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Sirtuin3 and Sirtuin7 are promising biomarkers in systemic sclerosis

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Abstract

Background Systemic sclerosis (SSc) is an autoimmune disease that results in micro-vasculopathy, leading to organ dysfunction. Sirtuins are known for their role in cellular processes such as the cell cycle, aging, and inflammation, Sirtuins also play an important role in regulating fibrotic responses, inhibiting collagen production and myofibroblast differentiation, implying that its dysregulation is involved in the pathogenesis of systemic sclerosis. The aim of this study was to determine the circulating Sirtuin3 and Sirtuin7 levels in patients suffering from systemic sclerosis with a focus on how they might be associated with the different clinical features and subsets of the disease.

Methods This prospective cross-sectional case–control study included 56 participants 41 SSc patients and 15 healthy controls. Demographics, clinical, and laboratory data were analyzed. Quantitative determination of human Sirtuin3 and Sirtuin7 concentrations was done.

Results Among systemic sclerosis patients, the age of SSc patients was 42.27 ± 10.46 years. The mean serum levels of Sirtuin3 and Sirtuin7 were significantly lower in SSc patients than in healthy controls ($p < 0.001$). SIRT3 and SIRT7 levels among SSc patients showed a statistically significant positive correlation ($p < 0.001$). SIRT7 level was insignificantly decreased in dcSSc (14.16 ± 5.93) than in lcSSc (20.01 ± 8.34). Regarding the SIRT3 level, there was an insignificant difference between dcSSc and lcSSc. Modified Rodnan's skin score correlated negatively with Sirtuin3 and Sirtuin7 levels. In systemic sclerosis patients with interstitial lung disease (56.1%), there was an insignificant difference in SIRT3 and SIRT7 levels (0.12 ± 0.01and 21.23 ± 8.23) compared with systemic sclerosis patients without interstitial lung disease (0.10 ± 0.01 and 17.47 ± 8.57), with $p = 0.408$ and 0.258, respectively. The receiver operating characteristic curve for SSc prediction with Sirtuin3 has an accuracy of 83.0%, sensitivity of 85.4%, and specificity of 80.0% and $p < 0.001$. Regarding Sirtuin7, it has an accuracy of 89.5%, sensitivity of 85.4%, and specificity of 93.3% and $p < 0.001$.

Conclusion Sirtuin3 and Sirtuin7 levels were found to have a significant positive correlation in SSc patients. Sirtuin3 and Sirtuin7 levels are both good diagnostic biomarkers for detecting and diagnosing SSc, with Sirtuin7 being more accurate, specific, and predictive of the disease than Sirtuin3. Sirtuin7 is thought to be a new biomarker for SSc disease.

Keywords Systemic sclerosis, Sirtuin3, Sirtuin7, mRSS

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Background

Systemic sclerosis (SSc) is an autoimmune disease that results in micro-vasculopathy, manifesting clinically with cutaneous and visceral fibrosis, Raynaud's phenomenon, ischemic digital ulcers, pulmonary artery hypertension, interstitial lung disease (ILD), and renal crisis, eventually causing significant organ dysfunction [1–3].

ILD is the main cause of death in patients with SSc, it is typically presented with interstitial pneumonia and peripheral bilateral reticulation with honeycombing mainly in the lower lobes, hypoxia, and reduced gas exchange due to lung architecture distortion, and finally respiratory failure and death [3–5].

Sirtuins (SIRTs), a remarkable regulator of metabolic processes, participate in gluconeogenesis, lipid metabolism, and mitochondrial activity, maintaining cellular energy supply homeostasis [6].

Sirtuins are seven nicotinamide adenine dinucleotide-dependent protein deacetylases. SIRT1, SIRT6, and SIRT7 are primarily located in the nucleus, while SIRT3, SIRT4, and SIRT5 are predominantly found in the mitochondria. SIRT2 primarily exists in the cytoplasm but transfers inside and outside of the nucleus [7–9]. They control the entire lipid metabolism process by eliminating the peroxisome proliferator-activated receptor as well as the peroxisome proliferator-activated receptor-gamma coactivator-1alpha [10, 11].

