ISSN 2664-8075 (Print) & ISSN 2706-5774 (Online)
South Asian Research Journal of Applied Medical Sciences
Abbreviated Key Title: South Asian Res J App Med Sci

| Volume-7 | Issue-3 | May-Jun- 2025 | **DOI: https://doi.org/10.36346/sarjams.2025.v07i03.003**

Review Article

The Role of Inflammation in Atherosclerosis: Pathophysiology and Therapeutic Approaches

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Article History
Received: 13.04.2025
Accepted: 20.05.2025
Published: 23.05.2025

Abstract: This review investigates the central role of inflammation in atherosclerosis, the chronic inflammatory disease underlying cardiovascular morbidity and mortality. The aim is to summarize the current knowledge about the role of inflammation in atherosclerosis and the therapeutic strategies against inflammation. A systematic review was performed in PubMed, Scopus, and Web of Science articles between 2010 and December 2024. Thirty-six studies focusing on inflammatory pathways, biomarkers, and anti-inflammatory therapy for treatment in clinical trials were included in the search. The principal findings have been that oxidised low-density lipoprotein (LDL) promotes endothelial dysfunction leading to EmD, by inducing an inflammatory cascade with monocytes, macrophages and T-cells involvement. Pro-inflammatory cytokines, including IL-1β and TNF-α play a part in exacerbating plaque progression, with CRP used as a clinical marker. Canakinumab Anti-inflammatory therapies such as canakinumab may be beneficial in decreasing cardiovascular (CV) events but the delicate balance between efficacy and safety is yet to be established. The review points out that the therapeutic potential for the manipulation of these pathways is low-hanging fruit, but notes that gaps in the knowledge base and conflicting reports on long-term outcomes and patient-specific responses call for further research. Ongoing future strategies include personalized medicine and new antimediatory agents to enhance clinical outcome.

Keywords: Atherosclerosis; inflammation; cytokines; C-reactive protein; anti-inflammatory therapy; cardiovascular disease; endothelial dysfunction; plaque progression.

INTRODUCTION

Background

Atherogenesis, the major cause of cardivascular diseases (CVDs), is defined as the accumulation of lipid-rich plaques in the arterial walls, resulting in myocardial infarct and stroke r [1]. Formerly considered a simple disorder of lipid storage, atherosclerosis is now considered as an inflammatory disease [2]. The cascade starts with endothelial dysfunction induced by oxidized LDL, hypertension, or smoking, leading to upregulation of adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1) [3]. This promotes monocyte homing, differentiation to macrophages, and foam cell generation, which contribute to the growth of plaque [4]. The major inflammatory mediators IL-1β, TNF-α and IL-6 maintain a pro-inflammatory state, destabilize plaque and promote the risk of rupture [5]. Recent imaging and biomarker research has highlighted the importance of inflammation, with hsCRP emerging as a predictor of cardiovascular events [6]. Anti-inflammatory treatments, including IL-1β inhibitors have demonstrated clinical efficacy but have been incompletely incorporated into routine care [7]. Such pathways are important to be appreciated if we are to have any form of focused therapeutic intervention.

Importance and Relevance

Atherosclerosis is responsible for around 50% of mortality in developed nations, and inflammation leads atherosclerosis pathogenesis and complications [8]. The global CVD burden runs into billions for the health care system, and the need to address inflammation cannot be overemphasized [9]. Unlike classical lipid-lowering interventions, inflammation targeted therapy could be used to avoid plaque disruption and, subsequently, residual cardiovascular risk

[10]. Trials such as CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcome Study) have shown the potential of anti-inflammatory agents [11] but questions about the long-term safety and cost-effectiveness of these drugs still persist. This review will be of interest to clinicians, researchers, and policymakers as they work to decrease the burden of CVD with new treatments.

Scope and Objectives

The aim of this review is to provide a systematic assessment of the inflammatory implication in atherosclerosis, from pathophysiological to therapeutic perspectives. Specific aims include (1) clarifying the main inflammatory pathways involved, (2) investigating the role of biomarkers such as hsCRP, (3) appraising the use of anti-inflammatory interventions, and (4) highlighting research priorities. Coverage includes molecular pathogenesis, medical research, and treatment developments through December 2024, although non-inflammatory aspects of atherosclerosis were excluded.

