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MINI-REVIEW OPEN ACCESS

Bacterial Infections and Atherosclerosis – A Mini Review

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Abstract

Atherosclerosis is the most challenging subsets of coronary artery disease in humans, in which risk factors emerge from childhood, and its prevalence increases with age. Experimental research demonstrates that infections due to bacteria stimulate atherogenic events. Atherosclerosis has complex pathophysiology that is linked with several bacterial infections by damaging the inner arterial wall and heart muscles directly and indirectly by provoking a systemic pro-inflammation and acute-phase protein. Repeated bacterial infections trigger an inflammatory cascade that triggers immunological responses that negatively impact cardiovascular biomarkers includes triglycerides, high-density lipoprotein, C-reactive protein, heat shock proteins, cytokines, fibrinogen, and leukocyte count. Herein, we intended to share the role of bacterial infection in atherosclerosis and evaluate existing evidence of animal and human trials on the association between bacterial infections and atherosclerosis on update.

Keywords: Atherosclerosis, Bacterial Infections, Inflammation

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INTRODUCTION

Atherosclerosis (Atheroma) is a multi-infectious and pathological condition of the inner arterial wall with a wide range of clinical manifestations[1-6] also identify and detect subclinical atherosclerosis[7,8] like coronary heart disease (CHD), myocardial infarction (MI), and stroke.[1] According to world estimates, around 8.38 million deaths because of CHD, and ischemic stroke account for 47.8 million disability-adjusted life years (DALYs).[9] Increased prevalence of CHD in urban areas of 10 to 12 percent and rural areas of 4 to 6 percent in India's momentous public health concerns.[10] Traditional and non-traditional risk factors include obesity, overweight, physical inactivity, sedentary lifestyle, smoking, hypertension, abnormally high blood glucose levels, alcohol, aging, gender, inflammatory C-reactive protein (CRP) or acute-phase proteins, homocysteine, and thrombogenic variables.[1,7,11,12] However, atherosclerosis can develop with the nonexistence of aggregated risk factors. Significant evidence suggests that infections prevalent in atherosclerotic lesions are either directly harmful or indirectly rely on host defense cause chronic inflammatory process.[4,13,14] Several human and animal tests have found a relationship between bacterial infection and atherosclerosis stated in cell culture system.[1] The pathogenic bacterium that causes atherosclerosis promotes molecular and cellular level activation, with inflammation playing a key part in the disease's pathogenesis. Due to disappointing results of antibiotic trials, the substantial significance of established predisposing factors, and infections acting via or along with them,[1,13,14] the researcher's keen interest in finding an inflammatory trigger remains hypothetical. The most current results on the impact of certain bacterial infections in the genesis and growth of fatty plaque in the inner wall of arteries are discussed in this article.

Bacterial Infections Causing Atherosclerotic Plaques

Several bacterial infections have been discovered by identifying nucleic acids or antigens in atherosclerotic plaque.[14] It includes *Chlamydia pneumoniae* (Cp), *Mycoplasma pneumoniae, Helicobacter pylori (H. pylori), Enterobacter hormaechei*, periodontal organisms like *Poryphyromonas gingivalis (P. gingivalis), Aggregatibacter actinomycetemcomitans, Prevotella intermedia, Tanerella forsythia, Fusobacterium nucleatum, Streptococcus sanguis,* and *Streptococcus mutans.*[15]

As an Inflammatory Trigger, Bacterial Infections

Several features of the gradual inflammatory response triggered by bacterial infection[16] are shared by atherogenic mechanisms. The defenceless hypothesis of bacterial infection is re-examined in this paper. In animal experimental studies, bacterial infections were proven to be the causation of atherosclerosis.[4,15] Blood infected with Cp, *P.gingivalis*, and *H. pylori,* spreads widely and eventually infects haemocytes and inner surface of the arteries, developing a continuous, latent, and recurrent infection. However, the aetiology of bacterial infection-induced atherosclerosis remains unknown. When a bacterial infection circulates in the blood, it's higher the inflammatory mediators, which allows WBC straight off or implicitly to invade the arterial vessel wall (Figure 1). Foam cells (mainly lipid-laden macrophages) and T-lymphocytes combine with the arterial inner wall[16] at an initial point of atherogenic lesions. Activated macrophages, reduced nitrous oxide bioavailability, and start releasing inflammatory markers via innate immunity receptors result in the generation of cellular adhesion molecules, the formation of chaperonins (HSP60) as an autoimmune response, and promotes leukocyte adhesion, cholesterol uptake by macrophages leads to lipid deposition in sub-endothelial spaces.[12,17,18] By stimulating murine macrophages, low-density lipoprotein interacts with Cp,[19] *P. gingivalis*,[20] and forms foam cells. Endotoxins produced by circulating microbial organisms can indeed help with adhesion. These cytokines boost inflammatory stimuli with oxygen radicals in necrosis, culminating in the creation of the complex necrotic core of advanced lesions, which is composed of necrotic and apoptosis cells and releases more inflammatory stimuli in endothelium. Upregulation of endothelial molecules and several inflammatory cytokines such as cachectin, interleukin-6,[21] monocyte chemoattractant protein1 (MCP-1), interleukin-8,[22] interleukin-1β[23] as a result of systemic effect of

