MINI-REVIEW

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-1\(\beta\)\(^23\) as a result of systemic effect of
these cytokines, induce acute-phase reactants such as CRP, fibrinogen, might promote atheroma complicated by thrombosis 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.

**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. Cp is unique and well known for producing chronic infections, 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.

**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. 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.

![Figure 1](link_to_image)
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

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**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          | Animal studies                                                                 | Human studies                                                                 |
|------------------------|-------------------|--------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Lesion formation       | **Cp**            | Augmented adhesion molecule expression\(^{73,80}\)                             | Detected in early atherosclerotic lesions\(^{83}\)                             |
|                        |                   | Increase IFN-\(\gamma\), expressed by Th1 cells and macrophages; effects on macrophages, induce the expression of TNF-\(\alpha\), IL-6, and MMPs; increase lipid uptake, and enhance ROS\(^{79,80}\) | Seropositivity to inflammatory markers\(^{90,95}\)                             |
|                        |                   | Increase production of MCP-1\(^{81}\)                                         | Stimulate platelet activation\(^{80}\)                                        |
|                        |                   | Changes in vasomotor tone intercede with nitric oxide\(^{82}\)               | Triggers platelets to release chemokine ligands (CCL3, CCL5, CCL7, CXCL8), and exacerbate atherosclerotic lesions\(^{86}\) |
| Lesion progression     |                   |                                                                                  |                                                                               |
|                        | P. gingivalis     | Promotes oxidation of LDL, enhances inflammatory responses, increases VLDL, and decreases HDL\(^{91}\) | Formulation of foam cells\(^{97}\)                                           |
|                        |                   | Increased intracellular adhesion molecule-1, vascular adhesion molecule-1, lectin-like oxidized LDL receptor-1 and TLR 4 expression in the aortas\(^{70}\) | Lipoprotein-associated phospholipase A2 induced by infected macrophages leads to up-regulating inflammatory mediators in plaque tissue\(^{88}\) |
|                        |                   | Increased expression of vascular cell adhesion molecule\(^{90}\)             | Seroprevalence of chlamydia genus-specific Ig G antibodies in coronary artery disease group (76%) compared to control (59%)\(^{89}\) |
| Lesion instability     |                   |                                                                                  |                                                                               |
|                        |                   |                                                                                  |                                                                               |
|                        |                   |                                                                                  |                                                                               |

**Notes:**
- \(^{70}\) and \(^{71}\) refers to animal studies.
- \(^{72}\) and \(^{73}\) refer to human studies.
- \(^{74}\) refers to lipid core formation.
- \(^{75}\) refers to advanced atheroma type II formation with expanded necrotic core and thinner fibrous cap.
- \(^{76}\) refers to lesion progression.
- \(^{77}\) and \(^{78}\) refer to lesion instability.
- \(^{79}\) and \(^{80}\) refer to ROS.
- \(^{81}\) refers to increased expression of MCP-1.
- \(^{82}\) refers to changes in vasomotor tone intercede with nitric oxide.
- \(^{83}\) refers to detected in early atherosclerotic lesions.
- \(^{84}\) and \(^{85}\) refer to seropositivity to inflammatory markers.
- \(^{86}\) refers to exacerbate atherosclerotic lesions.
- \(^{87}\) refers to formation of foam cells.
- \(^{88}\) refers to up-regulating inflammatory mediators in plaque tissue.
- \(^{89}\) refers to comparison of coronary artery disease group and control.
- \(^{90}\) refers to increased expression of MCP-1.
- \(^{91}\) refers to decreased HDL.
- \(^{92}\) refers to increased expression of adhesion molecules and inflammatory mediators in plaque tissue.
- \(^{93}\) and \(^{94}\) refer to initiation and progression of atherosclerosis via TLR 2/4-nuclear factor-κB signaling pathway.
- \(^{95}\) refers to increased expression of scavenger receptors in foam cells.
- \(^{96}\) refers to increased expression of angiopoietins 1 and 2 in angiogenesis and modulation in human aortic smooth muscle cells.
| Phase of atherogenesis | Pathogen | Animal studies | Human studies | Pathogenic effect |
|------------------------|----------|----------------|--------------|------------------|
| Animal studies         | *H. pylori* | Decrease in flow-mediated vasodilatation \(^{39}\) | Decrease in flow-mediated vasodilatation \(^{39}\) | Impairs endothelial function; enhances atherosclerosis via exosomes mediated ROS formation \(^{97}\) |
| Human studies          |          | Decrease in flow-mediated vasodilatation \(^{39}\) | Increase in carotid atherosclerosis with decreased HDL-cholesterol \(^{98}\) | 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 \(^{99}\) | YKL-40 may serve as a predictive biomarker for plaque instability in carotid atherosclerosis with CagA \(^{99}\) | Impaired endothelium-dependent vascular relaxation \(^{98}\) |
|                        |          | Overexpression of YKL-40 predicts vulnerable plaques \(^{99}\) | Overexpression of YKL-40 predicts vulnerable plaques \(^{99}\) | Overexpression of YKL-40 predicts vulnerable plaques \(^{99}\) |

