

Original Article



Lipid Profile and Its Correlation with Disease Severity in Kurdish Patients with Rheumatoid Arthritis

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Abstract

Introduction: Cardiovascular diseases (CVD) are considered a main cause of mortality and morbidity in the late stages of rheumatoid arthritis (RA). Changes in lipid profiles and dyslipidemia are associated with atherosclerosis in RA, and this is the cause of cardiovascular complications in some patients. This study aims to investigate the prevalence of dyslipidemia in Kurdish patients with RA and the association between lipid profiles and disease activity in 190 RA patients.

Methods: A cross-sectional study was conducted from 2020 to 2021 in the referral ward of Tohid Hospital and a private rheumatology clinic in Sanandaj. Plasma lipid profiles, including triglycerides (TG), total cholesterol (TC), and HDL-cholesterol, were measured by an auto-analyzer. Patients were classified into three groups based on Disease Activity Score at 28 joints (DAS28): remission ($DAS28 < 2.6$), low disease activity ($2.6 < DAS28 < 3.2$), and moderate/high disease activity ($DAS28 > 3.2$).

Results: As measured by LDL-C/HDL-C ratio and HDL-C, the atherogenic index significantly correlates with DAS28 in studied patients, whereas no correlations were detected with other lipid parameters. Besides, RA patients with high/moderate disease activity have significantly higher LDL-C/HDL-C and lower HDL levels compared to the patients in the remission group. There were no significant differences between the studied groups for other plasma lipid parameters. The prevalence of dyslipidemia was as follows: hypercholesterolemia 34.21%, hypertriglyceridemia 40.52%, hyper-LDL 24.73%, and hypo-HDL 13.68%. Even though only small samples were studied, these results suggest that disease severity correlates with lipid fractions, specifically HDL, and as a result, the LDL-C/HDL-C ratio in RA.

Conclusion: Higher rheumatoid arthritis disease activity was associated with an unfavorable lipid profile, especially the increased ratio of LDL-C/HDL-C and the decreased level of HDL-C. These findings support the potential value of atherogenic indices as indicators of cardiovascular risk in RA and should be confirmed in larger studies.

Keywords: Atherogenic index, Dyslipidemia, HDL cholesterol, Kurdistan, LDL cholesterol, Rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA), the most prevalent inflammatory joint disease, affects 0.3 to 1.2% of the general population and is approximately three times higher in women than in

men.¹ RA is characterized by polyarthritis with progressive joint damage, inflammation, disability, and extra-articular abnormalities. It is usually accompanied by other complications, like cardiovascular diseases (CVD), that



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contribute to mortality and morbidity in this devastating disease.² It has been shown that myocardial ischemic episodes and sudden cardiac deaths are more likely to happen in RA patients compared to healthy individuals. In general, CVD is accompanied by altered lipid profiles and an elevated atherogenic index (AI).³ However, the pattern of lipid abnormalities observed in patients with rheumatoid arthritis (RA) differs from that seen in other populations with a similar burden of cardiovascular disease (CVD). Studies have demonstrated higher mortality rates in RA compared to the general population. As such, circulating levels of total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), and high-density lipoprotein-cholesterol (HDL-C) are paradoxically reduced in RA patients, and cardiovascular events take place at lower lipid levels. This phenomenon is the so-called “*lipid paradox*” mentioned by many authors.⁴ This phenomenon usually leads to underestimation of cardiovascular (CV) risk assessment in RA patients. Several explanations have been proposed for the lipid paradox, one of which is higher levels of inflammation burden observed in RA patients. In this regard, it has been demonstrated that RA itself is an independent risk factor for coronary artery disease (CAD), and this association may be due to the effects of mediators of inflammation on the thickness of the carotid wall.⁵

