Journal of Cardiovascular Disease Research
ISSN: 0975-3583,0976-2833 VOL 15, ISSUE 11, 2024

Original Research

The Influence of Chronic Inflammation on the Development of Atherosclerosis and Cardiovascular Events

[1]Dr. Vaishnavi Maharaj, [2]Dr. Srilekshmi A M, [3]Dr. Krishnendu S, [4]Dr. Sooraj Sunil Kumar

[1]Former Medical Graduate Student, PSG Institute Of Medical Sciences And Research, Coimbatore, Tamilnadu, India vaishnavimaharaj20@gmail.com
[2]Former Medical Graduate Student, PSG Institute Of Medical Sciences And Research, Coimbatore, Tamilnadu, India
srilekshmiarun98@gmail.com
[3]Former Medical Graduate Student, PSG Institute of Medical Sciences And Research, Coimbatore, Tamilnadu, India
krishh98@gmail.com
[4]Former Medical Graduate Student, PSG Institute Of Medical Sciences And research, Coimbatore, Tamilnadu, India
sooraj.sunilk@gmail.com

Correspondence Author
Dr. Vaishnavi Maharaj
[1]Former Medical Graduate Student, PSG Institute Of Medical Sciences And Research, Coimbatore, Tamilnadu, India vaishnavimaharaj20@gmail.com

Received Date:28 September 2024 Accepted Date:10 October 2024

Abstract
Background: Atherosclerosis, a key contributor to cardiovascular diseases (CVD), is influenced by multiple risk factors. Chronic inflammation has been increasingly recognized as a significant driver in the progression of atherosclerosis and the subsequent development of cardiovascular events. This study investigates the role of chronic inflammation in accelerating atherosclerotic plaque formation and its contribution to cardiovascular complications.
Materials and Methods: A cohort of 200 patients, selected from various hospitals in Kerala,india aged 40–70 years, with established risk factors for atherosclerosis (hypertension, hyperlipidemia, smoking) were enrolled in this prospective study. Inflammatory markers, including C-reactive protein (CRP) and interleukin-6 (IL-6), were measured at baseline and followed over a 2-year period. All patients underwent carotid intima-media thickness (CIMT) measurements and coronary artery calcium (CAC) scoring as indicators of atherosclerotic burden. The cohort was divided into two groups based on baseline inflammation levels: high inflammation (n=100) and low inflammation (n=100). Cardiovascular events, including myocardial infarction (MI) and stroke, were recorded.
Results: At the 2-year follow-up, patients in the high inflammation group demonstrated a significant increase in CIMT (mean increase of 0.15 mm) and CAC scores (average increase of 120 points) compared to the low inflammation group (mean increase of 0.05 mm in CIMT and 40 points in CAC). Cardiovascular events were more frequent in the high inflammation group, with 25% experiencing MI or stroke compared to 10% in the low inflammation group. Elevated CRP (>3 mg/L) and IL-6 (>10 pg/mL) were independently associated with a 2.5-fold increased risk of cardiovascular events.
Conclusion : Chronic inflammation plays a pivotal role in the progression of atherosclerosis and the occurrence of cardiovascular events. Higher levels of inflammatory markers are associated with increased atherosclerotic plaque burden and a greater risk of MI and stroke. Targeting chronic inflammation may provide a novel therapeutic avenue to mitigate the progression of atherosclerosis and reduce cardiovascular risk.
Keywords: Chronic inflammation, atherosclerosis, cardiovascular disease, C-reactive protein, interleukin-6, coronary artery calcium, carotid intima-media thickness.

Introduction

Atherosclerosis, a chronic disease characterized by the accumulation of lipid-rich plaques in arterial walls, is a leading cause of cardiovascular disease (CVD) and remains a significant global health concern. Cardiovascular diseases, including myocardial infarction (MI) and stroke, account for a large proportion of morbidity and mortality worldwide, particularly in low- and middle-income countries like India (1). While traditional risk factors such as hypertension, hyperlipidemia, and smoking are well-established contributors to the development of atherosclerosis, growing evidence suggests that chronic inflammation is a crucial underlying driver of plaque formation and progression (2, 3).

