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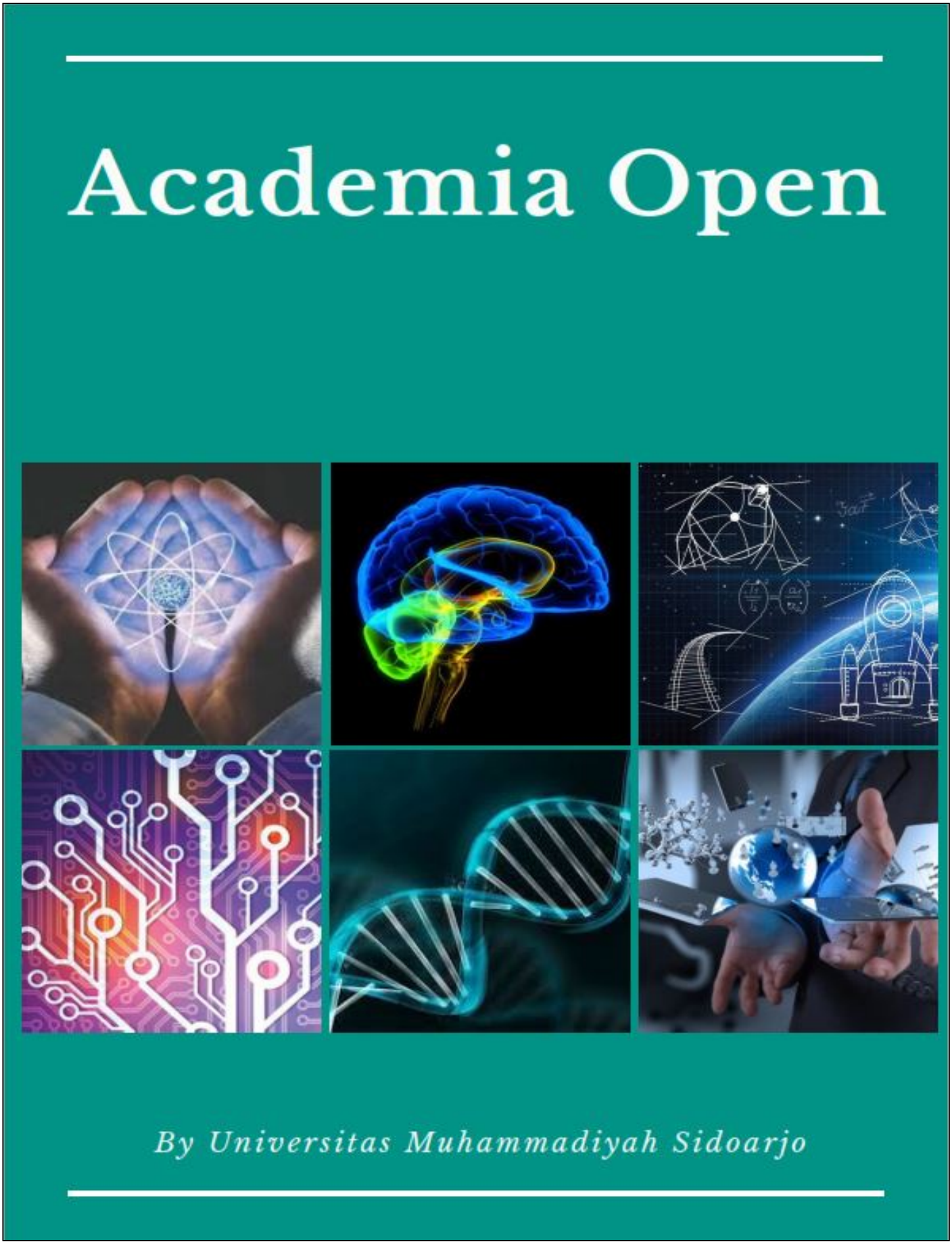

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Lipoprotein Ratios as Biomarkers for Assessing Chronic Atherosclerosis Progression

Rasio Lipoprotein sebagai Biomarker untuk Menilai Perkembangan Aterosklerosis Kronis

