Elevated Serum Levels of Syndecan-1 Are Associated with Renal Involvement in Patients with Systemic Lupus Erythematosus

Ki-Jo Kim, Ji-Young Kim, In-Woon Baek, Wan-Uk Kim, and Chul-Soo Cho

ABSTRACT. ***Objective.*** Syndecan-1 (SDC-1) is a major constituent of the endothelial glycocalyx, which plays a role in maintaining vascular homeostasis and functions as a glomerular filtration barrier. SDC-1 is readily shed into the blood under various conditions, but the clinical implication of circulating SDC-1 in patients with systemic lupus erythematosus (SLE) remains unclear. We aimed to investigate the association of serum SDC-1 level with certain clinical manifestations of SLE.

Methods. We measured serum SDC-1 levels by ELISA in 111 patients with SLE, 18 with rheumatoid arthritis (RA), and 20 healthy subjects, and investigated its association with clinical manifestations and laboratory variables.

Results. Serum SDC-1 levels were higher in patients with SLE than in those with RA and healthy controls (both $p < 0.001$) and were positively correlated with SLE Disease Activity Index (SLEDAI; $r = 0.367$, $p < 0.001$) and anti-dsDNA antibody level ($r = 0.259$, $p = 0.007$), but inversely correlated with serum C3 and CH50 levels ($r = –0.305$, $p = 0.001$ and $r = –0.244$, $p = 0.012$). Patients with active nephritis had higher serum SDC-1 levels than patients with inactive nephritis and those without nephritis (both $p < 0.001$). In addition, serum SDC-1 levels were correlated with renal SLEDAI score ($r = 0.540$, $p < 0.001$) and excretion of proteinuria as measured by spot urine protein/creatinine ratio ($r = 0.538$, $p < 0.001$). In 14 patients with lupus nephritis (LN) whose serum samples were obtained at the time of renal biopsy, there was a positive correlation between serum SDC-1 levels and activity index ($r = 0.632$, $p = 0.015$).

Conclusion. Serum SDC-1 levels are increased in SLE patients with nephritis, indicating that SDC-1 might be a useful serum biomarker for active LN. (J Rheumatol First Release Dec 15 2014; doi:10.3899/jrheum.140568)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS LUPUS NEPHRITIS SYNDECAN-1

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease that affects many organ systems. Lupus nephritis (LN), which occurs in over 50% of patients with SLE, is a severe manifestation of SLE with considerable morbidity and mortality[1]. Although recent advances in immunosuppressive treatment have significantly improved renal function and survival in patients with SLE, 10–26% patients with LN still progress to endstage renal disease[2]. Early detection of renal damage can improve clinical outcome, because delayed diagnosis of LN increases the risk of endstage renal disease[3]. Laboratory variables that have been used to measure renal damage include serum creatinine, urine sediments, 24-h proteinuria, levels of complements, and anti-dsDNA titers; however, these are neither sensitive nor specific enough to predict activity and flares of nephritis[4].

Renal biopsy is considered more informative than current laboratory variables for determining the activity and prognosis of LN that guide treatment decisions[5]. Nevertheless, repeated biopsy is not routinely performed because of invasiveness and risk of bleeding. A noninvasive, easily obtainable, and reproducible biomarker to predict the onset of nephritis and assess the activity and response to treatment would be useful for effective management. Several murine SLE studies have demonstrated the importance of cytokines, chemokines, and adhesion molecules in mediating renal inflammation and injuries[6,7]. A number of biomarkers with potential diagnostic value in LN have been identified in human studies; these include serum and/or urine levels of interleukin 18, monocyte chemoattractant protein-1, regulated upon activation normal T cell expressed and

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Accepted for publication October 23, 2014.

secreted (RANTES), interferon-γ, inducible protein-10 (IP-10)/CXCL10, and vascular cell adhesion molecule-1[4,8,9].

Syndecan is a member of the heparin-sulfate proteoglycan family, and plays divergent roles in several biological processes including inflammation, wound healing, development, and tumor progression[10]. Of the 4 subtypes of syndecans, syndecan-1 (SDC-1), also known as CD138, is predominantly expressed on the surface of plasma cells, endothelial cells, and epithelial cells[10]. The extracellular domain of SDC-1 can be readily shed from the cell surface and released into extracellular fluids under certain pathologic conditions. Elevated levels of soluble SDC-1 have been found in the blood of patients with multiple myeloma, diabetic nephropathy, and acute graft-versus-host disease, as well as in patients undergoing dialysis or major vascular surgery[11,12,13,14,15,16]. Serum SDC-1 levels were recently shown to be significantly higher in active SLE than in inactive SLE, and its levels were correlated with the ratio of CD138-positive plasma cells and SLE Disease Activity Index (SLEDAI)[17], but the association between SDC-1 levels and clinical manifestations of SLE was not assessed. In our study, we measured the serum level of SDC-1 in 111 patients with SLE to investigate its association with certain clinical manifestations of SLE.

