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Serum Sirtuin 1 as a potential indicator of disease activity and severity in systemic lupus erythematosus patients

Wafaa Soliman[1], Ayah T. Abdel-Zaher[2], Amira A. Moharram[3], Nada Saeed[4] and Aya Safar[1]

[1]Department of Physical Medicine, Rheumatology & Rehabilitation, Faculty of Medicine, Ain Shams University, Cairo, Egypt.

[2]Department of Internal Medicine, Rheumatology Division, Faculty of Medicine, Ain Shams University, Cairo, Egypt.

[3]Department of Clinical Pathology, Faculty of Medicine, Ain Shams University, Cairo, Egypt.

[4]Department of Medical Microbiology & Immunology, Faculty of Medicine, Ain Shams University, Cairo, Egypt.

Corresponding author: Aya Safar, Department of Physical Medicine, Rheumatology & Rehabilitation, Faculty of Medicine, Ain Shams University, Cairo,, Egypt.
Email: ayahamed@med.asu.edu.eg

Abstract

The aetiology and pathophysiology of systemic lupus erythematosus (SLE), are yet unclear. Autoantibodies that target various organs and tissues are produced as a result of SLE patients' poor immunological tolerance. Sirtuin-1 (SIRT1) is a histone deacetylase that has a major role in immune responses, apoptosis, and cell differentiation, through alteration of various signalling cascades, including nuclear factor κ-light chain enhancer and activator protein 1 of activated B cells cascades. According to recent data, SIRT1 is an immune system regulator factor, and its impaired action probably play a role in SLE pathogenesis. This study intended to determine whether SIRT1 can be an indicator for SLE severity and activity. This study comprised 30 SLE patients, with a mean age of 28.23 ± 5.21 years and 3.21 ± 1.2 years as duration of the disease. The normal control group consisted of 30 matched adults, aged 27.3±6.22 years (p=0.266). There was a significantly increase in the mean±SD of SIRT1 in SLE patients (28.72±5.83), compared to the control group (22.1±5.59) (p<0.05). **S**erum SIRT1 was significantly correlated to disease duration, SLEDAI, Katz score, ESR, CRP and renal biopsy classes. However, it was negatively correlated to C3, C4 and there was no correlation with age. A significant elevation was noted in the mean±SD of SIRT1 in active SLE patients (22.7 ± 13.77) compared to inactive SLE patients (6.02±11.27) (p <0.05). Also, the mean±SD of SIRT1 was significantly raised in patients with high SLE disease severity (17.94 ± 15.64) in contrast to those with low SLE disease severity (10.78±13.76) (p<0.05). In conclusion, SIRT1 serum levels were higher in patients with SLE, both with high and low disease severity. Thus, SIRT1 may be a serological indicator for the severity and activity of SLE.

Keywords: SLE, Sirtuin1; SLEDAI, Katz; Renal biopsy.

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Introduction

Systemic lupus erythematosus (SLE) is an immune-based illness identified by autoantibody synthesis, dysregulated stimulation of self-reactive T and B lymphocytes, and inadequate self-antigen tolerance.[1] Functional impairment of multiple

body organs and systems, including the central nervous system, joints, skin, kidneys, hematological system, and cardiovascular system, is a hallmark of SLE.[2]

Sirtuins are a class III histone deacetylase family that is a seven-member family naturally present inside most of the human body's cells and responsible for multiple cellular functions including metabolism, apoptosis, stress response, survival of cell, and stability of genome. Sirtuins are involved in mitochondrial biogenesis, aging, insulin sensitivity, endocrine signalling, osteoblast development, and the circadian rhythm. Additionally, they were linked to a number of disorders associated with aging, such as cancer, type 2 diabetes mellitus, and cardiac diseases.[3] The cell cytoplasm and nucleus have Sirtuin1 (SIRT1), the mitochondria contain Sirtuin 3-5, the nucleus has Sirtuin 6, and the nucleolus contains Sirtuin 7.[4]

Numerous biological processes, including metabolism, immunological control, and the release of inflammatory cytokines, depend on SIRT1 enzyme [5] A recent research study showed that blocking SIRT1 causes CD4+ T cells to produce less autoantibodies, which in turn reduces kidney injury. Consequently, it is hypothesized that SIRT1 is involved in SLE aetiology.[6] In the current investigation, serum SIRT1 levels in SLE patients were measured and associated with the disease severity and activity.

