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Implication of plasma gelsolin in systemic lupus erythematosus patients

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Abstract

Background: Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder with more than one organ involvement. Kidney is the foremost commonly affected one. Gelsolin is a protein that induces depolymerization of actin filaments thus preventing downstream stimulation of inflammatory reactions. The aim of this work was to detect the relation of plasma gelsolin to SLE disease activity and severity indices in order to find out if plasma gelsolin could be used as a biomarker of the disease. This study was conducted on 50 SLE female patients and 30 matched control. SLE disease activity Index (SLEDAI) and SLE damage index (SDI) were assessed. All lupus nephritis (LN) patients were subjected to an ultrasound-guided kidney biopsy. Plasma gelsolin level was measured.

Results: The mean age of the patients was 38.5 ± 6.3 years (26–51 years) with median disease duration of 5 (3–9.3) years. Eighteen patients had LN, 11 had cardiac manifestations and 12 had chest manifestations. The mean SLEDAI was 13.1 ± 4.5 (4–22) and the median SDI was 2 (1–3). Plasma gelsolin level was significantly lower in SLE patients (74.9 mg/l; 57.5–98.8 mg/l) compared to control (801.5 mg/l; 225–1008.3 mg/l) ($p < 0.001$). There were significant negative correlations of gelsolin levels with anti-ds DNA ($r = -0.63$, $p < 0.001$), SLEDAI ($r = -0.79$, $p < 0.001$), and SDI ($r = -0.74$, $p = 0.001$). Plasma gelsolin level was significantly lower in SLE patients with high/very high activity grades compared to those with low and moderate ($p = 0.007$ and $p < 0.001$ respectively). A gelsolin level of ≤ 78.95 mg/l significantly predicted renal affection ($p < 0.001$), with a sensitivity of 100%, specificity 71.9%, and a positive predictive value 66.7%.

Conclusion: A decreased gelsolin level is associated with disease activity in SLE patients. Plasma gelsolin was well related to disease activity and severity with a high predictive value for renal affection comparable to anti-ds DNA titre. Plasma gelsolin is a potentially important predictive biomarker for SLE and LN.

Keywords: Gelsolin, Plasma gelsolin, Systemic lupus erythematosus, SLE biomarkers, Lupus nephritis

Background

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder with more than one organ involvement, when becomes hyperactive forming antibodies attacking ordinary organs like the skin, kidneys, brain, joints, heart, lungs, and blood [1, 2]. Renal involvement is common in SLE with the kidney being the foremost commonly affected organ, and it is a significant cause of morbidity and mortality [3]. Lupus nephritis (LN) evolves whenever autoantibodies target the kidneys, which filter waste. This leads to renal inflammation which may result in blood or protein in the urine, elevated blood pressure, impaired kidney function, or finally kidney failure [4–6]. A lot of research is focusing at the discovery of the latest biomarkers for the early detection and tracking of SLE and LN [7].

Gelsolin is a multifunctional protein that has actin filament severing, capping, and nucleating functions [8–10]. This protein has two different isoforms: a cytoplasmic and a circulating isoform. Gelsolin induces the depolymerization of actin filaments; this would prevent the

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downstream stimulation of inflammatory reactions by these actin filaments [11, 12]. In conditions of acute damage or inflammation, gelsolin levels tend to decrease [13, 14].

Gelsolin is involved in the immune response and considered an anti-inflammatory modulator. Gelsolin depletion is additionally linked to the release of inflammatory mediators [15, 16].

Methods

Plasma samples and clinical data were collected from 50 female SLE patients attending the Rheumatology outpatient clinic and department inpatient of Benha University Hospitals diagnosed according to the European League against Rheumatism (EULAR)/American College of Rheumatology (ACR) SLE classification criteria [17]. Pregnant patients and cases with other immunological disorders or liver diseases were excluded. Thirty apparently healthy individuals represented the control group with a comparable age, sex, and social level**.**

All patients were subjected to full history taking and thorough clinical examination. The SLE disease activity index (SLEDAI) [18] was assessed and classified as low (score: 1–5), moderate (score: 6–10), high (score: 11–19), and very high (score $\geq$ 20). The SLE damage index (SDI) [19] was considered according to the systemic lupus international collaborating clinics/ACR (SLICC/ACR) score.

Laboratory evaluation included the complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum creatinine, blood urea, anti-nuclear antibodies (ANA), anti-ds DNA antibodies (titre) by enzyme-linked immunosorbent assay (ELISA) technique, complete urine analysis, protein/24 h urine, and protein/creatinine ratio.

