Coronary Artery Disease, Hyperlipidemia, Microorganisms and Statins

Oruc Alper Onk¹*, Reşit Coşkun² and Halis Süleyman³

¹Department of Cardiovascular Surgery, School of Medicine, Erzincan University, Turkey.
²Department of Cardiology, Bayburt State Hospital, Bayburt, Turkey.
³Department of Pharmacology, School of Medicine, Erzincan University, Turkey.

Authors’ contributions

This work was carried out in collaboration between all authors. Author OAO designed the study, wrote the protocol and wrote the first draft of the manuscript. Authors RC and HS managed the literature searches. All authors read and approved the final manuscript.

ABSTRACT

Coronary artery disease is a leading cause of death in the world. Inflammation has an important role in the pathogenesis of atherosclerosis. We have known that microorganisms are responsible in atherosclerosis and since they have been found in atherosclerotic plaques. Many studies on the effectiveness of statins in atherosclerosis treatment support that besides the antilipidemic activity of the statins, their pleiotropic activities (regulating endothelial function, stabilization of the plaque, decreasing oxidative stress, anti-inflammatory activity, decreasing thrombogenic response to inflammation and immunomodulatory activity) have an important role in their effectiveness on mortality and morbidity. As a result, it has been understood that microorganisms have an important role in the etiology of coronary artery occlusion. It has been found that hyperlipidemia is an early defense system against microbial damage of the vessel wall. Suppression of hyperlipidemia-related atherosclerosis or atherosclerotic plaque by drugs or methods not having antimicrobial activity is thought to trigger sudden vessel occlusion. Causes of sudden death associated with...
coronary artery and other forms of atherosclerosis have still not been fully elucidated. This study proposes that hyperlipidemia and atherosclerosis develop as a defense reaction to damage caused by micro-organisms in the coronary arteries. It also proposes that the treatment of atherosclerosis-associated subtotal obstruction of the coronary artery with hypolipidemic drugs exhibiting no antimicrobial activity, or in other ways (extreme weight loss in a short period of time), may cause sudden death.

Keywords: Coronary artery disease; hyperlipidemia; statins; microorganisms.

ABBREVIATIONS

CVD: Cardiovascular disease, CAD: Coronary artery disease, CMV: Cytomegalovirus, HSV: Herpes simplex virus (HSV), H. pylori: Helicobacter pylori (H. pylori), HIV: Human Immunodeficiency Virus, MI: Myocardial Infarction, LPS: Lipopolisaccharide, HSP: Heat shock protein, TNF: Tumor Necrosis Factor, hsCRP: High sensitive C-reactive peptide, EDM: Early defense mechanisms, RLDM: Rapid late defense mechanisms, MRSA: Methicillin-resistant S.

1. INTRODUCTION

The prevalence of the cardiovascular diseases (CVD) in the United States is 35%. In 2011, 5,802,000 people were hospitalized with a diagnosis of CVD, and 786,641 of them died [1]. Coronary artery disease (CAD), one of the CVDs, has a higher mortality rate than hypertension and cardiac failure [2]. The prevalence of CAD is 6.4%. Its high mortality rate is despite early diagnosis and improving treatment methods; one of every six adult deaths in the US is a result of CAD [1]. Hyperlipidemia, hypertension, older age, family history, and male gender are the classic risk factors for atherosclerosis, which causes CAD. However, 10-20% of CAD patients do not have the classic risk factors [3]. Experimental and clinical studies show that plaque ruptures as a result of the interaction between fibrous structure and platelets, monocytes, macrophages, and inflammatory components such as adhesion molecules. This situation shows that inflammation has an important role in the pathogenesis of atherosclerosis [4]. A study on inflammation and lipid metabolism pathways in atherosclerosis showed that inflammation was an important factor in CAD [5]. It has drawn attention to infections as a potential cause.

We have known that microorganisms are responsible for atherosclerosis since Streptococcus and Salmonella were found in the atherosclerotic plaques of rabbits by French researchers in the 1880s. The evidence supporting this idea has been increasing over time [4,6].