MATERIALS AND METHODS

Study population. One hundred eleven patients with SLE fulfilling the revised American College of Rheumatology (ACR) classification criteria for SLE[18] were included. Patients were excluded if any of the following conditions that might influence serum SDC-1 levels was present: pre-existing overt coronary artery disease (typical angina, myocardial infarction), transient ischemic attack, stroke, vasculitis, pregnancy, or active infection[14,16]. For comparison, 20 age-matched and sex-matched healthy control subjects, and 18 patients with rheumatoid arthritis (RA) who fulfilled the ACR classification criteria for RA[19], were included. All patients were recruited from the Division of Rheumatology of Yeouido St. Mary's Hospital, The Catholic University of Korea, in Seoul. Our study was carried out in accordance with the Helsinki Declaration and approved by the Institutional Review Board of Yeouido St. Mary's Hospital (No. SC12SISI0038). Written informed consent was obtained from all subjects.

Clinical and laboratory assessment. Clinical and laboratory data of patients with SLE and RA were obtained at the time of blood sampling. Disease duration and the presence of organ involvement and clinical features were recorded for these patients. Laboratory variables included urinalysis, complete blood count, serum creatinine, lipid profiles, erythrocyte sedimentation rate, and C-reactive protein. In patients with SLE, complement (C3, C4, CH50) and antibodies against dsDNA, Smith, ribonuclear protein, ribosomal P, SS-A/Ro, SS-B/La, cardiolipin, β_2-glycoprotein I and lupus anticoagulant were measured. Urine protein/creatinine (P/C) ratio was determined in a spot midstream urine sample as a substitute for 24-h urine protein estimation[20]. Renal biopsies were categorized according to the classification of the International Society of Nephrology/Renal Pathology Society[21] and activity and chronicity index were assessed[22]. SLEDAI and renal SLEDAI were used to estimate general disease activity[23] and renal activity[24], respectively. Current usage of medications was also retrieved, including glucocorticoids, hydroxychloroquine (HCQ), methotrexate (MTX), immunosuppressants [azathioprine (AZA), mycophenolate mofetil (MMF)], and statin. Serum samples were obtained and stored at –80°C until assay.

ELISA for serum SDC-1. Serum levels of SDC-1 were measured using a commercially available ELISA kit (Cell Sciences Inc.) according to the manufacturer's instructions. Briefly, 100 μl of serum and diluted standards were added to wells precoated with monoclonal antibody specific soluble CD138, followed by adding 50 μl of biotinylated anti-CD138 secondary antibody. After incubation for 1 h at room temperature and washing the plate 3 times, 100 μl of streptavidin-horseradish peroxidase was added to each well and left to incubate for 30 min at room temperature. After washing 3 times, 100 μl of tetramethylbenzidine substrate was added to the wells, followed by incubation for 15 min. The color reaction was stopped by adding H_2SO_4 and absorbance was measured at 450 nm. The standard curve ranged from 8 to 256 ng/ml. In selected samples, the results of serum SDC-1 determined by ELISA were verified by immunoprecipitation and Western blot analysis, which detected a band of about 100 kDa (data not shown).

Statistical analysis. Results for continuous data are presented as the means ± SD or medians with interquartile ranges (IQR) according to the distribution of the variables, and their comparisons between groups were made using Student t test or Mann-Whitney U tests. Categorical or dichotomous variables were summarized by frequency (in percentages) and were compared using the chi-squared test or Fisher's exact tests. Correlation between 2 variables was assessed using the Spearman's correlation coefficient. Two-sided p values of < 0.05 were considered statistically significant.