Patients and Methods

The study involved 30 SLE patients and 30 matched normal controls, who visited the rheumatology clinic as volunteers. The included 30 SLE patients were diagnosed based on the new ACR/ EULAR 2019 classification criteria.[7]

Patients with severe liver and kidney diseases, metabolic bone disorders, cardiovascular diseases, medications that affect bone metabolism or malignancy were excluded.

All included patients and controls were subjected to history taking of medical condition and demographic information, as well as thorough clinical examination. The Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score (active disease > 3) was used to evaluate disease activity.[8] The Katz score was used to measure the severity of the disease where < 4 was considered as low disease severity and ≥ 4 was considered as high disease severity. [9]

Collection and analysis of the Blood Samples

Every participant in the study provided two venous blood samples. After complete blood clotting, the first sample (4 ml) was placed into a serum separation tube (gel vacutainer) and centrifuged at 2683 g for 15 minutes. After that, the serum was collected and kept at -80°C until used for the evaluation of SIRT1, antinuclear antibody (ANA) titer, anti-DNA titre, C3, C4, C-Reactive Protein (CRP), serum creatinine, **b**lood urea nitrogen (BUN), aspartate aminotransferase (AST), and alanine aminotransferase (ALT). In order to determine the erythrocyte sedimentation rate (ESR), a second sample (2 ml) was collected in a sodium citrate vacutainer tube.

Sirtuin1 level in serum and additional laboratory indicators

Serum Sirtuin1 was evaluated using the human Sirtuin1 enzyme-linked immunosorbent assay (ELISA) commercial kits (catalogue Number: E2557Hu, provided by Bioassay Technology Laboratories, Shanghai Korain Biotech, China), according to the manufacturer's instructions. The optical density (OD) values of the samples were translated into ng/ml using the standard curve, which was plotted using five standards, provided in the kits.

Indirect immunofluorescence assays were utilized to check for anti-DNA and ANA titers using commercial kits (Inova Diagnostics, USA), according to the manufacturer's instructions. The Cobas c6000 autoanalyzer (Roche Diagnostics, Basel, Switzerland) was used to measure serum creatinine and BUN levels as well as AST and ALT activity. Quantitation of CRP, C3 and C4 levels was done using a nephelometry (Attelica Neph 630 system, Siemens Healthineers AG, Forchheim, Germany), according to the manufacturer's instructions and ESR was determined by the Westergren method.

Statistical Analysis

The data statistical analysis was performed using the Statistical Package for Social Science software (SPSS, version 25) on a Personal Computer. Non-numerical data are displayed as frequency and percentage, whereas parametric numerical data displayed as mean ± standard deviation and range. The statistical significance of the difference between the means of two research groups was ascertained using the Student T Test. The degree of correlation between two quantitative variables was ascertained using the Spearman's rho method. Linear relationship between two variables was calculated with the correlation coefficient denoted as "r". Strong correlations were defined as r = 0.6-0.79, moderate correlations as r = 0.40-0.59, weak correlations as r = 0-0.39, very weak correlations as r = 0-0.19, and very strong correlations as r = 0.8-1. The receiver operating characteristic (ROC) curve analysis was used to determine the sensitivity and specificity of diagnostic tests. The significance level was indicated at p <0.05.

Results

This study comprised 30 SLE patients, involving 26 females and 4 males. The average age was 28.23 ± 5.21 years (range: 20–40 years), and the average period of the illness was 3.21 ± 1.2 years (range: 1–5 years). The control group included 30 normal subjects with matched age (27.3 ± 6.22 years, 21 –38) (p=0.266).