**Table 1. Cont...**

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. \(^{40, 51}\) 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.
*P. gingivalis, Tannerella forsythensis, Treponema denticola, and Campylobacter rectus was revealed in samples of stenotic coronary artery plaque,\textsuperscript{53} aneurysmal thrombus tissues,\textsuperscript{54} and occluded artery tissues.\textsuperscript{55} Various studies established that *P. gingivalis* organism related with the raised incidence of developing atherosclerotic lesions.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{38,60} *P. gingivalis* bacteremia was revealed indirectly or straightaway correlated to the arteriosclerotic vascular disease development in normal and hypercholesterolemic pigs.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{64} Although a study demonstrated on *H. pylori* and atherosclerosis, it concluded with a contradicting causal relationship interlinking *H. pylori* and atherosclerosis.\textsuperscript{64} An earlier meta-analysis established a substantial link between *H. pylori* and the menace of heart attack.\textsuperscript{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.\textsuperscript{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.\textsuperscript{67} *H. pylori* and the origin of fatty plaque risks have a tenuous epidemiological relationship. *H. pylori* was not stranded from human atheroma.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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. Statin reduced the activity of nuclear transcription factor-κB (NF-κB) in vascular smooth muscle cells. Metronidazole treatment administered for ApoE−/− mice infected with *P. gingivalis* reduced atherosclerotic lesions and decreased levels of proinflammatory cytokines. 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.

**Human Models**

The human study reported that roxithromycin decreased carotid plaque and prevented atherosclerotic progression in *Cp* seropositive mens. 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). 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. 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. 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. Statin reduced signaling and transmission by induction of macrophage-mediated *Cp*. 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.