RESULTS

Characteristics of the study population. One hundred eleven patients with SLE and 20 age-matched and sex-matched healthy controls were enrolled in the study. We also included 18 patients with RA who showed no extraarticular manifestations, as a disease control group. Demographic and clinical characteristics of the study subjects are shown in Table 1. Of the 111 patients with SLE, 74 (66.7%) had mucocutaneous manifestations, 75 (67.6%) had hematologic manifestations, 54 (48.6%) had arthritic manifestations, and 21 (18.9%) showed pleuropericardial involvement. Fifty-three patients (47.7%) had renal involvement and 46 underwent kidney biopsy: 35 with class IV (1 superimposed on class V), 5 with class III, 3 with class II, and 3 with class V. Of the 53 with LN, 30 had active disease, while 23 had inactive LN according to the criteria of Bombardier, *et al*[23]. Neuropsychiatric manifestations and antiphospholipid syndrome were observed in 19 (17.1%) and 20 patients (18%), respectively. One hundred eight patients (97.3%) were taking glucocorticoid, 95 (85.6%) were receiving HCQ, 21 (18.9%) were receiving AZA, and 24 (21.6%) MMF. Fifteen patients (9.3%) were treated with MTX weekly.

Serum SDC-1 levels are increased in patients with SLE and are correlated with variables of disease activity. As shown in Figure 1, patients with SLE had significantly higher serum SDC-1 levels than did healthy controls [34.2 (20.9–54.0) vs 18.5 (14.5–27.6) ng/ml] and patients with RA [12.8 (8.7–21.5) ng/ml; both $p < 0.001$], while no difference was observed between healthy controls and patients with RA ($p > 0.05$). When patients with SLE were divided into 2 groups based on their SLEDAI score, the active SLE group ($n = 49$, SLEDAI score > 4) had significantly higher serum SDC-1 levels than did the inactive SLE group [$n = 62$, SLEDAI

Table 1. Demographic and clinical characteristics of the study groups. Values are presented as median (interquartile range) unless otherwise indicated.

Characteristics	SLE, n = 111	RA, n = 18	Controls, n = 20	p
Age, yrs, mean ± SD	36.4 ± 10.8	38.1 ± 7.8	36.3 ± 8.5	0.163†
Female, n (%)	97 (87.4)	15 (83.3)	18 (90.0)	0.401‡
Disease duration, yrs	9 (5–13)	4 (2–8)	NA	0.403§
SLEDAI	8 (4–16)	NA	NA	
Renal SLEDAI	4 (0–12)	NA	NA	
eGFR, ml/min	77.7 (44.3–91.4)	87.0 (83.4–89.5)	NA	0.589§
Urinary P/C ratio	1.36 (0.3–5.2)	NA	NA	
C3, mg/dl	59.0 (41.0–75.3)	NA	NA	
C4, mg/dl	10.8 (5.9–16.9)	NA	NA	
CH50, U/ml	26.1 (13.4–38.8)	NA	NA	
Anti-dsDNA titer, IU/ml	170.0 (73.8–400)	NA	NA	
ESR, mm/h	27 (11–42)	25 (13–35)	ND	0.316§
CRP, mg/l	0.76 (0.35–3.0)	4.9 (2.8–10.5)	ND	< 0.001§
Kidney biopsy, n (%)	46 (41.4)	NA	NA	
WHO classification				
II	3 (6.5)			
III	5 (10.9)			
IV	35 (76.1)			
V	3 (6.5)			
Activity score	8 (4–10)			
Chronicity score	3 (1.5–4.5)			
Medication				
Steroid, n (%)	108 (97.3)	12 (66.7)	NA	< 0.001‡
Prednisolone, mg	5 (5–10)	3.75 (0–5)	NA	< 0.001§
MMF, n (%)	24 (21.6)	0	NA	
AZA, n (%)	21 (18.9)	0	NA	
MTX, n (%)	15 (9.3)	17 (94.4)	NA	< 0.001‡
HCQ, n (%)	95 (85.6)	12 (66.7)	NA	0.083‡
ACEI/ARB, n (%)	42 (37.8)	1 (5.6)	NA	0.060‡
Statin, n (%)	24 (21.6)	2 (11.1)	NA	0.526‡

P values were obtained by †independent t test, ‡chi-square test, or §Mann-Whitney U test. SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; RA: rheumatoid arthritis; eGFR: estimated glomerular filtration rate; P/C ratio: protein/creatinine ratio; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; MMF: mycophenolate mofetil; AZA: azathioprine; MTX: methotrexate; HCQ: hydroxychloroquine; ACEI/ARB: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; NA: not applicable; ND: not done.

score ≤ 4; 42.1 (23.7–67.0) vs 29.8 (18.7–39.6) ng/ml, $p < 0.01$]. In correlation analyses, serum SDC-1 level showed positive correlation with SLEDAI score and anti-dsDNA antibody titer ($r = 0.367$, $p < 0.001$ and $r = 0.259$, $p = 0.007$, respectively), but negative correlation with C3 and CH50 levels ($r = –0.305$, $p = 0.001$ and $r = –0.244$, $p = 0.012$, respectively; Appendix 1). These correlations were still significant after adjustment for estimated glomerular filtration rate (eGFR), which was inversely correlated with serum SDC-1 level in our study ($r = –0.247$, $p = 0.010$). However, we did not find any association between serum SDC-1 and current use of medication (data not shown).

