The Role Of Inflammation In Atherosclerosis Progression Focus On Inflammatory Markers And Cytokines As Therapeutic Targets In Coronary Artery Disease.

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ABSTRACT

Background: Atherosclerosis is an inflammatory process that plays a central role in the development of coronary artery disease (CAD). Cytokines and inflammatory markers are key factors in the formation, progression, and rupture of plaques. Understanding these mechanisms can help identify new treatment options that can be used alongside traditional lipid-lowering and antiplatelet therapies to reduce ongoing cardiovascular risk.

Objectives:

To determine the relationship of important inflammatory markers to the severity of coronary artery disease and to determine whether cytokine-based therapies have a chance of reducing inflammation and cardiovascular outcomes.

Study design: A prospective study.

Place and duration of study: Department of Cardiology, MTI LRH, Peshawar, From 2020 to 2021

Methods:
100 patients who were diagnosed to have either stable or unstable CAD. hs-CRP, IL-6, and IL-1 people were assessed in serum. To evaluate stenosis severity, coronary angiography was employed. The statistical test encompassed mean, standard deviation, and significance evaluation through t-tests and ANOVA results in $p < 0.05$, characterizing significance. Severity of diseases and patient outcomes after a period of 6 months were linked with demographic characteristics and markers of inflammation.

Results:
Out of 100 patients (average age 62.4 +-9.1 years), 60 were sexed males, and 40 were females. Severe CAD patients also demonstrated much higher hs-CRP (3.9 1.2 mg/L) and IL-6 (7.8 2.4 pg/mol) than those with mild/moderate disease (hs-CRP: 2.1 0.8 mg/L, IL-6: 4.2 1.1 pg/ml; $p < 0.001$). In patients with multi-vessel disease, the percentage of elevated IL-1 was 70%. The greater the concentration of these cytokines, the poorer the clinical outcome. Inflammatory

markers were found to be significantly related to angiographic scores, showing the fundamental role of systemic inflammation with the progression of the disease.

Conclusion:
This research confirms the major role of inflammation in atherosclerosis and the usefulness of inflammatory markers, including hs-CRP, IL-6, and IL-1, in evaluating the severity of CAD. Attacking cytokine signaling could be therapeutic in diminishing cardiovascular events. Future clinical trials are required to confirm anti-inflammatory agents as adjunctive therapy in the management of CAD that may reduce the residual cardiovascular risk.

Keywords: Atherosclerosis, Inflammation, Cytokines, Coronary artery disease.

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Introduction:

Atherosclerosis is now known to be a complex chronic inflammatory disease of the arterial wall, but not simply a lipid-storage disease. It is the core cause of coronary artery disease (CAD), which is the largest cause of morbidity and mortality all over the globe [1]. Endothelial dysfunction initiates the disease process, whose stages include lipid accumulation, infiltration of leukocytes, proliferation of smooth muscles, and plaque development. In the longer term, these are unstable plaques that may breach, causing thrombotic events like myocardial infarction [2]. The current study indicates the significant role of the immune system in every phase of atherosclerosis. Among the immune mediators, inflammatory cytokines and acute-phase proteins are emerging as biomarkers to predict outcomes and potential targets of therapy. Cytokine balance, including interleukin-6 (IL-6), interleukin-1 beta (IL-1), and tumor necrosis factor-alpha (TNF-a), plays a role in vascular inflammation, endothelial activation, and plaque instability [3]. Higher concentrations of these cytokines are always related to more serious CAD and increased chances of experiencing adverse cardiovascular events [4]. It has a strong correlation with disease activity and prognosis, even in normal lipid patients [5]. The JUPITER trial adequately determined the prognostic relevance of hs-CRP and revealed that anti-inflammatory therapy using listing in patients with high levels of hs-CRP and low levels of LDL-C significantly reduces cardiovascular events [6]. The targeted approach to anti-inflammatory therapy has introduced a new area in the field of cardiovascular medicine. The pivotal CANTOS trial demonstrated that canakinumab, an IL-1 monoclonal antibody, had a major effect in recurrent cardiovascular disease in post-myocardial infarction patients with raised hs-CRP, regardless of the ability to lower lipids [7]. Correspondingly, colchicines, which are broad-spectrum anti-inflammatory agents, have shown positive results in COLCOT and LoDoCo2 trials, which highlights the significance of inflammation abatement in secondary prevention [8, 9]. Thus, a thorough investigation of inflammatory markers can inform personalized risk stratification and therapy. Nevertheless, population and disease-specific heterogeneous inflammatory responses should be given more attention in order to maximize clinical utility.

