





# Effect of IL-4, IL-5, IL-13, and IgE on Nasal Congestion in Patients with Allergic Rhinitis

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## Abstract

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**BACKGROUND:** Allergic rhinitis is a symptomatic nasal disease provoked by exposure of the nasal mucosa to allergens, resulting in IgE-mediated inflammation. Swelling of the nasal mucosa is caused by interstitial mucosal edema due to leakage of plasma fluid and congestion of the nasal mucosal vessels and imbibition of the perivascular space. The method for determining the cross-sectional area as a function of airway distance is known as acoustic rhinometry. Using this approach, it is possible to determine the area as a function of the distance in the airways.

**AIM:** The purpose of the study was to evaluate the concentration of serum and local IL4, IL5, IL13, and IgE and to analyze their effect on nasal congestion in patients with AR, comparing results with healthy controls.

**METHODS:** IL and IgE levels were measured in serum and nasal lavage with enzyme-linked immunosorbent assay (ELISA) – Invitrogen ELISA kit. The results were expressed as optical density (OD) at 450 nm and calculated according to the OD of the standard. For our study, A1 Acoustic Rhinometer, GM Instruments Ltd., Kilwinning, Scotland, was chosen. Data analysis was performed after two measurements were taken: before and after nasal decongestion, with drops containing 0.1% xylometazoline hydrochloride. Statistical analyses were performed using SPSS 16.0 for Windows (SPSS Inc.). All participants, after detailed presentation of the aims, tasks, and methodology of the study and the opportunity for discussion, signed an informed consent form.

**RESULTS:** The study was conducted on the territory of the University Hospital in Stara Zagora, Bulgaria, and 111 participants, aged from 19 to 84 years, were examined. Data analysis was performed after two acoustic rhinometry measurements, respectively, before and after nasal decongestion.

**CONCLUSION:** The published results show that there is an inverse relationship between the degree of nasal congestion (determined by acoustic rhinometry) and the serum concentration of pro-inflammatory cytokines.

## Introduction

Allergic rhinitis is a symptomatic nasal disease provoked by exposure of the nasal mucosa to allergens, resulting in IgE-mediated inflammation [1]. The classic symptoms of allergic rhinitis are recurrent episodes of sneezing, profuse nasal secretions, itching, and nasal congestion which occur after exposure to allergens. Of the listed, the symptom of itching is most indicative of an allergic etiology and can involve not only the nose but also the eyes, ears, palate, and throat [2].

Swelling of the nasal mucosa is caused by interstitial mucosal edema due to leakage of plasma fluid and congestion of the nasal mucosal vessels and imbibition of the perivascular space. The direct action of chemical mediators, such as histamine, platelet-activating factor (PAF), prostaglandin D2, quinine, and especially leukotrienes, is essential. Leukotrienes released by infiltrating inflammatory cells, most commonly eosinophils, play an important role in the pathogenesis of late-stage mucosal edema [3].

The method for determining the cross-sectional area as a function of airway distance is known as acoustic rhinometry. This is relatively simple and is based on the principle of computerized analysis of sound waves reflected from the nasal cavity walls. The impulse noise signal or sound from the auditory frequency range is compared with the reflections from the surface of the nasal cavity walls. The assessment is performed by measuring the minimum cross-sectional area (MCA) and the nasal cavity volume using acoustic reflection, and by analyzing the signal delay time. The data regarding the distance of narrowing from the sound source are obtained. Using this approach, it is possible to determine the area as a function of the distance in the airways [4], [5].

Allergic rhinitis is an immunological disease. Countless medical papers are published on this pathology, providing us with a detailed description of the pathophysiological mechanisms responsible for its development and manifestation. Thus, under cytological examination, the clinical picture is easily built, and other pathologies are ruled out. In contrast,

despite the growing amount of scientific research that analyzes the regulatory molecules of the immune system and their relationship to atopic diseases, the topic remains debatable [6], [7]. Such issues provoke our interest in studying the concentration of certain cytokine molecules and IgE considered to modulate the atopic immune response, comparing their serum and nasal lavage concentrations in patients with healthy volunteers, as well as analyzing the effect they have on the degree of nasal congestion.

The purpose of the study was to evaluate the concentration of serum and local IL4, IL5, IL13, and IgE and to analyze their effect on nasal congestion in patients with AR, comparing results with healthy controls. In addition, the study aimed to compare the differences between the two main clinical forms of AR – intermittent AR (IAR) and persistent AR (PAR).

