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Vitamin D and cathelicidin assessment in infection-induced asthma in Egyptian children

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Abstract

Introduction: Vitamin D deficiency was hypothesized to increase the risk of respiratory infections and asthma exacerbation through a reduced production of cathelicidin, a multifunctional anti-microbial peptide essential for normal immune responses to infections.

Aims: Evaluation of vitamin D status and its impact upon cathelicidin in children with infection-induced asthma through assessment of their serum levels.

Patients and methods: The study included 65 infection-induced asthmatic children aged 9.32 ± 2.35 years (33 in exacerbation and 32 severity matched in remission) and 25 healthy controls. All children were subjected to history taking, physical examination, pulmonary function tests, CBC, and assessment of serum levels of vitamin D (25(OH)D) and cathelicidin using ELISA.

Results: All asthmatics and controls were deficient in vitamin D (≤ 20 ng/ml), and no significant difference was found between controls (10.77 ± 5.6 ng/ml), remission group (9.8 ± 4.89 ng/ml), and exacerbation group (8.49 ± 5 ng/ml), $p = 0.29$. Cathelicidin was higher in the control group (7.69 ± 4.3 ng/ml) compared to that in the remission ones (6.88 ± 3.66 ng/ml), but not significant, while it was significantly higher in the exacerbation group (9.78 ± 3.03 ng/ml) compared to that in the remission ones ($p = 0.01$). No significant difference between the three groups regarding percentage having vitamin D level < 10 ng/ml ($p = 0.3$). There was no correlation between serum cathelicidin and vitamin D levels in either asthmatics or controls. Both levels had no correlation with spirometry indices and no relation to frequency of exacerbations.

Conclusion: Vitamin D deficiency cannot explain infection-induced asthma. Cathelicidin elevation in exacerbations seems to be independent of vitamin D.

Keywords: Vitamin D, Cathelicidin, Infection-induced asthma

Introduction

Bronchial asthma is considered one of the most common chronic diseases, and it affects about 300 million people all over the world (Global Strategy for Asthma Management and Prevention 2011). A significant number of asthmatic patients are at increased risk of asthma-related mortality and severe exacerbations; the intense rise in childhood asthma prevalence in recent decades in most countries is due to important environmental determinants affecting a genetically susceptible population (gene–environment interaction) (Braman 2006). Vitamin D is thought to be one of the environmental factors that increase the pattern of asthma, and many inconsistent results are raised (Adams and Hewison 2008). It may act through enhancing Th2 responses and inhibiting Th1 (Jirapongsananuruk et al. 2000), while inhibition of both Th2 and Th1 responses was proved by others (Urry et al. 2009). Due to its effects on adaptive and innate immunity, vitamin D was linked to

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host-defensive mechanisms against respiratory tract pathogens (Bener et al. 2012).

It also has a role in Toll-like receptor signaling due to infections by increasing the production of antimicrobial peptides as cathelicidin (Prentice 2008).

During bacterial infection, circulating 25 vitamin D is converted to 1,25(OH) vitamin D by macrophages; this is a direct stimulant of the expression of genes encoding for many antimicrobial peptides (mainly cathelicidin) (White 2010).

Children with vitamin D deficiency have been shown to be at higher risk of respiratory infections, which is the main stimulant of asthma exacerbation (Paul et al. 2012). However, the exact role of vitamin D in bronchial asthma is still not clearly determined (Mak and Hanania 2011; Miraglia del Giudice and Allegorico 2016).

Aim

The aim of this study was to assess vitamin D status and its impact upon cathelicidin anti-microbial peptide in children with infection-induced asthma through detection of their levels in serum.