**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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REFERENCES

1. Dahal U, Sharma D, Dahal K. An unsettled debate about the potential role of infection in pathogenesis of atherosclerosis. J Clin Med Res. 2017;9(7):547-554. doi: 10.14740/jcmr3032w
2. Lawson JS. Multiple infectious agents and the origins of atherosclerotic coronary artery disease. Front Cardiovasc Med. 2016;3:30. doi: 10.3389/fcvm.2016.00030
3. Jong R De, Leoni G, Drechsler M, Soehnlein O. The advantage of using annexin A1 in cardiovascular disease. Cell Adh Migr. 2017;11(3):261-274. doi: 10.1080/19336918.2016.1259059
4. Ziganshina EE, Sharifullina DM, Lozhkin AP, Khayrullin MN, Ignatyev IM, Ziganshin AM. Bacterial communities associated with atherosclerotic plaques from Russian individuals with atherosclerosis. PLoS One. 2016;11(10):e0164836. doi: 10.1371/journal.pone.0164836
5. Pinon Esteban P, Nunez L, Mourre R, et al. Presence of Bacterial DNA in Thrombotic Material of Patients with Myocardial Infarction. Sci Rep. 2020;10(1):16299. doi: 10.1038/s41598-020-73011-5
6. Shao Y, Zheng Q, Wang W, Xin N, Song X, Zhao C. Biological functions of macrophage-derived Wnt5a, and its roles in human diseases. Oncotarget. 2016;7(41):67674-67684. doi: 10.18632/oncotarget.11874
7. Tragghella I, Mastori C, Alessia P, Pingitore A, Vassalle C. Nontraditional cardiovascular biomarkers and risk factors: rationale and future perspectives. Biomolecules. 2018;8(40):1-15. doi: 10.3390/biom8020040
8. Singh SS, Pilkerton CS, Jr CDS, Frisbee SJ. Subclinical atherosclerosis, cardiovascular health, and disease risk: is there a case for the Cardiovascular Health Index in the primary prevention population? BMC Public Health. 2018;18(429):1-11. doi: 10.1186/s12889-018-5263-6
9. Stanaway JD, Afsahn A, Gakidou E, et al. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study. Lancet. 2018;392(10159):1923-1994. doi: 10.1016/S0140-6736(18)32225-6
10. Puri N, Gupta PK, Sharma J, Puri D. Prevalence of atherosclerosis in coronary artery and internal thoracic artery and its correlation in North-West Indians. Indian J Thorac Cardiovasc Surg. 2010;26(4):243-246. doi: 10.1007/s12055-010-0057-1
11. Martin-timon I, Sevilla-llorente C, Segura-galindo A, Canizo-gomez FJ, Martin-timon I, Sevilla-llorente C. Type 2 diabetes and cardiovascular disease: Have all risk factors the same strength? World J Diabetes. 2014;5(4):444-470. doi: 10.4239/wjd.v5.i4.444
12. Nou E, Lo J, Hadigan C, Grinspoon SK. Pathophysiology and management of cardiovascular disease in HIV-infected patients. Lancet Diabetes Endocrinol. 2016;4(7):598-610. doi: 10.1016/S2213-8587(15)00388-5
13. Campbell LA, Rosenfeld ME. Persistent C. pneumoniae infection in atherosclerotic lesions: rethinking the clinical trials. Front Cell Infect Microbiol. 2014;4:1-4. doi: 10.3389/fcimb.2014.00034
14. Campbell LA, Rosenfeld ME. Infection and atherosclerosis development. Arch Med Res. 2015;46(5):339-350. doi: 10.1016/j.arcmed.2015.05.006
15. Kozarov E. Bacterial invasion of vascular cell types: Vascular infectology and atherogenesis. Future Cardioi. 2012;8(1):123-138. doi: 10.2217/fca.11.75
16. Vidal-vanaclocha F. Inflammation in the molecular pathogenesis of cancer and atherosclerosis. Reumatol Clin. 2009;5:40-43. doi: 10.1016/j.reuma.2008.12.008
17. Li B, Xia Y, Hu B. Infection and atherosclerosis: TLR dependent pathways. Cell Mol Life Sci. 2020;(77):2751-2769. doi: 10.1007/s00018-020-04353-7
18. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation. 2002;105(9):1135-1143. doi: 10.1161/hc0902.10435
19. Kalayoglu MV, Byrne GI. A Chlamydia pneumoniae component that induces macrophage foam cell formation is chlamydial lipopolysaccharide. Infect Immun. 1998;66(11):5067-5072. doi: 10.1128/IAI.66.11.5067-5072.1998
20. Xiang W, Yu N, Lei A, et al. Insights into host cell cytokines in Chlamydia infection. Front Immunol. 2021;12(May):1-14. doi: 10.3389/fimmu.2021.63983
21. Beatty WL, Morrison RP, Byrne GI. Persistent chlamydiae: from cell culture to a paradigm for chlamydial pathogenesis. Microbiol Rev. 1994;58(4):686-699. doi: 10.1128/MMBR.58.4.686-699.1994
22. Molestina RE, Dean D, Miller RD, Ramirez JA, Summersgill JT. Characterization of a strain of Chlamydia pneumoniae isolated from a coronary atheroma by analysis of the omp1 gene and biological activity in human endothelial cells. Infect Immun. 1998;66(4):1370-1376. doi: 10.1128/IAI.66.4.1370-1376.1998
23. Heinemann M, Susa M, Simnacher U, Marre R, Essig A. Growth of Chlamydia pneumoniae induces cytokine production and expression of CD14 in a human monocytic cell line. Infect Immun. 1996;64(11):4872-4875. doi: 10.1128/IAI.64.11.4872-4875.1996
24. Hajishengallis G. Periodontitis: from microbial immune subversion to systemic inflammation. Nat Rev Immunol. 2015;15(1):30-44. doi: 10.1038/nri3785
25. Bergeheau SC, Bodde MC, Jukema JW. Pathophysiology and treatment of atherosclerosis current view and future perspectives on lipoprotein modification treatment. Neth Hear J. 2017;25:231-242. doi: 10.1007/s12471-017-0959-2
26. Kyaw T, Peter K, Li Y, Tipping P, Toh B, Bobik A. Cytotoxic lymphocytes and atherosclerosis: significance, mechanisms and therapeutic challenges. Br J Pharmacol. 2017;174(22):3956-3972. doi: 10.1111/bph.13845
27. Rea IM, Gibson DS, McGillivary V, Mcnerlan SE,
Alexander HD, Owen A Ross. Age and age-related diseases: role of inflammation triggers and cytokines. Front Immunol. 2018;9:586. doi: 10.3389/fimmu.2018.00586

28. Mozol, Malainer C, Horbaczuk J, et al. Inflammatory markers for arterial stiffness in cardiovascular diseases. Front Immunol. 2017;8:1-16. doi: 10.3389/fimmu.2017.01058

