Original Article

Immune response and leukocyte profile in patients infested with Sarcoptes scabiei in Duhok Province of Kurdistan region, Iraq

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Abstract

Introduction: Scabies is a skin condition that affects humans and many other mammalian hosts. It is brought on by the major obligate parasite *Sarcoptes scabiei*, which lives and reproduces in the epidermis and causes significant morbidity in both humans and animals.

Methodology: The current study aimed to determine the immunological responses of 60 patients who were clinically infested with scabies and who attended the Department of Dermatology at Azadi Teaching Hospital and the Gulan General Hospital at Akre. Serum samples were tested to measure the levels of total immunoglobulin E (IgE), interleukin 4 (IL-4), interleukin 5 (IL-5), complement protein 3 (C3), and complement protein 4 (C4) in all patients with scabies; and compared with non-infested healthy individuals as a control group. A fresh blood sample from each patient was tested for total white blood cell (WBC) count, lymphocytes, monocytes, neutrophils, eosinophils and basophils.

Results: The present study showed a significant increase in the mean of total WBCs and absolute eosinophil counts in patients infested with scabies when compared with controls ($p \le 0.05$). There were significant differences ($p \le 0.05$) in the mean of total IgE, IL4, II-5, C3, and C4 serum levels in patients infested with scabies when compared with the controls. Non-significant differences (p < 0.05) were recorded for the other parameters that were measured.

Conclusions: Scabies infection increased the levels of eosinophils and other immunological parameters, including IL4, Il-5, C3, C4, and total IgE.

Key words: scabies; crusted; ordinary; cytokines; complement and WBCs.

J Infect Dev Ctries 2025; 19(1):162-167. doi:10.3855/jidc.19348

(Received 06 October 2023 - Accepted 25 January 2024)

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Introduction

Scabies is a skin infestation caused by the burrowing ectoparasitic mite known as Sarcoptes scabiei variety hominis [1,2]. In 2010, it was estimated that over 100 million people worldwide had scabies. It has been reported to be more common in emerging nations and to have a significant negative influence on the health and social lives of indigenous populations in developed countries [3]. Scabies patients experience severe itching from allergic and inflammatory responses of the host against the mite and its products [2]. Scabies has a huge global impact and exhibits a wide variety of clinical symptoms, from mild to extremely damaging. However, the immunological and inflammatory responses linked to the various clinical presentations are still poorly understood [2]. Scabies can present in various clinical forms, and the two most frequently observed manifestations are ordinary scabies (OS) and crusted scabies (CS) [4]. The most prevalent type of scabies is OS and is thought to have a mite burden of fewer than 15 per person. Burrows, erythematous papules, and an allergic skin reaction with severe and widespread itching are the major clinical indicators [5]. On the other hand, CS is a relatively uncommon severe symptom of the condition and affects only a few thousand people [6].

An infestation of S. scabiei, commonly known as sarcoptic mange, triggers inflammatory and adaptive immune responses. These responses tend to occur relatively late in the infection, typically appearing around 4 to 6 weeks after the initial contact with the mite [7]. Scabies-related rash and itching resemble type I (immediate) and type IV (delayed) hypersensitivity reactions [2]. According to Walton et al., Langerhans cells (LCs) and eosinophils make up the initial inflammatory response to the mite and its products, while the numbers of monocytes, macrophages, and mast cells are much lower [8]. Studies that examined skin biopsies and circulating serum from scabies patients found complement elements C3 and C4 to be present [9]. The complement system plays a crucial and wide-ranging role in innate immunity, serving as the initial line of defense against invading pathogens [2]. The detection of these components in skin biopsies