Table 1 outlined the demographic, clinical, and laboratory information of the SLE patients. There was a significant increase in SIRT1 level among the SLE patients (28.72 ± 5.83) compared to the control group (22.1 ± 5.59) (p<0.05).

Table 1. Clinical, laboratory, and demographic characteristics of systemic lupus erythematosus (SLE) patients compared to normal controls.

Parameter	SLE Group		Healthy volunteers		*p*- value*
1. Demographic data					
Age (years) Mean ± SD	28.23 ± 5.21		27.3 ± 6.22		NS
Gender (%)	Male	Female	Male	Female	
	4 (13.3%)	26 (86.7%)	5 (16.7%)	25 (83.3%)	NS
2. Clinical and laboratory data (Mean ± SD)					
ESR	24.43 ± 9.59		11.17 ± 2.21		
CRP	9.33 ± 5.98		2.93 ± 1.31		
ALT	27.67 ± 3.77		26.93 ± 3.53		
AST	18.98 ± 3.17		17.8 ± 2.4		
BUN	22.97 ± 6.06		14.9 ± 2.12		
Creatinine	1.21 ± 0.48		0.67 ± 0.12		
Sirtuin 1 level	28.72 ± 5.83		22.1 ± 5.59		<0.001
C3	87.67 ± 8.79				
C4	24.07 ± 10.89				
Disease duration (years)	3.21±1.2				
SLEDAI (activity score)	23.23 ± 12.97				
Katz severity score	4.27 ± 1.76				

Table 1. Continued.

Parameter	SLE Group		Healthy volunteers	*p*- value*
Disease activity No. (%)	Active	Not Active		
	23 (76.7%)	7 (23.3%)		
ANA (positive) [No. (%)]	30 (100%)			
Anti dsDNA (positive) [No. (%)]	18(60%)			
Renal Biopsy [No. (%)]				
Class 1	6 (20%)			
Class 2	5 (16.7%)			
Class 3	6 (20%)			
Class 4	4 (13.3%)			
Class 5	4 (13.3%)			
No renal biopsy [No. (%)]	5 (16.7%)			

Student t test $p > 0.05$ is not significant (NS). Reactive Protein (CRP), blood urea nitrogen (BUN), erythrocyte sedimentation rate (ESR), aspartate aminotransferase (AST), and alanine aminotransferase (ALT). *****

Table 2 demonstrated significantly positive association between serum SIRT1 and disease duration, SLEDAI, Katz score, ESR, CRP and renal biopsy classes. However, Serum SIRT1 was negatively correlated with C3 and C4.

Table 3 revealed that SIRT1 levels were significantly greater in patients with active SLE (22.7 ± 13.77) compared to SLE patients in remission form (6.02 ± 11.27) (p<0.05). In addition, table 4 showed a significant increase in serum SIRT1 among patients with high disease severity (17.94 ± 15.64) compared to patients with low disease severity (10.78 ± 13.76) (p<0.05).

Table 2. Correlation of Serum Sirtuin-1 with other clinical and laboratory parameters.

Parameter	SIRT 1 (r value)	*p*-value*
Age	0.639	NS
Disease duration	0.709	≤0.001
SLEDAI	0.397	≤0.02
Katz score	0.286	≤0.001
ESR	0.139	≤0.02
CRP	0.087	≤0.001
C3	-0.359	≤0.001
C4	-0.815	≤0.022
Renal biopsy classes	0.609	≤0.001

*Student t test, $p > 0.05$ is not significant (NS).

Table 3. Comparison of Sirtuin-1 (SIRT1) serum levels in systemic lupus erythematosus (SLE) patients with activity versus SLE patients without activity.

	SLE patients with activity Mean±SD	SLE patients without activity Mean±SD	*p*-value*
SIRT1	22.7 ± 13.77	6.02 ± 11.27	p<0.001

*Student t test, $p \leq 0.05$ indicates statistical significance.

