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Relationship between Vitamin D, Inflammation and Lung Function In Patients with Severe Uncontrolled Asthma

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Abstract

BACKGROUND: Recently epidemiological studies showed that low vitamin D is linked to airway hyperresponsiveness, decreased lung function, poor asthma control, and steroid–resistant asthma.

AIM: We investigated the relationship between Vitamin D, inflammation with circulating IL-33 and lung function in 30 patients with severe uncontrolled asthma.

MATERIALS AND METHODS: The study included 30 patients with severe uncontrolled asthma. In each of them were measured serum levels of IL-33 and Vitamin D by the ELISA method. The pulmonary function is measured by basic spirometry parameters, FEV1. The results were statistically elaborated according to the Pearson's Correlation Tests.

RESULTS: The results showed statistically insignificant correlation between Vitamin D and IL-33, and Vitamin D with FEV1 (Vit.D/IL-33; r = 0.11323, p = 0.551); (Vit.D/FEV1; r = -0.1005; p = 0.597) Correlation between IL-33 and FEV1 is negative but statistically significant (IL-33/FEV1; r = -0.5248; p = 0.003).

CONCLUSION: Because there are little studies about the link between vitamin D and asthma, further research to clarify the mechanism how vitamin D control the activity of CD4+ T cells and the related Th2-type cytokines in the parthenogenesis of asthma.

Introduction

Asthma is the leading chronic respiratory diseases which affect more than 334 million people worldwide [1-3]. It is estimated that the number of people with asthma will grow by more than 100 million by 2025. Women were more likely than men and boys more likely than girls to have asthma [4]. Approximately 500,000 annual hospitalisations are due to asthma, and 250 000 deaths annually [3]. Five percentages or 100,000 of the Macedonian population have asthma [5, 6].

Characteristic mechanisms of asthma include inflammation, hyperresponsiveness and structural changes in the airways and the lung. Many cellular elements and different cells play a role (T lymphocytes, neutrophils, eosinophils, mast cells, macrophages, and dendritic cells). Recurrent episodes of wheezing, chest tightness, coughing and breathlessness, particularly at night or in the early morning are a clinical expression of this disease. These episodes are usually variable, and the airflow obstruction within the lung is often reversible with treatment or spontaneously [7].

Chronic inflammation of the asthmatic airway leads to epithelial desquamation, infiltration of the airway wall with T cells especially dominated Th2 helper CD4+ lymphocytes, smooth muscle, hypertrophy and hyperplasia, vascular congestion, oedema due to plasma leakage and mucus plugging [8-11]. All these changes could lead to thickening of

the airway walls due to subepithelial fibrosis and reduction of their lumen [12, 13].

More than 100 mediators and markers of inflammation are involved in this inflammation. Cytokines take place in complex pathophysiological process, and they are produced by cells like T cells, Tc, Th, Th1, Th2, NK, dendritic cells, B cells, endothelial cells, plasma cells, mast cells, bone marrow, tumor cells and thymus, together with, leukocytes, macrophages, fibroblasts, and monocytes [14, 15]. The interleukins are cytokines which can stimulate the proliferation and differentiation of immune cells. In asthma, T cells take a central place in coordinating the immune response. Cytokines present during activation of naïve CD4 + T cells from pathogens and many types of antigens differentiate them into subpopulations of T cells in T-follicular effector cells, Th1, Th2, Th9, Th17, and Th22. Th2 cells synthesise IL-4, IL-5, IL-13, IL-25, IL-31, IL-33 which are associated with asthma and allergic diseases [16-19].

Interleukin 33 (IL-33) is a new cytokine which was found in 2005. It belongs to the IL-1 family consisting of 11 members, high proinflammatory cytokines which activate the function of inflammation cell in the early asthmatic responses. IL-33 is a potent type 2 inducing cytokine. It is bind to ST2 receptors, which are expressed on mast cells and Th2 cells, and some various cells including epithelial, bronchial and endothelial cells, fibroblasts and some immune cells, as well as dendritic cells and macrophages [20-23]. It is assumed that IL-33 is one of the earliest released mediators and can orchestrate the immune cascade of asthma and stands out as an attractive candidate for discovering various therapeutic modalities, especially a new targeted therapy.

Vitamin D plays a role in the pathogenesis of asthma. Vitamin D is a potent immune system modulator and in the form of 1,25-dihydroxy vitamin D has been shown that it can be involved in the suppression of dendritic cell maturation and the development of consecutive Th1 cell [24-27]. Vitamin D may suppress the production of IL-12, which reduces the production of Th1 cells and potentially leading to increased proliferation of Th2 cells [25]. Additionally, studies with treatment of 1,25-dihydroxy vitamin D in mice showed reduced secretion of Th1-type cytokines IL-2 and IFN-γ and an increase in Th2-type IL-4. In asthmatic children, low vitamin D levels are associated with airway hyperresponsiveness, decreased lung function, worse asthma control, and steroid-resistant asthma and exacerbations. It remains unknown whether vitamin D is an association with increased airway hyperresponsiveness (AWH), inflammatory markers of asthma, decreased lung function, poor asthma control and steroid resistance in adult asthma patients [28-30].

