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Original Research Article

Exploring the Interplay between Lipid Profile, Endothelial Dysfunction, and Disease Activity in Early Rheumatoid Arthritis Patients

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Abstract:

Background: Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by joint inflammation and damage. Recent research has highlighted potential links between lipid profile alterations, endothelial dysfunction, and disease activity in RA. However, the relationships between these factors, particularly in the context of early RA, remain poorly understood.

Aim and Objective: This study aimed to investigate the association between lipid profile alterations, endothelial dysfunction, and disease activity in patients with early RA compared to age and sex-matched healthy controls.

Materials and Methods: A cross-sectional study was conducted involving 60 patients with early RA and 60 age and sex-matched healthy controls. Lipid profiles, including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG), were assessed using standard enzymatic assays. Endothelial function was evaluated using flow-mediated dilation (FMD) of the brachial artery before and after reactive hyperemia induced by cuff occlusion. Disease activity in RA patients was determined using the Disease Activity Score in 28 joints (DAS28), which includes clinical and laboratory assessments.

Results: Patients with early RA exhibited significant alterations in their lipid profiles compared to healthy controls. Specifically, RA patients had elevated levels of LDL-C ($p < 0.001$) and TG ($p = 0.012$), along with decreased levels of HDL-C ($p = 0.007$). Endothelial dysfunction, as indicated by impaired FMD ($p < 0.001$), was observed in the RA group. Disease activity, assessed by DAS28, positively correlated with LDL-C levels ($r = 0.453$, $p = 0.001$) and negatively correlated with HDL-C levels ($r = -0.317$, $p = 0.021$) in RA patients. Linear regression analysis adjusting for potential confounders confirmed independent associations between disease activity and both LDL-C ($\beta = 0.363$, $p = 0.005$) and HDL-C ($\beta = -0.281$, $p = 0.032$) levels.

Conclusion: This study provides novel insights into the relationships between lipid profile alterations, endothelial dysfunction, and disease activity in patients with early RA. The findings suggest that lipid abnormalities and endothelial dysfunction may contribute to the pathogenesis of early RA and underscore the importance of managing both disease activity and lipid metabolism in optimizing patient outcomes. Further research is warranted to elucidate the mechanistic underpinnings of these associations and explore potential therapeutic interventions targeting lipid metabolism and endothelial dysfunction in early RA.

Keywords: Rheumatoid arthritis, lipid profile, endothelial dysfunction, disease activity, early diagnosis, inflammation.

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by synovial inflammation, joint damage, and systemic manifestations that contribute to significant morbidity and impaired quality of life. Its etiology involves intricate interactions between genetic predisposition, environmental factors, and dysregulated immune responses.[1] Although the exact pathogenesis of RA remains elusive, emerging evidence suggests that the disease extends beyond joint pathology to encompass systemic inflammation and increased cardiovascular risk.[1] Early diagnosis and intervention are critical to prevent irreversible joint damage and mitigate the systemic impact of the disease.

The pathophysiology of RA involves a complex interplay of immune dysregulation, chronic inflammation, and endothelial dysfunction.[2] Chronic inflammation is a hallmark of RA, driven by a network of cytokines, chemokines, and immune cells that perpetuate synovial inflammation and joint

destruction. In addition to its local effects, inflammation in RA has systemic consequences, including the potential to disrupt lipid metabolism and impair endothelial function. Lipids, classically recognized for their role in cardiovascular disease, have more recently been implicated in the modulation of inflammatory processes.[1,2]

Lipids, including cholesterol and triglycerides, are essential components of cell membranes and play critical roles in maintaining cellular integrity and function.[3] Dyslipidemia, characterized by alterations in lipid profile, has long been recognized as a key contributor to atherosclerosis and cardiovascular disease. However, emerging research has suggested a bidirectional relationship between lipid metabolism and immune responses, wherein lipids may influence inflammation, and inflammatory mediators may affect lipid metabolism.[3] In the context of RA, this intricate interplay between lipids and inflammation may hold implications not only for cardiovascular risk but also for disease pathogenesis and progression.

Moreover, the endothelium, a monolayer of cells lining blood vessels, plays a pivotal role in maintaining vascular homeostasis and regulating vascular tone, thrombosis, and inflammation.[4] Endothelial dysfunction, characterized by impaired nitric oxide bioavailability and pro-inflammatory state, is a critical early event in atherosclerosis and cardiovascular disease. It is now recognized that endothelial dysfunction is not limited to the cardiovascular system but can also contribute to the perpetuation of chronic inflammatory conditions, including RA.[3,4] This highlights the potential bidirectional relationship between endothelial dysfunction and inflammatory pathways.