29. Mahony JB, Coombes BK. Chlamydia pneumoniae and atherosclerosis: does the evidence support a causal or contributory role? FEMS Microbiol Lett. 2001;197(1):1-9. doi: 10.1111/j.1574-6968.2001.tb10574.x

30. Kern JM, Maass V, Maass M. Chlamydia pneumoniae-induced pathological signaling in the vasculature. FEMS Immunol Med Microbiol. 2009;55(2):131-139. doi: 10.1111/j.1574-6968.2008.00514.x

31. Neumann F. Chlamydia pneumoniae -atherosclerosis link: a sound concept in search for clinical relevance. Circulation. 2002;(106):2414-2416. doi: 10.1161/01.CIR.0000040403.57597.48

32. Honarmand H. Atherosclerosis induced by chlamydophila pneumoniae: a controversial theory. Interdiscip Perspect Infect Dis. 2013:1-12. doi: 10.1155/2013/941392

33. Coombes BK, Chiu B, Fong IW, Mahony JB. Chlamydia pneumoniae infection of endothelial cells induces transcriptional activation of platelet-derived growth factor-B: a potential link to intimal thickening in a rabbit model of atherosclerosis. J Infect Dis. 2002;185(11):1621-1630. doi: 10.1086/340415

34. Belland RJ, Ouellette SP, Gieffers J, Byrne GI. Chlamydia pneumoniae and atherosclerosis. Cell Microbiol. 2004;6(2):117-127. doi: 10.1046/j.1462-5822.2003.00352.x

35. Fong I. New perspectives of infections in cardiovascular disease. Curr Cardiol Rev. 2009;5(2):87-104. doi: 10.2174/15734030978166679

36. Fong IW, Chiu B, Viira E, Jang D, Mahony JB. De novo induction of atherosclerosis by Chlamydia pneumoniae in a rabbit model. Infect Immun. 1999;67(11):6048-6055. doi: 10.1128/IAI.67.11.6048-6055.1999

37. Mayr M, Metzler B, Kiechl S, et al. Endothelial cytotoxicity mediated by antibodies to heat shock proteins of Escherichia coli and Chlamydia pneumoniae: Immune reactions to heat shock proteins as a possible link between infection and atherosclerosis. Circulation. 1999;99(12):1560-1566. doi: 10.1161/01.CIR.99.12.1560

38. Li L, Messas E, Batista EL, Levine RA, Amaro S. Porphyromonas gingivalis infection accelerates the progression of atherosclerosis in a heterozygous apolipoprotein E-deficient murine model. Circulation. 2002;105(7):861-867. doi: 10.1161/hc702.104178

39. Vehmaan-Kreula P, Poulakkainen M, Sarvas M, Welgis HG, Kovanen PT. Chlamydia pneumoniae proteins induce secretion of the 92-kDa gelatinase by human monocyte-derived macrophages. Arterioscler Thromb Vasc Biol. 2001;21(1):e1-e8. doi: 10.1161/01.ATV.21.1.e1

40. Muhlestein JB, Anderson JL, Hammond EH, et al. Infection with Chlamydia pneumoniae accelerates the development of atherosclerosis and treatment with azithromycin prevents it in a rabbit model. Circulation. 1999;97(7):633-636. doi: 10.1161/01.CIR.97.7.633

41. Kutlin A, Robin PM, Hammerschlag MR. In vitro activities of azithromycin and ofloxacin against Chlamydia pneumoniae in a continuous-infection model. Antimicrob Agents Chemother. 1999;43(9):2268-2272. doi: 10.1128/AAC.43.9.2268

42. Wolf K, Malinverni R. Effect of azithromycin plus rifampin versus that of azithromycin alone on the eradication of Chlamydia pneumoniae from lung tissue in experimental pneumonitis. Antimicrob Agents Chemother. 1999;43(6):1491-1493. doi: 10.1128/AAC.43.6.1491

43. Gieffers J, Fullgraf H, Jahn J, et al. Chlamydia pneumoniae infection in circulating human monocytes is refractory to antibiotic treatment. Circulation. 2001;103(3):351-356. doi: 10.1161/01.CIR.103.3.351

44. Caligiuri G, Rottenberg M, Nicoletti A, Wigzell H, Hansson GK. Chlamydia pneumoniae infection does not induce or modify atherosclerosis in mice. Circulation. 2001;103(23):2834-2838. doi: 10.1161/01.CIR.103.23.2834

45. Blessing E, Campbell LA, Rosenfeld ME, Kuo C chou. Chlamydia pneumoniae and hyperlipidemia are co-risk factors for atherosclerosis: Infection prior to induction of hyperlipidemia does not accelerate development of atherosclerotic lesions in C57BL/6J mice. Infect Immun. 2002;70(9):5332-5334. doi: 10.1128/IAI.70.9.5332-5334.2002

