Clinical Rheumatology
https://doi.org/10.1007/s10067-020-05033-3

ORIGINAL ARTICLE

Serum 14-3-3η protein is associated with clinical and serologic features of Sjögren's syndrome in patients with systemic lupus erythematosus: a cross-sectional analysis

Nevin Hammam[1] · Nada M. Gamal[1] · Mona H. Elzohri[2] · Amira M Elsonbaty[1] · Ahmed M. Rashed[1] · Zeiad H. Eldaly[3] · Dalia Tarik[4] · Tamer A. Gheita[5]

Received: 30 December 2019 / Revised: 30 December 2019 / Accepted: 5 March 2020

Abstract

Introduction/objectives Systemic lupus erythematosus (SLE) and Sjögren's syndrome (SS) may coexist and carry a higher risk for future comorbidities. Although 14-3-3η protein is recently a known diagnostic marker in rheumatoid arthritis (RA), its role has not been investigated in SLE. The aim of this study was to compare serum 14-3-3η protein level in SLE and RA patients and to examine its association with clinical and laboratory features in SLE patients.

Methods Eighty-four SLE patients and 39 RA patients were included. Sociodemographic, SLE disease activity index (SLEDAI), and damage index were assessed for SLE patients. Data about secondary SS were collected. 14-3-3η was measured by ELISA; titres above 0.19 ng/ml were considered positive.

Results Serum 14-3-3η protein in SLE was significantly lower than in RA (0.37 ± 0.09 vs 1.5 ± 0.51; $p < 0.001$). 14-3-3η protein level was comparable between SLE patients with and without arthritis (0.29 ± 0.8 vs 0.15 ± 0.08 respectively; $p = 0.20$). Serum 14–3-3η protein level was higher in SLE with secondary SS features compared to those without (0.22 ± 0.10 IU/ml vs 0.11 ± 0.04 IU/ml; respectively, $p < 0.001$). There were no differences in 14–3-3η positivity for other lupus criteria or correlation of 14–3-3η titer with SLEDAI. 14–3-3η protein at 1.11 ng/mL yield a secondary SS diagnostic accuracy of 71%.

Conclusions Serum 14–3-3η protein level is high in SLE-associated SS. The 14–3-3η protein level was able to distinguish patients with secondary SS among patients with SLE. Studying the role of 14–3-3η protein in Sjögren's syndrome would be considered in further larger scale studies to confirm the impact of any association.

Key Points
- *Serum 14-3-3η protein level is significantly higher in systemic lupus patients with secondary Sjögren's syndrome (SS) in comparison to those without.*
- *Serum 14-3-3η protein can be used as a useful marker to distinguish patients with secondary SS among patients with systemic lupus.*
- *14-3-3η protein level shows no difference between systemic lupus patients with and without arthritis.*

Keywords 14-3-3η protein · Arthritis · Sjögren's syndrome · Systemic lupus erythematosus

✉ Nevin Hammam
Nevin.Hammam@ucsf.edu

[1] Rheumatology and Rehabilitation Department, Assiut University Hospitals, Assiut Campus, Assiut, Egypt

[2] Department of Internal Medicine, Rheumatology & Clinical Immunology Unit, Assiut University Hospitals, Assiut, Egypt

[3] Department of Ophthalmology, Faculty of Medicine, Assiut University, Assiut, Egypt

[4] Clinical Pathology Department, Assiut University Hospitals, Assiut, Egypt

[5] Rheumatology Department, Faculty of Medicine, Cairo University, Cairo, Egypt

Introduction

Systemic Lupus Erythematosus (SLE) is an autoimmune inflammatory disease that affects mainly women. SLE is characterized with a chronic course of exacerbations and remissions and may lead to serious organ damages [1]. The heterogeneous clinical, serological presentation, and response to treatment suggest that different pathological mechanisms are responsible for the development and presentation of SLE in individual patients [2]. Among those with SLE, about 20% of patients have secondary Sjögren's syndrome (SS). Sjögren's syndrome develops as a result of accumulation of lymphocytes in the lacrimal and salivary glands. The most common

Published online: 23 March 2020

clinical findings include dryness of the mouth and/or the eyes. Although SLE and SS share clinical and immunogenetic features, they are two different conditions with mutual characteristics [3]. Apoptosis (programmed cell death), plays a fundamental role in the pathogenesis of SS, has been proposed as a possible mechanism for the impairment of secretory function and glandular damage [4]. In addition, the role of the apoptotic process seems critical throughout the disease in patients with SLE [5].

14-3-3η (eta), isoform of 14-3-3 protein family, is an intracellular protein involved in numerous cell processes including regulating the proliferation, differentiation, and apoptosis of cells [6, 7]. Extracellular 14-3-3η has been demonstrated to stimulate the expression of pro inflammatory cytokines including tumor necrosis factor-alpha (TNF-α) and matrix metalloproteinase (MMP) [8, 9]. Recent work has implicated that the serum 14–3-3η protein participates in the process of inflammation in rheumatoid arthritis (RA) and is significantly higher in RA patients as compared with patients with other inflammatory arthritis and healthy controls [10, 11]. Serum 14-3-3η levels, alone or in combination with other serological measurements, improves the diagnostic utility of patients with RA [12] and also is a prognostic radiographic damage biomarker [8, 13].

