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ORIGINAL ARTICLE

# Clinical significance of serum and urinary interleukin-6 in systemic lupus erythematosus patients

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**KEYWORDS**

Interleukin-6;
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**Abstract** *Background:* Previous studies reported higher interleukin-6 (IL-6) levels in systemic lupus erythematosus (SLE) patients than in healthy controls. However, the clinical relevance of IL-6 in SLE has not been clearly established.

*Aim of the work:* The present study aimed to evaluate the clinical significance of serum and urinary IL-6 and their usefulness as markers of disease activity in SLE.

*Patients and methods:* 63 SLE patients were included. Disease activity was assessed according to the Systemic Lupus Activity Measure (SLAM) score. Serum and urinary IL-6 were assessed by ELISA.

*Results:* The study included 63 Romanian patients, female to male ratio 9.5:1 with a mean age of 45.4 ± 12.6 years and disease duration of 8 (3–12.3) years. The median SLAM score at inclusion was 5 (range 3–8). Urinary IL-6 significantly correlated with proteinuria ($r = 0.25$; $p = 0.04$) and negatively with the platelet count, C3 and C4 levels ($r = -0.38$; $p = 0.002$, $r = -0.43$; $p = 0.001$, and $r = -0.46$; $p < 0.001$ respectively). Moreover, in patients with active lupus nephritis (LN), urinary IL-6 correlated with the SLAM ($r = 0.62$; $p = 0.01$). Patients with low urinary IL-6 levels (< 7.3 pg/ml) had a longer duration of treatment with corticosteroids or hydroxychloroquine (HCQ) (9.5 vs 4 years; $p = 0.02$ and 7 vs 4 years; $p = 0.02$). In a regression, only C3 was a significant determinant of urinary IL-6 level.

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*Conclusions:* Urinary but not serum IL-6 seems to be related to SLE activity in LN patients. Treatment with corticosteroids or HCQ therapy might reduce urinary IL-6 levels in SLE.



## 1. Introduction

Interleukin-6 (IL-6) is not only an important cytokine in the inflammation cascade [1], but has also pleiotropic functions in the regulation of the immune system [2]. For instance, IL-6 has pro-inflammatory properties as an important inductor of acute phase proteins [3,4] and, on the other hand, is involved in the anti-inflammatory responses [5,6].

Multiple studies have identified higher IL-6 levels in SLE patients in different samples analyzed: serum [7–9], urine [10,11], cerebrospinal [12] or bronchoalveolar lavage fluid [13]. Regarding the urinary IL-6 expression, there are data sustaining a local, renal, IL-6 production in SLE patients with active lupus nephritis (LN) [14,15]. However, the relationships between IL-6 levels and SLE disease activity are unsettled. Furthermore, IL-6 gene polymorphisms were reported in SLE patients [16].

Nevertheless, IL-6 was proposed as a therapeutic target in SLE [17]. Tocilizumab, an anti-IL-6 receptor antibody, initially used in patients with rheumatoid arthritis, was then tried in SLE [18]. However, anti-IL-6 therapy has not shown significant benefits in SLE, even if it decreased the disease activity and improved outcomes in SLE arthritis were noted [19]. Although a possible role of IL-6 as therapeutic target in SLE seems now improbable and this approach could be probably considered for future research only in selected patients, the involvement of IL-6 in SLE's pathogenesis cannot be denied and understanding its role could help clarify the heterogenic immunity of this disease.

The present study aimed to evaluate the usefulness of serum and urinary IL-6 levels as markers of disease activity in SLE.

## 2. Patients and methods

Sixty-three consecutive SLE patients fulfilling 2012 Systemic *Lupus* International Collaborating Clinics (SLICC) SLE criteria [20] were included in the study. Those with acute or chronic infectious conditions, pregnancy, neoplasia or overlap with another autoimmune disease were excluded. After patients signed the informed consent, the same protocol was applied to all. The study was approved by the ethics committee of Colentina Clinical Hospital and conforms to the Helsinki declaration.