Patients and methods

A cross-sectional, case-control study was designed, it included 65 asthmatic children aged 6–14 years attending Allergy Clinic, Abo Rish Hospital—Cairo University and Allergy Clinic, National Research Centre in the period between November 2015 and February 2016. All of them were chronic asthmatics according to GINA guidelines, 2011 (Global Strategy for Asthma Management and Prevention 2011). Exclusion criteria were parasitic infestations, autoimmune diseases, T.B., skeletal manifestations of vitamin D deficiency, chronic diseases that can affect the level of serum vitamin D (renal diseases, inflammatory bowel disease), children receiving vitamin D supplementation, or any drug (calcium, calcitonin, anticonvulsant) affecting its level during the last 6 months. We classified asthmatics patients into 33 patients in infection-induced exacerbation by symptoms of upper respiratory infection (URTI) and clinical examination and 32 patients in remission and 32 patients in remission. Criteria for clinical URTI were defined as two or more of the following symptom: fever, cough, headache, sneezing, runny nose and nasal congestion, pharyngeal hyperemia, and sore throat. The subgroups of asthmatic patients were severity matched in the last 3 months. Twenty-five normal healthy children of the same age and sex were included as a control group. Informed written consents were taken from all guardians of children. The study was approved by the ethical committee of the National Research Centre. All subjects were subjected to full history taking using the allergy sheet including personal history, history of upper respiratory symptoms, precipitating factors, asthma attacks (duration of asthma, frequency, and severity of attacks), protocol of asthma management and prevention, presence of systemic illness, vitamin D supplementation/any medication, and family history of asthma. Exposure to sunlight and its average duration in hours/day during the last month was recorded. Clinical examination with anthropometric measures (height, weight, and BMI) was calculated. Pulmonary function tests using a spirometer (Fukuda Denshi, Spirosift SP5000) were assessed. Laboratory investigations were assessed as follows: 5 ml peripheral venous blood was withdrawn from every patient and control subject under complete aseptic conditions, 1 ml was anticoagulated with EDTA tube for CBC, and the rest was centrifuged, aliquoted, and stored at − 20 °C for assessment of both serum vitamin D and cathelicidin antimicrobial peptide. Serum 25-hydroxy vitamin D levels were measured using a commercial enzyme-linked immunosorbent assay (ELISA) kit developed by Bioassay Technology Laboratory. Shanghai, China, catalog number EA1981 Hu. 25(OH)D is considered the best circulating biomarker of vitamin D status because it has longer half-life (2–3 weeks) than 1,25(OH)D (4 h) (Holick 2009). The normal range for 25-hydroxy vitamin D is 30–60 ng/ml. Insufficiency was diagnosed at level < 30 ng/ml, deficiency at level < 20 ng/ml and severe deficiency at level < 10 ng/ml (Holick 2007). Human cathelicidin antimicrobial peptide (CAMP) were measured using solid-phase enzyme-linked immunosorbent assay (ELISA), catalog number MBS013541. My Bio Source, Inc. P.O. Box 153308, San Diego, CA, 92195-3308, USA.

Statistical analysis

Data were analyzed using the statistical package version 15 (SPSS Inc., Chicago, IL, USA). Numerical data were expressed as mean and standard deviation. Qualitative data were expressed as frequency and percentage. The chi-square test (Fisher exact or chi-square test) as indicated were used to examine the relationship between qualitative variables. For quantitative data, the comparison between two groups was done using the Student *t* test. One-way ANOVA test was used to compare three or more independent means followed by post hoc test when there was a significance. Pearson correlation coefficient was used to examine the relationship between two quantitative variables. p value ≤ 0.05 was considered significant.

Results

The demographic data of the patient's group was presented in Table 1. Mean age was 9.32 ± 2.35 years (31 males and 34 females).

