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Colony Stimulating Factor-1 (CSF-1) in Lupus Patients and its Correlation with the Value of Proteinuria

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Abstract

Background: Kidney involvement is prevalent in systemic lupus erythematosus (SLE) and is the leading cause of disability and death. Colony-stimulating factor-1 (CSF-1) may be involved in the development of lupus nephritis (LN). This study aimed to evaluate serum CSF-1 levels in SLE patients with and without proteinuria and its correlation with the value of proteinuria.

Methods: A total of 75 subjects including 25 newly diagnosed SLE cases without renal involvement evidence, 25 new SLE with biopsy-proven LN, and also, 25 healthy controls were included in the study. Serum CSF-1 level was measured in all participants using a human CSF-1 ELISA kit.

Results: Analysis of variance (ANOVA) and post hoc analysis demonstrated significant differences between the three groups including healthy individuals, and SLE subjects with and without nephritis ($P=0.006$). The mean values of CSF-1 levels were increased among both participants without LN and patients with LN, compared to healthy individuals. However, a statistically significant greater mean concentration of CSF-1 was detected in individuals with LN compared to the healthy group ($P=0.004$). No significant statistical correlation was found between CSF-1 and 24-hour urine protein. Furthermore, when comparing the activity of SLE, a notable distinction was observed in the SLE disease activity index (SLEDAI) values between individuals with and without proteinuria ($P<0.0001$).

Conclusion: An upward trend in average CSF-1 levels was observed among both patients with and without LN, in comparison to healthy individuals. Significantly enhanced concentrations of CSF-1 were found in subjects with LN compared to healthy individuals.

Keywords: Lupus nephritis, CSF-1, Systemic lupus erythematosus, Proteinuria

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Introduction

Systemic lupus erythematosus (SLE) is an inflammatory multi-organ autoimmune disease without a well-known etiology, while it has diverse clinical and laboratory manifestations as well as various prognoses (1). Renal complications in SLE, recognized as lupus nephritis (LN), represent a significant challenge, with documented 5-year renal survival rates following successful treatment varying between 46% and 95% (2). LN stands as the primary driver of morbidity and mortality among individuals diagnosed with SLE. Despite advanced therapeutic options, end-stage renal disease (ESRD) is a common occurrence in individuals with LN, affecting as many as 26% of patients. Moreover, recurrences or exacerbations of LN are prevalent (ranging from 27% to 66%) and play a role in poor outcomes (3). Serial renal biopsies may be ideal for accurate follow-up of the progression of renal diseases. However, this may be difficult in practice with some complications (4). Within a decade of being diagnosed with SLE, approximately 5-20% of patients with LN experience kidney failure, while the various health problems resulting from immunosuppressive

treatment such as osteoporosis, various infections, and cardiovascular issues continue to be a cause for concern. To enhance the outcomes for SLE patients, it is crucial to promptly and accurately detect LN and begin treatment at an early stage (5). Given its importance for long-term LN outcomes, serum and urinary biomarkers have been an intense field of research (6). Colony-stimulating factor-1 (CSF-1), known as macrophage colony-stimulating factor (M-CSF) as well, was the initial hemopoietic growth factor discovered to regulate the growth and differentiation of macrophages from precursor cells located in the bone marrow (7). According to the study by Menke et al, an increase in the levels of CSF-1 in the bloodstream or urine, which is produced by renal tubular epithelial cells, might serve as an early indicator of renal disease activity. This could potentially occur even before any noticeable signs of glomerular dysfunction are observed, both during the initial occurrence of the disease and before its recurrence (8). Genetic findings have also reported additional data supporting the relationship between CSF-1 and the development of LN (9,10). The present study aimed to assess serum CSF-1 concentrations in SLE patients with and without proteinuria and its correlation with the value of proteinuria in new patients with LN.

Methods

Study design

In the study, 75 subjects including 25 newly diagnosed SLE cases without renal involvement evidence (according to urine analysis and 24-hour urine collection), 25 new SLE with biopsy-proven LN, and also, 25 healthy controls were included. To avoid any confusion caused by prior treatments, we restricted our study to include only patients who had not undergone any form of therapy before participating. All the patients were classified as SLE based on the Systemic Lupus International Collaborating Clinics (SLICC) criteria (11), and enrolled as new patients with SLE consecutively, who were referred to the Imam Reza hospital, Mashhad, Iran. All kidney biopsy samples underwent evaluation based on the 2003 ISN/RPS classification criteria for LN (12).

Demographic and laboratory indices

Demographic data including age and sex were gathered. Blood specimens were collected for a complete blood count, serum complement C3 and C4 levels, anti-nuclear antibodies (ANAs), and anti-double stranded DNA (anti-dsDNA). The ANA profile is requested as a screening test for all individuals suspected of having lupus. ANAs were analyzed by indirect immunofluorescence in Hep-2 cells. All study subjects were asked to collect a 24-hour urine sample to define the amount of proteinuria. Furthermore, serum samples were stored at -70 °C until sampling was completed. Following the guidelines provided by the manufacturer, human CSF-1 concentrations were assessed using a CSF-1 ELISA kit (ZellBio, GmbH).

