SAR Journal of Medical Biochemistry

Abbreviated Key Title: *SAR J Med Biochem*
Home page: https://sarpublication.com/journal/sarjmb/home
DOI: https://doi.org/10.36346/sarjmb.2026.v07i03.004

OPEN ACCESS

ISSN 2707-7721 (P)
ISSN 2709-6882 (O)

Original Reserach Article

Evaluation of Serum Spexin Levels and their Correlation with Annexin A2 in Men with Rheumatoid Arthritis

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Article History: | Received: 27.06.2026 | Accepted: 20.08.2026 | Published: 22.08.2026 |

Abstract: ***Background*:** Rheumatoid Arthritis is a chronic joint synovial arthritic joint deterioration. The identification of novel biomarkers is crucial for improving diagnostic accuracy and understanding disease pathogenesis. Spexin, a recently discovered adipokine, has been implicated in metabolic and inflammatory processes, While Annexin A2 is recognized to have a pro-inflammatory function in the pathophysiology of RA, Spexin, a recently identified adipokine, has been linked to metabolic and inflammatory processes. ***Objective***: The objective of this study was to investigate serum spexin levels and their correlation with Annexin A2 in males with rheumatoid arthritis compared to healthy controls, as well as to evaluate the diagnostic efficacy of these biomarker1s. ***Methods*:** A case-control study was undertaken including 42 male RA patients and 42 age- and BMI-matched healthy male controls (45-70 years). Serum concentrations of spexin, Annexin A2, anti-cyclic citrullinated peptide (ACCP), erythrocyte sedimentation rate (ESR), and uric acid were examined. Receiver operating characteristic (ROC) curve analysis, Pearson correlation, and independent t-tests were among the statistical methods used. ***Results*:** Results: The concentrations of serum spexin were significantly decreased in the RA group compared to the control group (4.201 ± 1.350 vs. 5.988 ± 1.666 ng/mL, $p < 0.0001$). On the other hand, the concentrations of serum Annexin A2 were significantly increased in the RA group (30.73 ± 6.543 vs. 21.21 ± 5.505 ng/mL, $p < 0.001$). Spexin had only poor analytical sensitivity (AUC = 0.221), whereas Annexin A2 had a good diagnostic value (AUC = 0.868). ***Conclusion*:** Lower serum levels of spexin and higher levels of Annexin A2 have been linked to RA in males. The inverse relationship between spexin and Annexin A2 levels implies possible interaction in the pathophysiology of RA. Annexin A2 can be used for diagnosing RA, whereas spexin may act as a treatment target.

Keywords: Rheumatoid Arthritis, Spexin, Annexin A2, Inflammation, Adipokines.

INTRODUCTION

Rheumatoid Arthritis RA is an autoimmune disease that is a systemic chronic condition, which mainly targets synovial joints, causing cartilage and bone destruction, disability, and excess mortality [1]. Rheumatoid arthritis affects between 0.5% to 1% of the world population, with a high prevalence among women but with considerable morbidity in males as well [2]. There are several factors that participate in the development of rheumatoid arthritis, which includes genetic predisposition, environmental factors, and autoimmune mechanisms, causing synovial inflammation, proliferation of synovial cells, and creation of pannus, which degrades the cartilage and bone [3].

The inflammatory microenvironment of RA is known to be one that involves the presence of immune cells, which include macrophages, T lymphocytes, and B lymphocytes in the synovial membrane, along with the release of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β [4]. Cytokines stimulate the activation of signal transduction pathways that include NF-κB and

Citation: Almuhammdi, M. M. F., Mohammed, N. B., & Alaaraji, S. F. T. (2026). Evaluation of Serum Spexin Levels and their Correlation with Annexin A2 in Men with Rheumatoid Arthritis, *SAR J Med Biochem*, *7*(3), 60-66. https://doi.org/10.36346/sarjmb.2026.v07i03.004

MAPK, which again contribute to the process of inflammation and cause fibroblast proliferation [5]. Inflammation thus results in joint damage and systemic involvement of the disease [6].