All LN patients ($n = 18$) were subjected to an ultrasound-guided kidney biopsy and samples evaluated according to the international society of nephrology/renal pathology society (ISN/RPS) classification [20].

The plasma gelsolin level was measured by a sandwich ELISA kit (Cat n°: E1233HU, Shanghai Crystal Day Biotech Co., Ltd., China**)** according to manufacturing instructions.

Statistical analysis: data were analyzed using the statistical package for the social sciences (SPSS) software, version 22.0 (IBM, Armonk, NY, USA). Categorical data were presented as numbers and percentages, mean $\pm$ SD (range) or median with interquartile range (IQR). Chi-square ($\chi 2$) and Fisher's exact tests were used for comparisons. Linear association between variables was assessed by Spearman's correlation coefficients. Receiver operating characteristics (ROC) curves were constructed to assess the ability of gelsolin to predict the activity and severity of SLE. Univariable and multivariable logistic regression analysis was run to detect the predictors of renal affection. A p value < 0.05 was considered significant.

Results

The mean age of the patients (38.5 $\pm$ 6.3 years; 26–51 years) was comparable to the age of the control (37.8 $\pm$ 7.5 years; 26–50 years, $p = 0.68$). The characteristics and laboratory findings of the patients are presented in Table 1. All patients were receiving steroids, 94% hydroxychloroquine, 24% azathioprine, 14% mycophenolate mofetil, 10% methotrexate, and 10% cyclophosphamide (CYC).

The median plasma gelsolin level (74.9 mg/l; 57.5–98.8 mg/l) was significantly lower in patients ($p < 0.001$) compared to the control (801.5 mg/l; 225–1008.3 mg/) (Fig. 1). The optimal cut-off level of plasma gelsolin level associated SLE disease was $\leq$ 152.6 mg/l, (88% sensitivity and 90% specificity; $p < 0.001$).

The median plasma gelsolin level was significantly lower in patients with LN (49.3 mg/l; 40.8–61.9 mg/l) than in those without (86.3 mg/l; 74.8–103.8 mg/l) ($p < 0.001$). The median level was highly significantly lower in LN patients class III and class IV LN (43.6 mg/l; 36.2–47.7 mg/l) (42.3 mg/l; 14.2–57.5 mg/l) in comparison to non-renal patients (86.3 mg/l; 74.8–103.8 mg/l) ($p = 0.001$) while it was significantly lower in LN patients class II LN (61.9 mg/l; 49.3–74.9 mg/l) in comparison to non-renal patients ($p = 0.049$). Non-significant differences were found among classes II, III, and IV LN ($p = 1$).

The median plasma gelsolin level was significantly lower in patients with musculoskeletal manifestations (69.4 mg/l; 46.5–83.2 mg/l) than in cases without (94 mg/l; 70.1–482.1 mg/l) ($p = 0.003$). Plasma gelsolin values were comparable between those with and without skin, cardiac, or pulmonary manifestations ($p = 0.07$, $p = 0.79$, and $p = 0.36$ respectively). The median plasma gelsolin level was significantly lower in patients with high and very high activity compared to those with a low/moderate grades ($p = 0.007$ and $p < 0.001$ respectively).

There was a significant negative correlation between gelsolin level with urinary protein/24 h ($r = -0.39$, $p = 0.004$), anti-dsDNA antibodies level ($r = -0.63$, $p < 0.001$), SLEDAI ($r = -0.79$, $p < 0.001$), and SDI ($r = -0.74$, $p < 0.001$) (Fig. 2). The relation to age ($r = 0.13$, $p = 0.38$), disease duration ($r = -0.19$, $p = 0.18$), and other laboratory parameters was insignificant. On regression analysis, plasma gelsolin and anti-ds DNA were found to be good predictors of LN (Table 2).

