ASTHMA ALLERGY IMMUNOLOGY
ASTIM ALLERJİ İMMÜNOLOJİ

doi: 10.21911/aai.2024.610
Asthma Allergy Immunol 2024;22:261-268

RESEARCH ARTICLE

Received: 08.07.2024 • Accepted: 09.08.2024
Online Published: 09.12.2024

Staphylococcus aureus-Specific IgE and Other Allergic Mediators Associated with Skin Allergy

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ABSTRACT

Objective: Many pioneers have mentioned that various organisms like bacteria, viruses, and fungi may complicate many allergic affections. This study aimed to show the association between bacterial infections and the determination of some immunological mediators in patients with skin allergies, among them total IgE and Specific IgE for *Staphylococcus aureus* dominated isolates from skin lesions of atopic dermatitis patients.

Materials and Methods: Eighty patients with skin allergies and twenty normal control individuals were included in this study. The study was done from October 2023 to January 2024 at the Department of Microbiology, College of Medicine, University of Anbar, Iraq. A skin swab and blood specimen were taken from each individual to be investigated. Total IgE and Specific IgE for *Staphylococcus aureus* dominated isolates from skin lesions of atopic dermatitis patients and control individuals using the ELISA test.

Results: Results revealed a significant difference between patients and control individuals in the titers of total IgE and Periostin, while there was no significant difference in the titers of IL-5. At the same time, results showed a significant correlation between basophils and total IgE, and a positive correlation between basophils and periostin as well as total IgE and periostin. Specific IgE to *Staphylococcus aureus* was detected in this study.

Conclusion: Bacterial infections concomitant with skin atopic dermatitis and other allergic reactions complicate these affections. So, total IgE, Periostin, and IL-5 undergo an increase. Detection of IgE specific to *Staphylococcus aureus* confirms that infections of different etiology can induce atopic reactions.

Keywords: *Staphylococcus aureus* specific IgE, total IgE, interleukin-5 (IL-5), periostin, eosinophils, basophils

INTRODUCTION

The term "allergy" is now commonly used with IgE-mediated allergies. Persons with atopy have a genetic propensity to develop IgE antibodies against common environmental allergens and have one or more atopic disorders, such as atopic dermatitis and atopic eczema. After exposure to the allergen, Allergy is characterized by a T-helper 2 (Th2)-mediated hypersensitivity response with a marked elevation in immunoglobulin E (IgE). Type 2 immune responses induce the expression of type 2 cytokines, such as interleukin (IL)-4, IL-5, IL-9, and IL-13. Contacting the bacteria during early development may be protective by inducing T-helper 1 (Th1) cell differentiation (1-3).

Clinically, the identification of allergen-specific IgE antibodies in the serum has been used to support a history-based diagnosis of allergic reactions, including food and insect sting allergies, asthma, dermatitis, urticaria, angioedema, ocular inflammation, and allergic forms of rhinitis (4). Measuring sIgE in response to pure native or recombinant allergens could provide a more targeted assay (5,6). IL-5 is the primary cytokine involved in eosinophil formation; it promotes eosinophil migration, activity, and

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survival (7). Although mast cells can also produce IL-5 in the airways, Th2 lymphocytes are the main source of the substance. Although mast cells can also produce IL-5 in the airways, Th2 lymphocytes are the main source of the substance (8). Periostin, an extracellular matrix protein of the fasciclin family, regulates multiple cellular processes, such as cell adhesion, proliferation, migration, and epithelial-to-mesenchymal transitions (EMT) (9). The extracellular matrix (ECM) protein periostin is involved in tissue remodeling in allergic inflammation and has recently been identified as a new mediator in chronic stages of allergic disorders (10). There is a need to reveal the role of bacterial infections associated with skin allergies and the effect of bacterial antigens in the mediation of specific IgE at the site of infection. So, this study was done to show the association between bacterial infections and the determination of some immunological mediators in patients with skin allergies. Among them are total IgE and specific IgE for *Staphylococcus aureus* isolated from skin lesions of atopic dermatitis patients.

MATERIALS and METHODS

A- Patients and Control individuals: Eighty patients with skin allergies and twenty normal control individuals were included in this study. The study was conducted during the period extending from October 2023 to January 2024 at the Department of Microbiology, College of Medicine, University of Anbar, Iraq. A questionnaire was followed to include patients in this study; inclusion criteria included patients with eczema, atopic dermatitis, and other skin allergies. Exclusion criteria were patients with other allergic diseases like asthma, allergic rhinitis, sinusitis, and psoriasis. Patients with cancer, parasitic infection, and other autoimmune diseases and patients who were taking immunosuppressant drugs were also excluded.