The current methods for the diagnosis of RA involve clinical examination, radiography, and serology including RF and ACCP [7]. Although the ACCP shows excellent specificity towards RA, it may not have complete sensitivity, and there are some patients who do not test positive for it [8]. Additionally, the common inflammatory biomarkers like ESR and CRP have no specificity since they can be found in many other diseases as well [9]. The discovery of novel biomarkers to aid in diagnostics and therapy monitoring is thus of prime importance in RA research.

Recently, adipokines (cytokines produced by fat cells) have become an important factor in inflammation and immunity in RA [10]. Some adipokines like adiponectin, leptin, and resistin are associated with the development of RA by participating in synovitis, cartilage destruction, and bone resorption [11]. Spexin, which is one of the novel adipokines, has attracted attention because of its possible involvement in metabolic and inflammatory diseases [10]. Spexin, which was first isolated as a neuropeptide, is found in almost all body tissues including fat cells, and it regulates energy metabolism and insulin sensitivity, and inflammation [10]. Spexin has anti-inflammatory activities and its levels differ in cases like obesity, type 2 diabetes mellitus, and cardiovascular diseases [10]. Nonetheless, there is little data about the involvement of spexin in RA, especially in male subjects.

Annexin A2 is an annexin superfamily member, and it is a calcium-dependent phospholipid-binding protein [12]. This protein is present in many cells such as endothelial cells, monocytes, macrophages, and synovial fibroblasts [13]. There are different biological functions of Annexin A2 like signal transduction, exocytosis, endocytosis, and fibrinolysis [12]. Interestingly, there are some evidences which support that Annexin A2 is involved in the development of various auto-immune and inflammatory diseases such as systemic lupus erythematosus and RA [14]. In rheumatoid arthritis (RA), Annexin A2 is highly expressed in synovial fluid and tissue and stimulates the proliferation, migration, and invasion into cartilage of synovial fibroblasts [12]. Mechanically, Annexin A2 is considered as an important molecule in discoidin domain receptor 2 (DDR-2)/ Annexin A2/ matrix metalloproteinase 13 (MMP-13) axis, which leads to joint destruction through the stimulation of FLS invasion [15]. Additionally, Annexin A2 acts in synergy with the epidermal growth factor receptor (EGFR) and stimulates inflammatory responses and chronic inflammation in RA [15]. Pro-inflammatory effect of Annexin A2 is proved through the relationship between Annexin A2 and anti-inflammatory Annexin A1 in the RA [15]. There was a significant increase in Annexin A2 level and a reduction in Annexin A1 level in naive RA patients compared to the control group [14].

Since spexin is being investigated as a new adipokine with anti-inflammatory effects and Annexin A2 as a pro-inflammatory factor in RA, it was anticipated that the serum concentration of spexin would be reduced whereas the serum concentration of Annexin A2 would be increased in RA patients in comparison to the controls, and the biomarkers will have correlation among themselves as well as with RA activity. The goals of this research were to: (1) compare the concentrations of spexin and Annexin A2 in the serum of male RA patients to healthy control subjects; (2) establish whether there is correlation between spexin and Annexin A2; and (3) assess the efficiency of spexin and Annexin A2 for the diagnosis of RA.

METHODOLOGY

Study Design and Participants

The case-control study was performed in Fallujah teaching hospital from September 2024 till May 2025. This study protocol was approved by the Institutional Review Board and written informed consent was obtained from all participants. The study comprised 42 men (age 45 – 70 years) who were found to have rheumatoid arthritis based on the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria [7]. Controls matched by age and body mass index (BMI) were 42 healthy men (age 45 – 70 years). The criteria for exclusion in both groups were presence of any other autoimmune disease, infection (acute or chronic), tumors, diabetes mellitus, and hepatic/renal insufficiency.

Collection Data

Demographic and clinical data were obtained from all participants, including age, BMI, disease duration, and current medications. The Disease Activity Score based on 28 joints (DAS28-ESR) was used to evaluate disease activity in RA patients.

