parents for recruitment in the study. All patients underwent general and systemic examination, and anthropometric measurements were assessed and applied to appropriate charts.¹¹

Laboratory Data

Blood samples (3 milliliters) from recruited subjects were collected using, Clot Activator with Gel Tube. A List of investigations was measured by spectrophotometer for the patients and control group: Serum calcium (Ca), phosphorus (Ph), Alkaline Phosphatase. Serum 25-OH Vitamin D measurement by Euroimmun 25-OH Vitamin D by ELISA kit Euroimmun AG, Seekamp 31,23560 Lübeck, Germany.¹²

Reference values¹³

Severe deficiency (≤ 5 ng/ml), deficiency (≤ 15 ng/ml), insufficient (15-20 ng/ml) and sufficient > 20

Data were analyzed using SPSS version 18

Results

A total of 75 infants and children, their ages ranged from 4-60 months are included in this study; 33 infants and children with history of

wheeze; more than three attacks, their mean age is 16 months with standard error 2.5; 17(51.5%) are males, and 16(48.5%) are females. The control group includes 42 healthy children, 22(52.4) are males and 20(47.6) are females, their mean age is 19.21 with standard error 2.1

Selected characteristics of patients with wheeze and control group

High frequency of breast feeding reported in the control group than children with recurrent wheeze, (38.1%, 27.3%) respectively but

statistically non-significant result, with significantly shorter duration of breast feeding less than 4 months in wheezy children than control group (39.1%, 5.6%) respectively p value 0.01. There is no significant difference in children with recurrent wheeze and control group regarding history of atopy (48.5%, 33.3%) with significant family history of allergic rhinitis and conjunctivitis (48.5%, 39.3%) in wheezy children than control group (14.3%, 7.1%) respectively as shown in (Table -1)

Table 1. Selected characteristics of wheezy children and control groups

Variables		Wheezy group		Control group		P value
		No.	%	No.	%	
Feeding history in 1 st two years	Breast	9	27.3	16	38.1	0.225
	Bottle	10	30.3	6	14.3	
	Mixed	14	42.4	20	47.6	
Duration of breast feeding (months)	< 4m	9	39.1	2	5.6	0.01
	4-12m	10	43.5	14	38.9	
	> 12m	4	17.4	20	55.5	
History of child atopy (atopic dermatitis)	Positive	16	48.5	14	33.3	0.137
	Negative	17	51.5	28	66.7	
Positive family history of atopy	Atopic dermatitis	14	42.4	7	16.7	0.13
	Allergic Rhinitis	16	48.5	6	14.3	0.001
	Allergic conjunctivitis	13	39.4	3	7.1	0.02
	Asthma	23	69.7	16	38.1	0.06

Biochemical parameters

(Table-2), shows that children and infants with recurrent wheeze have lower serum vitamin D level (21.69 ng/ml) than the control group (39.36ng/ml) with statistically significant result

(p-value 0.000), while mean serum calcium, phosphorus and alkaline phosphatase levels shows no significant difference.

Table 2. Biochemical parameters in patients and control

Variable	Patients	Control	P-value
	Mean ± SD		
Vitamin D (ng/ml)	21.69 ± 2.04	1.23 ± 0.48	0.000
Calcium (mg/dl)	8.5 ± 1.2	1.23 ± 0.48	0.261
Phosphorus (mmol/l)	1.23 ± 0.48	1.23 ± 0.48	0.534

Vitamin D status

Higher frequency of vitamin D deficiency; severe deficiency (12.1%) deficient (12.1%) and insufficiency (21.3%) recorded in children with recurrent wheeze than control group (4%); as well as sufficient level of vitamin D >20 ng/ml was recorded with higher frequency in control group than children with wheeze (97.6%,54.5%) respectively with statistically significant result (P-value 0.001). (Table-3)

Table 3. Vitamin D status in patients and control group

Variable	Severe deficiency < 5ng/ml	Deficient < 15 ng/ml	Insufficient 15-20 ng/ml	Sufficient >20 ng/ml	P value
Patients	4(12.1%)	4(12.1%)	7(21.3%)	18(54.5%)	0.001
Control	0(0%)	0(0%)	1(2.4%)	41(97.6%)	

Vitamin D and selected characteristics of patients with wheezes

(Table-4), shows no significant relation observed between mean Vitamin D level and selected variables of studied infants and children with recurrent wheeze; as age, sex, feeding history, history of atopy (p value > 0.0

Table 4. Vitamin D in relation to selected characteristics of patients

Variables		Vitamin D Mean (SE)	P-value
Age(months)	4m-12m	24.1(2.6)	0.198
	> 12m-24m	19.5(5.2)	
	24m-60m	17.2(2.6)	
Sex	Male	20(2.1)	0.095
	Female	22.4(3.5)	
Frequency of wheezing attacks	\leq 3 times	24.5(3.4)	0.297
	4-6 times	25.4(9.4)	
	> 6 times	18.6(2.5)	
Feeding history in 1st 2 years	Breast	17.3(2.8)	0.074
	bottle	22.6(4.8)	
	Mixed	23.8(2.7)	
Duration of breast feeding (months)	< 4m	22.7(3.1)	0.934
	4-12m	20.8(3.8)	
	> 12	16.2(5.9)	
History of child a topy	Positive	24.2(3.1)	0.321
	Negative	19.3(2.5)	
Positive family history of atopy	Atopic dermatitis	24.5(3.8)	0.355
	Allergic rhinitis	23.4(3.6)	
	Allergic conjunctivitis	19.3(3.6)	
	Asthma	22.2(2.5)	