these cytokines, induce acute-phase reactants such as CRP, fibrinogen,[24] might promote atheroma complicated by thrombosis[6,12,17,25,26] (Figure 2) by the hepatic system. Consequently, fibrinogen levels are accredited to the possibility of coronary events prospectively, and tissue plasminogen activator inhibitors enhance thrombus stability by inhibiting fibrinolysis.[27,28]

***Chlamydia pneumoniae* (Cp) Association**

In infected tissue, Cp stays longer and triggers a persistent inflammatory response. Cp can spread from the lungs to the arteries via infected mononuclear cells in the blood through peripheries, infecting endothelium cells, involuntary muscle cells, T-cells, and monocytes/ macrophages, and promoting the inflammatory atherogenic processes.[29,30] Cp is unique and well known for producing chronic infections,[31] and treatment failure is common and occurrence is regular. Long-term infections and treatment failures on account of the emergence of a non-replicating and non-cultivable growth stage, but viable state lead to higher antibody levels, recurring infections, enhanced antigen presentation, or any combination of these factors.[13,14,17,29,31–33].

Lab Experiment

Chlamydia pneumoniae (Cp) has been isolated in arterial plaques using immunohistochemistry, fluorescent in-situ hybridization (FISH), DNA extraction, electron microscope method, and culture medium, but it's only been recognized in normal arteries on rare occasions.[32,34,35] The study stated that the antibody-mediated response to bacterial HSPs, which lead to endothelial injury and exacerbate atherosclerosis development. Cp causes atherosclerotic plaques, which have 40-50 percent prevalence and do not correspond with conventional antibodies used in clinical research on coronary and other arteries. The previous study on clients with anti-chlamydial antibodies or clients with a chronic persistent infection associated with Cp has been underpowered.[35-37]

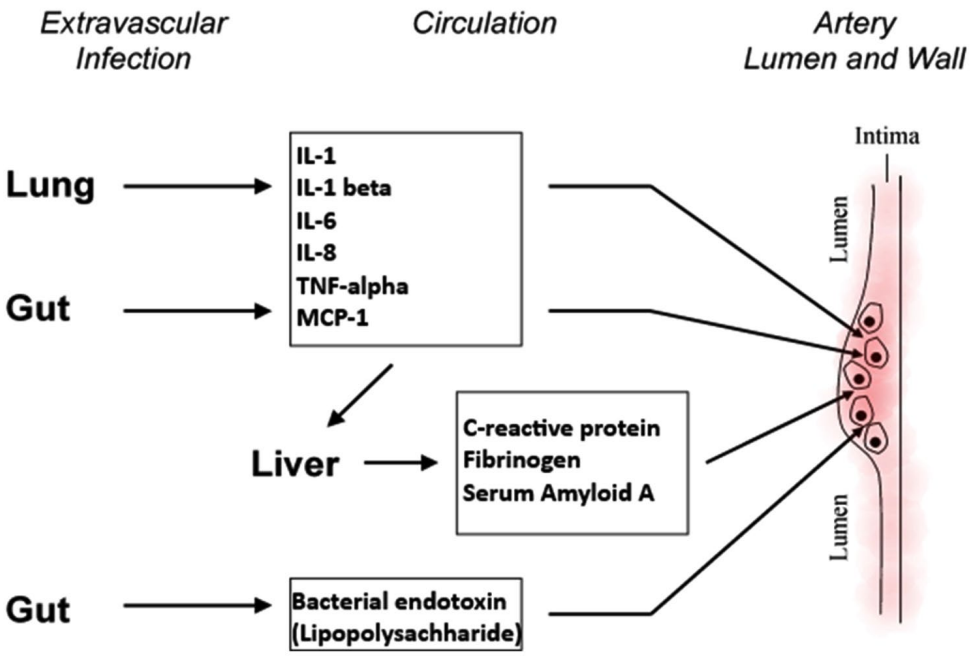

Figure 1. Bacterial products and cytokines released in response to extravascular infection. Extravascular infection stimulates the production of inflammatory cytokines that can elicit a secondary cytokine response from inflammatory cells in residence at sites of atherogenesis. Circulating bacterial endotoxin can also elicit a secondary response at the artery wall. Extravascular infection: cytokines stimulate the hepatic synthesis of acute-phase reactants and contribute to complicated atheroma formation or arterial thrombosis.