SIRT activation enhances mitochondrial oxidative metabolism as well as the resistance to oxidative stress. Furthermore, it fosters deoxyribonucleic acid damage restoration via anti-oxidant pathways including superoxide dismutase 2 in mitochondria and deacetylation or ADP-ribosylation of repair proteins [12]. SIRTs are best known for their role in cellular processes including the cell cycle, aging, metabolism of lipids, and inflammation through protein modifications such as deacetylation, mono-ADP-ribosyltransferase activity, and deformylation activity [6, 13], SIRTs also play an important role in controlling fibrotic responses, restricting the production of collagen as well as differentiation of myofibroblast, indicating that its dysfunction plays a role in SSc pathogenesis [14–16]. SIRT3 breaks down and weakens hypoxia-inducible factor-1α, affecting mitochondrial metabolic reprogramming. Because of the numerous roles that SIRT3 plays in controlling mitochondrial activity, metabolic processes, and dynamics, variations in SIRT3 levels within an aged lung will most likely result in a modified, or even impaired, reaction upon injury [17].

SIRT7 promotes neointimal formation after vascular injury and is essential in vascular smooth muscle cell proliferation. SIRT7 may thus be useful in the treatment and prevention of a number of vascular conditions [18]. Researchers observed a significant decrease in SIRT7 levels in lung cells from SSc-ILD patients and in mice with lung damage induced by bleomycin [19].

Numerous deficiencies in our understanding of SIRTs need to be filled in order to fully understand the importance of SIRTS in responses to inflammation and its mechanisms of action that could explain the various outcomes of autoimmune diseases.

Few earlier researches examined the function of SIRT3 in SSc patients, but this is the first study to our knowledge that analyzes the association between SIRT7 and diverse symptoms in SSc patients.

The goal of this research was to measure circulating SIRT3 and SIRT7 levels in SSc patients with a focus on how they might be associated with the different clinical features and subsets of the disease.

Patients and methods

In this prospective cross-sectional case–control research 56 participants were enrolled, from which 41 SSc patients were diagnosed according to the 2013 ACR/EULAR criteria for the classification of systemic sclerosis [20] after admission to the rheumatology and rehabilitation department in our university hospital from June 2022 to June 2023. Control involved 15 healthy individuals' sex and age-matched with the patients' group. The study excluded patients who were younger than eighteen, those with overlap syndrome or mixed diseases, patients with other rheumatologic diseases, and patients with intestinal lung disease not related to SSc. The study was conducted according to the Declaration of Helsinki's ethical principles after receiving acceptance from our faculty's local research ethics committee (IRP 17101143). The patients provided written informed consent to participate in the study.

Clinical examination and radiological assessment

All patients provided a full history, including their age, sex, occupation, marital status, smoking, disease duration, drug intake, and family history. The modified Rodnan skin score (mRSS) was used for evaluating skin involvement [21]. SSc patients underwent pulmonary function tests (PFT), chest x-rays, chest high-resolution computed tomography (HRCT), and echocardiography.

According to HRCT, patients were divided into SSc patients with ILD and the other group without ILD. ILD patients had different patterns in HRCT including septal thickening, ground glass opacities, cystic changes, honeycombing, tree in bud, consolidation, and distortion of lung architecture. For PFT, forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), and FEV1/FVC ratio were all measured. Patients were classified according to FEV1, which is the portion of the patient's vital capacity that can expire in the first second of forced expiration to complete FVC. Patients were classified based on FEV1 as mild (≤70), moderate (69–50), or severe (≤49). A restrictive ventilatory defect was defined based on spirometric findings of a 70% FEV1/FVC ratio and an 80% FVC [22].

Human SIRT3 and human SIRT7 assessment

Quantitative determinations of human SIRT3 and SIRT7 concentrations were done using SinoGeneClone Biotech Co., Ltd ELISA Kit, Catalog No: SG-10568 and SG-16125 respectively.

