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Trends in Lipid Parameters in Rheumatoid Arthritis Patients and Their Correlation withthe Disease Activity: a Hospital-Based Study

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Abstract
Background:*Rheumatoid arthritis (RA) is a chronicautoimmune disease associated with long-term morbidity and mortality. The present study aimed to assess the lipid parameters of RA patients and their correlation with the disease activity in a tertiary hospital in Bangladesh.*
Methods:*This study was conducted through a cross-sectional approach in the Department of Medicine, Rajshahi Medical College Hospital. A total of 96 adult RA patients were included as study patients according to the inclusion and exclusion criteria. The diagnosis of RA was confirmedby 2010 American College of Rheumatology/ European League Against Rheumatism (ACR/EULAR) classification criteria. Data collection was conducted through face-to-face interviews, physical examination, and laboratory investigations including lipid parameters and inflammatory markers. A pre-structured questionnaire was used. Disease activity was assessed through disease activity score 28 (DAS 28). For statistical analysis, SPSS v-25 was used. Declaration of Helsinki was followed in every aspect of this study.*
Results:*The mean age of the study patients was 42.13±9.38 (SD) years with a clear female predominance (83.3% female). The frequency of dyslipidemia was 86.5%. The pattern of dyslipidemia showed decreased high-density lipoprotein (HDL) (74%), raised total cholesterol (TC) (50%), raised low-density lipoprotein (LDL) (36.5%) and raised Triglyceride (TG) (25%). About 39.8% had single pattern dyslipidemia, 19.3% had dual pattern and 41% had triple pattern dyslipidemia. Average DAS score of the study patients was 3.91±0.97 (SD) where 18.75% had high disease activity, 36.45% had moderate, 38.54% had low and 6.25% were in remission phase. TC showed positive correlation with disease activity (DAS 28 score) (rs=.302, p<.05) and inflammatory markers both erythrocyte sedimentation rate (ESR) (rs=.322, p<.05) and C-reactive protein (CRP) (rs=.314, p<.05), while HDL exhibited a negative correlation (rs=-.289, p<.05 for DAS 28 score; rs=-.357, p<.05 for ESR; rs=-.339, p<.05 for CRP). TG also showed a positive correlation with CRP (rs=.302, p<.05).*
Conclusion:*This study reports a high prevalence of dyslipidemia in RA patients and reveals a significant positive linear relationship betweencertain lipid parameters and disease activity. Further investigation with larger cohorts is necessary to gain a comprehensive understanding of this relationship for our population.*

Keywords: *Rheumatoid arthritis, RA, Rheumatoid disease, Lipid profile, DAS 28 score*

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I. Introduction

Rheumatoid arthritis (RA), a chronic autoimmune disease of unknown etiology, poses a substantial burden on the affected individuals as well as associated peers [1]. The progressive nature of RAalong with the associated morbidity and mortality, significantly affects not only the physical health of affected individuals but also their mental well-being, social interactions, and economic status.The introduction of aggressive medical therapy with methotrexate leflunomide and other related biological agents improved the long-term prognosis of RAto a certain level but associated comorbidities still complicate the overall health condition and shorten the lifespan of the patients[2, 3].

As comorbidity, a higher incidence of cardiovascular disease (CVD) incidence among rheumatoid arthritis (RA) patients is well-documented with a significant associationwith the mortality associated with RA[4, 5].The pathological mechanism behind the occurrence and progression of CVD among RA patients is still unknown but traditionally age, systemic hypertension, smoking, obesity, and atherogenic lipid profile are considered risk factors for CVD in the general population[6, 7]. Among the patients with RA, an existence of lipid paradox has been reported in previous evidences wherepresence of a pro-inflammatory state in patients with active diseasecauses a reduction in total cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) in patients[8].However, the lower lipid levels do not necessarily confer a reduced risk of CVD as it occurs due to an active inflammatory process rather than improved lipid metabolism[5].On the contrary,anti-inflammatory therapies used for the management of RA may result in a rise of these lipid parameters[9]. Thus, there is a complex and dynamic interplay between the disease activity of inflammation level and lipid metabolism among RA patients.

