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Evaluation of serum 14-3-3 η protein and Sema3A levels in rheumatoid arthritis: diagnostic and prognostic value

Nivine Fathi Darwish¹, Shymaa Ahmed Hablas^{1*} , Nivin Naeem Baiomy² and El Sayed Mohamed Hamid Rageh¹

Abstract

Background: Serum 14-3-3 η protein plays an important role in the pathogenesis of rheumatoid arthritis (RA) as it is a joint-derived proinflammatory mediator. Semaphorin3A (Sema3A) plays an immune regulatory and bone remodeling role in many autoimmune diseases. Their role in rheumatoid arthritis needs to be evaluated for diagnostic and prognostic prospective values.

Results: The serum level of protein 14-3-3 η was significantly higher in patients with RA than those in healthy controls. Serum 14-3-3 η has a significant positive correlation with RF and ACPA, but not with either DAS28, ESR, or CRP. Serum 14-3-3 η levels were significantly correlated with radiographically assessed joint damage. Serum Sema3A levels were decreased in rheumatoid arthritis patients compared to controls. There were also negative correlations with disease duration and activity score (DAS28), ESR, CRP, and RF.

Conclusion: The discriminative ability of 14-3-3 η was comparable to RF and ACPA enhancing its diagnostic capacity. Sema 3A might serve as a predictive marker for radiographic severity and could have a potential therapeutic role in RA.

Keywords: Rheumatoid arthritis, Serum 14-3-3 η protein, Serum Sema3A, Proinflammatory mediators

Background

Rheumatoid arthritis (RA) is chronic autoimmune disease with a huge diversity in clinical picture, progression, and treatment response [1].

RA still constitutes an important cause of morbidity and mortality despite the great progression in treatment options [2].

The presence of autoantibodies to immunoglobulin G (rheumatoid factor—RF) and citrullinated proteins (anti-citrullinated protein antibodies—ACPAs) are characteristic to RA. However, they are absent in the sera of some patients [3].

An erosive joint damage can be detected in about 20% of early RA patients within 2 years and is also observed

even in patients with clinical remission [4]. The progression of joint damage is one of the most significant causes of morbidity in RA [5].

There is a great need for more diagnostic and prognostic markers that can diagnose the disease early and reflect the prognosis of the disease especially its erosive nature [6].

The 14-3-3 family of intracellular chaperone proteins consists of seven isoforms: alpha/beta (α/β), epsilon (ϵ), gamma (γ), eta (η), tau (τ), zeta (ζ), and sigma (σ) [7]. These proteins interact with more than 200 intracellular proteins to play a role in protein synthesis, cell cycle regulation, control of metabolism, protein trafficking, apoptosis, control of gene transcription, and cytoskeletal transport [8]. Serum 14-3-3 η level increases in patients with arthritis as it can induce proinflammatory cytokines, like interleukin 1 β (IL-1 β), tumor necrosis factor- α (TNF- α), and IL-6, and other factors leading to a joint

* Correspondence: shhablas@gmail.com

¹Physical Medicine, Rheumatology and Rehabilitation, Faculty of Medicine, Tanta University, Tanta, Gharbia Governorate, Egypt
Full list of author information is available at the end of the article

degradation including matrix metalloproteinase 9 and receptor activator of nuclear factor- κ B ligand (RANKL) [7, 9].

Semaphorins are a large family of proteins containing a Sema domain of ~500 amino acids and that function as regulatory signals for axonal/dendritic projections have been initially known as neural guidance molecules [10].

They are categorized into 7 classes, semaphorins 1 to 7 [11]. They are implicated in different biological activities like angiogenesis, immune cell responses, and regulation of tumor microenvironment. Sema3A is a member of this family which contributes in the development and regulation of nervous system [12].

It has been involved in immune responses, organogenesis, angiogenesis, and oncogenesis [13]. Sema3A applies its osteoprotective role by inhibition osteoclast differentiation and stimulating osteoblastic bone formation at the same time synchronously [14].

Our objective is to study the role of these two new markers in rheumatoid arthritis.

Methods

This case-control study included 45 RA patients (group I) fulfilling the 2010 American College of Rheumatology/European League against Rheumatism classification criteria for RA [15].

They were recruited from the outpatient clinic of the Rheumatology Department from December 2018 to February 2020. The study also included 35 age- and sex-matched apparently healthy individuals as a control group (group II).