Medical records were reviewed and complete laboratory data were collected. Blood and urine samples were collected at inclusion. In order to appreciate disease activity, the Systemic Lupus Activity Measure (SLAM), a SLE activity score [21] was computed at enrollment. SLAM scores several lupus impairments, like constitutional, mucocutaneous, ocular, reticuloendothelial, cardiovascular, pulmonary, gastrointestinal, neuromotor, and musculoskeletal. Renal involvement is evaluated into SLAM score related to serum creatinine and urinary sediment.

All clinical active involvements in SLE disease (i.e. cutaneous, joint, serositis) were defined according to 2012 SLICC criteria [20]. In case of renal SLE involvement, data on urine examination (urinary sediment and proteinuria in a 24 h collection) as well as estimated glomerular filtration rate (Modification of Diet in Renal Disease (MDRD) Study equation [22]) were available. LN was defined as proteinuria $\geqslant$500 mg/day and/or hematuria [20].

### 2.1. Serum and urinary IL-6 measurements

Peripheral blood samples were centrifuged 15 min at 4000 rpm. The biological samples were stored at −70°. Serum and urinary IL-6 levels were assessed by sandwich ELISA (DRG International, Inc. USA) according to manufacturer's instructions in the Immunology Laboratory of Colentina Research Center. For each sample, mean optical density at 450 nm was considered (BioRad Hercules, CA, USA).

### 2.2. Statistical analysis

The characteristics were summarized as mean and standard deviation (SD) or as median (quartile 1; quartile 3), (q1; q3), according to the distribution. Nominal data are presented as percentages. Subgroups of patients were defined based on the observed median urinary IL-6 (7.3 pg/ml), as reference data are not available and based on the presence of renal involvement, lupus nephritis (LN). Differences between subgroups were evaluated by Chi-squared test for categorical variables, T-independent test for normally distributed variables, and Mann–Whitney test for the others. The non-parametric Spearman test ($r$ = Spearman's rho coefficient) was used to analyze the bivariate correlations. Multivariate logistic regression models were used to assess the determinants of the urinary IL-6. Two-sided $p$-values $< 0.05$ were considered statistically significant. For all analysis, SPSS (Chicago, IL, USA) was used.

## 3. Results

The cohort consisted of 63 Romanian SLE patients, female to male ratio 9.5:1 with a mean age at inclusion of 45.4 ± 12.6 years. The median SLAM score at inclusion was 5 (range 3–8) (Table 1). The hematological manifestations were the most frequent at inclusion (42.9%), followed by the articular (39.7%), cutaneous (34.9%) and renal (23.8%) ones. Most of the patients were treated with corticosteroids (87.3%) and hydroxychloroquine (HCQ) (71.4%) for a median period of 6 years.

Serum IL-6 was not related to any of the investigated parameters (data not shown). Moreover, serum and urinary IL-6 levels were not correlated ($r = 0.02$; $p = 0.09$). In the whole cohort, urinary IL-6 was correlated with some indices

**Table 1** Demographic features, renal involvement, laboratory investigations, disease activity and medications received by systemic lupus erythematosus patients according to those with low and high urinary IL-6 levels.

