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Serum Calprotectin Level in Patients with Systemic Lupus Erythematosus and its Correlation with Disease Activity

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Abstract

Background: Neutrophils contribute to immune defense through phagocytosis and the formation of neutrophil extracellular traps (NETs), which can also trigger autoimmunity. Calprotectin (CLP), a key component of NETs, is released during inflammation and plays a role in modulating immune responses.

Aim of Study: This study aimed to compare serum CLP levels between systemic lupus erythematosus (SLE) patients and healthy controls, and to assess the relationship between CLP levels and SLE disease activity.

Patients and Methods: This cross-sectional study included 41 adult patients diagnosed with SLE and 41 healthy controls. All participants underwent clinical assessment, including comprehensive medical history and physical examination. Disease activity was measured using the SLE Disease Activity Index 2000 (SLEDAI-2K). Serum CLP levels were measured and compared between patients and controls. Correlations between CLP levels and clinical features of SLE were analyzed, and the diagnostic performance of CLP in distinguishing SLE patients from healthy individuals was evaluated.

Results: Serum CLP levels were significantly elevated in SLE patients compared to controls. A significant positive correlation was observed with the SLEDAI-2K score (p=0.002). Higher CLP levels were particularly noted in patients with arthritis, cognitive dysfunction, and positive anti-dsDNA antibodies. At a cutoff value of 3.45ng/dL, CLP demonstrated robust diagnostic performance, with a sensitivity of 87.8%, specificity of 75.6%, positive predictive value of 78.3%, negative predictive value of 86.1%, and overall accuracy of 87.1%.

Conclusion: CLP levels were higher in SLE patients and correlated with disease activity. Levels were elevated in those with arthritis, cognitive impairment, or positive anti-dsDNA, and showed good ability to distinguish SLE from controls.

Key Words: *Systemic Lupus Erythematosus – Calprotectin – SLEDAI-2K.*

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Introduction

SYSTEMIC Lupus Erythematosus (SLE) is a complex autoimmune disease characterized by a wide range of clinical manifestations, from mild symptoms affecting the skin and joints to severe, potentially life-threatening organ involvement **[1]**. Accurate assessment of disease activity is essential for guiding appropriate treatment strategies and improving patient outcomes.

Neutrophils play a central role in the innate immune response, acting as first-line defenders against pathogens through mechanisms such as phagocytosis and the release of cytoplasmic granular proteins with bactericidal properties **[2]**. One such mechanism involves the formation of neutrophil extracellular traps (NETs), which, while critical in pathogen defense, can also contribute to autoimmune pathology. In inflammatory conditions, NETs may promote autoimmunity by exposing nuclear and cytoplasmic autoantigens, including nucleic acids and proteins, to the immune system **[3]**.

Calprotectin (CLP), a key component of NETs, is a heterodimeric protein complex composed of the S100 family members S100A8 and S100A9 [4]. It is abundantly released by neutrophils and monocytes at sites of inflammation, where it plays a pivotal role in modulating the immune response [5,6]. Once in the extracellular space, CLP binds to receptors such the receptor for advanced glycation end-products (RAGE) and Toll-like receptor 4 (TLR4) on leukocytes and endothelial cells [7]. This interaction activates signaling pathways that stimulate the release of pro-inflammatory cytokines, including interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha (TNF-α), thereby amplifying inflammation [7].

Several studies suggest that serum CLP may serve as a useful biomarker for autoimmune diseases like rheumatoid arthritis and inflammatory bowel disease [6], and ankylosing spondylitis [8]. However, findings regarding its role in SLE are inconsistent. While some research indicates that serum CLP effectively differentiates SLE patients from healthy individuals [9], other studies report only modest diagnostic value [7]. Similarly, evidence regarding the relationship between CLP levels and anti-double-stranded DNA (anti-dsDNA) antibodies is conflicting with one study found a significant association [10], whereas another did not [7]. Discrepancies also exist in correlating CLP with disease activity: A weak positive correlation with the SLE Disease Activity Index (SLEDAI) was reported by Soyfoo et al. [11], but Wakiya et al. [12] observed no such association.