## Methods

The study was conducted on the territory of the University Hospital in Stara Zagora, Bulgaria, and 111 participants, aged from 19 to 84 years, were examined. We excluded patients with bilateral nasal polyposis, which affect the entire nasal passage, as well as patients with nasal septum deviation.

Patients with both forms of AR did not take any antiallergic, anti-histamine, topical or systemic corticosteroid drugs, and nonsteroidal anti-inflammatory drugs (NSAIDs), at least a month before the study.

All the participants, after detailed presentation of the aims, tasks, and methodology of the study and the opportunity for discussion, signed an informed consent form. The form was prepared in accordance with principles of Helsinki Declaration for Good Clinical and Laboratory Practice and approved at a meeting of Medical Ethics Committee at the Medical University, Stara Zagora.

We used the A1 Acoustic Rhinometer, GM instruments Ltd., Kilwinning, Scotland. Data analysis was performed after two measurements, respectively, before and after nasal decongestion, with nasal drops containing 0.1% xylometazoline hydrochloride. Biochemical analysis was performed with IL-4, IL-5, and IL-13 Sandwich ELISA kits of Affymetrix eBioscience. Measurement of IgE-total concentration was performed using an IgE-ELISA kit – NovaTec Immunodiagnostica GmbH.

The statistical analysis was performed with the statistical software IBM SPSS Statistics. The hypothesis was assessed for equality between two or more average variables and normal distribution by performing ANOVA analysis with Dunnett's *post hoc*. To compare averages in two independent samples,

we used Student's t-test. The non-parametric Mann-Whitney U-test was applied to detect a trend in a series of values. The achieved results were discussed at a level of statistical significance  $p < 0.05$ .

## Results

During the survey, 139 participants (111 with allergic rhinitis and 28 controls) were enrolled. In the group of patients, 54 (48.65%) were with IAR and 57 (51.35%) with PAR (Figure 1).

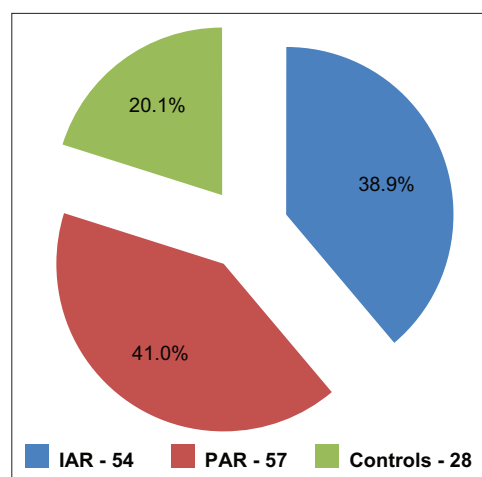


Figure 1: Distribution of patients in clinical groups

The mean age of patients with AR was  $46 \pm 16$  years (19–84), while in the control group, it averaged:  $46 \pm 15$  years (19–63). The clinical group consisted of 58 (52.3%) women and 53 (47.7%) men (Figure 2). There were no found differences in gender and age distribution between the clinical and control groups.

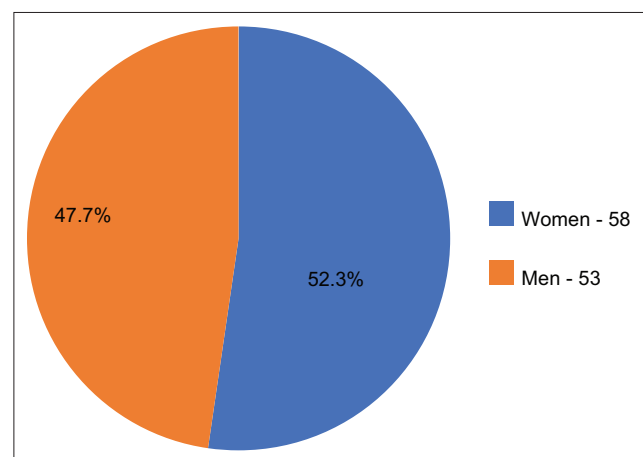


Figure 2: Gender distribution

The concentrations of the measured molecules in serum and lavage fluid in patients with the two main forms – intermittent and persistent allergic rhinosinusitis are presented in the following two charts (Figures 3 and 4).