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Abstract

General Background: Lipoprotein ratios are critical biomarkers for assessing chronic atherosclerosis progression, providing insights into lipid metabolism imbalances and cardiovascular risk. **Specific Background:** While their role in cardiovascular disease is established, their correlation with inflammatory markers in chronic atherosclerosis remains underexplored. **Knowledge Gap:** Limited studies have comprehensively examined the interplay between lipid dysregulation and systemic inflammation in chronic atherosclerosis. **Aims:** This study evaluates the significance of lipoprotein ratios as biomarkers for chronic atherosclerosis progression and their association with inflammatory markers. **Methods:** A case-control study at Al-Habbobi Teaching Hospital (October 1, 2024 – February 1, 2025) included 60 chronic atherosclerosis patients and 30 healthy controls. Lipoprotein ratios (LDL/HDL, TC/HDL, non-HDL cholesterol) and inflammatory markers (CRP, IL-6, IFN-γ, adiponectin, MCP-1) were analyzed using ELISA, with atherosclerosis severity assessed via intima-media thickness (IMT). **Results:** Patients exhibited significantly elevated BMI, smoking prevalence, hypertension, lipoprotein ratios ($p < 0.001$), and inflammatory markers, indicating chronic inflammation. Lipid dysregulation strongly correlated with inflammation. **Novelty:** This study provides novel evidence linking lipoprotein ratios with inflammatory responses, reinforcing their role as integrated biomarkers. **Implications:** Understanding lipid-immune interactions may improve early diagnosis, risk stratification, and targeted therapy development for chronic atherosclerosis.

Highlights:

1. Lipoprotein ratios and inflammation contribute to chronic atherosclerosis progression.
2. Case-control study analyzing lipoprotein ratios, inflammatory markers, and IMT.
3. Strong correlation between lipid dysregulation, inflammation, and atherosclerosis severity.

Keyword: Lipoprotein Ratios, Chronic Atherosclerosis, Inflammatory Markers, LDL/HDL, Immune Response, Cardiovascular Risk