Patient demographics and clinical data: The patients were from rural and urban residences, and their age, sex, occupations, and medication (cortisones and anti-allergics). Skin infections and complications were reported. Specimens were taken from patients attending dermatology clinics at Ramadi Teaching Hospital and private clinics suffering from various skin allergies. All patients attended dermatology units at the Ramadi Teaching Hospital and the private dermatology clinics in Ramadi City, Anbar Governorate. The senior dermatologist examined each patient and control individual in this study, and investigation results were reported.

Ethical approval: This study was approved by the Medical Ethics Committee of the University of Al-Anbar Governorate in Ramadi, Iraq, following the Helsinki Declaration (Ref: 8 in 18/01/2024). All research participants, including patients and their parents, provided signed informed consent.

B- Specimen collection

Five mL of venous blood specimens were taken from each individual in this study, both patients and control individuals, via venipuncture using 5 mL sterile plastic disposable syringes. Each blood specimen was divided into two parts: 2 mL was drawn in an EDTA tube for a complete blood count (CBC); the second portion (3 mL) was allowed to clot at room temperature and then centrifuged at 3000 rpm for 15 min. The pooled serum was taken and stored in sterile plastic white tubes and then kept at -20 ^{o}C to be used further for immunological tests.

Complete Blood Count (CBC) Test: The test was performed on blood specimens in EDTA tubes using the XN-350 Sysmex Automated Hematology Analyzer, and the results were reported.

Detection of Total IgE, IL-5, and Periostin in the sera of patients and control individuals: The Enzyme-Linked Immunosorbent Assay (ELISA) method was used to quantitatively detect total IgE, IL-5, and Periostin in the sera of patients and control individuals, following the steps mentioned in the kit for each one.

Detection of *Staphylococcus aureus* specific IgE

Staphylococcus aureus specific IgE was qualitatively determined in the patients' serum and healthy control individuals following the method mentioned in another article (11). An ELISA method was used to determine IgE specific for dominant *Staphylococcus. aureus* isolates from skin allergic lesions of patients.

Preparation of crude bacterial antigen

After thawing two milliliters of frozen crude *Staphylococcus aureus antigen*, 100 discs produced according to the instructions were impregnated with one milliliter of diluted bacterial crude antigen solution. To prepare paper discs with a paper puncher to obtain 0.5 cm in diameter, Watman Blotting Paper No.1 was utilized. An overnight UV light illuminator was used to sterilize these discs, and a sterility test was done for a sterilized disc sample. Ster-

ile discs were impregnated within the suspension of crude *Staphylococcus aureus* antigen, dried in an incubator at 37°C and kept cool in the refrigerator to be used soon for an ELISA test to determine IgE specific for *Staphylococcus aureus* antigen (11).

RESULTS

Hematological parameters

The blood of patients with skin allergies had a higher WBC mean count than that of the control individuals, 9.66±3.53 and 6.21±1.23 for each, respectively, p-value=0.0001. Patients also showed a higher eosinophil mean ratio of 4.09 ±3.20 in contrast to that of control individuals, 2.10±1.45, p-value=0.008. Regarding basophils, no significant difference was found between patients and control individuals, p-value=0.269 (Table I).

Table I: WBC and differential cell counts in the peripheral blood of patients and Control individuals.

	Skin allergy (n=80)	Controls (n=20)	p-value
WBCs (x10^3)	9.66±3.53 (4.21-19.50)	6.21±1.23 (4.50-9.00)	0.0001#
Eosinophil %	4.09±3.20 (0.3-13.7)	2.10±1.45 (0.3-4.3)	0.008#
Basophil %	0.39±0.64 (0.1-4.2)	0.23±0.13 (0.1-0.5)	0.269

#Significant difference between two independent means using Students-t-test at the 0.05 level.

Serological parameters

Total IgE: Patients showed a higher titer of total IgE in their sera than control individuals; 29 patients (36.3%) showed a sharp increase of total IgE in their sera to ≥1000 IU/mL.

The mean total IgE titer in patients was 648.62±528.17, while the mean total IgE in the sera of control individuals was 45.44±23.79 (Table II).

Specific IgE to *Staphylococcus aureus* antigen: Only two out of 18 tested sera from patients showed positive results for the IgE-specific antigen of *Staphylococcus aureus*-dominated bacterial isolates with skin allergies.