Principle

This ELISA kit used the Sandwich-ELISA technique. The micro ELISA plate included in this kit was pre-coated with an antibody specific to human SIRT3 and SIRT7. Standards or samples were added into the appropriate micro-ELISA plate wells and combined with the specific antibody. Then, horseradish peroxidase enzyme-labeled antibodies specific for human SIRT3 and SIRT7 were sequentially added to each microplate well and incubated. Following incubation, free components were washed out. The substrate solution (tetramethylbenzidine) was then added to each properly. The color has changed to blue. The enzyme–substrate reaction was stopped with the addition of a stop solution. The color alteration was determined as optical density using spectrophotometry at a wavelength of 450 nm. Calculation: The optical density value is proportional to the concentration of SIRT3 and SIRT7. The level of SIRT3 and SIRT7 in samples was determined by comparing the optical density to the standard curve.

Statistical analysis

The data was analyzed with the Statistical Package for Social Science, version 26.0 for Windows. Categorical data was provided in the form of frequencies and percentages, whereas numerical data were expressed using mean and standard deviation/standard error of the mean. Non-parametric tests were carried out after testing the data normality. The Mann–Whitney *U* test was applied for comparing the SIRT3 and SIRT7 levels in two independent groups. Spearman correlation was applied to investigate the correlation between SIRT3 and SIRT7 with various variables. The chi-square test was applied for comparing proportions among groups. A receiver operating characteristic (ROC) curve analysis was performed to determine SIRT3 and SIRT7's diagnostic ability to predict systemic sclerosis in a comparison with controls. The area under curve (AUC), sensitivity, specificity, positive predictive value, and negative predictive value were determined. *P*-values ≤ 0.05 was considered significant.

Results

The clinical characteristics of SSc patients

The current study enrolled 41 patients with systemic sclerosis and 15 healthy control subjects (sex and age-matched with the patients' group). The mean age of SSc patients was 42.27 ± 10.46 years and 39.47 ± 7.67 years in healthy controls. Among SSc patients and healthy controls, the percentage of females was 87.8% and 73.3%, respectively. 38 (92.7%) of the patients had limited cutaneous SSc (lcSSc), and 3 (7.3%) had a diffuse cutaneous SSc subtype (dcSSc). The mean duration of disease was 8.78 ± 1.1 years and ranged from 1 to 25 years, and the age of onset was 33.5 ± 10.48 years and ranged from 10 to 55 years. 4.9% were smokers. All patients were presented with Raynaud's phenomenon, and 80.5% had digital ulcers/scars.

Serum levels of SIRT3 and SIRT7

Serum level SIRT3

Serum levels of SIRT3 were significantly decreased in SSc patients at 0.11 ± 0.01 ng/mL compared to healthy controls at 0.74 ± 0.29 ng/mL($p < 0.001$; Fig. 1).

Serum level SIRT7

Serum levels of SIRT7 were significantly decreased in SSc patients at 19.58 ± 8.49 ng/mL compared to healthy controls at 164.46 ± 70.88 ng/mL ($p < 0.001$; Fig. 1).

SIRT3 and SIRT7 levels among SSc patients showed a statistically significant positive correlation ($r = 0.783$, $p < 0.001$).

Serum SIRT3 and SIRT7 levels with the severity of skin (scored with mRSS)

SIRT3 and SIRT7 levels and mRSS correlated negatively ($r = -0.201$, $p = 0.248$) and ($r = -0.211$, $p = 0.215$), respectively; however, it was not statistically significant (Table 2 and Fig. 2).

There was no statistically significant difference between SIRT3, SIRT7 levels, and SSc subtypes ($p > 0.05$); however, the SIRT7 level was decreased in dcSSc at 14.16 ± 5.93 than in lcSSc at 20.01 ± 8.34 (Table 1).

There was an insignificant difference in SIRT3 and SIRT7 levels (0.11 ± 0.01 and 20.10 ± 7.26), respectively, when SSc patients were stratified according to the presence of digital ulcers compared to patients without digital ulcers (0.13 ± 0.03 and 17.43 ± 4.53), respectively (Table 1).

Serum SIRT3 and SIRT7 levels with the severity of lung fibrosis

In systemic sclerosis patients with ILD (56.1%), on a high-resolution computed tomography scan of the chest, there was an insignificant increase in SIRT3 and SIRT7 levels (0.12 ± 0.01 and 21.23 ± 8.23), respectively, compared with systemic sclerosis patients without ILD (0.10 ± 0.01 and 17.47 ± 8.57), respectively ($p = 0.408$ and 0.258; Table 1).