All patients were subjected to full medical history taking, complete clinical examination, evaluation of disease activity using Disease Activity Score 28 (DAS28), ESR, visual analog scale (range, 0–100), and simplified disease activity index (SDAI) [16, 17].

Inclusion criteria

- 1- RA patients with disease duration less than 5 years.

Exclusion criteria

- 1- RA patients with other co-morbidities or chronic disease as diabetes mellitus or hypertension.
- 2- Patients who have received biological treatment.

Laboratory investigations

The laboratory investigations included the following: complete blood count, ESR, rheumatoid factor (RF), and C-reactive protein (CRP). Detection of serum anticyclicitrullinated peptide (anti-CCP) antibodies, liver function tests, and kidney function tests.

Serum 14-3-3 η levels were evaluated by the quantitative 14-3-3 η enzyme-linked immunosorbent assay (ELISA; Augurex Life Sciences Corp, Vancouver Canada) according to the manufacturer's protocol. Positivity for 14-3-3 η was defined by the manufacturer at \geq 0.19 ng/ml. Measurement of serum Sema3A level by Human SEMA3A (Semaphorin 3A) ELISA Kit supplied by MyBioSource, San Diego, CA, USA; Catalog No: MBS2510626 with coefficient of variation is $<$ 10% and detection range: 0.16–10 ng/ml.

Radiological investigations

The radiological studies included the following:

- (1) **Plain X-ray scan** on the hands and wrists (postero-anterior view) using the Modified Larsen Score (MLS) [18]
- (2) **Musculoskeletal ultrasonography using** (SAMSUNG MEDISON (UGE^{H60}) machine with linear array transducers (frequencies ranging between 9 and 12 MHz) by certified MSUS operator blinded to the study. The joints were examined according to the EULAR and JCR guidelines at the radiocarpal, metacarpo-phalangeal joints, and proximal interphalangeal joints to detect
 - a. Synovial thickening, effusion
 - b. Doppler flow by semiquantitative score [19].

Statistical analysis

Statistical presentation and analysis of the present study was conducted as continuous data and was expressed as mean \pm standard deviation or median. Comparison of continuous data between two groups was made by using Student's *t* test and Mann-Whitney tests, and for categorical variables, chi-square test was used. Spearman correlation between different parameters was used. Statistical significance was defined as a *P* value of \leq 0.05. The sensitivity, specificity, and accuracy were calculated by using receiver-operating characteristic analysis (ROC curve). Analyses were performed using SPSS program, version 17 (SPSS Inc., Chicago, IL, USA) and the GraphPad Prism software (GraphPad Prism Software Inc., San Diego, California, USA).

Result

The present study was conducted on 80 subjects. They were classified into two groups.

Group (I): rheumatoid arthritis patients ($n = 45$). Their ages ranged from 35 to 52 years with a mean age of 39.30 ± 6.81 , mean disease duration of 41.6 ± 6.7 months, and mean DAS28 score of 8.5 ± 12.2 . They were 37 females and 8 males.

Group (II): 35 healthy subjects age- and sex-matched served as a control group. Their ages ranged between 33

and 51 years with a mean age of 40.70 ± 4.0 . They were 29 females and 6 males.

The clinical and laboratory data of studied groups were illustrated in Table 1.

Serum 14-3-3 η protein levels

The serum levels of 14-3-3 η protein were significantly increased in RA patients compared to the control group ($P < 0.001^*$).

There were positive significant correlations with SDAI ($r = 0.485$, $P = 0.001^*$), synovitis ($r = 0.665$, $P < 0.001^*$), erosions ($r = 0.864$, $P < 0.001^*$), RF ($r = 0.374$, $P = 0.011^*$), and ACPA ($r = 0.474$, $P = 0.001$). There were no correlations with ESR, CRP, or DAS28 score.

For diagnosis of RA, ROC curve showed that serum 14-3-3 η protein at a cutoff value of greater than 0.24 ng/ml had a sensitivity of 88.89%, a specificity of 91.43%, a positive predictive value of 93%, and a negative predictive value of 86%, and AUC was 0.957 (Tables 2, 3, and 4; Fig. 1).

Serum Sema3A level

The serum levels Sema3A levels were significantly decreased in RA patients compared to the control group ($P < 0.001^*$).