Nowadays, with the accumulation of lipids within the vessel walls considered the main cause of atheromatous plaque formation, atherosclerosis is the primary cause of inflammation.⁶ Atherosclerosis is more prevalent in RA patients than in healthy populations, and it progresses as the inflammation continues.⁷ Lipid levels are inversely correlated with C-reactive protein (CRP) serum levels, and this happens as the inflammation continues during the RA’s course. In the preclinical phase of RA, serum lipids may be elevated before inflammation appears. As systemic inflammation increases, lipid levels tend to decline, whereas treatment with anti-inflammatory agents is often associated with a subsequent increase in serum lipid concentrations.⁸ However, RA patients experience a reduction in circulating levels of all cholesterol forms, while the atherogenic lipid profile increases. This phenomenon may be attributable, in part, to the distinct effects of inflammation on the synthesis and metabolism of different lipid subclasses. It has been shown that chronic inflammation promotes atherosclerosis by modulating well-defined risk factors such as LDL, and it also has direct effects on blood vessels.⁶ Triglyceride (TG) and TC serum levels appear to be normal or even lower in RA patients with high-grade inflammation. Additionally, in RA cases, greater disease severity inversely correlates with TC and HDL-C levels.³

Traditional disease-modifying antirheumatic medications (DMARDs) protect RA patients from the risk of cardiovascular disease (CV) through unclear mechanisms.⁹ The anti-inflammatory characteristics of anchor DMARDs, methotrexate, and other medications may account for the rise in plasma lipid levels. While DMARDs have the potential to reduce inflammation, and there are opposing data regarding the effects of DMARDs

on serum lipid profiles in RA patients, the atherothrombotic role of inflammation remains in question. These effects have been reported to be either beneficial or neutral in cohorts.¹⁰ While lipid profile remains a complex pathology in RA, the correlation of dyslipidemia with RA severity remains a question, and understanding this correlation could help in assessing CV risk and implementation of treatment strategies in RA. This study aimed to evaluate the correlation between changes in serum lipid profiles and disease activity in Kurdish people with RA. RA is the most prevalent inflammatory joint disease in this area, with a prevalence rate of 0.51%, which is modest compared to other parts of the world.¹¹ However, there is no report about the prevalence of dyslipidemia among RA cases in this geographical region; thus, in the present study, dyslipidemia was evaluated in RA patients of this ethnic group.

Methods

The study subjects included RA patients who were diagnosed according to the 2010 criteria of the American College of Rheumatology/European League Against Rheumatism Collaborative initiative for the classification of RA. Patients with other forms of arthritis were excluded from the study, as patients with RA were receiving biological drugs indicated for RA. This study was reviewed and approved by the central ethics committee of Kurdistan University of Medical Sciences. All participants and parents signed an informed consent to participate in the study.

A cross-sectional study was conducted from 2020 to 2021 in the referral ward of Tohid Hospital and a private rheumatology clinic in Sanandaj. The subjects included 190 RA patients in Kurdistan province, located in the northwest of Iran, all belonging to the Kurdish ethnicity. Demographic data, including age, sex, ethnicity, disease duration, family history of RA, smoking status, and co-morbidities, were obtained from all the patients at the clinic through clinical interviews and questionnaire reviews. The disease duration was considered to be the time between diagnosis and the time of the interview. A number of painful and swollen joints (28 joints) and patient/physician global assessments of pain (visual analog scale (VAS), ranging from 1 to 100) were utilized for evaluation by rheumatologists. The Disease Activity Score of 28 joints (DAS28) was used as a measure of disease severity. The DAS28 formula was calculated using joint swelling counts, joint tenderness counts of 28 joints, erythrocyte sedimentation rate (mm/h), and subjective assessment of the patient’s pain (VAS). Disease activity was classified into the following: DAS28 < 2.6 as clinical remission, 2.6 < DAS28 < 3.2 as low disease activity, 3.2 < DAS28 < 5.1 as moderate disease activity, and DAS28 > 5.1 as high disease activity. For comparison, the patients were divided into three groups based on DAS28: remission (R) (n = 70; DAS28 < 2.6), low disease activity (LDA) (n = 50; 2.6 < DAS28 < 3.2), and moderate/high disease activity (MHDA) (n = 70; DAS28 > 3.2). In order to analyze serum lipid levels, blood samples were taken early in the morning. Lipid profile tests,