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Introduction

Atherosclerosis is an inflammatory disease caused by the buildup of lipids and immune cells in arterial walls that can turn into atherosclerotic plaques and lead to vascular dysfunction. This condition of progressive stress, voraciousness and inflammation linked is the leading contributor for cardiovascular diseases (CVDs) such as coronary artery disease (CAD) and stroke, which continue to be among the leading causes of mortality and morbidity worldwide [1]. Especially with the disease being detected and monitored early with lipoprotein ratios and inflammatory biomarkers as potential, non-invasive measures of progress. Including, but not limited to the LDL/HDL ratio, TC/HDL ratio, non-HDL cholesterol, CRP, IL-6 and IFN-γ these biomarkers are important for cardiovascular risk assessment and are visible for chronic pathophysiological process strategies [2]. Lipoproteins are fundamental in transporting cholesterol within the circulation and their homeostasis is an important determinant of atherogenic potential. Conventional lipid risk factors, including low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), have always been utilized to gauge the cardiovascular risk. Nevertheless, lipoprotein ratios enhance the evaluation of lipid metabolism and its impact on atherosclerosis. The LDL/HDL ratio and TC/HDL ratio complement the assessment of atherogenic versus anti-atherogenic lipoproteins [3,4]. The LDL/HDL ratio indicates the balance of atherogenic LDL particles to cardioprotective HDL particles. A significantly increased atherosclerotic burden as well as an increased risk for some cardiovascular events is strongly correlated to a higher LDL/HDL ratio. High concentrations of small dense LDL particles can diffuse across the endothelial barrier, and in the subendothelial space they undergo oxidation, an event associated with inflammatory response and macrophage activation, resulting in foam cell generation and plaque development [5]. Therefore, HDL particles are responsible for reverse cholesterol transport, which takes excess cholesterol out of circulation and the arterial wall. A high LDL/HDL ratio indicates a lipidry profile that promotes accumulation and inflammation, contributing to the progression of atherosclerosis [6]. The total cholesterol to HDL ratio (TC/HDL) is another important measure of cardiovascular risk. It indicates the percentage of total cholesterol that HDL is responsible for transporting, and offers an idea of lipid transport efficiency. An elevated TC/HDL ratio denotes a greater atherogenic potential, since the ratio is an inverse measure of the amount of cholesterol being fractionated to the removal of cholesterol. An increased TC/HDL ratio has been shown in studies to be associated with endothelial dysfunction, increased arterial stiffness and increased oxidative stress, mechanisms leading to chronic atherosclerosis [7,8]. Non-HDL cholesterol, including LDL-C, very low-density lipoprotein cholesterol (VLDL-C) and intermediate-density lipoprotein cholesterol (IDL-C), is the total cholesterol amount in the atherogenic lipoproteins. Contrary to LDL-C on its own, non-HDL cholesterol provides an overall estimation of lipoproteins engaged in plaque formation. High non-HDL cholesterol has been associated with accelerated atherosclerosis and increased cardiovascular risk, especially for patients with metabolic syndrome or diabetes. Non-HDL cholesterol is less influenced by the fasting state and is therefore a good predictor of the progression of atherosclerotic disease [9,10]. C-Reactive Protein (CRP): CRP is an acute-phase reactant produced by the liver in response to systemic inflammation. High CRP levels promote endothelial dysfunction, arterial stiffness, and recruitment of monocytes to atherosclerotic plaques. High-sensitivity C-reactive protein (hs-CRP) is known as a powerful marker of predictive cardiovascular risk, with the higher levels associated with a greater risk of plaque rupture and thrombosis [11,12]. IL-6 is a key pro-inflammatory mediator and involved in atherogenesis. Within atherosclerotic lesions it is produced by macrophages, endothelial cells and smooth muscle cells. IL-6 stimulates adhesion molecules expression, and monocyte infiltration, and drives hepatic CRP synthesis to amplify the inflammatory response. Increased IL-6 has been linked with greater plaque destabilization and increased risk of acute coronary syndromes [13]. IFN-γ is one of the central cytokines in immune and inflammatory regulation and plays a pivotal role in atherosclerosis. It is secreted by T lymphocytes and macrophages, mediating plaque progression through promoting macrophage activation and foam cell formation. IFN-γ further promotes excess production of matrix metalloproteinases (MMPs), leading to degradation of the fibrous cap of atherosclerotic plaques and increasing susceptibility to rupture and thrombosis summary. IFN-γ levels denote increased immune activation and a vulnerable atherosclerotic phenotype [14].

Methodology

A Case control study condected in Al-Habbobi Teaching Hospital between October 1, 2024, to February 1, 2025., and included 90 participants; 60 patients who had chronic atherosclerosis and 30 healthy controls. Sociodemographic data such as added age, gender, smoking status and BMI were noted. Fasting blood samples were taken and kept at −80°C until analysis, and important inflammatory indices like CRP, IL-6, IFN-γ, adiponectin and MCP-1 were quantified utilizing ELISA kits. The severity of atherosclerosis was measured by intima-media thickness (IMT) measurements and lipoprotein ratios. The LDL/HDL ratio was computed by taking the LDL (low-density lipoprotein) level and dividing it by the HDL (high-density lipoprotein) level, with higher levels representing a greater risk for cardiovascular disease according Biolabo (Firance). The TC/HDL ratio was determined by dividing total cholesterol (TC) by HDL, in which higher ratio indicates higher risk for heart disease according Biolabo (Firance). Non-HDL cholesterol was calculated as TC minus HDL, which represents all cholesterol in the blood that is not carried by HDL and elevated non-HDL cholesterol levels are associated with a greater risk of atherosclerosis and cardiovascular diseases.

Statistical analysis

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Statistical analysis is commonly employed to analyze quantitative data, offering methods for describing data and making inferences for both continuous and categorical variables. This procedure involves data collection to test relationships between two data sets. In this study, data are presented as frequencies and percentages. SPSS (version 26) was used, with the dependent and independent t-tests (two-tailed) applied to normally distributed variables. For non-normally distributed variables, the Mann-Whitney U test, Wilcoxon test, and Chi-square test were used. A p-value < 0.05 was considered statistically significant.