Table 1 Demographic and clinical data of the asthmatic patients ($n = 65$)

Variable	Mean ± SD	Number/frequency (%)
Age (years)	9.32 ± 2.35	
Sex (males/females)		31/34
Duration of disease (years)	(7.27 ± 1.9)	
Frequency of attacks/month	(2.4 ± 0.64)	
Positive family history		50 (78.1%)
Positive parenteral consanguinity		10 (11.4%)
Fever/rhinitis before asthma		65 (100%)
Associated allergic disease		17 (26.6%)
Duration of exposure to sun (min/day)	(46.4 ± 45.6)	

The comparative data between patient's subgroups and control group were presented in Table 2 and there was a significant elevation regarding WBCs between patients (remission/exacerbation) compared to control. The absolute eosinophilic count was significantly elevated in patients with exacerbation compared to controls. All our studied groups were deficient in vitamin D (≤ 20 ng/ml), Fig. 1. Vitamin D was reduced in patients (both groups) compared to controls but not significant, cathelicidin was higher in control group than remission group but not significant, while it was significantly higher in the exacerbation group compared to remission ones (p = 0.01) (Fig. 1).

Comparing the percentage of children having vitamin D level < 10 ng/ml within each group revealed no significant difference between the three groups (Fig. 2).

Vitamin D and serum cathelicidin had no correlation with duration of the disease, absolute eosinophil counts, or spirometry indices apart from positive correlation between PEFR (% of predicted) and vitamin D (Table 3). There was no correlation between serum cathelicidin and vitamin D levels in either asthmatics (r = – 0.06 and p = 0.64) or in controls (r = .187, p = .418), also no correlation between both levels in either exacerbation or remission (p = 0.7 and r = 0.07; p = 0.4, r = 0.1) respectively. There was no correlation between BMI and cathelicidin (r = 0.24, p = 0.08).

Daily exposure to sun > 30 min significantly increased the level of vitamin D in the studied patients (exposed (10.16 ± 5.03 ng/ml) vs non-exposed (7.65 ± 4.65 ng/ml), p = 0.05. No difference between males and females was found regarding vitamin D or serum cathelicidin levels.

Discussion

Vitamin D deficiency has been recorded in many countries worldwide, even in those with excessive sun

Table 2 Comparison between asthmatics and control regarding demographic and laboratory data

Variable	Healthy control (group 1)	Patients in remission (group 2)	Patients in excerption (group 3)	p value (between groups)
Age	8.8 ± 2.2	9.3 ± 2.4	9.2 ± 2.3	0.7
Sex males/females	15/20	19/13	21/11	0.8
Weight (kg)	31.2 ± 11.1	30.6 ± 9.6	31.9 ± 12.7	0.9
Height (cm)	130.7 ± 11.2	125.7 ± 9.8	129.2 ± 9.7	0.2
BMI (kg/m$^{2)}$	17.7 ± 3.4	19.2 ± 5	18.5 ± 4.9	0.5
HB (gm/dl)	12.9 ± 1.6	12.7 ± 1.02	12.6 ± 0.9	0.9
RBCs (cells/mm^3)	4.70	4.76	4.73	0.63
WBCs (cells/mm^3)	5.8 ± 1.5	7.5 ± 2.5* (p = 0.03)	8.9 ± 4.2** (p = 0.001)	0.001
AEC (cells/mm^3)	207.8 ± 119.1	340.1 ± 312.3	389.7 ± 347** (p = 0.01)	0.04
Vitamin D (ng/ml)	10.77 ± 5.6	9.8 ± 4.89	8.49 ± 5	0.29
Serum cathelicidin (ng/ml)	7.69 ± 4.3	6.88 ± 3.66	9.78 ± 3.03*** (p = 0.01)	0.03

BMI body mass index, *AEC* absolute eosinophilic count
*Comparing healthy controls with patients in remission (groups 1 and 2)
**Comparing healthy controls with patients in exacerbation (groups 1 and 3)
***Comparing patients in remission with patients in exacerbation (groups 2 and 3)

