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RESEARCH ARTICLE

Infections May Cause Arterial Inflammation, Atherosclerosis, Myocarditis and Cardiovascular Disease

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ABSTRACT
Effective prevention and treatment of atherosclerosis and cardiovascular disease (CVD), the commonest cause of death in most countries, is still lacking. For many years we have studied the cholesterol hypothesis and found that there are many contradictions to this hypothesis. For instance, no trial has shown exposure response; the lipid values are not associated with degree of atherosclerosis, and people with high LDL-C live just as long or longer than people with low LDL-C. These facts together with the observation that inflammation is a common finding in atherosclerotic arteries have probably contributed to the hypothesis that CVD may be caused by inflammation. However, several trials with anti-inflammatory drugs have shown that such treatment increases the risk of CVD. Therefore, a relevant hypothesis is whether it is infections which cause the inflammation and whether CVD may be caused by infections because many human observations and animal experiments are in accordance with this idea. As cholesterol-lowering treatment is ineffective and may cause serious side effects, we believe that future research should elucidate the importance of infections in the etiology of CVD. A relevant method would be to perform a blood culture on all patients with an acute AMI and if it is positive, to treat the patient with an appropriate antibiotic.

Keywords: Adventitia; anti-inflammatory drugs; atherosclerosis; cardiovascular disease; infections; inflammation; LDL-cholesterol; macrophages; myocardial infarction; myocarditis, vasa vasorum.

Introduction

In a previous review much evidence has been presented in support of the view that elevated LDL-C is not the cause of CVD.[1] For instance, people with low LDL-C are just as atherosclerotic as people with high LDL-C; LDL-C of patients with acute CVD is lower than normal, and no cholesterol-lowering trial has shown exposure-response. If CVD, the commonest cause of mortality in most countries, was caused by elevated LDL-C, people with elevated LDL-C should of course have a shorter lifespan than those with a normal or low LDL-C. However, in a review including 19 studies where the authors had followed more than 60,000 elderly people after having measured their LDL-C, total mortality was unassociated or, in most cases, inversely associated with LDL-C. CVD mortality was recorded in seven of the studies as well and was unassociated or inversely associated with LDL-C in six of them.[2]

A common explanation of these findings has been that those with high LDL-C have been treated with statin drugs, but in the largest study, the authors found that those with the highest LDL-C lived even longer than those on statin treatment. Furthermore, after the publication of that review, nineteen more follow-up studies, including more than six million patients and healthy individuals of all ages have been published and with similar results, and in these studies, statin-treated participants were excluded, or the outcome was corrected for such treatment.[3] In three of the studies, which included only young and middle-aged subjects, the association between LDL-C and total mortality was U-shaped. However, the number with high LDL-C and early mortality included only 0.1 percent of the participants, and the number with low LDL-C and early mortality was significantly higher. CVD mortality was also recorded in seven of the studies. In five studies LDL-C was unassociated with CVD mortality, and in two studies CVD mortality was highest in the lowest LDL-C quartile.

The many cholesterol-lowering trials have been interpreted in support of the cholesterol hypothesis. However, in a meta-analysis of 37 statin trials, there was no exposure-response regarding cardiovascular or total mortality.[1] Cardiovascular mortality had even increased in seven trials, and total mortality had increased in ten trials, although not with statistical significance.

Familial hypercholesterolemia. It is a general view that the cause of premature CVD mortality in familial hypercholesterolemia (FH) is elevated cholesterol. However, on average, people with this abnormality live just as long as normal people, and the level of LDL-C of the few with early mortality does not differ from LDL-C of those with normal survival.[4] Furthermore, in past years when infectious diseases were the commonest cause of death, people with FH lived just as long or longer than those without this abnormality.[4] Only a few die prematurely and the cause of early mortality may be that those who die early have also inherited increased coagulation factors.[4] In accordance with this observation, rabbits with FH (Watanabe rabbits) have significantly higher levels of factor VIII and fibrinogen than normal rabbits, and in a trial with these rabbits, treatment with probucol prevented atherosclerosis by lowering these coagulation factors without lowering their cholesterol.[5]

The inflammation hypothesis. The many contradictory clinical observations and experiments have raised the question whether inflammation partakes in the creation of atherosclerosis and CVD, because inflammation is a frequent finding in atherosclerotic arteries.[6] The general view is that the entry of LDL-C into the subendothelial intimal layer is followed by its oxidation and that inflammation is caused by oxidized LDL-C. This hypothesis is apparently supported by the fact that oxidized LDL-C is prominently associated with atherosclerosis and CVD. However, if oxidized LDL-C were the cause of atherosclerosis, its lowering should of course be beneficial, but in the REVERSAL trial, where a low statin dose was compared with a high, the outcomes on arterial lumen size or atheroma volume were unchanged despite a significant reduction of oxidized LDL biomarkers.[7]