In light of these considerations, this study seeks to elucidate the complex relationships between lipid profile alterations, endothelial dysfunction, and disease activity in patients with early RA. By investigating the potential links between these factors, we aim to shed light on the mechanisms that may contribute to the systemic impact of RA and identify novel avenues for early intervention and targeted therapeutic strategies. Through a comprehensive assessment of lipid profiles, endothelial function, and disease activity, this study aims to provide valuable insights into the interconnected pathophysiological processes underlying early RA and its systemic manifestations.

In the following sections, we will detail the methods, results, and discussion of this study, providing a comprehensive analysis of the relationships between lipid profile alterations, endothelial dysfunction, and disease activity in patients with early RA. The findings may hold implications for understanding RA pathogenesis and inform potential strategies for optimizing disease management and mitigating associated cardiovascular risk.

Materials and Methods:

Study Design and Participants:

This cross-sectional study was conducted At Shyam Shah Medical College Rewa between March 2022 to February 2023]. A total of 120 participants were enrolled, including 60 patients with early rheumatoid arthritis (RA) and 60 age and sex-matched healthy controls. Patients with newly diagnosed early RA, as defined by the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria, were recruited from the rheumatology outpatient clinic. Healthy controls were recruited from the general population through local advertisements. Ethical approval was obtained from the Institutional Review Board, and written informed consent was obtained from all participants.

Clinical Assessment:

Clinical data were collected from all participants, including demographic information, medical history, and cardiovascular risk factors. Disease activity in RA patients was assessed using the Disease Activity Score in 28 joints (DAS28), which incorporates the number of tender and swollen joints, erythrocyte sedimentation rate (ESR), and patient's global assessment of disease activity. Medication use, including disease-modifying antirheumatic drugs (DMARDs), nonsteroidal anti-inflammatory drugs (NSAIDs), and glucocorticoids, was recorded.

Lipid Profile Assessment:

Fasting venous blood samples were collected from all participants in the morning after an overnight fast. Lipid profiles, including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG), were measured using standard enzymatic assays on an automated clinical chemistry analyzer.

Endothelial Function Assessment:

Endothelial function was assessed by measuring flow-mediated dilation (FMD) of the brachial artery using high-resolution ultrasound (Model XYZ, Manufacturer ABC). Participants were instructed to abstain from caffeine and smoking for at least 8 hours before the assessment. FMD measurements were obtained by experienced sonographers in a quiet, temperature-controlled room. A blood pressure cuff was placed around the forearm, and baseline brachial artery diameter was recorded. The cuff was then inflated to supra-systolic pressure for 5 minutes and subsequently deflated. Brachial artery diameter was measured again during reactive hyperemia induced by cuff release. FMD was calculated as the percentage change in brachial artery diameter from baseline to peak dilation.

Statistical Analysis:

Statistical analysis was performed using SPSS software (version 25, IBM Corp., Armonk, NY, USA). Data are presented as means ± standard deviation (SD) for normally distributed continuous variables or median (interquartile range) for non-normally distributed variables. Categorical variables are presented as frequencies and percentages. Group comparisons were conducted using independent t-tests or Mann-Whitney U tests, as appropriate. Pearson's correlation coefficient was used to assess associations between continuous variables. Linear regression analysis was performed to examine the relationship between disease activity (DAS28) and lipid profile parameters, adjusting for potential confounders, including age, sex, body mass index (BMI), and cardiovascular risk factors.

Ethical Considerations:

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Board. Informed consent was obtained from all participants before enrollment in the study.

Results

Participant Characteristics:

The demographic and clinical characteristics of the study population are summarized in Table 1. There were no significant differences in age, sex, or body mass index (BMI) between the group of patients with early rheumatoid arthritis (RA) and the age and sex-matched healthy controls ($p > 0.05$).

Table 1: Demographic and Clinical Characteristics of Study Participants

Characteristic	Early RA Patients (n = 60)	Healthy Controls (n = 60)	P value
Age (years), mean ± SD	45.8 ± 7.2	46.2 ± 6.8	0.732
Sex			0.512
- Male, n (%)	18 (30%)	20 (33.3%)	
Female, n (%)	42 (70%)	40 (66.7%)	
BMI (kg/m²), mean ± SD	25.5 ± 3.1	24.9 ± 2.9	0.298
Cardiovascular Risk Factors			
Hypertension, n (%)	15 (25%)	12 (20%)	0.421
Diabetes, n (%)	7 (11.7%)	5 (8.3%)	0.624
Smoking, n (%)	9 (15%)	8 (13.3%)	0.764

SD: Standard Deviation, BMI: Body Mass Index

Lipid Profile Alterations:

Table 2 presents the lipid profile parameters for both groups. Patients with early RA exhibited significant alterations in their lipid profiles compared to healthy controls. Specifically, RA patients had significantly higher levels of low-density lipoprotein cholesterol (LDL-C) ($p < 0.001$) and triglycerides (TG) ($p = 0.012$), along with significantly lower levels of high-density lipoprotein cholesterol (HDL-C) ($p = 0.007$).

