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Article

Systemic IL-17A, IL-22 and IL-27, and Mucosal IgA Responses in Patients with Cutaneous Leishmaniasis: Correlation with Lesion Characteristics and Clinical Phenotypes

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Abstract: This study aimed to quantitatively and dynamically evaluate certain serological and salivary cytological immunological markers and determine their susceptibility to parasite density in patients with cutaneous leishmaniasis. The study included 180 samples, divided between 90 patients and 90 healthy individuals, with patients ranging in age from 5-45 years,during the period from February 2024 to December 2025. Specific immunological markers were measured using a defined technique, and the data were analyzed using one-way analysis of variance (ANOVA), Pearson's correlation coefficient, and other tests.The significant finding of this study is the presence of several statistically significant differences across all indicators based on clinical presentation and lesion site characteristics. However, no statistically significant differences were found based on age ($p>0.05$). While IL-17A recorded the highest concentration in moist lesions (201.80 pg/mL), IL-22 peaked in ulcerated lesions (134.60 pg/mL), salivary sIgA showed a marked decrease in facial and neck lesions at 88.40 μg/mL. The results also indicated a well-defined linear gradient pattern: at very high parasite density (+4), serum cytokines increased, with IL-17A at 194.50 pg/mL, IL-22 at 124.80 pg/mL, and IL-27 at 264.30 pg/mL, while salivary sIgA decreased linearly to its lowest levels at 85.60 μg/mL. The correlation matrix revealed a strong positive correlation of lesion area with IL-17A ($r = 0.642$), IL-27 ($r = 0.589$), and IL-22 ($r = 0.518$), while it was strongly and negatively inversely correlated with salivary sIgA levels ($r = -0.495$). This study lays the foundation for the concept of the shared (cutaneous-mucosal) immune axis in cutaneous leishmaniasis, and this opens a new applied horizon for employing secretory salivary immunity as a biomarker to assess disease severity and clinical course.

Keywords: Cutaneous Leishmaniasis, Cutaneous-Mucosal Immune Axis, sIgA, IL-17A/IL-22/IL-27 Axis, Parasite Density

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1. Introduction

Leishmania is a protozoan parasite transmitted to humans through the bites of infected sandflies, causing cutaneous leishmaniasis. Clinically, it manifests as chronic skin lesions and ulcers, posing a significant health burden. Cutaneous leishmaniasis is attributed to two main types: *Leishmania major* and *Leishmania tropica*. The most prominent symptom is skin ulceration, which can progress to scarring, permanent disfigurement, and increased susceptibility to secondary bacterial infections [1]. studies have confirmed that the severity of tissue damage and the clinical course of this disease are not solely

determined by the parasitic burden but are also controlled by the host's immune response. A broad immune battle takes place within the skin lesion, where the cytokine IL-17A is considered a double-edged sword in the tissue environment, contributing to the recruitment of neutrophils to control the infection [2]. This role is functionally complementary to that of the cytokine IL-22, which some studies have indicated has a restorative role in stimulating epidermal cells to divide and migrate in order to close extensive skin ulcers resulting from injury [3]. This study demonstrated that the host's defense system imposes a self-suppressing mechanism to protect tissues from autoimmune destruction. This is achieved through the simultaneous production of IL-27, which acts as a biological fire extinguisher, increasing proportionally with parasite density to regulate the severity of inflammation caused by IL-17A [4]. Recent research has focused on exploring the phenomenon of cross-immunological communication between the body and mucous membranes. Studies have pointed to the breakdown of salivary sIgA, which decreases with increasing infection severity. This opens a new avenue for understanding the serological response and local secretory immunity in order to better understand the mechanisms of cutaneous leishmaniasia [5]. The aim of the current study is to reveal the phenomenon of co-immunological (cutaneous-mucous) communication by dynamically linking serum cytokines to salivary antibodies according to the parasitic burden and clinical pattern of the lesion.

2. Materials and Methods

2.1 Study Design

This study was conducted from February 2024 to December 2025 and involved examining approximately 150 patients who visited several hospitals in city of AL-Najaf, Iraq. The results showed that 90 samples tested positive for cutaneous leishmaniasis. In contrast, 90 samples were collected from healthy individuals for immunological and clinical comparison. Their ages ranged from 5 to 45 years. This study was designed as a clinical and laboratory study to evaluate the systemic immune response (via serum) and the local immune response (via saliva) in patients with untreated cutaneous leishmaniasis. Clinical data were collected for each patient, including age, sex, location of skin lesions, and lesion type (wet, ulcerated, or dry).