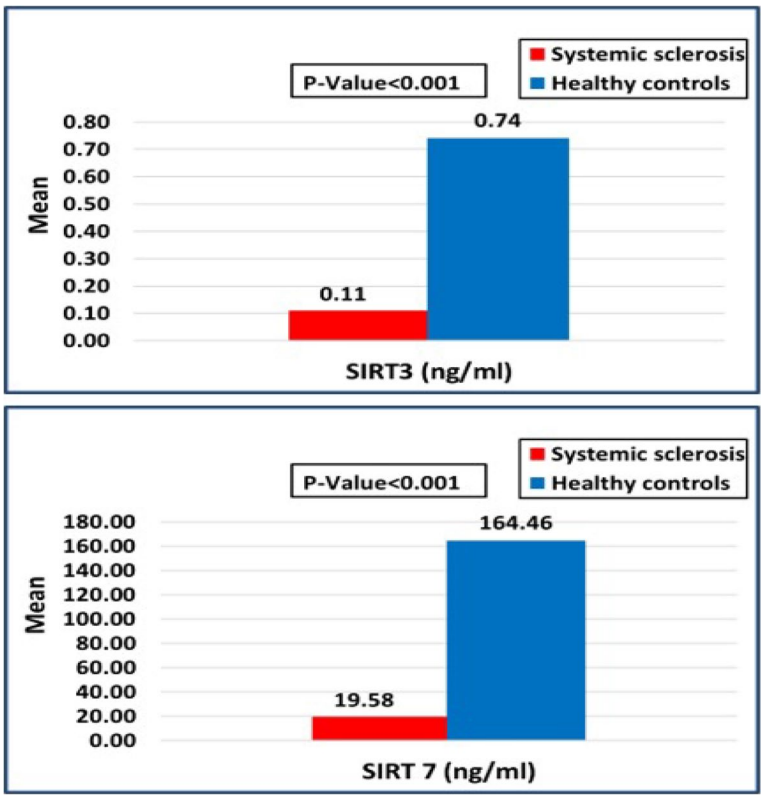

Fig. 1 Comparison of SIRT3 and SIRT7 levels between SSc patients and healthy controls

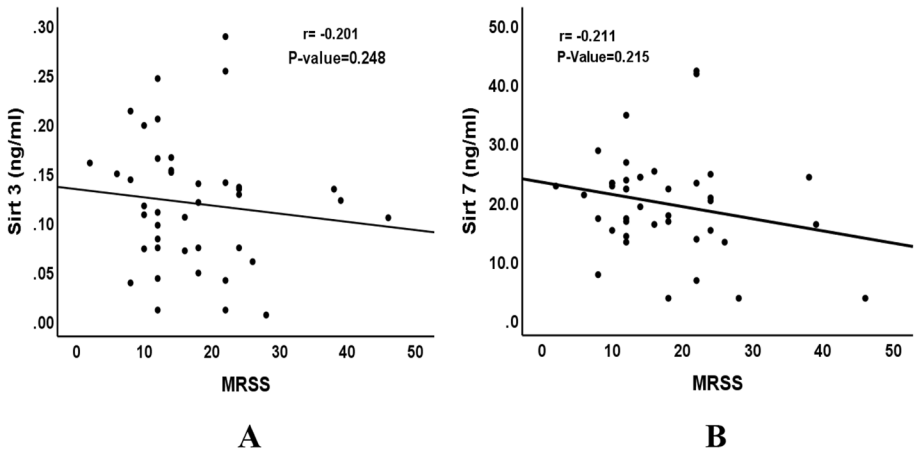

Fig. 2 **A** Scatter diagram for correlation between SIRT 3 and mRSS. **B** Scatter diagram for correlation between SIRT 7 and mRSS

Pulmonary function tests PFT showed 7.3% have mild restriction, 17.1% have moderate restriction, and 4.9% have severe restriction. PFT with abnormal findings was associated with SIRT3 (0.13 ± 0.02) and SIRT7 (20.37 ± 9.03). PFT with normal findings associated with SIRT3 (0.11 ± 0.01) and SIRT7 (19.25 ± 8.4); ($p = 0.422$ and $p = 0.796$; Table 1).