There were previous reports on the expression of 14-3-3η protein in other inflammatory arthritis, such as juvenile idiopathic arthritis (JIA) and psoriatic arthritis [14, 15]. Overall the utility of 14-3-3η protein in SLE and the association with SLE clinical and serological features has not been established in the existing literature [16]. Therefore, our primary aim was to compare the serum 14-3-3η protein levels in SLE and RA patients. The secondary objective was to evaluate the relationship between 14-3-3η protein with clinical and laboratory characteristics of SLE patients including secondary SS features.

Patients and methods

Study design and participants

This cross sectional study was carried out at the Rheumatology Department, Assiut University Hospitals, Assiut, Egypt. Eighty-four SLE patients aged ≥ 18 years fulfilling the Systemic Lupus International Collaborative Clinics (SLICC) classification criteria were enrolled [17]. Thirty-nine RA patients, diagnosed according to the 2010 American College of Rheumatology (ACR) classification criteria, were enrolled as a control group [18]. Patients with known hepatitis C or any other autoimmune diseases were excluded. The study ethics approval was obtained from the Faculty of Medicine Ethics Research Office (Pro17300290) and performed in accordance with 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all involved patients prior to their participation in the study.

Sociodemographic and clinical assessments

The sociodemographic data, disease characteristics, and current medications administration of all SLE patients were assessed. The disease activity and damage level of the patients were evaluated using Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [19] and Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index (SLICC/ACR-DI) [20], respectively. The presence of specific system activities based on their criteria presentation in SLEDAI within 10 days preceding the evaluation was measured. Furthermore, symptoms of dry eye and mouth were assessed based on classification criteria questionnaire [21] for more than 3 months.

Laboratory and serologic tests

Laboratory investigations included the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complete blood cell count (CBC), serum creatinine, and urinalysis. Complement C3 and C4 and relevant autoantibodies including anti-double-stranded DNA (anti-dsDNA), rheumatoid factor (RF), anti-Ro, and anti-La were measured by enzyme-linked immunosorbent assay (ELISA). Serum 14-3-3η protein levels were measured by quantitative 14-3-3η ELISA JOINTstat® supplied by Augurex Life Sciences Corp, Vancouver, BC, Canada. Positivity was assessed as per the manufacturer's suggested cutoff of ≥ 0.19 ng/ml [12].

Ophthalmologic examinations

Routine ophthalmic examinations, including tear function tests, were performed by an expert ophthalmologist and recorded. Tear function tests consisted of tear film break-up time (TBUT), Rose-Bengal (Van Bijsterveld) score, and the Schirmer-I test (Schirmer). For TBUT, a strip of moistened fluorescein paper was used to touch the inferior fornix for a short time with minimal stimulation. The tear film was observed under cobalt blue–filtered light. The interval (seconds) between the last complete blink and the first emergence of randomly distributed dry spots was averaged from triplicate measurements. This was followed by staining with 1% Rose-Bengal solution. Both fluorescein and Rose Bengal staining scores were recorded and ranged between 0 and 9 points. Schirmer was performed using standardized strips of filter paper which were placed in the lateral canthus away from the cornea and left in place for 5 min with the eyes closed. ST was positive when reading was recorded in millimeters of wetting for 5 min (mm/5 min).

The Schirmer test result ≤ 5 mm/5 min and/or a positive ocular color score (van Bijsterveld's score) ≥ 4 was considered positive ocular abnormalities.

Secondary SS evaluation

Secondary SS in this cohort of patients with SLE was defined by presence of symptoms of dry eye and dry mouth plus objective dry eye by ocular staining and/or ST, and positive serum anti-Ro and/or anti-La [21]. These findings were only considered valid in the absence of medications or certain diseases that might have overlap features.

Statistical analyses

Data were tested for normality by the Shapiro-Wilk test. Continuous data were presented as mean and standard deviation (SD) or median (interquartile range "IQR"), while categorical data were presented as frequency (%). When analyzing differences in protein levels, the independent samples *t* for continuous parameters and chi^2 tests for binary parameters and Mann–Whitney *U* test for non-parametric variables were used. Correlations were investigated by Spearman's rank correlation coefficient. Receiver operator characteristic (ROC) curves were used to detect the optimal threshold of 14-3-3η level for prediction of SLE patients with secondary SS from those without. A p value of ≤ 0.05 was considered significant. Data were analyzed using the STATA version 15 (Stata Corp., College Station, TX, USA).