including TC, TG, LDL-C, and HDL-C, were measured by an auto-analyzer during fasting. Atherogenic indices were calculated based on the TC/HDL-cholesterol and LDL-cholesterol/HDL-cholesterol ratios. ESR was measured by the Westergren method, and rheumatoid factor (RF IgM) was qualitatively measured by agglutination slides. Sera was used for the measurement of anti-cyclic citrullinated peptide antibodies (ACPA) using an ELISA method. The patients received standard triple therapy with DMARDs. Methotrexate was used as a main DMARD in 89.47% of the patients, with a mean dose of 10 mg/week (ranging from 7.5 to 15 mg/week). In 88.94% and 11.05% of the cases, hydroxychloroquine (ranging from 200 to 400 mg/day) and sulfasalazine (ranging from 1.5 to 2 g/day) were used, respectively. All the patients had taken a glucocorticoid (prednisolone, ranging from 7.5 to 15 mg/day) except for one patient who did not use any drugs. The prevalence of dyslipidemia among RA was defined according to the European Society of Cardiology (ESC) guidelines: serum TC ≥ 5.0 mmol/L, serum TG ≥ 1.7 mmol/L, serum LDL-C ≥ 3.0 mmol/L, and serum HDL-C < 1.0 mmol/L.¹²

Statistical analyses were accomplished using GraphPad Prism® version 9.0. Lipid serum levels of RA patients with remission, low, and high active disease were compared using one-way ANOVA with Tukey's multiple comparisons test. The distribution of quantitative variables was assessed for normality using the Shapiro–Wilk test. As the distribution was parametric, the correlations between lipid profiles and DAS28 were analysed using Pearson's correlation coefficient test. The data were summarised as dot plots showing the actual amounts of plasma lipids obtained, with error bars. In all analyses, $P < 0.05$ was considered significant.

Results

The subjects included 190 RA patients, with 164 females and 26 males. Patients' demographic statistics, clinical data, and lipid profiles are presented in Table 1. The number of patients was 70, 50, and 70 in remission, LDA, and MHDA, respectively. Mean DAS28 values were 2.07 ± 0.44 , 2.9 ± 0.17 , and 4.39 ± 0.95 in remission, LDA, and MHDA, respectively. Mean ESRs were 12 ± 7.06 , 23.3 ± 13.6 , and 38.3 ± 24.8 in remission, LDA, and MHDA, respectively. A statistically significant difference in ESR values was observed among the groups ($P < 0.05$). Hypertension, diabetes mellitus, fatty liver disease, and chronic kidney disease were recorded in 20.5, 13.7, 1, and 0.5 percent of patients, respectively. Qualitatively measured, IgM-RF and anti-CCP antibodies were positive in 40% and 50.52% of the cases, respectively. Dyslipidemia prevalence was as follows: hypercholesterolemia 65/190 (34.21%), hypertriglyceridemia 77/190 (40.52%), hyper-LDL 47/190 (24.73%), and hypo-HDL 26/190 (13.68%); 53.68% of patients had TC/HDL-C more than 3.5, and 14.73% had LDL-C/HDL-C more than 3.

HDL, and more clearly AI (LDL-C/HDL-C), were significantly different between the patients in remission and those in the MHDA group ($P < 0.05$, Table 2, Figure 1a and

