

Evaluation Serum Levels of Aggrecan, Fibulin-1, Lubricin, and β -Defensin 3 in Females with Rheumatoid Arthritis

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ABSTRACT

Background: Rheumatoid Arthritis (RA) is a chronic, systemic autoimmune inflammatory disease primarily affecting the joints. Despite the availability of diagnostic tools, identifying novel biomarkers that reflect joint pathology remains crucial for the accurate evaluation of RA.

Objectives: To assess the serum levels of novel joint-related biomarkers (aggrecan, fibulin-1, lubricin, and human beta-defensin 3 [HBD-3]) in females with RA, and to determine their diagnostic performance compared to healthy controls (HC).

Materials and methods: This case-control study included 60 female RA patients and 60 age-matched HC. Serum concentrations of aggrecan, fibulin-1, lubricin, HBD-3, and anti-citrullinated protein antibody (ACPA) were determined using ELISA kits. Erythrocyte sedimentation rate was measured via the standard Westergren method.

Results: Serum levels of aggrecan, fibulin-1, lubricin, and HBD-3 were significantly increased in RA patients compared to HC (P-value = 0.0001). For predicting disease status, the biomarkers yielded the following area under the receiver operating characteristic (AUROC) curve values: aggrecan (0.947, cut-off > 15.80 ng/mL), fibulin-1 (0.885, cut-off > 7.975 ng/mL), HBD-3 (0.885, cut-off > 325.2 pg/mL), and lubricin (0.719, cut-off > 169.4 pg/mL). Additionally, these biomarkers showed significant positive correlations with each other and with ACPA levels.

Conclusion: Serum aggrecan, fibulin-1, lubricin, and HBD-3 are significantly elevated in RA patients, indicating strong disease association and high diagnostic potential. Future longitudinal studies are required to establish definitive clinical utility in monitoring disease activity.

Keywords: Aggrecan; Fibulin-1; β -Defensin 3; Lubricin; Rheumatoid arthritis.

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INTRODUCTION

Arthritis is a disease that is prevalent and can manifest in a variety of forms, with rheumatoid arthritis (RA) being the most common. This autoimmune disease is characterized by chronic inflammation and the infiltration of immune and inflammatory cells into the synovial membrane, bone tissue, and cartilage, resulting in joint pain, deformity, and stiffness [1, 2]. RA contributes to functional disability and affects approximately 0.5–1% of the population. In women, RA is more prevalent and can manifest at any age. The primary clinical manifestations

of RA include symmetrical joint involvement characterized by erythema, arthralgia, edema, and a restricted range of motion [3, 4]. Furthermore, early diagnosis remains challenging, as no single definitive biomarker can independently confirm the condition with absolute certainty.

Rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA) are the two most notable autoantibodies in RA. ACPA is extremely predictive of the severity and progression of RA. ACPA and RF may be absent in 20–30% of RA cases; additionally, erosive RA may be present without these markers. RA disease phenotypes are therefore categorized into ACPA positive and negative RA. Although RF and ACPA have diagnostic utility, additional markers of pathogenesis will be needed to better understand the mechanisms involved in RA and to provide earlier diagnosis and treatment for patients with this disease [5–7].

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Aggrecan is a major glycoprotein of the extracellular matrix (ECM) of articular cartilage [8]. In joint disorders, aggrecan is degraded by principal enzymes such as aggrecanases and matrix metalloproteinases (MMPs), releasing fragments that are measurable in the serum and synovial fluid of affected individuals [9, 10]. Fibulin-1 is an ECM glycoprotein widely distributed throughout connective tissues, indicating a critical role in the process of matrix remodeling [11].

Similarly, lubricin is a mucin-like molecule [12] synthesized by chondrocytes and found in synovial fluid and membrane, contributing to joint integrity [13]. Defensins are antimicrobial peptides [14] and human beta-defensins (HBDs) identified in RA synovial membranes are associated with joint injury and cartilage remodeling through increased MMP synthesis and reduced TIMPs [15].