Blood Sampling and Laboratory Measurements

All subjects gave fasting venous blood samples from 8:00 to 10:00 AM. Serum was isolated by centrifugation at 3000 rpm for 10 minutes, and kept frozen at -20°C until analysis. Spexin and Annexin A2 were analyzed for serum level using commercialized enzyme linked immunosorbent assay (ELISA) kits following the manufacturer's protocol (Sunlong, China). The lowest detectable level and the intra- and inter-assay coefficients of variations (CVs) for the spexin assay kit were 0.25 ng/mL, < 8%, and < 10%, respectively. The lowest detectable level and the intra- and inter-assay CVs for the Annexin A2 assay kit were 0.156 ng/mL, < 8%, and < 10%, respectively. Anti-cyclic citrullinated peptide (ACCP) antibodies were analyzed in sera using a commercially available ELISA kit (Sunlong, China). ESR was measured using Westergren method. Serum

uric acid was quantified by a colorimetric enzymatic method using an automated analyzer.

Statistical Analysis

GraphPad Prism, version 8.02 (GraphPad Software, La Jolla, CA, USA) was used to evaluate quantitative data, which were then reported as mean ± standard deviation (SD). To ascertain if the mean values of the two study groups—RA patients and healthy controls—differed substantially, the independent samples t-test was employed. A P-value of less than 0.05 was deemed to be statistically significant. Furthermore, the strength and direction of the linear relationships between the serum levels of each biomarker were evaluated using the Pearson correlation coefficient. Lastly, the capacity of each parameter under study to differentiate RA patients from healthy people was evaluated using receiver operating characteristic curve (ROC curve) analysis. The area under the ROC curve (AUC), ideal cut-off value, sensitivity, specificity, and likelihood ratio (LHR) were calculated for every biomarker that was assessed.

RESULTS

Demographic and Clinical Characteristics

The demographic characteristics and serum concentrations of the studied parameters in RA patients and healthy controls are presented in Table 1. There were no significant differences between the RA patient group and the control group with respect to age (56.51 ± 7.820 vs. 55.07 ± 8.270 years, p = 0.417) or BMI (23.51 ± 1.942 vs. 22.73 ± 1.978 kg/m², p = 0.077), confirming successful matching of the study groups.

As expected, RA patients demonstrated significantly elevated inflammatory markers. The ESR was markedly higher in RA patients compared to controls (25.62 ± 3.988 vs. 15.57 ± 2.1662 mm/hr, p < 0.0001). In the same manner, levels of serum ACCP, which is a very specific indicator of RA, showed a significant increase in the patients (23.86 ± 3.593 vs. 13.17 ± 3.308 U/mL, p < 0.0001). Surprisingly, the levels of serum uric acid showed a significant decrease in the RA patients when compared with the control group (3.958 ± 0.

Table 1: Shows the demographics and blood levels of the parameters examined in patients with rheumatoid arthritis (RA) and healthy controls

Group Statistics					
Parameter	**no.**	**N**	**Mean**	**Std. D.**	**p-value**
Age years	controls	42	55.07	8.270	0.417
	patients	42	56.51	7.820	
BMI kg/m^2	controls	42	22.73	1.978	0.077
	patients	42	23.51	1.942	
ESR mm/hr.	controls	42	15.57	2.1662	<0.0001
	patients	42	25.62	3.988	
Uric Acid mg/mL	controls	42	4.244	0.5073	0.0016
	patients	42	3.958	0.2464	
ACCP U/mL	controls	42	13.17	3.308	<0.0001
	patients	42	23.86	3.593	
Spexin ng/mL	controls	42	5.988	1.666	<0.0001
	patients	42	4.201	1.350	
Annexin A2 ng/mL	controls	42	21.21	5.505	<0.001
	patients	42	30.73	6.543	

Serum Spexin and Annexin A2 Levels

The main results of this study can be associated with the concentration of spexin and Annexin A2 in the serum. Serum concentration of spexin was significantly decreased in RA patients than in the control group (4.201 ± 1.350 vs. 5.988 ± 1.666 ng/mL; p< 0.0001). The decrease in the concentration of this adipokine may indicate its involvement in RA development due to its anti-inflammatory effects. At the same time, serum concentration of Annexin A2 was significantly higher in RA patients than in the control (30.73 ± 6.543 vs. 21.21 ± 5.505 ng/mL; p< 0.001). This result confirms the results of previous studies about the upregulation of Annexin A2 in the synovial tissue and serum in RA [12].