Understanding the relationship between lipid metabolism and RA in a specific population is crucial for protection of the cardiovascular health of the diseased populationas well as for a broader understanding of RA as a systemic disease. Most of the current understanding is based on studies conducted in Western populations. However, given the genetic, dietary, and lifestyle differences, these findings may not be directly applicable to populations in other regions, such as Bangladesh. This gap highlights the need for region-specific studies to better understand the relationship between RA, lipid metabolism, and CVD risk. Therefore, our study aims to bridge this gap by exploring the lipid profiles of RA patients in a tertiary hospital in Bangladesh and examining their correlation with RA disease activity. If a clear correlation is established, a more targeted management could be introduced with a stronger emphasis on cardiovascular health, quality of life and the long-term better outcomes.

II. Methods

Study design and study population: The study was cross-sectional by design and conducted in the Department of Medicine, Rajshahi Medical College Hospital over a period of 1 year from January 2021 to December 2021. Adult patients attending the outdoor patient department (OPD) or admitted to the indoor ward with a confirmed diagnosis of rheumatoid arthritis (RA) were approached as the study population. RA was confirmed according to the 2010 American College of Rheumatology/ European League Against Rheumatism (ACR/EULAR) classification criteria[10]. For sampling Purposive convenient sampling was adopted. Patients with a diagnosis of diabetes mellitus, ischemic heart disease, chronic kidney disease, chronic liver disease, hypothyroidism, cushing syndrome, obesity, pregnancy, history of taking certain drugs including beta blocker, diuretics, cyclosporine, oral contraceptive pills (OCP), any lipid-lowering drugs, oral or intra-articular steroid (for more than 3 months) were excluded from this study. Finally, 96 RA patients were included as study patients following informed written consent.

Data collection: Data collection procedure was conducted through a detailed history taking, thorough physical examination and laboratory investigations. A pre-structured questionnaire was used for data collection. Socio-demographic (age, gender, residence) and clinical information (presenting clinical features, disease duration, etc.) was recorded from a face-to-face interview.Total number of tender and swollen joints were counted and noted through physical examination.A series of laboratory investigations were conducted including RA factor, Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP), fasting lipid profile (total serum cholesterol, TC; low density lipoprotein cholesterol, LDL; high density lipoprotein cholesterol, HDL and triglyceride,TG). Dyslipidemia will be defined as any or a combination of more than one component of lipid profile.

TC, TG and LDL level was considered to be raised or indicative to presence of dyslipidemia with a level of ≥240 mg/dl, ≥200 mg/dl and ≥160 mg/dl. HDL was considered to be low of indicative to presence of dyslipidemia with a level of <40 mg/dl. Single pattern dyslipidemia was defined as presence of dyslipidemia in only one or single lipid parameter (TG/LDL/HDL), while dual pattern was defined in any two lipid parameters. Triple pattern was defined with dyslipidemia inall of three- TG, LDL and HDL.

Visual Analogue Scale (VAS) was used to assess the pain condition ranging from 0-100 where 0 depicts no pain and 100 depicts extreme severe pain[11].

To determine the disease activity DAS 28 score was considered[12]. DAS-28 was calculated by using formulla-

DAS28= 0.56*√(TJC) + 0.28*√(SJC) + 0.70*Ln(ESR) + 0.014*VAS. [TJC-Tender joint count, SJC-Swollen joint count]

Finally, all information were recorded in designated information sheet for each patient.

Data processing and statistical analysis: Collected data were checked and verified for consistency following statistical analysis using statistical package for social science (SPSS) V-26. Data were presented as the proportion of valid cases for discrete variables and as means ± standard deviations and/or medians with inter quartile ranges for continuous variables. Spearman correlation test was conducted to determine the linear relation between lipid markers and disease activity indicators (DAS 28 score, ESR, CRP) and presented through scatter plot diagram. A p value of <0.05 was considered significant.