Plasma gelsolin level ($\leq$ 81.1 mg/l) had a significant predictive value in the differentiation of high/very high disease activity grade from low/moderate grades ($p < 0.001$) with sensitivity 78.1% and specificity 77.8%. At a

Table 1 Characteristics and laboratory findings of the systemic lupus erythematosus (SLE) patients

Parameter	SLE patients ($n = 50$)
Age (years)	Mean ± SD 38.5 ± 6.3 Range (26–51)
Disease duration (years)	Median (IQR) 5 (3–9.3)
Clinical manifestations:	**No.** (%)
Renal	18 (36)
Musculoskeletal	17 (34)
Skin	50 (100)
Cardiac	11 (22)
Chest	12 (24)
SLEDAI	Mean ± SD 13.1 ± 4.5 Range (4–22)
Low	**No.** (%) 2 (4)
Moderate	16 (32)
High	25 (50)
Very high	7 (14)
SDI	Median (IQR) 2 (1–3)
Laboratory findings	Median (IQR)
Hemoglobin (g/dl)	10.6 (9.2–12.9)
WBCs ($\times 10^3$/ml)	4.8 (3.7–8.4)
Platelets ($\times 10^3$/ml)	231 (199.5–302.8)
ESR (mm/h)	60 (47–75)
CRP (mg/dl)	10.3 (6.3–13)
Protein/24 h (mg/24 h)	255 (107–679)
Serum creatinine (mg/dl)	0.97 (0.84–1.12)
Blood urea (mg)	22.8 (20–41.3)
Protein/creatinine ratio	0.23 (0.12–0.52)
ANA positive	50 (100)
Anti-ds DNA positive	23 (46)
Plasma gelsolin (mg/l)	Median (IQR) 74.9 (57.5–98.8)
Renal biopsy done for 18	
Class I	**No.** (%) 0 (0)
Class II	6 (12)
Class III	5 (10)
Class IV	7 (14)

Results are presented as mean ± SD (range) or median ± IQR or *n* (%)

SLE systemic lupus erythematosus, *SLEDAI* SLE disease activity index, *SDI* SLE damage index, *WBCs* white blood cells, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *ANA* anti-nuclear antibodies, *anti-ds DNA* anti-double-stranded deoxyribonucleic acid

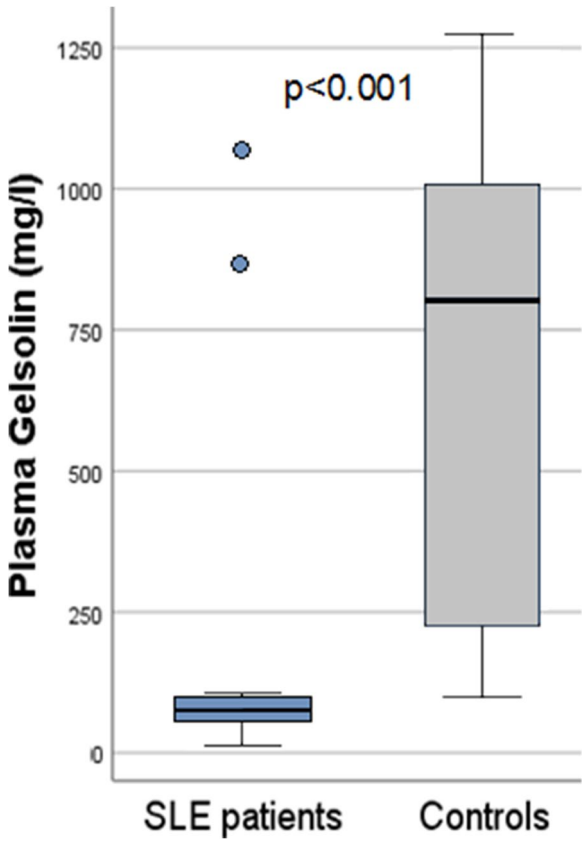

Fig. 1 Plasma gelsolin level in systemic lupus erythematosus (SLE) patients and controls

level of ≤ 78.95 mg/l, it had a significant predictive value of renal affection with 100% sensitivity and 71.9% specificity ($p < 0.001$). However, at an anti-ds DNA level ≥ 54 IU/ml the prediction of renal affection showed a sensitivity of 88.9% and specificity 59.4% ($p = 0.004$) (Table 3, Fig. 3).

Discussion

SLE is a chronic autoimmune inflammatory disease associated with various immunological events, characterized by a wide range of clinical manifestations with unpredictable flares and remissions that usually end by permanent injury [21]. In Egypt, SLE had a wide variety of clinical and immunological manifestations comparable to other nations and disparity across the country [22]. Assessment of renal function in SLE patients is imperative because early detection and management of renal involvement can essentially improve renal outcome [23]. The discovery, development, and validation of novel biomarkers which can expect clinical outcomes is a significant mission, particularly in SLE patients who develop heterogeneous clinical manifestations and must begin aggressive therapies [24].