Results

Patients and disease characteristics

A total of 84 SLE patients were included with a mean age of 31.1 ± 9.7 years; 80 (95.2%) were women, and mean disease duration of 5.2 ± 0.7 years. Average SLEDAI was 16.3 ± 1.5, with 22.2% of patients displaying moderate disease activity, and SLICC/ACR-DI score was 1.9 ± 0.3. The most frequent active systems were mucocutaneous (64.3%), renal (61.4%), and musculoskeletal (57.1%). Active arthritis and erythematous skin rash were present in 66.6% and 77.7%, respectively. Positive ds-DNA antibodies were detected in 60% of the patients. Thirty-four percent of patients were anti-La positive, and 27.7% were anti-Ro positive. Demographic data, clinical, and laboratory manifestations present in Tables 1 and 2.

Table 1 Demographic and clinical characteristics of SLE patients

Parameter Mean ± SD or *N* (%)		SLE patients ($n = 84$)
Age (years)		31.1 ± 9.7
Body mass index (kg/m^2)		25 ± 6.1
Disease duration (years)		5.2 ± 0.7
Clinical manifestations	Constitutional	56 (66.7)
	Mucocutaneous	54 (64.3)
	Musculoskeletal	48 (57.1)
	Lupus nephritis	51 (61.4)
	Neuropsychiatric	23 (27.4)
	Cardiac	12 (14.3)
	Chest	14 (16.6)
	Vascular thrombosis	10 (12)
	Sjögren's syndrome	20 (24)
	Hematological	66 (80.5)
SLEDAI score		16.3 ± 1.5
SLICC/ACR-DI		1.9 ± 0.3
Medications use	Steroids	62 (74)
	Hydroxychloroquine	78 (93)
	Cyclophosphamide	34 (42.5)
	Azathioprine	53 (63)
	Methotrexate	74 (88)

SLE systemic lupus erythematosus, *SLEDAI* SLE disease activity index, *SLICC/ACR-DI* Systemic Lupus International Collaborative Clinics/American College of Rheumatology damage index

Difference in serum 14-3-3η protein between SLE and RA

Thirty-nine RA patients, 87.2% were female, mean age of 37.7 ± 13 years, and mean disease duration of 9.6 ± 8 were included as the control group. As expected, serum 14-3-3η protein expression was significantly higher in patients with RA compared with SLE patients (1.5 ± 0.51 vs 0.37 ± 0.09; $p < 0.001$), Fig. 1. Moreover, the frequency of positive 14-3-3η protein was markedly higher in RA compared with SLE patients (66.7% vs 33.3%).

Relationships between 14-3-3η with clinical and serological parameters

Mean serum 14-3-3η protein expression in all SLE patients was 0.37 ± 0.09, and the frequency of positive 14-3-3η protein was 33.3%. Serum 14-3-3η levels were positively correlated with erythematous skin rash and ESR ($r = 0.24$, $p = 0.027$ and $r = 0.28$, $p = 0.009$, respectively). A significant correlation was observed between serum 14-3-3η protein levels and components of secondary SS including ocular sicca, anti-La, and anti-Ro ($p < 0.05$) (Table 3). Notably, 14-3-3η levels were significantly higher in SLE patients with secondary SS compared with those without (0.22 ± 0.10 vs 0.11 ± 0.04, $p < 0.001$), Fig. 2. SLE patients with and without current active arthritis have almost near14-3-3η protein levels (0.29 ± 0.8 vs 0.15 ± 0.08 respectively; $p = 0.20$). There were no

Table 2 Laboratory features of the systemic lupus erythematosus patients

Parameter Mean ± SD or *N* (%)	SLE patients ($n = 84$)
ESR (mm/1st h)	57 ± 34.7
CRP (mg/L)	19.1 ± 3.3
HGB (g/dl)	10.5 ± 2.2
TLC ($\times 10^3/mm^3$)	5.7 ± 2.7
PLT ($\times 10^3/mm^3$)	242 ± 108
AST (U/L)	34.1 ± 56.4
ALT (U/L)	33.9 ± 47.6
Albumin (mg/dl)	35.8 ± 10.3
SUA (mg/dl)	5.4 ± 2
Creatinine (mg/dl)	84.2 ± 67.0
Pyuria	19 (23)
Proteinuria (g/24 h)	1.2 ± 0.16
Hematuria	13 (15.7)
C3 (mg/dl)	63.3 ± 67.3
C4 (mg/dl)	6.8 ± 34.4
ACL (U/ml)	0.2 ± 0.4
Anti-La	74.7 ± 19
Positive anti-La	17 (34)
Anti-Ro	62.7 ± 17.1
Positive anti-Ro	13 (27.7)
ANA	84 (100)
Anti-ds DNA (IU/ml)	72.1 ± 76.8
Positive anti-dsDNA	49 (60)

SLE systemic lupus erythematosus, *ESR* erythrocyte sedimentation rate, *HGB* hemoglobin, *TLC* total leucocytic count, *PLT* platelets, *AST* aspartate transaminase, *ALT* alanine transaminase, *SUA* serum uric acid, *C* complement, *ACL* anti-cardiolipin, *ANA* anti-nuclear antibody, *anti-dsDNA* anti-double stranded deoxyribonucleic acid

significant correlation between 14-3-3η titer and other lupus criteria nor correlation of 14–3-3η protein with SLEDAI criteria or medications use.

