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To Estimate Serum Vitamin D3, Immunoglobulin E And Inflammatory Marker (Il-6) In Patients Of Allergic Rhinitis And Healthy Controls

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ABSTRACT

Background: Allergic rhinitis (AR) is the predominant non-infectious form of rhinitis characterized by symptoms such as sneezing, coughing, and flu-like manifestations. The precise pathophysiology of AR is yet unknown. Vitamin D3 insufficiency has been identified as a likely cause of allergy disorders because of its function in immunomodulation.

Aim: To estimate serum Vitamin D3 and inflammatory markers (IgE, IL-6) in patients of allergic rhinitis and healthy controls.

Materials and Methods; The present study was conducted in the Departments of Biochemistry and the Department of ENT, SGT Medical College, Hospital & Research Institute, Gurugram, Delhi-NCR, India. A written and informed consent was taken after explaining the purpose and details of the study to all the subjects of both the groups. A total of 160 individuals with clinically confirmed allergic rhinitis, aged between 18 and 55 years, were seen in the ENT outpatient department at SGT Hospital. A total of one hundred and sixty healthy volunteers, matched in terms of age and gender, was selected from the general public to serve as controls at SGT hospital. The measurement of Serum Vitamin D was conducted using a Competitive ELISA kit-based approach, whereas the measurement of Serum Interleukin 6 and IgE was conducted using a Sandwich ELISA kit-based method.

Results: It was observed that patients in the AR group had an average blood vitamin D level of 11.32±3.96 ng/ml, whereas participants without AR had a level of 27.15±16.26 ng/ml. The observed differences were found to be statistically significant with a p-value of 0.0001. The control group had a mean serum IgE level of 36.08±19.43 IU/ml, whereas the study group had a mean serum IgE level of 269.19±71.27 IU/ml ($p<0.0001$). The control group had a lowest value of 4.1 and a maximum value of 82.6, whereas the study group had a minimum value of 167.7 and a maximum value of 500.3. The mean serum IL6 levels in the control group were 6.67±6.55 IU/ml, but in the study group, they were 26.89±22.24 IU/ml ($p<0.0001$). The control group had a lowest value of 0.9 and a maximum value of 40.5, whereas the study group had a minimum value of 3.9 and a maximum value of 89.7.

Conclusion: Vitamin D insufficiency was detected in study group. The AR group exhibited considerably lower mean levels of serum vitamin D than the control group. However, upon stratification, the disparities were considerable.

Keywords: allergic rhinitis, vitamin d deficiency, Inflammatory markers (IgE, IL-6)

Introduction

Allergic rhinitis is one of the commonest chronic conditions with a significant impact on the quality of life.[1]It is an inflammatory disease of nasal membrane, is characterized by symptoms such as sneezing, rhinorrhoea, nasal congestion, and nasal itching.[2] Allergic disorders affect more than one-third of the world's population across all age groups and geographical locations. Allergic disorders can be triggered by various agents including respiratory allergens, food allergens, skin allergens and drugs. Many factors have been implicated in the development, progression and management of allergies. These include genetic predisposition, environmental influences, nutritional status and various biochemical factors.

Clemiers von pirquet in 1906 first termed the word allergy. AR is common health problem caused by inflammation reaction after allergen exposure and associated with an immunoglobulin E(IgE) mediated Immune response against allergens.[3]Although allergic rhinitis is not a life-threatening condition, complications can occur and the condition can significantly impair quality of life. It occurs when an atopic individual is exposed to allergen. Allergic rhinitis may be seasonal or perennial.[4]

The various treatment modalities for treatment of allergic rhinitis includes allergen avoidance, pharmacotherapy, immunotherapy and surgical intervention. Pharmacotherapy includes antihistamines, decongestants, steroids sprays, leukotriene receptor antagonist etc.[5] The Prevalence varies among countries due to geographic and aeroallergen differences.[6] Allergic Rhinitis is most common type of chronic rhinitis, affecting 10-20% of the population, and evidence suggests that the prevalence of the disorder is increasing. The prevalence is relatively low in low income and middle-income countries. Although prevalence is increasing steadily in these countries.[7] The disease affects both children and adults. The prevalence of allergic rhinitis is seen to vary due to use of varied definitions, study designs and different season.

