High Growth Differentiation Factor-15 (GDF-15) in Rheumatoid Arthritis Patients Potential Risk for Cardiovascular Disease

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Abstract

Rheumatoid arthritis (RA) is a chronic autoimmune disorder primarily affecting joints, leading to pain, stiffness, and functional disability. The inflammatory mechanisms underlying RA also impact various organ systems, with significant implications for morbidity and mortality. In this study, we analyzed the growth differentiation factor-15 (GDF-15), a cytokine implicated in inflammation and associated with RA and cardiovascular diseases. We conducted a case-control study involving 150 RA patients and 150 healthy individuals, assessing various biomarkers (ACPA, CRP, ESR, and RF) including GDF-15, lipid profile, and inflammatory markers. Our results demonstrated significantly elevated levels of GDF-15 in RA patients (309.44 pg/ml) compared to controls (64.40 pg/ml), indicating its potential role as a biomarker for RA and cardiovascular risk (p<0.001). Furthermore, RA patients exhibited dyslipidemia characterized by elevated total cholesterol, triglycerides, LDL cholesterol, and atherogenic indices, along with decreased HDL cholesterol levels, predisposing them to a higher risk of atherosclerosis and cardiovascular complications (p<0.001). Correlation analyses revealed associations between GDF-15 levels, lipid profile parameters, and disease severity markers, highlighting the intricate interplay between inflammation, lipid metabolism, and RA progression. These findings demonstrated the importance of early detection and management of dyslipidemia in RA patients to mitigate cardiovascular risk. Overall, our study contributes to understanding the pathophysiology of RA and identifies potential biomarkers for disease monitoring and risk stratification.

Keywords: Rheumatoid arthritis (RA), Growth differentiation factor-15 (GDF-15), C-Reactive Protein (CRP), Anti-cyclic citrullinated peptide (ACPA), Biomarkers, Cardiovascular risk

Significance | This study showed the high levels GDF-15, a clinical marker in rheumatoid arthritis, signified disease progression and heightened cardiovascular risk, implicating inflammation and tissue damage.

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disorder primarily affecting joints, characterized by pain, stiffness, and reduced mobility (Coutant & Miossec, 2020). It damages synovial tissues, leading to irreversible harm and progressive symmetric polyarthritis (Kugyelka et al., 2016; Mohammed, Maroof, & Al-Hafidh, 2022). Without timely identification and treatment, RA can decrease life expectancy, quality of life, and result in functional disability, morbidity, and mortality, posing a burden on society. Initially affecting small joints, RA progresses to larger joints and can impact various organs (Lee, Kim, Cho, & Lee, 2017; Sulaiman, Wong, Ahmad, & Ghazali, 2019). Although RA rarely

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directly causes death, its associated conditions such as heart and pulmonary issues can increase mortality rates (Conforti et al., 2021; Figus, Piga, Azzolin, McConnell, & Iagnocco, 2021; Yap et al., 2018a; Yap et al., 2018b). Joint damage from cartilage and bone loss can lead to deformities and deterioration (Zayed, Obaid, & Hamza, 2022). While genetic and environmental factors contribute to RA risk, its exact etiology remains unknown (Deane et al., 2017).

Clinical characteristics, radiographic findings, and laboratory results are pivotal in diagnosing rheumatoid arthritis (RA) (Poddar, Behera, & Ray, 2016). The 2010 ACR/EULAR Classification Criteria for RA is the standard classification tool (Aletaha et al., 2010). In 2019, 18 million people worldwide were afflicted with RA, with over 70% being female and 55% aged over 55 (Ralston, Penman, Strachan, & Hobson, 2018). A study by Alkazzaz in 2013 reported a cumulative RA risk of 22.74% in Hilla city, with incidence rates rising from 1.60% in 2001 to 3.02% in 2011 (Al_Badran, Algabri, Al Saeedi, & Alqazzaz, 2022). In 1975, 1% of Iraq's population had RA (Al-Rawi, Alazzawi, Alajili, & Alwakil, 1978; Halacoglu & Shea, 2020). From 1980 to 2019, urban areas had a higher RA prevalence (0.69%) than rural areas (0.54%), and high-income countries had higher prevalence rates (0.49%) compared to low-income countries (0.35%) (Almutairi, Nossent, Preen, Keen, & Inderjeeth, 2021). The prevalence of RA increases by 40–50% among individuals with first-degree relatives affected by the disease (Bemis et al., 2021).

Numerous studies have aimed to identify specific biomarkers for diagnosing and predicting the prognosis of RA, with a focus on cytokines, which play crucial roles in immune system signaling and are implicated in RA etiology. Cytokines produced by immune cells like B-cells and T-cells infiltrate synovial fluid, contributing to bone and cartilage erosion, inflammation, and pain (Al Ghuraibawi, Sharquie, & Gorial, 2023; McInnes & Schett, 2007, Luma et al., 2024).