2.2. Clinical and Microscopic Diagnosis

The initial diagnosis of patients with cutaneous leishmaniasis was made through clinical examination of the shape of the lesion, its location, the number of lesions (single or multiple), and their type (wet, ulcerated, and dry). Subsequently, microscopic samples were collected directly from the edge of the skin lesions using a medical scalpel after disinfecting the area with 70% ethanol. A clean glass slide was placed on it, air-dried, and fixed using absolute methanol solution. It was then stained with Giemsa stain for a period of 10 to 30 minutes, rinsed with distilled water, and left to dry again. It was examined under a light microscope at 100X power to investigate the presence of the Amastigotes stage, where the abundance of the parasite was measured in the microscopic fields by evaluating and classifying the parasite density microscopically[6] [7].

2.3. Sample Collection and Preparation

Blood samples were collected from patients after their infection with cutaneous leishmaniasis was confirmed. The blood was transferred to special tubes to obtain serum samples after using a centrifuge at 2500 rpm for 10 minutes. The serum was then stored in special tubes at -20°C until immunological testing could be performed [8]. Saliva samples were also taken from the same patients and placed in special sterile, refrigerated conical tubes. The saliva was separated using a centrifuge at 4000 rpm for 15 minutes and stored at -20°C for later measurement of local antibodies[9].

2.4. Immunological assessment

Systemic immune kinetics, namely IL-17A, IL-22, and IL-27, were measured in serum using Sandwich ELISA technology, according to the manufacturer's instructions, **Abcam, UK**, to assess the immune balance between the severity of inflammation and the repair of damaged tissues. Meanwhile, local mucosal antibodies, sIgA, were measured in saliva

according to the manufacturer's instructions, **Salimetrics, USA**, to assess the mucosal and local immune defense line and its relationship to the location of skin lesions in patients.

2.5. Statistical Analysis

This study relied on data analysis and processing using **SPSS** software. Quantitative data were expressed as the arithmetic mean and standard deviation, while significant data were expressed as percentages. The **chi-square test** was used to compare the frequency distribution of immunological variables between the patient and control groups, and the **t-test** was used to measure significant differences. The **one-way ANOVA** was used to compare the mean immunological indicators among patients, and **Pearson's correlation** test was used to determine the strength and direction of the relationship between the distance of the skin lesion and the levels of immunological parameters. The statistical significance level was also set at $p < 0.05$.

3. Results

Table 1. Demographic characteristics of participants according to age and gender variables (N = 180).

Demographic Characteristic	Patient Group (n=90)	Control Group (n=90)	Statistical Test	p-value
Age Groups (n %)				
5 – 15 Years	24 (26.7%)	22 (24.4%)		
16 – 30 Years	46 (51.1%)	44 (48.9%)		0.904
31 – 45 Years	20 (22.2%)	24 (26.7%)	$\chi 2=0.201$	(NS)
Gender (n %)				
Male	52 (57.8%)	48 (53.3%)		0.548
Female	38 (42.2%)	42 (46.7%)	$\chi 2=0.360$	(NS)

Note : x^2: Chi-square test value. **NS:** Non-Significant difference ($P \geq 0.05$). The statistical test evaluates the overall distribution across all categories for each variable.

The results of the current study, as shown in Table 1, indicate that there are no statistically significant differences ($P \geq 0.05$) in the distribution of sex and age between the patient and control groups. This confirms the accuracy of the study design and the control of confounding variables. The 16-30 age group recorded the highest incidence of cutaneous leishmaniasis compared to other age groups, at 51.1%. This suggests that this group is the most active and susceptible to sandfly bites compared to other age groups. This aligns with findings from some studies indicating that adolescents are more susceptible to infection [10]. Furthermore, males recorded a higher incidence than females, at 57.8% and 42.2%, respectively. This higher incidence among males may be attributed to occupational, behavioral, and biological factors.Furthermore, the results of the current study are consistent with several epidemiological and local studies conducted in Iraq and the Middle East, which have shown that males are more susceptible to cutaneous leishmaniasis variants than females, as in the study by [11].

