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The Relationship between Serum Vitamin D Levels with Allergic Rhinitis Incidence and Total Nasal Symptom Score in Allergic Rhinitis Patients

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Keywords: Allergic rhinitis; 25-hydroxyvitamin D; Allergic diseases; Total nasal symptom score; Cut-off points

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Abstract

BACKGROUND: Allergic diseases and vitamin D deficiency were found to have a relationship. However, there was limited number of studies on the relationship between vitamin D with allergic rhinitis (AR) and total nasal symptom scores (TNSS), particularly in determining the cut-off points of serum vitamin D levels which correlated to AR.

AIM: As this particular study has never been conducted in Indonesia, the main objective of this study was to investigate this issue.

METHODS: The research was conducted at Dr Soetomo Hospital, Surabaya in January 2017. A group of 30 subjects were recruited using consecutive sampling. Levels of serum vitamin D were measured using electrochemiluminescence immunoassay (ECLIA) method while the total nasal symptom scores were obtained by accumulating all the nasal symptoms. Data of serum vitamin D levels and TNSS were analysed statistically with the Pearson correlation test.

RESULTS: It was found that the mean of serum 25(OH) vitamin D levels (9.13 ng/mL) of the AR group was significantly lower than the non-AR group (26.22 ng/mL) (P = 0.000). The vitamin D cut-off points which correlated to AR was about 12.83 ng/mL (sensitivity = 80%; specificity = 100%). A Pearson correlation test found a strong, negative correlation between vitamin D levels and TNSS (P = 0.000; r = -0.800).

CONCLUSION: There was a strong, negative correlation between serum vitamin D levels with AR and TNSS. The cut-off points of serum vitamin D levels correlated to AR were approximately12.83 ng/mL. Thus, further research needs to be conducted.

Introduction

Allergic Rhinitis (AR) is one of the inflammation diseases of the nasal mucous, caused by immunoglobulin E (IgE) after allergens exposure, which affects 10-20% of total population and keeps increasing [1]. Severity measurement of the AR symptoms can be conducted subjectively by counting the total nasal symptom score (TNSS) and objectively by counting the serum IgE levels. Moderate to severe AR present in around 67.5% of the AR population and affects the quality of life [2].

Related to that, recent studies point out the relationship between allergic diseases and vitamin D deficiency. Vitamin D deficiency has been widely discussed as one of the world health problems which can lead to acute and chronic illnesses [1] [2]. Also, recently, new research was developed over a period of three years to deal with the function of the immunomodulatory role of calcitriol (the active form of vitamin D) that correlated with AR [3]. Vitamin D can regulate the body's immune cells which work on the pathophysiology of AR. Previous research in India discovered that there was vitamin D deficiency in 91% of AR samples; however, the incidence of vitamin D deficiency in AR in Indonesia has not been found yet [4].

Nevertheless, previous findings of the relationship between serum vitamin D levels and AR were still controversial. Most studies claimed that there was a significant difference in the levels of serum vitamin D between AR patients and normal people; thus, there was a relationship found between serum vitamin D levels and TNSS [5] [6] [7]. In contrast, some other studies showed different results in the response of interleukin IL-4 and IL-13 in mice bronchoalveolar secrete after being given vitamin D [8] [9]. In other words, the relationship between serum vitamin D levels with AR and TNSS is still unclear; hence, further study is needed to obtain more accurate results.

Although Indonesia is a tropical country that sunlit throughout the year, some research found that the percentage of vitamin D deficiency was 60% in young adult women, 35% in women aged over 65 years, and 78.3% in children [10] [11]. High rates of vitamin D deficiency can be occurred due to many factors affecting serum vitamin D levels, such as age, gender, skin elasticity, and others [10].