The aim of this work was to compare the level of serum CLP between SLE patients and controls and to assess the association of serum CLP with disease activity in SLE patients.

Patients and Methods

Study design and participants:

This cross-sectional study enrolled 41 consecutive adult patients diagnosed with SLE based on the 1997 revised American College of Rheumatology (ACR) classification criteria [13]. Patients were recruited from the Outpatient Rheumatology and Rehabilitation Clinic at Mansoura University Hospital. An equal number of age and sex-matched healthy volunteers were included as the control group. The study protocol was approved by the local ethics committee (MS.23.10.2579) and this study was conducted during 2024. All participants provided written informed consent after being fully informed about the study's objectives and procedures.

Exclusion criteria:

Participants under 18 years of age, as well as those with other autoimmune diseases, infections, malignancies, or medical conditions known to elevate serum CLP levels including diabetes mellitus, inflammatory bowel disease, lung fibrosis, and glomerulonephritis were excluded from the study.

Clinical assessment:

All subjects underwent comprehensive evaluation including detailed medical history, general clinical examination, and systemic examination. SLE related clinical features were reported. SLE disease activity was assessed using the SLE Disease Activity Index 2000 (SLEDAI-2K) [14], which comprises 24 items (16 clinical and 8 laboratory descriptors). Items are weighted as follows: eight items scored 8 points each, six items 4 points each, seven items 2 points each, and three items 1 point each, yielding a total score ranging from 0 to 105 [15]. Active disease was defined as a SLEDAI-2K score ≥6 [16].

Laboratory investigations:

Venous blood samples (8mL) were collected aseptically from the antecubital vein of all participants. The samples were divided as follows: 2mL into an EDTA tube for complete blood count (CBC), 2mL into a citrated tube for erythrocyte sedimentation rate (ESR) measurement using the Westergren method [17], and the remaining blood into a plain tube for serum separation after clotting and centrifugation. The serum was aliquoted into two parts: one for immediate analysis of complement components (C3, C4), C-reactive protein (CRP) which was quantified by immunoturbidimetric assay [18], and anti-dsDNA antibodies, which were detected by an ELISA assay employing recombinant human dsDNA for both quantitative and qualitative IgA detection; the other aliquot was stored at −20°C for later measurement of serum CLP using the Human CLP (CALPRO) ELISA kit.

Additionally, 24-hour urine samples were collected to assess proteinuria. Urine collection started at 8:00 AM after discarding the first void, followed by collection of all urine for the next 24 hours, ending with the sample at 8:00 AM the following day. Urine was analyzed for total protein content and examined microscopically for casts, red blood cells, and pyuria.

Statistical analysis:

Data analysis was conducted using SPSS version 20. Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile

range, IQR) as appropriate. Categorical variables were presented as frequencies and percentages. Group comparisons utilized the independent *t*-test for continuous data and chi-square test for categorical data. Correlations were evaluated using Pearson or Spearman correlation coefficients as suitable. The diagnostic performance of serum CLP (cutoff value 3.45mg/dL) was assessed by calculating sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, and receiver operating characteristic (ROC) curve analysis. Youden's Index was employed to determine the optimal cutoff. Statistical significance was set at $p<0.05$.

Results

Table (1) presents a comparison of demographic characteristics, BMI, and serum CLP levels between the SLE and control groups. Both groups were matched in terms of age and sex, with no statistically significant difference observed in BMI. Serum CLP levels in SLE patients ranged from 2.4 to 9.2ng/dl, with a mean of 5.6±2.4 ng/dl, whereas controls exhibited levels ranging from 1.3 to 4.2 ng/dl, with a mean of 3.0±0.7ng/dl. This difference was statistically significant (95% CI, 1.82 to 3.38; $p<0.001$).

Table (1): Comparison of the demographic data, BMI and serum CLP between the Control group and SLE group.