2. SOME MICROORGANISMS CAUSING ATHEROSCLEROSIS

At the beginning of the 20th century, it was reported that acute infection may cause acute myocardial infarction (MI) [7,8]. In the latter 20th century, Minick and Fabricant reported that Herpes virus caused atherosclerosis by fostering cholesterol accumulation in the smooth muscle cells in many vascular structures of chickens with Marek’s disease [9,10]. Just as the articles about the relationship between infections and atherosclerosis began to be published, epidemiologic and seroepidemiologic studies accelerated after pathogens were found in atherosclerotic vessels in humans. Cytomegalovirus (CMV), Herpes simplex virus (HSV) type 1 and type 2, Chlamydia pneumonia, Helicobacter pylori (H. pylori), hepatitis A, hepatitis C, HIV (Human Immunodeficiency Virus) and oropharyngeal pathogens are among the pathogens thought to be responsible for atherosclerosis [11,15].

A relationship has been propounded between Chlamidia pneumonia infection and atherosclerosis [16]. Chlamydia pneumoniae has been found in the coronary arteries and in other organs on autopsy [4,6]. Chlamydia pneumoniae can release LPS and heat shock protein (HSP) in the artery plaque. LPS and HSP trigger proliferation of pro-inflammatory agents in the vessels. Rats were infected by AR39 and MoP39 strains of C. pneumonia and then both strains were found in the rats’ aortas, but only AR39 strains caused atherosclerotic lesions [17,18]. Filardo and colleagues stated that the enhancing activity of C. pneumonia on inflammatory
response has a role in atherosclerosis. In the same study, it was reported that high sensitive C-reactive peptide (hsCRP), fibrinogen, IL-6 and \(C.\ pneumonia\) Ig A seropositivity are some markers of coronary artery disease [19]. In various studies, it has been stated that \(C.\ pneumonia\) increases oxidized LDL accumulation in the endothelium by activating lectin-like oxidized LDL receptors or increases the release of the inducible nitric oxide (iNOS) by decreasing the release of the endothelial-nitric oxide (eNOS) that provides tonus and unity for the endothelium and as a result causes atherosclerosis [20].

\(H.\ pylori\) is known as the etiologic factor for chronic gastric and duodenal ulcers and may cause gastric cancer [21-24]. In studies aiming to shed light on the cause of atherosclerosis, \(H.\ pylori\) was shown to increase the level of lipids that cause atherosclerosis [25,26]. The finding of \(H.\ pylori\) DNA in arterial plaque makes us think that \(H.\ pylori\) may be causing atherosclerotic plaques directly. In addition, long-lasting \(H.\ pylori\) infection increases the blood level of cytokines [18]. That explains how atherosclerosis is associated with \(H.\ pylori\) and with the resulting inflammation. Ayada and colleagues stated that Th-1 cells had increased immune response to the \(H.\ pylori\) HSP60 protein and facilitated migration of macrophages to the endothelium, their role in atherosclerosis.

Cytomegalovirus (CMV) infections are asymptomatic in people who are not immunesuppressed [27,28]. Various studies have shown that CMV are found in atherosclerotic plaques [29-34]. It has been reported that CMV increases the size of atherosclerotic lesions by increasing IFN-gamma and TNF-a in cases of hyperlipidemia [35-39]. Vliegen and colleagues found that in mice, CMV (MCMV) causes atherosclerosis by increasing systemic and local (in arcus aorta) cytokine release, which also supports the idea that CMV has a role in atherosclerosis [39].

It is claimed that Borellia, \(Burgdorferi\), \(Treponema pallidum\), hepatitis A virus and Herpes simplex virus type 1 and type 2 have a role in atherosclerosis development. [18,40]. As is known, the microorganisms grow better in a sugar-rich media. For this reason, wound healing is delayed and wounds even become chronic in patients with diabetes mellitus. Researches show a close relation between diabetes and atherosclerosis, and people are more prone to die of CAD if they have diabetes mellitus [41]. This information shows that atherosclerosis may be closely related with microorganisms.