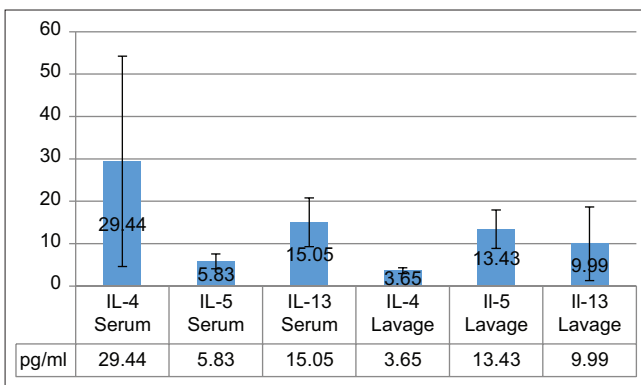


Figure 3: Cytokine concentration (pg/ml) in IAR patients

After statistical analysis of the results, we found higher serum IgE levels in patients with AR compared to the control (Figure 5); however, there was not a significant difference ( $237.84 \pm 38.71$  U/ml vs.  $175.44 \pm 79.89$  U/ml,  $p = 0.474$ , ANOVA).

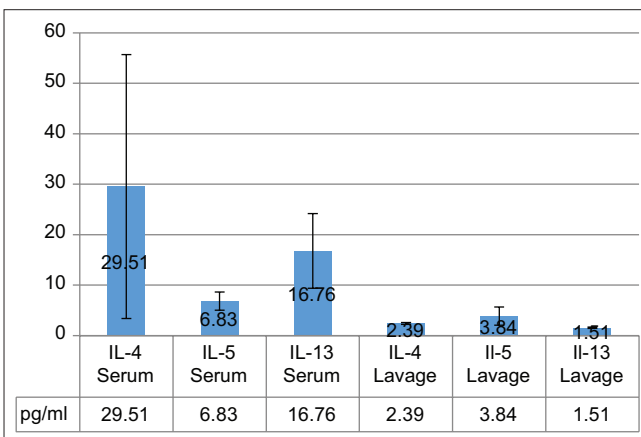


Figure 4: Cytokine concentration (pg/ml) in PAR patients

The results of IgE measurements in the nasal lavage fluid were  $1.6 \pm 0.40$  and  $1.1 \pm 0.37$ ,  $p = 0.312$ , ANOVA (Figure 3). We did not find a significant difference between the two subtypes – IAR and PAR (Figure 6) in blood serum  $261.27 \pm 57.79$  versus  $213.17 \pm 52.13$  ( $p = 0.532$ , ANOVA) and nasal lavage  $1.39 \pm 0.33$  versus  $1.82 \pm 0.41$  ( $p = 0.388$ , ANOVA).

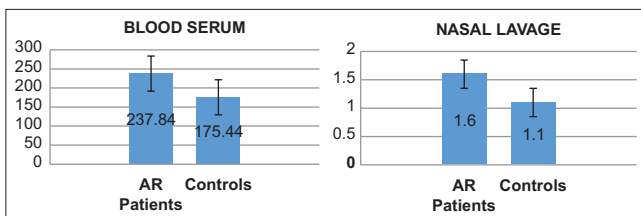


Figure 5: Serum and local IgE total concentration (UI/ml)

Measuring the concentration value of the IL-4 molecule in our study, the difference between healthy and atopic AR patients is notable but displays no statistical significance. In participants who did not exhibit any allergic and inflammatory pathologies, we measured a mean cytokine level of  $7.88 \pm 4.70$  pg/ml. In the blood serum of AR patients, the concentration of the pro-inflammatory molecule was  $29.48 \pm 17.77$  pg/ml ( $p = 0.188$ , Mann–Whitney U-test).

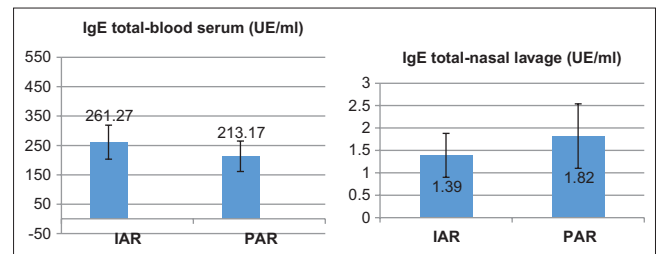


Figure 6: IgE total concentration AR patients

Regarding the serum and lavage fluid concentration of regulatory cytokines and their influence on the minimal cross-section area and the degree of nasal congestion, we found an inverse relationship, with a tendency for higher interleukin levels in subjects with nasal mucosal swelling smaller than the mean value defined for the clinical group (Figures 7 and 8).

