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CLINICAL AND IMMUNOLOGICAL INSIGHTS INTO THE ROLE OF INTERLEUKIN-6 IN SYSTEMIC SCLEROSIS

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КЛИНИЧЕСКИЕ И ИММУНОЛОГИЧЕСКИЕ АСПЕКТЫ РОЛИ ИНТЕРЛЕЙКИНА-6 ПРИ СИСТЕМНОЙ СКЛЕРОДЕРМИИ

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TIZIMLI SKLERODERMIYADA INTERLEYKIN-6 NING ROLI: KLINIK VA IMMUNOLOGIK TAHLIL

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Цель: *оценка клинического и иммунологического значения интерлейкина-6 у пациентов с системной склеродермией и его связи с активностью заболевания, степенью тяжести и поражением внутренних органов.* ***Материал и методы:*** *в исследование включены 79 пациентов с системной склеродермией и 30 здоровых лиц. Концентрацию ИД-6 в сыворотке крови определяли методом ИФА. Клиническое обследование включало оценку длительности заболевания, кожный счёт по модифицированной шкале Роднана (mRSS) и поражения внутренних органов.* ***Результаты:*** *уровень ИЛ-6 у пациентов с ССД был значительно выше, чем у лиц контрольной группы (p<0,001). Повышенные значения ИЛ-6 коррелировали с диффузной формой заболевания, высоким mRSS, интерстициальным заболеванием лёгких и увеличением воспалительных показателей (СРБ, СОЭ).* ***Выводы:*** *повышенный уровень ИЛ-6, который отражает активные воспалительные и фибротические процессы при системной склеродермии, может служить надёжным биомаркером активности заболевания и поражения органов. Регуляция пути ИЛ-6 представляет собой перспективное направление в терапии системной склеродермии.*

Ключевые слова: *системная склеродермия, интерлейкин-6, модифицированная шкала кожного счета Роднана, С-реактивный белок.*

Maqsad: *tizimli sklerodermiya bilan kasallangan bemorlarda interleykin-6 darajasining klinik va immunologik ahamiyatini o'rganish hamda uni kasallik faolligi, og'irligi va ichki a'zolar zararlanishi bilan bog'liqligini baholash.* ***Material va usullar:*** *tadqiqotga TS tashxisi qo'yilgan 79 nafar bemor va 30 nafar sog'lom shaxs jalb qilindi. Qon zardobida IL-6 miqdori ELISA usuli bilan aniqlangan. Klinik baholashda kasallik davomiyligi, Rodnan teri shkalasi (mRSS) va ichki a'zolar zararlanishi o'rganildi. Laborator tahlillar yallig'lanish markerlari va immun profillarni o'z ichiga olib, ularning IL-6 darajasi bilan bog'liqligi aniqlangan.* ***Natijalar:*** *tizimli sklerodermiya bemorlarida IL-6 darajasi sog'lom shaxslarga nisbatan sezilarli darajada yuqori ekanligi qayd etildi (p<0.001). Yuqori IL-6 darajalari diffuz teri shakli, yuqori mRSS bali, o'pkaning interstitsial kasalligi va yallig'lanish markerlari (SRO, ECHT) bilan bog'liq ekanligi aniqlandi.* ***Xulosa:*** *IL-6 ning oshishi tizimli sklerodermiyada faol yallig'lanish va fibroz jarayonlarini aks ettiradi hamda kasallik faolligi va ichki a'zolar zararlanishining ishonchli biomarkeri bo'lishi mumkin. IL-6 yo'lini modulyatsiya qilish tizimli sklerodermiyani davolashda istiqbolli terapevtik yo'nalish hisoblanadi.*

Kalit so'zlar*: tizimli sklerodermiya, interleykin-6, Rodnan teri shkalasi, C-reaktiv oqsil.*

Systemic sclerosis (SSc) is a rare but severe autoimmune connective tissue disease characterized by widespread vascular abnormalities, immune system dysregulation, and progressive fibrosis of the skin and internal organs. Although the prevalence of SSc varies geographically, it is estimated to affect approximately 50-300 individuals per million population, predominantly women in their fourth to sixth decades of life [1,3]. Despite its low prevalence, SSc is associated with significant morbidity and mortality, largely due to pulmonary, cardiac, and renal complications, making it a major clinical and research priority in rheumatology [2].

The pathogenesis of SSc is multifactorial, involving a complex interplay between genetic susceptibility, environmental triggers, epigenetic modifications, immune activation, and endothelial dysfunction. Early endothelial injury, driven by autoimmune-mediated inflammation and oxidative stress, leads to persistent vascular dysfunction, impaired angiogenesis, and tissue ischemia [5-7]. These vascular abnormalities create a pro-inflammatory microenvironment that promotes immune cell infiltration, including activated T and B lymphocytes, macrophages, and dendritic cells. The subsequent activation of fibroblasts and differentiation into myofibroblasts results in excessive synthesis and deposition of extracellular matrix components, predominantly collagen, leading to irreversible tissue fibrosis [4,8].