Diagnostic Performance of Biomarkers

The accuracy of serum ACCP, spexin, and Annexin A2 as markers to differentiate between RA patients and healthy controls is indicated in Table 2 and graphically presented in Figure 1. ACCP was found to be highly sensitive with an AUC of 0.987 (95% CI: 0.971 – 1.000). The sensitivity of ACCP at a cut-off level of > 18.65 U/mL was 92.68%, and its specificity was 92.68%. Similarly, Annexin A2 was found to be moderately sensitive with an AUC of 0.868 (95% CI: 0.794 – 0.941). At a cut-off point of > 24.42 ng/mL, Annexin A2 had a sensitivity of 73.17%, while its specificity was 71.43%. This shows that Annexin A2 can be used as a valuable marker for diagnosing RA, especially seronegative RA. Conversely, serum spexin was identified to have little diagnostic capability with an AUC of 0.221 (95% CI: 0.124 – 0.318). At a cut-off value of < 5.068 ng/mL, spexin had a sensitivity of 70.73%, and its specificity was 69.05%.

Table 2: Serum ACCP, Spexin, and Annexin A2 diagnostic performance in differentiating individuals with rheumatoid arthritis from healthy controls

Variable	AUC	Positive if Cut of Value	Sensitivity %	Specificity %	95 % Confidence Interval
ACCP U/mL	0.987	> 18.65	92.68	92.68	0.971 to 1.000
Spexin ng/mL	0.221	< 5.068	70.73	69.05	0.124 to 0.318
Annexin A2 ng/mL	0.868	> 24.42	73.17	71.43	0.794 to 0.941

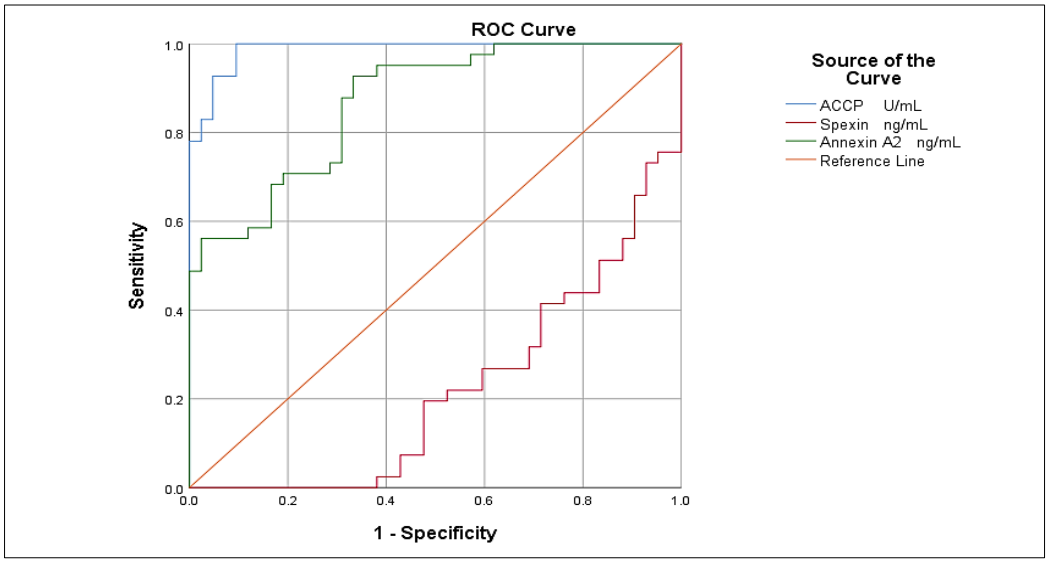


Figure 1: Receiver operating characteristic (ROC) curves of serum ACCP, Spexin, and Annexin A2 for the diagnosis of rheumatoid arthritis

Diagnostic Performance of ESR and Uric Acid

The diagnostic performance of ESR and uric acid is presented in Table 3 and illustrated in Figure2. ESR demonstrated excellent diagnostic accuracy with an AUC of 0.992 (95% CI: 0.9804 - 1.000). At a cut-off value of > 19.45 mm/hr, ESR had a sensitivity of 92.68% and specificity of 92.86%. Serum uric acid showed poor diagnostic performance with an AUC of 0.346 (95% CI: 0.226 - 0.465), consistent with its lower levels in RA patients.