| Variable | All ($n$ = 63) | Urinary IL-6 (pg/ml) | | $p$ |
|---|---|---|---|---|
| | | Low ($n$ = 33) | High ($n$ = 30) | |
| *Demographic* | | | | |
| F:M | 57:6 | 29:4 | 28:2 | 0.4 |
| Age (years) | 45.4 ± 12.6 | 48.0 ± 11.5 | 43.3 ± 13.6 | 0.3 |
| DD (years) | 8 (3–12.3) | 10 (5.5–14.5) | 6.0 (1.0–11.0) | **0.04** |
| *Lab. investigations* | | | | |
| TLC ($\times 10^3$/ml) | 6.8 (5.1–10.6) | 7.1 (5.2–10.2) | 6.7 (5–10.7) | 0.8 |
| LYM ($\times 10^3$/ml) | 1.6 (1.2–2.2) | 1.7 (1.2–2.3) | 1.5 (1.1–2.2) | 0.4 |
| Hb (g/dl) | 12.4 ± 2.1 | 12.6 ± 1.7 | 12.8 ± 2.5 | 0.7 |
| PLT ($\times 10^3$/ml) | 244.4 ± 89.2 | 268.8 ± 81.2 | 217.5 ± 91.3 | **0.02** |
| ESR (mm/1sth) | 19 (10–40) | 12.6 (12.3–13.4) | 14.5 (10–53.8) | 0.6 |
| CRP (mg/dl) | 2.3 (0.8–5.9) | 2.9 (0.8-6.6) | 2.2 (0.7–5.5) | 0.8 |
| C3 (g/l) | 1 (0.8–1.1) | 1.1 (0.9–1.2) | 0.8 (0.5–1.1) | **0.002** |
| C4 (g/l) | 0.2 (0.1–0.2) | 0.2 (0.2–0.3) | 0.1 (0.1–0.2) | **0.002** |
| sIL-6 (pg/ml) | 12.9 (1.6–20.7) | 9.1 (2.6–19.4) | 12.9 (6.5–20.7) | 0.6 |
| eGRF | 80.5 (58.1–113.5) | 91 (65.8–113.5) | 74.7 (52.7–105.7) | 0.3 |
| Proteinuria (mg/l) | 0 (0–30) | 0 (0–10) | 15 (15–50) | **0.03** |
| Hematuria | 9 (14.3) | 5 (15.2) | 4 (3.3) | 0.6 |
| *Lupus nephritis* | 15 (23.8) | 7 (21.2) | 8 (26.7) | 0.3 |
| *Disease activity* | | | | |
| SLAM score | 5 (3–8) | 5 (3.5–8) | 5 (5–9) | 0.9 |
| *Medications* | | | | |
| Steroids | 55 (87.3) | 28 (84.8) | 27 (90) | 0.4 |
| Duration (years) | 6 (1.3–11) | 9.5 (3.3–12.8) | 4 (0.7–9) | **0.02** |
| HCQ | 45 (71.4) | 25 (75.8) | 20 (66.7) | 0.3 |
| Duration (years) | 6 (0.5–10) | 7 (1.6–11) | 4 (0.1–6.5) | **0.02** |

IL-6: interleukin-6, F:M: female to male ratio, DD: disease duration, TLC: total leukocytic count, LYM: lymphocytes, Hb: hemoglobin, PLT: platelets, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, C: complement, sIL-6: serum IL-6, eGRF: estimated glomerular filtration rate, SLAM: Systemic Lupus Activity Measure, HCQ: hydroxychloroquine.
Low *vs.* high urinary IL-6. Results are presented as $n$ (%), mean ± SD or median (range). Low urinary IL-6 is $<7.3$ and high is $\geqslant 7.3$ pg/ml). The eGRF is calculated as ml/min/1.73 $m^2$. Bold values are significant at $p < 0.05$.

of SLE activity, i.e. with lower C3, C4, platelets, and higher proteinuria. However, the SLAM score was not related to urinary IL-6. Longer duration of both SLE and therapy with corticosteroids or HCQ was associated with lower IL-6 (Table 2).

When the subgroups of patients defined based on median urinary IL-6 were comparatively evaluated, patients with high IL-6 urinary levels had a shorter SLE duration, lower thrombocyte number, C3 and C4 levels, but higher proteinuria. They were treated for a shorter time with corticosteroids and HCQ. SLAM score and eGFR were similar in both groups. Notably, serum IL-6 levels were similar in the two subgroups (Table 1).

In a model of bivariate logistic regression only a lower C4 ($r = -0.87$, 95% CI 0.79–0.95; $p = 0.03$) correctly identified patients with a higher than median urinary IL-6 level in 62% of cases ($r = 0.21$; $p < 0.001$).

As IL-6 urinary but not serum levels were related to some of the investigated parameters, we supposed that local, intrarenal, production of IL-6 could have a contribution. Accordingly, we grouped the patients in respect to the presence of LN. In the subgroup of patients with active LN ($n = 15$) urinary IL-6 was negatively correlated with lymphocyte number, hemoglobin, C3, C4 level (Table 2 and Fig. 1). In regression analysis, the determinants of urinary IL-6 level were C3, lymphocytes number, and the duration of therapy with corticosteroids or HCQ, but only C3 had a significant contribution (Table 3).

