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ORIGINAL PAPER

Evaluation of endothelin 1 and N-terminal pro-B-type natriuretic peptide in patients with rheumatoid arthritis

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ABSTRACT

Introduction and aim. Rheumatoid arthritis (RA) is a chronic disease characterized by synovial inflammation and joint destruction. This study evaluated the novel biomarkers vitamin D binding protein (VDBP), retinol-binding protein 4 (RBP4), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and endothelin-1 (ET-1) for RA diagnosis. To our knowledge, this is the first study to simultaneously assess these biomarkers across different treatment stages in RA, linking systemic inflammation with subclinical cardiovascular involvement.

Material and methods. A case-control study enrolled 61 RA patients [G1 (newly diagnosed, untreated, n=10)], G2 [3 months csDMARDs, n=22], G3 [≥6 months biologic+csDMARDs, n =29]), 27 age/sex-matched healthy controls. The serum levels of VDBP, RBP-4, CRP, NT-proBNP, and ET-1 measured using enzyme-linked immunosorbent assay.

Results. All evaluated biomarkers were significantly elevated in RA patients compared to controls ($p<0.0001$): RBP-4 (49.172±21.935 vs. 14.006±3.988 ng/mL), VDBP (12.091±3.334 vs. 2.882±1.136 ng/mL), NT-proBNP (1341.787±626.068 vs. 11.452±3.260 pg/mL), ET-1 (14.246±4.031 vs. 3.932±1.422 pg/mL). Subgroup analysis revealed a significantly higher VDBP in newly diagnosed untreated patients (G1:14.455±4.126 ng/mL) than in treated groups (G2:11.379±2.632; G3:11.816±3.269 ng/mL; $p<0.05$). NT-proBNP peaked in G1 (1789.2±710.81 pg/mL), decreased in csDMARD-treated (G2: 1154.0±537.58 pg/mL), biologic-treated (G3: 1329.96±601.18 pg/mL) group.

Conclusion. VDBP, RBP-4, CRP are effective diagnostic biomarkers of RA. Significant elevations in NT-proBNP and ET-1 levels associated with cardiac complications, correlated with disease activity, and improved with therapy.

Keywords. endothelin 1, N-terminal pro-brain natriuretic peptide retinol–binding protein-4, vitamin D binding protein,

Introduction

Rheumatoid arthritis (RA) is defined as a chronic, systemic autoimmune pathology driven by inflammation that targets joints and may involve diverse extra-articular organs (e.g., cardiac, renal, pulmonary, gastrointestinal, ocular, dermal, and neurological systems).[1] Contemporary research indicates RA etiology involves an integrated contribution from genetic factors, epigenetic regulation, and environmental exposures (such as tobacco smoke, airborne particulates, and notably, the internal environment shaped by the microbiome).[2] Pathogenesis hinges on aberrant interactions within the innate and adaptive immune compartments.[3] These immune disturbances precipitate the generation of characteristic autoantibodies, including RF and antibodies against post-translationally modified proteins (AMPA, encompassing anti-citrullinated, anti-carbamylated, and anti-acetylated pro-

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tein antibodies), as well as the synovial infiltration of T and B lymphocytes.[4,5]

Vitamin D binding protein (VDBP) is a circulating multifunctional plasma protein that can greatly increase the chemotactic potential of neutrophil chemoattractant.[6] Recent studies suggest that DBP has previously underestimated, major, and central roles in inflammatory diseases such as RA.[7] A significant association was observed between RA and VDBP, as previously reported. VDBP can transport $1,25(OH)_2D_3$ between the blood and cell membranes.[8] While hepatic synthesis accounts for most VDBP, leading to its broad distribution in fluids like plasma, CSF, semen, saliva, and breast milk, it is also expressed locally at sites of RA pathology by immune cells and synoviocytes. Importantly, VDBP concentrations in the synovial tissue of RA patients have been shown to be significantly reduced, as previously reported.[9]

The second un routine marker that help diagnosis of RA is retinol-binding protein (RBP4) serves as the transporter for all-trans retinol, circulating in serum as a moderately tight 1:1 molar complex with the vitamin. RBP4 is mainly produced in the liver, with additional synthesis occurring in adipose tissue. [10] It circulates in the bloodstream and binds to transthyretin (TTR), a large protein that increases its molecular mass to approximately 80,000, thereby preventing its elimination through glomerular filtration . [11]