Interleukin-5 (IL-5): Forty-one patients showed similar values of IL-5 in their sera (10 pg/mL) while the value of control individuals was 10 pg/mL of IL-5 in their sera. Only one patient revealed more than 70 pg/mL of IL-5 in his serum. So, some patients showed higher mean values of IL-5 than control individuals (Table III).

Periostin: The mean value of periostin in the sera of patients was 149.50±164.49, which was more than in the control individuals, 44.78±13.73 (significant difference, p-value=0.048) (Table IV).

Table II: Total IgE in sera of patients and control individuals.

		Skin allergy (n=80)		Controls (n=20)		p-value
		n	%	n	%	
Total IgE (IU/mL)	<100 IU/mL	15	18.8	10	100	0.001*
	100-199	8	10.0	-	-	
	200-299	9	11.3	-	-	
	300-399	5	6.3	-	-	
	400-499	4	5.0	-	-	
	500-599	-	-	-	-	
	600-699	5	6.3	-	-	
	700-799	3	3.8	-	-	
	800-899	1	1.3	-	-	
	900-999	1	1.3	-	-	
	=>1000 IU/mL	29	36.3	-	-	
	Mean±SD (Range)	648.62±528.17 (1.056-1911.611)		45.44±23.79 (3.278-73.833)		0.001#

*Significant difference between percentages using Pearson Chi-square test (c^2-test) at the 0.05 level.
#Significant difference between two independent means using Students-t-test at the 0.05 level.

Table III: IL-5 in sera of patients and control individuals.

		Skin allergy (n=80)		Controls (n=20)		p-value
		n	%	n	%	
IL-5 (pg/ml)	<10 pg/ml	30	37.5	-	-	0.126
	10-19	41	51.2	10	100	
	20-29	3	3.8	-	-	
	30-39	4	5.0	-	-	
	40-49	-	-	-	-	
	50-59	1	1.3	-	-	
	60-69	-	-	-	-	
	=>70 pg/ml	1	1.3	-	-	
	Mean±SD (Range)	13.86±10.15 (2.693-71.273)		14.26±2.60 (10.818-17.693)		0.904

*Significant difference between percentages using Pearson Chi-square test (c^2-test) at 0.05 level.
#Significant difference between two independent means using Students-t-test at 0.05 level.

Table IV: Periostin in sera of patients and control individuals.

		Skin allergy (n=80)		Controls (n=20)		p-value
		n	%	n	%	
Periostin (pg/ml)	<10 pg/ml	-	-	-	-	0.019*
	10-19	1	1.3	-	-	
	20-29	1	1.3	2	20.0	
	30-39	13	16.3	2	20.0	
	40-49	8	10.0	2	20.0	
	50-59	6	7.5	3	30.0	
	60-69	14	17.5	1	10.0	
	70-79	3	3.8	-	-	
	80-89	4	5.0	-	-	
	90-99	2	2.5	-	-	
	=>100 pg/ml	28	35.0	-	-	
	Mean±SD (Range)	149.50±164.49 (17.857-700.238)		44.78±13.73 (13.733-23.543)		0.048#

*Significant difference between percentages using Pearson Chi-square test (c^2-test) at 0.05 level.
#Significant difference between two independent means using Students-t-test at 0.05 level.

At the same time, results revealed that twenty-eight (35%) patients showed more than 100 pg/mL of periostin in their sera in contrast to the values of the control group (Table IV) (Figure 1). Correlation relation between the studied parameters:

Basophils% and Total IgE

A significant positive correlation was found between basophil count and total IgE values of the patients, r=0.234, and a negative correlation between basophil count and total IgE values of the control individuals, r=-0.057.

Eosinophils% and IL-5

There was a negative correlation between eosinophil count and IL-5 value in patients and control individuals, r=-0.084 and -0.306 for each, respectively (Figure 2A).

Basophil % and periostin

There was a positive correlation between basophil count and periostin values of the patients, r=0.090, while there was a negative correlation between basophil count and periostin values of control individuals, r=-0.354 (Figure 2B).

Total IgE and Periostin

There was a positive correlation between total IgE and periostin values in patients and control individuals, r=0.114 and 0.137, respectively (Figure 2C).