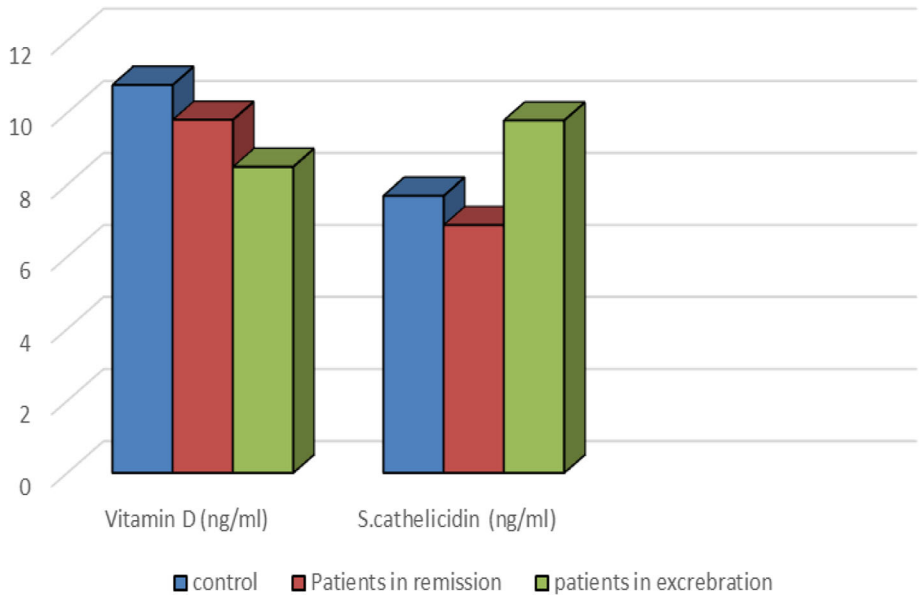

Fig. 1 Serum vitamin D and cathelicidin levels in the three studied groups

exposure (Brehm et al. 2009). The demonstration of the role of vitamin D in regulation of immune response and the parallel epidemiological pattern between vitamin D deficiency and asthma has led to the hypothesis that there is causal relationship between vitamin D and allergic respiratory diseases (Litonjua and Weiss 2007; Freishtat et al. 2010; Comberaiti et al. 2014).

In our study, vitamin D deficiency (< 20 ng/ml) was found in all the studied groups (asthmatics and controls), also the level was found to be < 10 ng/ml in 62.4%, 54.5%, and 52% of patients in remission, exacerbation, and healthy controls respectively.

Our results regarding vitamin D deficiency in controls agreed with many studies, an Indian one reported 25(OH)D level below 20 ng/ml in 62–82% of children (Harinarayan et al. 2008). The National Health and Nutrition Examination Survey (NHANES) 2001–2004, reported that 61% of US children had level between 15 and 29 ng/ml, while 9% had level below 15 ng/ml 19. 33.3% of healthy Egyptian children 6–16 years and 37.5% aged 2–18 years have insufficient vitamin D in spite of being a sunny country (Hamed et al. 2016; El-Menem et al. 2013). FAO/WHO Expert Consultation (2004), recorded that about 30 min of skin exposure (without sunscreen) of the face and arms to sunlight can supply all

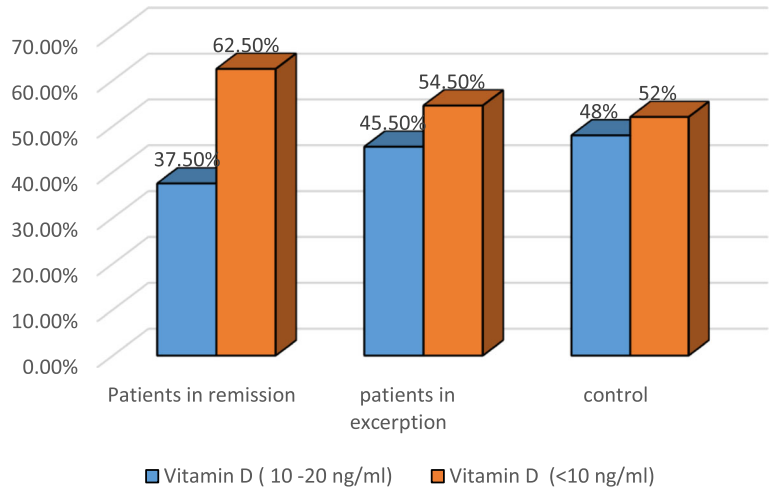

Fig. 2 Vitamin D classified levels in the studied groups

Table 3 Vitamin D and cathelicidin correlations with different spirometry indices in asthmatics