It has been demonstrated that growth differentiation factor-15 (GDF-15), a stress-responsive cytokine, is released by various cell types (Bootcov et al., 1997). Belonging to the transforming growth factor-β superfamily, it is expressed in multiple immune cells, tissues, and organs (Asrih et al., 2023; He & He, 2022). GDF-15 is produced and released from white adipose tissue in both mice and humans (Xiao, He, Zeng, Xia, & Pharmacotherapy, 2022). Initially identified as macrophage inhibitory cytokine-1 (MIC-1), GDF-15 regulates apoptosis in specific cell types and plays a crucial role in cell proliferation and signal transduction, implicating its involvement in inflammation (Elbarky, Hussien, Elgazzar, Mabrouk, & Elsaadany, 2021; Khalil, Elhanafy, Eigela, Nasr, & ELgendy, 2020; Tanrıkulu et al., 2017). GDF-15 has been linked to rheumatoid arthritis (RA), suggesting its role as a pro-inflammatory cytokine and an etiological factor for both RA and cardiovascular disease (El Shebiny et al., 2022). Elevated GDF-15

levels are observed during tissue injury and inflammation (Unsicker, Spittau, Krieglstein, & reviews, 2013). Cardiovascular disorders such as heart failure, atherosclerosis, hypertrophy, and endothelial dysfunction are associated with increased GDF-15 levels, which also correlate with disease development and prognosis (Adela & Banerjee, 2015; Ahmeda, 2020). GDF-15 possesses anti-apoptotic properties, promotes cell regeneration, and is elevated in obese individuals, indicating its association with cardiometabolic risk (Adela & Banerjee, 2015; Korkmaz, Şirin, Ayvaz Çelik, Erturan, & Yildirim, 2022; Yalcin et al., 2016).

In rheumatoid arthritis (RA), dyslipidemia is prevalent, characterized by elevated triglyceride (TG) and low-density lipoprotein (LDL) levels along with decreased high-density lipoprotein (HDL) levels. These lipoprotein disorders significantly influence the onset and progression of atherosclerosis and are associated with an increased risk of cardiovascular disease (Taskinen, 2003; Tziomalos, Athyros, Karagiannis, Kolovou, & Mikhailidis, 2009; Vergès, 2015; Yücel, İlanbey, & Discovery, 2022). Therefore, understanding the multifaceted aspects of RA, including its clinical presentation, diagnostic criteria, epidemiology, biomarkers, and associated cardiovascular risk factors, is crucial for effective disease management and improving patient outcomes.

Material and Methods

Study design

A case-control study was carried out in Babil Governorate, Iraq, from November 2022 to July 2023. The study included 150 individuals diagnosed with RA (29 male and 131 female) who attended the rheumatology section at Marjan Teaching Hospital in Babylon Province, Iraq. Additionally, 150 healthy individuals (31 male and 119 female) were included as a control group. RA diagnosis was based on the 2010 criteria established by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) (D Aletaha et al., 2010).

This study obtained written informed consent from patients or their first-degree relatives before commencement, following approval from the Faculty of Science, University of Kufa (Document No: 8215/2022) and Babylon Training and Human Development Centre, Babil, Iraq (Document No. 1502/2023). Ethical standards per the Declaration of Helsinki, Iraqi, international, and privacy regulations were adhered to, alongside guidelines from the World Medical Association, Belmont Report, CIOMS Guidelines, and ICH-GCP.

Exclusion Criteria:

None of the participants were smokers or consumed alcohol. Additionally, none had pre-existing medical conditions such as diabetes mellitus, hypertension, kidney problems, hyperthyroidism, or liver ailments. Participants with a body mass index (BMI) of 30

or above, and those using prescription drugs for lipid-lowering agents, beta-blockers, thyroxin, estrogen, vitamin E, and progestin were excluded. Patients with severe heart and kidney diseases, cancer, infections, nursing, pregnancy, autoimmune diseases like renal failure, Cushing's syndrome, lupus, inflammatory bowel disease, ankylosing spondylitis, allergies, various skin issues, inflammatory or infectious diseases, and cardiovascular disorders were also excluded, as well as patients undergoing biological therapy.

Inclusion Criteria:

Patients eligible for recruitment in the study had to meet specific diagnostic criteria for RA. This included a thorough evaluation to ensure compliance with the 2010 criteria established by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR), with a score of ≥ 6. All patients aged between 20 and 79, diagnosed by a rheumatologist, were considered for inclusion.

Measurements

Five milliliters of fasting venous blood samples were drawn from both the patients and the control group using plastic syringes and disposable needles after an overnight fast of 12-14 hours. The blood samples were then divided into two parts. Firstly, about two milliliters of whole blood were collected into a tube containing ethylene diamine tetraacetic acid (EDTA) for the erythrocyte sedimentation rate (ESR) measurement. Secondly, a sterile gel tube was filled with roughly 3 milliliters of fasting venous blood samples. After allowing the blood to clot at room temperature for fifteen minutes, it was centrifuged at 1500 xg for 10 minutes. Following coagulation, sera were separated and divided into three aliquots in Eppendorf tubes, then stored in a deep freeze at -20°C until analysis time.

The Westergren method was employed to measure the erythrocyte sedimentation rate (ESR) (Al-Marri & Kirkpatrick, 2000; Böttiger & Svedberg, 1967; Brigden, 1999; Gilmour & Sykes, 1951; Tishkowski & Gupta, 2023). Human growth differentiation factor-15 and human rheumatoid factor (RF) titers were determined using enzyme-linked immunosorbent assay (ELISA) based on the Sandwich ELISA principle. Specifically, the Human Growth Differentiation Factor-15-ELISA kit (Cat. No: E-EL-H0080, Elabscience; Biotechnology Inc. USA) and human RF kit (Cat. No E1389Hu Bio assay Technology, BTLAB, China) were utilized. Human C-Reactive Protein (CRP) and Human CCP-Ab (Anti-cyclic citrullinated peptide) levels were measured using commercial kits (Cat. No: E-EL-H0043, Elabscience Biotechnology Inc. USA) on BioTek ELX800 and ELX50 Absorbance Microplate Readers, along with an ELISA washer (BioTek Instruments, USA). Each kit exhibited an inter-assay coefficient of variation of less than 10% and was based on the sandwich technique, following the manufacturer's instructions. The concentrations of HDL-C, total cholesterol (TG),

and triglycerides (TG) were measured through enzymatic reactions using commercial analytical kits from BIOLABO SAS (02160 Miazy, France) (Allain, Poon, Chan, Richmond, & Fu, 1974; Lopez, 2013; Schettler & Nussel, 1975). The levels of LDL and VLDL cholesterol were determined using the Friedewald equations (Friedewald, Levy, & Fredrickson, 1972; Piva et al., 2011; Wilson, 1998).