Patients with active LN have increased serum SDC-1 levels. Because serum SDC-1 levels were correlated with SLEDAI score and the active nephritis group (n = 30) had a higher SLEDAI score [12 (8–16)] than the inactive nephritis (n = 23) and nonrenal groups [n = 58; 4 (4–6) and 4 (2–4), both $p < 0.001$], we compared the serum SDC-1 levels between the nephritis group and the nonrenal group. As shown in Figure 2A, patients with active nephritis had a significantly higher serum SDC-1 level [59.6 (40.5–143.0) ng/ml] than did patients with inactive nephritis [23.5 (16.8–36.5) ng/ml, $p < 0.001$] or without nephritis [30.1 (18.9–43.7) ng/ml, $p < 0.001$]. There was no difference in serum SDC-1 levels between the inactive nephritis group and the nonrenal group ($p > 0.05$). However, serum levels of SDC-1 did not differ between patients with and without rash, mucosal ulcer, arthritis, cardiopulmonary involvement, neuropsychological disorder, or hematological manifestation (data not shown).

To investigate whether serum SDC-1 level could distinguish patients with nephritis from those with an extrarenal flare, we compared serum SDC-1 levels among patients with active nephritis, extrarenal flare, and quiescent nonrenal SLE. As shown in Figure 2B, serum SDC-1 levels were significantly higher in patients with active nephritis (n = 30) than in those with extrarenal flare [n = 20; 59.6

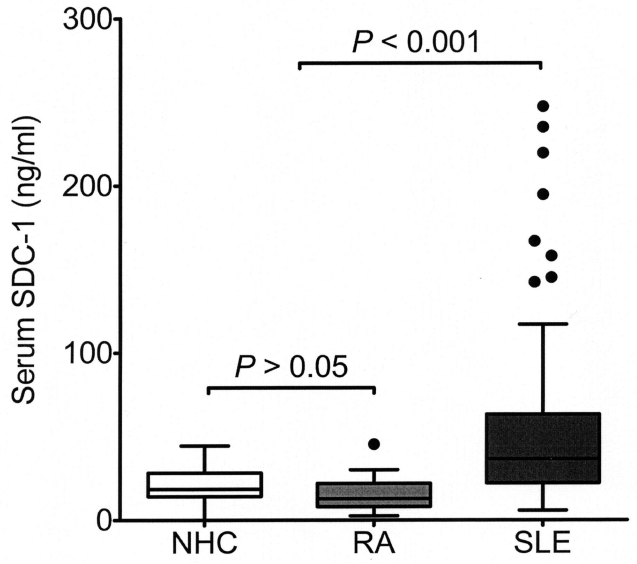

Figure 1. Serum syndecan-1 (SDC-1) levels in patients with systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and normal healthy controls (NHC). SDC-1 serum levels [median (interquartile range)] were significantly higher in patients with SLE [34.2 (20.9–54.0) ng/ml] than in patients with RA [12.8 (8.7–21.5) ng/ml] and NHC [18.5 (14.5–27.6) ng/ml]. P < 0.001 versus NHC and patients with RA. This difference was still significant after adjustment for estimated glomerular filtration rate (p < 0.001).

(40.5–143.0) vs 32.6 (19.0–61.8) ng/ml, p < 0.01], while there was no difference in serum SDC-1 levels between patients with extrarenal flare and quiescent nonrenal lupus [n = 44; 29.8 (18.7–38.5) ng/ml, p > 0.05]. As shown in Figures 2C and 2D, serum SDC-1 levels were correlated with renal SLEDAI score (r = 0.540, p < 0.001) and excretion of proteinuria measured by spot urine P/C ratio (r = 0.538, p < 0.001), respectively. Of note, these correlations were also observed in 20 patients with LN, whose serum was sampled after 12 months of treatment (r = 0.600, p = 0.005, r = 0.453, p = 0.045; Appendix 2). These results indicate that serum SDC-1 levels are increased in SLE patients with active nephritis, and its level primarily reflects renal activity.