Table 4. Comparison of Sirtuin-1 (SIRT1) serum levels in systemic lupus erythematosus (SLE) patients with varying degrees of disease severity.

	SLE patients (Mean±SD)		
	With high disease severity	With Low disease severity	*p* value*
SIRT 1	17.94 ± 15.64	10.78±13.76	*p*<0.03

*Student t test, *p* ≤0.05 indicates statistical significance.

The ROC curve analysis is displayed in Figure 1 with 86.7% sensitivity and 60.0% specificity. Serum SIRT1 exhibited good diagnostic performance in differentiating SLE patients from normal controls (cut-off value 22.77 ng/dl). Furthermore, Sirtuin1 demonstrated 56.5% sensitivity and 85.7% specificity in separating active from inactive SLE patients (cut-off value 29.60 ng/dl). Additionally, Sirtuin1 has a sensitivity of 66.7% and specificity of 83.3% for differentiating between high and low illness severity (cut-off value 29.60 ng/dl).

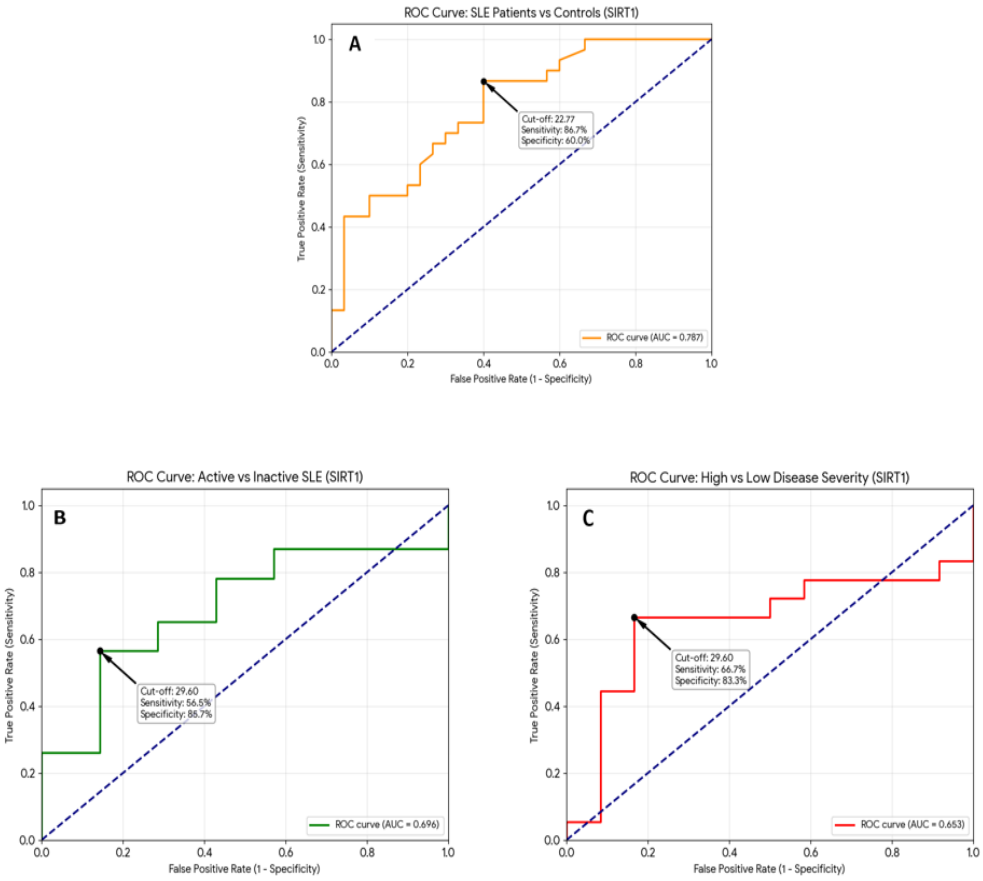

Figure 1. Receiver operating characteristic (ROC) curve analysis of serum Sirtuin1.
(A) discrimination between systemic lupus erythematosus (SLE) patients and normal controls, (B) differentiation between active and inactive SLE, and (C) discrimination between high and low disease severity. Each ROC curve displays the area under the curve (AUC), cut-off values, sensitivity, and specificity.