	SLE group	Control group	*p*
Age (years) (mean ± SD)	37.6±8.4	38.3±7.9	0.704
Females (n, %)	40, 97.6%	39, 95.1%	0.556
BMI (kg/m^2) (mean ± SD)	26.4±4.3	26.7±7.1	0.837
Serum CLP (ng/ml)	5.6±2.4	3.0±0.7	<0.001

Within the SLE cohort, serum CLP levels did not significantly correlate with age, BMI, or disease duration. However, a significant positive correlation was found between serum CLP levels and disease activity as measured by the SLEDAI-2K score ($p=0.002$) (Table 2, Fig. 1).

Table (2): Correlation of Serum CLP Levels with Age, BMI, Disease Duration, and Disease Activity (SLEDAI-2K) in patients with SLE.

	R/rho	*p*
Age	0.132	0.409
BMI	-0.048	0.765
SLE duration	-0.008	0.962
SLEDAI-2K	0.474	0.002

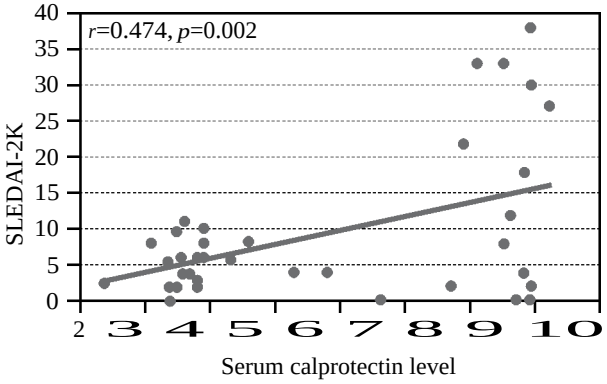

Fig. (1): Correlation between serum CLP level and the SLEDAI-2K score of the SLE group.

Further analysis, summarized in Table (3), revealed that SLE patients with arthritis exhibited significantly higher serum CLP levels compared to those without arthritis (6.9±2.3 vs. 5.2±2.3, respectively; $p=0.041$). Similarly, patients with cognitive impairment had elevated serum CLP levels relative to those without such impairment (6.3±2.4 vs. 4.2±1.9, respectively; $p=0.047$). Conversely, serum CLP levels did not differ significantly among SLE patients with or without other clinical manifestations.

Table (3): Comparison of the serum CLP level between SLE patients without and with the SLE-related clinical manifestation.

Manifestations	Serum CLP level in SLE patient		*p*
	Without manifestation	With manifestation	
Constitutional:			
Fatigue	6.7±2.5	5.5±2.4	0.414
Malaise	4.5±2.1	5.8±2.3	0.162
Loss of weight	6.1±2.4	4.8±2.2	0.117
Fever	5.8±2.5	5.2±2.2	0.475
Mucocutaneous:			
Photosensitivity	5.6±2.5	5.9±2.1	0.628
Malar rash	5.9±2.7	5.4±2.2	0.466
Alopecia	5.4±2.4	5.9±2.4	0.424
Oral Ulcer	5.5±2.4	5.9±2.4	0.558
Discoid lesion	5.7±2.4	4.8±2.1	0.392
Vascular:			
Vasculitic rash	5.7±2.4	5.9±2.6	0.762
Rynaud's phenomenon	5.2±2.3	6.5±2.3	0.095
Musculoskeletal:			
Arthralgia	5.1±2.3	6.6±2.2	0.059
Arthritis	5.2±2.3	6.9±2.3	0.041
Myalgia	5.7±2.4	5.3±2.4	0.571
Vascular necrosis	5.8±2.4	3.9±1.2	0.132
Neurological:			
Cognitive disorders	4.2±1.9	6.3±2.4	0.047
Mood disorder	5.8±2.5	4.6±1.1	0.209
Lupus headache	5.3±2.3	6.9±2.3	0.092
Cardiopulmonary:			
Pleuritis	5.6±2.4	5.6±2.3	0.931
Pericarditis	5.8±2.4	4.5±1.7	0.220
Dyspnea	5.6±2.4	5.7±2.4	0.847

Serum CLP also demonstrated a significant positive correlation with serum CRP levels (p<0.001) and an inverse correlation with serum C3 levels (p=0.006) (Table 4, Figs. 2,3). No significant associations were observed between serum CLP and other laboratory parameters, including hemoglobin concentration, white blood cell count, platelet count, ESR, serum C4 levels, serum creatinine, or 24-hour urine protein excretion.