Animal Model

Previous experiments on rabbits demonstrated that Cp can initiate early atherosclerotic, fatty streak changes in the aorta without inducing hyperlipidemia.[35,36] However, several animal studies demonstrated that Cp and *P. gingivalis* can progress atherosclerotic lesion (arterial stiffness) due to hyperlipidemia.[35,38] These microorganisms might theoretically cause acute cardiac events by destabilizing plaques via macrophage production of matrixins or gelatinase,[39] or by stimulating tissue factors to produce abrupt thrombosis, but no animal model has shown this effect. The current clinical trials were meant to avoid subsequent cardiac occurrence or precipitation caused by persistent Cp infection, which has never been done in animal experimental models.

Animal investigations confirmed that treating rabbits with azithromycin promptly after Cp infection prevented atherosclerosis progression, whereas prolonged treatment was unsuccessful in preventing atherosclerotic changes.[29,36,40] In addition, research demonstrated that single treatments (such as azithromycin or ofloxacin) cannot kill Cp is a persistent condition in either a continuous cell culture paradigm or an experimental murine pneumonitis model.[41,42] A recent trial on antibiotics showed that treating Cp with antibiotics is unproductive in eradicating Cp[43] in animal tissues or human monocytes. The optimum treatment regimen for chronic persistent Cp infection is currently unknown, but it may include rifampicin.[42] A prior investigation found that gatifloxacin, clarithromycin, and azithromycin were highly effective in avoiding atherosclerotic alterations in rabbits without hyperlipidemia.[36]

The mice infected with Cp not even showed signs of atherosclerotic progression,[44] however, infection aggravated aortic sinus lesions in C57BL/6J in mice fed with an atherogenic diet, and this occurred before the high-fat diet was introduced.[45] This implies that Cp infection and atherosclerotic alterations are dependent on arterial responses to hyperlipidemia. Cp was directly injected into the porcine coronary and pulmonary arteries, causing thickening of the temporal lobe of the large coronary artery, but not the pulmonary artery.[46] Additionally, Cp can decrease nitric oxide availability in ApoE gene deletion mice, resulting in endothelium-dependent relaxation injury. Apart from hyperlipidemia, this experimental research demonstrated that vascular injury which found as a precondition for Cp infection to cause atherosclerosis. Cp infection didn't increase lesion size in animals with