Cytokines serve as critical mediators in the pathological processes of SSc. Among them, interleukin-6 (IL-6) has emerged as a central regulator linking immune dysregulation, vasculopathy, and fibrosis. IL-6 is produced by multiple cell types implicated in SSc pathogenesis, including T and B lymphocytes, monocytes, endothelial cells, and fibroblasts. Acting through classic and trans-signaling pathways, IL-6 activates JAK/STAT3, MAPK, and PI3K/Akt cascades, promoting fibroblast proliferation, myofibroblast differentiation, and increased production of collagen and other extracellular matrix proteins. In addition to fibrotic processes, IL-6 contributes to endothelial activation and apoptosis, enhances the expression of adhesion molecules, and perpetuates a pro-inflammatory milieu, thereby amplifying vascular injury. Clinically, elevated serum and tissue IL-6 levels have been consistently associated with disease activity, extent of skin involvement assessed by the modified Rodnan skin score (mRSS), interstitial lung disease, and other organ complications in SSc patients [9,10]. Moreover, IL-6-driven pathways have been implicated in immune cell polarization and B cell hyperactivity, further sustaining autoimmunity and chronic inflammation. This dual role of IL-6 in both immune regulation and fibrosis underscores its potential as a biomarker for disease activity and as a therapeutic target. Indeed, pharmacological blockade of IL-6 signaling, for example with monoclonal antibodies such as tocilizumab, has

demonstrated clinical efficacy in reducing skin fibrosis and slowing progression of interstitial lung disease in clinical trials, highlighting the translational relevance of understanding IL-6-mediated mechanisms.

Given its central involvement in multiple pathogenetic pathways, elucidating the clinical and immunological significance of IL-6 in SSc is critical. A detailed understanding of IL-6 signaling not only provides insight into disease mechanisms but also informs potential therapeutic strategies aimed at modulating inflammation and fibrosis, offering hope for improved outcomes in a disease historically associated with limited treatment options.

Purpose of the study

To evaluate the clinical and immunological significance of interleukin-6 in patients with systemic sclerosis and its relationship with disease activity, severity, and organ damage.

Material and methods

This study was conducted at the Tashkent City Hospital No. 3 (Tashkent, Uzbekistan) between 2022-2025. A total of 79 patients fulfilling the 2013 EULAR/ACR-EUSTAR classification criteria for systemic sclerosis (SSc) were consecutively enrolled. In parallel, 30 age- and sex-matched healthy individuals without autoimmune or fibrotic disease history were included as a control group. All participants gave written informed consent. The study protocol was approved by the Institutional Ethics Committee of Tashkent City Hospital No. 3.

For SSc patients, demographic data (age, sex), disease duration (time from first non-Raynaud's symptom), SSc subtype (limited vs diffuse), and presence of internal organ involvement (interstitial lung disease, pulmonary arterial hypertension, cardiac involvement, renal crisis) were recorded. Skin involvement was assessed by the modified Rodnan Skin Score (mRSS) – a semi-quantitative clinical tool in which 17 body areas are each rated from 0 (normal) to 3 (severe thickening) by an experienced rheumatologist, giving a maximum possible total of 51. The mRSS provides a validated measure of skin fibrosis severity and correlates with disease activity and internal organ involvement. Peripheral venous blood was collected from all participants following overnight fasting. Serum was separated and stored at -80ºC until analysis. Interleukin-6 concentration was measured using a commercially available enzyme - linked immunosorbent assay (ELISA) kit [manufacturer name, catalogue number], according to the manufacturer's instructions. The assay sensitivity was [insert value] pg/mL, intra- and inter-assay coefficients of variation were < 10%. C-reactive protein (CRP) was measured by high - sensitivity immunoturbidimetric assay [insert instrument/model], and results expressed in mg/L. Erythrocyte sedimentation rate (ESR) was determined by the Westergren method and expressed in mm/hour. Additional routine laboratory parameters included: complete blood count, liver and renal function tests.

Results

The study included 79 patients who were treated as inpatients at Tashkent City Clinical Hospital No. 3 between 2022 and 2025. Of these, 73 patients (92.4%) were female and 6 patients (7.6%) were male. All patients were diagnosed with systemic sclerosis according to the 2013 ACR/EULAR classification criteria, with additional confirmation using the EUSTAR (European Scleroderma Trials and Research group, 2016) criteria. At the time of examination, the mean age of patients was 43.2±2.7 years, and the mean disease duration was 6.8±1.7 years. Based on the clinical form of systemic sclerosis, patients were divided into two groups: Group 1: patients with diffuse systemic sclerosis (n=39); Group 2: patients with limited systemic sclerosis (n=40).