Table (4): Correlation between Serum CLP level and the laboratory findings of the SLE group.

	r	*p*
Hg concentration	0.089	0.582
WBCs count	-0.021	0.895
Platelets count	0.266	0.092
Serum CRP level	0.595	<0.001
ESR	0.034	0.833
Serum C3 level	-0.424	0.006
Serum C4 level	-0.216	0.176
Creatinine	-0.208	0.193
24-hour urine protein	-0.016	0.920

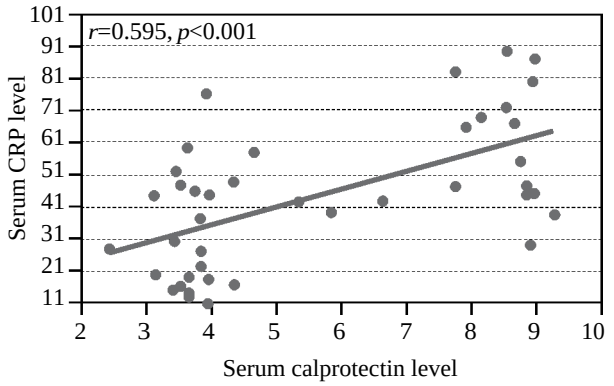

Fig. (2): Correlation between serum CLP level and the serum CRP level of the SLE group.

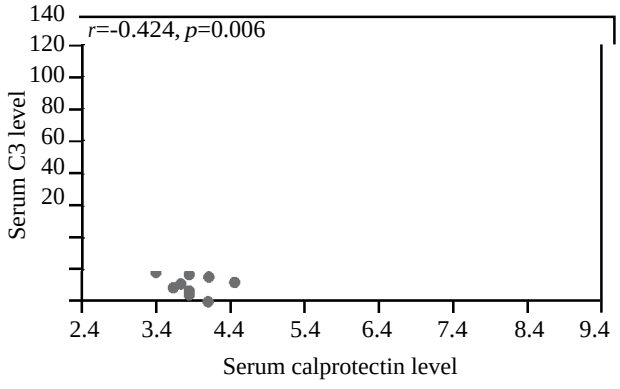

Fig. (3): Correlation between serum CLP level and the serum C3 level of the SLE group.

Additionally, SLE patients positive for anti-dsDNA antibodies had significantly higher serum CLP levels compared to the anti-dsDNA-negative patients (6.4±2.3 vs. 4.7±2.1; p=0.019). However, no significant differences in serum CLP levels were found in relation to anemia, leukopenia, lymphopenia, thrombocytopenia, pyuria, hematuria, or proteinuria status (Table 5).

Table (5): Comparison of the serum CLP level between SLE patients with negative and positive laboratory findings.

	Serum CLP level in SLE patient		*p*
	Negative laboratory findings	Positive laboratory findings	
Anemia	5.2±2.2	5.7±2.4	0.668
Leucopenia	6.2±2.5	4.8±1.9	0.079
Lymphopenia	5.1±2.1	5.8±2.5	0.518
Thrombocytopenia	5.9±2.5	4.9±2.0	0.241
Anti-dsDNA	4.7±2.1	6.4±2.3	0.019
Pyuria	5.8±2.4	4.5±2.1	0.228
Hematuria	5.5±2.3	6.2±2.7	0.486
Protein in urine	5.3±2.4	5.8±2.4	0.464

Youden's Index identified 3.45ng/dl as the optimal cutoff point for serum CLP to discriminate between SLE patients and healthy controls. ROC curve analysis confirmed the strong discriminative power of serum CLP, with an area under the curve (AUC) of 0.883 (Fig. 4).