3. ENDOGEN MECHANISMS CAUSING CORONARY ARTERY OCCLUSION

Infections can cause endothelial dysfunction. Endothelial dysfunction disturbs the barrier function of the endothelium between blood and the vessel wall. That leads to hyperlipidemia and atherosclerosis [42,43]. This information makes us think that hyperlipidemia and atherosclerosis are early defense mechanisms (EDM) preventing the contact of blood with the area where lesions have developed due to infection. Gradually increasing infection and growing inflammatory lesions due to infection destabilize the plaque and lead to its eventual rupture. Meanwhile, ruptured plaque is quickly repaired by the blood cells (monocytes, macrophages, platelets) and the cytokines [44,45]. These blood cells and cytokines that repair the ruptured plaque can be called rapid late defense mechanisms (RLDM). The activated RLDMs can cause occlusion of the vascular lumen in a short time in cases of endothelial rupture.

4. CAUSES OF SUDDEN DEATH IN CORONARY ARTERY ATHEROSCLEROSIS

As mentioned above, sudden death is thought to be due to the RLDMs blocking contact between the blood and the areas where lesions have developed due to infection. Not supressing the septic (microbial) lesion under the plaque together with thinning (diminishing) of the atherosclerotic plaque can be shown as the reason for sudden death in people being treated by hypolipidemic drugs and methods that do not have antimicrobial activity, as that causes the lesion to come in contact with blood. RLDMs activate to block the contact and mortal vascular occlusion may result. Vascular occlusion has been shown to result from loss of the endothelial cells covering the atherosclerotic plaque, uncovering of the subendothelial connective tissue and adhesion of platelets [46], which supports our opinion.

5. THE BENEFITS OF STATINS

Many studies on the effectiveness of statins in atherosclerosis treatment were done after statins were mentioned in 1987 (Merck’s lovastatin). The studies support that besides the antlipidemic activity of the statins, their pleotropic activities (regulating endothelial function, stabilization of
the plaque, decreasing oxidative stress, anti-inflammatory activity, decreasing thrombogenic response to inflammation and immunomodulatory activity) have an important role in their effectiveness on mortality and morbidity [47-51].

In vitro studies have demonstrated that statins inhibit the pathogen strains of *Pseudomonas aeruginosa*, and show pathogenicity against *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococcus [52,53]. Their effectiveness against Aspergillus and *Plasmodium falciparum* was also reported [54,55]. It is known that a certain dose of simvastatin is effective against *Streptococcus pneumonia* and *Moraxella catharrhalis* [56].

In an *in vivo* study done on Moray eels, simvastatin treatment in *C. pneumonia* infection was found to have immunomodulatory activity and also activity against *C. pneumonia* during the infection [57].

It has been shown that regression of atherosclerotic plaques occurs by decreasing hs-CRP levels in patients using statins [58]. Large-scale studies of statins also showed their anti-inflammatory properties to be mostly a result of their ability to decrease CRP activity [59]. The studies showed that patients with the largest inflamed lesions benefited most from the statins and they supported the use of statins in acute coronary syndromes [60]. Significant decreases in the number of cardiovascular events in patients with low LDL and high CRP levels as a result of statin use shows that suppressing the inflamed lesion is important [61]. Khot UN and colleagues reported that marked hyperlipidemia was not found in the half of patients who had myocardial infarction [62]. Rapid weight loss and significant decrease off at increased portal inflammation and fibrosis in patients with severe fatty infiltration [63]. It was reported that the total mortality rate is higher in people with low cholesterol; people with high cholesterol live longer [64,65]. In light of the obtained information, treatment of coronary artery occlusion by hypolipidemic drugs and methods with no antimicrobial activity is thought to be dangerous. Combined treatment with multidisciplinary approach just like many diseases at medicine will improve the outcome [66-68].

6. CONCLUSION

As a result, it has been understood that microorganisms have an important role in the etiology of coronary artery occlusion. It has been found that hyperlipidemia is an early defense system against microbial damage of the vessel wall. Suppression of hyperlipidemia-related atherosclerosis or atherosclerotic plaque by drugs or methods not having antimicrobial activity is thought to trigger RLDMs and sudden vessel occlusion. We think that statins at doses showing antimicrobial activity (high doses) can be useful in preventing death due to coronary artery atherosclerosis.

CONSENT

All authors declare that written informed consent was obtained from the patient (or other approved parties) for publication of this paper and accompanying images.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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