Table 3: Diagnostic performance of ESR and Uric Acid in distinguishing rheumatoid arthritis patients from healthy controls

Variable	AUC	Positive if Cut of Value	Sensitivity %	Specificity %	95% Confidence Interval
ESR mm/hr.	0.992	> 19.45	92.68	92.86	0.9804 to 1.000
Uric Acid mg/mL	0.346	< 4.020	60.98	54.76	0.226 to 0.465

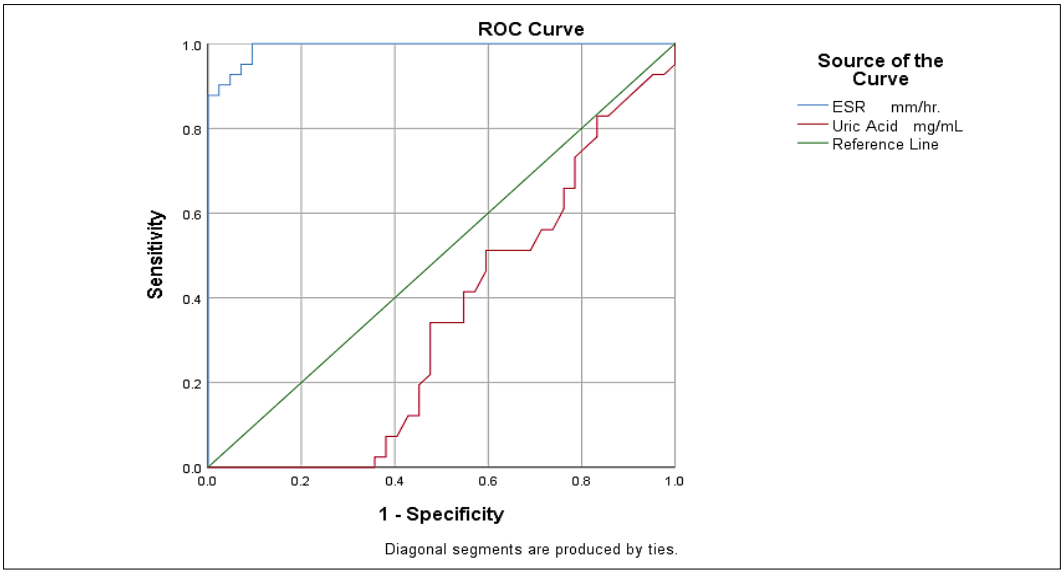


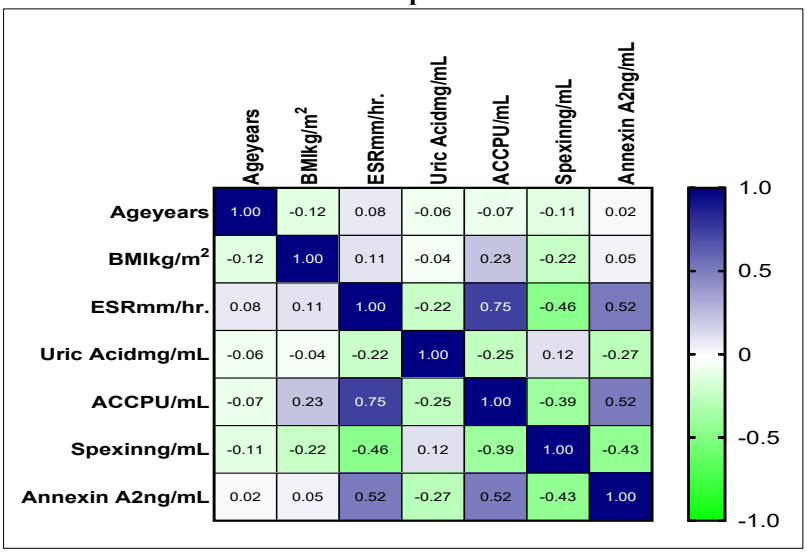
Figure 2: Receiver operating characteristic (ROC) curves of s ESR and Uric Acid for the diagnosis of rheumatoid arthritis

Correlation Analysis

Pearson correlation analysis was performed to evaluate the relationships between the studied biomarkers and clinical parameters in RA patients (Table 4). A significant negative correlation was observed between serum spexin and Annexin A2 levels ($r = -0.43$, $p < 0.01$). This reverse association suggests that reduced spexin levels may be related with increased Annexin A2 expression, possibly conducive to the pro-inflammatory environment in RA.