Relationship between serum SDC-1 level and renal biopsy index. To determine the association between serum SDC-1 levels and biopsy indices, we analyzed 14 patients with LN whose serum samples were obtained at the time of renal biopsy. Unfortunately, the relationship between serum SDC-1 levels and histologic types of LN could not be assessed because all patients had proliferative LN (1 with class III and 13 with class IV). However, serum SDC-1 levels were significantly correlated with activity index (r = 0.632, p = 0.015), but not chronicity index (r = 0.097, p = 0.742; Appendix 3). This significant association was not altered after adjustment for eGFR (r = 0.647, p = 0.012). Although the number of serum samples obtained simultaneously in patients who underwent renal biopsy was not enough to ensure the reliability of the analyses, these findings suggest that serum SDC-1 levels may be a valuable noninvasive biomarker for prediction of histological activity of LN.

DISCUSSION

In our present study, we corroborated and extended the study of Minowa, *et al*[17]; they showed that serum SDC-1 levels were significantly elevated in SLE patients with active disease compared to those with inactive disease, and were positively correlated with the percentage of CD138-positive plasma cells and SLEDAI score. In general, patients with active SLE can present a wide spectrum of manifestations that affect any of the major organ systems; however, the association between SDC-1 level and clinical manifestations of SLE was not evaluated in the previous study because of the relatively small numbers of patients studied (n = 22). In our study, we measured serum SDC-1 levels in 111 patients with SLE and determined the association between SDC-1 level and disease manifestations. We found that serum SDC-1 level was significantly higher in patients with nephritis than in those without nephritis, while it was not significantly different between patients with and without articular, cutaneous, cardiopulmonary, neuropsychiatric, or hematological involvement (data not shown).

Although serum SDC-1 level was positively correlated with SLEDAI score, SDC-1 level was not significantly elevated in SLE patients with extrarenal flare as opposed to renal flare, suggesting that a high serum SDC-1 level is relatively unique to nephritis in patients with SLE and not related to systemic inflammatory processes. This assumption is supported by our findings that serum SDC-1 level was not elevated in RA patients with evidence of systemic inflammation but no sign of kidney involvement, and that serum SDC-1 level was more strongly correlated with renal SLEDAI than total SLEDAI (r = 0.540, p < 0.001 vs r = 0.318, p = 0.020). Further, serum SDC-1 level was positively correlated with excretion of proteinuria as measured by the P/C ratio. These data indicate that high serum SDC-1 levels in patients with SLE may reflect renal activity, thus potentially serving as a useful serum biomarker in SLE patients with nephritis.

Endothelial glycocalyx, a carbohydrate-rich layer lining the luminal side of the endothelium, plays a role in the regulation of vascular adhesiveness and permeability. SDC-1, a transmembrane proteoglycan located on the luminal surface of endothelial cells, forms the backbone of the endothelial glycocalyx[25,26,27]. Serum SDC-1 is considered to be a marker of endothelial glycocalyx degradation because loss of endothelial glycocalyx was associated with increasing levels of circulating SDC-1[16,28]. Given that damage to the endothelial glycocalyx after systemic inflammation and/or ischemia/reperfusion leads to an increase in