Although these biomarkers are individually linked to joint pathology, their combined diagnostic value in RA remains unclear. Since RA involves coordinated inflammatory and destructive mechanisms, evaluating markers of cartilage degradation (aggrecan and lubricin), ECM remodeling (fibulin-1), and inflammation (HBD-3) may better reflect disease pathophysiology than single biomarkers alone. Therefore, this study assessed the serum levels of this biomarker panel in females with RA and evaluated its diagnostic performance compared with healthy controls.

MATERIALS AND METHODS

Study Design and Participants

The study protocol was approved by the Ethical Approval Committee of the University of Anbar (Reference number 190; 12 January 2024). Informed consent was obtained from all participants before enrollment. This cross-sectional case-control study initially estimated a minimum sample size of 27 participants using the Kish and Leslie formula ($N = Z^2 p(1-p) / d^2$), based on a 95% confidence level ($Z = 1.96$), 5% margin of error, and an estimated RA prevalence of 1.75% [16]. To strengthen biomarker evaluation, 60 female RA patients were subsequently recruited from the Rheumatology Clinic at Al-Ramadi Teaching Hospital between October 2024 and April 2025.

All RA cases were confirmed by consultant rheumatologists according to the 2010 American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) classification criteria [17], based on clinical assessment of joint involvement and laboratory investigations including RF, ACPA, and acute-phase reactants. Patients were receiving routine pharmacological treatment, mainly conventional synthetic disease-modifying antirheumatic drugs (DMARDs), as prescribed by their rheumatologists; however, detailed information regarding drug combinations and dosages was not systematically recorded. The patient group was matched with 60 healthy seronegative female controls of similar age and body mass index (BMI).

Inclusion and exclusion criteria

The RA patient group consisted of adult females who were diagnosed with RA as per the ACR/EULAR criteria. The control group consisted of age-matched females recruited from the medical and administrative staff at Al-Ramadi Teaching Hospital, with no clinical manifestations of autoimmune or joint disorders and with no family history of such disorders. The absence of such conditions was confirmed through a detailed self-reported medical history, the absence of any joint

pain or swelling, and negative results for routine inflammatory and rheumatic markers. Conversely, subjects were totally excluded from the study if they suffered from any other autoimmune or rheumatic disease (e.g., systemic lupus erythematosus, osteoarthritis, gout), any chronic infectious diseases (including hepatitis B, hepatitis C, human immunodeficiency virus), any severe hepatic or renal impairment, or any previous history of malignancies. Furthermore, pregnant or lactating women were also considered exclusion criteria due to the known effects on the immune response and serum protein levels. The exclusion criteria were rigorously assessed and applied using detailed medical history, routine clinical evaluation by the attending physician at the outpatient clinic, and baseline laboratory investigations.

Sample collection

Approximately 6 mL of venous blood was collected from each participant and divided into two tubes: an anticoagulated tube for erythrocyte sedimentation rate (ESR) measurement and a plain serum separator tube. After clot formation, the samples were centrifuged at 4000 rpm for 10 minutes to obtain serum. The separated serum was aliquoted into Eppendorf tubes and stored at -20°C until biochemical analysis.

Methods

Serum aggrecan, fibulin-1, lubricin, HBD-3, and ACPA concentrations were determined using commercially available enzyme-linked immunosorbent assay (ELISA) kits [18]. The specific kits used were aggrecan (Cat. No. MBS2703877), fibulin-1 (Cat. No. MBS162928), lubricin (Cat. No. MBS3801219), HBD-3 (Cat. No. MBS2600382), and ACPA (Cat. No. MBS2607572), all provided by MyBioSource, Inc. San Diego, CA, USA. ESR was measured using the standard Westergren method [19].

Statistical analysis

Quantitative data were analyzed using GraphPad Prism, version 8.02 (GraphPad Software, La Jolla, CA, USA) and expressed as mean $\pm$ standard deviation (SD) and standard error of the mean (SEM). The independent samples t-test was used to determine whether the mean values of the two study groups differed significantly (i.e., RA patients vs. healthy controls). Statistical significance was considered at a P-value of < 0.05 . Additionally, the Pearson correlation coefficient was used to assess the strength and direction of the linear relationships between the serum levels of the individual biomarkers. Finally, receiver operating characteristic curve (ROC curve) analysis was conducted to assess the ability of each studied parameter to distinguish RA patients from healthy individuals. For each evaluated biomarker, the area under the ROC curve (AUC), optimal cut-off value, sensitivity, specificity, and likelihood ratio (LHR) were determined.