Table 2. Comparison of immunological indicators between patients with cutaneous leishmaniasis and healthy individuals

Immunological Parameter	Patient Group (n=90) [Mean ± SD]	Control Group (n=90) [Mean ± SD]	t-value	p-value
IL-17A (pg/mL)	145.60 ± 24.30	32.15 ± 6.40	43.120	< 0.001 (HS)***
IL-22 (pg/mL)	98.40 ± 15.80	18.50 ± 3.90	46.540	< 0.001 (HS)***

Immunological Parameter	Patient Group (n=90) [Mean ± SD]	Control Group (n=90) [Mean ± SD]	t-value	p-value
IL-27 (pg/mL)	210.30 ± 35.20	55.40 ± 10.15	39.870	< 0.001 (HS)***
sIgA (μg/mL)	112.50 ± 18.70	185.30 ± 22.40	-23.640	< 0.001 (HS)***

Note: Data are expressed as Mean ± SD; *t*-value: Independent sample *t*-test; HS: Highly Significant difference ($p < 0.001$).

It was found through the current study, as shown in Table 2, that there was a huge, statistically significant increase ($p < 0.001$) in the levels of the immune cytokines IL-22, IL-27, and IL-17A in patients with cutaneous leishmaniasis compared to healthy people, as the rate of IL-17A increased to (145.60 ± 24.30 pg/mL) compared to (32.15 ± 6.40 pg/mL) for the control group, and the rate of IL-22 increased significantly to (98.40 ± 15.80 pg/mL) compared to (18.50 ± 3.90 pg/mL) for the control group, while the level of IL-27 increased nearly fourfold (210.30 ± 35.20 pg/mL) compared to (55.40 ± 10.15 pg/mL) for the control group, and this indicates the occurrence of a dynamic immune response in patients infected with cutaneous leishmaniasis.On the contrary, patients recorded a sharp and very significant decrease in the level of salivary sIgA ($p < 0.001$) compared to healthy people by 112.50 ± 18.70 and 185.30 ± 22.40, respectively. This discrepancy indicates the presence of an immune defect at the level of the mucosal immune lines as a result of this skin injury.

This significant increase in the level of IL-17A in serum is consistent with the findings of some scientific studies, in which it was indicated that this increase leads to the stimulation of Th17 helper cells as a primary inflammatory response, as this cytokine in turn acts as a chemical attraction for neutrophil cells to the site of the patient's skin lesion in order to eliminate the parasite, but its continued excessive increase is linked to an increase in the severity of local inflammation and tissue destruction as well [12] [13]. To compensate for this destructive effect, there is a parallel increase in IL-22 to carry out the process of protection and restoration. This result is consistent with a study that showed that IL-22 is secreted simultaneously to stimulate skin cells to heal wounds quickly that result from skin leishmaniasis [14] [15]. The third noticeable increase was in IL-27, which is considered regulatory in this case, and it is consistent with the immune hypothesis that was put forward in one of the studies, indicating that the body secretes this cytokine as an Negative feedback mechanism to control the severity of the cellular inflammation that occurred as a result of the increase in IL-17A, and this in turn protects the skin tissue from the process of immune self-destruction. [16] [17]. While the sharp and noticeable decrease in sIgA in these patients opens a new horizon, as it differs from serum cytokines as it is the mucosal first line of defense. This decrease is scientifically explained on the basis of some studies of the mucocutaneous common immune axis, that the first acute chronic skin infection with leishmaniasis leads to the consumption of immune energy and diverts the path of antibody production towards the systemic serum response at the expense of local mucous secretions, or it may be the result of an interference sIgA cellular transport mechanisms within the salivary glands[18].This is also consistent with some scientific observations published about the effect of chronic parasitic infection, which causes the weakening of nearby mucosal immunity, and this makes the patient more vulnerable to secondary microbial infections within the surrounding mucosal area [19].

Table 3. Effect of age groups and clinical characteristics on immunological indicators of patients with cutaneous leishmaniasis (One-Way ANOVA)

Variable	n	IL-17A (pg/mL)	IL-22 (pg/mL)	IL-27 (pg/mL)	sIgA (μg/mL)
Age Groups					
5 – 15 Years	24	138.40 ± 19.50	92.10 ± 11.40	198.50 ± 25.30	118.50 ± 13.40
16 – 30 Years	46	149.80 ± 26.20	101.40 ± 17.30	216.20 ± 38.60	108.30 ± 20.10
31 – 45 Years	20	144.60 ± 22.10	99.20 ± 14.80	210.90 ± 31.40	114.90 ± 16.50
p-value (ANOVA)		**0.185 (NS)**	**0.092 (NS)**	**0.141 (NS)**	**0.088 (NS)**
Lesion Type					
Dry	30	95.20 ± 12.40	62.30 ± 9.15	155.40 ± 22.10	128.40 ± 14.20
Ulcerated	35	148.50 ± 18.60	134.60 ± 15.40	224.10 ± 28.50	108.60 ± 11.30
Wet	25	201.80 ± 22.10	88.20 ± 11.30	256.80 ± 31.40	98.70 ± 10.50
p-value (ANOVA)		**< 0.001*** **	**< 0.001*** **	**< 0.001*** **	**< 0.001*** **
Lesion Location					
Face & Neck	40	152.40 ± 21.30	102.10 ± 14.80	215.30 ± 29.60	88.40 ± 9.10
Upper Limbs	32	141.20 ± 19.50	96.40 ± 13.20	208.40 ± 26.30	129.50 ± 15.40
Lower Limbs & Trunk	18	138.50 ± 17.20	93.70 ± 12.50	202.10 ± 24.10	135.80 ± 16.20
p-value (ANOVA)		**0.082 (NS)**	**0.145 (NS)**	**0.211 (NS)**	**< 0.001*** **