Serum SIRT3 and SIRT7 levels with the severity of gastrointestinal manifestation

Regarding the gastrointestinal features, the mean of the SIRT7 level was lower in patients with gastroesophageal reflux, nausea, vomiting, and constipation than those without these symptoms, with no statistically significant variation. Compared to patients without dyspepsia, those

Table 1 Association between the clinical characteristics of SSc patients and SIRT3 and SIRT7 levels

Variables	Systemic sclerosis ($n=41$)	
	SIRT3 (ng/ml)	SIRT7 (ng/ml)
SSc subtypes		
lcSSc: 38 (92.7%)	0.11 ± 0.01	20.01 ± 8.34
dcSSc: 3 (7.3%)	0.10 ± 0.01	14.16 ± 5.93
p-value	0.599	0.381
Dyspnea		
Yes: 32 (78%)	0.12 ± 0.01	20.29 ± 8.38
No	0.09 ± 0.02	17.05 ± 8.89
p-value	0.298	0.813
Chest discomfort/pain		
Yes: 15 (36.6%)	0.13 ± 0.02	22.60 ± 8.73
No	0.10 ± 0.01	17.84 ± 8.0
p-value	0.133	0.078
Cough		
Yes: 15 (36.6%)	0.11 ± 0.02	19.63 ± 8.38
No	0.11 ± 0.01	19.55 ± 8.72
p-value	0.871	0.818
ILD		
Systemic sclerosis without ILD	0.10 ± 0.01	17.47 ± 8.57
Systemic sclerosis with ILD: 23 (56.1%)	0.12 ± 0.01	21.23 ± 8.23
p-value	0.408	0.258
Pulmonary function tests		
Normal	0.11 ± 0.01	19.25 ± 8.40
Abnormal	0.13 ± 0.02	20.37 ± 9.03
p-value	0.422	0.796
Cardiac manifestations		
Yes: 9 (22%)	0.11 ± 0.02	20.00 ± 2.85
No	0.11 ± 0.01	19.46 ± 1.52
p-value	0.648	0.729
Arthritis		
Yes: 16 (39%)	0.12 ± 0.01	18.78 ± 6.50
No	0.11 ± 0.01	20.10 ± 9.64
p-value	0.446	0.377
Digital ulcer/scar		
Yes: 33 (80.5%)	0.11 ± 0.01	20.10 ± 7.26
No	0.13 ± 0.03	17.43 ± 4.53
p-value	0.502	0.432
Dysphagia		
Yes: 27 (65.9%)	0.11 ± 0.01	20.01 ± 9.23
No	0.12 ± 0.02	18.75 ± 7.10
p-value	0.762	0.611
Dyspepsia		
Yes: 22 (53.7%)	0.10 ± 0.01	16.47 ± 7.53
No	0.13 ± 0.02	23.18 ± 8.28
p-value	0.140	0.026
Gastroesophageal reflux		
Yes: (14 (34.1%)	0.11 ± 0.01	18.78 ± 7.28
No	0.12 ± 0.01	20.00 ± 9.15
p-value	0.680	0.670
Nausea/vomiting		
Yes: 5 (12.2%)	0.09 ± 0.01	17.50 ± 9.48
No	0.12 ± 0.01	19.87 ± 8.45
p-value	0.458	0.565
Constipation		
Yes: 5 (12.2%)	0.09 ± 0.03	12.80 ± 5.21
No	0.12 ± 0.01	20.52 ± 1.28
p-value	0.425	0.163
Diarrhea		
Yes: 3 (7.3%)	0.13 ± 0.01	22.33 ± 2.51
No	0.11 ± 0.01	19.36 ± 8.77
p-value	0.531	0.394
ANA		
Positive: 37 (90.2%)	0.11 ± 0.01	19.93 ± 7.30
Negative: 4 (9.8%)	0.23 ± 0.02	29.5 ± 12.5
p-value	0.034	0.360

Data expressed as mean ± SD/SE (range) or frequency (%)

Mann–Whitney *U* test

The *p* value was significant if < 0.05

SSc systemic sclerosis, *SIRT3* Sirtuin3, *SIRT7* Sirtuin7, *lcSSc* limited cutaneous SSc, *dcSSc* diffuse cutaneous SSc, *ILD* interstitial lung disease, *ANA* antinuclear antibodies

with dyspepsia had a statistically significant lower level of SIRT7 ($p=0.026$) compared to patients without dyspepsia (16.47 ± 7.53 vs 23.18 ± 8.28).