RESULTS

There were no significant differences between the RA patients and healthy controls regarding age (52.67 ± 7.61 vs. 50.83 ± 8.22 years, P-value = 0.294) and BMI (24.05 ± 1.89 vs. 23.63 ± 1.93 kg/m², P-value = 0.321). The results show that the serum concentrations of aggrecan (30.52 ± 11.99 vs. 10.26 ± 4.70 ng/mL), fibulin-1 (12.69 ± 5.82 vs. 5.63 ± 2.43 ng/mL), lubricin (226.75 ± 100.77 vs. 151.23 ± 76.30 pg/mL), HBD-3 (449.89 ± 140.86 vs. 235.58 ± 99.84 pg/mL),

Table 1. Demographic characteristics and serum concentrations of the parameters studied in rheumatoid arthritis (RA) patients and healthy controls*.

Variable	Healthy controls (n=60) Mean ± SD	CI 95%	RA patients (n=60) Mean ± SD	CI 95%	P-value
Age (years)	52.67 ± 7.61	50.75–54.59	50.83 ± 8.22	48.75–52.91	0.294
BMI (kg/m ²)	24.05 ± 1.89	23.57–24.53	23.63 ± 1.93	23.14–24.12	0.321
Aggrecan (ng/mL)	10.26 ± 4.70	9.07–11.45	30.52 ± 11.99	27.49–33.55	0.0001
Fibulin-1 (ng/mL)	5.63 ± 2.43	5.02–6.24	12.69 ± 5.82	11.22–14.16	0.0001
Lubricin (pg/mL)	151.23 ± 76.30	131.9–170.5	226.75 ± 100.77	201.2–252.2	0.0002
HBD-3 (pg/mL)	235.58 ± 99.84	210.3–260.8	449.89 ± 140.86	414.2–485.5	0.0001
ACPA (ng/mL)	6.11 ± 2.14	5.57–6.65	28.71 ± 11.26	25.86–31.56	0.0001
ESR (mm/H)	16.10 ± 3.38	15.24–16.96	37.70 ± 8.32	35.60–39.80	0.0001

* ACPA: Anti-citrullinated protein antibody; CI: Confidence interval; ESR: Erythrocyte sedimentation rate; HBD-3: Human beta-defensin 3; RA: Rheumatoid arthritis; SD: Standard deviation. P-value were determined using an independent samples *t*-test.

Table 2. Pearson correlation matrix of the evaluated serum biomarkers and clinical parameters in rheumatoid arthritis patients†.

		Correlations					
		Aggrecan	Fibulin-1	Lubricin	HBD-3	ACPA	ESR
Aggrecan	r	–	0.519**	0.395**	0.610**	0.641**	0.590**
	p	–	0.0001	0.0001	0.0001	0.0001	0.0001
Fibulin-1	r	–	–	0.510**	0.413**	0.558**	0.608**
	p	–	–	0.0001	0.0001	0.0001	0.0001
Lubricin	r	–	–	–	0.263*	0.398**	0.400**
	p	–	–	–	0.015	0.0001	0.0001
HBD-3	r	–	–	–	–	0.560**	0.572**
	p	–	–	–	–	0.0001	0.0001
ACPA	r	–	–	–	–	–	0.786**
	p	–	–	–	–	–	0.0001
ESR	r	–	–	–	–	–	–
	p	–	–	–	–	–	–

† ** Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed). p: P-value ACPA: Anti-citrullinated protein antibody; ESR: Erythrocyte sedimentation rate; HBD-3: Human beta-defensin 3.

and ACPA (28.71 ± 11.26 vs. 6.11 ± 2.14 ng/mL), as well as ESR (37.70 ± 8.32 vs. 16.10 ± 3.38 mm/H), were significantly greater in RA patients than in healthy controls (P-value = 0.0001 for all studied parameters; except lubricin, which had a P-value of 0.0002) as illustrated in Table 1.