Results from the International Study of Allergy and Asthma in Children (ISAAC) study showed that Indian children aged 13-14 years had an overall 10% prevalence of allergic rhinitis. In Delhi had a prevalence of 11.6%.10 Adults prevalence were estimated to be 11.7% in Delhi.[8]

In European study among general in adults population using Allergy Rhinitis and its impact on asthma (ARIA) definition for diagnosis the prevalence of allergic rhinitis was found to be around 25% in adults ranging from 17 % to 28.5%. In Asia Pacific Region (2008), the reported prevalence of allergic Rhinitis ranged from 10- 32% in adults.[9]

Many different attempts have been made to prevent allergic diseases, although most of these attempts have been unsuccessful. There is a need for further research in light of these contrasting findings. Some parameters are sensitive for allergy rhinitis and may be measured as markers such as vitamin D3, calcium, Trace elements (Zinc, Iron, Magnesium), IL6 and IgE.

Vitamin D has long been known to be an essential nutrient for the human body, particularly with regard to the absorption of dietary calcium and phosphate. Vitamin D has 2 major forms, cholecalciferol (VitaminD3) and ergocalciferol (VitaminD2). Both forms of vitamin D can be found in foods or supplements; however, only vitamin D3 is produced in skin.Recently many studies have reported that vitamin D may be associated with the development of allergy rhinitis. Vitamin D Deficiency is very common in India across all ages and both sexes, with a prevalence of 70-80%.[10]

In recent years, the world-wide increase in allergic diseases has been associated with low vitamin D. Vitamin D seems to have an immune-modulator effect by specifically regulating the mechanism which supresses the inflammatory response. **Haritosh et al**[11] demonstrated that vitamin D supplementation had a favourable impact on the treatment of allergic rhinitis with steroid sprays. Many investigators have used total serum immunoglobulin E (IgE) for evaluating allergic disease. Symptoms of AR are triggered by inflammatory mediators such as histamine and leukotrienes released as a result of increased immunoglobulin E(IgE) production from plasma cells. This increased production of IgE is mediated by cytokines released from inflammatory T cells invading the mucosa of the nasal cavity in response to the exposure of the mucosa to exogenous allergens.[12] B-lymphocytes generate Immunoglobulin E (IgE) in response to cytokine stimulation by interleukin-4 (IL-4) and interleukin-13 (IL-13). IgE is typically found in trace quantities inside the body, but its production is stimulated by foreign particles that function as allergens. Allergens stimulate heightened synthesis of IgE, leading to a hypersensitive reaction characterised by allergy and anaphylaxis. The typical serum concentration of IgE is within the range of 150-300 UI/ml (or below 110 ng/dL). IgE is mainly associated with hypersensitivity responses, but it also serves important functions in the immune system, including the stimulation of Th2 cells and the promotion of wound healing. The hypotension that occurs during anaphylactic shock is a protective mechanism that restricts blood flow, allowing the immune system sufficient time to address and remove the poison from the body.[13]Cytokine IL-6 is a T cell and macrophage derived protein with both pro and anti-inflammatory properties. It plays a significant role in inducing inflammation by increasing the synthesis of acute phase proteins while it also aids in the suppression of inflammation. However, the roles of these cytokines in the development of allergy remain unclear.[14] Many different attempts have been made to prevent allergic rhinitis, although most of these attempts have been unsuccessful. Therefore, this study will be aimed to analyze and examine potential role serum Vitamin D3, Calcium, Trace elements (Iron, Zinc, Magnesium) and inflammatory markers (IgE, IL-6) in allergy rhinitis.

Materials and Methods

The present study was conducted in the Departments of Biochemistry and the Department of ENT, SGT Medical College, Hospital & Research Institute, Gurugram, Delhi-NCR, India. Ethical clearance was taken from the Institutional Ethical Committee before the start of collecting the samples. A written and informed consent was taken after explaining the purpose and details of the study to all the subjects of both the groups.

Study Population: -

Using this formula below sample size has been calculated.