SIRT7 level was likewise lower in the patients with joint deformities and arthritis.

Patients with positive ANA (90.2%) had a statistically significant lower level of SIRT3 than patients with negative ANA (0.11 ± 0.01 vs. 0.23 ± 0.02, respectively) ($p=0.034$), while the SIRT7 level was lower in positive ANA patients without statistical significance.

The inflammatory markers and the levels of SIRT3 and SIRT7 exhibited a negative correlation that was not statistically significant, as shown in Table 2.

Concerning the medications that were administered to the patients, 30, 23, 21, 7, 2, and 1 patient used calcium channel blockers, azathioprine, methotrexate, steroids, angiotensin-converting enzyme (ACE) inhibitors, and cyclophosphamide, respectively. The number of patients who received combined therapy was 17 (41.5%). Patients received treatment for 9 years means with a range of 1 to 25 years. The level of SIRT7 in the SSc patients who take methotrexate (18.31 ± 8.77), and steroids (16.5 ± 5.33) decreased while, with azathioprine intake (21.17 ± 7.58), the level increased without significant differences.

Table 2 Correlations between SIRT3 and SIRT7 levels and parameters of SSc patients

Parameters	SIRT3 (ng/ml)		SIRT7 (ng/ml)	
	r	*p*-value	*r*	*p*-value
Patients' characteristics				
Age	0.044	0.787	0.193	0.227
Disease duration	0.093	0.565	−0.034	0.832
Age of onset	0.080	0.621	0.293	0.063
Laboratory investigation				
Blood urea (mmol/L)	0.028	0.864	0.026	0.870
Serum creatinine (µmol/l)	0.078	0.626	0.079	0.623
Erythrocyte sedimentation rate (mm/h)	0.014	0.929	−0.125	0.435
C-reactive protein (mg/l)	−0.030	0.851	−0.062	0.699
mRSS	−0.201	0.248	−0.211	0.215

Spearman correlation r (correlation coefficient)

The *p* value was significant if < 0.05

SSc systemic sclerosis, *SIRT3* Sirtuin3, *SIRT7* Sirtuin7, *mRSS* modified Rodnan's skin score

Figure 3 demonstrates the ROC curve of SIRT3 and SIRT7 levels for SSc prediction with SIRT3, at cut of point ≤ 0.16 ng/ml; it has an accuracy of 83.0%, sensitivity of 85.4%, specificity of 80.0%, positive predictive value of 92.1%, and negative predictive value of 66.7% with AUC = 0.898 and $p < 0.001$. Regarding SIRT7, at cut of point ≤ 24.5 ng/ml, it has an accuracy of 89.5%, sensitivity of 85.4%, specificity of 93.3%, positive predictive value of 97.2%, and negative predictive value of 70.0% with AUC = 0.909 and $p < 0.001$.

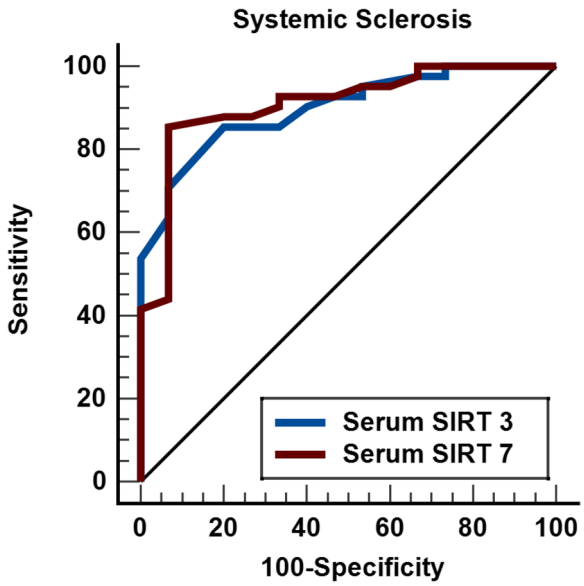

Fig. 3 ROC curve for the ability of SIRT 3 and SIRT7 in the prediction of systemic sclerosis in comparison to controls