Correlation analysis

All tested serum biomarkers were positively correlated with high significance levels. For example, there was a strong positive correlation between aggrecan and ACPA (r = 0.641; P-value = 0.0001), as well as a strong positive correlation between aggrecan and HBD-3 (r = 0.610; P-value = 0.0001). In addition, both fibulin-1 and lubricin were significantly and positively correlated with each of the other parameters that were tested (Table 2).

Diagnostic validity (ROC curve analysis)

The ROC curve analyses were conducted to evaluate the discrimination (diagnostic validity) of the new biomarker can-

didates (Figure 1). These results indicated excellent diagnostic accuracy for aggrecan as evidenced by an AUC of 0.947 (P-value = 0.0001). This equated to a sensitivity of 83.72%, and specificity of 83.33% using a cut-off value of > 15.80 ng/mL. The novel biomarkers, fibulin-1 and HBD-3, demonstrated good diagnostic capabilities, both achieving an AUC of 0.885 (P-value = 0.0001). However, lubricin had only moderate diagnostic utility (AUC = 0.719, P-value = 0.0001) as shown in Table 3).

DISCUSSION

RA is a complex, multifactorial disease that is significantly influenced by genetic and epigenetic factors. Consequently, it is challenging to diagnose early and accurately due to its intricate pathology. Traditional serological biomarkers that are employed in the diagnosis of RA are absent in up to one-third of patients, and the percentage is even higher in the early phases of the disease. Although 61.6% of individuals with RA test positive for ACPA during the initial phases of the disease, the specificity and sensitivity of the ACPA are