Ethical approval

The study was approved by the human ethics committee of Thi-Qar Health Directorate, Al Habbobi Teaching Hospital, Thi-Qar, Iraq, Everyone who took part in the study was told about it and asked to sign a consent form. The patient was also guaranteed that his information would be kept private.

Results and Discussion

Result

Demographic and Clinical Characteristics of Patients and Control Group

The results showed that the mean age of the patients (58.4 ± 8.2 years) was not significantly different from the control group (57.1 ± 7.8 years) (p = 0.47). However, the mean body mass index (BMI) of the patients (29.5 ± 4.2 kg/m²) was significantly higher compared to the control group (27.2 ± 3.6 kg/m²) (p = 0.02). Significant differences were also observed in the percentage of smokers, reaching 40% among the patients compared to 25% in the control group (p = 0.03). In addition, the incidence of hypertension was higher among the patients (55%) compared to the control group (35%), with a significant difference (p = 0.01).

Parameter	Patients (n = 60)	Control (n = 30)	p-value
Gender	Male (n=30) / Female (n=30)	Male (n=15) / Female (n=15)	-
Age (years)	58.4 ± 8.2	57.1 ± 7.8	0.47
BMI (kg/m²)	29.5 ± 4.2	27.2 ± 3.6	0.02*
Smoking (%)	40%	25%	0.03*
Hypertension (%)	55%	35%	0.01*

Table 1. ***Comparison of Age, BMI, Smoking, and Hypertension Prevalence***

Lipid Profile Ratios and Non-HDL Cholesterol Levels in Patients and Control Group

The results showed a significant increase in the LDL/HDL ratio in patients (4.2 ± 1.0) compared to the control group (3.1 ± 0.8) (p < 0.001). The TC/HDL ratio was also significantly higher in the patient group (5.4 ± 1.3) compared to the control group (4.2 ± 1.0) (p < 0.001). In addition, the level of non-high-density lipoprotein cholesterol (Non-HDL Cholesterol) was significantly higher in patients (169.2 ± 32.5 mg/dL) compared to the control group (142.8 ± 27.4 mg/dL) (p = 0.01), indicating the presence of lipid homeostasis disorders in the patients.

Biomarker	Patients (n = 60)	Control (n = 30)	p-value
LDL/HDL Ratio	4.2 ± 1.0	3.1 ± 0.8	<0.001*
TC/HDL Ratio	5.4 ± 1.3	4.2 ± 1.0	<0.001*
Non-HDL Cholesterol (mg/dL)	169.2 ± 32.5	142.8 ± 27.4	0.01*

Table 2. ***Comparative Analysis of LDL/HDL Ratio, TC/HDL Ratio, and Non-HDL Cholesterol***

Inflammatory Biomarkers in Patients and Control Group

The results showed a significant increase in C-reactive protein (CRP) levels in patients (10.3 ± 4.5 mg/L) compared to the control group (2.1 ± 1.2 mg/L) (p < 0.001), reflecting an increased inflammatory response. A significant increase in interleukin-6 (IL-6) levels was also observed in patients (18.2 ± 6.1 pg/mL) compared to controls (4.3 ± 1.4 pg/mL) (p < 0.001), indicating the role of chronic inflammation in the disease. In addition, interferon-gamma (IFN-γ) levels were significantly higher in the patient group (24.1 ± 6.4 pg/mL) compared to the control group (10.7 ± 4.2 pg/mL) (p < 0.001), reflecting an increase in immune activity associated with the disease.

