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The Pivotal Role of Interleukin-17 in the Pathogenesis of Systemic Lupus Erythematosus

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ABSTRACT

Background*: Systemic lupus erythematosus is a typical autoimmune illness distinguished by the development of many autoantibodies against various cellular components. Interleukin-17 (IL-17) is a powerful proinflammatory cytokine that has a key role in host immunological defense, tissue healing, and the etiology of inflammatory diseases.* ***Purpose:*** *This study aimed to investigate the significant role of IL-17 in SLE patients and compare its level between SLE patients and healthy controls.* ***Methods****: 126 participants were enrolled, including SLE patients with ages 10 to 60) years assembled from Merjan Teaching Hospital and AL-qassim general hospital during the period from 1 August 2024 to 31 January 2025. and matched healthy controls. Demographic data and IL-17 levels were collected and analyzed using appropriate non-parametric statistical tests to identify significant differences between groups. The concentrations of IL-17 were assessed using a sandwich (ELISA) test and a standard arc. The results were as follows, as stated by the enterprise (SUNLONG). This kit has been pre-coated with an antibody specific to IL-17.* ***Results****: Consistent with previous reports, the majority of SLE patients were female (96.8%) and primarily in the 21–40-year age range. While the sex distribution was similar between SLE cases and controls, a significant difference in age distribution was observed (p = 0.027). IL-17 levels (90.30) pg/ml are significantly higher in SLE patients compared to controls (36.70) pg/ml (p < 0.001), suggesting a foundation for future therapeutic strategies targeting this cytokine. The results was obtained by the chi-squared test. Appropriate analytical software (IBM SPSS V26) was used to show the descriptive analysis and statistics* ***Implications****: Further investigations should explore the synergistic effects of IL-17 with other inflammatory cytokines, particularly in lupus nephritis and neuropsychiatric SLE. Since the study suggests that IL-17 expression correlates with organ involvement, targeted therapies could be tailored to patients exhibiting IL-17-driven inflammation.* ***Additional materials****: the research was approved by the local Department of Ministry of Health, Babylon Health Directorate committee:1542.* ***Conclusion:*** *research demonstrates a strong association between IL-17 and lupus nephritis and its contribution to neuropsychiatric manifestations of SLE. IL-17 is a possible biomarker for disease severity, emphasizing its involvement in chronic inflammation mediated by T-helper 17 (Th17) cells. By elucidating the inflammatory pathways driven by IL-17, this study advances the body of scientific knowledge on SLE pathophysiology and provides a foundation for future therapeutic strategies targeting this cytokine.*

Keywords: Systemic lupus erythematosus, Interleukin-17, Cytokines

Article Information

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INTRODUCTION

Systemic lupus erythematosus is a prolonged immune-mediated disease marked by appearance of autoantibodies towards nuclear antigens, and immune complex deposition, leading to chronic inflammation and immune-mediated injury at classic target organs such as skin, joints, and kidneys. Approximately 3.4 million people worldwide have received a diagnosis of SLE [1]. Interleukin-17 (IL-17) is a cytokine that promotes inflammation and contributes strongly to the pathophysiology of systemic lupus erythematosus. Elevated levels of IL-17 have been observed in SLE patients, and its expression correlates with disease activity and organ involvement. Serum of IL-17 value in SLE case are high and have a favorable correlation with disease activity [2]. IL-17 was first discovered approximately 30 years ago. Members of this family have various biological functions, including driving an inflammatory cascade during infections and autoimmune diseases, as well as boosting protective immunity against various pathogens. IL-17 is a highly versatile proinflammatory cytokine necessary for vital processes, including host immune defenses, by inducing cytokines and chemokines, recruiting neutrophils, modifying T-cell differentiation, and stimulating the production of antimicrobial proteins, tissue repair, inflammatory disease pathogenesis, and cancer progression. IL-17-induced systemic lupus erythematosus in diagnosis and treatment [3] IL-17 has been implicated in various organ manifestations of SLE, such as contributing to the development of lupus nephritis by promoting inflammation and tissue damage in the kidneys. Additionally, IL-17 is associated with central nervous system involvement in SLE, suggesting its role in neuropsychiatric manifestations of the disease [4] IL-17 represents a potential therapeutic target. Interventions targeting the inhibition of IL-17 or its signaling pathways may help reduce inflammation and prevent organ damage in SLE patients[5]. Knowledge Gaps for these research mainly is mechanistic Specificity: While IL-17's association with inflammation is well-documented, the precise molecular pathways by which it exacerbates tissue damage in different organs (especially CNS and kidneys) remain insufficiently defined and temporal Relationship: It's unclear whether IL-17 elevation precedes clinical flares or merely reflects ongoing inflammation, limiting its use as a predictive biomarker.