Define the optimal 14-3-3η threshold to detect SLE with secondary SS

ROC curve analysis comparing patients with SLE with secondary SS and those without secondary SS demonstrated area under the curve (AUC) of 0.71 (95% confidence interval 0.60–0.81). At a cutoff of 1.11 ng/mL, the ROC curve yielded a sensitivity of 89.7% and specificity of 39% (Fig. 3).

Discussion

The real significance of 14-3-3η protein in inflammatory autoimmune disease, other than RA, their true specificity, the question of whether it is truly linked to arthritis, how accurately it reflects arthritis severity, and if it can differentiate specific

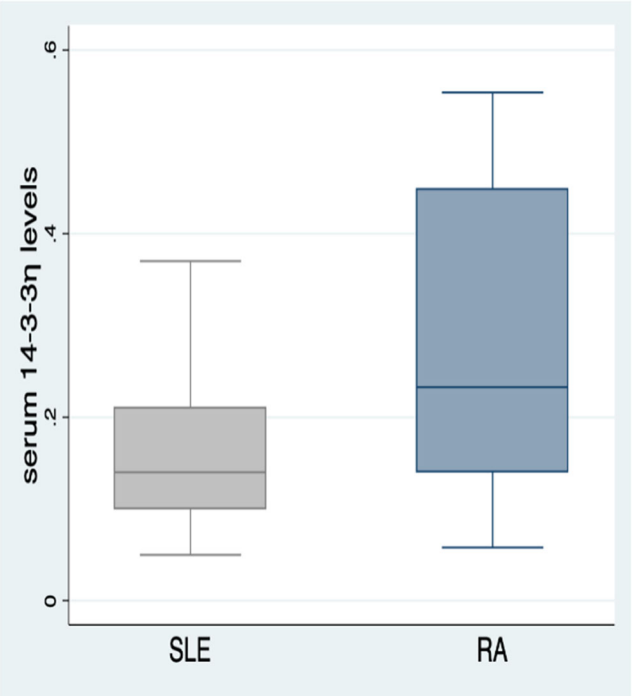

Fig. 1 Difference in serum 14-3-3η protein between systemic lupus and rheumatoid arthritis patients. Serum 14-3-3η protein is significantly higher in RA patients compared to SLE patients (1.5 ± 0.51 vs 0.37 ± 0.09; respectively, $p < 0.001$)

disease subsets are all questions that have been posed. This study shows that serum 14-3-3η protein can be used to enhance detection rate of patients with secondary SS among SLE patients. In the present study, our results demonstrate a significant association between serum 14-3-3η protein levels with clinical and laboratory components of secondary SS in patients with SLE. Of interest is that 14-3-3η protein is correlated with anti-La/SSB ($r = 0.50$, $p = 0.003$) greater than with anti-Ro/SSA ($r = 0.29$, $p = 0.04$), which is corresponding to that anti-La/SSB is more associated with SS [22]. Apart from the higher protein expression in SLE with secondary SS, there were no major differences in the protein levels between SLE patients with and without arthritis. To our knowledge, there is no prior study investigating the significance of 14-3-3η protein in relation to the clinical, laboratory characteristics of patients with SLE and associated SS.

Serum 14-3-3η proteins can play a fundamental role in the pathogenesis of primary SS through different mechanisms. 14-3-3 proteins are crucial regulators of intracellular protein trafficking and DNA damage response [23, 24]. 14-3-3 proteins play an additional role in regulating apoptosis and autophagy in inflammatory diseases [24] and have a protective function against mitochondria-mediated apoptosis, and higher 14-3-3η protein was found to be associated with reduced oxidative stress [25]. The uncontrolled apoptosis is the main pathogenesis in primary SS [4], and in line, oxidative stress was found to be significantly lower in Egyptian patients with

Table 3 Correlation between 14-3-3η protein and the clinical, and serological variables

Parameters	14-3-3η protein	
	r	*P* value
Age	0.080	0.469
Disease duration	− 0.088	0.431
Neuropsychiatric	0.132	0.231
Skin rash	0.240	*0.027*
Lupus nephritis	0.152	0.168
Arthritis	0.126	0.252
RF titer	0.068	0.724
ESR	0.284	*0.009*
CRP	0.003	0.988
ANA positive	0.122	0.312
ds-DNA positive	− 0.271	0.247
SLEDAI score	0.066	0.554
SLICC/ACR-DI	0.149	0.267
Ocular sicca	0.328	*0.015*
Anti-Ro	0.291	*0.046*
Anti-La	0.505	*0.003*
SS	0.601	*< 0.001*