Based on the above explanation, the relationship between allergic diseases and vitamin D deficiency was predicted to be associated with immune-modulatory effects of the derivatives of vitamin D. It has been revealed that the active form of vitamin D has some direct effects on antigen-presenting cell (APC), on mast cell, on T helper Th-2, on B-cell, and on proinflammatory interleukin**.** Vitamin D may modulate innate and adaptive immune response component functions played by T lymphocytes, both T helper Th1 and Th2 cells. Dendritic cells as an antigen-presenting cell (APC) can synthesise vitamin D by expressing vitamin D3-25-hydroxylase enzyme (CYP27A1) [12]. Vitamin D mechanism of action regulated the performance of macrophages, toll-like receptors (TLR) and natural killer cells (NK), as well as most of the Th2 cell-mediated components. The reaction of type I hypersensitivity of AR was characterised by releasing various mast cell mediators [1] [12]. Inhibition process of AR pathophysiology by vitamin D may reduce the clinical nasal symptoms [7] [13] [14]. Based on the description, this research was aimed to prove the relationship between serum vitamin D levels with AR incidence and TNSS.

Methods

This study was observational analytic with a cross-sectional approach. The subjects of the current study were AR and non-AR patients at ORL-HNS outpatient division of Allergy-Immunology at Dr Soetomo Hospital in January 2017. The AR patients were clinically diagnosed according to the criteria of *Allergic Rhinitis and its Impact on Asthma* (ARIA) [15]. Based on the formula to determine the minimum sample size, the result showed a minimum of 20 subjects: 10 subjects for each group. However, this study recruited 15 subjects in each group to find more reliable results which can be generalised to the population. Fifteen AR and fifteen non-AR patients in the age of 21-60 years, both gender, were included in the study. All patients were interviewed and undergone a complete *Ear Nose and Throat* (ENT) examination. The total nasal symptom scores of the AR patients were recorded. Also, the levels of serum vitamin D in all patients were also measured. Previously, the study has been approved by the Regional Committee of Medical Research Ethics. All subjects gave their informed consent before the study.

The exclusion criteria included acute respiratory tract infections, acute and chronic paranasal sinusitis, severe septal deviation, obstructive nasal disease, upper respiratory infection, asthma under treatment, hypercalcemia, severe hypertension, anaemia, coronary heart disease, renal and liver impairment, pregnant and lactating conditions, damaged blood preparation, or examination failure.

The total nasal symptom score (a runny nose, nasal congestion, sneezing and itchy nose) was assessed based on the severity of the symptoms. The severity degree of each symptom was based on the following scores: 0 = no symptom; 1 = mild, unobtrusive symptoms; 2 = moderate, disturbing but tolerable symptoms; and 3 = severe, disturbing, perceived to interfere with daily activities/sleep and difficult to tolerate. The maximum total nasal symptom score was 12.

The serum vitamin D levels were measured by employing the electrochemiluminescence immunoassays (ECLIA) method using Cobas E411 (fully automated) hormone-immunoassay analyser. Normal vitamin D is defined when 25(OH)D level ranges between 30-60ng/mL while vitamin D insufficiency is defined to be between 20 and 30ng/mL and vitamin D deficiency is defined to be under 20 ng/mL.

Data were analysed using the Software Package for the Social Sciences (SPSS). Pearson correlation test was used to analyse the relationship between serum vitamin D levels with AR and TNSS. The cut-off points were determined by ROC curve.

Results

Among 15 AR patients, there were 11 female patients (73.33%) and 4 male patients (26.67%) (Table 1). The AR patients were mostly found in the age group of 21-30 years, with the mean age of AR

patients was 28.87 (9.01) years. The distribution of patients according to age is summarised in Table 1. Severe AR was the most common classification found in 9 patients (60%).

Table 1: Demographic Characteristics

Variable	RA (*n* = 15)		Non-RA (*n* = 15)		*p*
	Mean	SD	Mean	SD	
Age	28.87	9.01	35.33	10.05	0.000*
	N	%	N	%	
Gender					
Male	4	26.67	11	73.33	
Female	11	73.33	4	26.67	
AR Classification	Mean	SD			
Mild inter-mittent	1	6.67			
Moderate-severe inter-mittent	1	6.67			
Mild persistent	4	26.66			
Moderate-severe persistent	9	60.00			

**P* <0.05 with independent t-test.

As shown in Table 2, the mean value of serum vitamin D levels in the AR group was 9.13 (5.06) ng/mL. While the minimum value was 3.64 ng/mL, the maximum value was 20.23 ng/mL. On the other hand, the mean value of serum vitamin D levels in the non-AR group was 26.22 (8.45) ng/mL.