Variant		Vitamin D (ng/ml)	Cathelicidin (ng/ml)
FVC % of predicted	*r*	0.119	− 0.032
	p	0.484	0.85
FVE1% of predicted	*r*	0.095	0.013
	p	0.576	0.938
FEV1/FVC%	*r*	0.223	0.048
	p	0.219	0.796
PEFR % of predicted	*r*	0.348	− 0.008
	p	0.035	0.961
FEF 25–75% of predicted	*r*	0.124	0.199
	p	0.466	0.237

FVC forced vital capacity; *FEV1* forced expiratory volume during first second; *PEFR* peak expiratory flow rate

the daily body requirements of vitamin D (FAO/WHO Expert Consultation 2004). In our study, daily exposure to sun 30 min, significantly increased vitamin D level in our patients; however, both groups are deficient in vitamin D. Duration of sun exposure was stated to be one of the risk factors of vitamin D deficiency (Arikoglu et al. 2015).The air pollution in our country may play a role in the prevention of ultraviolet rays from reaching the skin. No significant difference was found between males and females excluding the effect of clothing habits.

Vitamin D was reduced in our asthmatics compared to controls but was statistically insignificant. Our result agreed with many studies who found no significant difference between asthmatics and control regarding vitamin D insufficiency and deficiency (Braman 2006; Hamed et al. 2016; Soheila et al. 2011). Others found higher incidence of vitamin D deficiency among asthmatics compared to non-asthmatics (El-Menem et al. 2013; Arikoglu et al. 2015; Kolokotroni et al. 2015; Uysalol et al. 2013) and to controlled asthma group (Arikoglu et al. 2015).However, Alyasin et al. (2011) reported that high 25-hydroxy vitamin D levels were associated with elevated asthma immunological and inflammatory markers (Alyasin et al. 2011). Vitamin D less than 10 ng/ml was reported to be an asthma risk factor (Arikoglu et al. 2015); in our work, no significant difference was found between the three groups regarding percentage having vitamin D less than 10 ng/ml.

The exact role of vitamin D in asthma pathogenesis is still unclear and further assessments may be needed. Vitamin D plays critical roles in the support of the immune system (which may help to prevent acute asthma exacerbations), decreasing inflammation (which may reduce acute asthma symptomology), reducing remodeling (which can reduce chronic lung dysfunction), and enhancing glucocorticoid function (which may allow reduction of administered steroids doses (Iqbal and Freishtat 2011).