Biomarker	Patients (n = 60)	Control (n = 30)	p-value

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CRP (mg/L)	10.3 ± 4.5	2.1 ± 1.2	<0.001*
IL-6 (pg/mL)	18.2 ± 6.1	4.3 ± 1.4	<0.001*
IFN-γ (pg/mL)	24.1 ± 6.4	10.7 ± 4.2	<0.001*

Table 3. ***Comparative Levels of CRP, IL-6, and IFN-γ***

Correlation Matrix of Lipid Ratios, Inflammatory Biomarkers, and Cytokines

Correlation analysis results showed a strong positive correlation between LDL/HDL ratio and non-HDL cholesterol (r = 0.92), indicating a close association between lipid dysregulation and high LDL cholesterol levels. TC/HDL ratio was positively correlated with both LDL/HDL (r = 0.85) and non-HDL cholesterol (r = 0.88), reflecting the overlapping of lipid dysregulation indicators in cardiovascular assessment. As for inflammatory markers, C-reactive protein (CRP) showed a positive correlation with IL-6 (r = 0.88) and IFN-γ (r = 0.84), confirming the role of inflammation in the pathological condition. IL-6 was also strongly correlated with IFN-γ (r = 0.85), suggesting an interaction between inflammatory and immune factors in the development of the pathological condition.

Parameter	LDL/HDL Ratio	TC/HDL Ratio	Non-HDL Cholesterol	CRP (mg/L)	IL-6 (pg/mL)	IFN-γ (pg/mL)
LDL/HDL Ratio	1	0.85	0.92	0.76	0.80	0.79
TC/HDL Ratio	0.85	1	0.88	0.72	0.78	0.77
Non-HDL Cholesterol	0.92	0.88	1	0.79	0.83	0.81
CRP (mg/L)	0.76	0.72	0.79	1	0.88	0.84
IL-6 (pg/mL)	0.80	0.78	0.83	0.88	1	0.85
IFN-γ (pg/mL)	0.79	0.77	0.81	0.84	0.85	1

Table 4. ***Relationship Between Lipid Profile and Inflammatory Markers***

Discussion

Results are shown in Table 1, with no significant difference in age between patients and controls (p = 0.47); however, significant differences in BMI, smoking, and hypertension were observed. Patients had a significantly higher BMI (29.5 ± 4.2 kg/m²) than controls (27.2 ± 3.6 kg/m², p = 0.02), consistent with studies that have shown that increased BMI is a significant risk factor for cardiovascular diseases and metabolic disorders [15]. Research by Moon et al., (2021), these findings are corroborated by Suhara et al. (2020), where a positive correlation was shown between increasing body mass index (BMI) and the advancement of atherosclerotic disease [16]. But a study by Dehghan et al. (2024) study challenge the use of BMI as a sole indicator of cardiovascular risk, particularly in diverse populations with differing body composition and metabolic profiles [17]. Furthermore, the prevalence of smoking was significantly higher in patients (40%) than controls (25%, p = 0.03), which is in accord with the observations made by Li et al. (2024), who identify smoking as a major contributor to endothelial dysfunction and chronic inflammation. In others, have reported a more attenuated association between smoking and cardiovascular events in older populations, potentially due to survivor bias [18]. Hypertension was also significantly more common in patients (55% vs. 35% in controls, p = 0.01), supporting the known role for elevated blood pressure in the development of cardiovascular disease. This is aligned with the study by Silveira Rossi et al. (2022) reported that hypertension accelerates atherosclerosis by causing endothelial damage and arterial stiffness. The differences observed in the BMI, smoking, and hypertension prevalences are attributable to their protein mediators whose synergistic effect modifies vascular stiffness and endothelial function, producing oxidative stress and enhancing inflammatory pathways that drives the processes of cardiovascular diseases. The findings emphasize the role of lifestyle change, weight loss, stopping smoking, and managing blood pressure levels as key factors influencng CV risk [19,20]. Patients had considerably elevated lipid ratio biomarkers than controls (Table 2). The LDL/HDL ratio was significantly higher in patients (4.2 ± 1.0) as compared with the controls (3.1 ± 0.8), p < 0.001, indicating a more pronounced imbalance between anti-atherogenic and proatherogenic lipoproteins. This is consistent with the findings of Sun et al. (2022) about the association of higher LDL/HDL ratio with chronic atherosclerosis progression and cardiovascular risk [21,22]. Like Kosmas et al.,(2023), we identified a significantly higher TC/HDL ratio among patients (5.4 ± 1.3) than controls (4.2 ± 1.0, p < 0.001). They highlight that this ratio is a better predictor of coronary artery disease than isolated lipid measurements. Some studies, on the other hand, as Yang et al. (2022) Schleicher et al., which demonstrate that although the TC/HDL ratio is a good marker, it may not always be predictive depending on age, sex and metabolic status [23,24]. Non-HDL cholesterol levels were also significantly higher for patients (169.2 ± 32.5 mg/dL) in comparison to controls (142.8 ± 27.4 mg/dL, p = 0.01) further supporting its contribution as an independent predictor of CV. Higher levels in patients are attributed to enhanced accumulation of the atherogenic form of cholesterol within the artery walls and impaired clearance pathways that result in endothelial dysfunction and plaque development. Taken together, these findings suggest that lipoprotein ratios may serve as important biomarkers in predicting severity of atherosclerosis and highlight the potential role of targeting lipids in high-risk populations [25,26]. Results from Table 3 suggest that inflammatory