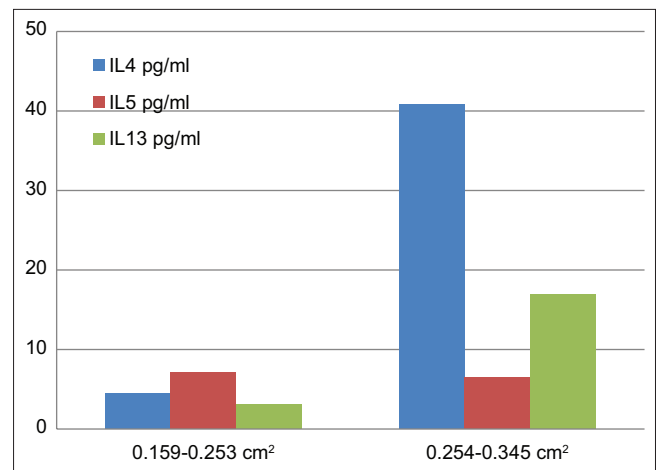


Figure 7: Distribution of serum cytokine levels by MCA

Serum levels of IL-4, IL-5, and IL-13 showed elevated values in the subgroup of patients with allergic rhinitis, where the total nasal cavity volume was greater in contrast to those subjects with minimal congestion where the cytokine values were significantly lower (Figure 9).

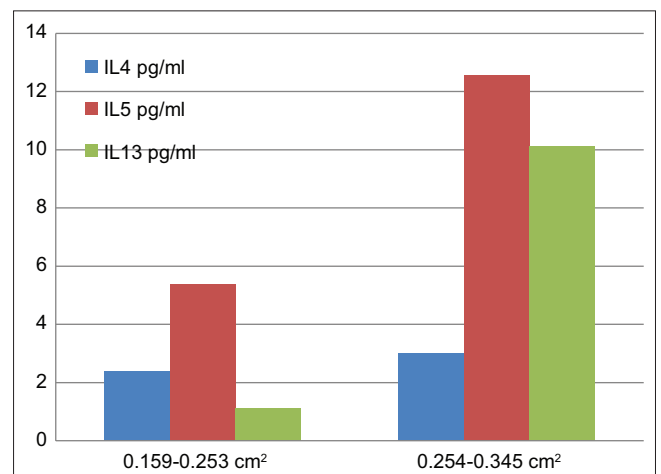


Figure 8: Distribution of nasal lavage cytokine levels by MCA

Concerning the concentration of total IgE molecules and their impact on nasal cavity reactivity, no direct relationship or no tendency of some dependence was established in our study (Figure 10).

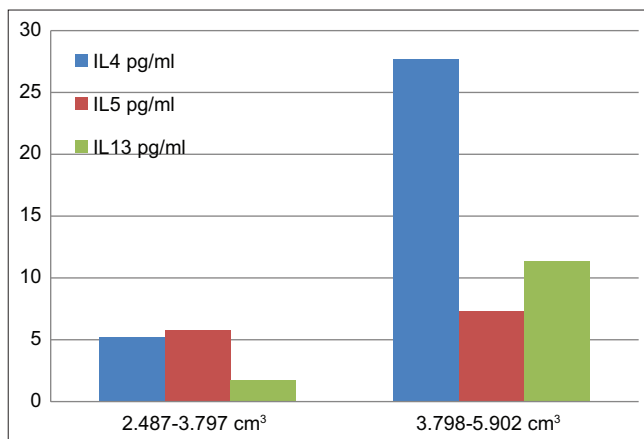


Figure 9: Distribution of serum cytokine levels by nasal cavity volume

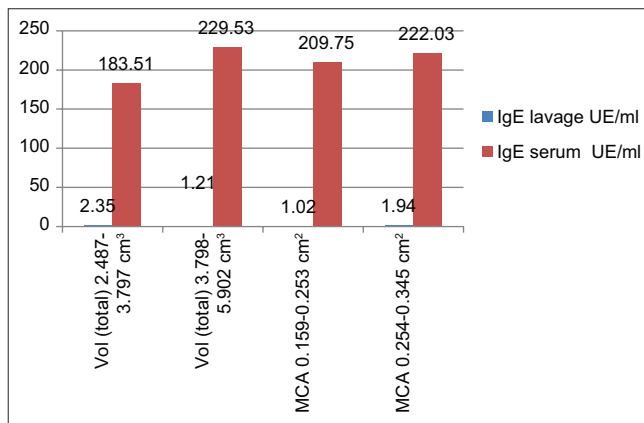


Figure 10: Distribution of serum and lavage IgE levels by MCA and nasal cavity volume