from patients suggests an activated complement system, which may be involved in the early inflammatory responses triggered by scabies. Interestingly, it has been reported that patients with scabies may have low levels of circulating C3 or C4, or both, which might seem counterintuitive [10]. A variety of innate effector cells have been identified in response to S. scabiei mites, including eosinophils, mast cells, basophils, neutrophils, dendritic cells (DCs), and macrophages [8,9,11]. Tissue eosinophilia is frequently observed in inflammatory areas linked to both disorders because eosinophils are frequently generated in significant numbers in allergic inflammation and helminth infections [12]. The identification of eosinophils is in line with the elevated expression of T helper 2 (Th2) cytokines such as interleukin IL-4, IL-5, and IL-13 in CS [8]. It has been demonstrated that eosinophils produce cytokines specific to Th2. The synthesis of IL-5, which is involved in the attraction, activation, and maturation of eosinophils, may represent an independent mechanism for facilitating the recruitment and survival of these granulocytes [13,14]. Eosinophils are essential for the body's defense against helminthic parasites, but they also play a role in tissue malfunction and destruction during allergies. However, it is still unknown how eosinophils contribute to the immunological and inflammatory reactions that cause OS and CS [2]. Skin lesions from scabies patients have been found to contain mast cells and basophils [15,16]. The primary molecules causing allergic Th2-type inflammation are TNF, IL-6, IL-4, IL-5, and IL-13, which are rapidly produced by activated mast cells and basophils [14,17]. Alternative macrophage activation is mediated by IL-4, IL-13, TNF, and IFN; these cytokines have been implicated in the immunological response to scabies. Macrophages have been found in the skin of scabies patients, but in small numbers [18-20]. Strong antibody-mediated immune responses are known to be elicited by scabies mite infestation, particularly in CS, which is connected to incredibly high levels of IgG and IgE that are specific for the antigen. However, little is known about when these responses occur and how important each one is in developing protective immunity [8,9]. An infection with scabies mites skews the Th1/Th2 immune response [19,21]. Th2 cells release IL-4, IL-5, and IL-13, and regulate the generation of antibodies to combat external parasites, mediating humoral immunity.

The aim of this study was to determine the immunological responses of patients infested with scabies in Duhok Province in Iraq. The total white blood cell (WBC) count; differential counts of lymphocytes, monocytes, neutrophils, eosinophils, and basophils; and serum levels of IL-4 and IL-5 were evaluated in all patients with scabies and compared with normal healthy individuals as a control group.

Methodology

Study population

The current study included 60 patients with scabies who had clinical features of the disease and who did not have other allergic diseases or helminthic infections. They attended the Department of Dermatology at Azadi Teaching Hospital, and Gulan General Hospital in Akre from September 2021 to late August 2022. Skin scraping was performed by using a disposable surgical blade after placing a drop of mineral oil. The specimen was placed on a microscope slide and examined by a light microscope to identify mites or eggs using 10% KOH. A group of healthy people was selected as controls. The population included both genders and all ages

Blood sample collection

Five mL of venous blood were collected from each patient and control. The blood sample was divided into two parts, the first part was collected in tubes with ethylene diamine tetra acetic acid (EDTA; 2 mL) to estimate the total WBC count and differential leukocyte count. The second part (3 mL) was allowed to clot, then centrifuged at 10,062 RCF to separate the serum into 3 to 5 aliquots, which were stored at -20 to -22 °C to be used for immunological investigations.

Immunological analysis

The enzyme linked immunosorbent assay (ELISA) which employs a quantitative sandwich enzyme immunoassay that measures different human cytokines (IL-4 and IL-5) in serum samples was used for immunological analysis following the manufacture's protocol (Bioassay Technology Laboratory, Shangahai, China; Cat. No. E3762Hu and Cat. No. E0091Hu). The optical density (OD) values were measured using an ELISA reader (Bio-Tek-Reader, Vermont, USA) at 450 nm and within 10 min after adding the stop solution. An automated chemiluminescence immunoassay was used for detection of total IgE and complement proteins (C3 and C4) using Cobas e 411 (Roch Diagnostic Company, Mannheim, Germany) according to the manufacture's protocol.