We aimed to investigate the relationship between Vitamin D, inflammation with circulating IL-33 and lung function in 30 patients with severe uncontrolled asthma.

Material and Methods

The study included 30 patients with asthma. They are diagnosis and treated at the Clinic of Pulmonology and Allergy in Skopje, Macedonia. All of them are a classification of uncontrolled moderate persistent asthma. In all patients, serum IL-33 level was measured by the ELISA, enzyme-linked immunosorbent assay method according to the manufacture's protocol at the Institute of Immunobiology and Human Genetics, Faculty of Medicine, in Skopje, Macedonia. Values within the reference range for IL-33 are 0pg/ml. Serum 25-hydroxyvitamin D was measured by ELISA method according to the manufacture's protocol at University Clinic of Clinical biochemist, Skopje, Macedonia.

At the Clinic of pulmonology and allergy in Skopje, was done the spirometry with turbine spirometer - Spirobank G, according to the standard methodology. In all patients was done and analysed FEV1 - Forced expiratory volume in the first second. Every patient is done three manoeuvres with three acceptable and three reproducible curves, according to guidelines for the measurement of Spirometry, with Flow-Volume and Time-Volume curve. The best curve has been automatically selected from the spirometer [31-33].

Inclusion Criteria: the patients are diagnosed and classified in uncontrolled moderate persistent asthma at PHI University Clinic of Pulmonology and Allergy according to the actual version of the Global Initiative for Asthma guidelines – GINA [7] and Guidelines for the Diagnosis and Management of Asthma (EPR-3) of NAEPP, National Asthma Education Prevention Program [33]. Uncontrolled asthma defined as at least one of the following [34].

Poor asthma symptom control: Asthma Control Questionnaire (ACQ) consistently >1.5, or Asthma Control Test <20 (or ''not well controlled'' by GINA - NAEPP guidelines over three months of evaluation:

- two or more bursts of systemic CS (3 days each) in the previous year - frequent severe exacerbations;
- at least one hospitalisation, required to stay on ICU or mechanical ventilation in the previous year - serious exacerbations; and
- after an appropriate bronchodilator withhold FEV1<80% predicted - airflow limitation.

All patients have stable asthma because there

has been no increase asthma symptoms or need for add another asthma medication for at least the past four weeks. Some of the patients have arterial hypertension, and they did not have other comorbidities, that could increase the IL-33 level. The age range of patients was 20-71 years old.

Exclusion criteria were severe diseases of renal, neurological, haematological, cardiac, gastrointestinal, endocrine or immune system, psychiatric disorders, and neoplastic diseases. Pregnancy is also exclusion criteria.

Statistical analysis

The results were statistically analysed by the statistical program SPSS for Windows 17.0. The results were statistically analyzed according to the Pearson's Correlation Tests. The significances values were taken $p < 0.05$.

Results

The study included 30 patients with severe uncontrolled asthma. The majority were females, 19 women (63.33%), and 11 were men (36.67%). The age of the patients was 20-71 years. The obtained values showed (Table 1):

Table 1: Mean values for Vitamin D, IL-33 and FEV1

N-30	mean	Std.Dv
Vitamin D	15.260	5.808
IL-33	33.461	8.851
FEV1	44.367	14.207

All patients had low serum vitamin D and their correlation with IL-33 showed statistically insignificant correlation (Vit.D/IL-33; r = 0.11323; p = 0.551) (Figure 1).

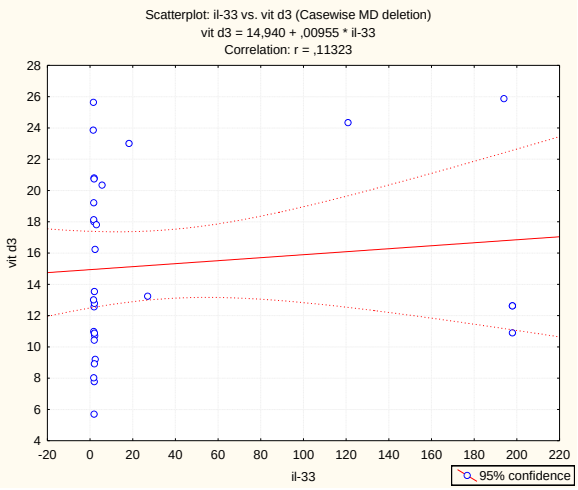

Figure 1: Correlation between Vitamin D and IL-33 in asthma patients. (r = -0.11323; p = 0.551)

Negative significant correlation between IL-33 and FEV1 (IL-33/FEV1; r = -0.5248; p = 0.003) (Figure 2).