Ethical consideration: Prior to the commencement of the study, ethical clearance was achieved from the ethical committee of Rajshahi Medical College, Rajshahi. The study was conducted with concordance of 'Declaration of Helsinki'.

III. Result

In this study, the average age of the RA patients was 42 years with over one-third of the patients were in 4th decade of life. There was a pronounced female predominance, as more than four-fifths of the participants were female. Majority of them reside in rural areas. In terms of nutritional status, nearly half of the patients had normal weight, while a significant one-third were overweight.The average duration of the RA among the participants was3.21±0.89 (SD)years.A majority of the patients were tested positive for the RA factor which was almost three-fourth of the total patients. Mean number of tender and swollen joints were 4.11±1.35 (SD) and 4.10±1.02 (SD) accordingly. Mean ESR was 29.28±8.81 (SD) mm at 1st hour, mean CRP was 12.13±3.98 (SD) mg/dl. Mean VAS score was 36.90±18.08. Regarding the disease activity according to DAS 28 score, 18.75% of patients were in high activity, 36.45% in moderate, 38.54% in low activity, and 6.25% were in remission while the mean DAS28 score was 3.91±0.97.

Table 1: Baseline characteristicsof the study patients with RA (n=96)

Variable	n (%)
Age (years)	
<30	14 (14.6)
31-39	21 (21.9)
40-49	35 (36.5)
≥ 50	26 (27.1)
Mean±SD	42.13±9.38
Gender	
Male	16 (16.7)
Female	80 (83.3)
Residence	
Rural	60 (62.5)
Urban	36 (37.5)
Nutritional status	
Underweight	11 (11.5)
Normal	45 (46.9)
Overweight	32 (33.3)
Obese	8 (8.3)
Duration of disease (years)	3.21±0.89
RA factor	
Positive	71 (73.95)
Negative	25% (26.05)
Tender joint count	4.11±1.35
Swollen joint count	4.10±1.02
ESR (mm at 1st hour)	29.28±8.81
CRP (mg/dl)	12.13±3.98
VAS score	36.90±18.08
DAS28 score	3.91±0.97
Level of disease activity	
High	18 (18.75)
Moderate	35 (36.45)
Low	37 (38.54)
Remission	6 (6.25)

ESR: Erythrocyte Sedimentation Rate, CRP: C-reactive protein, VAS: Visual Analogue Scale, DAS 28: Disease Activity Scale 28

The distribution of lipid parameters including total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglyceride (TG) have been depicted through a series of box plots. (Figure 1)The median value of TC, LDL, HDL and TG were 237.5 mg/dl, 146 mg/dl, 37 mg/dl and 130 mg/ml with a range of 160.00 mg/dL, 100.00 mg/dL, 12.50 mg/dL and 135.00 mg/dL accordingly. The TC and LDL were symmetrically distributed among the RA patients where more patients had higher HDL lower TG. (Figure 1)