To investigate the immunological features of systemic sclerosis, serum IL-6 levels were measured in both patient groups. In patients with diffuse systemic sclerosis, IL-6 concentrations were found to be approximately tenfold higher compared to healthy controls and threefold higher compared to patients with limited systemic sclerosis (Table).

Table

IL-6 levels in study groups

Groups	IL-6, pg/ml	p
Healthy individuals, n=30	3,8±0,87	
Diffuse systemic sclerosis, n=39	35,2±5,1	pa<0,05; pэ<0,001
Limited scleroderma, n=40	12,1±2,8	pэ<0,05
All patients, n=79	23,5±3,95	pэ<

Note. re – indicates statistically significant differences compared with healthy controls; ra – indicates statistically significant differences compared with Group 2 (patients with limited systemic sclerosis).

This significant elevation indicates pronounced and persistent inflammatory activity and is consistent with the observed internal organ involvement in this group. Notably, patients with limited systemic sclerosis also demonstrated a fourfold increase in IL-6 levels relative to healthy individuals, highlighting that even the limited form is associated with a measurable systemic inflammatory response.

When comparing the proportion of patients with elevated IL-6, 84.6% of those with diffuse systemic sclerosis exhibited increased cytokine levels, whereas 52.5% of patients with limited systemic sclerosis showed elevated IL-6 (Fig. 1). These findings suggest that IL-6, as a pro-inflammatory cytokine, is particularly elevated in diffuse disease and may reflect higher disease activity.

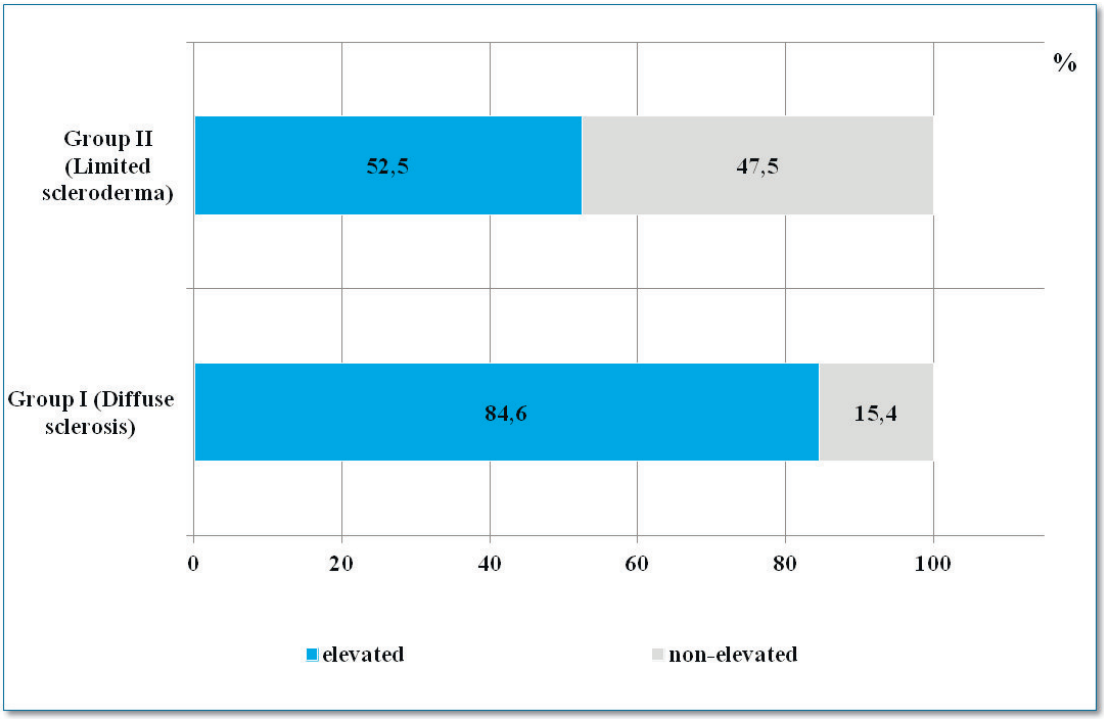


Fig. 1. Il-6 levels according to the clinical form of systemic sclerosis.

