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The Relationship between Vitamin D, Asthma and Total IgE in Children

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ABSTRACT Current researches have pointed out that vitamin D may play a role in multiple chronic illnesses, including symptoms involving the respiratory system. This study evaluated the interaction between vitamin D levels and severe asthma by proposing a clinical trial. The study population included 100 volunteer children, consisting of 50 asthmatic and 50 non-asthmatic children who were admitted to Kagithane State Hospital. The two groups were matched to each other by age. Subjects' ages ranged from six to sixteen years old with a fifty-eight percent female and forty-two percent male distribution. Serum vitamin D levels, eosinophile count, Total IgE, phosphorus, calcium in the asthmatic and non-asthmatic groups were compared. No evidence of any association of vitamin D with asthma was found.

INTRODUCTION

According to estimations in 2008, 300 million individuals seem to have been affected by asthma, which is a chronic inflammatory disorder targeting airways (Bateman et al. 2008). An increase in the hyper-responsiveness of the airways leads to recurrent wheezing, breathlessness and coughing in association with airflow obstruction in this commonly seen disease (Akinbami et al. 2009). Beginning from 1960s, asthma cases increased progressively reaching a peak in 1990. Since then, there has been no further increase in asthma cases (Akinbami et al. 2009). There is no clear explanation for this asthma epidemic (Paul et al. 2012). Apparently, pollution, tobacco smoke exposure, vitamin D deficiency, and early exposure to allergens play a role. Some patients are genetically predisposed to this disease (Gupta et al. 2012).

Recently, an association has been found between vitamin D levels and certain chronic illnesses. Asthma, atopy, several respiratory diseases show an association with vitamin D levels in epidemiological studies (Holick et al. 2007). An important data from the Third National Health and Nutrition Examination Survey (NHANES III) in a cross sectional study in USA population showed a positive correlation between vitamin D levels and forced expiratory volume in 1 second (Black et al. 2005). Although underlying mechanisms and the connections are still unclear in terms of lung function, the ability of vitamin D in regulation of inflammation and tissue remodeling (Xystrakis et al. 2006; Searing et al. 2010) also in induction of antimicrobial peptides (cathelidin and defensin-â 2) seems relevant (De Smet et al. 2005). Also, one must not forget the effect of vitamin D on muscle strength (Hopkinson et al. 2008; Finklea et al. 2011).

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According to generally accepted criteria, a serum vitamin D level below 30 ng/ml is considered as insufficiency of vitamin D. There are 1 billion people in the world meeting this criterion (Hollick et al. 2007).

Mechanistic relations of vitamin D with asthma and allergies is not fully illuminated but a statistically significant protection has been found against atopy with prenatal and post natal exposure to vitamin D (Camargo et al. 2007). Contrariwise, vitamin D supplementation have been found to increase the risk of allergy in some researches (Karen et al. 2016).

For children there was an inverse relationship between asthma severity and vitamin D levels and lung function improved with increasing levels of vitamin D in adults (Black et al. 2005). To further complicate this interaction, in some allergic conditions and atopic individuals increased serum vitamin D levels are shown (Hyponen et al. 2004; Gale et al. 2008; Back et al. 2009). Wjst et al. (1999) proposed increased not decreased vitamin D values as an explanation of global epidemic of allergic diseases.

From the viewpoint of childhood respiratory health, researchers assessed the role of vitamin D not in forme fruste and moderate cases but in severe asthma.

MATERIAL AND METHODS

Study Design

This is a randomized controlled trial (RCT). The study population included 100 volunteer children including 50 asthmatic and 50 non-asthmatic children who were admitted to Kagithane State Hospital Pediatrics Clinic for different reasons from January 2013 to June 2013. Before beginning the study, the researchers obtained an approval from Okmeydani Education and Research Hospital Ethics Committee (ÝSM.04. 34.61.12.900). Informed consents were obtained from all participants. Thorough bilateral interviews and questionnaire were used to gather information such as, age, gender, asthma and its severity. The researchers calculated the BMI of all children. The two groups were then matched to each other by age, with participants ranging between six and sixteen years old. When the target number of 50 patients who met the non-asthmatic group criteria was met, the addition of participants was terminated.