$n = Z2 \times P \times (1-P)/e2$

where:

n= Sample size

Z= Value from standard normal distribution, corresponding to desired confidence level (Z= 1.96 for 95% CI)

P= prevalence of allergic rhinitis

e= allowable error

Cases: - A total of 160 individuals with clinically confirmed allergic rhinitis, aged between 18 and 55 years, were seen in the ENT outpatient department at SGT Hospital. Diagnoses was made by

considering the patient's medical history, doing a physical examination, and performing laboratory tests.

Control: - A total of one hundred and sixty healthy volunteers, matched in terms of age and gender, was selected from the general public to serve as controls at SGT hospital.

Inclusion Criteria:

Clinically diagnosed cases of allergic rhinitis (signs and symptoms of nasal allergic rhinitis)

Exclusion criteria:

- Nasal pathology
- Pregnant Women
- Chronic smoker & alcoholics
- Asthma

Methodology

Both the control group and the case group were adequately informed about the study's objective, and signed permission was then acquired. A venous blood sample of five (5) ml was taken from the participants using a sterile disposable syringe and needle by venepuncture, ensuring aseptic conditions. The serum was isolated using centrifugation at a speed of 3500 revolutions per minute for a duration of 15 minutes. The samples were kept at a temperature of -20°C.

The measurement of Serum Vitamin D was conducted using a Competitive ELISA kit-based approach, whereas the measurement of Serum Interleukin 6 and IgE was conducted using a Sandwich ELISA kit-based method.

Statistical Analysis

The levels of Vitamin D, trace elements, calcium, and different parameters were examined using SPSS software (USA inc.) version 23. The mean and standard deviation of all parameters were computed. The chi-square test was used for non-parametric variables. The statistical method used to compare two groups was the Student t-test. The Pearson correlation coefficient was used to determine the correlation.

Results

Table 1: Age wise distribution of Study Subjects

Age Group	Control Group	Study Group
<25 years	21	32
25-35 year	64	50
36-45 years	36	40
>45 years	39	38
Total	160	160
Mean	34.23	33.31

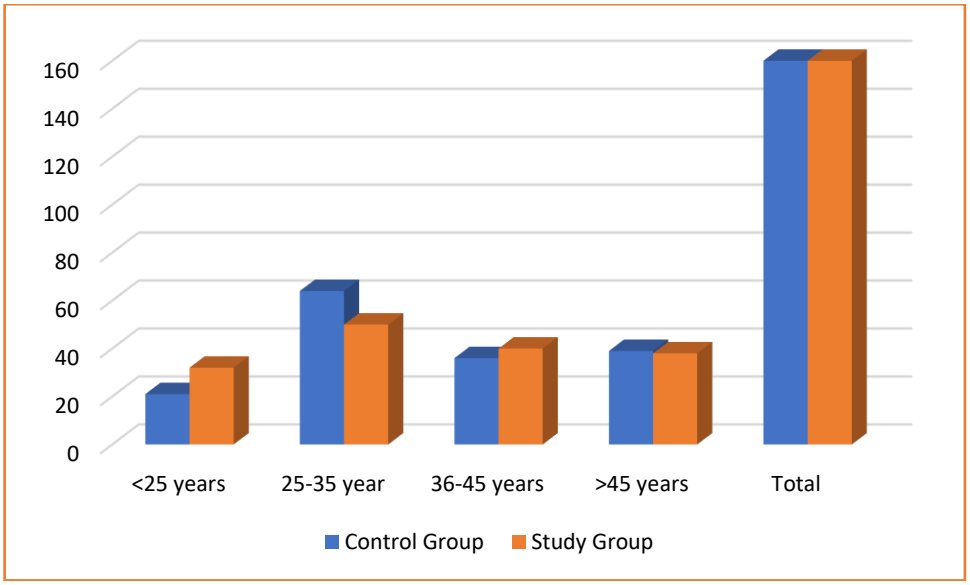

Figure 1. Age wise distribution of Study Subjects

A total of 320 individuals were recruited for the research, all of whom visited the outpatient department at our facility. The participants were categorized into two groups, namely cases and controls, each consisting of 160 patients. Out of a total of 160 participants, 84 were male and 76 were female in the control group. Therefore, this research demonstrates a higher proportion of males compared to females, with a male to female ratio of 1.13 to 1. Out of the total of 160 participants, 87 were male and 73 were female in the study group. Therefore, this research demonstrates a higher proportion of males compared to females, with a ratio of 1.19 males for every 1 female.