Table 2: Relationship Between Serum Vitamin D Levels and Allergic Rhinitis

Group	*n*	Vitamin D		*p*
		Mean	SD	
AR	15	9.13	5.06	0.000*
Non-AR	15	26.22	8.45	

**p* <0.05 with independent t-test.

The analysis results found a significant difference in the serum vitamin D levels between AR and non-AR patients (P = 0.000). The examination techniques of serum vitamin D levels were using ECLIA method. The ROC analysis curve in Table 3 and Figure 1 showed that the cut-off points related to AR were 12.83 ng/mL with 100% sensitivity and 80% specificity.

Table 3: Vitamin D Cut-Off Points That Correlated to AR

	Cut-off Points	Sensitivity (%)	Specificity (%)	*p*
Vitamin D of AR	</ 12.830	100	80	0.000*

**P* <0.05 with ROC.

The results of this study showed a significant negative relationship between serum vitamin D levels and TNSS of the AR patients (*p*=0.000). The correlation coefficient (*r*) between the two variables was -0.8 which indicated that the two variables had a strong negative correlation (Table 4).

Table 4: The Relationship Between Serum Vitamin D levels and TNSS

TNSS	*n*	Vitamin D		Statistical analysis	*p*
		Mean	SD		
4-6	5	11.87	7.14		
7-9	6	8.74	3.56	*r*=-0.80	0.000*
10-12	4	6.29	2.61		

**p* <0.05 with Pearson correlation test.

It also indicates that vitamin D has an important role in AR symptoms because the level could be detected in the blood of AR patients and the value was inversely proportional to TNSS.

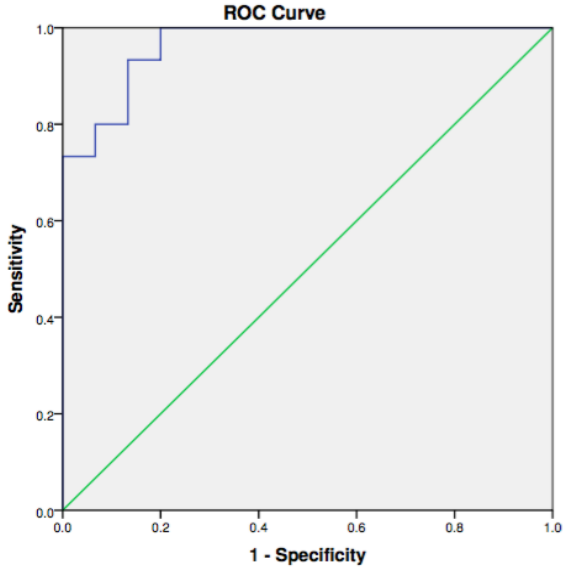

Figure 1: Receiver Operating Characteristic Curve

Discussion

This study found a significant difference between the serum vitamin D levels of the AR and non-AR patients. Similarly, a study by Yalcinkaya et al. showed that the serum vitamin D levels of AR patients were lower than the non-AR group. The mean value of serum vitamin D levels in the AR group was 15.39 ng/mL whereas the mean value in the non-AR group was 53.80 ng/mL. Furthermore, a study in India found that vitamin D deficiency occurred in 91% of the total AR samples and a significant improvement shown in TNSS after vitamin D supplementation [4] [16].