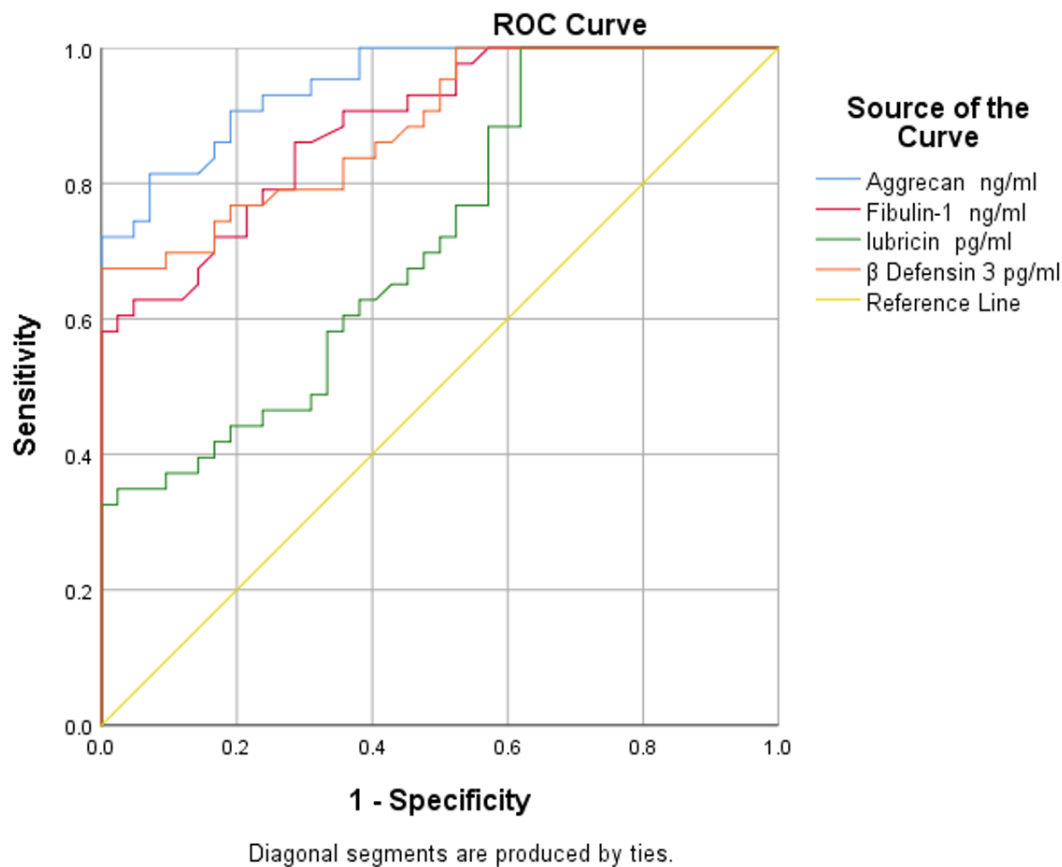


Figure 1. Receiver operating characteristic (ROC) curves of serum aggrecan, fibulin-1, lubricin, and HBD-3for the diagnosis of rheumatoid arthritis.

Table 3. Diagnostic performance of serum aggrecan, fibulin-1, lubricin, and HBD-3 in distinguishing rheumatoid arthritis patients from healthy controls*.

Biomarker	AUC	95% CI	P-value	Correlations			
				Cut-off Value	Sensitivity (%)	Specificity (%)	Likelihood Ratio
Aggrecan (ng/mL)	0.947	0.906–0.988	< 0.0001	> 15.80	83.72	83.33	5.023
Fibulin-1 (ng/mL)	0.885	0.818–0.952	< 0.0001	> 7.975	79.07	79.07	3.778
Lubricin (pg/mL)	0.719	0.612–0.826	0.0001	> 169.4	62.79	61.90	1.648
HBD-3 (pg/mL)	0.885	0.817–0.953	< 0.0001	> 325.2	76.74	76.19	3.223

* AUC: Area Under the curve; CI: Confidence interval; HBD-3: Human beta-defensin 3; RA: Rheumatoid arthritis; ROC: Receiver operating characteristic. *This table provides a summary of all the ROC coordinates from the four biomarkers, including likelihood ratios and 95% CI.

considerably greater than those of the RF test [20]. RF is also employed to diagnose other inflammatory diseases [21]. Consequently, it is crucial to identify novel biomarkers with high specificity and sensitivity, as the rapid progression of joint injury can be slowed in 90% of patients through early diagnosis and targeted treatment of RA [22].

In this study, we identified promising biomarkers, with high specificity and high sensitivity, for diagnosing RA by combining aggrecan, fibulin-1, lubricin, and HBD-3 with traditional RA biomarkers. Our findings demonstrate a concurrent and significant elevation of all these novel biomarkers in patients with RA, reflecting two interconnected pathological hallmarks

of the disease: active ECM remodeling and chronic joint inflammation. Regarding ECM degradation, loss of aggrecan is considered one of the earliest events preceding cartilage disintegration [23], highlighting its pathogenic importance and value as an indicator of early cartilage damage in RA. This process is further supported by the elevated fibulin-1 levels observed in the present study. To our knowledge, studies evaluating serum fibulin-1 in RA remain limited; therefore, our findings provide novel insights into its association with the disease. Recent evidence indicates that ECM remodeling plays a central role in RA pathogenesis, with matrix components contributing to synovial auto-aggression [2]. Further-

more, elevated ECM proteins such as fibulin-1 may reflect pathological alterations in the rheumatoid joint environment [24].

Lubricin levels were also significantly higher in RA patients than in controls. Previous studies demonstrated that lubricin acts as an immunomodulator through binding to cluster of differentiation 44 (CD44) [25] and interaction with Toll-like receptors (TLRs), thereby preserving the anti-inflammatory phenotype of synovial cells and reducing pro-inflammatory cytokine production [26]. Conversely, Ekinici *et al.* [12] discovered that serum lubricin levels were significantly higher in active juvenile idiopathic arthritis patients, in comparison to the juvenile idiopathic arthritis patients in remission and control groups. A systematic review comprising sixty-two studies, thirty-eight of which assessed endogenous lubricin in osteoarthritis or joint injury. There were nineteen papers that reported a decrease, while nineteen found an increase or no change in lubricin [27].