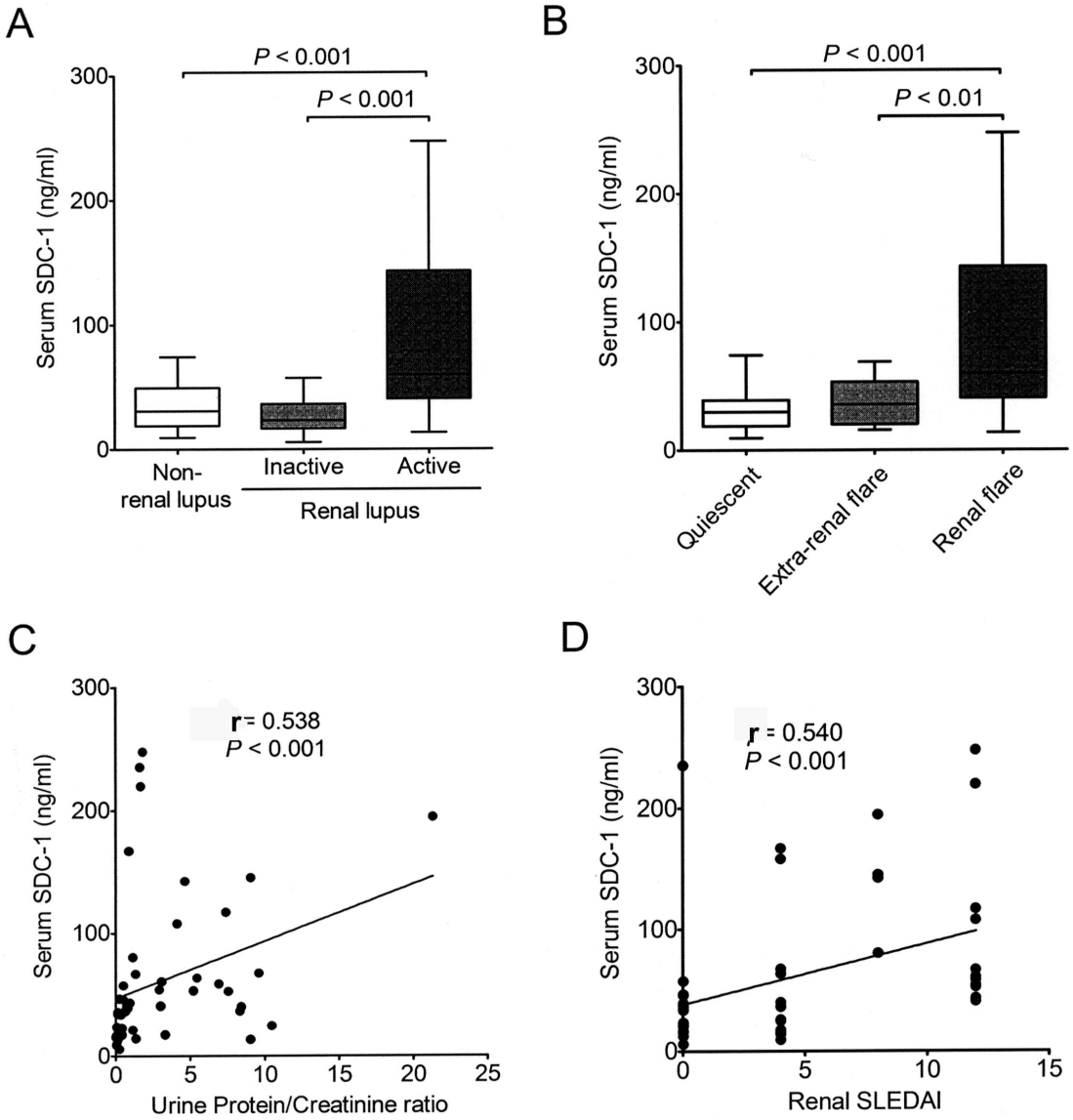

Figure 2. Elevated serum SDC-1 levels in SLE patients with LN and the correlation between serum SDC-1 level and renal disease activity. A. Patients with active LN [n = 30, 59.6 (40.5–143.0) ng/ml] had a higher serum level of SDC-1 than that of patients with inactive LN [n = 23, 23.5 (16.8–36.5) ng/ml, p < 0.001] and those without LN [n = 58, 30.1 (18.9–43.7) ng/ml, p < 0.001]. B. Serum SDC-1 levels in patients with active LN [n = 30, 59.6 (40.5–143.0) ng/ml] were higher than those in patients with extrarenal flare [n = 20, 32.6 (19.0–61.8) ng/ml, p < 0.01] or quiescent nonrenal SLE [n = 44, 29.8 (18.7–38.5) ng/ml, p < 0.001]. Values are medians with IQR. C and D. Serum SDC-1 levels were positively correlated with urine P/C ratio (r = 0.538, p < 0.001) and renal SLEDAI (r = 0.540, p < 0.001). These differences or associations remained significant after adjustment for eGFR (data not shown). SDC-1: syndecan-1; SLE: systemic lupus erythematosus; LN: lupus nephritis; IQR: interquartile range; P/C: protein/creatinine; SLEDAI: SLE Disease Activity Index; eGFR: estimated glomerular filtration rate.

vascular permeability and promotes inflammation by enhancing the leukocyte adhesion to endothelial cells[29,30], elevated serum SDC-1 levels in patients with LN may reflect the damage of the glomerular endothelial glycocalyx, which constitutes the glomerular filtration barrier[31]. In accordance with this proposition, disruption of the endothelial glycocalyx has been shown to be associated with albuminuria[32], and most forms of glomerular endothelial cell injury, including preeclampsia, thrombotic microangiopathy, and diabetic nephropathy, can cause proteinuria[32,33]. Conversely, protection of the glycocalyx with hydrocortisone and antithrombin, which reduce the glycocalyx shedding[34], alleviates the vascular leakage, tissue edema, and inflammation[35].