## 4. Discussion

In this study, higher urinary not serum IL-6 were related to indices of SLE activity (lower C3 and C4), mostly in patients with kidney involvement, pointing to a renal source of IL-6. Lower IL-6 was also associated with longer duration of HCQ therapy, supporting an inhibitory action of HCQ on IL-6 production. Patients in the present study were subgrouped into low and high urinary IL-6 based on the median level (7.3 pg/ml) as reference data on serum or urinary IL-6 levels in SLE patients were not consistent [10,23–27].

Although previous studies concordantly reported higher IL-6 levels in SLE than in healthy controls, regardless the type of biological samples assessed, its diagnostic utility is still uncertain, as data were heterogeneous [7–13]. For instance, serum determinations of IL-6 levels largely varied from 0.3 to 9.8 pg/ml [10,23–27], such as 3.2 pg/ml in the new onset active SLE patients, 3.6–4.0 pg/ml in those with renal involvement [26], and 12.9 pg/ml in patients with Jaccoud's arthropathy [28]. Accordingly, the currently available data do not allow defining IL-6 cut-off level for SLE activity.

In the present study there was no significant correlation between serum IL-6 levels and disease activity or flare occurrence. The published data are contradictory as some reported a positive correlation [10,29–31] while others described no relation [24]. A correlation between serum [32] or urinary [33] IL-6 and the presence of LN has been reported. Consequently, it is

**Table 2** The relationships between urinary IL-6 levels and the investigated parameters in the total SLE patients and in those with lupus nephritis.

| Parameters $r$ ($p$) | SLE patients | | | |
|---|---|---|---|---|
| | All ($n$ = 63) | | LN ($n$ = 15) | |
| DD (years) | −0.35 | **(0.01)** | −0.4 | (0.2) |
| LYM ($\times 10^3$/ml) | −0.12 | (0.3) | −0.66 | **(0.01)** |
| Hb (mg/dl) | −0.14 | (0.3) | −0.67 | **(0.01)** |
| PLT ($\times 10^3$/ml) | −0.38 | **(0.002)** | −0.33 | (0.2) |
| C3 (g/l) | −0.43 | **(0.001)** | −0.67 | **(0.01)** |
| C4 (g/l) | −0.46 | **(< 0.001)** | −0.87 | **(< 0.001)** |
| Proteinuria (mg/l) | 0.25 | **(0.04)** | 0.28 | (0.3) |
| Steroids (years) | −0.39 | **(0.002)** | −0.6 | **(0.02)** |
| HCQ (years) | −0.38 | **(0.003)** | −0.52 | **(0.05)** |
| SLAM score | 0.048 | (0.71) | 0.62 | **(0.01)** |

SLE: systemic lupus erythematosus, LN: lupus nephritis, IL-6: interleukin-6, DD: disease duration, LYM: lymphocytes, Hb: hemoglobin, PLT: platelets, C: complement, HCQ: hydroxychloroquine, SLAM: Systemic Lupus Activity Measure. Bold values are significant at $p < 0.05$.

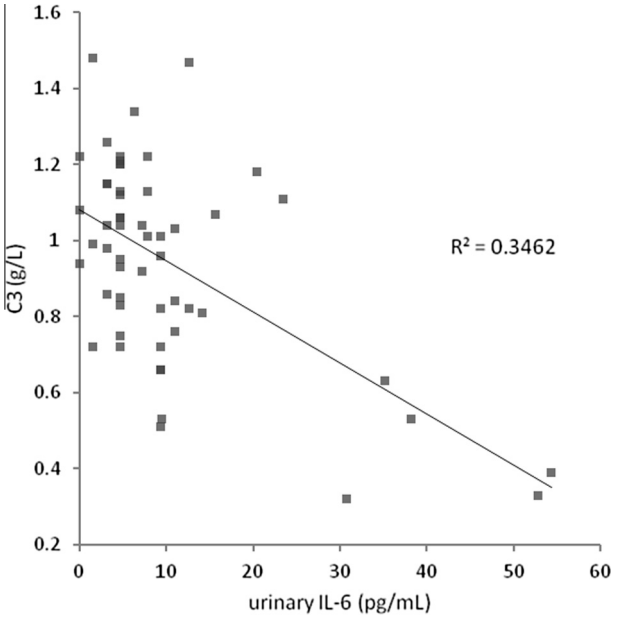


**Figure 1** Correlation between urinary IL-6 and C3 levels in SLE patients.

difficult to establish the significance of serum IL-6 in respect to lupus disease activity. We can only assume that there might be subgroups of SLE patients with certain clinical features in which the serum IL-6 kinetics might correlate with disease activity.