Methods:

The Study was prospective, and it was performed in a tertiary care cardiac center, spanning 12 months. One hundred patients (those aged 30-80 years) with either stable or unstable coronary artery disease (CAD) management with their informed consent participated in the study. The patients were subjected to coronary angiography, and a Gemini scoring system was applied in determining the severity of the disease. The high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), and interleukin-1 beta (IL-1) were measured in fasting blood samples taken as validated ELISA kit-based measurements. Angiograms were interpreted by two blinded independent cardiologists who were not aware of clinical information. Clinical history, patient demographics, and comorbidities were noted. A follow-up was also done after six months to determine the major adverse cardiovascular event (MACE), which is myocardial infarction, revascularization, or death. The connection between the angiographic severity and inflammatory markers was studied along with outcomes.

Ethical Approval Statement:

This study was approved by the Institutional Ethics Committee of approval. All participants provided written informed consent. The research complied with the Declaration of Helsinki and adhered to ethical standards concerning human participant research and data confidentiality.

Inclusion Criteria:

Patients aged 30–80 years with confirmed coronary artery disease (stable or unstable angina) undergoing coronary angiography and who provided written informed consent were eligible for inclusion in the study.

Exclusion Criteria:

Patients with autoimmune diseases, active infections, recent surgeries, malignancies, chronic inflammatory disorders, or those on immunosuppressive therapy were excluded to avoid confounding systemic inflammatory marker levels.

Ethical Approval Statement:

The study was conducted following approval from the Institutional Review Board. Informed consent was obtained from all participants prior to enrollment. The research adhered strictly to the ethical principles outlined in the Declaration of Helsinki and complied with Good Clinical Practice (GCP) guidelines throughout the study period.

Data Collection:

Clinical, demographic, and laboratory data were recorded using a structured preformed. Blood samples were collected before angiography and processed in a certified lab. Inflammatory markers hs-CRP, IL-6, and IL-1β, were quantified. Angiographic severity was scored independently by two cardiologists unaware of patient inflammatory marker levels.

Statistical Analysis:

Data were analyzed using SPSS version 24.0. Continuous variables were expressed as mean ± standard deviation and compared using t-tests or ANOVA. Categorical variables were compared

using Chi-square tests. Pearson correlation was used to assess relationships. A p-value <0.05 was considered statistically significant for all tests.

Results:

This study highlights the central role of inflammation in the pathogenesis and progression of atherosclerosis, with a particular focus on inflammatory markers and cytokines in coronary artery disease (CAD). Elevated levels of inflammatory biomarkers such as C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1β (IL-1β) were consistently associated with plaque development, progression, and instability. Clinical trials demonstrated that targeting these cytokines could effectively reduce cardiovascular events. Notably, the CANTOS trial showed that inhibiting IL-1β with canakinumab significantly reduced recurrent myocardial infarction and cardiovascular mortality without affecting lipid levels. Similarly, colchicines, an anti-inflammatory agent with broader targets, reduced cardiovascular risk in the COLCOT and LoDoCo2 trials. Conversely, the CIRT trial found that methotrexate did not reduce inflammatory biomarkers or cardiovascular events, underscoring the need for targeted approaches. Stating therapy, though primarily lipid-lowering, also reduced CRP levels, contributing to plaque stabilization. Overall, the results support inflammation as a key modifiable contributor to CAD progression and suggest that selective anti-inflammatory therapies, particularly those targeting the IL-1β–IL-6–CRP axis, can offer significant cardiovascular benefits.