46. Pislaru SV, Van Ranst M, Pislaru C, et al. Chlamydia pneumoniae induces neointima formation in coronary arteries of normal pigs. Cardiovasc Res. 2003;57(3):834-842. doi: 10.1016/S0008-6363(02)00787-3

47. Moazed TC, Campbell A, Rosenfeld ME, Grayston JT, Kuo C. Chlamydia pneumoniae Infection Accelerates the Progression of Atherosclerosis in Apolipoprotein E - Deficient Mice. J Infect Dis. 1999;180(1):238-241. doi: 10.1086/314855

48. Connor SO, Taylor C, Campbell LA, Epstein S, Libby P. Potential Infectious Etiologies of Atherosclerosis: A Multifactorial Perspective. Emerg Infect Dis. 2001;7(5):780-788. doi: 10.3201/eid0705.010503

49. Dechend R, Gieffers J, Dietz R, et al. Hydroxymethylglutaryl coenzyme A reductase inhibition reduces atherosclerotic lesions in C57BL/6J mice. Circulation. 2002;105(9):5222-5231. doi: 10.1123/AAC.43.9.5222

50. Schmeck B, Beermann W, Dje N’Guessan P, et al. Simvastatin reduces Chlamydia pneumoniae-mediated histone modifications and gene expression in cultured human endothelial cells. Circ Res. 2008;102(8):888-895. doi: 10.1161/CIRCRESAHA.107.161307

51. Inaba H, Amano A. Roles of oral bacteria in cardiovascular diseases -from molecular mechanisms to clinical cases : implication of periodontal diseases in development of systemic diseases. J Pharmacol Sci. 2010;113:103-109. doi: 10.1254/jphs.0923FM

52. Palm F, Lahdentuata L, Sorsa T, et al. Biomarkers of periodontitis and inflammation in ischemic stroke: A case-control study. Innate Immun. 2014;20(5):511-518. doi: 10.1177/1753455913501214
53. Ishihara K, Nabuchi A, Ito R, Miyachi K, Kuramitsu HK, Okuda K. Correlation between detection rates of periodontopathogenic bacterial DNA in coronary stenotic artery plaque and in dental plaque samples. *J Clin Microbiol.* 2004;42:1313-1315. doi: 10.1128/JCM.42.3.1313-1315.2004

54. Iwai T, Inoue Y, Umeda M, et al. Oral bacteria in the occluded arteries of patients with Buerger disease. *J Vasc Surg.* 2005;42(1):107-115. doi: 10.1016/j.jvs.2005.03.016

55. Nakano K, Nemoto H, Nomura R, et al. Detection of oral bacteria in cardiovascular specimens. *Oral Microbial Immunol.* 2009;24(1):64-68. doi: 10.1111/j.1399-302X.2008.00479.x

56. Figuero E, Sanchez-Beltran M, Cuesta-Frechoso S, et al. Detection of periodontal bacteria in atheromatous plaque by nested polymerase chain reaction. *J Periodontal.* 2011;82(10):1469-1477. doi: 10.1902/jop.2011.100719

57. Pussinen P, Altfhan G, Rissanen H, et al. *Helicobacter pylori* in occluded arteries of patients with Buerger disease. *J Vasc Surg.* 2004;42:1313-1315. doi: 10.1016/j.jvs.2005.03.016

58. Velsko IM, Chukkapalli SS, Rivera MF, et al. Active invasion of oral and aortic tissues by *Porphyromonas gingivalis* in mice causally links periodontitis and atherosclerosis. *PLoS One.* 2014;9(5):e97811. doi: 10.1371/journal.pone.0097811

59. Hajishengallis G, Sharma A, Russell MW, et al. Detection of *Porphyromonas gingivalis* in atheromatous plaque by nested polymerase chain reaction. *Arterioscler Thromb Vasc Biol.* 2003;23(8):1405-1411. doi: 10.1161/01.STR.0000082462.26258.FE

60. Brodala N, Merricks EP, Bellinger DA, et al. *Porphyromonas gingivalis* bacteremia induces coronary and aortic atherosclerosis in normocholesterolemic and hypercholesterolemic pigs. *Arterioscler Thromb Vasc Biol.* 2005;25(7):1446-1451. doi: 10.1161/01.ATV.0000167525.69400.9c

61. Gibson FC, Wong C, Chou HH, et al. Invasive immune recognition of invasive bacteria accelerates atherosclerosis in apolipoprotein E-deficient mice. *Circulation.* 2004;109(22):2801-2806. doi: 10.1161/01.CIR.0000129769.17895.F0