Statistical analysis

Statistical analysis was conducted using SPSS version 16. Mean and standard deviations were utilized to represent quantitative data. Analysis of variance (ANOVA) and post hoc analyses were applied to compare the means among the three groups including SLE patients with and without nephritis and healthy controls. The correlation between the CSF-1 and 24-hour urine protein secretion was assessed using the Pearson correlation coefficient.

Results

General characteristics of study participants

In total, 25 newly diagnosed SLE patients without LN (2 males and 23 females), 25 new LN patients (3 males and 22 females), and 23 individuals (2 males and 21 females) in the healthy group were recruited in the present study. The mean age of 32 ± 9 and 29.7 ± 8 years was reported in patients without LN and with LN, respectively, and the mean age was 32 ± 7 years in the healthy group. No notable distinction was found in terms of age ($P = 0.06$) and sex ($P = 0.88$) among the study groups.

Characteristics of laboratory indices

Generally, 84% of the patients with proteinuria and 23 individuals (95.8%) without proteinuria were ANA positive with ELISA, and the difference between the two groups was found to be significant ($P = 0.001$) (Table 1). Moreover, 22 individuals (88%) in the LN group with proteinuria and 11 patients (45.8%) without proteinuria possessed positive anti-ds DNA. There was a statistically significant difference between these two groups ($P = 0.002$). From the perspective of reducing complement proteins C3 and C4, there was no significant difference between the two groups of LN and lupus patients without proteinuria. The P values for C3 and C4 levels were noted as $P = 0.76$ and $P = 0.5$, respectively. Meanwhile, the comparative evaluation of the values of the SLE disease activity index (SLEDAI) between the two study groups (with and without proteinuria) showed a significant difference between the two groups of subjects, one with proteinuria and the other without ($P < 0.0001$).

Serum CSF-1 levels across healthy individuals, SLE patients with and without nephritis

The mean values of CSF-1 concentrations were 46.35 ± 30.54 among patients without LN, 58.93 ± 22.82 pg/mL in patients with LN, and 34.34 ± 22.32 pg/mL within healthy individuals. The ANOVA results indicated a significant difference among the three study groups ($P = 0.006$). Overall, in post-hoc analysis, the mean concentration of CSF-1 was notably elevated in patients with LN in comparison to the healthy group ($P = 0.004$) (Figure 1).

Table 1. Demographic characteristics and laboratory indices of studied groups

Variables	Without LN (n=25)	LN (n=25)	Control (n=23)	*P* value
Gender/Female, n (%)	23 (92)	22(88)	21(91.3)	0.88
Age (y)	32±9	29.7±8	32±7	0.066
Positive anti-dsDNA, n (%)	11 (45.8)	22 (88)	-	0.002
Positive ANA, n (%)	23 (95.8)	21 (84)	-	0.001
SLEDAI (mean+SD)	8.8±7.7	37±19.9	-	<0.0001

Abbreviations: LN, lupus nephritis; SLEDAI, systemic lupus erythematosus disease activity index; ANA, anti-nuclear antibody; Anti-dsDNA, anti-double-stranded DNA antibody.

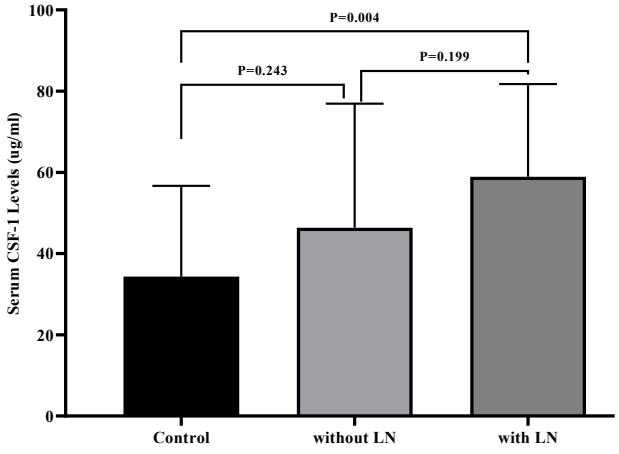

Figure 1. CSF-1 levels among study groups including healthy controls, SLE patients with and without nephritis

In addition, no correlation was found between CSF-1 and 24-hour urine protein ($r=0.37$, $P=0.86$).