Table 2: Gender wise distribution of study participants

Group	Male	Female
Control study	84	76
Study Group	87	73

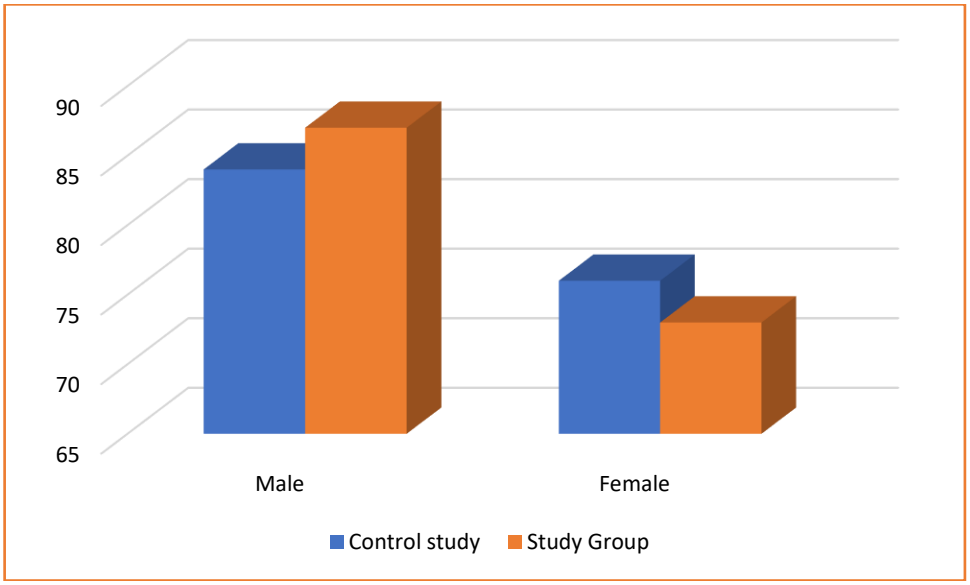

Figure 2: Gender wise distribution of study participants

The research examined the levels of vitamin D3 in both study groups. It was observed that patients in the AR group had an average blood vitamin D level of 11.32±3.96 ng/ml, whereas participants without AR had a level of 27.15±16.26 ng/ml. The observed differences were found to be statistically significant with a p-value of 0.0001. Indeed, both research groups had insufficient or deficient levels of vitamin D3.

Table 3 : Vitamin D level among study participants

Group	Minimum	Maximum	Mean	SD	P value
Control study	6.22	91.1	27.154	16.26	< 0.0001
Study Group	4.9	21.9	11.32	3.96	

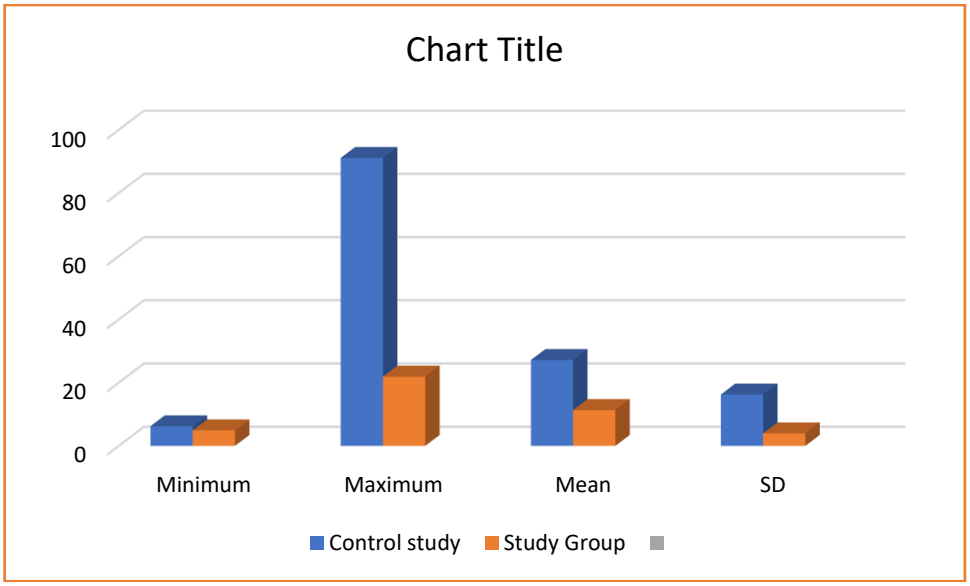

Figure 3 : Vitamin D level among study participants

The control group had a mean serum IgE level of 36.08±19.43 IU/ml, whereas the study group had a mean serum IgE level of 269.19±71.27 IU/ml (p<0.0001). The control group had a lowest value of 4.1 and a maximum value of 82.6, whereas the study group had a minimum value of 167.7 and a maximum value of 500.3.