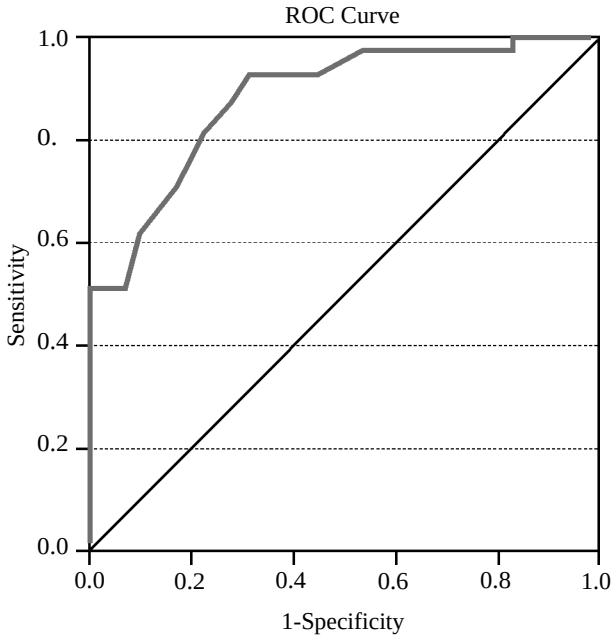

Fig. (4): ROC curve analysis for the ability of the CLP to discriminate between healthy and SLE (AUC=0.883).

At a cutoff value of 3.45ng/dl, serum CLP demonstrated a high sensitivity of 87.8% (95% CI: 73.8% to 95.9%) and a moderate specificity of 75.6% (95% CI: 59.7% to 87.6%). The PPV and NPV were 78.3% (95% CI: 67.5% to 86.2%) and 86.1% (95% CI: 72.8% to 93.5%), respectively, yielding an overall diagnostic accuracy of 87.1% (95% CI: 71.6% to 89.4%) (Table 6).

Table (6): The diagnostic value of the serum CLP for discrimination between SLE patients and controls.

Statistic	Value	95% CI
Sensitivity	87.8%	73.8% to 95.9%
Specificity	75.6%	59.7% to 87.6%
PPV	78.3%	67.5% to 86.2%
NPV	86.1%	72.8% to 93.5%
Accuracy	81.7%	71.6% to 89.4%

Discussion

The main findings of our study were as follows: (a) SLE patients had significantly higher serum CLP levels compared to matched healthy controls; (b) serum CLP levels were significantly correlated with the SLEDAI-2K score and serum CRP levels, while inversely correlated with C3 levels; (c) SLE patients with arthritis or cognitive impairment had significantly higher serum CLP levels compared to those without these conditions; (d) SLE patients with positive anti-dsDNA had significantly higher serum CLP levels than those with negative anti-dsDNA; and (e) ROC curve analysis demonstrated that serum CLP levels had strong discriminatory power between SLE patients and healthy controls, with an AUC of 0.883.

Neutrophils play a central role in immune defense through mechanisms such as phagocytosis and the formation of NETs. While NETs are essential for trapping and neutralizing pathogens, they have also been implicated in the initiation and propagation of autoimmune responses. CLP, a major component of NETs, is released during inflammation and has been shown to modulate both innate and adaptive immune responses. However, findings regarding the role of CLP in SLE have been inconsistent. To address this, we conducted a study to compare serum CLP levels between SLE patients and healthy controls, and to investigate the association between CLP levels and SLE disease activity.

The results of the present study demonstrated that serum CLP levels were significantly elevated in patients with SLE compared to matched healthy controls. This finding is consistent with a growing body of evidence indicating that CLP may serve as a valuable biomarker for SLE.

Several studies support this observation. One previous study reported significantly higher serum CLP concentrations in 59 SLE patients compared to 52 healthy controls, suggesting CLP as a potential rapid diagnostic marker *[9]*. Similarly, another study found elevated CLP levels in 44 SLE patients relative to 43 healthy volunteers *[7]*. These findings have been corroborated by additional research *[11, 19–20]*, all consistently demonstrated significantly increased serum CLP levels in SLE cohorts. Furthermore, Pruenster et al. *[6]* highlighted that CLP levels are elevated in various inflammatory diseases, including SLE.