Statistical Analysis

The dates were analyzed using the statistical software SPSS (version 26, SPSS Inc., Chicago, Illinois, USA). The analysis categorized the variables into two types based on their statistical distribution: normally distributed variables and nonparametric variables, determined using the Kolmogorov-Smirnov test. Normally distributed results were expressed as mean ± standard deviation (SD), and the pooled t-test was employed to compare the patient and control groups. Pearson's correlation coefficients (r) were used to estimate the correlation between parameters. For nonparametric variables, percentiles and medians ranging from 25% to 75% were calculated. The Mann-Whitney U test was utilized to compare measurement parameters between the control and patient groups. Spearman's correlation coefficients (rho, ρ) were calculated to ascertain the correlation between nonparametric variables.

Results

Comparison Study (RA Patients and Controls)

Demographic Parameters Comparison

Table 1 presented the demographic data results for both RA patients and healthy controls. The analysis revealed no significant difference between the RA patients and the control group in terms of age, height, weight, BMI, residence, sex ratio, marriage status ratio, and residency. These results were obtained by precisely selecting the control group, which eliminated the potential effects of any covariate and ensured that any change in any measured biomarker was solely related to the presence of RA disease.

Clinical Parameters Comparison

Table 2 presented the findings from the clinical data of RA patients and healthy controls (HC). The findings indicated a significant difference between the ACPA (p<0.001), CRP (p<0.001), ESR (p<0.001), and RF (p<0.001) levels in RA patients compared to the control group. Furthermore, all participants evaluated for ACPA, RF, CRP, and ESR showed a significant increase (p<0.001) to confirm the diagnoses. Specifically, there were 113 ACPA-positive and 37 ACPA-negative cases, 106 CRP-positive and 44 CRP-negative cases, and 102 RF-positive and 48 RF-negative cases among RA patients. Additionally, 97 cases had elevated ESR (>20 mm/h) while 53 cases had normal ESR (<20 mm/h) in RA patients. The severity assessment using DAS-28-CRP revealed 25 patients in low disease activity, 56 patients in moderate disease activity, and 69 patients in high disease activity. All patients were receiving

conventional disease-modifying anti-rheumatic drugs (DMARDs) for their RA and were undergoing treatments including folic acid, methotrexate, sulfasalazine, prednisolone, and hydroxychloroquine (HCQ) as detailed in Table 2.

GDF-15 Comparison

The results of the concentration of GDF-15 in healthy controls and RA patients were presented in Figure 1. The findings indicated a statistically significant difference ($p<0.001$) in GDF-15 concentration between RA patients (309.44 [171.67-396.45] pg/ml) compared to the control group (64.40 [47.49-85.52] pg/ml).

Lipid Profile Comparison

The results of lipid profile parameters and atherogenic indices levels in patients and healthy groups with RA patients were presented in Table 3. The findings of this study demonstrated that RA patients had significantly higher levels of lipid profile (TC, TG, VLDL-C, and LDL-C) and atherogenic indices (CRI-I, CRI-II, AIP, and AC) compared with the control group. These findings indicated a susceptibility to an increased risk of heart disease and atherosclerosis. Additionally, a significant decrease was observed in the HDL-C level in RA patients compared with the control group, which further increased the risk of atherosclerosis.

Correlation Study

Biomarkers and Demographic Parameters Correlation

Table 4 presented the findings of the associations between the measured biomarkers and the demographic characteristics. The results of correlation coefficients in RA patients revealed a positive correlation between GDF-15 and Age ($r=0.161$, $p<0.05$). Conversely, a negative correlation was observed between GDF-15 and Residency ($r=-0.164$, $p<0.05$). Additionally, there was a negative correlation between family history and each of CRI-I ($r=-0.170$, $p<0.05$) and AC ($r=-0.170$, $p<0.05$). However, no correlation was found among the other parameters as shown in Table 4.

Biomarkers Correlation

The results of the correlations among the studied biomarkers of RA patients were presented in Table 5. In the current study, a weak positive correlation was observed between GDF-15 and TC ($r=0.251$, $p<0.01$), as well as between GDF-15 and LDL-C ($r=0.245$, $p<0.01$). Additionally, GDF-15 showed a positive correlation with atherogenic indices including CRI-I ($r=0.281$, $p<0.01$), CRI-II ($r=0.262$, $p<0.01$), AIP ($r=0.211$, $p<0.01$), AC ($r=0.281$, $p<0.01$), and atherogenic risk ($r=0.194$, $p<0.05$). However, a significant negative correlation was found between GDF-15 and HDL-C ($r=-0.164$, $p<0.05$).