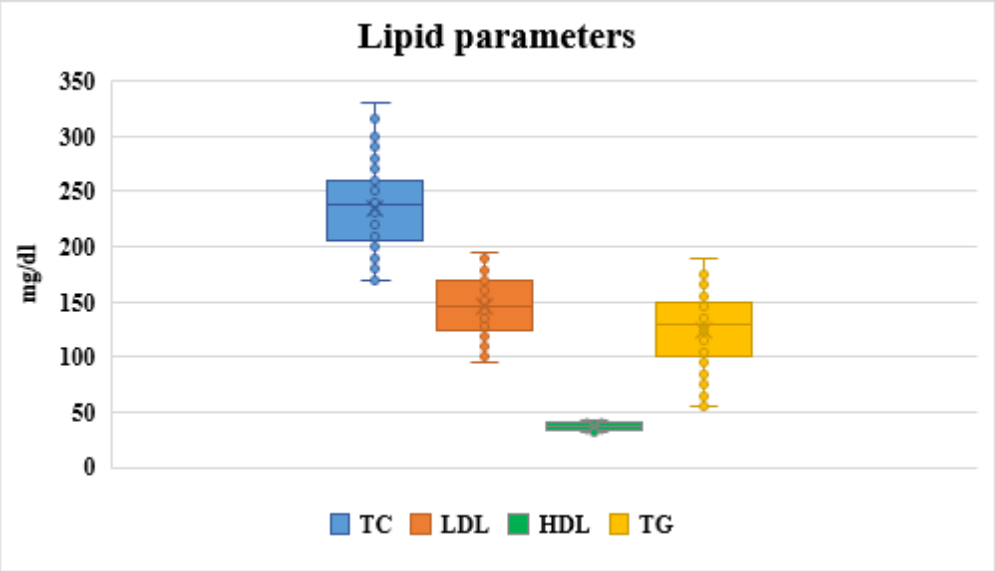

Figure 2: Box plot of lipid parameters among study patients with RA (n=96)

Abnormal lipid parameters were observed as raised TC, raised LDL, decreased HDL, raised TG in 50%, 36.5%, 74%, 25% and 86.5% of patients accordingly. A total of 86.5% of patients had dyslipidemia.

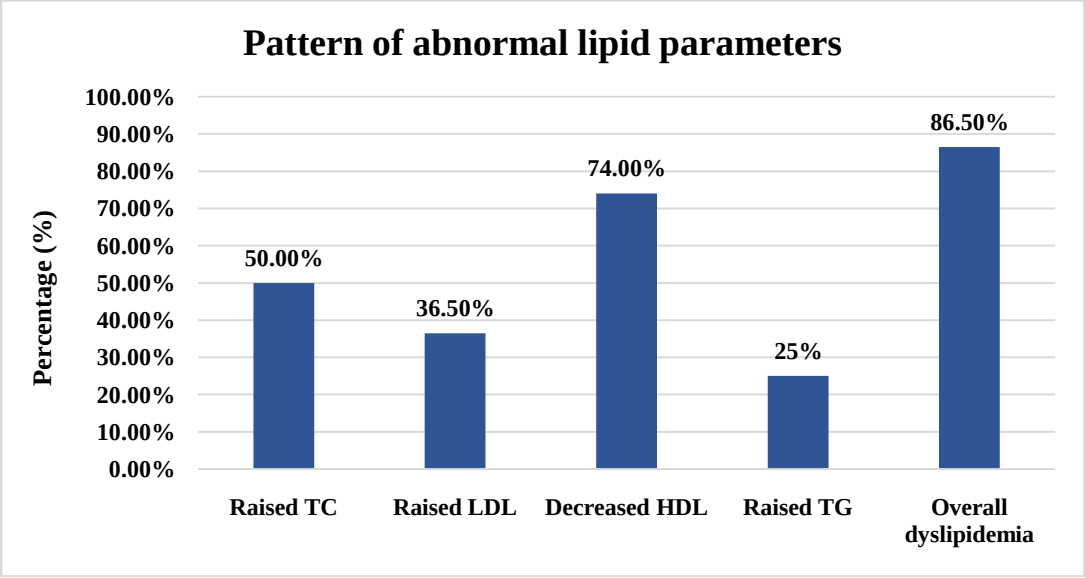

Figure 3a. Pattern and frequency of dyslipidemia among study patients with RA (n=96)