Hematological analysis

Fresh blood samples were collected from the scabietic patients and directly examined for complete

Parameters	Cases (mean ± S.E) N = 60	Control (mean ± S.E) N = 30	<i>p</i> value
Lymphocyte	$34.248 \pm 1.7700 \text{ cells/mm}^3$	$34.933 \pm 1.6870 \text{ cells/mm}^3$	0.781
Monocyte	$5.036 \pm 0.4133 \text{ cells/mm}^3$	$5.006 \pm 0.3170 \text{ cells/mm}^3$	0.955
Neutrophils	$52.586 \pm 1.5706 \text{ cells/mm}^3$	$52.753 \pm 3.8193 \text{ cells/mm}^3$	0.968
Eosinophils	$8.668 \pm 1.3599 \text{ cells/mm}^3$	$1.680 \pm 0.3948 \text{ cells/mm}^3$	0.010
Basophils	$0.908 \pm 0.0833 \text{ cells/mm}^3$	$0.633 \pm 0.1140 \text{ cells/mm}^3$	0.101

Table 1. Mean \pm SE of total and absolute leukocytes counts for scabies patients and controls.

SE: standard error; WBC: white blood cells.

blood counting (lymphocyte, monocyte, neutrophils, eosinophils, and basophils) using the Medonic M Series-Hematology Analyzer (Boule Diagnostics, Stockholm, Sweeden) according to the manufacturer's instructions.

Statistical analysis

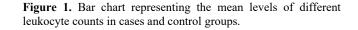
Statistical analyses were performed with the Statistical Package for Social Sciences (SPSS) software version 27 (IBM Corp, Armonk, NY, USA). The descriptive analysis included the mean \pm standard error (SE) for each variable. Independent Student's t-tests were conducted to compare each variable between the two groups. Pearson correlation analysis was utilized to assess the degree of correlation between the measured variables within each group.

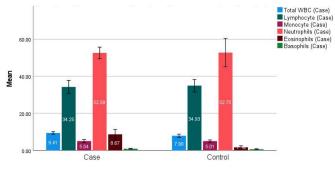
Ethical consideration

The study was approved by the Ethical Committee in Duhok Directorate General of Health under the reference number 13072021-7-8, issued on 13 July 2021.

Results

There was a significant (p = 0.03) increase in the mean of total WBC in patients infested with scabies (9.414 ± 0 .3479 (10³/mL)) when compared with the control group (7.900 ± 0.4447 (10³/mL)). The absolute leukocyte counts in scabies-infested patients were





WBC: white blood cells.

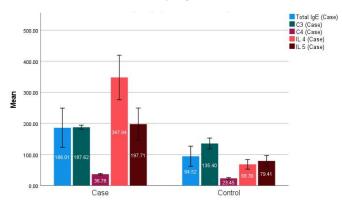
recorded compared to the control group (Figure 1). Notably, a significantly (p = 0.01) higher difference was observed only in the eosinophil levels when compared with the control group, while the differences in other parameters were non-significant (p < 0.05), as shown in Table 1.

Total IgE was measured in both cases and controls; with the median value of 186.006, and a geometric mean value of up to 100 IU/mL was considered normal. The difference between total IgE for cases and controls was statistically significant (p < 0.0120). There were significant ($p \le 0.05$) differences in the mean of IL-5 serum levels in the patients infested with scabies when compared with the control group. Significant ($p \le 0.05$) differences were observed in the mean serum IL-4 levels of the patients infested with scabies when compared to the control group. In addition, there were significant (p > 0.05) differences in the levels of complement proteins C3 and C4 in patients infested with scabies compared to controls as shown in Figure 2 and Table 2.

Discussion

This study included 60 clinically positive scabies patients, and found a significant (p = 0.0120) difference in total IgE levels between cases and controls, with a median value of 186.006. In an effort to characterize purported serum IgE levels in healthy, non-allergic adult populations, Nye *et al.* [22] and Barbee *et al.* [23]

Figure 2. Bar chart representing mean level of different immune molecules in cases and control groups.