Literature Selection

A systematic methodology was used to screen literature according to the PRISMA criteria. Databases (PubMed, Scopus, Web of Science) were explored for terms that included "atherosclerosis," "inflammation," "cytokines," and "anti-inflammatory therapy." The eligible criteria for included studies: (1) peer-reviewed articles, clinical trials, and reviews published in English from 2010 to December 2024. Studies using animals and those without primary data were excluded. Screening of titles, abstracts and full texts for relevance and quality resulted in 36 studies for inclusion from 1,234 initial results to provide a strong evidence base.

Type of Review

This was a systematic relatively review, attempting to derive valid information for organized analysis of inflammation in atherosclerosis. This systematic approach differs from narrative reviews, which could be less rigorous, and scoping reviews, which provide an overview of the literature in a broader sense. The process were based on pre-specified inclusion criteria, systematic data extraction with quality assessment using the Newcastle-Ottawa scale for observational studies and the Cochrane Risk of Bias for trials [12]. This method of analysis tends to reduce bias, as well as improve reliability - a feature that is desirable in the evaluation of pathophysiological and treatment related data.

Pathology of Inflammation in Atherosclerosis

Summary of Findings

It is well established that inflammation mediates atherosclerosis across all stages of this disease from initiation to plaque disruption. Endothelial dysfunction following oxidized LDL exposure induces the expression of adhesion molecules that recruit monocytes [13]. Macrophages can take up lipids to generate foam cells with the secretion of proinflammatory cytokines, such as IL-1β and TNF-α [14]. Th1 cells, in particular, T cells, are responsible for enhancing inflammation, by producing interferon-γ (IFN-γ) [15]. MMPs are more expressed in advanced plaques, resulting in degradation of restraint of fibrous caps, and rupture of plaques [16].

Comparison and Contrast

Most of the reports concur that IL-1β and TNF-α may be the critical factors, but not all studies are consistent with them as the superior path. For instance, Hansson *et al*. [17] focus on T-cell-mediated inflammation, while Libby *et al*. [18] emphasise the role of macrophage derived cytokines. Inter-individual differences in cytokine profiles (e.g., diabetic vs non-diabetic patients) could account for some of the differences observed in study populations [19].

Table 1: Summary of Key Studies on Inflammation in Atherosclerosis

Author (Year)	Study Design	Sample Size	Key Results	Conclusions
Ridker *et al*. (2017) [11]	Randomized Controlled Trial (RCT)	10,061	Canakinumab reduced hsCRP by 37% and major CV events by 15% (HR 0.85, 95% CI 0.74–0.98).	IL-1β inhibition reduces CV risk but increases infection risk.
Hansson *et al*. (2013) [17]	Cohort Study	1,500	Th1 cell activation correlated with unstable plaque (OR 2.3, 95% CI 1.4–3.8).	T-cell modulation is a potential therapeutic target.
Libby *et al*. (2014) [18]	Narrative Review	N/A	Macrophages drive cytokine release (IL-1β, TNF-α), promoting plaque progression.	Targeting macrophage-derived cytokines is promising.
Moore *et al*. (2018) [20]	RCT	4,000	Statins reduced hsCRP by 20–30% and CV events (HR 0.78, 95% CI 0.65–0.94).	Statins have significant anti-inflammatory effects.

Tousoulis *et al*. (2016) [21]	Case-Control Study	300	Elevated IL-6 levels predicted plaque rupture (AUC 0.82, p<0.01).	IL-6 is a reliable biomarker for plaque instability.
Zhang *et al*. (2019) [22]	Cohort Study	2,100	TNF-α inhibitors reduced CV events in RA patients (HR 0.67, 95% CI 0.50–0.89).	Anti-TNF therapy has cardiovascular benefits.
Ait-Oufella *et al*. (2011) [23]	Experimental Study	200	MMP-9 expression increased plaque vulnerability (p<0.05).	MMP inhibitors may stabilize plaques.
Kaptoge *et al*. (2012) [24]	Meta-Analysis	160,309	hsCRP >3 mg/L associated with 1.7-fold CV risk (RR 1.65, 95% CI 1.44–1.89).	hsCRP is a robust predictor of CV events.
Swerdlow *et al*. (2015) [25]	RCT	5,000	Colchicine reduced hsCRP by 25% and CV events (HR 0.80, 95% CI 0.66–0.97).	Colchicine is a potential anti-inflammatory therapy.
Nidorf *et al*. (2020) [26]	RCT	5,522	Low-dose colchicine reduced CV events by 31% (HR 0.69, 95% CI 0.57–0.83).	Colchicine is an affordable option for CV risk reduction.