RF rheumatoid factor, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *ANA* antinuclear antibody, *SLEDAI* systemic lupus erythematosus disease activity score, *SLICC/ACR-DI* Systemic Lupus International Collaborative Clinics/American College of Rheumatology damage index, *SS* Secondary Sjögren's syndrome. Italic values are significant at $p < 0.05$

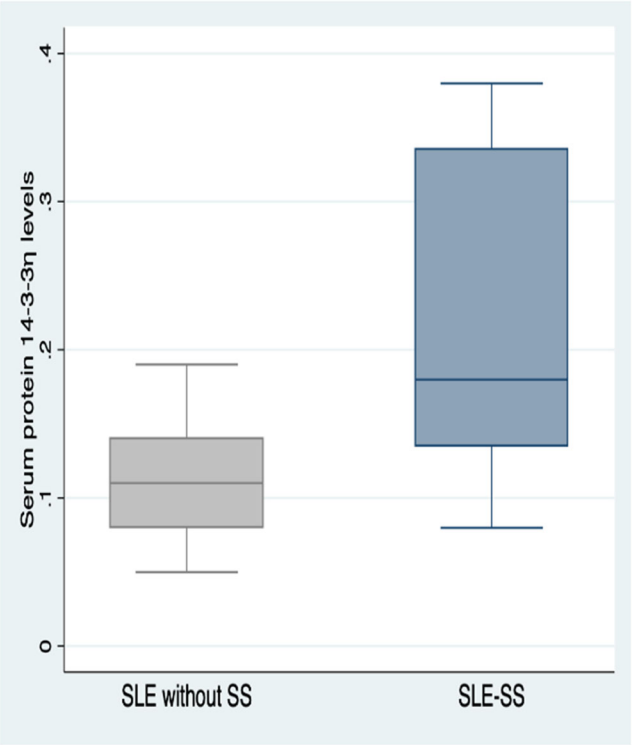

Fig. 2 Difference in serum 14-3-3η protein between systemic lupus with and without secondary Sjögren's syndrome. Serum 14-3-3η protein is significantly higher in SLE patients with secondary Sjögren's syndrome compared with SLE without Sjögren's syndrome patients (0.22 ± 0.10 vs 0.11 ± 0.04; respectively, $p < 0.001$) (Fig. 2)

secondary SS compared with those with RA [26]. Moreover, 14-3-3 protein is critical for B cell survival and potentially leading to or stimulating the production of antibodies. 14-3-3η protein may stimulate the proinflammatory cytokines as TNF-α [9]. The role of various cytokines, such as TNF-α, is considered in the development of primary SS, and it has an important role in the pathogenesis of the disease and has not been described in SLE [27]. Deutsch et al. detected that 14-3-3 protein had a 2- to 3-fold difference in expression level in oral fluid in patients with primary SS compared with controls [28]. The risk of B cell non-Hodgkin lymphoma is 44 times greater in patients with primary SS than in a healthy population [29]. 14-3-3 protein isoforms have been implicated in the pathogenesis and response to treatment in B cell lymphoma [30]. Primary SS is strongly linked to lymphoma while lupus is not [27]. Further investigations for the role of 14-3-3η protein in the pathogenesis of primary SS are required.

In the present work, 14-3-3η significantly correlated with ocular sicca, anti-Ro, anti-La, and ESR, which all components of secondary SS. The presence of these associations between 14-3-3η protein and secondary SS but not with SLE features increase lines of evidence that SLE and secondary SS are wholly distinct diseases and occasionally overlap as a result of shared organ or serologic manifestations [29]. The subset of patients with SLE and secondary SS has higher frequency of photosensitivity, oral ulcers, anti-Ro antibodies, and anti-La antibodies and a lower frequency of renal disease and anti-dsDNA antibodies [21, 31]. ESR is elevated in 80% of secondary SS patients [29]. These results may support the fact of different mechanisms attributed to these symptoms in patients with SLE and secondary SS. This has raised the question of whether 14-3-3η proteins may serve as a biomarker for detection, as well as for unveiling possible mechanisms involved in secondary SS.

Furthermore, we support the evidence that 14-3-3η protein is a diagnostic marker to identify RA patients from other inflammatory arthritis such as SLE. The higher 14-3-3η protein levels in RA patients compared with SLE patients was in line with the literatures [13, 32]. 14-3-3η protein level is specific biomarker to enhance detection of patients with RA [12]. 14-3-3η is detected extracellularly in arthritis and behaves as a marker that are involved in joint damage, and thus, it is expressed at higher levels in patients with erosive RA. Previous researches in RA patients revealed that serum 14-3-3η expression was significantly higher in patients with radiographic damage [8, 9, 29]. Moreover, previous work demonstrates higher levels of serum 14-3-3η protein in erosive psoriatic arthritis but not in non-erosive psoriatic subjects per