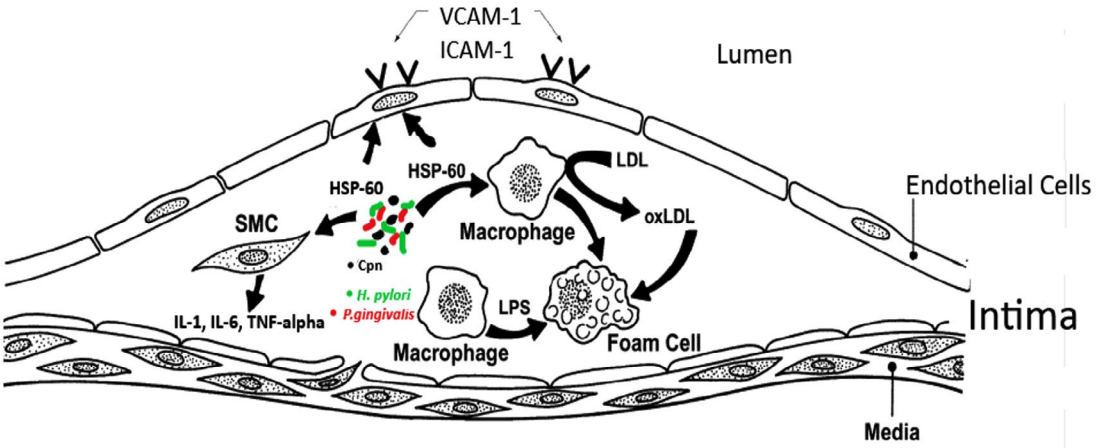

Figure 2. Direct effects of bacterial agents (Cpn, *H.pylori*, and *P.gingivalis*) on a blood vessel wall components. Bacterial infection augments endothelial cell production of inflammatory cytokines and expression of adhesion molecules, e.g., vascular cell adhesion molecule (VCAM)-1, enhancing leukocyte recruitment to the arterial wall. Bacterial endotoxin (Lipopolysachharides) may promote macrophage foam cell formation at the site. Bacterial heat shock protein (HSP- 60) may elicit pro-inflammatory functions from arterial wall macrophages, endothelium, and smooth muscle cells (SMC), and also promote macrophage oxidation of lipoproteins.

Table 1. Effects of major bacterial pathogens on atherosclerosis

Phase of atherogenesis	Pathogen	Pathogenic effect	
		Animal studies	Human studies
Lesion formation • Activation of endothelium[70,71] • Direct invasion into vascular cells and leukocytes[72] • Leukocyte migration[73] • Lipid core formation[74] • Advanced atheroma type II formation with expanded necrotic core and thinner fibrous cap[75] • Expression of inflammatory gene via acetylation of histone H4 and phosphorylation[50] **Lesion progression** • Proliferation of smooth muscle cells[76] **Lesion instability** • Plaque rupture[77] • Thrombosis[78]	Cp	• Augmented adhesion molecule expression[79,80] • Increase IFN-γ, expressed by Th1 cells and macrophages; effects on macrophages, induce the expression of TNF-α, IL-6, and MMPs; increase lipid uptake, and enhance ROS[79,80] • Increase production of MCP -1[81] • Changes in vasomotor tone intercede with nitric oxide[82]	• Detected in early atherosclerotic lesions[83] • Seropositivity to inflammatory markers[84,85] • Stimulate platelet activation[80] • Triggers platelets to release chemokine ligands (CCL3, CCL5, CCL7, CXCL8), and exacerbate atherosclerotic lesions[86] • Formation of foam cells[87] • Lipoprotein-associated phospholipase A2 induced by infected macrophages leads to up-regulating inflammatory mediators in plaque tissue[88] • Seroprevalence of chlamydia genus-specific Ig G antibodies in coronary artery disease group (76%) compared to control (59%)[89] • Rapidly activates P44/P42 mitogen-activated protein kinases by TLR 4 and stimulates proliferation of VSMCs *in vitro*[76] • Resistance to apoptosis[90] • Stimulate thrombosis[78]
	P. gingivalis	• Promotes oxidation of LDL, enhances inflammatory responses, increases VLDL, and decreases HDL[91] • Increased intracellular adhesion molecule-1, vascular adhesion molecule-1, lectin-like oxidized LDL receptor-1 and TLR 4 expression in the aortas[70] • Increased expression of vascular cell adhesion molecule[60]	• Increase expression of adhesion molecules and up-regulation of TLR4 induced by GroEL (belongs to heat shock protein 60) in human coronary artery endothelial cells[70] • Initiation and progress of atherosclerosis via the TLR 2/4-nuclear factor-κB signaling pathway[92] • Uptake by macrophages and promotes foam cell formation[93,94] • 78.57% DNA detection from bacteria[56,95] • Expression of scavenger receptors leads to increase uptake of oxidized LDL[70,94] • Expression of angiopoietins 1 and 2 in angiogenesis and modulation in human aortic smooth muscle cells[96]

Table 1. Cont...

Phase of atherogenesis	Pathogen	Pathogenic effect	
		Animal studies	Human studies
	H. pylori	• Impairs endothelial function; enhances atherosclerosis via exosomes mediated ROS formation[97] • Impaired endothelium-dependent vascular relaxation[98] • Overexpression of YKL-40 predicts vulnerable plaques[99]	• Decrease in flow-mediated vasodilatation[98] • Dysregulated lipid metabolism, lower HDL-cholesterol, and earlier vessel wall changes[100] • YKL-40 may serve as a predictive biomarker for plaque instability in carotid atherosclerosis with CagA$^+$ *H. pylori* infection[99] • Vascular endothelial injury due to increased expression of GATA3-dependent CHI3L1 up regulation[101] • Seropositivity to inflammatory markers with C-reactive protein[102]

IFN-γ: interferon-γ. Th1: t-helper type1. TNF: tumor necrosis factor. IL: interleukin. MMPs: matrix metalloproteinases. ROS: reactive oxygen species. MCP-1: monocyte chemoattractant protein-1. TLR: toll-like receptor. VSMCs: vascular smooth muscle cells. LDL: low-density lipoprotein. VLDL: very-low-density lipoprotein. HDL: high-density lipoprotein. CHI3L1: chitinase 3 like 1.

advanced atherosclerosis, but it decreases the size of the fibrous cap of atheroma and the synthesis of matrix metalloproteinases, indicating that the severity of Cp-promoting lesions decreased as atherosclerosis progressed.[47] However, whereas Cp infection increased the size of sores in mice, anti-infective treatment (azithromycin) did not lower the aortic lesion size.