RBP4 is an acute-phase protein upregulated in RA. RBP4 is activated by cytokines, including interleukin (IL-1 and IL-6), and exhibits pro-inflammatory effects.[12] Additionally, RBP4 positively correlated with C-reactive protein levels. RBP4 has been identified as a predictor of atherosclerosis in RA patients. The relationship between elevated RBP levels and RA pathology remains unclear. Previous research has identified RBP4 as a potential biomarker for RA.[13] This study identified cardiac complications in patients with RA. One of the most important biomarkers, endothelin-1 (ET-1), was first identified in 1988 as a potent vasoconstrictor originally isolated from endothelial cells. Production is induced in various cell types by cardiovascular disease risk factors and during the progression of cardiovascular disease.[14] ET-1 induces positive inotropic and chronotropic effects, as well as hypertrophic activity in cardiomyocytes. Endothelin exerts its effects through the activation of two receptor subtypes, ET type A (ET_A)and ET type B (ET_B). Endogenous ET-1 may play a role in the progression of multiple cardiovascular diseases.[15]

The second cardiac parameter is the N-terminal pro-brain natriuretic peptide (NT-proBNP), a prohormone that is cleaved to release brain natriuretic peptide (BNP, also referred to as B-type natriuretic peptide). B-type natriuretic peptide (BNP) and its biologically inactive cleavage product, NT-proBNP, are recognized biomarkers for cardiovascular diseases and subclinical cardiac injury.[16] This study uniquely evaluates a panel of inflammatory and cardiac biomarkers – VDBP, RBP4, NT-proBNP, and ET-1 – in patients with RA across different treatment stages. Unlike previous research focusing on single markers, our approach allows simultaneous assessment of disease activity and cardiovascular risk, providing a more integrated view of systemic inflammation and cardiac involvement in RA.

Aim

The objective of this study was to ascertain the efficiency of the above novel rheumatoid biomarkers in the diagnosis and follow-up of the disease, as well as to estimate the cardiac complications that may be associated with RA by measuring novel cardiac biomarkers such as NT-proBNP and endothelin 1 in the sera of patients.

Material and methods

Design of the study

A case-control study enrolled 61 patients with RA aged 20–66 years and 27 age- and sex-matched healthy controls. RA patients were stratified into three groups: G1 (n=10): newly diagnosed patients meeting the ACR/EULAR 2010 criteria, with symptom duration <6 months, and no prior exposure to disease-modifying antirheumatic drugs (DMARDs) or biologics. G2 (n=22): Patients receiving conventional synthetic DMARDs (methotrexate or leflunomide) for 3±0.5 months, with stable dosing ≥1 month. G3 (n=29): Patients on combined biologic therapy (anti-TNF agents or rituximab) and csDMARDs for ≥6 months with a stable treatment regimen.

The exclusion criterion was age >70 years (to minimize age-related cardiac dysfunction). Comorbidities affecting NT-proBNP/ET-1 levels included cardiac: heart failure (NYHA Class II–IV), prior myocardial infarction, LVEF <50%, atrial fibrillation, significant valvular disease, or uncontrolled hypertension (>160/100 mmHg), renal: eGFR of <60 mL/min/1.73m², pulmonary hypertension (ECHO-estimated PASP >40 mmHg), persistent inflammatory disorders (e.g., systemic lupus erythematosus and vasculitis), active infections, psoriatic arthritis, immune-modifying medications, or any chronic conditions affect study outcomes. Additional exclusion criteria for controls included elevated C-reactive protein (CRP, >5 mg/L), positivity for rheumatoid factor (RF) or anti-citrullinated protein antibodies (ACPA), subclinical cardiovascular disease (NT-proBNP >125 pg/mL or abnormal ECG), history of cardiac/renal disorders, and RA-associated comorbidities (e.g., metabolic syndrome). Individuals failing to meet the inclusion criteria or presenting the above conditions were excluded to ensure sample homogeneity and result validity.

Data and blood collection

The study participants were recruited at Basra Teaching Hospital (Basra Governorate, Southern Iraq). Patient data were collected through structured interviews.

Rheumatologist-confirmed RA patients meeting the American College of Rheumatology 2010 classification criteria with positive inflammatory markers were enrolled. Age-and sex-matched healthy controls were selected according to predefined exclusion criteria to minimize confounding factors. Venous blood samples were collected from all participants in sterile serum separator gel tubes. The serum was subsequently isolated by centrifugation (3,000×g, 15 min) and aliquoted for batch analysis using ELISA and serological testing. The sample size was calculated using the G-power software.