One of the suggested mechanisms of vitamin D in asthma pathogenesis is the reduction in cathelicidin production and increase risk to infection. Cathelicidin is a multifunctional host defense molecule essential for normal immune responses to infections. It has many immunomodulatory properties, as inhibition of neutrophil apoptosis, chemoattractant function, cytokine release, and tissue regeneration (Yeung et al. 2011). This peptide is a part of the innate immunity and it is secreted by peripheral blood immune cells respiratory epithelial cells and regulated by vitamin D (Iqbal and Freishtat 2011). Cathelicidin expression could be inducible or constitutive by microbial, developmental, and inflammatory stimulations. However, the molecular mechanisms of gene regulation are still not clearly known (Ewa et al. 2012). Cathelicidin level was higher in our normal children compared to those in remission, but statistically not significant. Despite low levels of vitamin D in all studied groups, serum cathelicidin levels were significantly higher in the infection-induced exacerbation group compared to remission ones. Also, there was no significant correlation between vitamin D and cathelicidin in all studied groups that did not support the hypothesis that vitamin D deficiency can increase the frequency of infection-induced asthma attacks by reducing cathelicidin production (knowing that 1,25(OH)D is the trigger for activation of cathelicidin and not 25(OH)D which was assessed in our work as the latter is the form that reflect status of vitamin D in the body (Holick 2009). Randomized controlled trials found some weak evidence to support the role of vitamin D supplementation in the reduction of asthma exacerbations (Riverin et al. 2015). High levels of serum cathelicidin in our exacerbation group may reflect activation of the immune system in acute attacks of asthma independent of vitamin D levels. Many studies recorded that cathelicidin can be considered as a strong marker for a systemic immune response in bacterial or viral infections (Zhang et al. 2012; Chalmers et al. 2013). Our study goes parallel with Tugba et al. (Arikoglu et al. 2015), who reported that the serum cathelicidin levels were significantly higher in the attack group than in the controlled asthma group. On the opposite side, a low level of cathelicidin was found to be due to vitamin D deficiency that may predispose to infectious complications in healthy children as well as asthmatic children (Bozzetto et al. 2012; Hart et al. 2011; Hewison 2010).

In different studies, the correlation between PFT and vitamin D had many controversies. In our work, there was no correlation found between vitamin D level and pulmonary function indices apart from positive correlations with PEFR. Lack of correlations goes parallel with

many studies (Arikoglu et al. 2015; Boonpiyathad et al. 2016), who reported that there was no observed association between serum vitamin D levels and lung function. A significant association between 25-OHD levels and PEFR were detected in the cross-sectional analyses in women and men (Van Schoor et al. 2012). PEFR was found to be a marker for improvement post-vitamin D administration in the deficient group (Najmuddin and Lahiri 2017; Yadav and Mittal 2014). Yao et al. 2014 (Yao et al. 2014) found a significant relationship between low serum vitamin D levels and impaired lung functions. Serum 25(OH)D level less than 50 nmol/L was recorded to be significantly associated with a lower FEV1/FVC (Larose et al. 2015).

It was reported that there is a significant positive correlation between body mass index (BMI) and serum levels of cathelicidin in all asthmatic patients (Arikoglu et al. 2015). Other showed that expression of cathelicidin m-RNA was significantly positively correlated with body mass index (BMI) that may be caused by the proinflammatory cytokines produced by adipose tissue, e.g., leptin that may stimulate the cathelicidin production (Benachour et al. 2009). In contrast to this result, our study showed no correlation between BMI and serum cathelicidin.

Conclusion

Vitamin D deficiency was common in asthmatic patients but was not the leading cause of infection-induced asthma exacerbations. Cathelicidin elevation in asthma exacerbations seems to be independent of vitamin D.

Recommendation

Further study on a larger number of patients and controls is needed to prove our results.

Limitation of a study

Lack of a group of non-asthmatic control during their infection for comparison with asthma exacerbation group may add a different data.

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Availability of data and materials

All the data of patients are available.

Authors' contributions

This work was carried out in collaboration between all authors. Authors AAM and AMAA-A designed the study and wrote the protocol. Authors AAM, HMH, and AMAA-A managed the literature searches. All pediatric team managed the patient's recruitment and pulmonary function. Authors MAMA and RNY did the lab assessment. Author HMH performed the statistical analysis. Authors AAM and HMH wrote the first draft of the manuscript. Author AMAA-A revised and edited the manuscript. Authors AAM, HMH, and AMAA-A managed the analyses of the study and executed the manuscript in its final form. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Informed consent was obtained from the parents and/or caregivers of all participants before the procedure, according to the guidelines of the ethical committee of the National Research Centre and Ain Shams University.

Consent for publication

I am and all authors have approved the manuscript for submission to your journal hoping that it is going to be accepted for publication.

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

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