If inflammation were the cause of atherosclerosis and CVD, a logical treatment would consist of administering therapeutic anti-inflammatory drugs. However, several large case-control studies, meta-analyses, and controlled trials including more than 800,000 CVD patients and controls have demonstrated that such treatment increases the risk of CVD.[8-11] In two recent systematic reviews and meta-analysis of similar trials, the authors claimed that anti-inflammatory therapy can reduce the incidence of the primary outcome in patients with CAD.[12,13] However, mortality was unchanged, the risk of infections was increased and the authors have ignored the four large meta-analyses with the opposite result mentioned above.

The infection hypothesis

A common view is that LDL-C enters the arterial wall from the inside of the artery. If so, inflammation

should be most pronounced in the intima and media. However, by microscopic analysis of the arterial walls of patients with CVD, Higuchi et al.[14,15] and Maiellaro et al.[16] have demonstrated that inflammation commences within the adventitial layer where vasa vasorum are situated. Furthermore, in a study by Hirata et al., infiltration of macrophages and pro-inflammatory cytokines were enhanced in the epicardial adipose tissue of patients with coronary artery disease (CAD) but not in non-CAD patients.[17] Furthermore, in a study of fresh cadaveric hearts, Ito et al. found that fibro-lipid coronary plaques are associated with local inflammation in the adventitia.[18] As we shall demonstrate in the following, these findings are also in accord with the infection hypothesis.

A century ago, infections were considered to be the major cause of atherosclerosis.[19-21] The main arguments were the high frequency of arterial lesions in patients who died from typhoid fever and the high prevalence of arteriosclerotic radial arteries in those who survived. More recent studies have shown that early atherosclerosis in children is significantly associated with infectious diseases and that those who were treated with antibiotics during their acute illness had less carotid thickening than the untreated.[22,23]

In accordance, periodontal infections are associated with an increased risk of CVD and treatment of these infections may improve endothelial dysfunction and lower the carotid intima-media thickness.[24-27] Furthermore, CVD mortality increases during influenza epidemics; a third of patients with acute CVD have had an infectious disease immediately before onset; serological markers of infection are increased in patients with CVD; and bacteremia and sepsis are found frequently in patients with cardiogenic shock caused by AMI.[28.29] Recently, several studies have found that AMI and stroke are commonly seen after sepsis and other types of infections.[30,33] That infections may participate in the pathogenesis of atherosclerosis is also in accord with the findings of more than 50 types of bacteria and viruses within the arterial plaques and the absence of microorganisms in normal arteries.[34,35]

Experimental evidence. In accordance with the findings in human studies, early atherosclerosis can be produced in animals by bacteria and viruses. More than a dozen animal experiments have succeeded with the creation of early atherosclerosis by infecting the animals with various types of bacteria and virus.[36] In two experiments, the atherosclerotic changes were decreased by immunization or treatment with antibiotics.[37,38] In one of the experiments where minipigs were infected with Chlamydia pneumoniae alone or together with Influenza virus, vascular damage and endothelial dysfunction were most prominent in the co-infected animals, and the changes were less pronounced in the hypercholesterolemic than in the normocholesterolemic pigs.[37]

An apparent contradiction is that most trials using antibiotics or vaccination have failed. However, it is unlikely that a single antibiotic should be able to eliminate more than 50 different microorganisms. Furthermore, by curing periodontal infections, Piconi et al. have demonstrated that treatment of periodontal disease with the correct antibiotic protocol improved endothelial function and reduced intimal-medial thickening to a much higher degree than seen in any cholesterol-lowering trial.[39]

The role of LDL. A relevant question is why elevated LDL-C is beneficial in prevention of atherosclerosis. The answer is that more than a dozen research groups have demonstrated that both animal and human lipoproteins participate in the immune system by adhering to and inactivating almost all kinds of microorganisms and their toxic products.[28,29] When complexed with LDL, the microorganisms are phagocytosed by macrophages, which are subsequently converted to foam cells .[28] This phenomenon explains why people with FH lived just as long or longer than other people in the past, when infections were the most important cause of death.[4]

Because of the high tissue pressure around the arterial vasa vasorum, the aggregates of microorganisms and LDL-C together with macrophages phagocytosing these aggregates may impair the blood flow in vasa vasorum causing local ischemia of the arterial wall.[28] This process is enhanced if the blood contains an increased level of homocysteine, because homocysteine reacts with LDL to form homocysteinylated LDL aggregates which increases the aggregation of LDL complexed with microorganisms.[40] When microorganisms are phagocytosed by macrophages, they are inactivated by oxidation, and, as they are complexed with LDL, the LDL may become oxidized as well. Therefore, a high level of oxidized LDL-C may be attributed to infections and the resulting inflammatory process; it is not the very cause.