There were negative correlations with duration of the disease ($r = -0.372$, $P = 0.012^*$), disease activity (DAS28 score) ($r = -0.703$, $P < 0.001^*$), and simplified disease activity index (SDAI) ($r = -0.581$, $P < 0.001^*$), synovitis (GSN) ($r = 0.501$, $P < 0.001^*$), and erosions ($r = 0.652$, $P < 0.001^*$). ESR ($r = -0.535$, $P < 0.001^*$), RF ($r = -0.645$, $P < 0.001^*$), CRP ($r = -0.668$, $P < 0.001^*$), and ACPA ($r = -0.787$, $P < 0.001^*$).

For diagnosis of RA, ROC curve showed that serum Sema3A at a cutoff value of lesser than or equal to 5.8 ng/ml had a sensitivity of 82.82%, a specificity of 80%, a positive predictive value of 84.1%, and a negative predictive value of 77.8%, and AUC (area under the curve) was 0.854 (Tables 2, 3, and 4; Fig. 1).

Discussion

The need of new diagnostic markers for RA is crucial in particular subsets of rheumatoid arthritis patients such as those having an undifferentiated form of arthritis or those who progressively develop severe erosive disease. In such cases, serum 14-3-3 η protein was suggested by some authors as a novel detected biomarker for RA that has a diagnostic and prognostic value and the need for studies confirming this potential diagnostic and prognostic role seemed urgent [7, 20–24].

As for serum 14-3-3 η , we detected significant increased levels in our patients in comparison to controls with specificity value of 91.43% in comparison to 88.57% for ACCP, and also there were positive correlations with RF factor, ACPA. However, there were no correlations with DAS28, ESR, or CRP (Tables 1 and 2). In addition, there was a positive correlation between increased serum 14-3-3 η levels and radiological changes (Table 3).

Our results strongly suggest the pathogenic and diagnostic role of serum 14-3-3 η in RA and are in agreement with Van Beers-Tas et al. (2016) who found serum 14-3-3 η in the pre-clinical phase of arthritis and detected association between the positivity of this marker and ACPA- and/or RF-positive subjects with arthritis, compared with subjects with no arthritis. This can be explained by the ability of 14-3-3 η protein to provoke inflammatory and degenerative factors [7, 20, 25].

Carrier et al. (2016) observed in their study the same increase in 14-3-3 η protein in serum and synovial fluid of RA patients. Also, the association of production of inflammatory mediators like tumor necrosis factor α (TNF α), osteoclast-activating factors, and interleukin 6 (IL-6) in the patients' group [23]. Also, the persistent increase of 14-3-3 η protein level despite treatment could point out to patients at high risk of joint damage. The association between increased CRP and 14-3-3 η protein levels was considered by them as a bad prognostic indicator particularly in older individuals [23].

We found a positive correlation between increased serum 14-3-3 η levels and radiological damage that were

Table 1 Comparison between the two studied groups according to different clinical and laboratory parameters

	Patient group N = 45	Control group N = 35	Test of significance	p
ESR 1st h (mm/h)	34.1 \pm 16.9	4.7 \pm 1.32	10.25	< 0.001*
RF (IU) median (min-max)	50 (0–150)	5 (2–9)	U = 205.5*	< 0.001*
CRP (mg/dl) median (min-max)	60 (2–96)	1.0 (0.0–2.0)	U = 6.5	< 0.001*
ACCP (U/ml) Median (min-max)	70 (10–220)	17 (10–27)	U = 228.5*	< 0.001*
Serum 14-3-3 η (ng/ml) Median (min-max)	0.45 (0.14–0.69)	0.14 (0.07–0.34)	U = 68.5*	< 0.001*
Serum Sema3A (ng/ml) Median (min-max)	3.9 (1.8–6.1)	6.5 (2.1–8)	U = 1345.0*	< 0.001*

U Mann-Whitney test

Table 2 Agreement (sensitivity, specificity) for different parameters to predict cases (vs control)

	AUC	<i>p</i>	95% C.I	Cut off	Sensitivity	Specificity	PPV	NPV
RF	0.870	< 0.001*	0.778–0.961	> 7	80.0	85.71	87.8	76.9
ACCP	0.855	< 0.001*	0.764–0.946	> 22	84.44	88.57	90.5	81.6
14-3-3η	0.957	< 0.001*	0.916–0.997	> 0.24	88.89	91.43	93.0	86.5
Sema3A	0.854	< 0.001*	0.755–0.953	≤ 5.8	82.82	80.0	84.1	77.8