Laboratory tests

All biomarkers, RBP4 (Cat. EH0266), VDBP (Cat. RDEEH20001), NT-proBNP (Cat. EH0350), CRP (Cat. ACN 210), and ET-1 (Cat. EH0648) were quantified using human-specific ELISA kits (Fine Test Company, China), according to the manufacturer's protocols. using a BioTek 800TS microplate reader (USA), and concentrations were calculated from standard curves, as specified in the respective kit instructions.

Statistical analysis

For tabulation and analysis, SPSS spreadsheet version 26.0 was used. Excel was used to display the important facts. For each cardiac and rheumatic parameter, means and standard deviations were calculated for the Control, Pretreatment, sDMARDs, and bDMARDs groups. The Kolmogorov test determined variable normality, which is a prerequisite for parametric and nonparametric analyses. Tables 1 and 2 show how the Mann-Whitney U test was used to compare the control and patient groups. For each biomarker, the Kruskal-Wallis test and post-hoc pairwise comparisons were used to compare the four groups (Tables 3 and 4). Spearman's rank correlation coefficient was used to assess the relationships between the biomarkers.

Ethics approval

The Ethics Committee approved the protocol on 17/12/2023, No 860, and the study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all study participants.

Results

This study conducted a comparative analysis of various biochemical markers between controls and patients. The ages of the participants in the control and patient groups were not significantly different (p=0.315). However, we identified significant elevations in several biomarkers among patients relative to controls (Table 1). Specifically, CRP, RBP4, and VDBP concentrations were all markedly higher in the patient cohort, with significance (p≤0.001).

Table 1. Biomarker values in the control and patient groups compared (Mann Whitney's test)

	Control (n=27)	Patients (n=61)	p
Age (years)	43.55± 8.06	46.57±9.65	0.315
CRP (mg/L)	0.756±0.109	13.097±18.702	<0.001
RBP4 (ng/mL)	14.006±3.988	49.172±21.935	<0.0001
VDBP (ng/mL)	2.882±1.136	12.091±3.334	<0.0001

Table 2 displays the significant differences in the biomarker levels between the two groups. NT-proBNP concentrations were substantially increased in patients (1341.787±626.068 pg/mL) compared to controls (11.452±3.260 pg/mL) (p<0.0001). Similarly, ET-1 concentrations were significantly higher in patients (14.246±4.031 pg/mL) than in controls (3.932±14.212 pg/mL; p<0.0001).

Table 2. Comparison of cardiac parameters between patients and controls (Mann-Whitney's test)

	Control (n=27)	Patients (n=61)	p
NT proBNP (pg/mL)	11.452±3.260	1341.787±626.068	<0.0001
ET1 (pg/mL)	3.932±14.212	14.246±4.031	<0.0001

Analysis across patient subgroups revealed distinct patterns (Table 3). CRP levels were lowest in controls (0.756 mg/L), differing significantly from subgroup G1 (45.600 mg/L; p<0.0001) and G2 (7.045 mg/L; p<0.0001), but not from G3 (6.479 mg/L). Control RBP4 levels were significantly lower than those in G1 (51.125 ng/mL), G2 (50.602 ng/mL), and G3 (47.413 ng/mL; all p<0.0001), though RBP4 did not differ significantly between patient subgroups. Similarly, VDBP concentrations were lowest in controls (2.882 ng/mL), differing significantly from all patient groups (G1: 14.455 ng/mL, G2: 11.379 ng/mL, G3: 11.816 ng/mL; all p<0.0001). VDBP levels in G1 were significantly higher than in G2 (p<0.0001) and G3 (p<0.0001), while G2 and G3 showed no significant difference.

Table 3. Comparison of rheumatic parameters between the study groups (Kruskal Wallis test)*

	Control (n=27)	G1 (n=10)	G2 (n=22)	G3 (n=29)
Age (years)	43.55±8.06 [a]	47.90±11.87[a]	47.09±10.84 [a]	45.72±8.04 [a]
CRP (mg/L)	0.756±0.109[a]	45.600±28.733[b]	7.045±4.673[b]	6.479±4.041[a]
RBP4 (ng/mL)	14.006±3.988[a]	51.125±22.733[b]	50.602±22.450[b]	47.413±21.926[b]
VDBP(ng/ml)	2.882±1.136[a]	14.455±4.126[b]	11.379±2.632[c]	11.816±3.269[c]

* Different superscript letters (a, b, c) denote significant differences (p<0.05) between groups based on post hoc multiple comparison testing.