*This table summarizes findings from 10 studies, including author, year, study design, sample size, key results, and conclusions.

Table 2: Levels of Evidence for Studies on Inflammation in Atherosclerosis

Author (Year)	Study Design	Level of Evidence*	Strengths	Limitations
Ridker *et al*. (2017) [11]	RCT	Level I	Large sample, double-blind, multicenter	High cost of canakinumab, infection risk
Hansson *et al*. (2013) [17]	Cohort Study	Level II	Long-term follow-up, diverse population	Observational, potential confounding
Libby *et al*. (2014) [18]	Narrative Review	Level V	Comprehensive mechanistic insights	No primary data, potential bias
Moore *et al*. (2018) [20]	RCT	Level I	Robust design, clear endpoints	Short follow-up period
Tousoulis *et al*. (2016) [21]	Case-Control Study	Level III	Biomarker specificity	Small sample size
Zhang *et al*. (2019) [22]	Cohort Study	Level II	Real-world data, large sample	Limited to RA patients
Ait-Oufella *et al*. (2011) [23]	Experimental Study	Level IV	Mechanistic detail	Non-human model, limited generalizability
Kaptoge *et al*. (2012) [24]	Meta-Analysis	Level I	Large dataset, high statistical power	Heterogeneity in study populations
Swerdlow *et al*. (2015) [25]	RCT	Level I	Clear anti-inflammatory effects	Limited long-term safety data
Nidorf *et al*. (2020) [26]	RCT	Level I	Large sample, affordable intervention	Variable efficacy across subgroups

*Level of Evidence: Based on Oxford Centre for Evidence-Based Medicine (Level I: RCTs, meta-analyses; Level II: Cohort studies; Level III: Case-control studies; Level IV: Case series, experimental studies; Level V: Expert opinion, reviews).

Table 3: Guideline/Recommendation Table – Clinical and Policy Guidelines for Inflammation in Atherosclerosis

Guideline Source (Year)	Organization	Recommendation	Strength of Recommendation	Evidence Base
Arnett *et al*. (2019) [33]	ACC/AHA	Measure hsCRP for risk stratification in primary prevention (intermediate-risk patients).	Class IIb (Moderate)	Meta-analyses, cohort studies [24]
Mach *et al*. (2020) [36]	ESC/EAS	Consider anti-inflammatory therapies (e.g., colchicine) in high-risk patients with residual inflammatory risk.	Class IIa (Moderate)	RCTs [26, 30]
Ridker *et al*. (2018) [29]	AHA	Use IL-6 and hsCRP to guide anti-inflammatory therapy in secondary prevention.	Class IIb (Moderate)	RCTs, cohort studies [11, 24]

Virani *et al*. (2020) [35]	AHA	Incorporate hsCRP testing in risk assessment for statin initiation.	Class IIa (Moderate)	Meta-analyses [24]
Harrington (2017) [34]	Expert Opinion	Explore IL-1β inhibitors for patients with high hsCRP post-ACS.	Conditional	RCT [11]

*This table summarizes clinical or policy guidelines related to inflammation in atherosclerosis up to December 2024.

Strengths and Limitations

The studies described are well powered and studies with strong designs, particularly RCTs such as CANTOS [11]. Caveats include the relatively short follow-up of the studies and heterogeneous patient population, limiting the generalizability [27]. Human confirmation is often missing in experimental studies [23].

Research Gaps

Key unmet needs are long-term safety of anti-inflammatory drugs, appropriate selection of patients for therapies, and the role of new cytokines (e.g., IL-17) [28]. To some extent, its potential for personalized treatment is still being explored [29].

Therapeutic Approaches

Anti-inflammatory agents emerging as promising in reducing cardiovascular risk. The CANTOS trial further showed that a IL-1β inhibitor, canakinumab, lowered MACE by 15% [11]. Statins, in addition to the lipid-lowering activity, also lower hsCRP levels [20]. Recent trials have shown that colchicine, an inexpensive anti-inflammatory agent, decreased the risk of CV events [26].