AUC Area under a curve, *p* value probability value, CI Confidence intervals, NPV Negative predictive value, PPV Positive predictive value

*Statistically significant at $p \leq 0.05$

detected by both X-ray and musculoskeletal U/S (Tables 3 and 4). This can be due to 14-3-3η protein which activates several proinflammatory signaling cascades involved in the pathogenesis of RA. It also stimulates matrix metalloproteinase which participate in the joint damage cascade [7, 10].

We demonstrated the relation between disease activity score DAS28 results, gray scale synovitis assessment, and Doppler flow signal to both serum 14-3-3η and Sema3A in (Table 4 and Fig. 2a–d).

Maksymowych et al. (2014) reported the same increase in serum 14-3-3η level in both early and established rheumatoid which was explained by the stimulation of extracellular regulated kinase 1,2 that leads to more joint damage through the production of interleukin 1 (IL-1), IL-6, receptor activator of nuclear factor κB ligand, and matrix metalloproteinase 1 [7].

Maksymowych et al. found that 14-3-3η correlated significantly with rheumatoid factor (RF) and anticitrullinated protein antibodies (ACPA) in RA, but not with C-reactive protein (CRP) or the Disease Activity Score in 28 joints. The levels were higher in patients with more joint damage and can be used as a marker for

radiographic progression and probably a new therapeutic target [7].

In this study, the discriminative ability of serum 14-3-3η is comparable to RF and ACPA, enhancing its diagnostic capacity (Table 2).

This agreed with El-Sherif et al. (2019) who observed increase in serum 14-3-3η protein levels in patients who were seronegative for RF and ACPA which could enhance the sensitivity of RA diagnosis [26].

Guan et al. (2019) also found that the detection rate of RA patients can be improved using serum 14-3-3η protein.

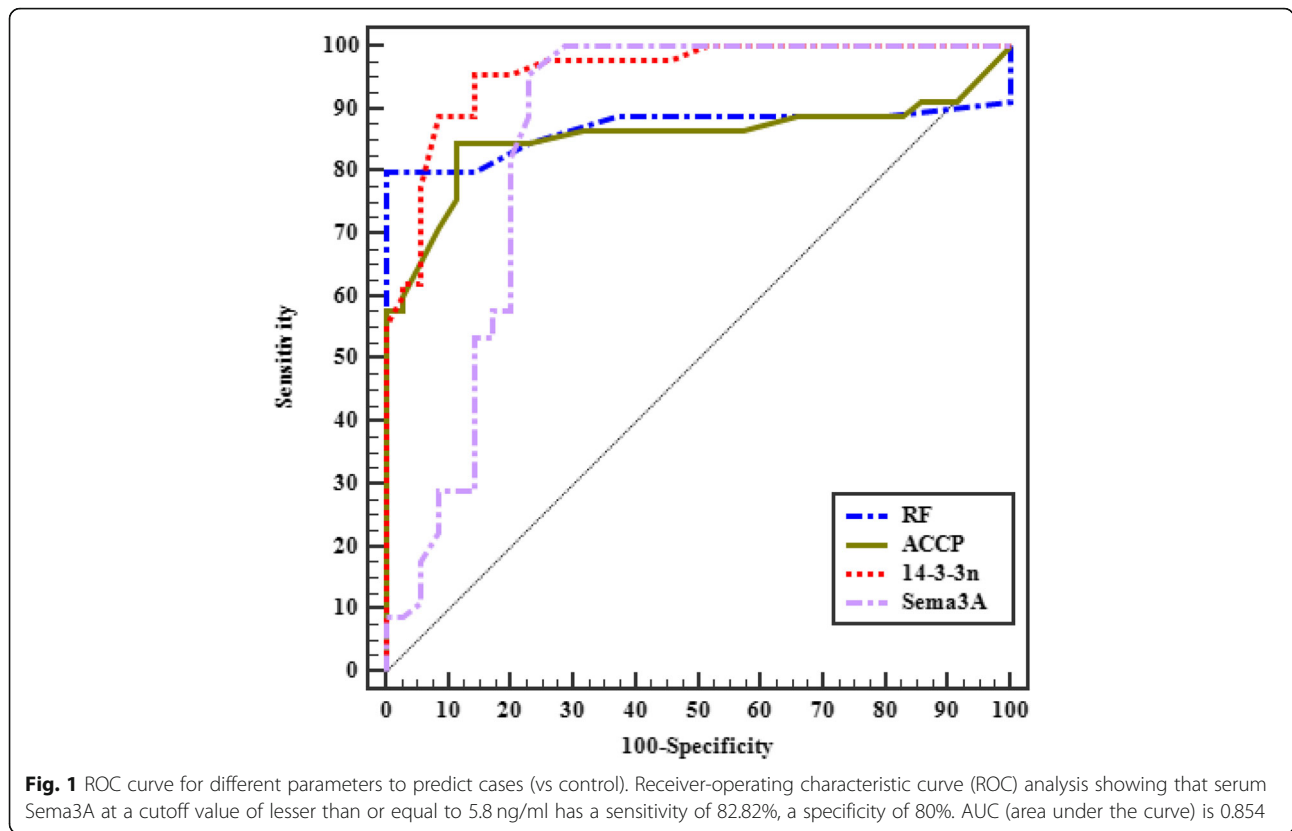
Zeng and Tan (2018) stated that the diagnostic capture of RA patients improved through combining serum 14-3-3η protein with rheumatoid factor and anticitrullinated peptide antibody [27].