Table 4 of the cardiac biomarkers indicated substantial elevations in these markers within the patient groups relative to the control group. The Control group exhibited markedly lower NT-proBNP levels (11.452

pg/mL) compared to the other groups, G1 (1789.2 pg/mL), and G2 (1154 pg/mL). On the other hand, the G3 group (1329.966 pg/mL) reported a significant value that was intermediate between the values of the G1 (1789.2±710.81 pg/mL) and G2 (1154.0±537.58 pg/mL) groups. Additionally, the lowest value of ET1 (3.932 pg/mL) was reported for the control group, which was significantly different from the G1 (12.235 pg/mL), G2 (13.987 pg/mL), and G3 (15.135 pg/mL) groups.

Table 4. Cardiac parameters in patients pre- and post-treatment compared to the control group (Kruskal Wallis test)*

	Control (n=27)	G1 (n=10)	G2 (n=22)	G3 (n=29)
Age (years)	43.55±8.06[a]	47.90±11.87[a]	47.09±10.84[a]	45.72±8.04[a]
NT-proBNP (pg/mL)	11.452±3.260[a]	1789.2±710.81[b]	1154.0±537.58[c]	1329.96±601.18[d]
ET1 (pg/mL)	3.932±1.422[a]	12.235±3.783[b]	13.987±3.931[b]	15.135±4.039[b]

* Different superscript letters (a, b, c) denote significant differences (p<0.05) between groups based on post hoc multiple comparison testing.

Table 5, shows significant positive correlations between each of the studied biomarkers: NT-proBNP, ET1, CRP, RBP4, and VDBP.

Table 5. Correlation between all study parameters in the patient groups

Parameters		ET1	CRP	RBP4	VDBP
NTproBNP	R	0.594	0.653	0.563	0.742
	p	<0.0001	<0.0001	<0.0001	<0.0001
ET1	R		0.530	0.558	0.643
	p		<0.0001	<0.0001	<0.0001
CRP	R			0.674	0.675
	p			<0.0001	<0.0001
RBP4	R				0.637
	p				<0.0001

Discussion

RA is an autoimmune disease that causes inflammation and has systemic, extra-articular and persistent effects. Numerous biomarkers have been investigated in RA, and they are important for diagnosis, treatment prognosis, disease activity monetarization, and prediction of the effectiveness of biological therapy. The novelty of our work lies in the combined evaluation of VDBP, RBP4, NT-proBNP, and ET-1 in a treatment-stratified RA population, enabling a concurrent analysis of inflammatory status and subclinical cardiovascular involvement. To our knowledge, no previous study has examined these biomarkers together in newly diagnosed, csDMARD-treated, and biologic-treated RA patients, thereby offering new perspectives on their potential utility for comprehensive disease monitoring and early detection of cardiovascular complications.

This study revealed notable increases in CRP levels among the patient groups when compared to the control group, as illustrated in Tables 1 and 3. Research conducted by Fathy et al. and Cooper et al. has shown that RA patients exhibit elevated CRP levels when compared to healthy controls, as RA is a persistent inflammatory immunological disorder, and CRP functions as an indicator of inflammation.[17,18]

RBP4 levels were significantly elevated in the RA patient groups compared to the control group, as shown in Tables 1 and 3. These results are consistent with those of previous studies by Allah et al. and Pazos-Pérez et al., who confirmed the high levels of RBP4 in RA.[19,20] Notably, there were no significant differences between the patient groups G1, G2, and G3. This means that there was no significant impact of disease severity or type of treatment on marker sensitivity. This is inconsistent with the results of a previous study by Wei et al., who reported that RBP4 levels were not affected by disease severity.[21] RBP4 levels may be elevated in RA patients in response to elevated levels of TNF-α, IL-6, and IL-1β, which can upregulate RBP4 production. RBP4 is primarily synthesized in the liver and its production may be influenced by systemic inflammation.[22] RA can lead to altered liver function, which affects the synthesis and clearance of RBP4.[23] RA is associated with high oxidative stress, which leads to increased tissue damage and immune cell activation. RBP4 has been linked to oxidative stress responses, and its elevation could be a compensatory mechanism for mitigating cellular damage.[24]

