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The Association between Interleukin-37 and Allergic Rhinitis and its Severity.

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Abstract

Introduction: In response to allergen contact, the membranes lining the nose become inflamed, which is known as immunoglobulin E (IgE) mediated allergic rhinitis. In 1929, it was established that sneezing, nasal blockage, and mucous discharge are the three primary signs of allergic nasal reactions. Worldwide, allergic rhinitis is a major cause of serious sickness and disability. Allergic rhinitis affects people of all ages, nationalities, and ethnic groups. Sleep, job, education, and social life are all impacted.

Aim of the study: To assess the association between interleukin-37 (IL-37) and allergic rhinitis and its severity.

Subjects and Methods: This study is a controlled observational study that was conducted on 80 participants in the Fayoum University Hospital. All participants were informed of the study's methods and goals, after receiving the patients' informed consent and the research committee's approval, participants were divided into two groups:

- Group (A): Case group:(40) Patients presented with allergic rhinitis.
- Group (B): control group: (40) Patients without evidence of allergic rhinitis

Results: Our results showed that a statistically significant difference with allergic rhinitis and controls, with low mean nasal lavage and blood serum interleukin -37 expression among patients (downregulation).

Conclusions: This study investigated the relationship between IL-37 levels and various health factors among participants. The results demonstrated significant differences in IL-37 levels between cases and controls, both in blood and after nasal lavage, suggesting a potential role of interleukin -37 as an anti-inflammatory cytokine

1. Introduction

Immunoglobulin E (IgE)-mediated allergic rhinitis is a condition in which the membranes lining the nose become irritated in reaction to allergen exposure [1].

Sneezing, nasal blockage, and mucous discharge are the three hallmark signs of allergic nasal responses, according to a 1929 definition. One of the leading causes of severe illness and disability in the world is allergic rhinitis. People of various ages, nations, and ethnicities are susceptible to allergic rhinitis. Social life, work, education, and sleep are all affected [2].

The economic impact of allergic rhinitis is often underestimated because it does not lead to higher direct expenses. However, the indirect expenses are substantial [1].

Both allergic rhinitis and asthma are long-term inflammatory conditions that commonly co-occur. Although asthma and other allergy diseases have existed since ancient times, hay fever is relatively new.

A conservative estimate places the number of people with allergic rhinitis at about 500 million. Globally, allergic rhinitis is becoming more common, particularly in areas where its prevalence is low or moderate. On the other hand, it may be plateauing or even dropping in areas with the highest frequency. There are specific initiatives in the European Union and countries like Canada to better understand, treat, and prevent allergy diseases [4].

Allergy disorders and rhinitis are now considered serious. Indoor and outdoor allergens, as well as occupational pollutants, can cause rhinitis and other allergic diseases. It is yet unclear how indoor and outdoor pollutants contribute to the onset of the disease and its symptoms, but it is probably conclusive. While it can sometimes be difficult, the diagnosis of allergic rhinitis is usually simple. Due to their inability to identify rhinitis symptoms as indicators of a disorder that disrupts their social, academic, and professional lives, many people [5].

Growing knowledge about allergic disorders has made it easier to see how important the interleukin [IL] family is to the onset and progression of these conditions [6].

Initially known as IL-1F7, (IL)-37 is a new member of the IL-1 family that has been demonstrated to naturally decrease inflammatory and innate immune responses [7].

2. Subjects and Methods

2.1.Subjects

This study is a controlled observational study that was conducted on 80 participants in the Fayoum University Hospital. All participants were informed of the study's methods and goals, after receiving the patients' informed consent and the research committee's approval, participants were divided into two groups:

- Group [A]: Case group: 40 Patients presented with allergic rhinitis.
- Group [B]: control group: 40 Patients without evidence of allergic rhinitis.

Inclusion criteria

- Adults aged over 16.
- Evidence of allergic rhinitis.
- Patients who are not treated with corticosteroids or anti-histaminic [topical or systemic] for at least four weeks.