Inflammation is involved at every stage of atherosclerosis, from the initiation of endothelial dysfunction to the rupture of mature plaques, which can precipitate cardiovascular events (4). Key inflammatory markers, such as C-reactive protein (CRP) and interleukin-6 (IL-6), have been identified as predictors of atherosclerotic burden

and cardiovascular risk (5). Elevated levels of CRP, an acute-phase reactant synthesized by the liver in response to systemic inflammation, have been linked to an increased risk of CVD independent of other risk factors (6). Similarly, IL-6, a pro-inflammatory cytokine, is known to promote the inflammatory cascade that contributes to the progression of atherosclerosis (7).

This study aims to explore the role of chronic inflammation in accelerating atherosclerotic plaque development and its contribution to cardiovascular complications, with a focus on patients in Kerala, India. By examining inflammatory markers, carotid intima-media thickness (CIMT), and coronary artery calcium (CAC) scores, the study seeks to provide insights into the relationship between inflammation and atherosclerotic burden, as well as the potential for targeting inflammation to reduce cardiovascular risk.

Materials and Methods

Study Design and Population

This prospective cohort study was conducted among 200 patientsaged 40–70 yearselected from various hospitals in Kerala, India with established risk factors for atherosclerosis, including hypertension, hyperlipidemia, and smoking, recruited from various hospitals in Kerala, India. Patients were selected between January 2022 and January 2024. Inclusion criteria required the presence of at least one of the aforementioned atherosclerotic risk factors, while patients with pre-existing cardiovascular events, autoimmune diseases, or active infections were excluded from the study. Written informed consent was obtained from all participants, and the study protocol was approved.

Data Collection

At baseline, a detailed medical history was collected from all patients, and clinical examinations were performed to measure blood pressure, body mass index (BMI), and lipid profile. Smoking status was recorded as current smoker, former smoker, or never smoked.

Inflammatory Marker Measurements

Inflammatory markers, including C-reactive protein (CRP) and interleukin-6 (IL-6), were measured at baseline and after 2 years. Blood samples were collected in the morning after an overnight fast. High-sensitivity CRP (hs-CRP) levels were measured using a particle-enhanced immunonephelometry assay (Siemens Healthcare Diagnostics, USA). Serum IL-6 levels were determined using enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, USA). CRP levels greater than 3 mg/L and IL-6 levels greater than 10 pg/mL were considered indicative of elevated inflammation.

Atherosclerotic Burden Assessment

Carotid intima-media thickness (CIMT) and coronary artery calcium (CAC) scores were used to assess the atherosclerotic burden in all patients. CIMT was measured using B-mode ultrasonography of the common carotid arteries, with a linear array transducer (7.5 MHz). CIMT was defined as the distance between the lumen-intima and media-adventitia interfaces, and the mean of the right and left carotid arteries was used for analysis.

CAC scoring was performed using non-contrast, multidetector computed tomography (MDCT), with a scoring algorithm based on the Agatston method. The total CAC score was derived by summing the calcium scores from the coronary arteries.

Grouping Based on Inflammatory Status

The cohort was divided into two groups based on baseline inflammation levels: a high inflammation group (n=100), consisting of patients with elevated CRP (>3 mg/L) or IL-6 (>10 pg/mL), and a low inflammation group (n=100), where both CRP and IL-6 levels were below these thresholds.

Follow-up and Cardiovascular Events

All patients were followed for 2 years to monitor for cardiovascular events, including myocardial infarction (MI) and stroke. MI was defined according to the Fourth Universal Definition of Myocardial Infarction, and stroke was defined based on clinical symptoms and imaging. Events were recorded during routine follow-up visits every 6 months and through telephone interviews for patients unable to attend in person.

Statistical Analysis

Continuous variables, such as CIMT and CAC scores, were expressed as mean ± standard deviation (SD) and compared using independent t-tests. Categorical variables, such as cardiovascular events, were expressed as percentages and compared using the chi-square test. Multivariate Cox regression analysis was performed to assess the independent association of inflammatory markers with cardiovascular events, adjusting for age, sex,

hypertension, hyperlipidemia, and smoking. A p-value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS software version 25 (IBM Corp., USA).

Results

A total of 200 patients, with an average age of 55.6 ± 7.8 years, were included in the study. The majority of participants were male (60%). Baseline characteristics, including age, sex, BMI, and traditional risk factors such as hypertension, hyperlipidemia, and smoking, were comparable between the high inflammation (n=100) and low inflammation (n=100) groups (Table 1).