The mean serum IL6 levels in the control group were 6.67±6.55 IU/ml, but in the study group, they were 26.89±22.24 IU/ml (p<0.0001). The control group had a lowest value of 0.9 and a maximum value of 40.5, whereas the study group had a minimum value of 3.9 and a maximum value of 89.7.

Table 4 Inflammatory markers level among study participants

		Minimum	Maximum	Mean	SD	P-value
IGE	Control study	4.1	82.6	36.08	19.43	< 0.0001
	Study Group	167.7	500.3	269.194	71.27	
IL6	Control study	0.9	40.5	6.67	6.55	< 0.0001
	Study Group	3.9	89.7	26.89	22.24	

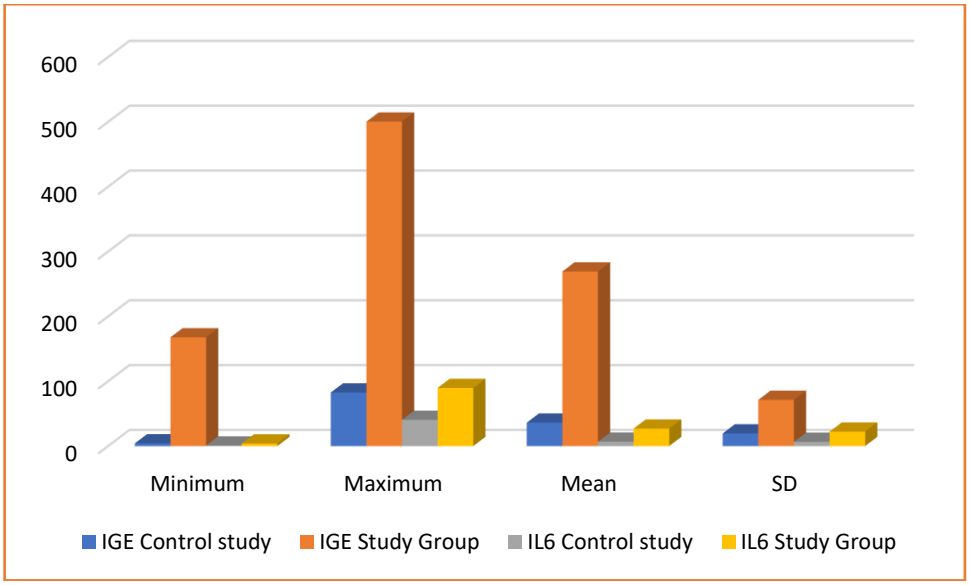

Figure 4 Inflammatory markers level among study participants

Discussion

Allergic rhinitis is a significant health issue that has a noticeable impact on people's daily lives. The allergens that cause it include: domestic allergens (such as mites, domestic animals, insects, or of plant origin), outdoor allergens (such as pollens and moulds), occupational allergens (such as latex), tobacco smoke, automobile exhaust (containing ozone, oxides of nitrogen, and sulphur dioxide), aspirin, and other non-steroidal anti-inflammatory drugs (NSAIDs). The condition consists of four primary symptoms: rhinorrhoea, sneezing, nasal itching, and nasal congestion. These symptoms lead to sleep disruption, weariness, low mood, irritability, and impaired cognitive function. Additional disorders such as conjunctivitis, postnasal drip, Eustachian tube dysfunction, otitis media, sinusitis, and in infants, dental malocclusions and facial abnormalities may be linked to it.[15]

A total of 320 participants were included in the research, all of whom visited the outpatient department at our institution. The participants were categorized into two groups, namely cases and controls, each consisting of 160 patients. Out of the total of 160 participants, 84 were male and 76 were female in the control group. Therefore, this research demonstrates a higher proportion of males compared to females, with a male to female ratio of 1.13 to 1. In the research group, there were 87 male individuals and 73 female subjects out of a total of 160. Therefore, this research demonstrates a higher proportion of males compared to females, with a ratio of 1.19 males for every 1 female.

