Vitamin D Status in Children with Recurrent Wheeze

Ghufran Tahir Salman, MBChB, CABP, Dr. Sawsan Issa Habeeb, MBChB, FICMS.

1. Misan Health Directorate / Al-Zahrawi hospital
2. Professor of pediatrics, College of Medicine, University of Basrah, Iraq

Received: 11.05.2020 Accepted: 09.06.2020

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

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. 

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. 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 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 Euroimmun25-OH Vitamin D by ELISA kitEuroimmun 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 1st 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 (39.36 ng/ml) with statistically significant result (p-value 0.000), while mean serum calcium, phosphorus and alkaline phosphatase levels shows no significant difference.
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Table 2. Biochemical parameters in patients and control

| Variable       | Patients Mean ± SD | Control Mean ± SD | P-value |
|----------------|-------------------|------------------|---------|
| 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         |                     |         |
| ≤ 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. 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. Much attention
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has focused on the strong association between atopic tendency and childhood wheezing.\textsuperscript{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.\textsuperscript{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 al\textsuperscript{21} 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 al\textsuperscript{22}, a family history of atopy was significantly frequent among children with wheeze than the controls as well as in UK study bySherriff et al\textsuperscript{23}; 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 byTan TN et al\textsuperscript{24}, also a study done by Bessa et al inBrazil,\textsuperscript{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 in consistent to a study carried out by Dogru, et al \textsuperscript{26} and in Sweden by Stenberg et al\textsuperscript{27} 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 al \textsuperscript{28} 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. \textsuperscript{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.\textsuperscript{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. \textsuperscript{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 خفض تركيز 25-هيدروكسي فيتامين د في المصل يرتبط بارتفاع خطر الإصابة بالالتهابات الجهاز التنفسي العلوي والسفلي عند الأطفال

تم إجراء دراسة مقارنة لتقدير تركيز فيتامين (د) وعلاقته بالعلامات البيوكيميائية المختلفة 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 الين وأربعين فطاً من الأطفال الأصحاء، وقد تم قياس قائمة من التحاليل للرضع والمجموعة الضابطة: الكالسيوم، والفوسفور، والفسفاطوزي القلوي وفيتامين (د).

التاريخ الغذائي للمريض في الستة الأول من العمر كشف أن الرضاعة الطبيعية تحدد أقل عدد الأطفال الذين يعانون من الأزيز المتكرر فيه. في المجموعة الضابطة مع مدة أقصر (أقل من 4 أشهر) للرضاعة الطبيعية للفحص الأطفال مع نتيجة معنوية معنوية بحث (0.01). كان تركيز فيتامين (د) منخفضًا بشكل ملحوظ عند الأطفال المصابين بأزيز متكرر عن المجموعة الضابطة. (69،21 نانوغرام / مل، 39.36-110 نانوغرام / مل) على التوالي مع نتيجة معنوية معنوية بحث (0.000).

وكان يتم ذلك بفضل 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 معنوية بحث (0.01). بينما قيمة الكالسيوم والفسفور المحلي والفوساطوزي القلوي ظهرت عدم وجود فرق كبير. لا توجد علاقة ملموسة بين متوسط تركيز فيتامين (د) والمتغيرات المختلفة للمرض والأطفال الذين يعانون من الأزيز (قيمة معنوية 0.05).

الخلاصة: يمكن اعتبار وصف مكملات فيتامين (د) للأطفال والرضع والأطفال الذين يعانون من الأزيز المتكرر.

الكلمات المفتاحية: فيتامين د، الأزيز متكرر، الأطفال

http://dx.doi.org/10.33762/mjbu.2020.127089.1014