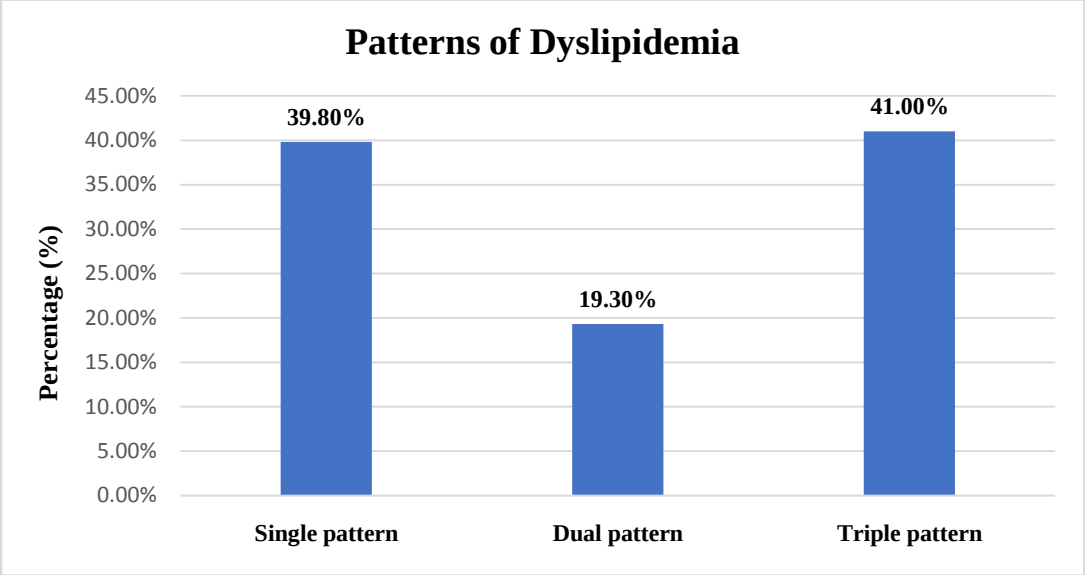

Figure 3b: Pattern of dyslipidemia among study patients with RA (n=96)

Scatter plot diagram showed the linear relationships between lipid parameters das 28 score, ESR and CRP. (Figure 4) BothTC and HDLexhibited significant correlation with DAS 28 score, ESR and CRP. TC showed positive correlation with DAS 28 score (r_s=.302, p<.05), ESR r_s=.322, p<.05) and CRP (r_s=.314, p<.05). HDL showed negative correlation with DAS 28 score (r_s=-.289, p<.05), ESR (r_s=-.357, p<.05) andCRP (r_s=-.339, p<.05). (Figure 4a, 4b, 4c)A significant positive correlation was also observed between TG and CRP (r_s=.302, p<.05). (Figure 4c) p value was determined by spearman's rank test.

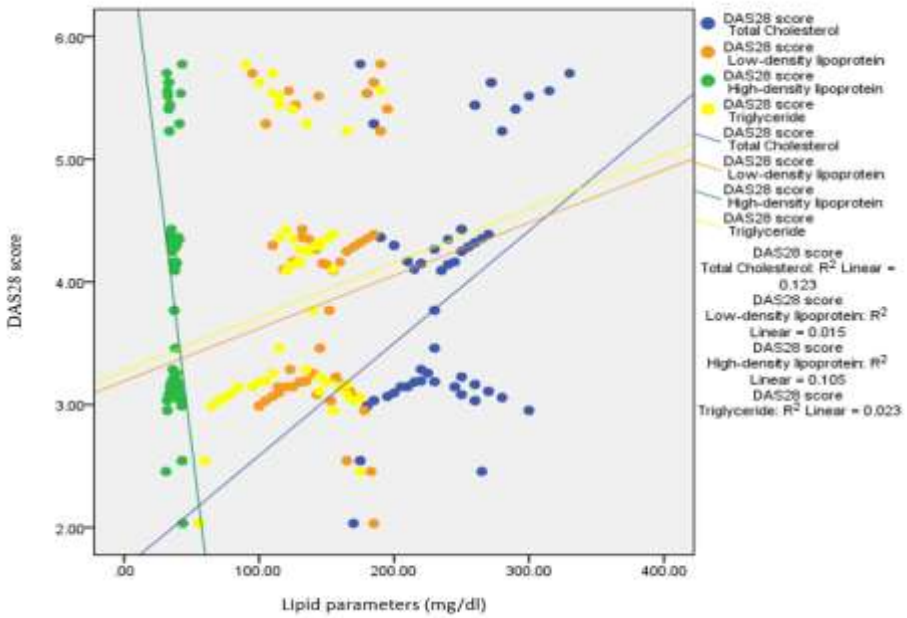

Figure 4a: Scatter plot diagram showing correlation between lipid parameters and DAS28 score (n=96)