Regarding the above findings, the improvement of AR symptoms was occurred due to immunomodulatory effects of vitamin D on the immune system. Milovanovic et al. stated that there was a significant negative correlation between serum vitamin D levels and IgE [17]. That study result was from the study conducted by Yip et al., which found that vitamin D could suppress the activity of IgE-mediated mast cells [6]. Besides, Vasiliou et al. also found a similar finding: serum vitamin D levels were associated with another allergic disease, asthma [18]. Also, an increase in serum vitamin D levels after given UV-B to mice was associated with a decrease in airway inflammatory and hyperresponsive reactions compared to the samples which were not exposed to UV-B [5].

The cut-off points from the ROC analysis curve obtained in this study with chi-square were insignificant ($P > 0.05$), but the symmetric measure was significant ($P = 0.000$). The result of cut-off points is considered as valid if the test result shows an insignificant chi-square and significant symmetric measure. Therefore, the cut-off points in this study were valid [19].

Even though the previous paradigm claimed that vitamin D was exclusively produced from kidney as the result of pre-vitamin D metabolism from the sun and food intake, the new paradigm stated that vitamin D could be produced from some types of immune cells with vitamin D receptor (VDR), namely APC and T-cells. Vitamin D receptor itself is expressed by T-cells, B-cells, APC, and mast cells. The levels of vitamin D produced by these cells varied by genetic influence. This vitamin regulates two thousand different genes, one of which is a gene that plays a role in the pathophysiology of allergies [20]. Vitamin D encodes chromosome 12 which is closely related to allergic rhinitis and asthma. This vitamin regulates chromosomes played by IgE, 13Q14 and 7Q14 [5] [21].

This study found evidence of a strong, negative relationship between serum vitamin D levels with AR incidence and TNSS. It indicates that vitamin D plays an important role in the AR symptoms because the level could be detected in the AR patients serum and the value was inversely proportional to TNSS. Furthermore, the results of this study were by the study by Thakkar et al., which also found a negative relationship between serum vitamin D levels with TNSS with moderate correlation strength [7].

The action mechanism of vitamin D can be explained by its ability to control Th2-mediated cell regulation. It controls the APC by decreasing lipopolysaccharide activity (LPS), enhancing the tolerogenic phenotype of dendritic cells, and inhibiting APC differentiation [22]. Vitamin D inhibits mast cell differentiation and can cause mast cell apoptosis within 30-40 days. The inhibitory pathway of other mast cells was by inhibiting IgE and IL-4 [18]. Research in Australia with mice samples suggested the suppression of degranulation of IgE-mediated mast cells after vitamin D administration [6]. The study by Hypponen et al. found that serum vitamin D levels had a significantly negative correlation with IgE [23]. Inhibition of histamine binding to its receptor in the nasal mucosa and the induction IL-10 activity leads to suppression of Th2 activity in the initial phase [6]. Anti-inflammatory IL-10 can be produced by APC, Th2 cells, and mast cells [23].

Still, in controlling the Th2-mediated cell regulation, vitamin D can inhibit the proliferation and differentiation of B-cells into plasma cells by inducing IL-10 and inhibiting the action of IgE, IL-2, IL-4, IL-6 and pro-inflammatory chemokines [22]. In the late phase, vitamin D can inhibit the recruitment of blood eosinophils into mucose, thus inhibiting the differentiation of B-cells into plasma cells. Interleukin 5 inhibition by vitamin D causes resistance to the process of differentiation, maturation, migration, and infiltration of eosinophils into the nasal mucosa [6].

In addition to working on Th2, it also has a role in enhancing the Th1-mediated cell regulation, such as NK cells, TGF-β and IL-10, resulting in the suppression of inflammatory responses [6]. Vitamin D may also inhibit Th1-mediated cells, such as IFN-γ which decrease MHC class II activation and inhibit TLR. This process leads to decreased regulation of proinflammatory cytokines [23].

In conclusion, a strong, negative correlation was found between serum vitamin D levels with AR and TNSS. The cut-off points of serum vitamin D levels related to AR were 12.83 ng/mL. However, further randomised controlled trials are needed. Vitamin D as a potential therapeutic regimen for allergic rhinitis treatment may reduce the severity of the disease and control the frequent attacks of allergic rhinitis.

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