Serum spexin levels also showed significant negative correlations with ESR ($r = -0.46$, $p < 0.05$) and ACCP ($r = -0.39$, $p < 0.05$), indicating that lower spexin levels are associated with higher disease activity and autoantibody production. Annexin A2 showed significant positive correlations with ESR ($r = 0.52$, $p < 0.01$), ACCP ($r = 0.52$, $p < 0.01$), confirming its association with disease activity and severity. These correlations support the role of Annexin A2 as a marker of inflammation and joint damage in RA. No significant correlations were observed between uric acid and other biomarkers.

Table 4: Pearson correlation matrix of the evaluated serum biomarkers and clinical parameters in rheumatoid arthritis patients



DISCUSSION

The present study investigated the serum levels of spexin and Annexin A2 in male RA patients and their potential as diagnostic biomarkers. The main findings were significantly lower serum spexin levels and elevated Annexin A2 levels in RA patients compared to healthy controls; a significant negative correlation between spexin and Annexin A2; good diagnostic performance of Annexin A2, while spexin showed limited diagnostic utility and correlations of both biomarkers with disease activity markers.

The decrease in the serum level of spexin in RA patients is a novel observation, indicating that there may be a possible involvement of spexin in the etiology of this disease. Spexin, which is an adipokine, has already been reported to have anti-inflammatory as well as metabolic activities [10]. Studies have reported that spexin acts as an anti-inflammatory molecule by regulating the release of pro-inflammatory cytokines and enhancing insulin sensitivity [3]. The low levels of spexin found in RA patients could possibly be indicative of its anti-inflammatory activity being compromised [3].

The reverse relationship found between spexin and Annexin A2 in this study lends further credence to this hypothesis. Annexin A2 has been identified as a pro-inflammatory factor in rheumatoid arthritis, and increased levels of Annexin A2 in synovial tissue lead to cell proliferation, vascularization, and joint damage [12]. The reverse relationship between spexin and Annexin A2 indicates that spexin could play a role in restraining the expression or function of Annexin A2.

In addition, the highly significant negative correlations between spexin and ESR and ACCP show that the decrease in spexin concentration corresponds to an increase in disease activity and formation of autoantibodies. This result supports the theory that spexin can be a protective factor in the development of RA because the reduction of spexin concentrations can aggravate the condition of the patient. Furthermore, the negative correlation between spexin and the disease duration shows that spexin can decrease during the progression of the disease [16].

The exact mechanisms by which low concentrations of spexin are achieved in patients with RA have not yet been explained. One hypothesis suggests that constant inflammation can inhibit spexin synthesis via the action of cytokines on the fat tissue [10]. Another possible explanation for the observed

phenomenon is that spexin synthesis in RA is regulated by genes or epigenetics.

The increased concentration of Annexin A2 in serum from RA patients found in this study is in line with findings of study [12]. Annexin A2 is a multi-functional protein involved in several physiological functions such as inflammation, angiogenesis, and fibrinolysis [12]. It is upregulated in RA at the level of synovium and synovial fluid, facilitating proliferation and invasion of synovial fibroblasts and causing cartilage/bone damage [17].

From a functional point of view, it is worth mentioning the importance of Annexin A2 as a central component of the DDR-2/Annexin A2/MMP-13 pathway that mediates joint destruction by facilitating FLS migration and invasion [8]. Annexin A2 binds to DDR-2 and, according to the study of Zhao *et al*., it becomes phosphorylated, causing the release of MMP-13, which mediates cartilage degradation [12]. Suppression of Annexin A2 resulted in substantial decrease in joint destruction in experimental collagen-induced arthritis [17].