Furthermore, significant positive correlations were observed between TC and each of CRI-I ($r=0.757$, $p<0.001$), CRI-II ($r=0.775$, $p<0.001$), AIP ($r=0.190$, $p<0.05$), and AC ($r=0.757$, $p<0.001$). Additionally, TG showed a positive correlation with AIP ($r=0.844$, $p<0.001$), while HDL-C exhibited significant negative correlations

with CRI-I ($r=-0.669$, $p<0.001$), CRI-II ($r=-0.625$, $p<0.001$), AIP ($r=-0.500$, $p<0.01$), and AC ($r=-0.669$, $p<0.001$).

Moreover, VLDL-C showed a significant positive correlation only with AIP ($r=0.844$, $p<0.001$), while LDL-C exhibited positive correlations with CRI-I ($r=0.827$, $p<0.001$), CRI-II ($r=0.871$, $p<0.01$), and AC ($r=0.827$, $p<0.001$). Additionally, CRI-I showed a strong positive correlation with CRI-II ($r=0.986$, $p<0.001$), as well as negative correlations with AIP ($r=-0.448$, $p<0.01$) and AC ($r=1.000$, $p<0.01$).

Furthermore, CRI-II exhibited significant positive correlations with CRI-I ($r=0.986$, $p<0.001$), AIP ($r=0.297$, $p<0.01$), and AC ($r=0.986$, $p<0.001$), while AIP showed positive correlations with CRI-I ($r=0.448$, $p<0.01$), CRI-II ($r=0.297$, $p<0.01$), and AC ($r=0.448$, $p<0.01$).

Finally, AC displayed significant positive correlations with CRI-I ($r=1.000$, $p<0.01$), CRI-II ($r=0.986$, $p<0.001$), and AIP ($r=0.448$, $p<0.01$), while atherogenic risk exhibited positive correlations with CRI-I ($r=0.423$, $p<0.01$), CRI-II ($r=0.309$, $p<0.01$), AIP ($r=0.802$, $p<0.001$), and AC ($r=0.423$, $p<0.01$).

Discussion

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic synovial inflammation leading to joint deterioration and bone erosion. RA is associated with alterations in various inflammatory biomarkers. Growth differentiation factor-15 (GDF-15), belonging to the transforming growth factor-β superfamily, is expressed in multiple immune cells, tissues, and organs. This study aimed to assess the levels of GDF-15 and lipid profile in RA patients.

The findings of our study suggest that elevated GDF-15 levels may contribute to the incidence of atherosclerosis by promoting lipid increase. Our research indicates that RA patients exhibit higher risk atherogenic indices and a pro-atherogenic lipid profile, thereby increasing their susceptibility to cardiovascular diseases associated with atherosclerosis.

Comparison of demographic and clinical parameters between RA patients and controls revealed no significant differences in age, height, weight, BMI, sex ratio, marital status, or residency. However, RA patients demonstrated elevated lipid profiles (TC, TG, VLDL-C, LDL-C) and atherogenic indices (CRI-I, CRI-II, AIP, AC), which are indicative of increased cardiovascular risk.

Correlation analysis further highlighted associations between GDF-15, lipid profile components, and atherogenic indices, underscoring their clinical significance in the management of RA. These findings underscore the importance of monitoring lipid profiles and atherogenic indices in RA patients for early detection and management of cardiovascular risk.

Table 1. Data describing the demographics characteristic of individuals with RA patients and healthy controls (HC). Results expressed as mean ± standard deviation for normally distributed data. F/χ2: F-statistics value for continuous variables or Chi-square statistic value for categorical variables, df: degree of freedom between groups/within the group, p: probability value. Binomial data were expressed as ratios and analyzed by Chi-squared test. MWUT: Mann-Whitney U test. F/M: female/male, BMI: body mass index.

Parameters	Control	Patients	F/χ²	df	p-value
Age (years)	44.39±9.99	45.71±10.30	1.256	1/298	0.263
Weight (kg)	75.57±13.58	77.72±10.58	0.135	1/298	0.714
Height (cm)	165.77±6.85	166.06±6.98	2.317	1/298	0.129
BMI (kg/m²)	27.57±5.17	28.19±3.52	1.482	1/298	0.224
Sex (F/M)	119/31	121/29	0.083	1	0.773
Married/Single	142/8	145/5	0.724	1	0.395
Urban/Rural	123/27	118/32	0.527	1	0.468
Family History (Yes/No)	0/150	119/31	197.238	1	<0.001

Table 2. Clinical information from RA patients and healthy controls (HC).

Parameters	Control	Patients	F/χ²	df	p-value
ACPA (IU/ml)	12.34(10.41-13.63)	172.42 (24.89-293.89)	MWUT	-	<0.001
ACPA (+/-)	0/150	113/37	181.283	1	<0.001
CRP (mg/dl)	3.33 (1.38-4.83)	10.17 (4.52-11.75)	MWUT	-	<0.001
CRP (+/-)	0/150	106/44	163.018	1	<0.001
ESR (mm/hour)	10 (9-12)	33.50 (20-45.5)	MWUT	-	<0.001
ESR (>20, <20)	0/150	97/53	143.35	1	<0.001
RF (U/ml)	3.33 (3.08-3.80)	27.29 (10.21-34.42)	MWUT	-	<0.001
RF (+/-)	0/150	102/48	154.505	1	<0.001
Folic Acid (Yes/No)	-	135/15	-	-	-
Methotrexate (Yes/No)	-	135/15	-	-	-
Sulfasalazine (Yes/No)	-	22/128	-	-	-
Prednisolone (Yes/No)	-	34/116	-	-	-
HCQ (Yes/No)	-	44/106	-	-	-
Severity (DAS28-CRP) (Severe/Moderate/Mild)	-	69/56/25	-	-	-

Table 3. The results of the lipid profile and atherogenic indices of patients and controls.