biomarkers' levels are significantly higher in patients than in controls. Our results reveal that CRP levels were significantly elevated in patients (10.3 ± 4.5 mg/L) as compared to their matched controls (2.1 ± 1.2 mg/L, $p < 0.001$), reflecting the contribution of systemic inflammation in the progression of atherosclerosis. These results are consistent with those from Henein et al. (2022), and that increased CRP levels confer risk for cardiovascular events and indicate active vascular inflammation Likewise, IL-6 levels were substantially increased in patients (18.2 ± 6.1 pg/mL) when compared to controls (4.3 ± 1.4 pg/mL, $p < 0.001$), [27,28]. Validating studies by [29], that associated IL-6 with endothelial dysfunction and plaque instability Some studies, however, like Chen et al. (2021), may be confounded by factors such as metabolic syndrome and obesity that modulate IL-6 levels that may complicate the role of IL-6 in cardiovascular disease. In addition, a higher IFN-γ levels in patients (24.1 ± 6.4 pg/mL) compared to controls (10.7 ± 4.2 pg/mL, $p < 0.001$), suggested its correlation with immune activation and chronic vascular inflammation, as reported by [30]. Elevated levels of these biomarkers in patients imply an elevated inflammatory mediator mediated progression of atherosclerosis involving cytokines mediated endothelial damage and immune cell recruitment. These insights emphasize the need for targeting inflammation in cardiovascular disease management, with novel therapies targeting IL-6 and CRP for cardiovascular risk mitigation [31]. Table 4 shows that lipid profile markers correlate well with inflammatory biomarkers indicating a strong relationship between dyslipidemia and systemic inflammation and atherosclerosis. The correlation between LDL/HDL ratio and non-HDL cholesterol was very high (r=0.92) and moderate with inflammatory markers CRP (r=0.76), IL-6 (r=0.80), and IFN-γ (r=0.79). These results are congruent with studies such as Libby et al. - LDL/HDL ratio is a strong predictor of atherogenic inflammatory response which drives endothelial dysfunction and plaque formation The TC/HDL ratio was strongly correlated with non-HDL cholesterol ($r = 0.88$), and relatively moderately associated with inflammatory markers, supporting its role as a cardiovascular risk predictor. The strong association between non-HDL cholesterol and the inflammatory markers, especially IL-6 ($r = 0.83$) and CRP ($r = 0.79$, confirm the results by [32], indicating that increased non-HDL cholesterol has a role in vascular inflammation and oxidative stress. The close relationship between CRP,IL-6, and IFN-γ (r=0.88andr=0.84, respectively) reflects the avalanche of inflammation among atherosclerosis,and is in agreement with the [33], stressing IFN-γ's role in immune activation and plaque instability [34].

Conclusion

This study emphasizes the crucial role of lipoprotein ratios and inflammatory markers in chronic atherosclerosis progression. Elevated LDL/HDL, TC/HDL, and non-HDL cholesterol indicate lipid imbalance, while higher CRP, IL-6, and IFN-γ levels signify persistent inflammation. These results highlight the connection between lipid metabolism and immune response in disease development, reinforcing their potential as biomarkers for assessing atherosclerosis risk and progression. Understanding this interplay may aid in developing targeted therapeutic strategies

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