METHODS

Study design: Case-Control study

Timeline: a period from 1st August 2024 to 31th January 2025.

Specimens' collection:

63 blood samples for IL-17 identified from cases suffering from systemic lupus erythematosus as well as control selection 63, both sexes with ages varying between 10 and 60 years in AL-Merjan teaching hospital and Al-qassim general hospital a period from 1st August 2024 to 31th January 2025.

Diagnostic criteria:

Patients were enrolled from both the Rheumatology Consultation Clinic and the Biological Injection Unit at Marjan Teaching Hospital. Data were collected through in-person interviews, using a structured questionnaire developed by the researcher. Each participant provided a venous blood sample (5 ml) following the interview.

ELISA protocol specifics:

The concentrations of IL-17 were assessed using a sandwich (ELISA) test and a standard arc. The results were as follows, as stated by the enterprise (SUNLONG). This kit has been pre-coated with an antibody specific to IL-17

Demographic Parameters

Sex and age distributions were recorded directly from patient records. Data were categorized into age groups (11–20, 21–30, 31–

40, and 41–50 years) to assess the distribution among SLE patients and controls.

Serology based techniques

Levels of IL-17 were assessed using a sandwich (ELISA) test and a standard arc. The results were as follows, as stated by the enterprise (SUNLONG). This kit has been pre-coated with an antibody specific to IL-17. To assess IL-17 levels, a sandwich ELISA technique was used. The microplate wells were pre-coated with IL-17-specific antibodies. First, a series of standards was prepared by serial dilution to generate a range of known concentrations. Patient and control samples were then diluted and pipetted into designated wells alongside the standards. Following sample addition, the plate was incubated at 37°C for 30 minutes to allow antigen binding. After incubation, the wells were washed multiple times to remove unbound components. A horseradish peroxidase (HRP)-linked detection antibody, specific to IL-17, was added and allowed to bind. Another incubation step at 37°C for 30 minutes followed, after which the wells were washed again to eliminate excess conjugate. A chromogenic substrate was then introduced, initiating a color reaction in wells where IL-17 was present. After a 15-minute incubation, the reaction was halted with a stop solution, turning the color from blue to yellow. Absorbance was measured at 450 nm using a microplate reader. IL-17 concentrations in the samples were determined by comparing absorbance values to the standard curve, accounting for dilution factors.

Statistical method

The statistical tools were conducted using SPSS version 28 (IBM Corp., Armonk, NY, USA) or an equivalent statistical software package was used to process and evaluate the data. The differences between the systemic immune responses to systemic lupus erythematosus were analyzed using a paired Z-test, and Mann-Whitney test. Significances are defined as p-values of fewer than 0.05 .

RESULTS

Table 1. shows a comparative analysis of SLE patients (cases) and healthy individuals (controls) based on sex and age, The majority of participants in both groups are female (96.8%), with only 3.2% being male. This identical distribution in both cases and controls results in a p-value of 1.000, referring to no statistically significant difference in SLE occurrence based on sex. The age distribution varies between cases and controls, with the highest proportion of participants falling within the 21–40 age range. Among SLE patients, (34.9%) are aged 21–30 years, while (31.7%) are in the 31–40 age group. In contrast, the control group shows a higher percentage in these categories, with (42.9%) in the 21–30 range and (44.4%) in the 31–40 range. Notably, a significant difference is observed in the 41–50 age group, where (28.6%) of cases belong, compared to only (7.9%) in controls. The p-value for age distribution is 0.027, suggesting a statistically significant association between age and SLE occurrence.

Table 2. shows a comparative analysis of inflammatory markers between systemic lupus erythematosus (SLE) disease cases and healthy controls using the Mann-Whitney U test. The markers analyzed include IL-17. The mean rank for IL-17 in SLE patients (90.30 pg/ml) was significantly higher than in the control group (36.70 pg/ml).

The Mann-Whitney U test value was 296.000, with a Z-score of -8.240 and a p-value of 0.000, referring to a statistically significant difference aligning to recent studies have indicated that individuals with systemic lupus erythematosus (SLE) exhibit higher levels of interleukin-17 (IL-17) compared to healthy individuals. For instance, a 2021 study analyzed blood IL-17 Levels in 30 SLE patients and discovered significantly higher amounts than in healthy control as those of study by [10].