Agarwal S et al performed a research in which participants were recruited from the outpatient department of our institution. The participants were separated into two groups, with 40 individuals in each group. Among the 40 cases, 2 were dismissed during the subsequent investigation. Therefore, there were a total of 38 instances. Out of a total of 80 individuals, there were 50 men and 28 girls. Therefore, this research demonstrates a higher proportion of males compared to females, with a ratio of 1.78 males for every 1 female.[16] Furthermore, a further investigation was out by Gupta et al. in India in 2016 included the participation of 27 individuals diagnosed with allergic rhinitis, with an average age of 26.47 ± 9.25 years.[17]

This research examined the levels of vitamin D3 in both study groups. It was observed that patients in the AR group had an average blood vitamin D level of 11.32±3.96 ng/ml, whereas people without AR had a level of 27.15±16.26 ng/ml. The observed differences were statistically significant, with a p-value of 0.0001. Indeed, both research groups had insufficient or deficient levels of vitamin D3.

Bhat VS et al. did a research comparing the levels of vitamin D3 across two groups. The study found that patients in the AR group had an average blood vitamin D level of 15.8±7.4 ng/ml, whereas participants without AR had an average level of 18.1±6.6 ng/ml. The observed differences were found to be statistically significant with a p-value of 0.003. Both research groups contained patients with insufficient or low levels of vitamin D3.[18] A research done by Hollams et al. in Australia in 2012 examined the blood vitamin D level and its correlation with allergic rhinitis. This research successfully established a correlation between vitamin D insufficiency and allergic rhinitis.[19] In a related study done by Agarwal S et al, the researchers noted that the average blood vitamin D level in 38 patients at the beginning of the trial was 20.15 ± 10.26 ng/ml. After 3 months of supplementation, the average serum vitamin D level increased to 38.05 ± 14.6 ng/ml. This increase was statistically significant (p = 0.0001). No substantial alteration was seen in the controls.[16]
The average serum IgE levels in the control group were 39.00±42.65 IU/ml, but in the study group they were 9.00±71.49 IU/ml (p<0.0001). The control group had a lowest value of 8.1 and a maximum value of 515, whereas the study group had a minimum value of 4.86 and a maximum value of 176.4. Awan N U et al reported that the average IgE levels were 378.36±132.84 IU/ml, ranging from a low of 103 to a high of 740 IU/ml. The mean serum IgE levels in group A were 383.69±154.86 IU/ml, whereas in group B, they were 373.03±106.83 IU/ml (p=0.0001).[20]

The IL 6 gene is situated on the p15-21 region of the short arm of chromosome 7. The length of the file is around 5 kilobytes and it is composed of 4 exons and 6 introns. The mite's sensitivity phenotype was shown to be associated with the 4q12 area in the British population and the 4q27 region in the German population. Both locations are significant contenders in terms of the mite sensitivity phenotype. The association between the 7q35 area and HDM allergens (Dermatophagoides farinae) has previously been reported in a specific group of persons with asthma. On the other hand, IL 8 is produced by a gene situated on chromosome 4 inside the q13-q21 region. This gene consists of four exons, three introns, and a proximal promoter region. IL 8 has a total length of 5.25 kilobase pairs (kbp).[21] The research found that the average serum IL6 levels in the control group were 6.67±6.55 IU/ml, whereas in the study group they were 26.89±22.31 IU/ml (p<0.0001). The control group had a minimum value of 2.05 and a maximum value of 20.6, whereas the study group had a low value of 7.65 and a maximum value of 31.1. In their investigation, Dey et al. discovered that the average serum IL-6 level in the sick group was 51.66 ± 12.09 pg/mL, while it was 4.65 ± 1.78 pg/mL in the control group (t = 15.06, p < 0.0001).[21]

Conclusion

Vitamin D insufficiency was detected in study group. The AR group exhibited considerably lower mean levels of serum vitamin D than the control group. However, upon stratification, the disparities were considerable.

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