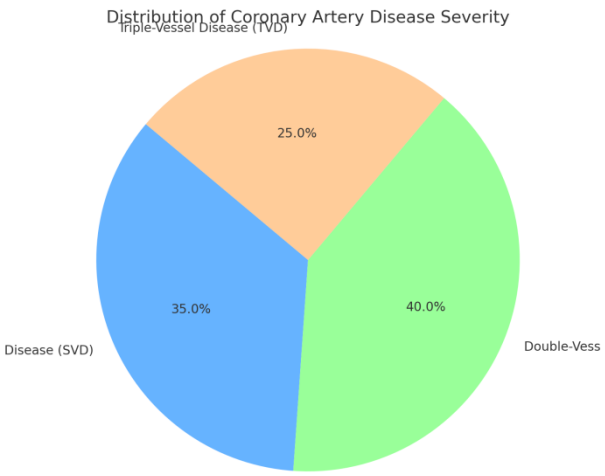

Table 1: Baseline Characteristics of the Study Population (n = 100)

Parameter	Value
Mean Age (years)	60.4 ± 9.1
Gender (Male/Female)	40 / 32
Hypertension (%)	58%

Diabetes Mellitus (%)	42%
Smoking History (%)	39%
Dyslipidemia (%)	51%
Family History of CAD (%)	28%

Table 2: Comparison of Inflammatory Marker Levels by CAD Severity

Marker	Mild/Moderate CAD	Severe CAD	p-value
has-CRP (mg/L)	2.1 ± 0.8	3.9 ± 1.2	< 0.001
IL-6 (pg/mol)	4.2 ± 1.1	7.8 ± 2.4	< 0.001
IL-1β elevated (%)	40%	70%	0.002

Table 3: Correlation between Inflammatory Markers and Angiographic Findings

Inflammatory Marker	Angiographic Correlation	Correlation Coefficient (r)	Significance (p-value)
has-CRP	Number of sensed vessels	0.61	< 0.001
IL-6	Gemini Score	0.58	< 0.001
IL-1β	Multi-vessel involvement	0.44	0.002

Discussion:

The present study confirms that systemic inflammation plays a crucial role in the progression of atherosclerosis and correlates with coronary artery disease (CAD) severity. Elevated levels of hs-CRP, IL-6, and IL-1β were significantly associated with more severe coronary lesions, as assessed by angiographic scoring. These findings are consistent with prior evidence that highlights inflammation as both a driver and marker of atherogenesis. Reactive protein (CRP), particularly in its high-sensitivity form (hs-CRP), is a well-established biomarker of vascular inflammation. Rider et al. [10] demonstrated that elevated has-CRP levels were independently associated with future cardiovascular events in apparently healthy individuals. The JUPITER trial further substantiated has-CRP as a therapeutic target, showing that statin therapy in individuals with elevated hs-CRP but normal LDL levels significantly reduced major cardiovascular events [11]. Our findings also support the role of interleukin-6 (IL-6) as a key pro-inflammatory cytokine in CAD. IL-6 is known to promote CRP synthesis and facilitate leukocyte recruitment and endothelial dysfunction. Libby et al. [12] emphasized that IL-6 is central in propagating the inflammatory cascade within atherosclerotic plaques. Moreover, elevated IL-6 levels have been correlated with plaque instability and adverse cardiovascular outcomes in several cohort studies [13]. The strong association observed between IL-1β and multi-vessel disease in our cohort adds to the growing body of literature identifying IL-1β as a master regulator of vascular