Sema3A has a role in autoimmune diseases through regulating lymphocytic function and an osteoprotective effect by stimulation of phospholipase C PLCγ or suppression of RhoA signaling [28]. When its expression levels are distorted, it becomes responsible for abolishing the functions of regulatory T cells and allowing the infiltration and focal aggregation of autoreactive

Table 3 Correlation between the two markers and different parameters in patients group ($n = 45$)

	Serum 14-3-3η		Serum Sema3A	
	r_s	<i>p</i>	r_s	<i>p</i>
Age (years)	− 0.040	0.792	0.103	0.500
Duration of the disease (months)	0.184	0.227	− 0.372*	0.012*
DAS 28	0.358	0.06	− 0.703*	< 0.001*
ESR	0.237	0.117	− 0.535*	< 0.001*
ACPA	0.474*	0.001*	− 0.787*	< 0.001*
RF	0.374*	0.011*	− 0.645*	< 0.001*
CRP	0.307	0.065	− 0.668*	< 0.001*
SDAI	0.485*	0.001*	− 0.581*	< 0.001*
SYNOVITIS	0.665*	< 0.001*	− 0.501*	< 0.001*
Erosions	0.864*	< 0.001*	− 0.652*	< 0.001*

Serum 14-3-3η protein levels: There were positive significant correlations with SDAI ($r = 0.485$, $P = 0.001^*$), SYNOVITIS ($r = 0.665$, $P < 0.001^*$), degree of erosion ($r = 0.864$, $P < 0.001^*$), RF ($r = 0.374$, $P = 0.011^*$), and ACPA ($r = 0.474$, $P = 0.001^*$). There were no correlations with ESR, CRP, or DAS score. Serum Sema3A level: There were negative correlations with duration of the disease ($r = 0.372$, $P = 0.012^*$), disease activity (DAS28 score) ($r = -0.703$, $P < 0.001^*$), SDAI ($r = -0.581$, $P < 0.001^*$), GSN scale ($r = 0.501$, $P < 0.001^*$), and degree of erosion ($r = 0.652$, $P < 0.001^*$). ESR ($r = -0.535$, $P < 0.001^*$), RF ($r = 0.645$, $P < 0.001^*$), CRP ($r = -0.668$, $P < 0.001^*$), and ACPA ($r = -0.787$, $P < 0.001^*$)



lymphocytes in the synovial membrane. Subsequently, Sema3A levels in RA patients can be of an important significance [11, 28–30].

In this study, serum Sema3A levels were decreased in rheumatoid arthritis patients compared to controls. Also, there were also negative correlations with duration of the disease and disease activity score (DAS28), ESR, CRP, and RF (Tables 3 and 4).

Our results are compatible with Teng et al. (2017) who found a significant negative correlation between serum Sema3A levels and RF, CRP, and DAS28 in addition to lower levels of serum Sema3A detected in RA patients compared to osteoarthritis controls [31].

