Review
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A Review of the Association Between Coronary Artery Disease and Infection

Koroner Arter Hastalığı ile Enfeksiyon Arasındaki İlişki Üzerine Bir Derleme

Coronary Artery Disease and Infection

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Özet

Koroner arter aterosklerozunun kronik inflamasyon-onarım kaskadları gibi çeşili inflamatuvar süreçlerle ilişkisi üzerinde uzun süredir durulmaktadır. İnsanlarda ateroskleroz gelişiminde belirli inflamatuvar yolakların rolüne işaret eden çok sayıda kanıt mevcuttur. Bununla birlikte, enfeksiyon ile koroner arter hastalığı arasındaki nedensellik ilişkisi daha az dikkat çekmiştir. Klamidya pnömoni, helikobakter pilori, herpes simplex virüs ve sitomegalovirus gibi bazı enfeksiyöz ajanların koroner arter hastalığının gelişimi ve şiddetiyle önemli bir ilişki içerisinde olduğu gittikçe daha sık olarak bildirilmektedir. Belirli mikroorganizmalarla enfeksiyon ve ateroskleroz arasındaki ilişkiye dair yayınlanmış olan deneysel ve otopsi çalışmalar mevcut olsa da, enfeksiyöz etiyolojinin koroner arter hastalığının gelişiminde hayati bir rol oynayıp oynamadığı henüz netlik kazanmış değildir. Günümüzdeki veriler K. Pnömoni enfeksiyonu ile ateroskleroz arasında bir nedensellik ilişkisinin varlığına işaret etmekle birlikte H. Pilori ve herpesvirus infeksiyonunun da koroner arter hastalığının progresyonu ve şiddetinden sorumlu olabileceğine dair ikna edici kanıtlar ortaya konulmuştur.

Anahtar Kelimeler

Ateroskleroz; Enfeksiyon; İnflamasyon

Abstract

Atherosclerotic involvement of the coronary arteries and its association with various inflammatory processes such as chronic inflammation-repair cascades have long been considered. There has been a growing body of evidence regarding the role of certain inflammatory pathways in the development of atherosclerosis in humans. The causal relationship between infection and coronary artery disease has drawn less attention. A number of infectious agents including chlamydia pneumoniae, helicobacter pylori, herpes simplex virus, and cytomegalovirus (CMV) have increasingly been reported as having significant causal relationships with the development and severity of coronary artery disease. Despite experimental and autopsy studies of the association between infection and certain microorganisms and atherosclerosis, it is still unclear whether infectious etiology plays a crucial role in the development of coronary artery disease. Current data particularly indicate the causal relationship of C. pneumoniae with atherosclerosis and there has also been convincing evidence that H. pylori and herpesviruses may be responsible for disease progression or severity.

Keywords

Atherosclerosis; Infection; Inflammation

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Introduction

Ischemic heart disease (IHD) is responsible for the vast majority of heart disease related deaths with its proportional mortality ratio being higher than that of hypertension and heart failure [1, 2]. The incidence of IHD has gradually increased in the last few decades and primary prevention strategies have become increasingly important [3, 4]. There is a growing body of evidence regarding the role of certain inflammatory pathways in the development of atherosclerosis in humans [5]. It is now well known that acute myocardial infarction is related to the activation of a culprit plaque that possesses specific features that do not cause marked stenosis, but rather a progressive narrowing of a critically involved culprit vessel [6].

Although there has been intensive research about the association of inflammation and coronary artery disease, the causal relationship between infection and coronary artery disease has drawn less attention. Actually, an interactive relationship among coronary artery disease, the presence of infection, and ongoing inflammation has been proposed [7]. A number of infectious agents including chlamydia pneumoniae, helicobacter pylori, herpes simplex virus, and cytomegalovirus (CMV) have increasingly been reported as having significant causal relationships with the development and severity of coronary artery disease. Thus, infection has emerged as a new therapeutic target in patients with coronary artery disease [8].

This review outlines previous knowledge and recent data regarding the association between infection and coronary artery disease, specifically focusing on the relationship between infection and sudden death.