The subjects included 50 asthmatic patients who were diagnosed on the basis of the following diagnostic asthma criteria of recurring bouts (that is, more than two) of wheezing, coughing, dyspnea, or a combination of these conditions, and reversal of these symptoms with bronchodilators. The 50 non-asthmatic subjects selected had neither a history of allergic disorders personally nor relatives with such conditions. Also, children with any chronic disease were not included in this group. Subjects who consumed vitamin D in a prescription or as fortified foods and patients who used drugs, which alter the metabolism of vitamin D, such as anticolvunsants or steroid, were also excluded. Comparisons in terms of vitamin D between groups were made regarding eosinophil counts, forced expiratory volume in one second (FEV1), forced vital capacity (FVC), use of non-steroid anti-inflammatory drugs, any hospitalization in the past year and duration and severity of the disease. For description purposes, the researchers classified vitamin D levels into three groups as deficient (<20 ng/mL), insufficient (≥20 and <30 ng/mL), or sufficient (≥30 ng/mL) (Holick et al. 2007; Vieth et al. 2007). Serum 25(OH) D levels were measured to define the vitamin D state of individuals.

Peripheral Blood Eosinophil Count

A peripheral smear with Wright staining was done in asthmatic and non-asthmatic children for eosinophil counts.

Pulmonary-function Testing

In asthma, airways blockage results in reduced airflow and smaller partial-expiratory lung volumes. Therefore, in asthmatic subjects, spirometry was conducted in accordance with the American Thoracic Society (ATS) recommendations using a spirometer (Jaeger, flow screen, Würzburg, Germany). The best FEV1, FVC, and FEV1/FVC values were selected for analysis in agreement with the National Asthma Education and Prevention Program (NAEPP) guidelines sponsored by the U.S. National Institutes of Health (Expert Panel Report 2007).

Statistical Evaluation

For statistical analysis, NSCC 2007 and PASS 2008 statistical software programs were used. In the evolution of the study results to compare quantitative data in the two groups, Student t-test was used for parameters showing normal variation and Mann Whitney test for parameters not showing normal variation, besides statistical defining methods (mean, standard deviation median, frequency, ratio, minimum and maximum vitamin D values). To compare qualitative data, Yates' Continuity Correction Test was used. Significance was rated at $p<0.01$ and $p<0.05$ levels.

RESULT

This study was completed on 50 non-asthmatic and 50 asthmatic subjects, totaling 100 participants. Subjects' ages ranged from six to sixteen years old with a fifty-eight percent female (n: 58) and forty-two percent male (42) distribution (Table 1).

Table 1: Distribution of identifying characters

	N	*%*
Sex		
Girl	58	58.0
Boy	42	42.0
Group		
Normal	50	50.0
Asthma	50	50.0
	Med±SD	*Min-Max*
Age	11.5±2.3	6-16
BMI	20.7±4.0	14.6-35.6

BMI values of subjects ranged from 14.6 kg/m2 to 35.6 kg/m2 with a mean value of 20.75 ± 4.00 kg/m^2. No statistically significant difference was observed, according to age, sex, and BMI between the two groups (Table 2).

Table 2: Comparison of groups according to sex, age, and BMI

	Normal		*Asthma*		*p*
	n	*%*	*n*	*%*	
Sex					^{a}*0.068*
Girl	24	48.0	34	68.0	
Boy	26	52.0	16	32.0	
	Med±SD	*Min-Max*	*Med±SD*	*Min-Max*	
Age	11.7±2.4	7-16	11.4±2.1	6-15	^{b}*0.467*
BMI	20.3±3.7	14.6-30.1	21.1±4.2	14.7-35.6	^{b}*0.329*

[a]Yates' Continuity Correction Test [b]Student's t Test

Statistically, FVC percentage, FVC Lt, FEV percentage and FEV Lt values of non-asthmatic subjects were significantly higher than asthmatic subjects' values. Again, FEV/FVC percentage values of non-asthmatic subjects were significantly higher than the asthmatic group. Between subjects of non-asthmatic and asthmatic groups, no statistically significant difference was observed as to Ca^{++}, phosphor and vitamin D values. Eosinophil counts and Total IgE values of non-asthmatic subjects were lower than asthmatic subjects at statistically significant levels (Table 3). Distribution of asthmatic subjects is as follows:

- Step 1: Thirty-four percent (n=17)
- Step 2: Thirty-four percent (n=17)
- Step 3: Thirty-two percent (n=16)

In asthmatic subjects, no statistically significant difference was observed among the three-step groups of asthma regarding the sex, age and BMI (Table 4).

Statistically, very significant differences were observed in FEV Lt Values between step groups. Calcium, phosphorus, and vitamin D values of the groups also showed no statistically significant differences. Eosinophil values in all asthma step groups showed statistically significant differences at high levels. According to Mann Whitney U Test, which was performed to detect the group creating diversity, eosinophil counts of step 1 group subjects were significantly lower than step 3 group subjects. Total IgE values in the step groups showed highly significant differences statistically. According to the Mann Whitney Test, which was carried out to determine the difference-creating group, total IgE values of step 1 group of subjects were significantly lower than step 2 and step 3 groups of subjects. Total IgE values of step 2 subjects were also significantly lower than step 3 group subjects' values (Table 5).