A larger study involving 249 SLE patients observed significantly elevated CLP levels in serum, urine, and saliva, with serum concentrations being 2.7-fold higher than in healthy controls *[21]*. Similarly, Davies et al., reported elevated serum CLP levels in 243 SLE patients, noting particularly high urine CLP concentrations in individuals with lupus nephritis *[22]*.

Regarding diagnostic performance, Homa-Mlak et al., reported a high sensitivity (89.8%) but moderate specificity (53.8%) for serum CLP in distinguishing SLE from healthy individuals *[9]*. Šumová et al., reported moderate sensitivity and specificity (63.6% and 64.1%, respectively) *[7]*. In the current study, at a cutoff of 3.45mg/dL, serum CLP showed high sensitivity (87.8%), moderate specificity (75.6%), a PPV of 78.3%, a NPV of 86.1%, and overall accuracy of 87.1%, reinforcing its potential as a diagnostic biomarker.

In the present study, serum CLP levels showed a significant correlation with SLE disease activity, as measured by the SLEDAI-2K score. Positive associations were also observed with CRP and anti-dsDNA antibodies, alongside an inverse correlation with C3. These findings align with those of Homa-Mlak et al., who reported significant, albeit weak, correlations between CLP levels, C3, and anti-dsDNA *[9]*. Further supporting the association between CLP and disease activity, several previous studies have demonstrated that CLP levels reflect both disease severity and autoantibody levels *[21, 23–24]*. Notably, Ometto et al. *[23]* suggested that CLP may be more sensitive than CRP in detecting residual inflammation and predicting disease flares. In support with these findings, Tydén et al. *[10]* collected serum samples from 100 SLE patients at different disease activity states and found higher CLP levels during active phases, suggesting its utility in monitoring treatment response. Conversely, one

previous study found no correlation between CLP and disease activity, possibly due to the low disease activity in their patient population [12].

Cellular studies further support the role of CLP in SLE. Elevated CLP expression in B cells from patients with active disease was found to correlate with SLEDAI-2K scores and to decrease following treatment, highlighting its potential as a marker of disease activity [25].

The role of NETs in SLE pathogenesis has also been linked to CLP. Impaired NET degradation has been associated with increased disease activity, elevated anti-dsDNA antibody levels, and decreased C3 and C4 levels [26], findings that are consistent with the results of the present study. Further evidence from Tydén et al. [10] suggests that anti-dsDNA antibodies may contribute to elevated serum CLP levels by enhancing phagocytosis and promoting polymorphonuclear cell activation. However, this association is not universally observed; for instance, Šumová et al. [7] did not find a significant correlation between CLP and anti-dsDNA level.

Clinical associations further underscore the relevance of CLP in arthritis. In the present study, SLE patients with arthritis exhibited significantly higher serum CLP levels compared to those without arthritis, in line with findings reported by previous studies [7,19]. Similar associations have been observed in rheumatoid arthritis; Hammer et al. [27] reported that CLP levels correlated with joint inflammation. Additionally, our study noted elevated CLP levels in patients with arthralgia, although this difference did not reach threshold of statistical significance, suggesting a potential role for CLP as an early marker of joint involvement. In addition, our results indicated that serum CLP levels were significantly elevated in SLE patients with cognitive impairment, aligning with findings from Muñoz-Grajales et al. [28], who showed that CLP levels could effectively differentiate patients with cognitive dysfunction.

Soyfoo et al. [11] reported a weak positive correlation between serum CLP levels and disease activity, as measured by the SLEDAI. Additionally, Haga et al. (20) found a significant correlation between serum CLP levels, CRP and disease activity in SLE patients. These findings were consistent to the findings of the current study. Camins-Fàbregas et al. [29] argued that patients with higher anti-dsDNA levels had elevated CLP levels, and accordingly, suggested that CLP determination, being faster than measuring anti-dsDNA levels, could be useful in assessing inflammatory activity.