Furthermore, the pro-inflammatory nature of Annexin A2 is demonstrated through its reciprocal expression to Annexin A1, which is known for being an anti-inflammatory molecule [14]. There is evidence showing the occurrence of high amounts of Annexin A2 but low amounts of Annexin A1 in naive RA patients in contrast to the amounts found in normal individuals [10]. Knockdown of Annexin A2 using either siRNA or antibodies has been demonstrated to induce the expression of cellular Annexin A1 followed by its translocation to the membranes leading to the development of anti-inflammatory effects [14].

In addition, there has been found an interaction between the epidermal growth factor receptor (EGFR) and Annexin A2 in RA, which is enhanced by the down-regulation of Annexin A1 [15]. The discovery that the butyric acid, produced by the gut microflora, could reduce the expression of EGFR and Annexin A2 and increase the expression of Annexin A1 suggests a therapeutic approach for interference with this pro-inflammatory mechanism [15].

Moreover, the positive correlations seen in the present study between Annexin A2 and the indicators of disease activity such as ESR, ACCP, and DAS28-ESR suggest more evidence of the association of Annexin A2 with disease activity. This can be an indicator that Annexin A2 might be a good biomarker for disease activity in RA patients [18]. The diagnostic potential of the above-mentioned markers was assessed via the ROC curve analysis technique. ACCP and ESR proved to be highly effective in terms of diagnosing RA and assessing inflammation as their AUCs were calculated at 0.987 and 0.992, correspondingly.

The diagnostic performance of annexin A2 was good with AUC of 0.868, implying that this marker can help as a valuable add on biomarker in the diagnosis of RA, especially in seronegative cases. The sensitivity and specificity were 73.17% and 71.43% respectively, at cut off > 24.42 ng/mL. Both the sensitivities and specificities have either similar or superior values compared to certain conservative markers, thus annexin A2 is a well-respected addition to the diagnostic battery of RA.

On the contrary, serum spexin showed low discriminatory capability with an AUC of 0.221. Low AUC values suggest that spexin alone cannot be considered a effective biomarker for diagnosing RA. But based on the presence of significant alterations in spexin levels in RA subjects compared to control individuals and the correlation of this biomarker with RA disease activity markers, spexin can be useful in monitoring disease progression and/or can be used as a therapeutic target. Spexin as a potential therapeutic target is based on the anti-inflammatory properties and negative correlation with inflammatory markers in RA [19]. These findings have some clinical applications. Since the level of Annexin A2 is high in RA patients and its association with the markers of disease activity, it can serve as a biomarker to evaluate disease activity and treatment response [5]. Since there is an inverse association between spexin and Annexin A2, it is possible that methods employed to enhance the level of spexin would reverse the inflammation caused by Annexin A2.

Future research should assess the changes in the levels of spexin and Annexin A2 over time with respect to the course of the disease and its treatment [20]. In addition, the influence of DMARDS and biological treatments on the biomarker levels should be assessed. It is also important to conduct more extensive research including both male and female RA patients [21]. It would be interesting to explore the possible use of spexin as a target in RA therapy. One can make use of animal models of RA in order to establish whether the treatment with spexin can decrease the severity of the disease. It would be interesting to study the mechanisms through which spexin is able to regulate Annexin A2 expression/activation [22, 23].

CONCLUSIONS

This study shows that there are elevated raised serum levels. The potential interplay between these molecules may contribute to the interplay between these molecules between these molecules. While spexin may be a potential therapeutic target despite its weak diagnostic efficacy, Annexin A2 exhibits promise as a diagnostic biomarker with good discriminative ability. These results underline the possibility of creating novel diagnostic and treatment approaches for this crippling illness and add to the increasing amount of data demonstrating the involvement of adipokines and annexins in the pathophysiology of RA.

Author Contributions

- **Maryam:** Research, Writing, and Original Draft Preparation.
- **Nibras:** Formal analysis, data curation, and investigation.
- **Shakir:** Project management, writing, review, and editing, conceptualization, and supervision.

Funding: No funding.

ACKNOWLEDGEMENT

We would like to thank the universities of Fallujah and Anbar for the continuous support they provide to their researchers.

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