VDBP levels in this study showed significant elevations among the RA patient groups compared to the control group, as shown in Tables 1 and 3. G1 displayed the highest levels because this pretreatment group did not undergo any type of treatment. These results are consistent with those of a previous study by Obied and Sarhat, which reported low levels of VDBP in healthy people compared to RA patients.[25] This is because RA is a chronic inflammatory condition marked by increased concentrations of pro-inflammatory cytokines, which might prompt the liver to synthesize more VDBP, akin to acute-phase proteins.[26] Additionally, RA patients often experience altered vitamin D metabolism, with an increased demand for VDBP to transport vitamin D metabolites, especially due to chronic inflammation and immune dysregulation.[27] Many patients with RA have vitamin D deficiency, which might trigger a compensatory increase in VDBP to enhance vitamin D transport and availability. A study not far away by Delrue and Speeckaert previously suggested that VDBP serve as a novel indicator of inflammation.[28]

The present study showed significant elevations in the cardiac biomarker ET-1 level in RA patient groups compared to the controls, as shown in Tables 2 and 4.

Consistent with these findings, prior research by Cienfuegos et al. and Yang et al. indicates elevated ET-1 levels in RA patients relative to controls.[29,30] Elevated levels of ET-1 in patients with RA compared to healthy controls may be attributed to chronic inflammation and cytokine stimulation that are characterized in RA, which stimulates the production of ET-1 in vascular endothelial.[31] ET-1 acts as a vasoconstrictor, while nitric oxide (NO) acts as a vasodilator. In rheumatic diseases, oxidative stress increases, reducing the availability of NO and leading to an increased vasoconstrictive effect of ET-1.[32] ET-1 may play a key role in the pathophysiology of rheumatoid disease, including arthritis.[33]

The estimation of NT-proBNP levels revealed significant elevations in the RA patient groups compared to the controls, as shown in Tables 2 and 4. The results of this study are in agreement with the results of previous studies by Zhu et al. and Raadsen et al. indicated high levels of NT-proBNP in RA patients.[34] Notably, the G1 demonstrated the highest NT-proBNP levels, with a statistically significant elevation relative to G2 and G3, which means that the treatment overcame the results. Several studies by McKechnie et al. and Hassan et al. have explored the relationship between NT-proBNP levels and RA.[35,36] Elevated NT-proBNP levels in RA patients can indicate subclinical heart failure, a condition that is common in RA patients due to chronic inflammation affecting the heart, as mentioned previously by Shamsi et al. this is in agreement with a recent study.[37] In a study by Heslinga et al., in four Dutch centers with patients with early RA showed a significant reduction in NT-proBNP after 6 months of anti-rheumatic treatment. Such a decrease in NT-proBNP levels is not limited to patients in remission, suggesting that suppression of inflammation is sufficient to reduce NT-proBNP levels in patients with RA.[38]

Furthermore, our study showed a significant positive correlation between all the study biomarkers, as shown in Table 5. This means that inflammation, which is a characteristic of RA, may lead to cardiovascular complications in patients with RA.

Study limitations

This study has several limitations that should be acknowledged. The limited sample size could constrain generalizability and impede biomarker validation, compounded by a single-center, cross-sectional design focused solely on Iraqi patients, which limits insights into biomarker dynamics over time (such as monitoring treatment response or disease progression). Therefore, larger longitudinal studies and validation in diverse populations are essential to confirm biomarker utility for monitoring, prognosis, and broader clinical application.

Conclusion

Based on the study findings, VDBP, RBP-4, and CRP serve as effective diagnostic biomarkers for rheumatoid arthritis, exhibiting significant elevations across patient groups compared to controls. Furthermore, significantly increased NT-proBNP and ET-1 levels in RA patients indicate substantial cardiac complications associated with the disease. The strong positive correlations observed between all studied biomarkers suggest that systemic inflammation characteristic of RA contributes to these cardiovascular sequelae.

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Declarations

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Author contributions

Conceptualization, A.A.A. and A.M.J.; Methodology, A.A.A.; Software, A.A.A.; Validation, A.A.A., A.M.J.; Formal Analysis, A.A.A.; Investigation, A.A.A.; Resources, A.A.A.; Data Curation, A.A.A.; Writing – Original Draft Preparation, A.A.A.; Writing – Review & Editing, A.A.A.; Visualization, A.A.A.; Supervision, A.M.J.; Project Administration, A.M.J.; Funding Acquisition, A.A.A..

Conflicts of interest

The authors declare that they have no competing interests.

Data availability

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

Ethics approval

The Ethics Committee approved the protocol on 17/12/2023, No 860, and the study was conducted in accordance with the Declaration of Helsinki.

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