Plasma gelsolin is one of the most important actin-binding proteins in the actin-clearing system that plays important roles in body protection and internal environment balance. Plasma gelsolin has been pronounced to play vital roles in serious situations, such as acute inflammation, trauma, burns, and sepsis [25]. The depletion of gelsolin during the rapid increase of globular and filamentous actin in the clearance cycle is a possible mechanism for the reduction of plasma gelsolin levels in severe diseases [26]. In addition, decreased plasma gelsolin

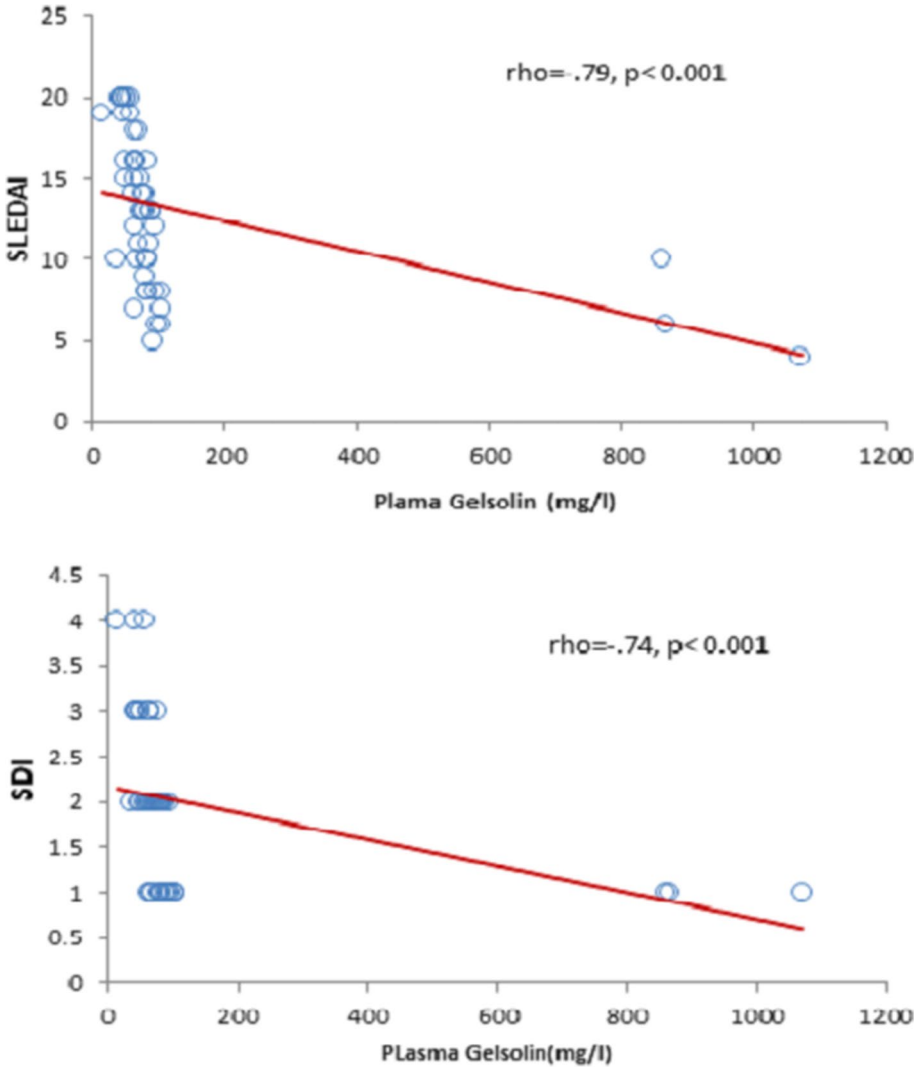

Fig. 2 Correlation of plasma gelsolin with the systemic lupus erythematosus disease activity index (SLEDAI) and SLE damage index (SDI) in SLE patients

Table 2 Logistic regression analysis for the predictors of renal affection in systemic lupus erythematosus patients

Variable	SLE patients ($n = 50$; LN $n = 18$)					
	Univariate			Multivariate		
	OR	95%CI	*p*	OR	95%CI	*p*
Plasma gelsolin	1.18	(1.06–1.3)	**0.002**	1.15	(1.03–1.28)	**0.009**
Anti-ds DNA titre	1.04	(1.01–1.07)	**0.006**	1.09	(1.02–1.19)	**0.028**
ESR	1.03	(0.98–1.35)	.35	–	–	–
Serum creatinine	1.19	(0.26–5.4)	0.82	–	–	–
Protein/24 h urine	1.04	(1.01–1.1)	**0.006**	1.01	(0.99–1.01)	1.03