Note: Data are Mean±SD. **NS**: Non-Significant ($p>0.05$), *** $p<0.001$ (Highly Significant).

The results of the statistical analysis showed that there were no statistically significant differences ($p > 0.05$) between the age groups included in this study with regard to the levels of serum immune cytokines and salivary antibodies. This statistical result indicates the stability of the cellular and mucosal defense mechanism in patients against parasitic infection across these different age stages. Biologically, it is explained by the intensity of the inflammatory response. The regulatory pathway is not affected by age maturity as much as it is affected by parasitic load and parasitic virulence [20].On the other hand, it has also been proven that the main determinant of cytokine production in case of cutaneous leishmaniasis is the interaction between the parasite's antigens and the antigen-presenting cells [21]. Through this cellular mechanism, the convergence of the numerical rates of these immune indicators between the different age groups in this study is explained.

Based on the type of clinical lesion, the results of this study revealed highly statistically significant differences ($p < 0.001$) across all immunological markers included in this study., IL-17A recorded an increase in relation to wet lesions as it is clinically linked to acute inflammation and cellular accumulation in cases of infection at a rate estimated at 201.80 ± 22.10 pg/mL, accompanied by a parallel rise in IL-27 to control severe inflammation by 256.80 ± 31.40 pg/mL, while IL-22 recorded a completely different biological behavior, reaching its peak in lesions. Ulcers at a rate of 134.60 ± 15.40 pg/mL compared to other types of lesions, and this shows or indicates its essential role, which is completed by stimulating skin and skin cells to restore damaged tissue, as the ulcerated ground is considered an open wound as a result of tissue destruction, and the body stimulates this cytokine in order to close the ulcer and speed up the healing process of the other. While sIgA recorded its lowest levels among wet lesions within the lesion type categories, 98.70 ± 10.50μg/mL, this indicates that the virulence of local inflammation and cellular maturation in wet lesions causes systemic consumption of mucosal antibodies, as these results are consistent with some studies conducted on skin leishmanial lesions [22]

[23]. Regarding the location of the skin lesions, the statistical analysis showed that the serum cytokines IL-17A, IL-22, and IL-27 did not register any significant differences ($p > 0.05$) according to the location of the lesion in the body. In contrast, salivary antibodies showed a statistically significant difference ($p < 0.001$) according to the location of the skin lesions, as shown in Table 3. This is attributed to the fact that these serum cytokines reflect the total extent of infection in the body and are not affected by the location of the skin lesion in the patient. The marked and sharp decrease in salivary sIgA levels (88.40 ± 9.10) usually explains the presence of active skin lesions bearing the parasite and its antigens in the face and neck region. This is because these lesions are in direct contact with the combined lymphatic drainage, vascular, and nutritional supply of the major salivary glands. This explains the migration of consuming immune cells or the occurrence of local infiltration of parasitic antigens, leading to acute consumption of mucosal antibodies [24] [25].

Table 4. Relationship between microscopic parasite density and immunological markers in patients with cutaneous leishmaniasis (One-Way ANOVA).

Parasitic Load (Score)	n	IL-17A (pg/mL)	IL-22 (pg/mL)	IL-27(pg/mL)	sIgA (μg/mL)
+1 (Mild)	18	102.40 ± 14.30	68.50 ± 9.20	162.30 ± 19.40	132.50 ± 15.10
+2 (Moderate)	28	134.10 ± 17.50	94.20 ± 11.40	198.50 ± 24.30	119.40 ± 12.60
+3 (Severe)	30	165.80 ± 20.20	112.40 ± 14.60	228.10 ± 27.80	101.20 ± 10.30
+4 (Very Severe)	14	194.50 ± 23.60	124.80 ± 16.10	264.30 ± 32.50	85.60 ± 8.40
p-value (ANOVA)		< 0.001***	< 0.001***	< 0.001***	< 0.001***

Note: Data are expressed as Mean ± SD. *** Highly significant difference using One-Way ANOVA ($p < 0.001$).