DISCUSSION

The results showed a higher WBC mean count in the blood of patients with skin allergies than in control individuals. This status was due to the allergic inflammatory reaction leading to the activation of WBCs in circulation. WBC activation was due to DAMP release, which causes WBC activation in circulation (12). Patients showed a higher eosinophil mean ratio in contrast to control individuals. These results can be explained by the role of eosinophils in allergic reactions related to different skin conditions. Eosinophils also contribute to tissue edema by releasing toxic granule proteins and generating leukotrienes, which directly regulate blood vessels or indirectly stimulate mast cells (13). Patients with atopic dermatitis are often found to have a higher ratio of circulating eosinophils; a possible explanation for the eosinophil increase seen in atopic dermatitis may be the inhibition of eosinophil apoptosis, which GM-CSF and IL-5 likely mediate. So, patients with allergies have an increased inflammatory response, and eosinophils infiltrate their skin (14). In addition, the attraction of eosinophils during allergic reactions is due to the release of type 2 cytokines such as IL-5 and IL-13 (13). These results can also be explained by the fact that IL-5 is essential for eosinophil development, maturation, and proliferation in the bone marrow (15). The nonsignificant difference in basophil number between patients and control individuals might be due to the study's size and duration.

Regarding serological results, patients showed a higher titer of total IgE in their sera than control individuals. These findings can be explained by the Th2-mediated reaction switch on and the yield of IgE in allergic patients (15). IgE is a critical link between the adaptive immune system's role in recognizing antigens and the effector roles played by mast cells and basophils at mucosal and cutaneous sites of environmental exposure. IgE roles have made it an attractive target for pharmaceutical intervention, with the potential for IgE blockage to be used in various therapeutic contexts (16). Other pioneers found similar findings, such as high titers of total IgE in sera of patients with atopic affections (17). Regarding specific IgE in this study, only two out of 18 tested sera from patients showed positive results for the IgE-specific antigen of *Staphylococcus aureus* bacterial antigen. These results were in accordance with the findings of another article (18), which found that patients

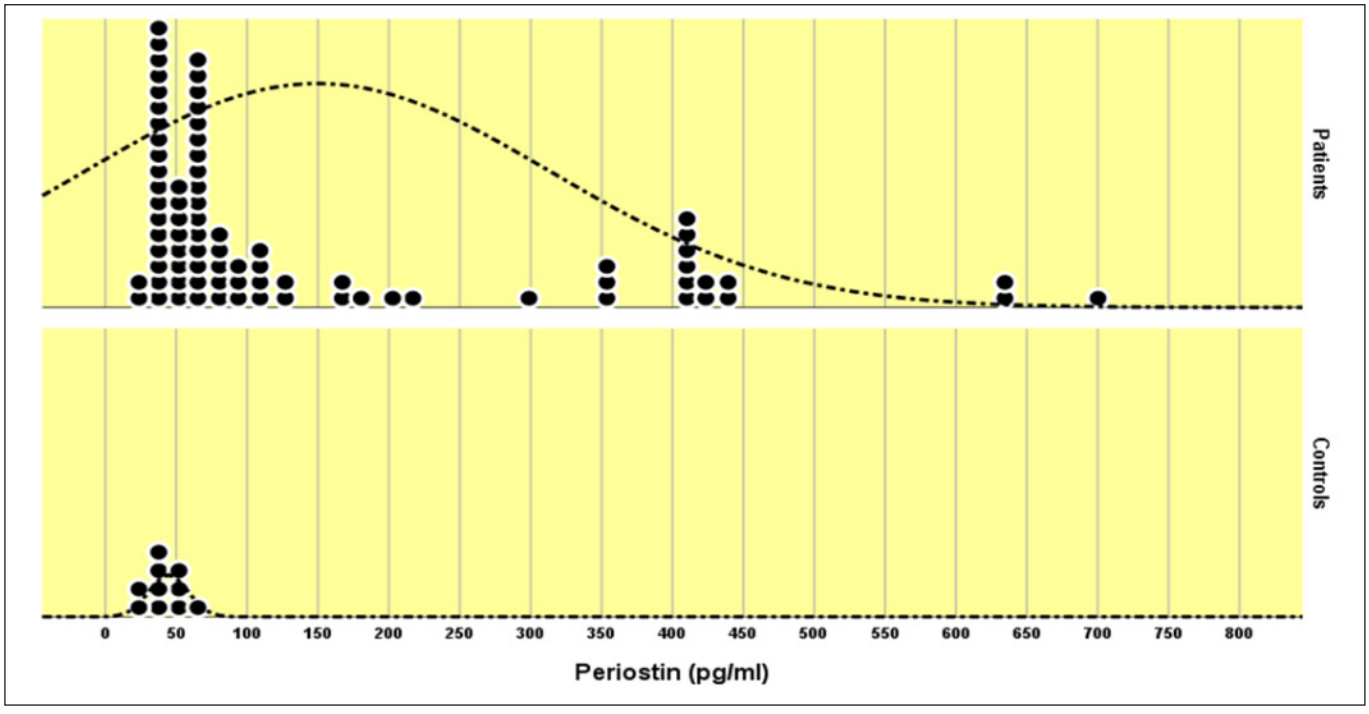

Figure 1. Periostin in sera of patients and control individuals.