The trial delivered a brief course of placebo or azithromycin to male survivors of acute MI who had raised antibody titers to Cp infection. In follow-up (18 months) study, it was determined that azithromycin medication significantly decreased unfavorable cardiovascular events.[40] However, some studies reported that treating Cp at an early stage of infection has a positive effect, and this is depending on the actuality of confounding risk factors in a subject.[34,48]

The therapy on anti-infective trial is also dependent on adjunctive medication such as selective -blockers, antiplatelet medicines (i.e. aspirin), high-density lipoprotein, and statins. Study showed that "statins" block Cp in cell culture medium and diminish the atherosclerosis-related serological response.[49] Simvastatin inhibits Cp-mediated histone modification and gene expression (DNA synthesis) in endothelial culture cells, thereby inhibiting release of cytokines involved in the beginning and accelerating atherosclerosis.[50]

Animal research has its constraints, such as models demonstrating that atherosclerotic lesions are associated with an extremely early pathologic process that does not correspond to the lesions that cause human atherosclerotic alterations. In animals, there is no clear evidence that Cp infection promotes plaque rupture. Atherosclerotic lesions do not rupture or evolve into clinical disease in most animal models.

Oral Pathogens

Extensive studies demonstrated persistent mouth infections (e.g., periodontitis) and increased the development of atherosclerotic diseases in the host.[48,51] Periodontal diseases are inflammatory disorders attributable to polymicrobial dysbiosis, where the host's defensive reaction to the bacteria damages the surrounding tissues.[52] Bacterial DNAs encoding periodontal pathogens such as *Aggregatibacter actinomycetemcomitans, P.*

gingivalis, Tannerella forsythensis, Treponema denticola, and *Campylobacter rectus* was revealed in samples of stenotic coronary artery plaque,[53] aneurysmal thrombus tissues,[54] and occluded artery tissues.[55] Various studies established that *P. gingivalis* organism related with the raised incidence of developing atherosclerotic lesions.[56,57] According to one study, clients with severe periodontitis detected *P. gingivalis* in stenotic coronary artery plaque sample was 5-fold risk than those clients with medium periodontitis.[53]

Lab Experiments

Using the FISH technique, researchers discovered *P. gingivalis* in aortic plaque and observed that persistent dental infection causes a particular immune reaction, and also massive increases in oral bone loss, aortitis, and plaque growth.[58] *P. gingivalis*-induced anti-inflammatory cytokine production inhibited by identical immunoglobulins to Toll-like receptors 2 and 4, a cluster of differentiation 14, and β2 integrin.[59]

Animal Models

Experiments on apolipoprotein E-deficient rats fed a high-fat food revealed that *P. gingivalis* microbes enhanced the initiation and progression of atherogenic plaque.[38,60] *P. gingivalis* bacteremia was revealed indirectly or straightaway correlated to the arteriosclerotic vascular disease development in normal and hypercholesterolemic pigs.[61] Research indicated that *P. gingivalis* was found using PCR analysis in several localized tissues and also demonstrated specific blood IgG in clients with elevated *P. gingivalis* levels.[62] *P. gingivalis* can thus have a direct or indirect impact on the pathogenesis of atherosclerosis by invading gingival tissues and other bloodstreams. Periodontitis and atherosclerotic disease are more common in people who have hyperinflammatory characteristic.[48] Thus, oral bacteria might cause atherosclerosis directly by invading endothelial cells or secondarily by stimulating vascular cells. *P. gingivalis* and *S. sanguis*, for example, both express a platelet-aggregation factor. The connection between oral diseases and atherosclerosis, on the contrary, further investigation is needed in the lab and human research.