Exclusion criteria

- Patients below 16 Years old.
- Previous endoscopic sinus.
- Immunocompromised patients like renal failure.
- Diseases with known immune-related etiologies, craniofacial abnormalities.

2.2.Study design

This study is a controlled observational study.

2.3.Statistical Method

After a thorough history-taking process and clinical examination, allergic rhinitis is was identified. From each research that was included, we gathered two types of information: the baseline and demographic information on of the participants, including their age and gender, is the first category. The results of the analysis were included in the second category. An extensive statistical analysis was carried out in this study to look at the linkages and relationships between the variables of interest. The characteristics of the research participants and the factors under examination were summarized using descriptive statistics. A summary of the data distribution was created using metrics including mean, standard deviation, range, and frequency distribution. The means of interleukin-37 (IL-37) levels before and after nasal lavage in both.

Patients and controls were compared using paired sample t-tests. Cross-tabulations were also used to investigate any

connections between the cardinal symptoms, a nasal cavity inspection, and the levels of IL-37 obtained following nasal lavage. To evaluate the independence of categorical variables, the chi-square test was employed. Additionally, correlation analyses were carried out to look at the correlations between IL-37 levels and the total scores of cardinal symptoms and sequelae. The proper software (SPSS version 26.1) was used for all statistical analyses, and a significance threshold of 0.05 was taken into account for assessing statistical significance. The current study recorded demographic data, such as age, gender, the length of the allergic rhinitis, and family history of allergic disorders, in a prepared checklist. The mean blood level and nasal lavage of IL-37 in the two groups (case group) and (control group) were compared to each other to find out our results.

3. Results

3.1.Comparison of IL-37 levels between cases and control

Table 1 illustrates that The Median of IL-37 in blood serum of allergic patients was 39.91 (7.646-142.112) and the Median of controls was 92.29 (49.65-241.59). There was a statistically significant difference with ($p \leq 0.001$) between patients and controls with low mean among patients (downregulation).

The median of IL-37 in the nasal lavage of allergic patients was 54.96 (0-117.343) and the median of controls was 140.27 (99.720 - 214.074). There was a statistically significant difference with ($p \leq 0.001$) between patients and controls with low mean among patients (down regulation) as shown in **Table 1**.

Table 1: Median (IQR) of cases Interleukin-37 levels.

Marker	Mean	SD	Median [IQR]	Range	*P*- value
Interleukin-37 Blood serum level in Cases [ng/ml]	40.776	30.79	39,91	7.646-142.112	**<0.001**
	102.549	44.988	92.29	49.650-241.590	
Interleukin-37 level in water after nasal lavage in	61.132	35.459	54.96	0.00-117.343	**<0.001**
	150.244	31.506	140.27	99.720 - 214.074	

Cases [ng/ml]

