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Infectious and coronary artery disease

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Review Article

Abstract

BACKGROUND: Atherosclerotic event is one of the most causes of death in the world. Coronary artery disease (CAD) is one manifestation of atherosclerosis. It is well-known that several risk factors, such as diabetes mellitus (DM), smoking, hypertension (HTN), have effects on it. It is proposed that infection can lead to atherosclerosis or even make its process faster. Here, we discuss about the effect of some of infectious agents on the atherosclerosis and CAD.

METHODS: In this study, first we did a comprehensive search in PubMed, Scopus, and Science Direct using some related keywords such as atherosclerosis, CAD, myocardial infarction (MI), infection, and name of viruses and bacteria. After finding the related papers, we reviewed the correlation between some microbial agents and risk of CAD.

RESULTS: Literature has reported several infectious agents (viruses, bacteria, and parasites) that can be associated with risk of CAD. This association for some of them like Helicobacter pylori (H. pylori), Chlamydia pneumonia (C. pneumoniae), and Cytomegalovirus (CMV) is a very strong. On the other hand, there are some other agents like influenza that still need to be more investigated through original studies. Furthermore, different mechanisms (general and special) have been reported for the association of each agent with CAD.

CONCLUSION: Based on the studies in databases and our literature review, it is so clear that some microbes and infectious agents can be involved in the process of atherosclerosis. Therefore, controlling each type of infections especially among people with a traditional risk factor for atherosclerosis should be taken into account for reducing the risk of CAD and atherosclerosis.

Keywords: Infection, Coronary Artery Disease, Atherosclerosis

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Introduction

Development of plaques related to the athermanous in the inner layer of arteries is called atherogenesis. The traditional risk factors for the process of atherosclerosis can act on the different places of this process. For instance hypertension (HTN) as major risk factors for this process can increase the tension of arterial wall. It can prevent from appropriate repair process. It is proposed that cigarette smoking and diabetes can effect on the biology of the vasculature, but there are not enough details about their mechanisms.[1] It is said that traditional risk factors such as smoking, diabetes mellitus (DM), and HTN cannot be considered alone for all cases of atherosclerosis.[2]

Today atherosclerosis is considered as a chronic inflammatory disease of blood vessels. Two mechanisms for the effect of inflammation on the atherosclerosis are considered. Direct mechanism is related to the inflammation at the site of vessel wall.[3] Many studies in databases suggest that microbes have an important role in vascular disease and atherosclerosis.[4] Infection in the vessel wall can act in the category of the direct mechanism. Infectious agents have effects on the formation of atherosclerotic plaque, making its process faster. Infectious agents can also lead to final complication of these plaques like plaque rupture and thrombosis.[2] The second and indirect mechanism is related to the inflammation at non-vasculature places that can lead to increase secretion of cytokines.[3] Until now impact of many infectious agents on the atherosclerosis are investigated, and there are many original and even secondary articles

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in this field.[2] Effects of some microbes such as Helicobacter pylori (H. pylori), Chlamydia pneumonia (C. pneumoniae), Cytomegalovirus (CMV), hepatitis C virus (HCV) on the atherosclerosis has been reviewed widely but evidence about some other agents seems to be inadequate. Table 1 shows some of the available meta-analyses in databases regarding the correlation of infection and atherosclerosis.

Materials and Methods

In this narrative review, electronic databases and resources including PubMed, Scopus and Science Direct and Google Scholar were searched using appropriate combination of some keywords like "atherosclerosis," "coronary heart disease (CHD)," "cerebrovascular disease (CVDs)," "microbe," "infection," "bacteria," "virus" and name of some infectious agents based on the literature review. Furthermore, in related papers, we investigated the references of them for finding other related papers. Before including each paper, we evaluated them regarding methodology and study design. After finding the related papers, the correlation between some microbial agents and coronary artery disease (CAD) were evaluated in 11 separate parts.