Sema3A also decreases the expression of many inflammatory cytokines secreted by peripheral blood mononuclear cell PBMCs. This role explains the negative

correlations with disease duration and disease activity score (DAS28), ESR, and CRP [31].

Li et al. (2017) showed that Sema3A can be a hopeful biomarker for monitoring the RA activity as it is expressed in all skeletal lineages' cells and then secreted locally and in the blood flow [32].

Sema3A becomes an immunosuppressive regulator that can initiate an immune inhibitory response by making a complex with neuropilin-1 and plexin-A4 [33]. This action was proven in several studies through the induction of Sema3A expression in animal models with arthritis and reported reduced severity and damage of articular surface [34].

In contrast to our results, Ha et al. (2018) found higher serum levels of Sema3A in patients with RA than those in healthy controls and showed a negative

Table 4 Relation between DAS 28 with 14-3-3n and Sema3A in patients' group (n = 45)

	DAS 28				H	p
	Clinical remission (< 2.6) (n = 7)	Low disease activity (2.6–3.2) (n = 10)	Moderate disease activity (3.2–5.1) (n = 5)	High disease activity (> 5.1) (n = 23)		
14-3-3n						
Median (Min.–Max.)	0.28 (0.25–0.47)	0.25 (0.14–0.60)	0.55 (0.26–0.67)	0.59 (0.16–0.69)	17.928*	< 0.001*
Sema3A						
Median (Min.–Max.)	5.5 (3.8–5.8)	5.9 (5–6.1)	4.1 (2.6–6.1)	2.9 (1.8–4.7)	28.918*	< 0.001*

H H for Kruskal Wallis test, p p value for association between different categories

*Statistically significant at p ≤ 0.05

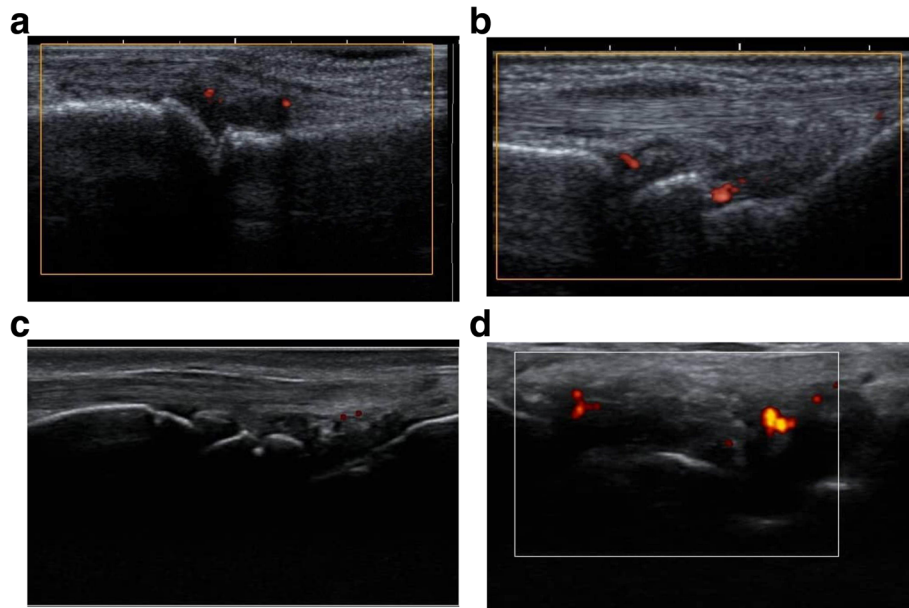


Fig. 2 Relation between the gray scale ultrasound scan and Doppler flow signal with Sema3A and 14-3-3 η protein levels. **a** Longitudinal scan of the metacarpophalangeal joints showing synovitis grade 3 with Doppler signal grade 1 (low-disease activity score). The 14-3-3 η protein level showed an increase up to 0.49 ng/ml (controls 0.14 ng/ml) and Sema3A level showed mild decrease 5.1 ng/ml (controls 6.5 ng/ml). **b** Longitudinal scan of the radiocarpal and intercarpal joints showing synovitis grade 2 Doppler signal grade 1 (low-disease activity score). Serum 14-3-3 η protein level is 0.46 ng/ml and Sema3A level is 4.1 ng/ml. **c** Longitudinal scan of the intercarpal joints showing erosion and grade 2 synovitis and grade 1 Doppler signal (low-disease activity score with erosions). The 14-3-3 η protein level is 0.5 ng/ml, and Sema3A level is 5.9 ng/ml. **d** Longitudinal scan of the wrist showing grade 3 synovitis and grade 2 Doppler signal with effusion (moderate disease activity score). The 14-3-3 η protein level is 0.61 ng/ml, and Sema3A level is 3.5 ng/ml