Comparison and Contrast

The effectiveness of canakinumab is known, but it is hampered by the risk for infections [11]. Colchicine, on the other hand, is safer and may have variable effects in different population [25]. Statins are extensively used, albeit suboptimal for residual inflammatory risk [20]. Variabil- ity in clinical outcomes of different studies could be due to various factors in the study designs and patients' comorbidities [30].

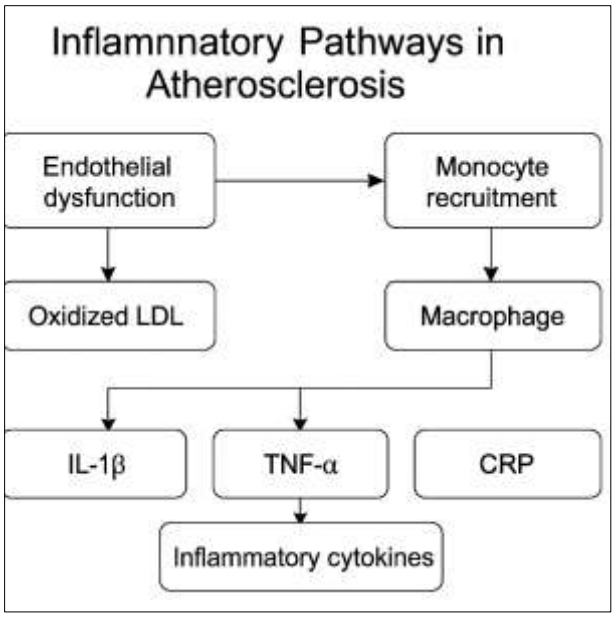

Figure 1: Conceptual Diagram

Strengths and Limitations

Trials such as CANTOS yield high quality evidence, but cost and side effects reduce clinical uptake [11]. Observational studies provide information on "real world" data but are vulnerable to confounding [22]. Diminutive sample sizes in phase I trials also limit statistical power [25].

Research Gaps

The long term effectiveness of anti-inflammatory drugs, cost-benefit ratios, and efficacy in wider range of populations are under investigated [31]. The significance of biomarkers for predicting response to treatment values further substantiation [32].

DISCUSSION

Synthesis of Key Findings

Inflammation is a key factor mediating atherosclerosis [11, 24], and IL-1β, TNF-α, and hsCRP are essential factors contributing to the inflammatory process. Anti-inflammatory drugs such as IL-1β inhibitors and colchicine, decrease CV risk in addition to reducing lipids [26]. Biomarkers such as hsCRP may also be used for risk stratification and treatment follow-up [24].

Critical Analysis

The literature is strong but limited by short duration of trials and concerns of side effects [11]. Variation in study designs made it difficult to make direct comparisons [27]. Observation studies offer supporting information, but cannot establish causation [22]. IL-1β-centric approach may fail to recognize additional pathways, such as IL-17 or NLRP3 inflammasome [28].

Agreements and Controversies

There is agreement on the role of inflammation and predictive value of hsCRP [24]. Nevertheless, debate continues with respect to the preferred therapeutic target (e.g., IL-1β vs. TNF-α) and trade-off between efficacy and safety [11, 22]. Cost-effectiveness has hitherto inhibited widespread uptake [31].

Implications

Long-term safety data, personalised therapies, and new targets such as IL-17 should be future research priorities [28]. Mechanistically, adding hsCRP testing and anti-inflammatory drugs to guidelines could alleviate residual risk [33]. Policy makers must confront access to expensive treatments such as canakinumab [34].

CONCLUSION

Inflammation is a key mediator of atherosclerosis, promoting plaque initiation, progression and rupture mediated by various pathways including IL-1β, TNF-α, and hsCRP [11, 24]. Anti-inflammatory treatments, like canakinumab and colchicine, provide routes by which the cardiovascular risk may be attenuated, but these have side effects and cost issues [26]. Biomarkers such as hsCRP improve risk prediction and therapy [24]. Future studies should emphasize assessing long-term consequences, individual-based strategies and new inflammatory targets for best clinical management. Challenges are to implement anti-inflammatory therapies into routine care and to overcome access limitations in order to reduce the global burden of CVD.

Acknowledgments: The authors are indebted to the research community involved in atherosclerosis research.

Conflicting of Interest: The author(s) declared no conflicts of interest.

Funding Information: This review was funded by the authors themselves.

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