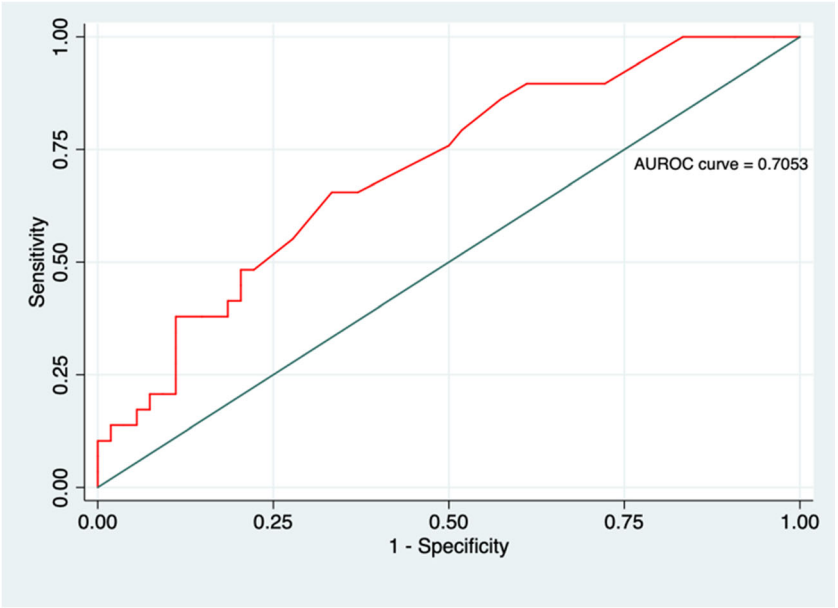

Fig. 3 ROC analysis showing serum 14-3-3η protein as a predictor of secondary Sjögren's syndrome in systemic lupus patients. Serum 14-3-3η protein is a predictor of SLE with secondary SS demonstrated area under the curve (AUC) of 0.71 (95% confidence interval: 0.60–0.81). At a cutoff of 1.11 ng/mL, the ROC curve yielded high sensitivity of 89.7% but with low specificity of 39%

radiographic assessment. 14-3-3η was independently associated with erosive status in psoriatic arthritis after adjusting other factors [15].

The present study could not find a relationship between 14-3-3η protein and arthritis in patients with SLE. Hitchon et al. [16] examined serum 14-3-3η titer from 265 patients with SLE. Results of this study showed that 14-3-3η positivity was similar across the three arthritis groups (active/inactive/never present); however, they found that highest quartile of 14-3-3η was associated with active arthritis. The relationship between 14-3-3η protein and arthritis in patients with SLE could interpret with caution. While the majority of arthritis in SLE is non-erosive arthritis, few patients can develop erosive arthritis indistinguishable from RA. These patients have often been called "rhupus" [15]. The lack of relationship of 14-3-3η protein and SLE arthritis in the current study may reflect differences in cohort size and absence of underlying overlap erosive arthritis and rhupus patients. Further work explores the associations of 14-3-3η protein with erosive arthritis in lupus is in need.

Furthermore, there was no correlation of 14-3-3η titer with other lupus criteria nor SLEDAI or specific system activity, which was consistent with the previous work in systemic lupus [16] and in RA patients [32, 33]. Inflammatory status and the immunological stages are uncoupled process along the course of the disease. 14-3-3η protein may influences the clinical and immunological features of secondary SS, but it does not appear to affect disease activity.

To our knowledge, this is the first study to investigate the 14- 3-3η protein levels in SLE patients and confirm its relation to secondary SS. We could draw a discovery that 14-3-3η protein was elevated in patients with secondary SS in SLE patients, and it may represent a new biomarker for secondary SS. A limitation to this study is the relatively small sample of secondary SS patients, and it is recommended to perform the study on a larger number of patients. Moreover, data regarding salivary gland biopsy pathology are lacking, and the number of SLE patients with secondary SS could thus be underestimated. While Sjögren's syndrome in this study was defined by the 2002 SS classification criteria [34], combinations of clinical symptoms and objective manifestations predict classification by the research criteria very well [35].

Conclusion

In conclusion, 14-3-3η protein titers are higher in SLE with secondary Sjögren's syndrome, suggesting the precise role of these 14-3-3η proteins in secondary SS pathogenesis. No difference in serum 14-3-3η protein in SLE patients with and without arthritis was found. This study opens a window for the association between 14-3-3η protein and secondary SS, and examining this association in primary SS could be more specific.

Compliance with ethical standards

Informed consent The study conforms to the 1995 Helsinki declaration and was approved by Assiut Faculty of Medicine ethical committee. Informed consent was obtained from all patients.

Disclosures None.