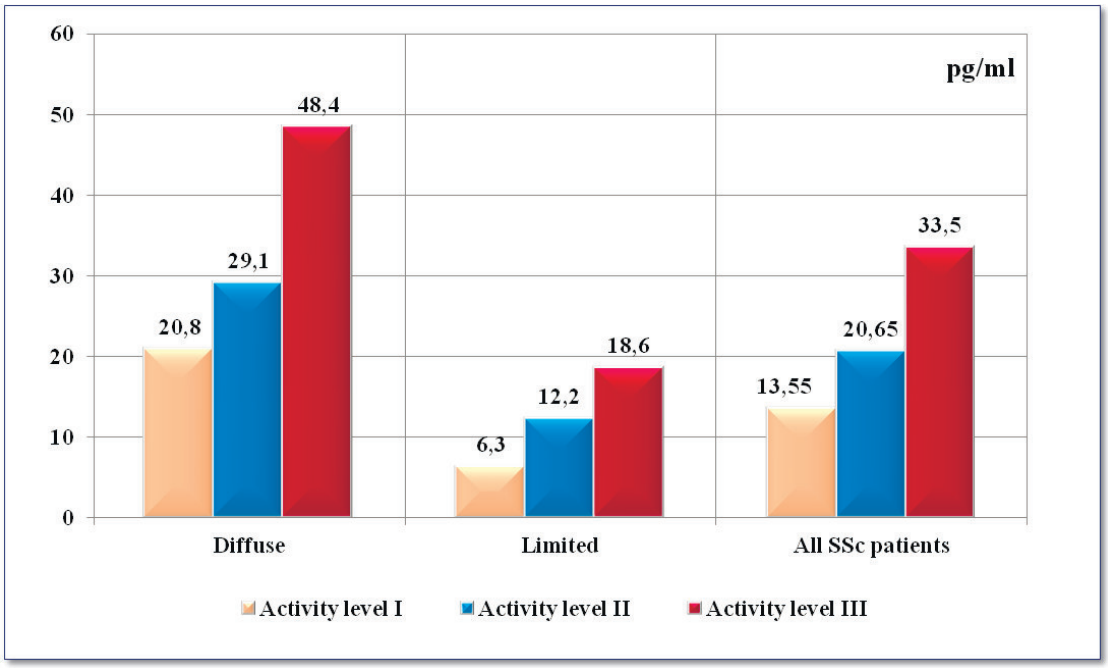


Fig. 2. Serum IL-6 levels according to disease severity in study groups.

Further analysis stratified by disease activity revealed a positive correlation between IL-6 levels and disease severity in both groups (Fig. 2). Increases in IL-6 were consistently associated with higher disease activity scores. Moreover, patients with diffuse systemic sclerosis exhibited significantly higher IL-6 concentrations than those with limited disease at comparable activity levels, reinforcing the role of IL-6 as a key mediator of inflammation and fibrotic progression in more severe forms of systemic sclerosis.

Conclusion

1. The present study demonstrates that IL-6 is markedly elevated in patients with systemic sclerosis, particularly in those with the diffuse form of the disease. Elevated IL-6 levels correlate with increased disease activity, more extensive skin involvement as assessed by the modified Rodnan skin score, and greater internal organ involvement. Even patients with limited systemic sclerosis exhibit significant IL-6 elevation compared to healthy controls, indicating that IL-6 contributes to systemic inflammation across all clinical subtypes.

2. These findings highlight IL-6 as a central mediator linking immune dysregulation, inflammation, and fibrosis in systemic sclerosis. Measurement of serum IL-6 may serve as a useful biomarker for disease activity and severity, supporting its potential role in patient stratification and monitoring. Furthermore, the data underscore

the therapeutic relevance of targeting IL-6 signaling pathways, offering a promising strategy to mitigate inflammation and fibrosis in patients with systemic sclerosis.

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Objective: *To investigate the clinical and immunological significance of interleukin-6) in patients with systemic sclerosis and to evaluate its relationship with disease activity, severity, and organ involvement.* ***Material and methods:*** *The study included 79 patients diagnosed with SSc and 30 healthy individuals. Serum IL-6 levels were measured using enzyme-linked immunosorbent assay (ELISA). Clinical assessment included disease duration, modified Rodnan skin score (mRSS), and evaluation of organ involvement. Laboratory parameters such as inflammatory markers and immune profiles were analyzed to determine their association with IL-6 concentration.* ***Results:*** *Serum IL-6 levels were significantly elevated in patients with SSc compared with healthy controls (p<0.001). Increased IL-6 concentrations were correlated with diffuse cutaneous form, higher mRSS values, interstitial lung disease, and elevated inflammatory indicators (CRP, ESR).* ***Conclusion:*** *Elevated IL-6 reflects active inflammation and fibrosis in systemic sclerosis and may serve as a reliable biomarker of disease activity and internal organ involvement. Modulation of IL-6 signaling could represent a promising therapeutic target in systemic sclerosis management.*

Key words*: systemic sclerosis, interleukin-6, modified Rodnan skin score, C-reactive protein*

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