Discussion

In this study, we assessed the serum CSF-1 levels in SLE patients with and without nephritis, and in a control group. According to the findings, a rising pattern can be observed in the mean values of CSF-1 levels among both patients without LN and patients with LN compared to healthy subjects. However, it is notable that the mean level of CSF-1 was significantly elevated in patients with LN in comparison to the control group. In addition, the comparison of SLE disease activity showed a significant difference in SLEDAI values between individuals with and without proteinuria. Cytokines have a notable impact on the development of SLE and LN, which has recently become a very attractive area of research. The use of cytokines as indices of disease activity in SLE and LN is interesting (13). Timely treatment, therefore, improves the outcomes in LN. Besides, there is a robust connection between a delayed diagnosis and an increased occurrence of ESRD (3). Although kidney biopsy is ideal for the careful monitoring of LN, it is not a flawless procedure and carries complications such as infection and hemorrhage. Hence, a non-invasive method is needed to forecast the initiation and recurrence of LN before the onset of evident kidney damage (13). CSF-1, known as M-CSF, was the initial hematopoietic growth factor recognized to control the development and maturation of macrophages originating from precursor cells situated in the bone marrow (7). Its levels increase in the serum, urine, and kidneys of individuals with LN (14). CSF-1 has a wide range of distribution and can be produced by different types of cells such as epithelial and endothelial cells, neurons, fibroblasts, and osteoblasts (15,16). The CSF-1 gene, which is found on chromosome 1p13-p21 in humans, is highly conserved, as shown by comparing its sequence with that of other species. CSF-1 exists in three main biological forms, which are a result of various mRNA splicing and posttranslational modification (17). From a mechanistic point of view, CSF-1 binds with its distinct receptor, CSF-1R, in a water-soluble manner. This interaction leads to the process of CSF-1R dimerization and phosphorylation. Simultaneously, CSF-1R can facilitate CSF-1 removal either by internalization or rapid renal clearance (18). A recent study (10) aimed to understand the relationship between the clinical characteristics of LN and the urinary expression levels of APRIL signaling factors that are in turn induced by CSF-1 (19), suggesting that the expression levels of APRIL in the urine could be considered a helpful biomarker for detecting LN. Furthermore, CSF-1 facilitates the movement of monocytes towards the growth of pro-inflammatory macrophages (20). Studies on both human and murine models have shown enhanced concentrations of CSF-1 in urine, serum, and kidneys of MRL/lpr mice and LN patients. Additionally, these elevated levels of CSF-1 are linked to various histopathological factors (20).

On the other hand, CSF-1 plays a fundamental function in the growth and development of macrophages in the glomerulus, contributing to kidney damage (8) and exacerbating the severity of LN (21). A study conducted by Liao et al demonstrated the correlation between CSF-1 and miR-145 using a dual luciferase reporter assay. It was observed that in individuals with LN and in human renal mesangial cells induced by LPS, the expression of miR-145 is typically reduced. In theory, miR-145 has the potential to reduce inflammatory dysfunction by suppressing CSF-1, thereby preventing the development of LN in living organisms via the JAK-STAT signaling pathway facilitated by CSF1 (9). Genetic findings have revealed that miR-145 controls the progression of LN through the CSF-1-mediated JAK/STAT signaling pathway. Therefore,

targeting miR-145 could potentially represent a novel therapeutic approach for LN (9). According to the results of the present study, increased average concentrations of CSF-1 were detected in both patients without LN and patients with LN when compared to healthy individuals. Nevertheless, significantly higher concentrations of CSF-1 were found in patients with LN compared to the healthy group. However, no substantial association was found between CSF-1 and proteinuria, which is consistent with the findings of the study by Mirfeizi et al (22). In a clinical study by Menke et al, the CSF-1 concentrations were evaluated in two separate groups, revealing heightened concentrations of CSF-1 in the urine and serum of individuals with SLE in comparison to healthy subjects across both cohort studies (8). The researchers monitored serum CSF-1 before and after LN flares specifically, excluding flares in other presentations of SLE. They found that both urine and serum concentrations of CSF-1 significantly increased before LN flares (8). Consistently, a cohort study conducted by Tian et al demonstrated that elevated levels of M-CSF in urine following initial remission could predict a recurrence of kidney inflammation in individuals with SLE and diffuse proliferative glomerulonephritis. These findings suggest that monitoring pro-inflammatory indicators in urine could guide treatment strategies for LN patients (14). The results of the present study revealed that assessing the CSF-1 level enables the identification of patients with LN from healthy individuals. Hence, this information can be valuable for preventive measures against the development of SLE cases with renal involvement. A constraint of this research is the comparatively limited sample size, which restricted the exploration of CSF-1 levels across different manifestations of lupus. Additionally, conducting longitudinal studies could provide insights through repeatedly monitoring serum CSF-1 levels and their correlation with lupus activity and remission over time.

Conclusion

According to the findings of the present study, there is an increasing trend in the average CSF-1 levels among both patients without LN and subjects with LN, when compared to the control group. Notably, the average concentration of CSF-1 was significantly elevated in patients with LN in comparison to healthy individuals. Moreover, a notable difference in SLE disease activity was observed, as evidenced by the contrasting SLEDAI values, between individuals with and without proteinuria. To gain valuable insights, it would be beneficial to perform prospective studies with larger populations and involve the evaluation of serum concentrations of CSF-1 and their correlation with lupus activity over an extended period.

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Authors' Contribution

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Competing Interests

The authors declared no conflict of interest.

Ethical Approval

The study was approved by the Ethics Committee of Mashhad University of Medical Sciences (Ethical code: IR.MUMS.fm.REC.1396.604). Informed consent was obtained from the patients before entering the study.

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