References

1. Petri M (2002) Epidemiology of systemic lupus erythematosus. Best Pract Res Clin Rheumatol 16:847–858

2. Mok CC, Lau CS (2003) Pathogenesis of systemic lupus erythematosus. J Clin Pathol 56:481–490. https://doi.org/10.1136/jcp.56.7.481
3. Aggarwal R, Anaya J-M, Koelsch KA, Kurien BT, Scofield RH (2015) Association between secondary and primary Sjögren's syndrome in a large collection of lupus families. Autoimmune Dis 2015:298506. https://doi.org/10.1155/2015/298506
4. Manganelli P, Fietta P (2003) Apoptosis and Sjogren syndrome. Semin Arthritis Rheum 33:49–65. https://doi.org/10.1053/sarh.2003.50019
5. Gheita TA, Bassyouni IH, Bassyouni RH (2012) Plasma concentrations of growth arrest specific protein 6 and the soluble form of its tyrosine kinase receptor Axl in patients with systemic lupus erythematosus and Behcets disease. J Clin Immunol 32:1279–1286. https://doi.org/10.1007/s10875-012-9743-7
6. Aitken A (2006) 14-3-3 proteins: a historic overview. Semin Cancer Biol 16:162–172. https://doi.org/10.1016/j.semcancer.2006.03.005
7. Yang X, Lee WH, Sobott F, Papagrigoriou E, Robinson CV, Grossmann JG, Sundström M, Doyle DA, Elkins JM (2006) Structural basis for protein-protein interactions in the 14-3-3 protein family. Proc Natl Acad Sci U S A 103:17237–17242. https://doi.org/10.1073/pnas.0605779103
8. Maksymowych WP, van der Heijde D, Allaart CF, Landewé R, Boire G, Tak PP, Gui Y, Ghahary A, Kilani R, Marotta A (2014) 14-3-3eta is a novel mediator associated with the pathogenesis of rheumatoid arthritis and joint damage. Arthritis Res Ther 16:R99. https://doi.org/10.1186/ar4547
9. Kilani RT, Maksymowych WP, Aitken A, Boire G, St-Pierre Y, Li Y, Ghahary A (2007) Detection of high levels of 2 specific isoforms of 14-3-3 proteins in synovial fluid from patients with joint inflammation. J Rheumatol 34:1650–1657
10. Zeng T, Tan L (2018) 14-3-3eta protein: a promising biomarker for rheumatoid arthritis. Biomark Med 12:917–925. https://doi.org/10.2217/bmm-2017-0385
11. Guan S-Z, Yang Y-Q, Bai X, Wang Y, Feng KQ, Zhang HJ, Dong M, Yang HW, Li HQ (2019) Serum 14-3-3eta could improve the diagnostic rate of rheumatoid arthritis and correlates to disease activity. Ann Clin Lab Sci 49:57–62
12. Maksymowych WP, Naides SJ, Bykerk V, Siminovitch KA, van Schaardenburg D, Boers M, Landewé R, van der Heijde D, Tak PP, Genovese MC, Weinblatt ME, Keystone EC, Zhukov OS, Abolhosn RW, Popov JM, Britsemmer K, van Kuijk A, Marotta A (2014) Serum 14-3-3eta is a novel marker that complements current serological measurements to enhance detection of patients with rheumatoid arthritis. J Rheumatol 41:2104–2113. https://doi.org/10.3899/jrheum.131446
13. van Schaardenburg D, Maksymowych WP, Boers M et al (2014) THU0244 14-3-3Eta is an independent predictor of radiographic changes in early RA and higher titres inform a higher likelihood of joint damage progression. Ann Rheum Dis 73:266 LP–266266
14. Dalrymple AM, Tuttle P IV, Feller L, Zhukov OS, Lagier RJ, Bridgforth R, Williams GJ, Popov JM, Naides SJMT (2017) 14-3-3η (eta) Protein in juvenile idiopathic arthritis (JIA) patients. Arthritis Rheumatol 69
15. Marotta A, Kuijk AW, Maksymowych WP, Tak PP (2013) SAT0309 serum 14-3-3 ETA: an independent biomarker associated with joint damage in psoriatic arthritis. Ann Rheum Dis 71:576 LP–576576. https://doi.org/10.1136/annrheumdis-2012-eular.3256
16. Hitchon C, Robinson D, El-Gabalawy H et al (2017) 215 active arthritis is associated with 14–3–beta titre in patients with systemic lupus erythematosus. Lupus Sci & Med 4:A99 LP–A99A99
17. Petri M, Orbai A-M, Alarcon GS et al (2012) Derivation and validation of the systemic lupus international collaborating clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 64:2677–2686. https://doi.org/10.1002/art.34473
18. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO III, Birnbaum NS, Burmester GR, Bykerk VP, Cohen MD, Combe B, Costenbader KH, Dougados M, Emery P, Ferraccioli G, Hazes JM, Hobbs K, Huizinga TW, Kavanaugh A, Kay J, Kvien TK, Laing T, Mease P, Ménard HA, Moreland LW, Naden RL, Pincus T, Smolen JS, Stanislawska-Biernat E, Symmons D, Tak PP, Upchurch KS, Vencovský J, Wolfe F, Hawker G (2010) 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 62:2569–2581
19. Gladman DD, Ibañez D, Urowitz MB (2002) Systemic lupus erythematosus disease activity index 2000. J Rheumatol 29:288–291
20. Gladman DD, Goldsmith CH, Urowitz MB, Bacon P, Fortin P, Ginzler E, Gordon C, Hanly JG, Isenberg DA, Petri M, Nived O, Snaith M, Sturfelt G (2000) The systemic lupus international collaborating clinics/American College of Rheumatology (SLICC/ACR) damage index for systemic lupus erythematosus international comparison. J Rheumatol 27:373–376
21. Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, Daniels TE, Fox PC, Fox RI, Kassan SS, Pillemer SR, Talal N, Weisman MH, European Study Group on Classification Criteria for Sjögren's Syndrome (2002) Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 61:554–558. https://doi.org/10.1136/ard.61.6.554
22. Franceschini F, Cavazzana I (2005) Anti-Ro/SSA and La/SSB antibodies. Autoimmunity 38:55–63. https://doi.org/10.1080/08916930400022954
23. Cau Y, Valensin D, Mori M et al (2018) Structure, function, involvement in diseases and targeting of 14-3-3 proteins: an update. Curr Med Chem 25:5–21. https://doi.org/10.2174/0929867324666170426095015
24. Jia H, Liang Z, Zhang X, Wang J, Xu W, Qian H (2017) 14-3-3 proteins: an important regulator of autophagy in diseases. Am J Transl Res 9:4738–4746
25. Sreedhar R, Arumugam S, Thandavarayan RA, Giridharan VV, Karuppagounder V, Pitchaimani V, Afrin R, Miyashita S, Nomoto M, Harima M, Gurusamy N, Suzuki K, Watanabe K (2015) Myocardial 14-3-3eta protein protects against mitochondria mediated apoptosis. Cell Signal 27:770–776. https://doi.org/10.1016/j.cellsig.2014.12.021
26. Gheita TA, Kenawy SAB, El Sisi RW et al (2014) Subclinical reduced G6PD activity in rheumatoid arthritis and Sjogren's syndrome patients: relation to clinical characteristics, disease activity and metabolic syndrome. Mod Rheumatol 24:612–617. https://doi.org/10.3109/14397595.2013.851639
27. Scheinfeld N (2006) Sjögren syndrome and systemic lupus erythematosus are distinct conditions. Dermatol Online J 12:4
28. Deutsch O, Krief G, Konttinen YT et al (2015) Identification of Sjogren's syndrome oral fluid biomarker candidates following high-abundance protein depletion. Rheumatology (Oxford) 54:884–890. https://doi.org/10.1093/rheumatology/keu405
29. Shovman O, Gilburd B, Watad A et al (2018) Decrease in 14-3-3eta protein levels is correlated with improvement in disease activity in patients with rheumatoid arthritis treated with tofacitinib. Pharmacol Res. https://doi.org/10.1016/j.phrs.2018.11.009
30. Maxwell SA, Li Z, Jaye D, Ballard S, Ferrell J, Fu H (2009) 14-3-3zeta mediates resistance of diffuse large B cell lymphoma to an anthracycline-based chemotherapeutic regimen. J Biol Chem 284:22379–22389. https://doi.org/10.1074/jbc.M109.022418
31. Baer AN, Maynard JW, Shaikh F, Magder LS, Petri M (2010) Secondary Sjogren's syndrome in systemic lupus erythematosus defines a distinct disease subset. J Rheumatol 37:1143–1149. https://doi.org/10.3899/jrheum.090804