The results of Kim et al. [21] showed that high S100A8 expression was correlated with low hemoglobin levels, high ESR, low complement, and elevated anti-dsDNA antibodies. In contrast to these findings, our study did not find a significant correlation between serum CLP level and hemoglobin concentration or ESR as ESR can be affected by treatment in our patients.

This study has several limitations that should be acknowledged. First, the relatively small sample size may limit the generalizability of the findings. Second, SLE disease activity was assessed exclusively using the SLEDAI-2K score, while other validated indices of disease activity were not included, potentially overlooking broader aspects of disease severity. Additionally, the single-center, cross-sectional design restricts the ability to infer causality or evaluate longitudinal changes in serum CLP levels. To strengthen and validate these findings, future studies should involve larger, multi-center cohorts and adopt a longitudinal design. Further research is also warranted to explore the relationship between serum CLP levels and alternative measures of disease activity, and to determine whether dynamic changes in CLP levels can effectively reflect treatment response over time.

Conclusion:

Patients with SLE demonstrate significantly higher serum CLP level as compared to healthy people. Serum CLP level was strongly correlated with the SLEDAI-2K score and serum CRP levels, while inversely correlated with C3 levels. SLE patients with arthritis, cognitive impairment, or positive anti-dsDNA antibodies showed notably higher serum CLP levels. Serum CLP levels have a strong ability to differentiate between SLE patients and healthy controls.

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مستوى كالبروتيكتين المصلى فى مرضى الذئبة الحمراء وعلاقته بنشاط المرض

يُعد مرض الذئبة الحمراء الجهازية من الأمراض المناعية الذاتية التى تتسم بتنوع واسع فى الأعراض، بدءًا من الحالات الخفيفة التى تؤثر على الجلد والمفاصل، وصولًا إلى حالات أكثر خطورة قد تهدد الحياة. يتميز هذا المرض بإنتاج أجسام مضادة ضد مكونات نوى الخلايا، مما يؤدى إلى ترسب معقدات مناعية تتسبب فى تلف أنسجة متعددة. يُعد التقييم الدقيق لنشاط المرض أمرًا أساسيًا لتوجيه العلاج المناسب. تلعب العدلات دورًا محوريًا فى الجهاز المناعى، وتُنتج شبكات عدلية خارج الخلايا، قد تكون ذات تأثيرات سامة. ويُعد الكالبروتيكتن أحد البروتينات التي تُفرز فى موقع الالتهاب وله دور فى تنظيم الاستجابة الالتهابية. تهدف هذه الدراسة إلى تقييم مستويات الكالبروتيكتن في مصل الدم لدى مرضى الذئبة الحمراء مقارنة بالأصحاء، ودراسة علاقته بنشاط المرض. شملت الدراسة واحدًا وأربعين مريضًا وواحدًا وأربعين شخصًا سليمًا، مع جمع بيانات سريرية وتحليل عينات دم، واستخدام مقياس نشاط الذئبة الحمراء الجهازية (سيلداى٢ك) لتقييم النشاط المرضى. أظهرت النتائج ارتفاعًا معنويًا فى مستويات الكالبروتيكتن لدى المرضى، وارتباطه الإيجابي مع درجة النشاط المرضي والبروتين المتفاعل – سِى (سى آر بى)، وسلبيًا مع مستويات البروتين المتمم ٣ (سي ٣). كما ارتفعت مستوياته لدى المرضى الذين يعانون من التهاب المفاصل أو اضطرابات إدراكية، وكذلك لدى المرضى الإيجابيين للأجسام المضادة (أنتى دبل ستراند دى أن أى). أظهرت النتائج قدرة الكالبروتيكتن على التمييز بدقّة بين المرضى والأصحّاء، ممّا يجعله مؤشّرًا حيويًا واعدًا فى تقييم ومتابعة مرض الذئبة الحمراء الجهازية.