History

The association between infectious diseases and atherosclerotic involvement of arteries was first addressed in the first two decades of the 20th century. It is likely that infection with certain microorganisms such as tubercle bacilli was thought to be responsible for arterial wall disease. Frotingham's report in 1911 was among the first documents focusing on this issue. The unanswered question in this report was whether the arterial disease was due to the actual presence of the microorganism in the artery wall or if the disease was the result of some toxins released by the microorganism [9].

Despite these earlier considerations, the relationship between atherosclerosis and microorganisms had not drawn attention until the 1970s. Fabricant et al. was probably the first to demonstrate this relationship in an animal model for which they infected chicken subjects with Marek's disease herpes virus. The authors saw easily visible atherosclerotic lesions in the large coronary arteries and also in great arteries elsewhere [10]. However, the first demonstration of the causal relationship between atherosclerosis and infectious disease was through laboratory evidence that Chlamydia pneumoniae can infect cultured human vascular endothelial cells and stimulate procoagulant activity [11].

An epidemiologic study reported that antibodies against cytomegalovirus (CMV) were found to be higher in those patients requiring vascular surgery for atherosclerotic disease [12]. Seven years later, infection with CMV was suggested to be a major risk factor for fast-growing allograft vasculopathy following heart transplantation [13].

Various microorganisms associated with atherosclerosis

Although the association between certain microorganisms and coronary artery disease has been proposed several times, a clinically relevant causal relationship requires convincing evidence based on positive laboratory diagnosis. This is particularly true for viruses. Their direct isolation is not always possible, making it difficult to determine whether a previous episode of a viral disease constitutes a virtual etiology in the pathogenesis of atherosclerosis [14].

Chlamydia pneumoniae

Chlamydial microorganisms are small gram-negative obligate intracellular organisms. Chlamydia pneumoniae may be the cause of mild upper respiratory tract infections in adolescents and young adults but it may cause more severe disease in older adults. In the United States, C. pneumoniae accounts for about 1%-20% of community-acquired pneumonia cases in adults; its presence may be the cause of as much as 50% of community-acquired pneumonia cases in children [15, 16].

There have been several clinical investigations suggesting evidence for the association of C. pneumonia infection and coronary artery disease. In an earlier study, Saikku et al. [17] demonstrated that IgG and IgA positivity against C. pneumonia was much more common in patients with acute myocardial infarction or chronic coronary artery disease than in controls. More recently, one clinical study of 100 patients and 60 healthy controls sought to determine whether IgG seropositivity against C. pneumoniae shows any correlation with the presence of coronary artery disease and blood inflammatory markers including C-reactive protein, fibrinogen, and cholesterol levels. In this study, IgG seropositivity against C. pneumoniae was found to be significantly correlated with inflammatory markers of atherosclerosis, indicating that C. pneumoniae infection constitutes an important risk for the development of coronary artery disease by its association with the atherogenic lipid profile and procoagulant activity [18]. Results of this study were confirmed by Al-Ghamdi et al. [19] in a similar study where C. pneumoniae specific IgG levels were found to be significantly correlated with hsCRP and cholesterol levels in coronary artery disease patients. This study underscored the effect of C. pneumonia on lipid profile and also its proinflammatory effects on the development of atherosclerosis.

Altannavch et al. [20] hypothesized that chlamydial infection may be relatively more common in diabetic patients with unstable angina pectoris since these patients more frequently tend to have impaired immune responses. This study provided supportive clinical evidence for the association of C. pneumonia infection and coronary artery disease because patients with unstable angina pectoris also had significantly higher seroprevalance against C. pneumoniae. Moreover, the study demonstrated that IgG antibodies against C. pneumoniae were significantly higher in diabetic patients than in non-diabetic patients. However, the authors emphasized that their study did not suggest any positive correlation between C. pneumoniae sero-positivity and angina severity.

One Japanese study [21] investigated the association between hyperhomocysteinemia and chlamydia pneumoniae infection with carotid atherosclerosis and coronary artery disease. This study confirmed that IgG seropositivity against C. pneumoniae was significantly more common in patients with coronary artery disease than in controls. Moreover, it was found that IgG seropositivity against C. pneumoniae was well-correlated with total plasma homocysteine concentration.