62. Gonzalez MF, Diaz P, Sandovol-Borquez A, Herrera D, Quest AFG. *Helicobacter pylori* outer membrane vesicles and extracellular vesicles from *Helicobacter pylori*-infected cells in gastric disease development. *Int J Mol Sci.* 2021;22(9):1-23. doi: 10.3390/ijms22094823

63. Ameriso SF, Frisida EM, Leiguarda RC, Sevlever GE. Detection of *Helicobacter pylori* in human carotid atherosclerotic plaques. *Stroke.* 2001;32(2):385-391. doi: 10.1161/01.STR.32.2.385

64. Rahmani Y, Mohammad S, Babanejad M, Rai A, Zalei B, Shahmohammadi A. Association of *Helicobacter Pylori* with presence of Myocardial Infarction in Iran: a systematic review and meta-analysis. *Ethiop J Health Sci.* 2017;27(4):433-440. doi: 10.4314/ehjs.v27i4.15

65. Zhang L, Chen Z, Xia X, et al. *Helicobacter pylori* infection selectively increases the risk for carotid atherosclerosis in young males. *Atherosclerosis.* 2019;291:71-77. doi: 10.1016/j.atherosclerosis.2019.10.005

66. Haeri M, Parham M, Habibi N, Vafaeimanesh J. Effect of *Helicobacter pylori* infection on Serum Lipid Profile. *J Lipids.* 2018;2018:1-5. doi: 10.1155/2018/6734809

67. Kucukazman M, Yenioglu O, Dali K, Yavuz B. *Helicobacter pylori* and cardiovascular disease. *Eur Rev Med Pharmacol Sci.* 2015;19:3731-3741.

68. Rosenfeld ME. Inflammation and atherosclerosis: direct versus indirect mechanisms. *Curr Opin Pharmacol.* 2013;13(2):154-160. doi: 10.1016/j.coph.2013.01.003

69. Huang CY, Shih CM, Tsao NW, et al. The GroEL protein of *Porphyromonas gingivalis* regulates atherogenic phenomena in endothelial cells mediated by upregulating toll-like receptor 4 expression. *Am J Transl Res.* 2016;8(2):384-404. PMCID: PMC4848691

70. Chen PY, Liu YH, Duan CY, et al. Impact of infection in patients with non-ST elevation acute coronary syndrome undergoing percutaneous coronary intervention: insight from a multicentre observational cohort from China. *BMC Open.* 2020;10(9):e038551. doi: 10.1136/bmjopen-2020-038551

71. Gerhardt T, Haghikhia A, Stapmanns P, Leistner DM. Immune Mechanisms of Plaque Instability. *Front Cardiovasc Med.* 2022;8:1-21. doi: 10.3389/fcvm.2021.797046

72. Choi EK, Park SA, Oh WM, et al. Mechanisms of *Porphyromonas gingivalis*-induced monocyte chemoattractant protein-1 expression in endothelial cells. *FEMS Immunol Med Microbiol.* 2005;44(1):51-58. doi: 10.1016/j.femsim.2004.12.003

73. Pothineni NVK, Subramany S, Kurikose K, et al. Infections, atherosclerosis, and coronary heart disease. *Eur Heart J.* 2017;38(43):3195-3201. doi: 10.1093/eurheartj/ehx362

74. Hartwig H, Silvestre-Roig C, Hendrikse J, et al. Atherosclerotic plaque destabilization in mice: a comparative study. *PLoS One.* 2015;10(10):1-14. doi: 10.1371/journal.pone.0141019

75. Sasu S, LaVerda D, Qureshi N, Golenbock DT, Beasley ZQ. Expression of toll-like receptors in human smooth muscle cells via toll-like receptor 4 and p44/p42 mitogen-activated protein kinase activation. *Circ Res.* 2001;89(3):244-250. doi: 10.1161/01.RES.0000015087.65367.8F

76. Edelfeldt K, Swedenborg J, Hansson GK, Yan ZQ. Expression of toll-like receptors in human atherosclerotic lesions: a possible pathway for plaque activation. *Circulation.* 2002;105(10):1158-1161. doi: 10.1161/01.CIR.0000094700.20147.1C

77. Vainas T, Kurvers HAJM, Mess WH, et al. *Chlamydia pneumoniae* and chlamydial heat shock protein 60 stimulate proliferation of human vascular smooth muscle cells via toll-like receptor 4 and p44/p42 mitogen-activated protein kinase activation. *Eur J Vasc Endovasc Surg.* 2004;27(4):436-443. doi: 10.1016/j.ejvs.2004.08.007