Discussion

SIRTs are a type of deacetylase that controls a number of biological processes, including inflammation, metabolism, cell proliferation, and senescence [6, 23, 24], by enzymatic targeting if multiple intracellular proteins. SIRT3 is now recognized as important players in various fibrotic disorders due to their capability to control routes that contribute to the activation of fibroblast as well as fibrogenesis of tissue [25], that is of special interest to SSc. Several studies have found a link between reduced SIRT3 levels and the development of fibrosis, in addition to a protective, antifibrotic function for SIRT reconstruction [3, 25, 26]. SIRT7 is the most recent and least researched SIRT [27]. SIRT7 acts with other factors to positively regulate Ribosomal deoxyribonucleic acid transcription and may influence both ribonucleic acid polymerase 2 and ribonucleic acid polymerase 1 transcription [28]. Furthermore, both circulating SIRT3 and SIRT7 are being considered as biomarkers of disease in a variety of pathological conditions, such as those involving the lungs [3, 17, 29–31].

Recent research shows that lower SIRT3 levels may be associated with a poor prognosis in patients with COVID-19, a disease that appears to share multiple pathological mechanisms with SSc, which lends support to the hypothetical utilization of serum SIRT3 as a marker of the degree of severity of SSc-related lung disease [32–34].

We found serum levels of SIRT3 and SIRT7 were significantly decreased in SSc patients compared to healthy controls ($p < 0.001$).SIRT3 and SIRT7 levels among SSc patients showed a statistically significant positive correlation ($p < 0.001$).

There was no statistically significant difference between SIRT3, SIRT7 levels, and SSc subtypes ($p > 0.05$); however, SIRT7 levels were lower in dcSSc than in lcSSc. Manetti et al., study in 2022 showed that serum SIRT3 decreased in patients with dcSSc with respect to patients with lcSSc [3]. In our study, only 7% of the patients had dcSSc.

In line with other studies that found SIRT3 levels to be significantly reduced in SSc patients who had digital ulcers and vascular dysfunction than those without such ischemic problems [3, 10], patients with digital ulcers, scars or gangrene, telangiectasia, hypopigmentation, and hyperpigmentation had insignificantly lower levels of SIRT3 in our study. SIRT7 levels increased insignificantly with digital ulcers and scars.

We observed a negative correlation between SIRT3 and mRSS, as well as SIRT7 and mRSS, a semi-quantitative method for measuring the involvement of skin which is crucial for SSc diagnosis and prognosis. Other studies have discovered that SIRT3 disruption contributes to skin fibrosis [3, 32], whereas another study observed

no correlation between SIRT3 protein expression in SSc patients and mRSS, which could be attributed to the personal interpretation and biological samples utilized to measure this protein's levels [16].

Insignificant difference in serum SIRT3 and SIRT7 levels of SSc patients with ILD versus patients without ILD. Our findings contradict previous researches, which found that SIRT3 and SIRT7 decreased pulmonary fibrosis [3, 14, 16, 19, 25, 26, 29–32, 35, 36], this could be explained by our study's small sample size and our patients regularly received their treatment since diagnosis, with a period ranging from one to nine years (the medications that were administered to the patients were calcium channel blockers, azathioprine, methotrexate, steroids, angiotensin-converting enzyme (ACE) inhibitors, and cyclophosphamide, and 17 patients (41.5%) received combined therapy). Many studies showed the effect of some molecules on the SIRTs, which increased and activated them [37]. Other studies excluded SSc patients who were receiving several medications from their study [3]. In addition, research findings indicate that elevated SIRT3 expression reduces mitochondrial DNA damage and promotes the infiltration of fibrotic monocytes into the lungs, thereby lessening pulmonary fibrosis [36]. Increased SIRT3 levels cause a decrease in mothers against decapentaplegic homolog 3 (Smad3) levels, which decreases transforming growth factor beta 1 (TGF-β1's) effects [14]. SIRT7 overexpression also lowers the levels of Smad3 messenger ribonucleic acid (mRNA) and protein [19].