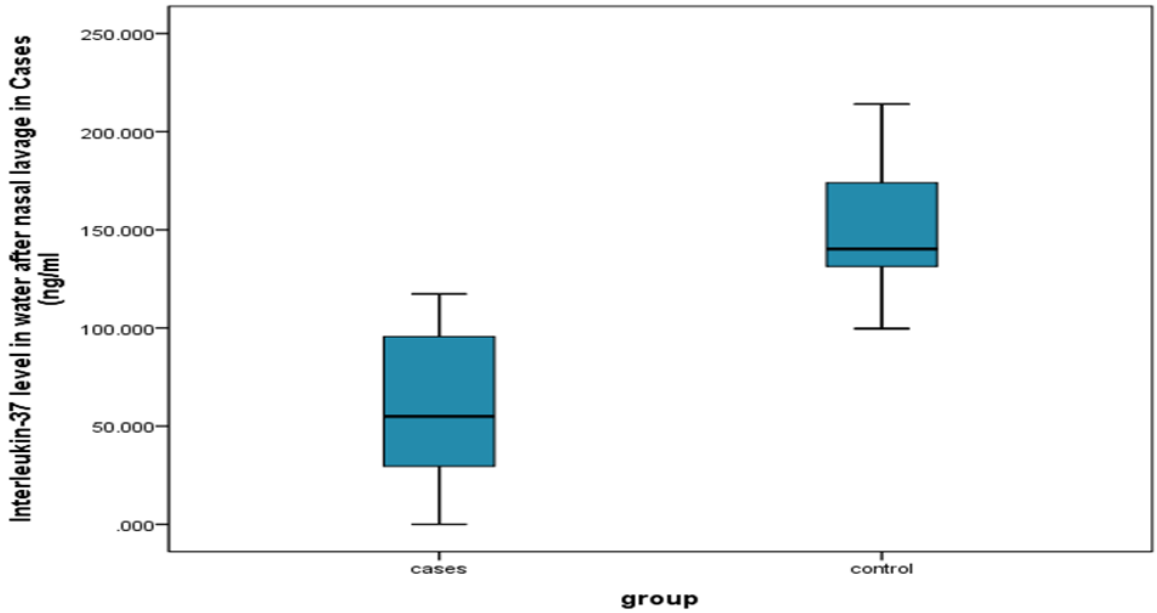

Figure 1: Box blot shows nasal lavage level of IL-37 in both cases and control.

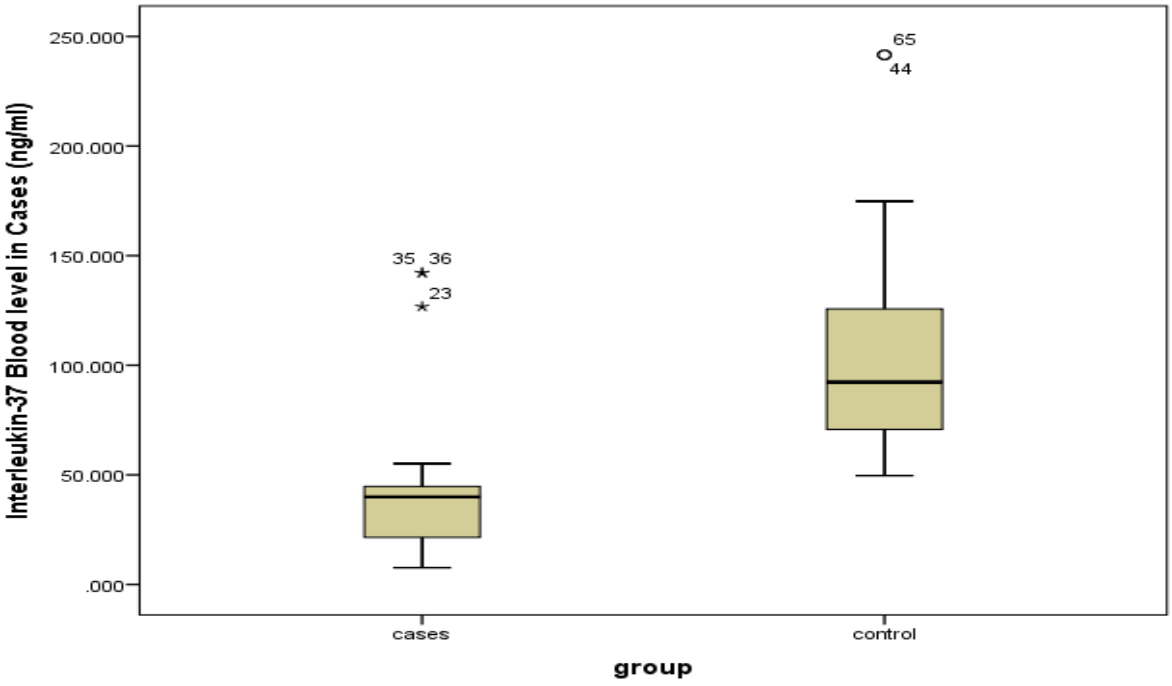

Figure 2: Box blot shows blood serum level of IL-37 in both cases and control.