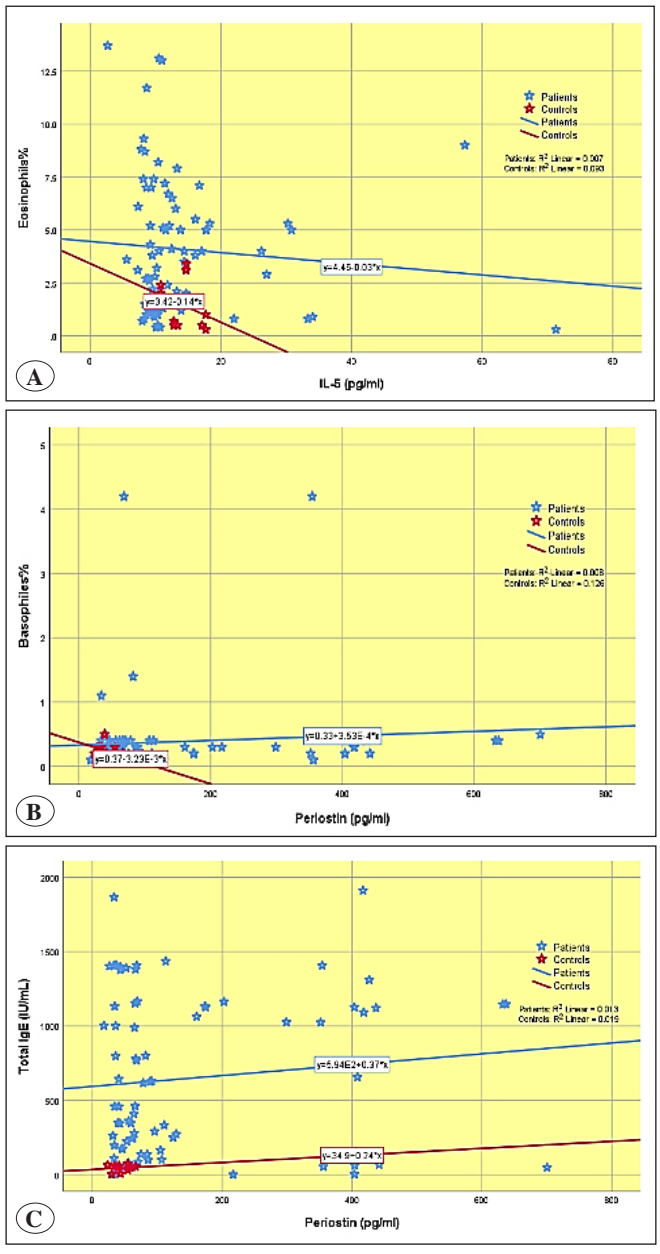

Figure 2. A) Correlation between Eosinophil % and serum IL-5. **B)** Correlation between Basophils % and serum periostin. **C)** Correlation between serum Total IgE and periostin.

with positive swab cultures from both sexes and two age groups showed more IgE specific for *S. aureus* crude antigen (65.5%) than that of the *S.aureus* standard strain. Our explanation for the positive result was that some bacterial antigens act as an allergen mediating type 1 hypersensitivity reaction at the site of the infection (11,19). Nine of the patients showed higher values of IL-5 than control individuals, while the majority of patients (41) showed values of IL-5 in their sera similar to those of control individuals. This result disagreed with the finding of another article (20), who found that the serum levels of IL-5 were significantly higher (p=0.021). These results can be explained by the fact that IL-5 is essential for eosinophil development, maturation, and proliferation in the bone marrow in addition to tissue accumulation, activation, and survival (21). The variation of IL-5 values in patients might be due to the short half-life of IL-5 in serum, thus exposing the released amount to undergo disintegration faster than other mediators (22). The increased values of periostin in the patients' sera can be explained by the fact that periostin plays a special role as an inflammatory mediator that links resident cells and immune cells together. It is commonly recognized that allergic inflammation is primarily mediated by type 2 (T2) immunity. Interleukins IL-4, IL-5, and IL-13 are essential components in the pathophysiology of numerous allergic inflammatory disorders, humoral immunity and protection against helminth infection. T helper 2 (Th2) cells, follicular helper T cells, eosinophils, mast cells, and basophils are the cells that produce IL-4, IL-5, and IL-13 (23,24). Either directly or indirectly, periostin expression is upregulated when IL-4 and IL-13 bind to their receptors. This process is dependent on SOX11 and STAT-6. Additionally, it has been documented that periostin facilitates the adhesion and migration of αMβ3 integrin-mediated eosinophils induced by IL-5. Remarkably, periostin was found to chemotactically recruit macrophages to the site of allergic responses in a peripheral nerve experiment (25). However, in that experimental scenario, the lack of periostin resulted in less macrophage infiltration, which reduces inflammation and slows the progression of the disease. This implies that periostin primarily draws macrophages that promote inflammation; this may also be true for other organs and inflammatory conditions (26,27).