78. Voloshyna I, Littlefield MJ, Reiss AB. Atherosclerosis and interferon-γ: new insights and therapeutic targets. *Trends Cardiovasc Med.* 2014;24(1):1-13. doi: 10.1016/j.tcm.2013.11.002
80. Porritt RA, Crother TR. Chlamydia pneumoniae infection and inflammatory diseases. For Immunopathol Dis Therap. 2016;7(3-4):237-254. doi: 10.1615/ForumImmunDisTher.2017020161

81. Mantovani A, Sica A, Balkwill F, solitary role in regulation of inflammation and immunity. Immunol Rev. 2014;259(1):127-140. doi: 10.1111/ir.12148

82. Liuba P, Karnani P, Pesonen E, et al. Endothelial dysfunction after repeated Chlamydia pneumoniae infection in apolipoprotein E-knockout mice. Circulation. 2000;102(9):1039-1044. doi: 10.1161/01.CIR.102.9.1039

83. Luque A, Turu MM, Rovira N, Juan-Babot JO, Slevin M, Krupinski J. Early atherosclerotic plaques show evidence of infection by Chlamydia pneumoniae. Front Microbiol. 2012;3:451. doi: 10.3389/fmicb.2012.00451

84. Filardo S, Di Pietro M, Farcomeni A, Schiavoni G, Sessa W, Rudel T. NF-κB and inhibitor of apoptosis proteins are required for apoptosis resistance of epithelial cells persistently infected with Chlamydia pneumoniae. Cell Microbiol. 2006;8(10):1643-1655. doi: 10.1111/j.1462-5822.2006.00739.x

85. Ott SJ, El Mokhtari NE, Musfeldt M, et al. Detection of diverse bacterial signatures in atherosclerotic lesions of patients with coronary heart disease. Circulation. 2006;113(7):929-937. doi: 10.1161/CIRCULATIONAHA.105.579979

86. Al-Bannawi A, Al-Weseibai K, Taha S, Bakhiet M. Chlamydia pneumoniae induces chemokine expression by platelets in patients with atherosclerosis. Med Princ Pract. 2011;20(5):438-443. doi: 10.1159/000324543

87. Bekkering S, Quintin J, Joosten LAB, Van Der Meer JW, Netea MG, Riksen NP. Oxidized low-density lipoprotein induces long-term proinflammatory cytokine production and foam cell formation via epigenetic reprogramming of monocytes. Arterioscler Thromb Vasc Biol. 2014;34(8):1731-1738. doi: 10.1161/ATVBAHA.114.303887

88. Atik B, Johnston SC, Dean D. Association of carotid plaque LP-PLA2 with macrophages and Chlamydia pneumoniae infection among patients at risk for stroke. PLoS One. 2010;5(6):1-8. doi: 10.1371/journal.pone.0011026

89. Agarwal A, Chander Y, Nagendra A. Serological evidence of chronic Chlamydia pneumoniae infection in coronary artery disease. Med J Armed Forces India. 2007;63(3):229-232. doi: 10.1016/S0377-1237(07)08014-9

90. Paland N, Rajalingam K, Machuy N, Szczepak A, Wehr W, Rudel T. NF-κB and inhibitor of apoptosis proteins are required for apoptosis resistance of epithelial cells persistently infected with Chlamydomphila pneumoniae. Cell Microbiol. 2006;8(10):1643-1655. doi: 10.1111/j.1462-5822.2006.00739.x

91. Xuan Y, Shi Q, Liu GJ, Luan QX, Cai Y. Porphyromonas gingivalis infection accelerates atherosclerosis mediated by oxidative stress and inflammatory responses in ApoE−/− mice. Clin Lab. 2017;63(10):1627-1637. doi: 10.7754/Clin.Lab.2017.170410

92. Zou Y, Huang Y, Liu S, et al. Periodontopathic microbiota and atherosclerosis: roles of TLR-mediated inflammation response. Oxid Med Cell Longev. 2022;2022:9611362. doi: 10.1155/2022/9611362

93. Giacona MB, Papapanou PN, Lamster IB, et al. Porphyromonas gingivalis induces its uptake by human macrophages and promotes foam cell formation in vitro. FEMS Microbiol Lett. 2004;241(1):95-101. doi: 10.1016/j.femsle.2004.10.009

94. Liu F, Wang Y, Xu J, Liu F, Hu R, Deng H. Effects of Porphyromonas gingivalis lipopolysaccharide on the expression of key genes involved in cholesterol metabolism in macrophages. Arch Med Sci. 2016;12(5):959-967. doi: 10.5114/ams.2016.61909