Discussion

The effects of vitamin D deficiency in pediatrics have become increasingly apparent and extend beyond skeletal health. Vitamin D modifies airway inflammation and appears to be important in building immunity against respiratory infections, so is potentially beneficial in asthma.¹⁴ The present study reveals that; the frequency and duration of breast feeding was reported less in wheezy child than control group, this is in consistent with Silvers et al¹⁵, and Sonnenschein-van et al¹⁶ studies respectively. It is possible that the effect of breastfeeding on early wheeze reflects protection against respiratory infection, the predominant trigger of wheezing in early childhood.^{17,18} Much attention

has focused on the strong association between atopic tendency and childhood wheezing.¹⁹ Current study shows no significant difference of atopic tendency in children with recurrent wheeze and control group; similar result was concluded by Linneberg, et al study in Denmark.²⁰ They found most risk factors had opposite direction of their effects on wheeze and atopic dermatitis. For example, breast-feeding was associated with a decreased risk of wheezing but an increased risk of atopy. Hence, these findings support the hypothesis that wheeze and atopic dermatitis have a different etiology. In contrast to a study carried out in Hong Kong by Wang SS et al²¹ who concludes that vitamin D deficiency is associated with childhood atopic dermatitis. There was no significant difference regarding family history of atopic dermatitis and asthma among wheezy children and control group in contrast to a study carried out in Italy by Esposito, et al²², a family history of atopy was significantly frequent among children with wheeze than the controls as well as in UK study by Sherriff et al²³; atopy and a family history of asthma emerged as the main predictors of wheeze that developed after 6 months of age. In this study there is significant family history of allergic rhinitis and conjunctivitis in wheezy children, these finding is inconsistent with other study in Singapore done by Tan TN et al²⁴, also a study done by Bessa et al in Brazil,²⁵ demonstrated a statistically significant association between wheeze and family history of rhinitis. Vitamin D level is significantly lower in children with recurrent wheeze than control group as well as vitamin D status as severe deficiency, deficiency, and insufficiency significantly recorded in children with recurrent wheeze. This is consistent to a study carried out by Dogru, et al²⁶ and in Sweden by Stenberg et al²⁷ who shows that preschool children

admitted to hospital with acute wheeze had significantly lower levels of vitamin D than children with no wheeze in an age-matched control group. In the current study the mean serum calcium, phosphorus and alkaline phosphatase levels shows no statistically significant difference between patients and control group. These results are in accordance with Smith, et al²⁸ in England. Vitamin D stimulates protein synthesis, such as filaggrin, that is necessary for stratum corneum barrier formation. Therefore, vitamin D deficiency might exacerbate atopic dermatitis via disturbed epidermal barrier function and immunologic dysregulation, with subsequent impaired defense against infections.²⁹ In this study history of atopic dermatitis in wheezy children with low vitamin D is not significant. A study in Australia by Allen, et al.³⁰ also did not find significant association between eczema and low serum 25(OH) D levels. While Lee et al, in Korea found an inverse correlation between serum concentration of vitamin D and severity of the disease in children with atopic dermatitis associated with food allergy.³¹ We conclude that vitamin D supplementation may be considered in infants and children with recurrent wheeze.

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فيتامين (د) عند الأطفال الذين يعانون من الأزيز المتكرر

أن انخفاض تركيز 25-هيدروكسي فيتامين د في المصل يرتبط بارتفاع خطر الإصابة بالتهابات الجهاز التنفسي العلوي والسفلي عند الأطفال. تم إجراء دراسة مقارنة لتقييم تركيز فيتامين (د) وعلاقتها بالعلامات البيوكيميائية المختارة عند الرضع والأطفال الذين يعانون من الأزيز المتكرر. ثلاثة وثلاثون مريضاً ، تراوحت أعمارهم بين (4-60) شهراً ؛ خلال الفترة من 1 مارس 2014 إلى نهاية يونيو 2014. تم اختيار عينة ضابطة للعمر والجنس من اثنين وأربعين طفلاً من الأطفال الأصحاء وقد تم قياس قائمة من التحليلات للمرضى والمجموعة الضابطة: الكالسيوم ، والفوسفور ، والفوسفاتيز القلوي و فيتامين(د).

التاريخ التغذوي للمرضى في السنتين الأولى من العمر كشف ان الرضاعة الطبيعية بمعدل اقل عند الاطفال الذين يعانون من الأزيز المتكرر منه في المجموعة الضابطة مع مدة اقصر (اقل من 4 اشهر) للرضاعة الطبيعية لهؤلاء الاطفال مع نتيجة معنوية معتد بها احصائيا (0.01). كان تركيز فيتامين (د) منخفضاً بشكل ملحوظ عند الأطفال المصابين بأزيز متكرر عن المجموعة الضابطة. (21،69 نانوغرام / مل ، 39،36 نانوغرام / مل) على التوالي مع نتيجة معنوية معتد بها احصائيا (0.000)

وكانت شدة نقص فيتامين (د) عند الأطفال المصابين بأزيز متكرر، ونقص حاد في فيتامين(د) أقل من 5 نانوغرام / مل تم تسجيله في 4 (100٪)، قيمة معنوية معتد بها احصائيا (0.001). بينما قيمة الكالسيوم والفوسفور المصلي والفوسفاتيز القلوي اظهرت عدم وجود فرق كبير. لا توجد علاقة ملحوظة بين متوسط تركيز فيتامين د والمتغيرات المختارة للرضع والأطفال الذين يعانون من الأزيز (قيمة معنوية 0.05)

الخلاصة: يمكن اعتبار وصف كمالات فيتامين (د) للرضع والأطفال الذين يعانون من الأزيز المتكرر.

الكلمات المفتاحية: فيتامين د ، ازيز متكرر ، الأطفال