Table 1. Demographic characteristics of RA patients

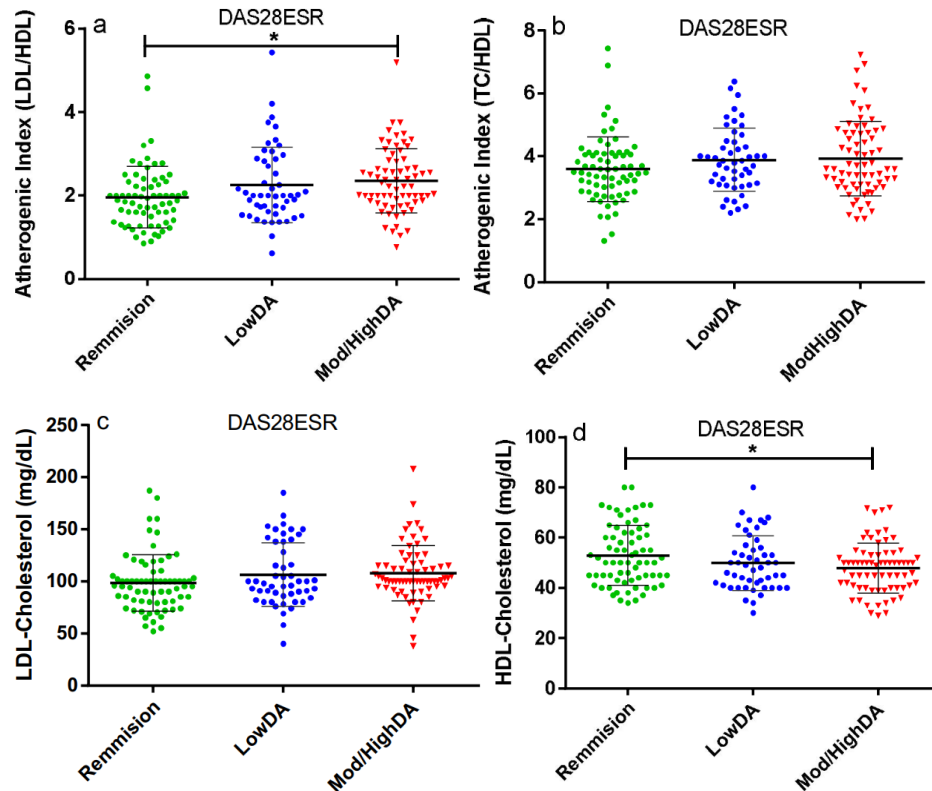
Variable	RA patients (N = 190)	RA patients with Normal Lipid Value (N = 54)	RA patients with Dyslipidemia (N = 136)
Women, n (%)	164 (86.31%)	44 (26.83%)	120 (73.17%)
Men, n (%)	26 (13.69%)	10 (38.46%)	16 (61.54%)
Age, years	52 $\pm$ 13	48.9 $\pm$ 15.4	52 $\pm$ 12.1
Family history of RA, n (%)	50 (26.31%)	11 (21.11%)	39 (29.5%)
Disease duration, Months, n (%)	92 $\pm$ 69.2	90.4 $\pm$ 67.8	92.2 $\pm$ 69.9
Smoker, n (%)	10 (5.26%)	1 (1.9%)	9 (6.8%)
VAS	48.6 $\pm$ 28.3	45.9 $\pm$ 27.5	49.3 $\pm$ 28.4
28 Tender Joint	0.6 $\pm$ 2.2	0.04 $\pm$ 0.3	0.6 $\pm$ 2.3
28 Swollen Joint	2.5 $\pm$ 3.5	2.3 $\pm$ 3.8	2.5 $\pm$ 3.5
ESR (mm/hrs)	24.3 $\pm$ 20.4	23.2 $\pm$ 21.6	24.5 $\pm$ 19.8
DAS28	3.1 $\pm$ 1.2	2.9 $\pm$ 1.1	3.1 $\pm$ 1.2
RF positive, n (%)	76 (40%)	26 (50%)	50 (37.8%)
ACPA positive, n (%)	96 (50.52%)	31 (59.6%)	65 (49.2%)
TC	184 $\pm$ 41	156.2 $\pm$ 19.2	194.6 $\pm$ 42.6
TG	146 $\pm$ 74	99.8 $\pm$ 28.8	164.5 $\pm$ 78.1
LDL-C	104 $\pm$ 27.8	86 $\pm$ 15.5	111.6 $\pm$ 27.8
HDL-C	50 $\pm$ 11.2	54.5 $\pm$ 9.3	48.4 $\pm$ 11.4
TC/HDL-C	3.82 $\pm$ 1.07	2.9 $\pm$ 0.4	4.1 $\pm$ 1
LDL-C/HDL-C	2.2 $\pm$ 0.81	1.6 $\pm$ 0.3	2.4 $\pm$ 0.8