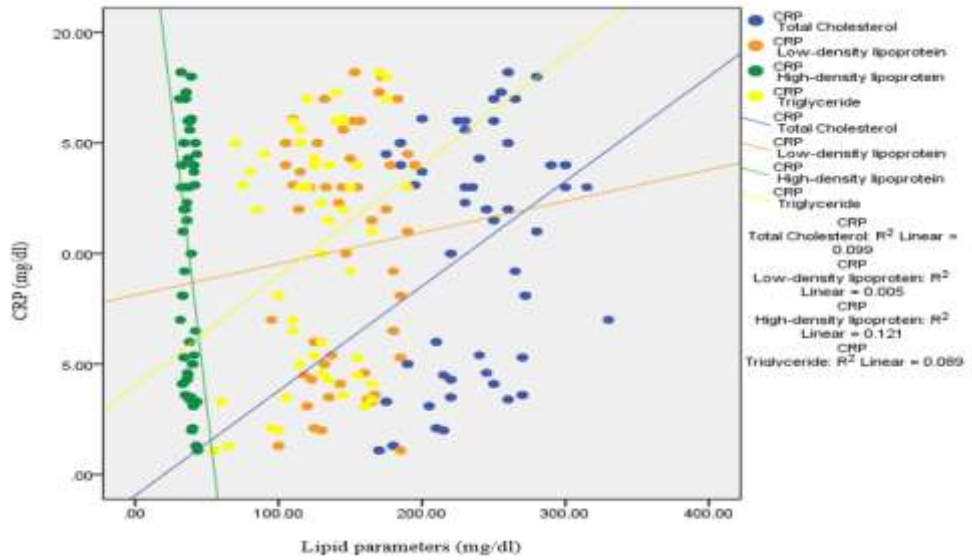

Figure 4b: Scatter plot diagram showing correlation between lipid parameters and CRP (n=96)

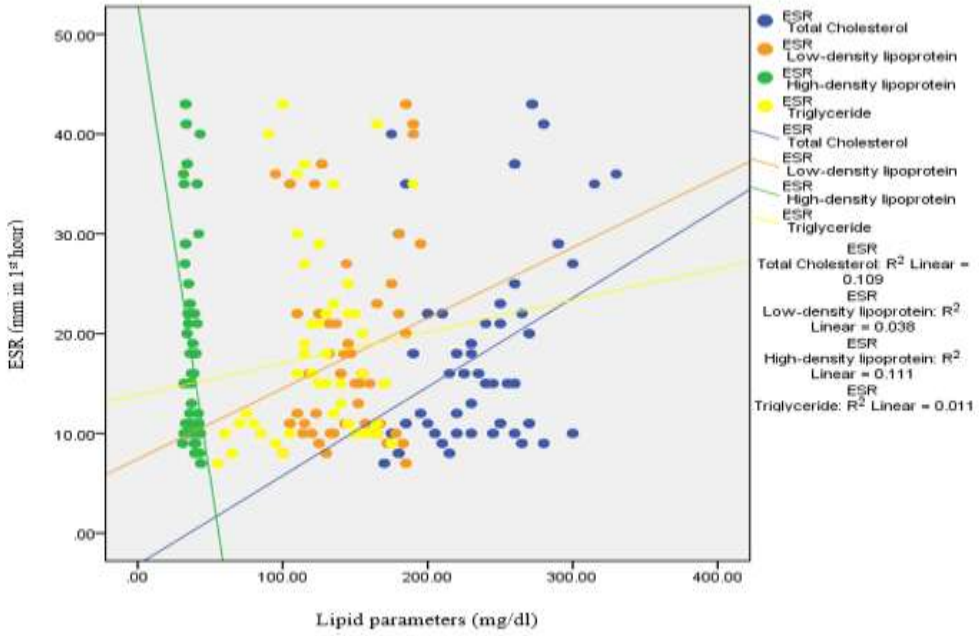

Figure 4c: Scatter plot diagram showing correlation between lipid parameters and ESR (n=96)