## Discussion

In the blood serum of patients with allergic rhinitis in our study, the detected concentration of total IgE was  $237.84 \pm 38.71$  UE/ml. Despite the lack of a statistically significant difference ( $p = 0.474$ , ANOVA), in the blood of volunteers without allergic pathology, we found a lower by about 25% or 1/4 mean value of the antibody –  $175.44 \pm 79.89$  UE/ml. Regarding the presence of immunoglobulin E in the nasal lavage, no significant differences were found between the two values, and in the patients' group, we measured levels of  $1.6 \pm 0.40$  UE/ml, compared to  $1.1 \pm 0.37$  UE/ml for the controls ( $p = 0.312$ , ANOVA). Comparing the concentrations of the molecules in the two main forms of AR, we found a slight increase in participants with the intermittent form –  $261.27 \pm 57.79$  UE/ml, compared to those with persistent, where the measured concentration was  $213.17 \pm 52.13$  UE/ml ( $p = 0.532$ , ANOVA). This could be considered as an indication of increased manifested allergic activity caused by pollen exposure.

In some studies, elevated levels of IL-4 and IL-13 in nasal secretions have been demonstrated in

patients with allergic rhinitis. For example, Scavuzzo *et al.*, examining nasal mucus in 30 patients with AR, reported significantly elevated values of the IL-4 molecule compared to healthy ( $25.5 \pm 3.6$  pg/ml vs.  $15.2 \pm 2.3$  pg/ml,  $p < 0.001$ ) [8]. Ciprandi *et al.* also reported a positive significant correlation between the concentration of IL-4 and IL-5 in patients with AR and inflammatory eosinophils in lavage fluid [9]. Although, there are some studies in the literature where the authors suggest that there is no increase in the values of the leukotriene C4, and B4, prostaglandin E2, and cytokines IL-4, IL-6, and IL-8 in atopic rhinitis [10], [11] and presence of other studies which suggest that after 2 weeks of administration of intranasal steroids, no change in cytokine activity can be found and a change is present only in the eosinophils number [12].

Measuring the values of the IL-4 molecule concentration in our study, the difference between healthy and patients with atopic AR is remarkable. In participants who had all allergic and inflammatory pathologies ruled out, we measured a mean cytokine level of  $7.88 \pm 4.70$  pg/ml. The concentration of the pro-inflammatory molecule in the blood of patients with AR was  $29.48 \pm 17.77$  pg/ml ( $p = 0.188$ , Mann–Whitney U-test). Between the two subtypes of the disease, we did not find any differences in serum concentration, and minimal discrepancies in the reported values were found in the lavage fluid –  $3.65 \pm 0.67$  pg/ml compared to  $2.39 \pm 0.2$  pg/ml, respectively, in the intermittent and persistent AR ( $p = 0.271$ , ANOVA). Like immunoglobulin E, the data indicate enhanced inflammatory activity in the pollen-induced form.

When analyzing the distribution of IL-5 in the serum of the patients and the control group, we did not find any significant differences, as in the first group, the measured concentration was  $6.31 \pm 1.24$  pg/ml, compared to  $5.61 \pm 2.2$  pg/ml,  $p = 0.842$  in the second. Of interest is the tendency for significantly higher IL-5 levels in nasal lavage fluid in patients with intermittent allergic rhinitis –  $13.43 \pm 4.77$  pg/ml compared to participants with persistent rhinitis –  $3.84 \pm 1.81$  pg/ml ( $p = 0.088$ , t-test).

Concerning IL-13, we found elevated blood concentrations of participants in both sub-forms of the disease, but without significant differences between them. Thus, in patients with IAR, the serum level was  $15.05 \pm 5.77$  pg/ml, and in those with PAR –  $16.76 \pm 7.4$  pg/ml ( $p = 0.433$ , ANOVA). In comparison, in healthy volunteers, the mean measured value of IL-13 was  $5.04 \pm 3.75$  pg/ml ( $p = 0.296$ , Mann–Whitney U-test). Similar observations of IL-5 were made in the distribution of the molecule in the nasal lavage. In patients with IAR, the mean concentration was  $9.99 \pm 8.68$  pg/ml and the measured concentration in the clinically healthy group was  $1.81 \pm 0.56$  pg/ml ( $p = 0.213$ , Mann–Whitney U-test).

## Conclusion

The published results show that there is an inverse relationship between the degree of nasal congestion (determined by acoustic rhinometry) and the serum concentration of pro-inflammatory cytokines. In all three interleukins tested, a significant increase in values of the group of patients with a minimal cross-section greater than the mean determined in the clinical group was reported. The results obtained were similar to the total volume of the nasal cavity. The data led us to conclude that the concentration of IL-4, IL-5, and IL-13 in the nasal secretions is related to the degree of nasal congestion not only in the area of the lower concha and the anterior 2/3 of the nasal cavity but in the degree of swelling of the entire nasal cavity mucosa.

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