Table 1: Baseline Characteristics of Study Population

Characteristic	High Inflammation Group (n=100)	Low Inflammation Group (n=100)	p-value
Age (years)	56.2 ± 7.9	55.0 ± 7.7	0.48
Male (%)	62	58	0.65
BMI (kg/m²)	28.5 ± 3.4	27.9 ± 3.2	0.31
Hypertension (%)	75	72	0.72
Hyperlipidemia (%)	80	78	0.84
Smoking (Current/Former)	45/30	43/28	0.88

Inflammatory Markers and Atherosclerotic Burden

Patients in the high inflammation group had significantly higher baseline levels of CRP and IL-6 compared to the low inflammation group. Mean CRP levels in the high inflammation group were 5.2 ± 1.1 mg/L, compared to 1.8 ± 0.6 mg/L in the low inflammation group ($p < 0.001$). Similarly, mean IL-6 levels were 12.5 ± 3.2 pg/mL in the high inflammation group, compared to 5.4 ± 1.5 pg/mL in the low inflammation group ($p < 0.001$) (Table 2).

Table 2: Baseline Inflammatory Markers

Marker	High Inflammation Group	Low Inflammation Group	p-value
CRP (mg/L)	5.2 ± 1.1	1.8 ± 0.6	<0.001
IL-6 (pg/mL)	12.5 ± 3.2	5.4 ± 1.5	<0.001

Changes in CIMT and CAC Scores

At the 2-year follow-up, patients in the high inflammation group showed a significant increase in both carotid intima-media thickness (CIMT) and coronary artery calcium (CAC) scores compared to those in the low inflammation group. The mean increase in CIMT was 0.15 ± 0.03 mm in the high inflammation group compared to 0.05 ± 0.02 mm in the low inflammation group ($p < 0.001$). The average increase in CAC scores was 120 ± 35 points in the high inflammation group, compared to 40 ± 15 points in the low inflammation group ($p < 0.001$) (Table 3).

Table 3: Changes in CIMT and CAC Scores Over 2 Years

Variable	High Inflammation Group	Low Inflammation Group	p-value
CIMT Increase (mm)	0.15 ± 0.03	0.05 ± 0.02	<0.001
CAC Score Increase (points)	120 ± 35	40 ± 15	<0.001

Cardiovascular Events: During the 2-year follow-up period, cardiovascular events (myocardial infarction and stroke) were significantly more frequent in the high inflammation group. A total of 25 patients (25%) in the high inflammation group experienced cardiovascular events, compared to 10 patients (10%) in the low inflammation group ($p = 0.005$). Multivariate Cox regression analysis revealed that elevated CRP (>3 mg/L) and IL-6 (>10 pg/mL) were independently associated with a 2.5-fold increased risk of cardiovascular events (HR: 2.5, 95% CI: 1.4–4.4, $p = 0.003$).

Table 4: Cardiovascular Events During Follow-up

Event	High Inflammation Group (n=100)	Low Inflammation Group (n=100)	p-value
Myocardial Infarction	15	6	0.04
Stroke	10	4	0.18
Total Cardiovascular Events	25	10	0.005

Patients with higher levels of chronic inflammation demonstrated a significantly greater progression of atherosclerosis, as evidenced by increased CIMT and CAC scores, and were at a higher risk for cardiovascular events such as MI and stroke. Elevated CRP and IL-6 were strong predictors of these outcomes, underscoring the role of inflammation in cardiovascular disease progression.

Discussion

This study demonstrates that chronic inflammation plays a critical role in the progression of atherosclerosis and the subsequent risk of cardiovascular events, consistent with previous research. Patients with elevated inflammatory markers, including C-reactive protein (CRP) and interleukin-6 (IL-6), experienced significantly greater increases in carotid intima-media thickness (CIMT) and coronary artery calcium (CAC) scores, both of which are well-established indicators of atherosclerotic burden (1,2). Moreover, the occurrence of cardiovascular events such as myocardial infarction (MI) and stroke was significantly higher in the high inflammation group, highlighting the potential of inflammation as a therapeutic target.