Bold values are significant at $p \leq 0.05$

SLE systemic lupus erythematosus, *LN* lupus nephritis, *anti-dsDNA* anti-double-stranded deoxyribonucleic acid, *ESR* erythrocyte sedimentation rate

Table 3 Plasma gelsolin level versus anti-double-stranded deoxyribonucleic acid (anti-dsDNA) in the prediction of renal affection in systemic lupus erythematosus patients

Parameter	SLE patients ($n = 50$)							
	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)	Acc. (%)	AUC	95%CI	*p*
Plasma gelsolin ≤ 78.95 mg/l	100	71.9	66.7	100	82	0.95	0.897–1	**< 0.001**
Anti-ds DNA ≥ 54 IU/ml	88.9	59.4	55.2	90.5	70	0.75	0.61–0.88	**0.004**

Bold values are significant at $p \leq 0.05$

SLE systemic lupus erythematosus, *Sens* sensitivity, *Spec.* specificity, *PPV* positive predictive value, *NPP* negative predictive value, *Acc* accuracy, *AUC* area under the curve

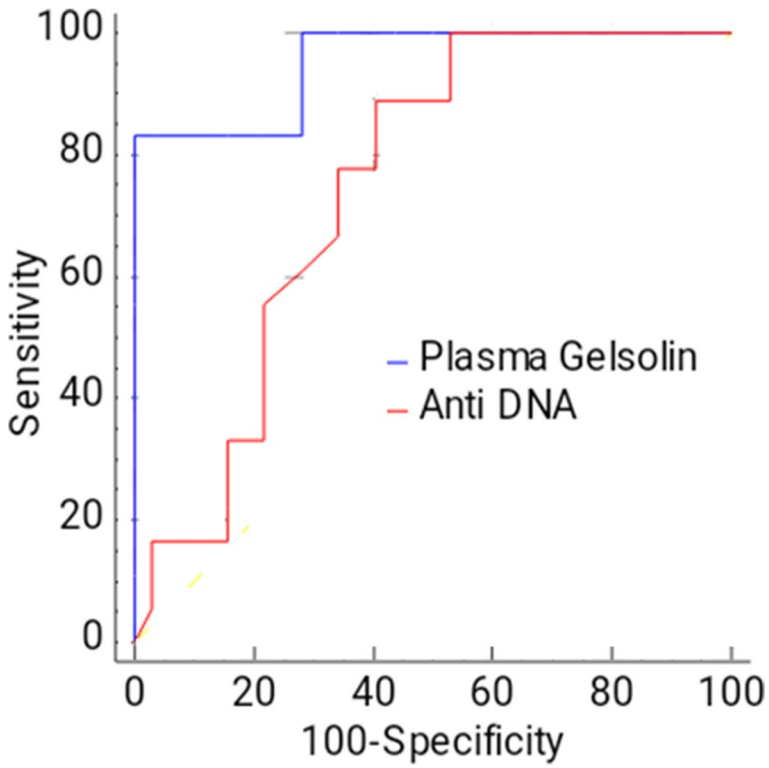

Fig. 3 Receiver operating characteristic (ROC) curves of plasma glesolin level versus anti-double-stranded deoxyribonucleic acid (anti-ds DNA) in the prediction of renal affection in systemic lupus erythematosus (SLE) patients

levels in the circulation have been reported in chronic inflammatory diseases [27].

In this study, the plasma gelsolin was significantly lower in patients compared to control and this result coincided with the study of Parra et al. [28] and Mitto et al. [29]. In addition, Hu et al. [26] demonstrated that plasma gelsolin levels in patients with SLE and RA were significantly decreased compared to controls. This was also observed in the study of Osborn et al. [30] who observed that the mean circulating plasma gelsolin levels were significantly lower in patients with RA. Esawy et al. [30] demonstrated that plasma gelsolin levels were decreased in psoriatic arthritis (PsA) patients compared to the controls, while Haung et al. [31] found that the expression level of gelsolin in both serum and whole blood cells was decreased in primary Sjogren's syndrome patients.