Parameters	Control	Patients	F/χ²	df	
TC (mM)	4.81±0.65	5.63±0.81	93.563	1/298	<0.001
TG (mM)	1.50±0.29	2.02±0.49	123.607	1/298	<0.001
HDL-C (mM)	1.21±0.18	0.89±0.15	267.039	1/298	<0.001
VLDL-C (mM)	0.69±0.13	0.92±0.22	123.607	1/298	<0.001
LDL-C (mM)	2.92±0.64	3.82±0.88	102.783	1/298	<0.001
CRI-I	4.08±0.86	6.49±1.55	279.642	1/298	<0.001
CRI-II	2.49±0.79	4.44±1.45	206.029	1/298	<0.001
AIP	0.11(0.05-0.16)	0.38(0.26-0.44)	MWUT	-	<0.001
AC	3.09±0.86	5.49±1.55	279.642	1/298	<0.001

Table 4. Shows the biomarkers' correlation with demographic variables. *: Significant correlation p<0.05.

Parameters	GDF-15	CRI-I	CRI-II	AIP	AC
Age	0.161*	-0.134	-0.138	-0.002	-0.134
Height	-0.044	-0.040	-0.052	0.022	-0.040
Weight	-0.031	-0.016	-0.015	-0.046	-0.016
BMI	0.007	0.015	0.023	-0.057	0.015
Sex	0.031	-0.031	-0.012	-0.119	-0.031
Residency	-0.164*	0.029	0.021	0.046	0.029
Duration of the Disease	0.076	0.134	0.118	0.136	0.134
Family History	-0.011	-0.170*	-0.154	-0.147	-0.170*

Table 5. Correlation between the studied biomarkers. *: Significant correlation p<0.05, **: Significant correlation p<0.01, ***: Significant correlation p<0.001.

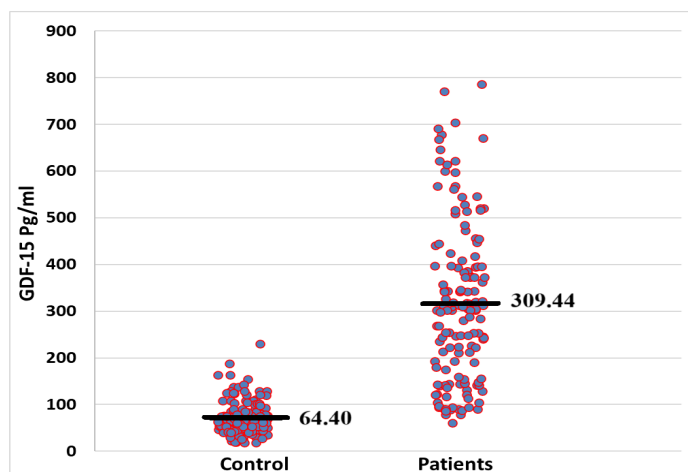| Parameters	GDF-15	CRI-1	CRI-11	AIP	AC
GDF-15	1	0.281**	0.262**	0.211**	0.281**
TC	0.251**	0.757***	0.775***	0.190*	0.757***
TG	0.131	0.109	-0.040	0.844***	0.109
HDL-C	-0.164*	-0.669***	-0.625***	-0.500**	-0.669***
VLDL-C	0.131	0.109	-0.040	0.844***	0.109
LDL-C	0.245**	0.827***	0.871***	0.078	0.827***
CRI-I	0.281**	1	0.986***	0.448**	1.000**
CRI-II	0.262**	0.986***	1	0.297**	0.986***
AIP	0.211**	0.448**	0.297**	1	0.448**
AC	0.281**	1.000**	0.986***	0.448**	1
Atherogenic Risk	0.194*	0.423**	0.309**	0.802***	0.423**

Figure 1. Comparison among of concentration GDF-15 in healthy controls (HC) group and RA patients group.

Comparison Study among RA Patients and Controls - Demographic Parameters

The age range of the studied groups was between 20 and 79 years. After 40 years, age-related changes in RA develop due to a number of variables, such as tension, reduced immunity, and exposure to various antigens, such as tobacco, which activate autoreactive lymphocytes (Hassan, Abdullah, & Zakair, 2022; Xia et al., 2015). Additionally, there were non-significant differences in BMI between the two studied groups as shown in Table 1. This finding is consistent with Mohammed et al. (2022), who found no significant differences in BMI among RA patients and controls (Mohammed et al., 2022). The mean ± S.D of BMI for patients with RA was 28.19±3.52, which is in line with earlier studies showing a connection between rheumatoid arthritis and obesity. Obesity seems to be linked to a higher chance of getting rheumatoid arthritis, although obesity itself may not aggravate rheumatoid arthritis. However, clinical assessments indicate that obesity may decrease the likelihood of remission due to its impact on disease activity indices (Mahdi et al., 2023).

According to the findings of this research, the majority of RA patients were females (121) compared to males (29), resulting in a female-to-male ratio of 4.1:1. This corresponds to the results of previous investigations (Ghasak Ahmed Ali & Al-Turaihi, 2022; Attar & Al Ghamdi, 2010; Gorial, Ahmad, & Abbood, 2021). Additionally, Dessie et al. (2020) showed that the risk of developing RA was three times greater in women than in men between the ages of 40 and 60 (Dessie et al., 2020), while Al-Bedri et al. (2016) reported a women-to-men ratio of 7.6:1 (Al-Bedri, Al-Quriashi, Gorial, & Younis, 2015). The cause is related to environmental factors, and female sex hormones, such as progesterone and estrogen, which have a role in the pathophysiology of RA. Inflammatory responses and cytokine production in the synovium have a direct effect on cartilage. The increased incidence of RA in women suggests that hormonal factors specific to women have a role in the development of the disease and may influence blood protein levels that promote inflammation. For instance, it has been suggested that estrogen influences T and B cells, which are involved in the immunological response, and may have a pro-inflammatory effect (Yu et al., 2020).