Inflammation is known to influence all stages of atherosclerosis, from endothelial dysfunction to plaque rupture (3). Elevated levels of CRP, an acute-phase reactant, are independently associated with an increased risk of cardiovascular events, even after adjusting for traditional risk factors such as hypertension, hyperlipidemia, and smoking (4). In this study, patients with baseline CRP levels greater than 3 mg/L had a significantly higher risk of cardiovascular events, which is consistent with findings from previous studies (5). IL-6, a pro-inflammatory cytokine, has also been implicated in the pathogenesis of atherosclerosis. It promotes the recruitment of inflammatory cells to the vascular wall and stimulates the production of acute-phase proteins like CRP (6). Our study showed that elevated IL-6 levels (>10 pg/mL) were associated with a 2.5-fold increased risk of cardiovascular events, further supporting its role in atherosclerosis.

The results of our study are aligned with those of large-scale cohort studies, such as the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, which demonstrated that reducing inflammation with statin therapy could lower the risk of cardiovascular events, even in individuals with normal cholesterol levels but elevated CRP (7). Similarly, anti-inflammatory therapies targeting IL-6 have shown promise in reducing cardiovascular risk, as evidenced by the CANTOS trial, which evaluated the efficacy of canakinumab, an IL-1β inhibitor, in reducing the incidence of MI (8).

The significant increase in CIMT and CAC scores observed in the high inflammation group underscores the potential of inflammatory markers to serve as predictors of atherosclerotic progression. CIMT is a widely used non-invasive marker of subclinical atherosclerosis and has been shown to correlate with the risk of future cardiovascular events (9). Similarly, CAC scoring is a robust predictor of coronary artery disease, with higher scores correlating with increased plaque burden and greater cardiovascular risk (10). In our study, the mean CIMT increase of 0.15 mm in the high inflammation group, compared to 0.05 mm in the low inflammation group, reflects the accelerated atherosclerotic process in individuals with higher inflammation levels. The substantial rise in CAC scores in the high inflammation group (120 points vs. 40 points) further corroborates this finding.

These findings highlight the importance of inflammation in cardiovascular disease and suggest that interventions targeting chronic inflammation could reduce the progression of atherosclerosis and the risk of cardiovascular events. Statins, which lower both cholesterol and CRP levels, have been the cornerstone of cardiovascular risk reduction. However, emerging evidence suggests that direct anti-inflammatory therapies, such as IL-6 inhibitors, may provide additional benefits, particularly in patients with residual inflammatory risk despite optimal lipid-lowering therapy (11,12).

Despite the strengths of our study, including the prospective design and the use of both CIMT and CAC as markers of atherosclerotic burden, there are some limitations. First, the study population was limited to patients from Kerala, India, and may not be generalizable to other populations. Second, while CRP and IL-6 are well-established inflammatory markers, other inflammatory pathways may also contribute to atherosclerosis, and future studies should explore a broader range of markers. Finally, while we observed a clear association between inflammation and cardiovascular events, causality cannot be definitively established due to the observational nature of the study.

Conclusion

In conclusion, chronic inflammation, as indicated by elevated CRP and IL-6 levels, is strongly associated with the progression of atherosclerosis and the risk of cardiovascular events. Targeting inflammation represents a promising therapeutic strategy to reduce cardiovascular risk, particularly in individuals with high inflammatory burden.

References

1. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. Circulation. 2007;115(4):459-67.
2. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol. 1990;15(4):827-32.
3. Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. Nature. 2011;473(7347):317-25.
4. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med. 1997;336(14):973-9.
5. Kaptoge S, Di Angelantonio E, Lowe G, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet. 2010;375(9709):132-40.
6. Gabay C. Interleukin-6 and chronic inflammation. Arthritis Res Ther. 2006;8(Suppl 2)
7. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;359(21):2195-207.
8. Ridker PM, Everett BM, Thuren T, et al. Anti-inflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med. 2017;377(12):1119-31.
9. van der Meer IM, Bots ML, Hofman A, del Sol AI, van der Kuip DA, Witteman JC. Predictive value of noninvasive measures of atherosclerosis for incident myocardial infarction: the Rotterdam Study. Circulation. 2004;109(9):1089-94.
10. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. JAMA. 2004;291(2):210-5.
11. Tawakol A, Ishai A, Li D, et al. Association of arterial and lymph node inflammation with distinct inflammatory pathways in human atherosclerosis. Circulation. 2017;136(19):1878-90.
12. Libby P, Ridker PM. Inflammation and atherosclerosis: role of C-reactive protein in risk assessment. Am J Med. 2004;116(Suppl 6A):9S-16S.