32. van Beers-Tas MH, Marotta A, Boers M, Maksymowych WP, van Schaardenburg D (2016) A prospective cohort study of 14-3-3η in ACPA and/or RF-positive patients with arthralgia. Arthritis Res Ther 18:1–7. https://doi.org/10.1186/s13075-016-0975-4
33. Hammam N, Salah S, Marotta AFKE (2017) Evaluation of synovial fluid 14-3-3η protein as a marker of joint damage in rheumatoid arthritis patients. Arthritis Rheumatol. 69
34. Shiboski SC, Shiboski CH, Criswell LA, Baer A, Challacombe S, Lanfranchi H, Schiødt M, Umehara H, Vivino F, Zhao Y, Dong Y, Greenspan D, Heidenreich AM, Helin P, Kirkham B, Kitagawa K, Larkin G, Li M, Lietman T, Lindegaard J, McNamara N, Sack K, Shirlaw P, Sugai S, Vollenweider C, Whitcher J, Wu A, Zhang S, Zhang W, Greenspan J, Daniels T, Sjögren's International Collaborative Clinical Alliance (SICCA) Research Groups (2012) American College of Rheumatology classification criteria for Sjögren's syndrome: a data-driven, expert consensus approach in the Sjögren's International Collaborative Clinical Alliance cohort. Arthritis Care Res (Hoboken) 64:475–487
35. Al-Hashimi I, Khuder S, Haghighat N, Zipp M (2001) Frequency and predictive value of the clinical manifestations in Sjogren's syndrome. J Oral Pathol Med 30:1–6