DISCUSSION

As a classical knowledge over two hundred years, one knows that vitamin D participates in bone mineralization, turnover and Ca metabolism like an endocrine hormone. As years passed, most researches detected vitamin D receptors and á 1 hydroxylase activity in muscle cells, cells of the immune system, including macrophages and neutrophil leucocytes and epithelial cells of the lungs and gut. The active form of vitamin D

Table 3: Comparison of clinical and laboratory values between groups

	Normal		Asthma		p
	Med±SD	*Min-Max*	*Med±SD*	*Min-Max*	
FVC %	89.3± 8.5	64-111	82.2± 10.1	56-109	a0.001**
FVC Lt	2.6± 0.8	1.2- 5.0	2.1± 0.5	1.0- 3.4	a0.001**
FEV %	97.3± 9.4	68-115	86.3± 12.6	44-108	a0.001**
FEV Lt	2.5± 0.7	1.2- 4.5	2.0± 0.5	0.8- 3.1	a0.001**
FEV / FVC %	107.0± 5.8	91-118	102.6± 8.2	75-115	a0.003**
Calcium	10.2± 0.3	9.5- 11.0	10.1± 0.3	9.3- 10.9	a0.089
Phosphor	4.5± 0.6	3.1- 6.5	4.6± 0.6	3.2- 5.8	a0.363
Vitamin D; (median)	11.2± 5.8	4.0-28.0(10.3)	9.1± 3.6	4.0-19.0(9.0)	b0.090
Eosinophile; (median)	168.9±116.3	20-519(140.0)	347.4±298.1	28-1020(233.5)	b0.007**
Total IgE; (median)	96.3±192.1	3-1301.0(41.0)	387.6±533.9	3.3-2500.0(157.9)	b0.001**

Student's t Test a: b:Mann Whitney U Test **p<0.01

Table 4: Comparison of step groups as to age, sex, and BMI

	Step 1		Step 2		Step 3		p
	n	*%*	*n*	*%*	*n*	*%*	
Sex							*a0.648*
Girl	13	76.5	11	64.7	10	62.5	
Boy	4	23.5	6	35.3	6	37.5	
	Med± SD	*Min- Max*	*Med± SD*	*Min- Max*	*Med± SD*	*Min- Max*	
Age	11.8±2.1	7-15	11.7±1.5	8-14	10.6±2.5	6-15	*b0.207*
BMI	21.4±5.0	16.1-35.6	21.9±3.8	16.3-30.6	19.9±3.8	14.7-27.3	*b0.393*

[a]Pearson Chi-Square Test [b]Oneway ANOVA Test

can inhibit inflammation through enhancing secretion of anti-inflammatory cytokines and chemokines. So, vitamin D's endocrine, autocrine, paracrine and immune-modulating activity emerged in the body (Paolo et al. 2016).

Clinical trials on vitamin D and asthma formerly showing impaired pulmonary physiology, increased bronchoconstrictor response to irritants and resistance to glucocoticoids, lately stated otherwise. In a review based on 46 epidemiological and observational articles thorough search engines until 2015, a linkage that cannot be explained as a chance event between vitamin D and asthma exists (Mohammed et al. 2016).

Since decreased sun exposure showed an association with asthma incidence, vitamin D defi-

Table 5: Comparison of step groups' clinical values

	Step 1		Step 2		Step 3		p
	Med±SD	*Min-Max*	*Med±SD*	*Min-Max*	*Med±SD*	*Min-Max*	
FEV %	98.2± 6.45	84-108	86.5± 6.0	70- 97	73.4± 9.8	44-88	*a0.001***
FEV Lt	2.2± 0.5	1.3- 3.1	2.0± 0.4	1.1- 2.8	1.6± 0.4	0.8- 2.5	*a0.001***
Calcium	10.1± 0.4	9.3- 10.8	10.0± 0.3	9.4- 10.9	10.1± 0.2	9.7-10.6	*a0.733*
Phosphor	4.5± 0.8	3.2- 5.6	4.7± 0.5	3.9- 5.7	4.6± 0.6	3.5- 5.8	*a0.684*
Vitamin D; *(median)*	8.9± 3.5	4-18 (9.10)	9.3± 4.3	4-19 (8.70)	9.2± 3.1	4-18 (9.2)	*b0.912*
Eosinophile; *(median)*	221.8± 264.9	28-960 (118)	336.5± 283.4	39-950 (252)	492.5±298.8	80-1020 (436.5)	*b0.008***
Total IgE; *(median)*	149.7±255.4	3-1033 (44.90)	286.1±372.8	6-1493 (136.90)	748.2±706.3	47-2500 (511.6)	*b0.001***

[a]Oneway ANOVA Test [b]Kruskal-Wallis Test

ciency was blamed in the etiology of asthma (Litonjua et al. 2007). Fundamentally, asthma is a complex disease with various phenotypical expressions and outcomes under the influence of a high number of factors (Bateman et al. 2008; Brehm et al. 2009).