Results

H. pylori

Vcev et al.[10] in a randomized, multicenter study with evaluation of 180 subjects (90 CAD and 90 healthy parsons as a control group) observed that H. pylori has more seroprevalence in patients group compared to control group. They also investigated the association between this infection and CAD risk factors and showed that body mass index, smoking, HTN, DM, total cholesterol, and socio-economic status in both groups of study have not a significant association with H. pylori infection. And at the end, they suggested more studies in this field. But Jin et al.[11] in their study showed that some risk factors for CAD [gender, age, smoking, and high-density lipoprotein (HDL) cholesterol] have a meaningful difference in patients with CAD (n = 175) compared to control group (n = 88). They reported a non-significant difference between two groups about the presence of H. pylori infection.

In a cohort study, Zhu et al.[12] followed up 929 patients with CAD (antibodies to H. pylori were found in 56% of cases) for 3 years and investigated them for acute myocardial infarction (AMI) and death. Finally, they showed that there is no meaningful association between H. pylori infection and incidence of AMI or death and concluded that this infection cannot be a major risk factor for CAD, AMI or death.

In some studies, it has been proposed a mechanism for the association of H. pylori with CAD that we explain it with more details here. It is understood that hyperhomocysteinemia can be an important risk factor for CAD and atherosclerosis.[13] This condition can result from inhibition of the methionine synthase reaction due to the low-level of folate serum.[14] On the other hand, we know that H. pylori infection can result in low ascorbic acid level in gastric juice[15] which reduces absorption of folate.[16] Furthermore, there is a meaningful association between folate level of serum and CHD.[17] Therefore, we think that effect of prescribing ascorbic acid on decreasing the atherosclerosis process can be studied and with consideration of all available data about the association of H. pylori and CAD, we suggest that these patients especially those with a conventional risk factor for CAD should take a good care for CAD. Another proposed mechanism for H. pylori infection is related to H. pylori strains with cytotoxin-associated gene A. However, a study revealed that colonization with this battery cannot considered as an independent risk factor for severe CAD.[18] Power full studies like meta-analysis studies in a different aspect of this association like the progression of atheroma, development of CAD and its effect on risk factors of CAD is helpful about this issue. A meta-analysis in 2012 showed that there is an association between H. pylori infection and ischemic stroke[6] while another one in 2014 rejected this correlation.[19]

Table 1. Some available meta-analyses regarding correlation of infection and atherosclerosis

First author	Publication year	Microorganism	Evaluated outcome	Reported results
Zhang et al.[5]	2008	H. pylori (Cag A)	IS and CAD	Significantly associated
Wang et al.[6]	2012	H. pylori	IS	Significantly associated
Chen et al.[7]	2013	C. pneumoniae	CVD	Significantly associated
Huang et al.[8]	2014	Hepatitis C	Carotid atherosclerosis	Significantly associated
Filardo et al.[9]	2015	C. pneumoniae	Atherosclerosis	Significantly associated

H. pylori: Helicobacter pylori; C. pneumoniae: Chlamydia pneumoniae; CAD: Coronary artery disease; CVD: Cardiovascular disease; IS: Ischemic stroke

Streptococcal pneumonia

Eurich et al.[20] in a population-based cohort study investigated 6171 patients of community-acquired pneumonia. During the follow-up, they observed acute coronary syndrome (ACS) events in 175 patients. They showed that pneumococcal polysaccharide vaccination can reduce the ACS events (about 60%) in patients with pneumonia. There is a possible mechanism for this protective effect of pneumococcal vaccination based on an experimental study. The similarity between epitope of S. pneumoniae and oxidized low-density lipoprotein (Ox-LDL) propose a molecular mimicry theory so that pneumococcal vaccination can result in a reduction of anti-Ox-LDL immunoglobulins (Igs) and finally decrease in the atherosclerosis process.[21]

There is a possibility for hereditary component-2 deficiency (C2D) that can play a role for progression of atheroma. On the other hand, Jonsson et al.[22] investigated 40 persons with C2D. They reported severe infection as the most clinical presentation for these patients. Septicemia or meningitis caused by S. pneumonia made up the majority of previous reported infections. Moreover, they also reported pneumonia and recurrent pneumonia in their follow-up of these patients.