Besides endothelial cells, SDC-1 (CD138) is also expressed in plasma cells and is a well-recognized marker of

plasmacytic differentiation[36]. An earlier study showed that SDC-1 is highly expressed in malignant plasma cells and is shed from the surface of myeloma cells into serum[37]. As mentioned[17], serum SDC-1 levels were found to be elevated in patients with SLE and were positively correlated with percentage of circulating CD138+ plasma cells, suggesting that serum SDC-1 might be derived from CD138+ plasma cells. Several studies have provided evidence that CD138 may be involved in LN pathology. For instance, a large number of anti-dsDNA antibody–secreting plasma cells were present in the kidneys of NZB/W mice, and their numbers were correlated with the serum dsDNA-IgG titer[38]. In patients with LN, CD138+ cells were located around the glomeruli or the tubulointerstitium of the margin between the renal cortex and the medulla[39]. CXCR3 chemokine receptor, which is crucial for trafficking of Th1 cells into inflamed tissue, was preferentially expressed by CD138high/MHCII+ IgG-secreting plasma cells[40]. Taken together, it is conceivable that high expression of the cognate chemokine, IP-10/CXCL10, in the kidneys of patients with LN[41] may enhance the chemotaxis of these cells to areas of inflammation in the kidneys, thereby contributing to renal pathology by local production of IgG autoantibody. It is notable that expressions of inflammatory mediators such as matrix metalloproteinase-9, RANTES, and heparanase, which are known to enhance SDC-1 shedding from cell surfaces[42,43,44], are upregulated in the kidneys of patients with LN[6,45,46].

Although SDC-1 is the major syndecan expressed in epithelial cells, it is unlikely that increased serum levels of SDC-1 are derived from the keratinocyte, because there was no discernible association of serum SDC-1 levels with cutaneous manifestations (data not shown). SDC-1 is also expressed in tubular epithelial cells of the kidneys. Compared with control kidney tissue, SDC-1 expression was increased on tubular epithelial cells of kidney biopsies obtained from renal allograft[47] and proteinuric renal disease, including IgA nephropathy, minimal change nephropathy, and LN[48]; however, the increase of SDC-1 expression in renal biopsies of proteinuric patients was not reflected in the urine because the concentration of SDC-1 shed into the urine was not different between controls and proteinuric patients.

It is unclear whether the increase in soluble SDC-1 levels in patients with SLE is merely a marker of renal damage or plays a distinct role in glomerular pathology. Previous studies showed that soluble SDC-1 promoted growth of myeloma tumors *in vivo*[49], and increased cell invasion of breast cancer cells[50], indicating that the proteolytically shed SDC-1 ectodomain remains biologically active. In fact, shed SDC-1 ectodomains have been shown to induce neutrophil chemotaxis and impair alveolar wound healing following asbestos or bleomycin exposure, whereas SDC-1 expressed on cell surface promoted alveolar wound healing[51]. On the basis of these data, it is interesting to speculate that SDC-1, shed either from plasma cells that infiltrate the kidney or the glomerular endothelial glycocalyx, could in turn enhance the survival of plasma cells and increase neutrophil recruitment into the kidneys, thereby perpetuating the inflammatory response in the kidneys of patients with LN. However, another study in sepsis model reported that shed SDC-1 ectodomains facilitated the resolution of inflammation by neutralizing a number of proinflammatory mediators, such as proteases, chemokines, and cytokines through binding to their heparin sulfate chains[52]. This discrepancy might be attributed to the different disease settings, inciting stimuli (infection vs inflammation) and inflammation status (acute vs chronic).

We demonstrated that serum SDC-1 levels are elevated in SLE patients with nephritis compared to those without nephritis and that this reflects the renal activity, as evidenced by the correlation between serum SDC-1 levels and renal SLEDAI and urinary P/C ratio, as well as the histologic activity index. These data suggest that serum SDC-1 could be used as a potential biomarker of active renal inflammation in LN and can provide additional information about renal activity to that provided by established markers. Further studies are needed to confirm these results in a longitudinal large-cohort study of patients with SLE and to elucidate the mechanistic role of soluble SDC-1 in LN.