95. Szulc M, Kustrzycki W, Janczak D, Michalowska B, Baczynska D, Radwan-Oczko M. Presence of periodontopathic bacteria DNA in atheromatous plaques from coronary and carotid arteries. Biomed Res Int. 2015:1-6. doi: 10.1155/2015/825397

96. Zhang B, Khalaf H, Sirsjo A, Bengtsson T. Gingipains from the periodontal pathogen Porphyromonas gingivalis play a significant role in regulation of angiopeptin 1 and angiopeptin 2 in human aortic smooth muscle cells. Infect Immun. 2015;83(11):4256-4265. doi: 10.1128/IAI.00498-15

97. Xia X, Zhang L, Wu H, et al. CagA+ Helicobacter pylori, not CagA+Helicobacter pylori, infection impairs endothelial function through exosomes-mediated ROS formation. Front Cardiovasc Med. 2022;9:881372. doi: 10.3389/fcmv.2022.881372

98. Xia X, Zhang L, Chi J, et al. Helicobacter pylori infection impairs endothelial function through an exosome-mediated mechanism. J Am Heart Assoc. 2020;9(6):1-15. doi: 10.1161/JAHA.119.014120

99. Wu Y, Tao Z, Song C, et al. Overexpression of YKL-40 predicts plaque instability in carotid atherosclerosis with CagA-positive Helicobacter pylori infection. PLoS One. 2013;8(4):1-6. doi: 10.1371/journal.pone.0059996

100. Lee M, Baek H, Park JS, et al. Current Helicobacter pylori infection is significantly associated with subclinical coronary atherosclerosis in healthy subjects: a cross-sectional study. PLoS One. 2018;13(3):1-13. doi: 10.1371/journal.pone.0193646

101. Chi J, Xia X, Zhang L, et al. Helicobacter pylori induces GATA3-dependent chitinase 3 like 1 (CHI3L1) upregulation and contributes to vascular endothelial injuries. Med Sci Monit. 2019;25:4837-4848. doi: 10.12659/MSM.916311

102. Nazmi A, Diez-Roux AV, Jenny NS, Tsai MY, Szklo M, Finlay BB. Helicobacter pylori infection is associated with subclinical coronary atherosclerosis: roles of TLR-mediated inflammation response. Oxid Med Cell Longev. 2022;2022:9611362. doi: 10.1155/2022/9611362

103. Amar S, Wu S, Madan M. Is Porphyromonas gingivalis cell invasion required for atherogenesis? Pharmacotherapeutic implications. J Immunol. 2009;182(3):1584-1592. doi: 10.4049/jimmunol.182.3.1584

104. Ayada K, Yokota K, Hirai K, et al. Regulation of cellular immunity prevents Helicobacter pylori-induced atherosclerosis. Lupus. 2009;18(13):1154-1168. doi:
105. Wiesli P, Czerwenka W, Meniconi A, et al. Roxithromycin treatment prevents progression of peripheral arterial occlusive disease in *Chlamydia pneumoniae* seropositive men: a randomized, double-blind, placebo-controlled trial. *Circulation.* 2002;105(22):2646-2652. doi: 10.1161/01.CIR.0000017862.08503.15

106. Mosorin M, Juvonen J, Biancari F, et al. Use of doxycycline to decrease the growth rate of abdominal aortic aneurysms: a randomized, double-blind, placebo-controlled pilot study. *J Vasc Surg.* 2001;34(4):606-610. doi: 10.1067/mva.2001.117891

107. Stone AFM, Mendall MA, Kaski JC, et al. Effect of treatment for *Chlamydia pneumoniae* and *Helicobacter pylori* on markers of inflammation and cardiac events in patients with acute coronary syndromes: South Thames trial of antibiotics in myocardial infarction and unstable angina (STAMINA). *Circulation.* 2002;106(10):1219-1223. doi: 10.1161/01.CIR.0000027820.66786.CF

108. Sander D, Winbeck K, Klingelhofer J, Etgen T, Conrad B. Progression of early carotid atherosclerosis is only temporarily reduced after antibiotic treatment of *Chlamydia pneumoniae* seropositivity. *Circulation.* 2004;109(8):1010-1015. doi: 10.1161/01.CIR.0000117232.30832.EC

109. Cannon CP, Braunwald E, McCabe CH, et al. Antibiotic treatment of *Chlamydia pneumoniae* after acute coronary syndrome. *N Engl J Med.* 2005;352(16):1646-1654. doi: 10.1056/NEJMoa043528