correlation with Dkk-1 and tumor necrosis factor- α and found non-significant correlation with radiographic damage assessed using the modified Larson score [35]. Our explanation is that there might be longitudinal changes in the serum level during the disease course that we were not able to detect in our study. Also, the longer disease duration of their patient that reached 81 months might play a factor in enhancing the release of this marker.

Using the ROC curve analysis, our study revealed a higher discriminative ability of serum Sema3A compared to RF and ACPA which enhances its diagnostic capacity (Fig. 1).

According to Gao et al. (2018), serum Sema3A level was significantly higher in RA patients than healthy controls, and its mRNA expression level was increased in RA patients' PBMC than controls. The serum Sema3A level was positively correlated with platelet counts, ESR, RF, IgM, Larson score, and bone mineral density (BMD) of the lumbar spine. It was also significantly increased in anti-CCP-positive groups compared to negative groups [36].

These conflicting results might be due to different sample sizes and heterogeneous RA patients in individual studies.

Our results showed a significant negative correlation between Sema3A levels and ultrasound detected bony erosions (Table 3).

Teng et al. (2017) examined the effects of Sema3A on macrophages, fibroblasts, and osteoclasts which are the cells primarily involved in the pathogenesis of RA and revealed that Sema3A-supported IL-4 stimulated M2 macrophage polarization, while inhibited LPS/IFN- γ stimulated M1 polarization. Sema3A prevents endothelial cell proliferation and migration, represses fibroblast function, delays osteoclastogenesis, and performs a protective role in RA. Teng et al. concluded that Sema3A administration diminishes joint tissue damage and the severity of experimental arthritis and offers promising preventive and therapeutic strategies in arthritis [31].

Conclusion

Measuring serum 14-3-3 η protein and Sema3A levels seem to have higher discriminative diagnostic utility in RA. Addition of these markers to ordinary known tests might lead to better diagnosis and evaluation of RA. Sema3A offers a potential therapeutic role for further studies to confirm these promising results.

Recommendations

Future long-term studies are to follow-up patients and to study whether these markers could have a prognostic value. Also, the relation between these markers and the pathogenesis of RA needs to be investigated.

Abbreviations

RA: Rheumatoid arthritis; RF: Rheumatoid factor; ACPAs: Anti-citrullinated protein antibodies; IL-1 β : Interleukin 1 β ; TNF- α : Tumor necrosis factor- α ; DAS28: Disease Activity Score 28; ESR: Erythrocyte sedimentation rate; SDAI: Simplified Disease Activity Index; PBMCs: Peripheral blood mononuclear cells; ROC curve: Receiver-operating characteristic

Acknowledgements

Not applicable

Authors' contributions

NF set the design, collected the data, and performed the data analysis. SA collected the data and performed the analysis and drafting. NN performed the analysis and interpretation of the data and drafting. ER suggested the study design, performed the blind ultrasonographic evaluation for all cases, and shared in the drafting. The authors read and approved the final manuscript.

Funding

We did not receive any funds for this study.

Availability of data and materials

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

Ethics approval and consent to participate

The study was implemented in agreement with the ethical principles of Helsinki and was approved by the local Research Ethics Committee of Faculty of Medicine, Tanta University (approval code 31084/07/19). All of the participants gave written informed consent after a full explanation of the study.

Consent for publication

Not applicable

Competing interests

No competing interest to disclose.

Author details

¹Physical Medicine, Rheumatology and Rehabilitation, Faculty of Medicine, Tanta University, Tanta, Gharbia Governorate, Egypt. ²Department of Clinical Pathology, Faculty of Medicine, Tanta University, Tanta, Egypt.

Received: 29 July 2020 Accepted: 19 October 2020

Published online: 11 December 2020

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