In terms of marital status, the majority of the patients were married, with married individuals having a higher risk of RA than unmarried ones among patients, which agrees with Karahan et al. (2016), who found that the majority were married (91.9%) (Karahan et al., 2016).

Regarding residences, this study indicates that RA affected urban areas (118) more than rural areas (32) as shown in Table 1, possibly due to poor case findings in areas with low healthcare or variations in the risk environment (Almutairi et al., 2021).

There were more patients with family histories in the current study than those without. Although the etiology of RA is uncertain, environmental and genetic factors have been demonstrated to play an important role in the disease's development (Almurshedi et al., 2023; Scherer, Häupl, & Burmester, 2020). Family history is still a significant predictor of the development of RA, although it may not be as strongly correlated with disease activity (Deane et al., 2017).

Comparison of Clinical Data Parameters between Groups

The current study's findings revealed higher levels of ESR, RF, CRP, and ACPA in RA patients compared to controls, consistent with prior research (N. U. G. Mohammed, Khaleel, & Gorial, 2022; Shen et al., 2015). Elevated ACPA levels in RA patients were also observed, aligning with the results of Alwan & Ghali (2021), indicating the significance of ACPA antibodies as diagnostic and prognostic markers for RA (Alwan & Ghali, 2021; Shafaghi et al., 2014).

The study found elevated levels of ESR in RA patients compared to normal values. This elevation is attributed to the nonspecific nature of ESR as an indicator of inflammation, reflecting the presence of acute-phase reactants in the blood. In RA, systemic inflammation resulting from the autoimmune response targeting the synovial tissue leads to tissue damage and inflammation. Cytokines like IL-6 stimulate the liver to produce acute-phase reactants such as CRP and fibrinogen, consequently raising ESR levels. Thus, increased ESR serves as a marker for the systemic inflammation characteristic of RA (Madhuvan, Rangaswamaiah, & Manigandan, 2022).

Consistent with a study by Khater et al. (2022), the CRP titers in RA patients were higher compared to the control group, indicating an elevated inflammatory response (Khater & Al Sheik, 2022). CRP levels rise as part of the host's inflammatory response, contributing to its elevation (Sproston & Ashworth, 2018).

Moreover, CRP, particularly in long-term female patients, has been suggested as a more accurate indicator of RA activity than ESR (Castrejon et al., 2008). Studies have shown a correlation between patient age and ESR, with ESR values increasing with age (Crowson, Rahman, & Matteson, 2009). Some research suggests that CRP is a more precise indicator of acute disease activity in RA compared to ESR (Khadim & Al-Fartusie, 2021; Skogh, Gustafsson, Kjellberg, & Husberg, 2003; Ward, 2004).

The elevated ESR and CRP values observed in the current study may be influenced by various factors, including age, the duration and severity of the illness, inflammation, and treatment dosage and duration. These variables may collectively impact disease activity (Khater & Al Sheik, 2022).

The findings are consistent with Dessie et al. (2022), wherein patients with RA exhibited significantly higher levels of the inflammatory marker CRP compared to controls. Elevated CRP levels suggest systemic inflammation, indicative of an increased risk of atherosclerotic events in RA patients. This underscores the

heightened systemic inflammation and dyslipidemia observed in RA patients compared to the control group. Both indices in RA patients indicate the presence of atherosclerotic events (G. Dessie, Tadesse, Demelash, Genet, & Reviews, 2020).

In rheumatoid arthritis (RA), the immune system inadvertently attacks the synovium, the lining of the joints, leading to inflammation. This inflammatory process triggers the release of cytokines and other inflammatory molecules. In response, the immune system generates antibodies like rheumatoid factor (RF) to help eliminate the damaged tissue. However, prolonged production of RF can contribute to persistent inflammation and joint damage (Alattabi, Abood Jaber, Zenki, & Development, 2019). The presence of anti-cyclic citrullinated peptide (anti-CCP) antibodies, as indicated in the study by Al-Dabbagh and Hashim (2018), may signify certain pathophysiological characteristics and ongoing immune activation, while RF seropositivity is associated with inflammation (AL-DABBAGH & HASHIM, 2018).

The current results of these parameters are likely attributable to the inflammatory activity and severity of the disease. Acute phase reactants such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) increase in response to inflammation and tissue damage. In patients with rheumatoid arthritis (RA), these levels are typically elevated during active disease and can serve as markers for monitoring disease activity and response to therapy. Autoantibodies like rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (ACPA) are used as diagnostic markers for RA, as they are commonly found in RA patients and have been associated with disease severity. Monitoring routine parameters such as RF, ESR, CRP, and ACPA can be valuable in managing RA, providing essential information about disease activity. Regular monitoring of these biomarkers can assist in making therapeutic decisions and optimizing disease control (Ali & Abbas, 2022; Almurshedi et al., 2023).