The HBD-3 levels in RA patients were significantly higher than in the control group. This finding aligns with the findings of Mohammed *et al.* [14] who reported that serum levels of HBD-3 were significantly higher in RA patients than in healthy subjects. Also, this result agrees with Santos *et al.* [28] who reported in an *in vitro* study that HBD-3 plays a role in RA by inducing the production of proinflammatory cytokines and MMP by chondrocytes, which degrade the ECM of cartilage. The promotion of the secretion of proinflammatory cytokines by HBD could play a role in the cytokine imbalance that leads to synovium destruction in RA [29]. Another study shows that the presence of proinflammatory cytokines in the affected joints may elucidate the heightened expressions of HBD-3 and other AMPs. Increased expression of HBD-3 may furthermore contribute to the recruitment of immune cells and enhance the inflammatory reaction within the joint [29]. In typical physiological conditions, HBD-3 and other AMPs are expressed at an extremely low level. However, they can be induced by a variety of stimulants, including host inflammatory stimuli like tumor necrosis factor- α (TNF- α) and interleukin-1 beta (IL-1 β). In this regard, the mechanism by which HBD-3 is related to the existence of bone erosion may consist only of its capacity to enhance the production of TNF- α and IL-6, thus causing the inflammatory cytokines to contribute to bone destruction and the swollen joints seen in RA [28]. Farhan *et al.* [15] found in a study conducted on Iraqi patients that RA patients exhibit elevated serum HBD-2 concentrations in comparison to control participants, and these levels are associated with disease activity. In the diagnosis of RA, serum level of HBD-2 levels can be a useful biomarker.

There was a highly significant positive correlation among aggrecan, fibulin-1, lubricin, and HBD-3, with ACPA and ESR (traditional diagnostic markers). These strong positive correlations demonstrate that these markers increase concurrently in response to disease development and progression. The synchronous elevation of these biomarkers highlights their strong association with RA and supports their potential role as complementary diagnostic markers alongside conventional parameters. However, several limitations should be considered. The relatively small sample size, single-center design, and inclusion of only female participants may limit the generalizability of the findings. In addition, the cross-sectional design precluded assessment of the long-term prognostic value of these biomarkers or their utility in monitoring disease progression. Important clinical and confounding vari-

ables, including disease duration, DAS28 scores, BMI, smoking status, minor comorbidities, and detailed medication regimens, were not systematically evaluated, limiting comprehensive adjustment for potential confounders. Furthermore, the sample size calculation was based on disease prevalence rather than biomarker effect sizes or anticipated AUC values, which may have reduced the statistical power of the diagnostic evaluation. Therefore, larger multicenter longitudinal studies, particularly in early, or undiagnosed RA populations, are warranted to validate these findings and further establish their clinical significance.

CONCLUSION

The study demonstrated significantly elevated serum levels of aggrecan, fibulin-1, lubricin, and HBD-3 in RA patients, indicating their strong association with the disease. While these biomarkers successfully differentiate established RA patients from healthy controls in this cohort, their definitive diagnostic utility should be interpreted cautiously due to the cross-sectional case-control study design. Therefore, further prospective, longitudinal studies involving early or undiagnosed cohorts are necessary to fully establish their clinical applicability and diagnostic value in real-world settings.

ETHICAL DECLARATIONS

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Ethics Approval and Consent to Participate

The Ethical Approval Committee of the University of Anbar approved the study protocol (Reference number: 190, Date: 12-1-2024). An information sheet was completed, and informed consent was obtained from all participants, both patients and controls.

Consent for Publication

Not applicable.

Availability of Data and Material

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

Competing Interests

The authors declare that there is no conflict of interest.

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Use of Artificial Intelligence

During the preparation of this work, the authors used artificial intelligence (AI) tools solely to improve the English language and readability, including rephrasing the abstract to meet word count limits. After using these tools, the authors thoroughly reviewed, edited, and validated the content. The authors declare that AI tools were not used to generate data or scientific conclusions, and they take full responsibility for the final content of the publication.

Authors' Contributions

I.A.S. performed the experimental work, data collection, and drafted the manuscript. S.F.T.A. designed the study, supervised the practical work, and critically revised the manuscript. S.A.S.A. contributed to data analysis, performed

the literature search, participated in the final revision of the manuscript, and provided financial support for publication. All authors read and approved of the final version of the manuscript.

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