If the level of LDL-C is too low, some of the microorganisms may be viable and capable of

infecting hypoxic areas of the arterial wall, resulting in formation of vulnerable plaques, which have many of the characteristics of micro-abscesses.[28] In accordance, the temperature of vulnerable plaques is higher than the surrounding tissues indicating that some of the microorganisms are still viable.[41] If a vulnerable plaque ruptures, a thrombosis may be created and the microbes may be able to enter the myocardium (Table 1). This interpretation is in accord with the well-known fact that neutrophils accumulate around necrotic myocardium within 12-24 hours after an AMI and that patients with AMI often have similar clinical and laboratory signs as patients with an infection, such as low-grade fever, sweating, elevated erythrocyte sedimentation rate, elevated C-reactive protein and leukocytosis. If LDL-C is too low to be able to obstruct vasa vasorum and if the number of living microorganisms is too high, myocarditis may be the result, an hypothesis which is supported by the many clinical, electrocardiographic and laboratory similarities between myocarditis and myocardial infarction.

Table 1. A short summary describes the proposed effects of infection in people with high or low LDL-C

Microorganisms entering the body of an individual with high LDL-C	Microorganisms entering the body of an individual with low LDL-C
↓	↓
The microorganisms are complexed immediately with LDL, facilitating phagocytosis by the leucocytes. Therefore, most viable microbes do not enter the blood circulation	As some of the microorganisms are not complexed with LDL directly, they may be able to enter the circulation. When they become complexed with LDL in the circulation, aggregation occurs together with macrophages phagocytosing these complexes, particularly in the presence of hyperhomocysteinemia
↓	↓
Local inflammation may occur in the skin, gut or lungs	Because of the high extravascular pressure around the arteries, these complexes may occlude the arterial vasa vasorum, creating local ischemia of the arterial wall
↓	↓
Healing of the infection	As some of the microorganisms still may be viable, they may enter the ischemic part of the arterial wall, creating an abscess, the vulnerable plaque
↓	↓
A scar may be created	If the vulnerable plaque bursts, an arterial thrombus may be created. If the thrombus blocks the blood flow completely, a myocardial infarction is created.If the thrombus does not block the blood flow in vasa vasorum, a myocarditis may be created. If the vulnerable plaque heals, an arterial plaque may be created.

Other factors may contribute to obstruction of vasa vasorum during atherogenesis. Mental stress for instance may cause hypertension and increased platelet aggregation, leading to AMI.[42,43] The prevailing view is that the cause of AMI in people with mental stress is attributable to elevated blood cholesterol, since elevated LDL-C is associated with AMI in young and middle-aged people and mental stress is able to raise blood cholesterol by 10-50%,[44,45] but as mentioned, mental stress may cause cardiovascular disease in another way. In agreement with this observation, more than 35 follow-up studies have shown that elderly people with elevated LDL-C live just as long or longer than those with normal or low LDL-C,[2,3] probably because retired citizens may be less stressed than young and middle-aged people. The reason why most studies of the association between cholesterol and CVD have shown the opposite is that very few trials have included elderly people.

The benefit of cholesterol-lowering has also been exaggerated because in almost all trials, it has been expressed as the relative risk reduction (RRR) instead of the absolute risk reduction (ARR).[46] If for example one patient die in a treatment group of 100 individuals and two die in the control group of

similar size, the ARR is only one percent, whereas the RRR is 50% because one is 50% of two.

Conclusion

Entry of oxidized LDL-C into the arterial intima is unlikely to be the cause of inflammation in CVD because inflammation is most pronounced in the adventitia. It is also unlikely that inflammation is the cause of atherosclerosis and CVD because many types of anti-inflammatory drugs increase the risk of CVD. Abundant evidence supports the view that infectious diseases are a major cause of atherosclerosis, AMI and myocarditis and that inflammation is a protective reaction against infection, rather than the very cause. As bacteremia and sepsis have been found in many patients with serious AMI,[47] we suggest that blood cultures should be performed in all patients with AMI or stroke, and if positive, the patient should be treated with a suitable antibiotic. There are also good reasons to change the official guidelines.[48]

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