Helicobacter pylori

H. pylori is a spiral microaerophilic bacteria, the gram-negative organism that colonizes and produces a prolonged systemic inflammatory reaction in gastric mucosa of human.[63] Although a study demonstrated on *H. pylori* and atherosclerosis, it concluded with a contradicting causal relationship interlinking *H. pylori* and atherosclerosis.[64] An earlier meta-analysis established a substantial link between *H. pylori* and the menace of heart attack.[65] *H. pylori* infection was an independent predictor of carotid atherosclerosis in males <50 years, and young males were affected by an aggravation of infection with identifiable atherosclerotic plaques.[66] A study resulted on 2573 clients with serological positive for *H. pylori* (66.5%) showed increased level of cholesterol (LDL) and connected with raising incidence of CHD in mens.[67] *H. pylori* and the origin of fatty plaque risks have a tenuous epidemiological relationship. *H. pylori* was not stranded from human atheroma.[64] According to a detailed inquiry, only few case-control studies found a link between CHD and *H. pylori*, while a vast number of cohort studies found no link. There is still a topic of debate on this subject.[68]

Pathogenic Effects of Bacterial Infections

The presence of bacterial pathogens in atherosclerotic plaque has been demonstrated in numerous investigations. Pathogens can be latent or multiply in cells such as macrophages, triggering a chronic inflammatory response. Because they function from within the cell, evading the immune system, intracellular bacteria are the most commonly implicated species.[14,69] Effects of major pathogens of various bacterial organisms on atherosclerosis have been shown in Table 1.

Effective Bacterial Target in Atherosclerosis

Anti-infective therapy experiments have been done in both animal and human models of atherosclerotic disease.

Animal Models

Cp infection increased intimal wall thickening and atherosclerosis severity; more crucially, therapy with azithromycin reduced

atherosclerosis severity shown in rabbit experiment.[40] Statin reduced the activity of nuclear transcription factor-κB (NF-κB) in vascular smooth muscle cells.[49] Metronidazole treatment administered for ApoE$^{+/-}$ mice infected with *P. gingivalis* reduced atherosclerotic lesions and decreased levels of proinflammatory cytokines.[103] The study done on mice indicates that triple medication therapy (lansoprazole, amoxicillin, and clarithromycin) could reduce the atherogenic consequences of *H. pylori* infection in the gastrointestinal tract.[104]

Human Models

The human study reported that roxithromycin decreased carotid plaque and prevented atherosclerotic progression in Cp seropositive mens.[105] A pilot study done on Cp with doxycycline treatment showed unaffected by antibody titers and CRP levels were considerably lower than baseline levels at 6-month follow-up (P =.01).[106] The study found that a one-week course of antibiotic amoxicillin (500 mg twice a day) or azithromycin (500 mg once a day) reduced adverse cardiovascular complications in patients with acute coronary syndromes, with no effect on Cp or *H. pylori* seropositivity and no response to antibody titer effect.[107] Long-term roxithromycin therapy of 30 days trial on patients with Cp positive and negative with ischemic stroke yielded limited effect on early atherosclerosis progression and negative result at 4-year clinical end point.[108] Gatifloxacin (400 mg) initial therapy over two weeks followed by 10 days every month up to 2 years of primary clinical endpoint 23.1% compared to placebo 25.1%, but there was no improvement in the cardiac events.[109] Statin reduced signaling and transmission by induction of macrophage-mediated Cp.[49] As shown in a previous analysis, the most anti-infective therapeutic trials in people have failed to demonstrate any significant cardio-protection. Each investigation included varied treatment options, durations, and cardiovascular results. In the initial human trials using macrolide antibiotics, short antibiotic regimens were used. There was no change in the end-points of CHD events or cardiac death in large trials.[74]

CONCLUSION

Numerous shards of evidence exist about persistent infections with bacteria and their molecular mechanism, which plays a significant part in the development of arterial disease with atherosclerotic plaques. Sufficient data indicates that infectious organisms are discovered in the narrowed blood vessel wall, an infectious agent such as Cp, *P. gingivalis*, and *H. pylori*, and their particular antibodies, are connected to CHD. Nonetheless, there is insufficient evidence regarding how infections serve a role in the formation of fatty plaques, when their natural history begins, pathophysiological progression, the indirect effects of infection on atherosclerosis progression, and medical treatment. Long-term treatment, pharmaceutical resistance, late-onset clinical effects of medicines, recurring infection, or slow long-term inflammation could all be factors of CHD. To fully comprehend the role of bacterial infections in atherosclerosis, more clinical research is required.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

GM drafted the manuscript, compiled information from the literature and designed the figures. RS supervised, copy-edited, and approved this mini review before sending it for publication.

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ETHICS STATEMENT

Not applicable.

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