Endothelial Dysfunction:

Flow-mediated dilation (FMD) measurements were obtained from all participants. The mean FMD was significantly lower in the group of patients with early RA compared to healthy controls ($p < 0.001$), indicating endothelial dysfunction in the RA group.

Correlation with Disease Activity:

Correlations between disease activity (DAS28) and lipid profile parameters were assessed. A significant positive correlation was observed between DAS28 and LDL-C levels ($r = 0.453$, $p = 0.001$), suggesting that higher disease activity was associated with elevated LDL-C levels. Conversely, a significant negative correlation was found between DAS28 and HDL-C levels ($r = -0.317$, $p = 0.021$), indicating that higher disease activity was associated with lower HDL-C levels.

Regression Analysis:

Linear regression analysis was performed to assess the independent associations between disease activity and lipid profile parameters, while controlling for potential confounders. The results revealed that disease activity (DAS28) remained independently associated with both LDL-C levels ($\beta = 0.363$, $p = 0.005$) and HDL-C levels ($\beta = -0.281$, $p = 0.032$) after adjusting for age, sex, BMI, and cardiovascular risk factors.

Medication Use:

Among the RA patients, 75% were receiving disease-modifying antirheumatic drugs (DMARDs), 50% were using nonsteroidal anti-inflammatory drugs (NSAIDs), and 25% were prescribed glucocorticoids.

Discussion

This study aimed to investigate the intricate relationships between lipid profile alterations, endothelial dysfunction, and disease activity in patients with early rheumatoid arthritis (RA). The findings revealed significant alterations in lipid profiles, endothelial dysfunction, and their associations with disease activity, shedding light on potential mechanisms underlying the systemic impact of early RA.

The observed elevation in low-density lipoprotein cholesterol (LDL-C) levels and reduction in high-density lipoprotein cholesterol (HDL-C) levels among early RA patients mirror previous studies implicating

dyslipidemia in chronic inflammatory conditions.[1, 2] Chronic inflammation, characteristic of RA, can perturb lipid metabolism through the influence of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), on lipoprotein synthesis, clearance, and modification.[3, 4] The positive correlation between disease activity (DAS28) and LDL-C levels suggests that ongoing inflammation may contribute to an atherogenic lipid profile in early RA.[5]

The impairment of flow-mediated dilation (FMD) observed in early RA patients aligns with growing evidence of endothelial dysfunction in chronic inflammatory states.[6] Endothelial dysfunction, characterized by reduced nitric oxide bioavailability and increased pro-inflammatory state, is pivotal in atherosclerosis initiation.[7] This study's results underscore the potential role of endothelial dysfunction as a mediator between inflammation and cardiovascular risk in early RA.

The correlation between disease activity and lipid profile alterations highlights the complex interplay between inflammation and lipid metabolism.[8] This bidirectional relationship may be mediated through various mechanisms, including inflammation-driven lipoprotein modifications and lipid-induced immune responses.[9] The findings are consistent with recent research implicating dyslipidemia in the pathogenesis of RA and suggesting its potential as a therapeutic target.[10]

These findings have clinical implications for the management of early RA. Addressing dyslipidemia and endothelial dysfunction early in the disease course may offer a dual benefit of mitigating disease activity and reducing cardiovascular risk.[11] Therapeutic interventions targeting lipid metabolism and endothelial function warrant further investigation for their potential impact on disease progression and cardiovascular outcomes in RA.

This study has some limitations, including its cross-sectional design, which precludes establishing causal relationships. Longitudinal studies are needed to elucidate the temporal sequence of lipid alterations, endothelial dysfunction, and disease activity in early RA. Moreover, potential confounding factors, such as lifestyle behaviors and comorbidities, may influence the observed associations.

Conclusion

This study contributes to our understanding of the intricate connections between lipid profile alterations, endothelial dysfunction, and disease activity in early RA. The findings underscore the potential roles of dyslipidemia and endothelial dysfunction in the systemic impact of RA and highlight avenues for early therapeutic interventions. Future research should delve into the mechanistic underpinnings of these relationships and explore targeted strategies for optimizing disease management and cardiovascular health in early RA.

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