1d). LDL-C/HDL-C was significantly *lower* in the remission group compared to the MHDA group (1.95 vs. 2.35, $P < 0.05$, Table 2). Although not statistically significant, this difference was also found between the remission and the LDA group (1.95 vs. 2.25, $P > 0.05$, Figure 1a) or the LDA group and the MHDA group (2.25 mg/dL vs. 2.35 mg/dL, $P > 0.05$, Figure 1a). Conversely, HDL-C was significantly *higher* in the remission compared to the MHDA group (52.91 mg/dL vs. 47.97 mg/dL, $P < 0.05$, Table 2). These differences were not significant in terms of HDL-C between the remission and the LDA group (52.91 mg/dL vs. 49.86 mg/dL, $P > 0.05$, Figure 1d) or the LDA and MHDA (49.86 mg/dL vs. 47.97 mg/dL, $P > 0.05$, Figure 1d). In contrast to this data, no significant differences were detected between TC ($P = 0.74$), TG ($P = 0.88$), and LDL ($P = 0.1$) in patients with different disease activities (Table 2). In fact, TCs were 182.5, 187.3, and 182.0 in the remission, LDA, and MHDA groups, respectively. TGs were 143.8, 150.1, and 144.2 in the remission, LDA, and MHDA, respectively. LDL-C values were 98.41, 106.4, and 107.8 in the remission, LDA, and MHDA, respectively. Besides, no statistically significant differences were observed for TC/HDL-C when the comparison was made between the three studied groups ($P = 0.13$, Table 2).

A study of the association between disease activity and lipid profiles also showed that the LDL/HDL ratio has a positive correlation with DAS28 ($R = 0.21$, $P = 0.003$, Figure 2a). Serum HDL was inversely correlated with DAS28 ($R = -0.20$, $P = 0.005$, Figure 2d). In contrast, serum levels

Table 2. Lipid profiles in RA patients stratified by disease severity

Variable	DAS28 < 2.6 (N=70)	2.6 < DAS28 < 3.2 (N=50)	DAS28 ≥ 3.2 (N=70)	P
Total Cholesterol (mg/dL)	182.5 ± 48.24	187.3 ± 49.73	182.0 ± 39.12	0.74
Triglyceride (mg/dL)	143.8 ± 35.05	150.1 ± 38.19	144.2 ± 38.81	0.88
LDL-Cholesterol (mg/dL)	98.41 ± 26.56	106.4 ± 29.67	107.8 ± 26.97	0.1
HDL-Cholesterol (mg/dL)	52.91 ± 12.19	49.86 ± 10.68	47.97 ± 10.11	0.03*
Atherogenic Index (TC/HDL)	3.58 ± 1.17	3.88 ± 1.29	3.93 ± 1.19	0.13
Atherogenic Index (LDL/HDL)	1.95 ± 0.83	2.25 ± 0.90	2.35 ± 0.77	0.01*

**Figure 1.** Differences in lipid profiles in remission, low disease activity, and moderate/high disease activity groups. Differences in the serum levels of LDL-C/HDL-C (a), TC/HDL-C (b), LDL-C (c), and HDL-C (d) ratios between patient groups. LowDA: Low disease activity; Mod/HighDA: Moderate or high disease activity. The data are summarized in dot plots representing the real amount of obtained plasma lipids with error bars.

of TC, TG, and LDL were not correlated to DAS28 ($P > 0.05$, Figure 2d). Besides, TC/HDL-C was not significantly correlated to DAS28 ($P > 0.05$, Figure 2b).

Discussion

The main objective of this study was to investigate the relationship between disease activity and lipid profile parameters in patients with RA. RA disease activity is typically assessed using measures such as the DAS28, which includes counts of tender and swollen joints, the ESR or CRP levels, and patient-reported outcomes. Increased systemic inflammation, a feature of active RA, is correlated with higher DAS28. RA patients frequently have a unique lipid profile: they have a higher risk of CVD even when their TC and LDL-C values are lower than those of the general population. This paradox can be partially explained by the pro-inflammatory state of RA, which adversely affects lipid metabolism and function. According to the data obtained in this study, the differences between active and inactive patients in AI (LDL-C/HDL-C) and, more clearly, HDL

indicated a certain effect of the disease activity parameter, DAS28, on atherogenesis and HDL-C. Interestingly, this is not observed for TC/HDL or LDL, which may indicate the importance of HDL cholesterol instead of LDL. This result is more interesting when one considers that most current lipid-lowering drugs target LDL-C but not HDL-C. In line with this, it has been demonstrated that low HDL levels are good predictive signs of cardiovascular risk when LDL is sufficiently low.¹³ Besides, TC/HDL-C was not significantly different between RA patients in the three studied groups (Fig. 1b), and this is in contrast with the results obtained by a Japanese group.¹⁴ This may be a good reason for HDL, but not LDL, for the difference between disease activities that was observed in the studied groups.