Based on these studies, an association between S. pneumonia with CAD can be suggested but this association and its mechanism is still unclear and more original studies, and evidence is needed to clarify all aspect of this association.

C. pneumoniae

C. pneumoniae infection is another bacterial infection that is proposed for playing a role for developing CAD. In a cross-sectional study Haider et al.,[23] evaluated 63 patients with CVDs including angina and MI and 40 healthy subjects as control group for detection of C. pneumoniae IgA antibodies and interferon γ (IFN-γ) with enzyme-linked immunosorbent assays (ELISA). According to their observation C. pneumoniae, IgA was seen in 66.7% of subjects in control groups and in 41.4% in subjects in control groups. The mean amount of IFN-γ was 32.12 pg/ml in patients group compared to 11.32 pg/ml in control groups. An important finding in this study was about increased IFN-γ in patients group. We also know that the value of IFN-γ can be higher in patients with ACS and stable angina compared with healthy persons.[24] Hence, it can be said the C. pneumoniae can have some effects on the development of CAD especially by elevation of IFN-γ values. However, there are some studies that concluded this relationship cannot be very strong. For example, Sadeghian et al.[25] by a case-control study investigated 30 patients with coronary atherosclerosis and the same number in the control group. They observed only one patient with positive polymerase chain reaction (PCR) for C. pneumoniae in cases group. In the control group, there were no positive cases.

Also, it has been showed that there is a cross reactivity between Bartonella quintana and C. pneumoniae. Hence, there is possibility that the association between C. pneumoniae and CAD can be related to the B. quintana. But, Badiaga et al.[26] in a case-control study demonstrated that C. pneumoniae is an independent risk factor for CAD and only in some cases there is a co-infection not cross-reactivity.

These differences must be evaluated in more powerful studies like a meta-analysis. For instance in a meta-analysis in 2013 a significant association between CVDs and serum specific IgG for C. pneumoniae has been reported.[7] Different issues in this topic should be evaluated in other studies. One of them is related to the different methods (PCR, serological markers, culture from vascular tissue) that used in different studies. The other important problem is the use of standard method in studies.[27]

Mycoplasma pneumoniae (M. pneumoniae)

Basinkevich et al.[28] measured antibodies and antigen to M. pneumoniae in patients with CHD and persons without it and demonstrated that there is more seropositivity for M. pneumoniae in cases group compared with control group. So, they concluded that this type of infection can be associated with CHD.

M. pneumoniae and C. pneumoniae usually is reported together in different studies related to CAD.[28,29] Momiyama et al.[30] investigated the interaction of M. pneumoniae infection with chlamydial infection. They concluded that M. pneumoniae is a more prevalent in persons with CAD compared with control group and they showed that this prevalence can be dependent on co-infection by M. pneumoniae and C. pneumoniae. Therefore, this co-infection is considered as an important factor for development CAD.

For confirming the association of M. pneumoniae with CAD and also the interaction of M. pneumoniae infection with chlamydial infection, more original studies is still needed. But now consideration of reducing the CAD risk factors in

these patients should be noticed.

Human immunodeficiency virus (HIV)

Another important organism that is mentioned to have an association with atherosclerosis is HIV. Neumann et al.[31] investigated 101 HIV-infected patients with coronary angiography and demonstrated that there is CAD in 59.1% of all patients. Also, it has been said that some factors like simultaneous infections with other viruses or vitamin D deficiency/insufficiency can make a stronger correlation between HIV infection and CAD.[32] Escaut et al.[33] in a cohort of 840 patients showed that there were a higher proportion of coronary event in HIV-infected subjects and concluded that metabolic disturbances due to drugs and smoking of tobacco is the important factors for this association. Lai et al.[34] in their study demonstrated that long-term exposure to the antiviral therapy and use of cocaine is associated with the development of CAD. At this time, there are some studies proposed the relationship between HIV and CAD and each one suggests some factors affecting on this relationship so it seems that meta-analysis for doing subgroup analysis in this field can be more helpful. An available meta-analysis about this issue in 2009 revealed that HIV infection cannot be a strong risk factor for subclinical atherosclerosis.[35]