Patients with dyspnea and chest pain had insignificantly lower levels of SIRT3 and SIRT7 than patients without these manifestations.

SIRT7 has been linked to SSc-ILD and recently suggested as an innovative regulator of pulmonary fibrosis. SIRT7 expression was significantly reduced in both fibroblasts from SSc-ILD patients and pulmonary tissue from bleomycin-challenged mice, suppressing SIRT7 increased the production of collagen and smooth muscle actin, while overexpression significantly decreased the levels of these profibrotic molecules within human pulmonary fibroblasts. The results indicate that SIRT7 can be protective against SSc-related pulmonary fibrosis when combined [3, 19].

In the present research, patients with dyspepsia had a statistically significant decreased level of SIRT7 than patients without dyspepsia ($p=0.026$) whereas gastroesophageal reflux, nausea, vomiting, and constipation had insignificantly lower levels of SIRTs.

Furthermore, positive ANA patients had a statistically significantly lower level of SIRT3 than negative ANA patients, and positive ANA patients had a lower level of SIRT7 without statistical significance. Inflammatory markers and SIRT3 and SIRT7 levels showed a negative correlation, which was not statistically significant but could be an indicator of disease activity. These notices will require future research to validate those ideas. SIRTs can cooperate to support specific immune functions. These outcomes, along with the results of the ROC curve analysis, demonstrated that these two SIRTs act as good diagnostic biomarkers for the detection and diagnosis of SSc. We also discovered that SIRT7 is more accurate and specific and has a better ability to predict the disease than SIRT3.

Based on the information provided above, we believe that SIRT3 and SIRT7 have significant importance in SSc, particularly SIRT7. In this study, we investigated SIRT7 levels in relation to various SSc manifestations and discovered that it could be a novel biomarker for the disease. There are a few limitations to this study, including the small sample size and lack of patient follow-up. Further prospective research on larger cohorts of SSc patients is necessary to determine if variations in circulating SIRT3 and SIRT7 levels correlate with the progression of the disease in such patients over time. More researches are required to determine if changes in SIRTs cause the emergence and progression of rheumatologic diseases and to fully comprehend the crucial function of the SIRTS in the response to inflammation.

Conclusion

SIRT3 and SIRT7 levels were found to have a significant positive correlation in SSc patients. SIRT3 and SIRT7 levels are both good diagnostic biomarkers for detecting and diagnosing SSc, with SIRT7 being more accurate, specific, and predictive of the disease than SIRT3. SIRT7 is thought to be a new biomarker for SSc disease.

We recommend further studies to find if modulation of the expression of SIRT3 and SIRT7 could provide new targeted therapeutic approaches for the treatment of the SSc.

Abbreviations

ANA	Antinuclear antibody
AUC	Area under curve
dcSSc	Diffuse cutaneous systemic sclerosis
FVC	Forced vital capacity
FEV1	Forced expiratory volume in the first second
HRCT	High-resolution computed tomography
ILD	Interstitial lung disease
lcSSc	Limited cutaneous systemic sclerosis
mRNA	Messenger ribonucleic acid
mRSS	Modified Rodnan's skin score
PFT	Pulmonary functions tests
ROC	Receiver operating characteristic
SIRTs	Sirtuins
Smad3	Mothers against decapentaplegic homolog 3
SSc	Systemic sclerosis
TGF-β1's	Transforming growth factor beta 1

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Authors' contributions
Conceptualization: Marwa Mahmoud Abdelaziz, Nihal Fathi; methodology: Mai H. El-Morabaa, Eman R. Badawy; formal analysis and investigation: Yasmine S. Makarem, Gehan Ibrahim Salem; writing — original draft preparation: Yasmine S. Makarem; writing — review and editing: Marwa Mahmoud Abdelaziz; Resources: Mai H. El-Morabaa; supervision: Nihal Fathi, Marwa Mahmoud Abdelaziz, Yasmine S. Makarem.

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Availability of data and materials
The data will be available upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was conducted according to the Declaration of Helsinki's ethical principles after receiving acceptance from our faculty's local research ethics committee (IRP 17101143). The patients provided written informed consent to participate in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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