Table 1. Distribution of SLE patients and control according to age groups and sex.

Variable		Case (n=63)	Control(n=63)	Total	P-Value
Sex	Female	61(96.8%)	61(96.8%)	122(96.8%)	1.000
	Male	2(3.2%)	2(3.2%)	4(3.2%)	
	Total	63(50%)	63(50%)	126(100%)	
Age groups/ years	11-20	3(4.8%)	3(4.8%)	6(4.8%)	0.027
	21-30	22(34.9%)	27(42.9%)	49(38.9%)	
	31-40	20(31.7%)	28(44.4%)	48(38.1%)	
	41-50	18(28.6%)	5(7.9%)	23(18.3%)	
	Total	63(50%)	63(50%)	126(100%)	

Table 2. Comparison of Inflammatory Markers Between SLE Patients and Controls.

Parameters	Case (n=63) Mean Rank	Control(n=63) Mean Rank	Mann-Whitney	Z	P-Value
IL-17 (pg/ml)	90.30	36.70	296.000	-8.240-	0.000
* Level of significant variance (P < 0.05), P values were computed by the Mann-Whitney test					

DISCUSSION

Table 1 shows Sex Distribution: No Significant Difference (p = 1.000). The study shows that 96.8% of SLE patients and healthy controls are female, with only 3.2% being male. The absence of a statistically significant difference suggests that the study population has an inherently high proportion of female participants, making it difficult to assess whether SLE disproportionately affects women compared to men. However, previous research has established that SLE is more common in women, with a women-to-men ratio of about 9:1. Possible reasons for this female predominance: Hormonal influence: Estrogen is thought to contribute to immune system dysregulation, increasing susceptibility to autoimmune diseases aligning to [6] delves into how sex hormones impact the pathogenesis and clinical characteristics of SLE. The study highlights that estrogen can enhance immune responses by promoting the activation and survival of autoreactive B cells and the production of autoantibodies, contributing to the development and exacerbation of SLE.

Genetic factors: The X chromosome carries immune-related genes, and since females have two X chromosomes, this could increase the risk. Immune system differences: Females generally have stronger immune responses, possibly predisposing them to autoimmunity similar to [7] shows by its study that Females possess two X chromosomes, while males have one X and one Y chromosome. Although one X chromosome in females is typically inactivated to balance gene expression, some immune-related genes can escape this inactivation, leading to a double dose of these genes in females. This increased expression can enhance immune responsiveness, potentially increasing susceptibility to autoimmune diseases.

Age Distribution: Significant Association (p = 0.027). Most SLE patients fall within the 21–30 (34.9%) and 31–40 (31.7%) age groups, which aligns with the peak onset age reported in most epidemiological studies. The significant difference is observed in the 41–50 age group, where 28.6% of SLE patients belong, compared to only 7.9% of controls. Possible Reasons for Age-related Differences: Peak Onset Age: SLE typically develops in young adulthood (15–45 years), which explains the higher proportion of cases in the 21–40 range. This is the period when hormonal activity is at its peak, particularly estrogen, which plays a crucial role in immune system regulation and may aid in the onset of the disease [8]. Delayed Diagnosis in Older Patients (41–50 years group) The significant difference in the 41–50 group suggests that some SLE cases may have been undiagnosed or misdiagnosed earlier, leading to an accumulation of cases in this age range. Older patients may have atypical presentations, delaying recognition [9]. Environmental and Occupational Exposures:

Table 2. The mean rank for IL-17 in SLE patients (90.30) was markedly higher than in the control group achieved a score of 36.70. The results from the Mann-Whitney U test were 296.000, accompanied by a Z-score of -8.240 and a p-value of 0.000, indicating a notable difference. IL-17 Levels in SLE Patients (Higher Than Controls). Significance IL-17 is crucial in autoimmune inflammation by activating and attracting immune cells, which leads to tissue damage. Recent studies have indicated that individuals with systemic lupus erythematosus (SLE) exhibit higher levels of interleukin-17 (IL-17) compared to healthy individuals. For instance, a 2021 study analyzed blood IL-17 Levels in 30 SLE patients and discovered significantly higher amounts than in healthy controls.[10]. In a similar vein, a 2020 study involving 60 adult SLE patients reported increased IL-17 levels, suggesting that this cytokine might have a key role in SLE progression [11]. These findings underscore the importance of IL-17 in the inflammatory mechanisms linked to SLE. Increased levels of Interleukin 17 in patients with SLE indicate enhanced activation of Th17 cells, a subset of T-helper cells associated with autoimmune disorders. Recent research has emphasized the significance of IL-17 and T-

helper 17 cells in the development of systemic lupus erythematosus (SLE). A meta-analysis released in 2024, which reviewed 35 studies involving 2,617 SLE patients, found elevated levels of T-helper 17 cells, a higher Th17/Treg ratio, and increased amounts of IL-17, IL-21, IL-6, and IL-10 in SLE patients in comparison to healthy individuals. In contrast, levels of T transforming growth factor-beta [TGF-β] were found to be lower. This discrepancy implies that the enhanced activation of Th17 cells plays a role in the autoimmune responses' characteristic of SLE [12].