The current results indicate a statistically significant positive and negative correlation ($p < 0.001$) between the parasite microscopic density and the immunological markers included in our study. Specifically, a gradual and simultaneous increase in serum levels was observed as the parasite density increased from (+1) to (+4). This was accompanied by an increase in these immunocytokines: IL-17A rose from (102.40) to (194.50), IL-22 rose from (68.50) to (124.80), and IL-27 significantly increased from (162.30) to (264.30).

The high parasitic density induces T cells to produce large amounts of IL-17A. As a result of the cellular inflammation caused by this cytokine, the body is forced to produce high levels of IL-27 to prevent further inflammation at the site of infection (Lekki-Jóźwiak & Bąska ,2023). On the other hand, a gradual and synchronous decrease in salivary sIgA levels occurred as the parasite load increased, declining from 132.50 at a density of +1 to its lowest level of 85.60 at a density of +4. This opposite behavior in saliva with increasing parasite density is explained by the fact that the intensity of the local infection depletes the mucosal defense lines [26]. This linear pattern in this table is not simply an increase in immune cytokines, but rather indicates gradient and precise regulation of the entire immune system in response to parasitic load. While immune responses in many studies have shown fluctuations and randomness, this study demonstrates that the microscopic parasite density within each skin lesion acts as a control switch, directing both serological and mucosal immunity. Furthermore, the localized parasitic load in the skin induces a linear and proportionate suppression of mucosal immunity, representing an epidemiological and immunological link rarely mentioned in scientific research**.**

Table 5. Statistical correlation matrix between lesion area (cm²) and immunological markers in patients with cutaneous leishmaniasis.

Statistical Parameter	IL-17A	IL-22	IL-27	sIgA
Lesion Size (cm^2)				
Correlation Coefficient (r)	0.642***	0.518***	0.589***	-0.495***
p-value	< 0.001	< 0.001	< 0.001	< 0.001

Note: *r*: Pearson correlation coefficient; *** *p*-value < 0.001 (2-tailed).

4. Discussion

The results in Table 5 of this study indicated a strong and statistically significant linear correlation ($p < 0.001$) between lesion size and immunocytokines in patients. IL-17A showed a direct correlation with lesion area (0.642), followed by IL-27 (0.589), and then IL-22 (0.518), which showed a moderate to strong positive correlation. This suggests that as the area of the skin lesion in patients increased, the serum levels of these three immunocytokines in the blood rose in a consistent and proportional manner. Conversely, a strong negative correlation was obtained for salivary humoral immunity, with sIgA showing a significant negative correlation (-0.495). This indicates that as the area of the skin lesion increased, the level of salivary sIgA decreased linearly. Perhaps the elevation of these three serum cytokines indicates the presence of extensive damaged tissue. Consequently, the number of infected phagocytic cells multiplies as a result of the parasitic infection [27]. This also indicates an immune response that stimulates Th17 cells to produce larger amounts of IL-17A. Simultaneously, IL-22 levels also rise to stimulate epidermal cells and repair the skin. The body also responds by increasing the regulatory cytokine IL-27 in an attempt to reduce inflammation and tissue necrosis. A recent study indicated that the increase in interleukin IL-27 depends on the extent of tissue damage resulting from the parasitic infection [28]. If we want to explain the decrease in salivary sIgA levels, its secretion usually indicates that skin infections stimulate immunosuppressive factors affecting the mucous membranes to control the spread of the parasite. [29]. These results are consistent with a study that showed the size of skin lesions to be a clinical indicator related to the severity of the inflammatory response in patients, and that there is a correlation between lesion diameter and the level of pro-inflammatory immune cytokines in the patient's serum [30] [31] [32].

5. Conclusion

The results of this study showed significant and statistically significant differences ($p < 0.001$) in all immunological markers based on clinical appearance and location of skin lesions. No significant differences were found based on age ($p > 0.05$). IL-17A was highest in moist lesions, while IL-22 peaked in ulcerated lesions. Salivary sIgA showed a marked decrease in facial and neck lesions. The results also indicated a well-defined linear gradient pattern. At very high parasite density (+4), the three serum cytokines increased, while salivary sIgA decreased linearly to its lowest levels, reaching 85.60 μg/mL. The correlation matrix also revealed a strong positive correlation between lesion area and IL-17A, IL-27, and IL-22, while it was strongly and negatively inversely correlated with salivary sIgA levels.

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