The TC/HDL-C ratio is widely regarded as the most critical predictor of cardiovascular disease (CVD). A large international study conducted in the general population demonstrated that the atherogenic index (TC/HDL-C) is a better predictor of myocardial infarction than HDL-C levels alone.¹⁵ However, studies on lipid profiles in rheumatoid

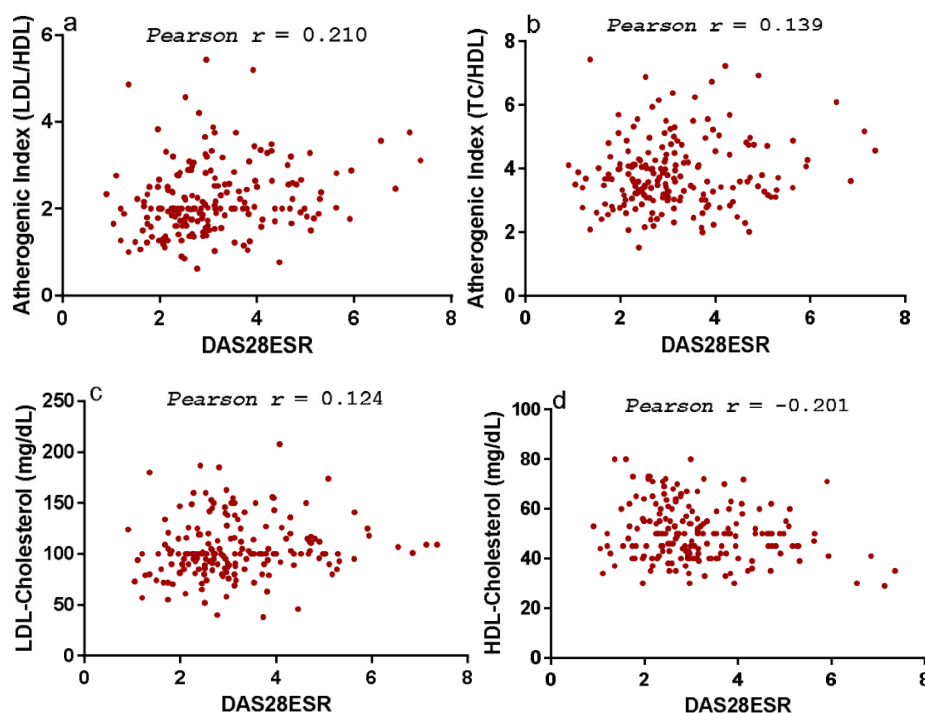


Figure 2. Correlations between DAS28 and lipid profiles. Correlation between DAS28 and LDL-C/HDL-C ratio ($R=0.21$, $P=0.002$) (a), TC/HDL-C ratio ($R=0.139$, $P=0.073$) (b), LDL-C levels ($R=0.124$, $P=0.074$) (c), and HDL levels ($R=-0.201$, $P=0.002$) (d). Pearson's correlation coefficient test was applied for analysis.

arthritis (RA) patients show inconsistent results. While some studies find progression without changes in the atherogenic index when disease activity is managed, others show a similar trend between lipid profiles and disease activity.¹⁶ However, it has been observed that the phenotypes of HDL, rather than cholesterol alone, differ between RA patients and healthy individuals. This difference may contribute to the inflammatory processes in RA.¹⁷ Anti- and pro-inflammatory phenotypes of HDL have been demonstrated to be at lower and higher levels, respectively, in RA patients compared to controls.¹⁹ RA patients often exhibit higher levels of dysfunctional HDL and increased oxidative stress, which can modify HDL particles, making the particles pro-inflammatory.¹⁸ Impaired cholesterol efflux capacity is another reason for pro-inflammatory HDL particles in RA patients. Myeloperoxidase (MPO) is an enzyme in oxidative pathways and is involved in atherosclerosis.¹⁹ Vivekanandan-Giri et al. showed that cholesterol efflux capacity decreased as MPO activity increased in RA patients.²⁰ This may be an explanation for the lipid paradox in RA.⁴ Despite statin therapy, which targets LDL-C as the main body lipid, HDL-C concentration remains an important CV risk factor, and serum HDL-C, strongly and independently of LDL-C, predicts CV events.²¹ In patients with RA, reduced HDL-C levels have been shown to correlate with increased disease activity. It has been established that all lipid fractions tend to be decreased in active RA and are more abundant in HDL-C than in other lipid measures. Boers et al. showed that TC and HDL-C tend to be inversely correlated with disease activity in RA patients.²² In contrast, in the present study, no differences were observed between serum TC levels of RA patients that were related to the grade of disease (Table 2). Elevated CRP levels and inflammation in RA correlate with high Lp(a)