3.2.Association of IL-37 and allergic rhinitis in blood serum and nasal lavage

As shown in **Table 2** and **Figure 2, t**he ROC (Receiver Operating Curve) curves, demonstrates the association between IL-37 and allergic rhinitis in blood serum with sensitivity of 92.5% and specificity of 94.1% and p <0.001 (highly significant association). Also. it demonstrates the association of IL-37 and allergic rhinitis in nasal lavage with sensitivity a 95% and specificity 82.1% and p <0.001 (highly significant association).

Table 2: the association of IL-37 and allergic rhinitis Sensitivity and Specificity.

Markers	AUC	Cut off point	Sensitivity	Specificity	*P*- value
IL-37 Blood level in Cases [ng/ml]	0.936 [0.859-1]	55.24	92.5%	94.1%	<0.001
IL-37 level in nasal lavage in Cases [ng/ml	0.98 [0.958-1]	111.89	95%	82.1%	<0.001

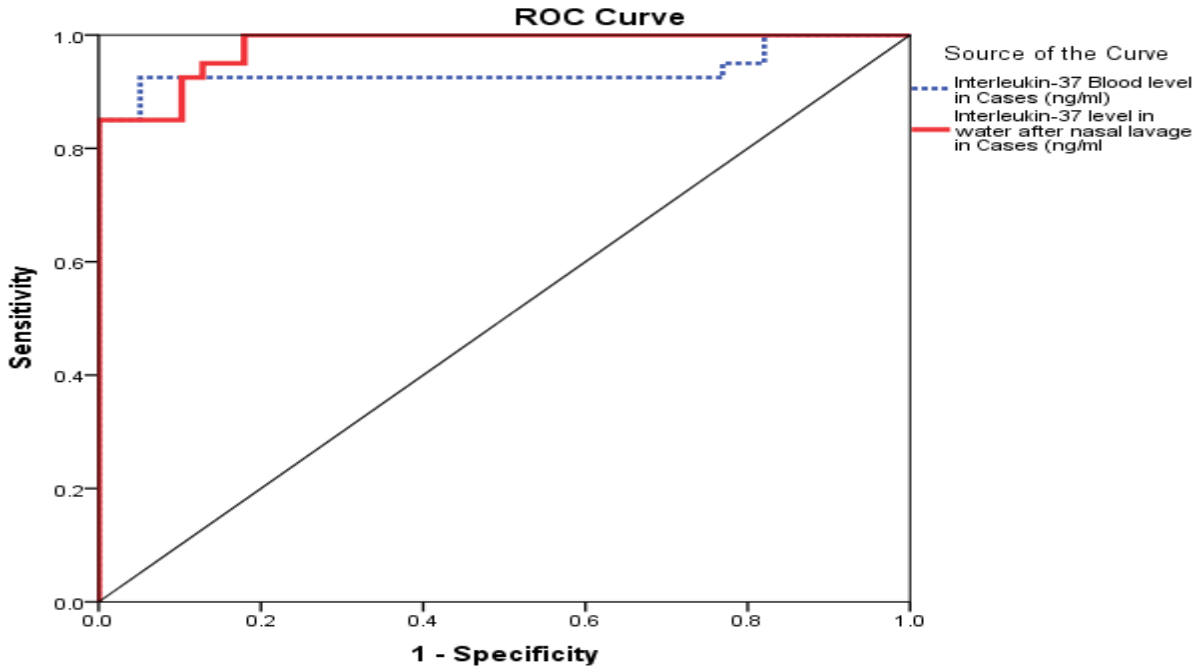

Figure 3: ROC curve shows the role of markers in the studied group.

3.3. Correlation between IL-37 levels and allergic rhinitis severity according total nasal score system (TNSS)

Table 3 illustrates that there was significant negative correlation between disease severity and IL-37 Blood level in Cases with $p < 0.001$. IL-37 Blood level decreases as the severity increases according to TNSS. On other side there was no significant Correlation between disease severity and IL-37 level in nasal lavage in Cases with $p > 0.05$.