The study results revealed that growth differentiation factor-15 (GDF-15) levels were significantly higher in rheumatoid arthritis (RA) patients compared to controls. Several studies have indicated an association between GDF-15 and disease activity in RA patients (Brown et al., 2007; Khalil et al., 2020). Elevated GDF-15 levels are considered a potential marker of RA and are believed to be a pro-inflammatory cytokine and a potential causative factor for both RA and cardiovascular disease due to its association with RA (El Shebiny et al., 2022). GDF-15 is released at high concentrations in response to mitochondrial dysfunction, oxidative stress, and metabolic stress, often stimulated by pro-inflammatory cytokine activation (Arkoumani et al., 2020; W.-W. Jiang et al., 2021; Schwarz, Kinscherf, & Bonaterra, 2023).

Comparison of GDF-15 between Healthy Controls (HC) and RA Patients

These results suggest a potential association between GDF-15 and the pathophysiology of rheumatoid arthritis (RA). Our findings align with several studies that have investigated GDF-15 serum levels in RA patients (He & He, 2022; Xu, Su, He, & Huang, 2018; Xu et al., 2021). In Iran, Esalatmanesh et al. (2020) conducted a study on RA patients, indicating that GDF-15 concentration may serve as a biomarker for predicting the severity of RA disease activity (Esalatmanesh, Fayyazi, Esalatmanesh, & Khabbazi, 2020). Similarly, a study in Turkey by Xu et al. (2018) assessed serum GDF-15 concentrations in RA patients, finding higher levels compared to the control group (Xu et al., 2018). These findings collectively suggest a plausible link between GDF-15 and the pathophysiology of RA, including joint damage (He & He, 2022). Oxidative stress plays a significant role in the pathophysiology of RA, as autoimmune processes in this condition lead to the generation of reactive oxygen species and reactive nitrogen species (Albabawaty, Majid, Alosami, & Mahmood, 2020).

Comparison of the Lipid Profile between Healthy Controls (HC) and RA Patients

The study findings revealed significantly elevated levels of lipid profile parameters and atherogenic indices (TC, TG, VLDL-C, LDL-C, CRI-I, CRI-II, AIP, and AC) in RA patients compared to the control group. Conversely, a significant decrease was observed in HDL-C levels in RA patients compared to controls, increasing the risk of atherosclerosis. Dyslipidemia is commonly observed in RA, likely due to the chronic inflammatory state associated with the condition (Erum, Ahsan, & Khowaja, 2017), which is closely linked to atherosclerosis (Kypreos et al., 2019; Popescu et al., 2023). The prevalence of dyslipidemia in RA patients appears to increase with the duration of the disease (Spanakis et al., 2006), possibly due to aging, which is a known risk factor for lipid profile disorders (Higashi et al., 2012), and prolonged inflammation (Toosi et al., 2018; Turesson, Jacobsson, Matteson, & management, 2008). Epidemiological studies indicate that women, especially those who are menopausal, are more susceptible to compromised lipid profiles, significantly heightening the risk of atherosclerotic events (Rørholm Pedersen et al., 2016). This suggests that factors beyond inflammation, such as gender, hormones, and genetics, may contribute to abnormal blood lipids in RA (Yan et al., 2023).

In RA patients, the indices indicate the presence of atherosclerotic events. Patients with RA face an elevated risk of atherosclerotic events, as evidenced by increased values of atherogenic indices. Moreover, RA patients exhibit higher levels of systemic inflammation and dyslipidemia compared to the control group. Consequently, elevated disease activity in RA patients leads to elevated levels of bilateral dyslipidemia (TC, LDL-C) and accelerated atherosclerosis. Various factors, including genetics, inflammation, and medications, may render individuals with RA more vulnerable to dyslipidemia than the general population,

thereby increasing the risk of atherosclerosis and cardiovascular disease, potentially leading to premature mortality.

Correlation Study

Correlation between the Biomarkers and the Demographic Parameters

The results revealed a positive correlation between GDF-15 and age, as depicted in Table 4. This finding is consistent with prior research (Doerstling, Hedberg, Öhrvik, Leppert, & Henriksen, 2018; Kempf et al., 2012; Vila et al., 2011), suggesting that GDF-15 expression may be associated with aging through both physiological and pathological mechanisms. Evidence indicates that elevated GDF-15 levels in the bloodstream may serve as a biomarker for aging and age-related cognitive decline (Yasunori Fujita et al., 2016; J. Jiang, Wen, & Sachdev, 2016). Elevated GDF-15 levels may signal mitochondrial dysfunction, a hallmark of aging and a contributing factor to various age-related diseases (Yasunori Fujita et al., 2016; Ji et al., 2017). Additionally, as individuals age, they may experience cellular senescence, hormone dysregulation, oxidative stress, protein glycation, and inflammation (Simm et al., 2008). Considering aging-related characteristics such as telomere length or mitochondrial function may provide further insights into the role of aging (Bao et al., 2019; Blasco, 2007). In healthy individuals, GDF-15 concentrations gradually increase with age and do not seem to be influenced by sex or ethnicity (di Candia et al., 2021; Ho et al., 2012).

Furthermore, the study identified a negative correlation between GDF-15 and residency, as indicated in Table 4. This finding may be attributed to the impact of social and environmental factors following war conflicts in the area of Iraq (Al_Badran et al., 2022). This lipid variation was associated with a family history of RA, characterized by hypertriglyceridemia, dyslipidemia, high quantities of small dense low-density lipoprotein particles, and mild high-density lipoprotein cholesterol contents.