IV. Discussion

This hospital based cross-sectional study assessed the lipid parameters of 96 rheumatoid arthritis (RA) patients and revealed a notably high incidence of dyslipidemia, affecting 86.5% of the study patients. Among the various dyslipidemia patterns, the most prevalent was a reduced high-density lipoprotein (HDL), observed in almost three-quarters of the patients. Both of total cholesterol (TC) and HDL showed significant correlation with disease activity (DAS 28 score) and inflammatory markers (ESR and CRP).

The high frequency of dyslipidemia observed in this study highlights the significant impact of RA on lipid metabolism. Lipid levels among RA patients showed inconsistent findings in different studies[8, 13]. High frequency of dyslipidemia and significant correlation between abnormal lipid profile and disease activity was reported in certain studies[14–18]. But in present study a positive correlation was observed between TC and disease activity while a negative correlation was observed between HDL and disease activity. This findings are contrary to some of the previous studies where a higher disease activity level were associated with lower TC and higher HDL[17, 18]. The reasons behind these inconsistency might be the confounding effects of

differences in age, obesity, smoking, gender, sample size, duration and history and duration of receiving treatment for RA, etc.

RA is characterized by chronic inflammation which causes changes in lipid metabolism by altering the production and metabolism of lipoproteins in the liver. In RA, pro-inflammatory cytokines like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha) level increase and interfere with normal lipid metabolism and transport leading to an increased production of TC, and decreased clearance of LDL. Moreover, medication with corticosteroids and disease-modifying antirheumatic drugs (DMARDs), can also affect lipid metabolism by increasing TC and decreasing HDL. Another reason could be the decreased physical activity due to joint pain and stiffness, which may contribute to weight gain and alteration of lipid profiles.This study didn't observe any significant relation of LDL with disease activity and inflammation markers. According to DAS 28 score, almost three-fourth of the study patients had low and moderate disease activity. The demographic profile of study patients revealed a typical RA presentation with middle age and female predominance [16, 19–22].

The relation between lipid parameters anddisease activity in RA patients reflect a complex relationship between inflammation and lipid metabolism in RA. But this study was not beyond limitations.Due to cross-sectional design, this study could not establish any causality in and there might be lack of generalizability in the findings due to single centered sample patients. Future longitudinal and cohort studies are warranted to explore the causal relationship and the impact of RA disease activity on lipid metabolism and cardiovascular risk as well.

The study assessed complexity of the relationship between RA and lipid metabolism in Bangladesh. The findings indicate that clinicians could consider lipid profiles as an integral part of managing RA, especially for the prevention of cardiovascular morbidities.

V. Conclusion

This study observed a higher frequency of dyslipidemia in RA patients along with a positive correlation of high-density cholesterol and total cholesterol with disease activity. The findings indicate the necessity of understanding the lipid paradox mechanism in RA patients of our population through further larger study.

Declarations:

Ethics approval: The study protocol was reviewed and approved by the Ethical Review Committee of Rajshahi Medical College. Ethical issues were maintained in accordance with the Helsinki Declaration.

Consent for publication: none

Availability of data and materials: The data and other necessary details are available and can be found upon reasonable request to the corresponding authors.

Conflict of interest: None

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Investigation: MAH, MAY, MSS, MMR
Formal analysis: MAH, MAY, MSS, MMR
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Supervision: MAH, MAY, MSS, MMR
Writing – original draft: MAR, SKN, DMKR, DMZH
Writing – review & editing: MAH, MAY, MSS, MMR

Use of ChatGPT: ChatGPT 3.5 was used for language editing and to improve clarity of the manuscript.

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