In this work, the median plasma gelsolin level was significantly lower in patients with renal and with musculoskeletal manifestations than in those without. There were no significant differences according to the presence and absence of skin, cardiac, or pulmonary manifestations. Also, there was an insignificant relation of plasma gelsolin levels with the patients' ages, disease duration, and other laboratory parameters.

There were significant negative correlations of plasma gelsolin level with anti-dsDNA antibodies titers, SLEDAI

and SDI. In agreement, Parra et al. [28] demonstrated that plasma gelsolin decreased in SLE patients when they developed a clinical flare. Hu et al. [26], showed a significant negative correlation between plasma gelsolin levels and SLEDAI. Meanwhile, they found no correlation between plasma gelsolin levels and RA disease activity. Also, Osborn et al. [32] documented the lack of a correlation between plasma gelsolin levels and disease activity in RA. This suggested the potential clinical application of plasma gelsolin in SLE diagnosis and disease activity evaluation. Esawy et al. [30] notified that a significant negative correlation between plasma gelsolin and PsA activity was detected. The median of plasma gelsolin level was significantly lower in SLE patients with a high/very high activity compared to those with low /moderate grade. At a level of $\leq$ 81.1 mg/l, there was a significant predictive value differentiating high/very high disease activity from low/moderate.

In the present study, there is a significant negative correlation between plasma gelsolin level and urinary protein/24 h in SLE patients. The median plasma gelsolin level was significantly lower in LN patients with class II, III, and IV in comparison to non-renal patients. Meanwhile, differences of plasma gelsolin levels among these histopathological classes were non-significant. The optimal cut-off point of plasma gelsolin in this study associated with the SLE disease was $\leq$ 152.6 mg/l with a validated sensitivity of 88% and 90% specificity. Dimitrijevic et al. [33] demonstrated that plasma gelsolin deposits were detected and varied in samples with significant association between these deposits and LN morphologic classifications indicating their potential biological marker value in LN severity and glomerular injury.

In the current work, it was found that plasma gelsolin and anti-ds DNA antibodies were good predictors of renal affection. Plasma gelsolin level ($\leq$ 78.95 mg/l) significantly predicted renal affection with 100% sensitivity and 71.9% specificity, while anti-dsDNA titer ($\geq$ 54 IU/ml) would predict with 88.9% sensitivity and 59.4% specificity. Misra et al. [34] declared that plasma gelsolin may be better used as a severity biomarker for the evaluation of glomerulonephritis than anti-dsDNA. The general existence of plasma gelsolin deposits in patients with LN morphologic classification I to V indicated that plasma gelsolin should be better used as a biomarker for LN disease activity rather than a specific diagnosis index. All these pieces of evidence indicate that plasma gelsolin might be used as an inflammatory marker.

Among the study limitations is the lack of full information about the anti-phospholipid status and medications received by the patients. Further larger-scale longitudinal studies are warranted to explain role of gelsolin in SLE pathogenesis and treatment outcomes. Additional work can consider gelsolin deposits in renal tissue in parallel with plasma. More studies can focus on the reversal of plasma gelsolin reduction which may be a new therapeutic target for SLE patients.

Conclusion

A decreased plasma gelsolin level was associated with clinical disease activity in SLE patients. It was well related to SLE disease activity and severity. Plasma gelsolin had a high sensitivity and specificity associated with SLE disease as well as a high predictive value for renal affection. Gelsolin level was comparable to anti-ds DNA titre as predictors of renal affection. Plasma gelsolin might be used as a biological marker for SLE and predictive biological marker for lupus nephritis.

Abbreviations

SLE: Systemic lupus erythematosus; SLEDAI: SLE Disease Activity Index; SDI: SLE Damage Index; LN: Lupus nephritis; SLICC/ACR score: Systemic Lupus International Collaborating Clinics/ACR; CBC: Complete blood count; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; ELISA: Enzyme-linked immunosorbent assay; ISN/RPS: International Society of Nephrology/Renal Pathology Society.

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Authors' contributions

Idea suggestion and study design: Samia M. Abdel moneam, Amal F. Soliman and Arwa S. Amer. Data collection and analysis: Ghada M. Mosaad, Arwa S. Amer, and Seham G. Ameen. Manuscript writing and final revision: Samia M. Abdel moneam, Amal F. Soliman, Arwa S. Amer, and Ghada M. Mosaad. All authors have read and approved the final manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

An informed written consent was taken from all patients and subjects' participating in this study and the protocol was approved by the ethical committee of Benha Faculty of Medicine no. MS 11-5-2020.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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