Correlation between the Biomarkers

The study findings suggest that atherogenic indices can serve as biochemical markers for predicting and managing cardiovascular disease (CVD) risk in rheumatoid arthritis (RA) patients. Established cardiovascular risk factors and atherogenic indices (AIP, CRI-I, CRI-II, AIP, and AC) exhibited a statistically significant association in this investigation. Lipid profiles such as triglycerides (TG) and low-density lipoprotein cholesterol (LDL-C) can be utilized as biochemical indicators to monitor and evaluate CVD risk (Cure et al., 2018). Moreover, oxidized LDL-C levels are elevated in inflamed synovial fluid, and both intracellular and extracellular oxidized LDL-C are detected in the rheumatoid synovium. Recent research has demonstrated a common genetic predisposition for dyslipidemia and RA, indicating a correlation between dyslipidemia and the pathogenesis of RA (Park, Cho,

Emery, & Kim, 2013). Additionally, there is evidence that lipids directly regulate inflammation, with increased levels of circulating inflammatory cells caused by hypercholesterolemia triggering inflammation (Drechsler, Megens, van Zandvoort, Weber, & Soehnlein, 2010; Swirski et al., 2007).

Chronic inflammation in RA patients leads to dyslipidemia, characterized by elevated LDL-C and reduced high-density lipoprotein cholesterol (HDL-C) levels (Rezuş, Macovei, Burlui, Cardoneanu, & Rezuş, 2021). Systemic inflammation is a primary contributing factor to increased cardiovascular risk in RA patients, as it is associated with lipid-salvage processes, arterial stiffness, and atherosclerotic plaque destabilization (Błyszczuk & Szekanecz, 2020; Mahtta et al., 2020). Therefore, alterations in HDL-C levels influenced by inflammation may lead to increased adipose bulk and further adipose dysfunction (Bag-Ozbek, Giles, & reports, 2015).

Assessing CVD risk in RA patients based solely on disease activity can be challenging due to its fluctuating nature. Atherogenic indices, which change comparably to disease activity, offer a better means of measuring CVD risk (Popa, Arts, Fransen, & van Riel, 2012). The logarithmically converted ratio of TG to HDL cholesterol molar concentrations, known as AIP, exhibits a strong correlation with other atherogenic indices and is highly predictive of CVD risk in RA (Alifu et al., 2023; Dobiásová, 2006).

Higher levels of atherogenic indices, including CRI-II and AIP, correlate with an increased risk of CVD (Hajian-Tilaki, Heidari, & Bakhtiari, 2020). Despite AIP being the preferred index, both CRI-II and CRI-I play important roles in assessing CVD risk (Targońska-Stępniak, Piotrowski, Zwolak, Drelich-Zbroja, & Majdan, 2018; Tecer et al., 2019; Venetsanopoulou, Pelechas, Voulgari, & Drosos, 2020). Estimating AIP is considered a useful biochemical measure for managing and evaluating CVD risk in RA patients, as per the EULAR report (Popa et al., 2012).

Overall, atherogenic indices hold promise as reliable indicators for estimating CVD risk in RA patients, particularly considering the fluctuating influence of disease activity. Rather than relying solely on individual lipid profiles, studying atherogenic indices may provide a more comprehensive assessment of CVD risk in RA patients (Dessie, 2022).

Conclusions

In summary, the comparative analysis between rheumatoid arthritis (RA) patients and healthy controls showed a complex relation with RA, inflammatory biomarkers, lipid profiles, and cardiovascular risk. The demographic analysis revealed no notable changes between RA patients and controls with age, BMI, sex ratio, marital status, or residency, denotoing that observed differences in biomarkers were not influenced by these factors. However, RA patients showed markedly high levels of inflammatory biomarkers

(ACPA, CRP, ESR, RF) compared to controls, indicating potential systemic inflammation characteristic of RA.

The significant high levels of growth differentiation factor-15 (GDF-15) in RA patients compared to controls, suggested its potential implication in the pathophysiology of RA and its association with cardiovascular risk. Furthermore, correlation analysis showed connections between GDF-15, demographic parameters, lipid profile components, and atherogenic indices, showing their clinical relevance with preventing RA.

Additionally, RA patients showed adverse lipid profiles characterized by high total cholesterol (TC), triglycerides (TG), very-low-density lipoprotein cholesterol (VLDL-C), and low-density lipoprotein cholesterol (LDL-C), alongside reduced high-density lipoprotein cholesterol (HDL-C), predisposing them to heightened cardiovascular risk. The assessment of atherogenic indices further highlighted the pro-atherogenic lipid profile in RA patients, showing susceptibility to atherosclerosis and cardiovascular diseases.

However, monitoring inflammatory biomarkers, lipid profiles, and atherogenic indices is crucial in RA for early cardiovascular risk detection and management. Targeted interventions to reduce inflammation and dyslipidemia could lessen cardiovascular burden in RA. Further research into mechanistic links is vital for improving therapeutic strategies and outcomes in this autoimmune condition.

Author contribution
G.A.O.A., M.A.H., S.R.M. collected samples, performed tests, and wrote the article, conducted the study design, reviewed and edited the manuscript.

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The authors have no conflict of interest.

Abbreviations
ACPA, Anti-Cyclic Citrullinated Peptide Antibodies; CRP, C-reactive protein; ESR, Erythrocyte Sedimentation Rate; RF, Rheumatoid Factor; HCQ, Hydroxychloroquine; DAS28-CRP, Disease Activity Score-28-C-Reactive Protein. TC, Total cholesterol; TG, Triglyceride; HDL-C, High density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; VLDL-C, Very low density lipoprotein; AC, Atherogenic coefficient; AIP, Atherogenic index of plasma; CR-I, CR-II Castelli's risk indexes.

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