CMV

Basinkevich et al.[29] in their study measured the level of IgM antibody to CMV in patients with MI, unstable angina, stable angina and in healthy subjects as control group and showed that seropositivity frequency is more in patients group compared with control group. Furthermore, there are some studies have shown the presence of CMV and its replication in the atherosclerotic plaque.[36] There is a mechanism that has been proposed for the effect of CMV in the process of atherosclerosis. It has been said that antibodies specific for CMV can trigger a pathway and induce genes expressing the molecules implicated in the activation of endothelial cell apoptosis that this damage to the endothelial cell can be consider for atherosclerotic pathogenicity.[37] It is proved that poor control of glucose level in type 2 diabetic patients can lead to developing CMV infection of arterial wall.[38] Another important issue is related to the existence of CMV infection in immunosuppressive patients like kidney transplant patients. This infection also is related to the development of atherosclerosis among kidney transplant patients.[39,40] After all a meta-analysis in 2012 with inclusion of 55 studies showed that CMV infection can be effective in the process of atherosclerosis.[41]

Herpes simplex virus type 1 (HSV-1) and 2

Al-Ghamdi[42] for revealing the association of HSV-1 and atherosclerosis measured the level of IgG antibody specific for HSV-1 among 40 patients with acute and chronic CAD, 20 with peripheral arterial disease and 20 with cerebral stroke and compared it with 15 subjects as control group. In the results of this study, in spite of a high seropositivity for HSV, the seropositivity had not a statistically meaningful difference between the two groups. Also Sorlie et al.[43] reported that there is no association between HSV1 antibody level and CHD. Some studies have different results. For example, Siscovick et al.[44] in a nested case-control study observed that existence of antibody to HSV-1 can increase the risk of incident MI and CHD death 2 times in older patients. Some studies also proposed a mechanism for effect of HSV-1 on atherosclerosis process. A major receptor for Ox-LDL is lectin-like Ox-LDL receptor-1 (LOX-1) in the endothelial cell. It has been said that this receptor is more expressed in the atherosclerosis process and therefore there may be a possible role in the atherosclerosis for this receptor.[45]

On the other hand, it has been shown that in HSV-1 infected patients, due to the more expression of LOX-1, the uptake of Ox-LDL will increase and therefore it can lead to activation and dysfunction of endothelial cells and eventually atherosclerosis.[46] But ultimately with consideration of this available data, we suggest more original studies and long-term follow-up of HCV-1 infected patients for a better understanding of association between HSV-1 and CAD. Sun et al. in a cross-sectional study with evaluation of 1244 subjects (488 with essential HTN and 756 normotensive) demonstrated that HSV-2 can be considered as an independent risk factor for HTN[47] and we know that HTN is a traditional risk factor for CAD. So, it can be supposed that HSV-2 can develop CAD by HTN. Also it has been shown that seropositivity of HSV-2 antibody can be related to the risk of death due to the CVD in the future.[48]

Biopsies from CAD have been investigated for inflammatory cells and also for the antigen to HSV-2. And it is demonstrated that there is a meaningful correlation between the presence of antigen to HSV-2 and infiltrate.[49] But in some studies also reported that seropositivity to HCV-2 antibody is not different between ischemic heart disease (IHD)

patients compared with healthy subjects.[50] At this time, we need more original studies for clarifying the association of HSV-2 with atherosclerosis process and CAD.