Table 3: Correlation between IL-37 levels and allergic rhinitis severity according TNSS.

IL-37 level (ng/ml)		**TSNN**
Blood serum levels	R	-.581**
	P- value	**.<0.001***
Nasal lavage	R	.101
	P- value	.535

4. Discussion

Over the last few decades, the prevalence of allergy disorders has skyrocketed globally, becoming a significant public health concern **[8]**.

Comorbid diseases such as asthma, rhinosinusitis, nasal polyposis, and sleep difficulties are known to be associated with AR, which can lead to significant medical and social issues **[9]**.

Proinflammatory cytokines were the subject of the majority of research on the pathophysiological mechanism of AR, but anti-inflammatory cytokines were given less consideration **[10]**.

Growing knowledge about allergic disorders has made it easier to see how important the interleukin [IL] family is to the onset and progression of these conditions **[6]**.

Research has demonstrated that IL-37, a new member of the IL-1 family that was first known as IL-1F7, naturally suppresses innate immunity and inflammatory reactions **[7]**.

The biggest variety, known as IL-1F7b, is called IL-37 in this study. IL-37 has five splice variants [IL-1F7a-e] and interacts with the cell surface receptors **[11].**

Several disorders linked to inflammation have been found to exhibit aberrant IL-37 expression., inflammatory bowel disease **[11]**, systemic lupus erythematosus **[12]**, ankylosing spondylitis [24], and rheumatoid arthritis**,** Graves' disease **[13]**.

Furthermore, Lunding et al. showed that IL-37 inhibited the hallmarks of experimental asthma in mice as well as a Th2 cell-directed allergic inflammatory response, indicating that IL-37 may be essential for the pathophysiology of asthma **[14]**.

These results suggest that IL-37 could play a part in allergic illness and inflammatory reactions. Nevertheless, further research is necessary to determine whether IL-37 and AR are correlated.

The current study sought to measure the levels of IL-37 in both serum and nasal lavage in patients with AR.

Our results showed that a statistically significant difference ($P \leq 0.001$).

Between patients with allergic rhinitis and controls with low mean nasal lavage and blood serum IL-37 expression among patients (downregulation).

According to a study by Liu et al., children with AR had significantly lower levels of IL-37b expression in their serum and nasal lavage. In line with these conclusions **[15]**.

Furthermore, Shen Y et al. findings indicate that PBMCs from AR patients showed substantial reductions in IL-37 expression at both the mRNA and protein levels. It was also shown that IL37 is a significant cytokine implicated in the pathophysiology of AR. For AR, it might be protective **[14,16]**.

The association between IL-37 and allergic rhinitis is shown in the current study by the ROC curve. It demonstrated the association Serum level of interleukin37 and allergic rhinitis with sensitivity 92.5% and specificity 94.1% and p <0.001 (highly significant association). It also demonstrated the association between IL-37 in nasal lavage and allergic rhinitis with sensitivity 95% and specificity 82.1% and p <0.001 (highly significant association).

From our knowledge, it is the first research to evaluate correlation between IL-37 and allergic rhinitis's severity. In our study there was significant negative correlation between disease severity and IL-37 serum level in Cases with $p < 0.001$. Interleukin-37 Blood level decreases as the severity increases

according to TNSS. On other side there was no significant Correlation between disease severity and IL-37 level in nasal lavage in Cases with p >0.05.

When conducting correlation analyses of patients with allergic rhinitis symptoms with low levels of IL-37, there were no significant correlations with p >0.05 between sex, asthma and chronic diseases as HTN, DM, and IL-37 levels both in serum and nasal lavage.

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5. Conclusion

This study investigated the relationship between IL-37 levels and various health factors among participants. The results demonstrated significant differences in IL-37 levels between cases and controls, both in blood and after nasal lavage, suggesting potential role of IL-37 as anti-inflammatory cytokine in development of allergic rhinitis disease and its severity**.**

AI declaration statement: None declared.

Ethical approval: approved

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