Correlation results showed a significant correlation between the basophil count and total IgE values of patients, r=0.234, and a negative correlation between the basophil count and total IgE values of control individuals, r= -0.057. These results can be explained by the role of basophils in IgE-mediated reactions; basophil granulocytes are the effector cells in allergic reactions. These cells have high-affinity immunoglobulin E (IgE) binding sites and store histamine in their granules. Furthermore, blood basophils can release their mediators when reacting to an allergen or other stimuli (15,28). Basophils undergo an increase in individuals with allergic asthma, rhinitis, or contact der-

matitis, and they often exhibit symptoms of anaphylactoid degranulation. Additionally, basophils may gather in impacted tissues during the latter stages of an allergic reaction that follows an antigen challenge (15).

A negative correlation exists between eosinophil count and IL-5 value in patients and control individuals, r=-0.084 and -0.306 for each, respectively. This status might be due to the release of Th1 mediators, with antagonist IL-5 activity (atopic dermatitis concomitant infections may lead to such a result. There is a positive correlation between the basophil count and periostin values of patients, r=0.090, and a negative correlation between the basophil count and periostin values of control individuals. This result can be explained by the role of basophils and periostin in allergic reactions (15). Finally, a positive correlation exists between total IgE and Periostin values in patients and control individuals, r=0.114 and 0.137, respectively. This result can be explained by the fact that cytokines, such as TSLP, are produced by keratinocytes when periostin activates on αv integrin, Type 2. This result is explained by the fact that periostin is a downstream molecule of interleukin (IL)-4 and IL-13, which are highly expressed cytokines in allergic disorders (type 2 immune response). Notably, periostin facilitates communication between fibroblasts and keratinocytes in skin tissues, which is essential for amplifying and retaining of allergic inflammation. Type 2 immune responses are triggered when allergens invade hosts. Type 2 cytokines, such as IL-4 and IL-13, stimulate fibroblasts to produce periostin. The pro-inflammatory cytokines released by keratinocytes then amplify pro-inflammatory immune responses. Therefore, periostin and pro-inflammatory cytokines such as TSLP, IL-4, and IL-13 form a vicious cycle in allergic skin inflammation (26,29).

CONCLUSION

Bacterial infections concomitant with skin atopic dermatitis and other skin allergic reactions complicate these affections through ThI and Th2-mediated reactions. So, total IgE, Periostin, and IL-5 undergo an increase. Specific IgE to bacterial antigens, particularly specific IgE to *Staphylococcus aureus* in this study, was detected. These results confirm that infections of different etiologies can induce atopic reactions. In this study, eosinophil, Basophil, and total leukocyte count underwent an increase in the peripheral blood of patients. This study confirmed that the studied hematological and immunological factors are related to and in correlation with different skin allergic diseases.

Conflict of Interest

Authors indicate no such interest.

Funding

None.

Authorship Contributions

Concept: **Hanan Jamal Hasan, Shehab Ahmed Lafi, Abdullah Salih Hasan,** Design: **Hanan Jamal Hasan, Shehab Ahmed Lafi, Abdullah Salih Hasan,** Data collection or processing: **Hanan Jamal Hasan, Abdullah Salih Hasan,** Analysis or Interpretation: **Hanan Jamal Hasan, Shehab Ahmed Lafi,** Literature search: **Hanan Jamal Hasan, Shehab Ahmed Lafi,** Writing: **Hanan Jamal Hasan, Shehab Ahmed Lafi,** Approval: **Hanan Jamal Hasan, Shehab Ahmed Lafi, Abdullah Salih Hasan.**

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