lipoprotein and low HDL-C.²³ Charles-Schoeman and colleagues demonstrated that HDL from RA patients with $\text{DAS28} > 5.1$ had a decreased ability to transport cholesterol compared to HDL from RA patients with $\text{DAS28} < 2.6$. They also detected a significant inverse correlation between ESR and DAS28 with the anti-inflammatory capacity of HDL, as measured by antioxidant enzyme capacity.²⁴ Furthermore, systemic inflammation is likely to alter the protein cargo of HDL particles, and this may transform anti-inflammatory forms of HDL-C to the pro-inflammatory form.⁷ These may explain the increased CV risk and mortality among RA patients. In other words, RA patients with more active disease and more systemic inflammation have higher atherogenic lipids and are more prone to be at risk for CVD, such as atherosclerosis. Significant differences were observed in LDL/HDL and HDL, but not LDL, in patients with $\text{DAS28} < 2.6$ and patients with $\text{DAS28} \geq 3.2$ (Fig. 1a, 1c, and 1d). In line with these findings, Botta et al. showed that high disease activity in RA alters the markers of HDL functionality and arterial stiffness.²⁵ On the contrary, other studies revealed that RA patients had higher levels of large HDL particles and lower levels of small HDL particles, which inversely correlated with inflammation markers like CRP.²⁶ Based on the presented data, it seems that changes in the atherogenic index do not originate in TC but in HDL-C (Table 2). Even though lipid profile pattern fluctuations during the RA course and predicting CV risk assessment are not very clear, we suggest that LDL/HDL could be used as a risk predictor in these patients. This may necessitate designing experimental studies to change lipid levels, mainly targeting HDL.

Conclusion

In summary, the atherogenic index, as measured by the

LDL-C/HDL-C ratio and HDL-C in studied patients, significantly correlates with DAS28, whereas no correlations with other lipid parameters were detected (Fig. 2). Besides, RA patients with high/moderate disease activity have significantly higher LDL-C/HDL-C and lower HDL levels compared to the patients in the remission group (Fig. 1). The results of the present study demonstrated a significant correlation between RA disease severity and both lipid profile parameters and the atherogenic index. As disease control with common DMARDs or glucocorticoids could decline plasma lipid levels and, hence, atherosclerosis in RA patients, we suggest performing larger studies to support the evaluation of disease activity for predicting CV events in RA patients and to treat hyperlipidemia not only with the current dyslipidemia therapeutics but also with novel drugs that target specific portions of pathologic lipids in RA patients. This may be applicable by increasing HDL through novel therapeutic approaches. Using such approaches could reduce CV mortalities and help increase the survival rate of this devastating disease. Although the current results are sufficient for statistical analysis, larger cohorts are required to better define the influence of RA disease activity on lipid profile markers and other atherosclerosis markers. Limitations of this study include the lack of detailed information on lipid-lowering medication use, dietary habits, physical activity, cardiovascular comorbidities and menopausal status. The potential influence of menopause-related changes in lipid metabolism could not be evaluated, given that the majority of participants were women and the mean age of the study population was within the menopausal age range. Residual confounding from these unmeasured factors cannot be ruled out entirely and should be taken into account in the interpretation of the results.

Competing Interests

The authors declare that there are no conflicts of interest.

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Writing—Review & Editing: Ebrahim Mohammadi

Ethical Approval

This study was approved by the ethics committee of Kurdistan University of Medical Sciences (Ethical Code: IR.MUK.REC.1394/83).

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