Recommended daily allowances for vitamin D is 400 IU for children. Several recent studies showed harm or no benefit from high dose vitamin D, warning against high dose prescription (Karen et al. 2016; Gartner et al. 2003).

In these kind of studies, adjustment for age, gender, ethnicity, height and BMI have been made as BMI affects both lung functions and Vitamin D concentration (Black et al. 2005). This research did not observe any meaningful difference among the three step groups relating to sex, age and BMI. An experimental research on rats showed a dose-dependent effect, explaining the controversial results in the medical literature about the effect of vitamin D on asthma. While appropriate doses of vitamin D were beneficial, with higher doses the useful effect of vitamin D on asthma and allergy was reversed. Histologically, inflammatory cell infiltration, especially eosinophilia infiltration, mucosal edema, smooth muscle hyperplasia were seen in high dose vitamin D group, but in low and normal dose groups, eosinophilic infiltration and edema were much lower (Chen et al. 2015).

Certain studies showed a significant relationship between asthma and Vitamin D (Brehm et al. 2009). Some studies found no relationship between asthma and Vitamin D (Deverux et al. 2010) and the current findings were in agreement with these studies. The study further compared the Vitamin D and asthma steps, and could not find any relation. In this study, no significant difference between the asthma severity step groups with respect to vitamin D levels was observed.

The measurement of total eosinophil count has been reported to be helpful in the management of asthma since 1967. The prevalence of significant peripheral eosinophilia has been documented in asthmatic patients with resolution in response to steroid administration (Barry et al. 1973). According to Wardlow et al. (2000), evidence showed without doubt that eosinophil is closely connected intimately with asthma and some atopic ilnlesses. This is not to mean that eosinophil cause asthma but the answer is being awaited with interest (Wardlaw et al. 2000; Barry et al. 1973).

Hypponen et al. (2009) found a significant positive relationship between IgE and vitamin D. But Felicia Montero et al. (2013) did not find a connection between vitamin D levels and some allergy markers, including eosinophil count and immunoglobulin E. When the asthma subgroups were compared, significant differences were noticed between them with regards to eosinophil count and immunoglobulin E levels. Both parameters rose progressively as asthma worsened. But when vitamin D and asthma subgroups were compared, no differences were found. Some studies showed that inorganic elements whose metabolisms are directly related to vitamin D, like phosphorus and calcium, do not differ between normal and asthmatic children (Brehm et al. 2003), this study correlated with the findings. When the calcium and phosphors levels were compared between the levels of asthma subgroups, no statistical differences were observed.

Vitamin D is now accepted as a modulator of the immune system and this role created an impetus regarding its potential effect in the etiology of asthma (Gupta et al. 2012). Recent evidences have accumulated signaling links between vitamin D and lung function. Markers of inflammation, immunomodulation and response to steroids were also governed by vitamin D. However, to prove the notion that insufficient serum vitamin D levels have a role in the genesis and exacerbations of preschool wheezing, asthma, and response to glucocorticoid therapy, further clinical steroid trials are required (Gupta et al. 2012).

Finally, vitamin D deficiency is still on the agenda of public health workers in spite of the sunny climate in many regions of Turkey (Hatun et al. 2005; Alyasin et al. 2011). This cross-sectional study found an excessive prevalence of vitamin D deficiency in an epidemic form, with values well below 20 ng/ml in both asthmatic and non-asthmatic children in Turkey.

CONCLUSION

Researchers' hypothesis at the beginning was that vitamin D has an association with asthma as researches accumulate regarding the role of vitamin D in disease mechanisms and its effects on immune cells, chemokine production and tissue remodeling. But researchers could not find a close link between asthma and vitamin D levels perhaps due to the widespread vitamin D deficiency in the district from which this study group emerged. Also, no connection was found between asthma severity and vitamin D levels.

RECOMMENDATIONS

Although this is not a decisive study for the controversy upon asthma and vitamin D relation, when considering the diverse metabolic effects of vitamin D, vitamin D assay must be included in pediatric routine checkups and vitamin D must be added to children's diets accordingly.

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