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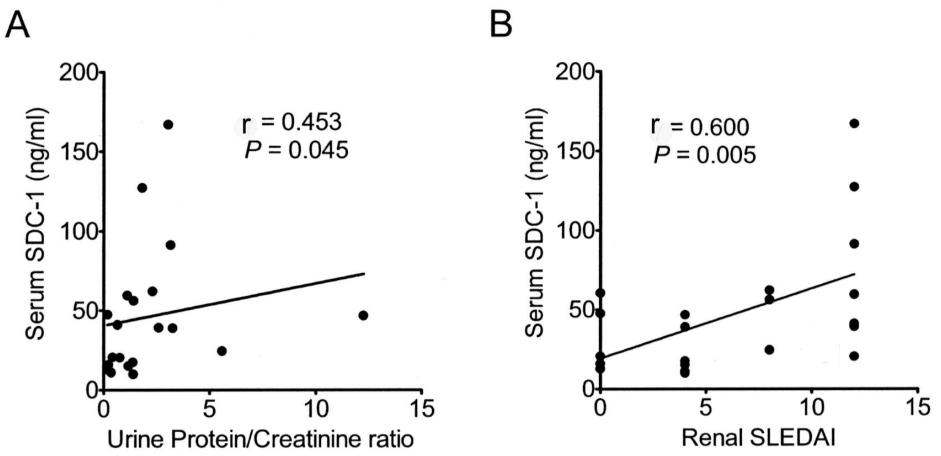
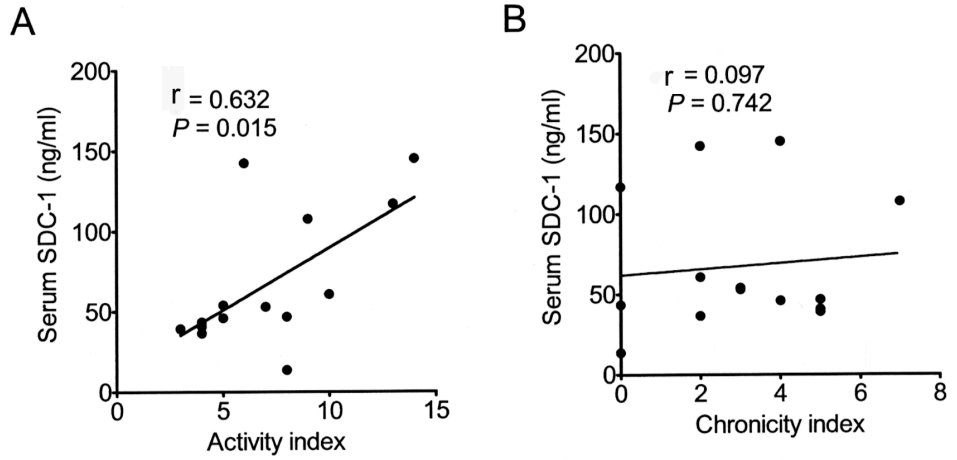
APPENDIX 1. Correlation between serum SDC-1 level and systemic lupus erythematosus (SLE) disease activity indices.

	Univariate		Adjusted for eGFR	
	r	p	r	p
SLEDAI	0.367	< 0.001	0.350	< 0.001
Anti-dsDNA, IU/ml	0.259	0.007	0.350	< 0.001
C3, mg/dl	–0.305	0.001	–0.311	0.001
C4, mg/dl	–0.128	0.190	–0.172	0.082
CH50, U/ml	–0.244	0.012	–0.251	0.010

r = Spearman's correlation coefficient. SDC-1: syndecan-1; SLEDAI: SLE Disease Activity Index; eGFR: estimated glomerular filtration rate.



APPENDIX 2. Twenty patients were followed up after 12 months of treatments, and correlations between serum SDC-1 level with urine P/C ratio (A) and renal SLEDAI (B) were significant. SDC-1: syndecan-1; P/C: protein/creatinine; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.



APPENDIX 3. Relationship of serum SDC-1 level to activity and chronicity indices of renal histology. Serum SDC-1 levels were significantly correlated with activity index (r = 0.632, p = 0.015; panel A), but not chronicity index (r = 0.097, p = 0.742; panel B) in patients with lupus nephritis. This association remained significant after adjustment for estimated glomerular filtration rate. SDC-1: syndecan-1.