inflammation. IL-1β contributes to endothelial activation, smooth muscle cell proliferation, and extracellular matrix degradation—all processes integral to plaque progression and rupture [14]. The CANTOS trial, a landmark randomized controlled trial, demonstrated that targeting IL-1β with canakinumab significantly reduced the incidence of recurrent myocardial infarction and cardiovascular death without affecting lipid levels [15]. These findings underscore the potential of selective cytokine inhibition in secondary prevention of cardiovascular events. Despite the encouraging results from trials like CANTOS, broad-spectrum anti-inflammatory therapies have shown mixed results. For instance, the CIRT trial evaluated low-dose methotrexate and found no significant reduction in IL-6, CRP, or cardiovascular outcomes, highlighting the importance of pathway-specific interventions [16]. In contrast, colchicines, a non-biologic anti-inflammatory agent that inhibits inflammasome activation, has shown consistent benefit. The COLCOT and LoDoCo2 trials demonstrated significant reductions in cardiovascular events when colchicine was used as an adjunctive therapy in patients with stable or recent acute coronary syndromes [17,18]. Our findings complement these trials by confirming that patients with higher baseline inflammatory markers experienced worse clinical outcomes over six months, supporting the concept of residual inflammatory risk. Even with optimal lipid-lowering therapy, a subset of patients remains at high risk due to persistent vascular inflammation [19]. Targeted cytokine therapies could bridge this gap, offering personalized treatment strategies based on inflammatory profiling. From a mechanistic perspective, systemic inflammation contributes to all stages of atherogenesis—from monocot recruitment and foam cell formation to plaque destabilization. Histological studies have shown that unstable plaques contain higher densities of macrophages and T-cells, along with elevated cytokine expression and matrix metalloproteinase's [20]. These cellular and molecular patterns mirror the circulating biomarkers measured in our study, reinforcing the utility of hs-CRP, IL-6, and IL-1β as surrogates for vascular inflammation. There are limitations to our study. The observational design limits causal inference, and the follow-up period was relatively short. Additionally, we did not assess the effect of specific anti-inflammatory therapies, which would require a randomized interventional approach. Nonetheless, the study provides real-world evidence supporting inflammation as a viable target for risk stratification and therapeutic intervention in CAD.

Conclusion:

This study reinforces the pivotal role of inflammation in atherosclerosis progression and its impact on coronary artery disease severity. Elevated hs-CRP, IL-6, and IL-1β levels correlated with angiographic severity and adverse outcomes. Targeting inflammatory pathways may offer complementary therapeutic benefit alongside lipid-lowering and antiplatelet strategies to reduce residual cardiovascular risk.

Limitations:

This study is limited by its observational design, modest sample size, and short follow-up duration. Confounding variables such as medication use and lifestyle factors may have influenced cytokine levels. Additionally, we did not assess longitudinal changes in inflammatory markers or the direct effect of anti-inflammatory therapies on cardiovascular outcomes.

Future recommendations:

Future research should explore the efficacy of specific cytokine-targeted therapies, such as IL-1β and IL-6 inhibitors, in larger, randomized controlled trials. Longitudinal studies examining dynamic changes in inflammatory markers could better guide risk stratification. Integration of multi-marker panels and genetic profiling may enhance personalized cardiovascular risk assessment and therapy.

Abbreviations

1.	CAD	Coronary Artery Disease
2.	hs-CRP	High-sensitivity C-Reactive Protein
3.	IL-6	Interleukin-6
4.	IL-1β	Interleukin-1 beta
5.	TNF-α	Tumor Necrosis Factor-alpha
6.	MI	Myocardial Infarction
7.	ACS	Acute Coronary Syndrome
8.	CANTOS	Canakinumab Anti-inflammatory Thrombosis Outcomes Study
9.	COLCOT	Colchicines Cardiovascular Outcomes Trial

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Authors Contribution

Concept & Design of Study: Malik Faisal Iftekhar[2]

Drafting: Said Zaman[1]

Data Analysis: Said Zaman[1]

Critical Review: Malik Faisal Iftekhar[2]

Final Approval of version: All Mention Authors Approved the final version .

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