Parameters	Cases (mean ± SE) N = 60	Control (mean ± SE) N = 30	<i>p</i> value
Total IgE	$186.006 \pm 31.6411 \text{ IU/mL}$	94.523 ± 16.2208 IU/mL	0.012
IL-5	$197.711 \pm 25.9448 \text{ pg/mL}$	$79.407 \pm 8.4614 \text{ pg/mL}$	0.010
IL-4	$347.935 \pm 35.8580 \text{ pg/mL}$	$68.385 \pm 7.7650 \text{ pg/mL}$	0.010
C3	$187.616 \pm 3.3321 \text{ mg/dL}$	$135.400 \pm 8.7847 \text{ mg/dL}$	0.010
C4	$36.776 \pm 1.1853 \text{ mg/dL}$	$23.556 \pm 1.3808 \text{ mg/dL}$	0.010

Table 2. Mean ± SE of IgE, IL-5, IL-4, C3, and C4 levels in serum for patients infested with scabies and controls.

SE: standard error.

found a significant range in serum IgE levels. In general, studies examining humoral immunity in individuals with scabies have yielded conflicting and inconsistent findings [8]. Several researchers have observed higher total IgE levels in cases with common scabies in recent investigations [9,19]. Others claimed that the levels decreased following therapy [24,25] or had no differences [26]. Previous research has demonstrated that scabies infection increases the amount of circulating IgE antibodies, but the findings were quite inconsistent. Only 2% of the 91 OS cases in a more recent investigation with ELISA analysis had circulating IgE antibodies bound to S. scabiei var. canis antigens [27]. In contrast, CS has regularly shown substantial increases in total IgE levels [28]. The total IgE data from the current study appear to be in contradiction with those provided by Walton et al. who claimed that the initial clinical evaluation of a suspected host seemed to have no advantage over total serum IgE [8]. However, the severity of cutaneous lesions was positively correlated with total IgE according to our findings.

The results of the current study showed that except for eosinophils, mean WBC counts in patients with scabies infection increased non-significantly. This is because parasite infection stimulates the host's humoral and cellular immune responses [29,30]. Previous research has suggested that scabies patients have higher total leucocyte counts [1,8,31]. Other studies observed elevated levels of basophils, eosinophils, lymphocytes, and monocytes in scabies patients [32,33]. The current study found that the mean eosinophil count was significantly higher in scabies patients than in controls. This observation may be linked to the presence of allergic reactions, which are among the symptoms of S. scabiei infection and could be a result of the body's cellular response to the parasite infestation [1,8]. The number of inflammatory cells in local tissues and blood circulation during immunological or inflammatory reactions of the host can be affected by extracts of dead or living mites [34]. The current investigation found a marked increase in the levels of inflammatory mediators such as IL-4 and IL-5 in the serum of scabiesinfected patients. Similar results were reported by Abood *et al.* [35].

The inflammatory mediators IL-1, IL-6, IL-8, IL-10, and TNF are produced by dermal microvascular endothelial cells as a result of S. scabiei infestation, as demonstrated by Arlian and Morgan [34]. These mediators are involved in the control of inflammatory and immunological responses. Cadman and Lawrence observed that mast cells, basophils, and eosinophils can be easily drawn to infection sites and draining lymph nodes, where they can produce IL-4 and/or IL-5; which were in charge of starting and maintaining the control of Th2 responses [32]. It has been demonstrated that complement plays a crucial role in the host's defense against a variety of infections [36]. In this study, it was found that patients with scabies infestations had significantly higher levels of C3 and C4. When complement fragments C3a and C4a interact with certain receptors, local inflammatory reactions result. In addition. C3a and C5a can stimulate mast cells to release inflammatory mediators such as histamine and tumor necrosis factor-alpha (TNF-alpha) [18]. Given the significant inflammatory nature of crusted scabies, this finding contradicts Walton's evidence that showed that people with the illness have lower amounts of C3 and C4, and is intriguing [8].

Conclusions

In the present study, scabies infestation generated immunological reactions in patients, including both cellular and humoral immune response. These responses significantly affected the levels of inflammatory mediators, including IL-4 and IL-5, as well as total and differential leukocytes, in patients when compared to the control. Scabies is still regarded as the most serious public health issue with negative social and psychological effects in poor countries and among displaced people.

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Conflict of interests

No conflict of interests is declared.

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