Discussion

This research was designed to evaluate serum SIRT1 level in individuals with SLE and correlate it with activity and severity of SLE disease. Our study revealed that SIRT1 might function as a positive regulatory mechanism in the lupus disease. The results imply higher SIRT1 levels in patients with SLE compared to normal controls. Also, there was a positive correlation between serum SIRT1, disease duration, SLEDAI, Katz score, ESR, CRP and renal biopsy classes. However, there was negative correlation with C3, C4, but there was no correlation with age.

Our study indicated that elevated SIRT1 levels in serum of SLE patients was in line with other research that assessed SIRT1 expression in B cells from people with subacute lupus erythematosus and CD4+ T cells from SLE patients.[10] Thus, our results imply that SIRT1 may be a biomarker in individuals with SLE and that SIRT1 is implicated in the pathophysiology of SLE.

In the current study, raised serum SIRT1 level was positively linked to disease activity and disease severity. Higher serum SIRT1 levels were present in patients with active SLE compared to patients in remission. Also, there was higher SIRT1 levels in SLE patients with higher severity scores compared to SLE patients with reduced disease severity score. This comes in parallel with findings of a study by Yang and his colleagues.[11]

It was noticed that patients who had arthritis, headache, haematuria, leukocyturia, and positive anti-dsDNA, had significantly higher levels of SIRT1 in comparison to patients without these characteristics. This indicated the involvement of SIRT1 in organ and system damage in SLE individuals which is particularly responsible for haematological system, central nervous system and joints affection. Additionally, a prior research study revealed that SIRT1 was highly expressed in a variety of autoimmune conditions.[12] SLEDAI score, lupus nephritis, and increased mortality in SLE patients could be linked to SIRT1 gene polymorphism.[13] A previous research suggested that proliferation of B lymphocytes, suppression of apoptosis, and up-regulation of tumor necrosis factor-α (TNFα) could be attributed to SIRT1 overexpression.[14]

Excessive inflammation in lupus patients was positively connected with SLE disease activity and may have encouraged increased production of SIRT1. Elevated SIRT1 expression may positively control T cell and macrophage cytokine output, hence exacerbating inflammation.[15] In addition to upregulating IL-17A and IL-22 in CD4+ T cells, SIRT1 activation results in an imbalance between Th-17 and T-reg.[16]

In the meantime, Anti-dsDNA, C3, and C4 were useful in tracking of SLE disease activity. However, there is little accuracy in diagnosing SLE, particularly in terms of sensitivity. [17] Given that serum SIRT1 was elevated in both active SLE patients and SLE patients with severe disease, it may serve as an indicator for both disease activity and severity.

Although this study ended up with remarkable findings, it faced some limitations. As there was a restriction on the number of patients. Also, we did not assess SIRT1's activity in preclinical and early-stage SLE patients which would have shown SIRT1's diagnostic or prognostic relevance. Longitudinal studies observing changes in serum SIRT1 expression in SLE patients with varying disease activity may help to strengthen such evidence and to get more understanding of SIRT1's function as a dynamic biomarker for tracking SLE progression.

In conclusion, in the current study, patients with SLE had considerably higher serum SIRT1 concentrations, and higher levels were linked to more severe and active disease. All of these results suggested that SIRT1 may serve as a biomarker for evaluating the severity and activity of SLE.

Author Contributions

WS contributed to clinical examination, analysis and interpretation of patient’s data. ATA and AAM performed and analyzed laboratory data. NS shared in analysis of data. AS clinically examined the Patients and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

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Ethical approval

The study protocol was reviewed and approved by the Research Ethical Committee of the Faculty of Medicine, Ain Shams University.

Informed consent

The study participants were eligible according to the inclusion criteria and each participant provided a written informed consent before being included in the study.

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