Hepatitis viruses

Hepatitis viruses seem to be involved in the process of atherosclerosis. It has been shown that hepatitis A virus (HAV) can be related to the development of atherosclerosis process and therefore leading to CAD. Zhu et al.[51] showed in their study that CAD has statistically more prevalence among HAV-infected patients compared with patients without HAV seropositivity. So according to this conclusion, prevalence of CAD and HAV infection should be associated to each other but the prevalence of HAV infection and CVD is not similar in different places.[52] Furthermore, there are some studies with consideration of CAD prevalence have concluded that HAV infection cannot be a predictor for atherosclerosis and it's not related to CAD.[53,54]

Ishizaka et al. in their study concluded that hepatitis B virus (HBV) is not associated with C-reactive protein (CRP) level and atherosclerosis. In contrast, HBV infection and seropositivity to HBV surface antigen has been proposed as a risk factor for developing atherosclerosis.[55] About involving HBV in atherosclerosis process, there are some reasons. Infection with HBV can have some extra liver manifestation like vasculitis and there are some evidences that show the presence of HBV in endothelial cells.[56,57] Also, we know that chronic liver disease can lead to increase of oxidative stress level.[58] So by this ways, it seems that hepatitis B infection can help the atherosclerosis process. But it also has been said the effect of HBV on atherosclerosis is duo to the liver failure and it cannot be an independent risk factor for CAD.[59]

Arcari et al.[60] in their cohort study with the investigation of 582 subjects concluded that HCV infection has not any relationship with AMI. Also Butt et al.[61] showed that patients with HCV infection has a younger age, lower lipid level and lower HTN prevalence than healthy control subjects. Even after adjusting conventional risk factor for CAD they concluded that HCV infection can be associated with developing CAD. Another study in 2013, by Miyajima et al.[62] demonstrates that HCV can be associated with mild atherosclerosis. We know that presence of inflammatory markers like CRP and interleukin-6 (IL6) can be a trigger for atherosclerosis process[63,64] and on the other hand, it has been shown that these markers have a more level in the HCV-infected patients.[65,66] So, this can be a possible mechanism for developing atherosclerosis by HCV infection. Also a meta-analysis in 2012 showed that HCV infection is an independent risk factor for carotid atherosclerosis.[8]

Influenza A

It has been shown that level of IL-6 and IL-8 can increase due to infection of monocyte with influenza A\H1N1 and it can lead to systemic inflammation and further developing the atherosclerosis process.[67] Perhaps this can activate the second or indirect mechanism about the role inflammation in the process of atherosclerosis that we pointed it before. Some other studies have reported that infection with influenza (A or B) cannot be a risk factor for developing CAD.[68] on the other hand it is shown that vaccination against influenza can be a protective factor for developing atherosclerosis during the seasons related to the flu.[69,70] of course this is soon to be used generally for the suspected CAD patients and its effect should be investigated in further studies. Also more studies about relationship of CAD and influenza are still needed.

Organism causes dental infection

Some studies have suggested that oral and dental infection can be an important risk factor for CAD.[71,72] So that they have also mentioned some of the organisms that cause oral or dental infection can be found in the coronary arteries of patients with atherosclerosis. Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans, Prevotella intermedia, Tannerella forsythensis, are microorganisms implicated in dental infection and also have been seen in the coronary artery biopsy samples.[73] Zhang et al.[74] also reported in their study some other microorganism like T. forsythensis, Bacteroides forsythus, Campylobacter rectus, Fusobacterium nucleatum, Treponema spp. and Streptococcus sanguis simultaneously in both coronary atherosclerotic plaques and subgingival plaque in patients with CAD.[74] Based on these studies, the association between these infections and CAD can be concluded and dental health in particular in patients with CAD risk factors should be considered.

Conclusion

Based on the studies in databases and our literature review, it is so clear that some microbes and

infectious agents can be involved in the process of atherosclerosis. Some agents still need more studies for investigation of their effects on atherosclerosis and also secondary studies is required in some other agents. We think that the infectious agents can be involved in both direct and indirect mechanisms of inflammation effect on the process of atherosclerosis. On the other hand, it is shown that some other agents like H. pylori have some especial mechanisms for affecting on the process of atherosclerosis. We believe that infection should be considered as an important risk factor for atherosclerosis. Therefore, controlling each type of infections especially among people with a traditional risk factor for atherosclerosis should be taken into account for reducing the risk of CAD and atherosclerosis.

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Conflict of Interests

Authors have no conflict of interests.

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