Peterson et al. found no correlation between serum and urinary IL-6 in SLE patients. Nevertheless, they observed that urinary IL-6 expression correlated with renal impairment as well as with lupus activity evaluated by SLAM score [10]. Furthermore, high urinary IL-6 levels were found not only in SLE patients with glomerulonephritis, but also in those with interstitial disease [34]. Even so, other authors did not identify

**Table 3** Determinants of urinary IL-6 in patients with lupus nephritis.

| | LN patients ($n$ = 15) | | |
|---|---|---|---|
| | $R$ | 95% (CI) | $p$ |
| (Constant) | | (43.7–86.4) | 0.001 |
| C3 (mg/dl) | −0.54 | (−0.5 to 0) | **0.048** |
| LYM count | −0.36 | (−0.02 to 0) | 0.08 |
| Steroids (years) | −0.95 | (−5.5 to 0.2) | 0.07 |
| HCQ (years) | 0.66 | (−1.4 to 5.2) | 0.21 |

LN: lupus nephritis, CI: confidence interval, C3: complement factor 3, LYM: lymphocytes, HCQ: hydroxychloroquine. Bold values are significant at $p < 0.05$.

urinary IL-6 as a reliable marker for LN [11]. The discordance between serum and urinary IL-6 levels focused the search for a renal, local source, of IL-6. IL-6 was found by immunostaining in the monocyte–macrophage infiltrates in kidney biopsies [35] and also in the mesangial cells and glomerular immune deposits, but not in the normal renal tissue [14]. Activated monocytes may induce IL-6 synthesis in mesangial cells through a CD40 ligand [15]. It was postulated that IL-6 expression in mesangial cells may be enhanced by the anti-DNA antibodies [35].

In our study, there was a significant association of urinary, not of serum, IL-6 with proteinuria and complement fractions, but not with SLE activity. Moreover, in patients with LN, IL-6 was inversely correlated with C4 and, in logistic regression, C4 level was the independent determinant of LN. Accordingly, a particular IL-6 kinetic in the subgroup of SLE patients with renal involvement, kidney lesions being the main source, can be assumed. Thus, urinary IL-6 might be a marker of LN activity.

Even if the HCQ mechanism of action is not understood, its benefits in SLE are well known [36]. In our data, urinary IL-6 levels were lower in patients with a longer total duration of therapy with HCQ. This is in line with other reports, where a decrease in serum and salivary IL-6 [37] as well as a decline in IFN-α levels [24] was described under HCQ therapy. Regarding a possible impact of HCQ on IL-6 production, it was proposed that HCQ might inhibit the production of IL-6 by T cell and monocyte [38]. More recently, da Silva et al. demonstrated *in vitro* that HCQ inhibits the production of pro inflammatory interleukins and suggested that HCQ might have an impact on the antigen presentation [39]. Thus, urinary IL-6 could also be used as a marker for the efficacy of HCQ therapy.

The presented data should be interpreted with caution, as longer SLE duration could be related to kidney disease activity and to the duration of therapy, and both could influence IL-6 urinary levels. One of our study limits was the low number of patients, especially of those with renal impairment. Moreover, the renal involvement was defined only on the urine examination (according to 2012 SLICC criteria); we did not have data on the renal biopsies of these patients. Even so, we identified some correlations between urinary IL-6 and renal impairment in SLE and we observed an interesting relation between the HCQ treatment and urinary IL-6 expression. Prospective follow-up of SLE patients is necessary to evaluate the long-term impact of high IL-6 levels.

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## 5. Conclusion

Urinary IL-6 could be a useful auxiliary parameter to assess disease activity in the subgroup of SLE patients with renal involvement as its expression seems more related to a renal origin. HCQ could act by inhibiting IL-6 production, as lower urinary IL-6 was observed in patients with longer HCQ therapy duration.

## Conflict of interest

None.

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