Another investigation examined the role of signal transducer and activator of transcription 3 [STAT3] signaling in SLE. The researchers discovered elevated IL-17 concentrations and an increased count of Th17 cells in SLE patients. They also observed that STAT3 is essential for the differentiation of Th17 cells, while the suppressor of cytokine signaling 3 (SOCS3) negatively influences this process. These results imply that dysfunction in the STAT3/IL-17 pathway may play a part in Th17 cell activation in SLE. [13]. Collectively, these studies suggest that elevated IL-17 value in SLE cases are linked to increased Th17 cell activation, highlighting this pathway's role in the disease's development.

The excessive expression of IL-17 has been associated with the severity of disease in SLE, linking it to kidney impairment (lupus nephritis) and systemic inflammation. Recent studies have shown a strong relationship between heightened interleukin-17 (IL-17) levels and the worsening of symptoms in systemic lupus erythematosus (SLE), especially regarding kidney complications such as lupus nephritis (LN) aligning with study publication in 2024 about evaluated serum IL-17 value in LN cases and SLE cases without nephritis [14]. In addition, IL-17 contributes to the persistence and maturation of B cells, promoting their capacity to produce antibodies. This activity may intensify the production of autoantibodies, which is a characteristic feature of SLE. Furthermore, a disrupted balance between Th17 cells and regulatory T cells (Tregs) is thought to play a significant role in the breakdown of immune self-tolerance observed in lupus [15].

CONCLUSION

The current investigation contributes to the understanding of interleukin-17 (IL-17) in the pathophysiology of systemic lupus erythematosus. The results indicate that IL-17 levels in the blood are markedly increased in SLE cases compared to healthy, underscoring its role in disease activity and organ impairment. These results align with earlier studies that show a notable connection between IL-17 and lupus nephritis, along with its involvement in the neuropsychiatric dimensions of SLE. This research enhances our insight into IL-17 as an important biomarker for disease intensity and emphasizes its role in the chronic inflammation associated with T-helper 17 (Th17) cells. By clarifying the inflammatory pathways influenced by IL-17, this study enriches the existing scientific framework on SLE pathophysiology and lays the groundwork for future therapeutic approaches focused on this cytokine.

Research Limitations

1. Small sample size and restricted geographical coverage: One notable limitation of this study is the relatively small sample size, which may restrict the generalizability of the findings. With fewer participants, statistical power is reduced, making it more challenging to detect subtle associations or control for potential confounding variables. This limitation should be considered when interpreting the results, and future research with larger cohorts is recommended to validate and expand upon these observations.
2. The cross-sectional design reduces the ability to monitor disease progression.

3. Insufficient functional investigation of IL-17 signaling pathways.
4. Potential complicating factors, such as medication usage : One key limitation of this study lies in the potential influence of ongoing pharmacological treatments on IL-17 expression levels. Since many participants were under immunosuppressive or corticosteroid therapy, it is possible that these medications modulated cytokine activity, thereby affecting serum IL-17 concentrations. This factor may have masked the natural variations linked to disease activity, and thus, should be considered when interpreting the results.
5. Gender disparity among the study population.

Recommendations for Future Research

1. Longitudinal studies monitor IL-17 levels over time.
2. Larger, multi-center research with greater application.
3. Mechanistic research on the involvement of IL-17 in SLE pathogenesis.
4. Clinical studies for IL-17-targeted therapeutics.
5. Examining IL-17 expression in male SLE patients.

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Ethical approval

The present study Which is conducted by authors (Duaa Sami Segatri[1] , Dr-Eman Hasani AL- Salami[2]) was approved by the Ministry of Health, Babylon Health Directorate Committee (Approval No. 1542) and the local Department of Medical Microbiology committee. All the patients were informed about the aim of the present work and the possibility of publication of the results of the outcome of the study. All the patients willingly agreed to participate and a written consent to indicate their willingness to participate has been signed by all of them.

Statement of Permission and Conflict of Interests

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