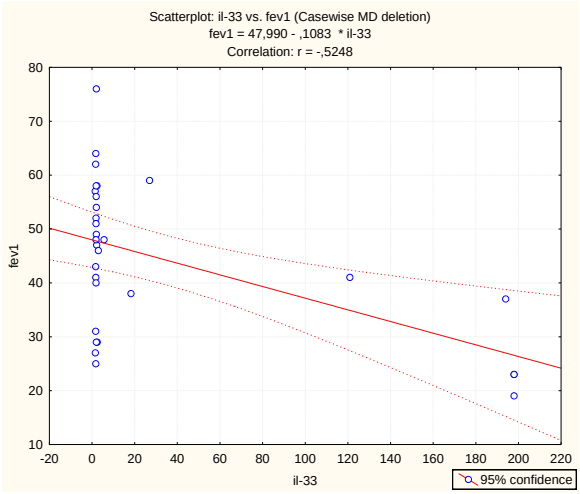

Figure 2: Correlation between IL-33 and FEV1 in asthma patients. (r = -0.5248; p = 0.003)

Negative insignificant correlation between serum levels of vitamin D and FEV1 (Vit.D/ FEV1; r = -0.1005; p = 0.597) (Figure 3)

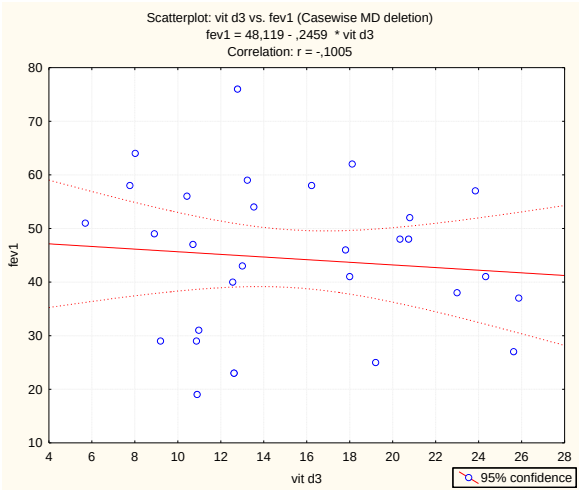

Figure 3: Correlation between Vitamin D and FEV1 in asthma patients. (r= -0.1005; p = 0.597)

Discussion

The studies which investigate vitamin D status, inflammatory markers of asthma and lung function are scarce. The studies which investigated the direct mechanistic links between vitamin D and lung diseases are limited. Cross section of data indicate that low level of vitamin D in patients with mild and moderate asthma is associated with more frequent exacerbations, poor asthma control, decreased lung function, steroid–resistant asthma, and consequent increased steroid use [24-26, 35-37].

A couple study presented that the low level of vitamin D has an association with airway obstruction and corticosteroid requirement, influencing the severity in asthmatic patients. Our study showed that serum vitamin D level was lower (level of vitamin D < 30 ng/ml) in these 30 patients with asthma but their correlation with IL-33 was statistically insignificantly. Anna Bonanno et al. in their study showed that Vitamin D it is not involved in IL-33/IL-31, Th2-type cytokines activity implicated in bronchial and nasal allergic disease [24]. Felicia M.A. et al. in their study they did not find a link between allergy markers (allergic rhinitis, eosinophil count, total IgE) and vitamin D levels [38].

Vitamin D inhibits the synthesis and releases cytokines which are Th1-associated and some other molecules, like IL-17, which lead to decreased inflammation and proliferation of smooth muscle cell [35, 38, 39]. Recent studies have shown that low level of vitamin D is linked with increased expression of the pro-inflammatory cytokine TNF-α, enhancing a pro-inflammatory effect in patients with asthma [35, 40]. This vitamin promotes regulatory T cells and also increases synthesis of IL-10, which lead to an inhibition of Th2 responses as well as airway inflammation and airway hyperresponsiveness [35, 41].

Larose et al. in HUNT, prospective cohort study, found that low serum 25(OH) D level was not correlated with airway obstruction in most asthmatics adults except men with asthma but without allergic rhinitis [42]. In our study, there was an insignificant correlation between serum levels of vitamin D and FEV1. Laura et al. also showed in their study that the vitamin D level did not correlate with lung function and markers of allergy in asthmatic patients [43]. Some studies show a significant direct relation between vitamin D level and both FEV1 and FEV1/FVC [43, 44].

In this study, we found that serum IL-33 was increased in patients with asthma and they positively correlated with asthma severity with the significant negative correlation between IL-33 and FEV1. In human studies of allergic asthma, serum IL-33, bronchoalveolar lavage fluid and lung tissue have found to be higher in patients with asthma compared to healthy controls and correlate with asthma severity [45-50], which was confirmed in our study

In conclusion, despite the limitation of this study with a small number of patients, we found an increased serum IL-33 in patients with asthma and it is positively related to the severity of asthma (FEV1), but we did not find a correlation between levels of vitamin D and FEV1 and IL-33. Because there are little studies about the link between asthma and vitamin D, further studies are necessary to explain the mechanism how vitamin D can control the activity of CD4+ T cells and the related Th2 type cytokines in the pathogenesis of the allergic disease, including asthma.

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