The association of C. pneumoniae infection with coronary artery disease was also investigated in large-volume clinical studies. In a recent Indian study, 192 patients with coronary artery

disease were compared with age and sex matched controls in regard to IgG and IgA seropositivity against C. pneumoniae and helicobacter pylori infection. The study supported previous findings that IgG and IgA seropositivity were more common in patients with coronary artery disease than in controls. However, it was found that hs-CRP levels were higher in coronary artery disease patients with IgA seropositivity than those with IgG seropositivity, suggesting that chronic infection with these organisms plays a role in the development of coronary artery disease [22]. In a retrospective cross-sectional study including a total of 400 age and sex matched patients, a multiple regression model was constructed to investigate the effect of the presence of IgG seropositivity against cytomegalovirus, chlamydia pneumoniae, and helicobacter pylori on coronary artery disease [23]. In contrast to the above studies, this study found that C. pneumoniae infection was not independently associated with the presence of coronary artery disease whereas H. pylori infection was among significant risk factors.

Helicobacter pylori

The association between H. pylori infection and coronary artery disease has long been addressed. The possible mechanism was reported as decreased methylation due to vitamin and folate deficiency, characteristic of chronic gastritis. The resultant increase in plasma homocysteine levels produces toxic effects in endothelial cells leading to the development of coronary artery disease [24]. However, this causal relationship was not supported by earlier clinical investigations. In one prospective controlled study, Khurshid et al. [25] investigated whether positive serology for H. pylori was an independent predictor of angiography-proven coronary artery disease. Contradicting previous studies, this study found no significant relationship between H. pylori infection and coronary artery disease. These results were supported by another study where the odds ratio of H. pylori infection for the presence of coronary artery disease was found to be 1.3 within a 95% confidence interval of 0.82 to 2.16 [26]. Although there have been a few more studies contradicting the positive association between H. pylori infection and coronary artery disease [27, 28], some others suggested the presence of such a relationship. Kowalski et al. [29] reported that H. pylori seropositivity was present in 81.5% vs. 51% of patients with and without coronary artery disease, respectively. The authors also reported that H. pylori eradication caused a significant attenuation in coronary artery lumen reduction after percutaneous coronary angioplasty, possibly by the elimination of chronic inflammation and by decreasing proinflammatory cytokine release. A screening study of 2,029 subjects investigated the association of H. pylori seropositivity and coronary artery calcium score and found that H. pylori seropositivity was significantly associated with the coronary artery calcification score. This study particularly emphasized that the association was more applicable for early coronary atherosclerosis [30].

Based on myocardial perfusion imaging studies, one recent study presented important evidence regarding the relationship between H. pylori infection and coronary artery disease. The study, which included a total of 300 patients, revealed that H. pylori infection was independently associated not only with coronary artery disease positivity but also with fixed perfusion defects on myocardial perfusion imaging, indicating a positive relationship between previous myocardial infarction and H. pylori seropositivity [31]. Although these studies support the view that H. pylori gastritis indirectly stimulates endothelial damage by causing deficiency of certain substances, clinical evidence still awaits confirmation by well-designed studies since all of the referenced studies are subject to criticism due to design limitations.

Herpesviruses

Herpesviruses constitute a large family of DNA viruses that can infect animals and humans. A number of species from the Herpesviridae family are widespread in humans including herpes simplex virus 1 and 2, varicella zoster virus, Epstein-Barr virus, cytomegalovirus, and human herpes viruses 6 and 8 [32]. In earlier studies it was demonstrated that herpes virus-infected human endothelial cells lead to thrombus formation and the increased adherence of platelets and granulocytes [33, 34]. In some other studies, CMV DNA was found in the arterial walls of patients with coronary artery disease [35]. About two decades ago, it was also suggested that there is an important relationship between CMV infection and carotid intima thickness [36].

In one animal study, Alber et al. [37] infected 3-4 week old apolipoprotein E deficient mice with murine γ-herpesvirus-68 (MHV-68). The study showed that herpesviruses-infected mice had accelerated atheroma formation within a 24-week period compared to uninfected mice. Moreover, acceleration of atherosclerosis was reduced by antiviral drug administration. This study was the first to show the casual relationship between herpesvirus infection and atherosclerosis. In an autopsy study where aortic tissues of 33 cadavers were studied for herpes simplex virus type 1 (HSV-1), Epstein-Barr virus (EBV), and cytomegalovirus (CMV), virus isolation was more common in the atherosclerotic than in the non-atherosclerotic group. The authors reported that virus DNA cells were detected more extensively in atherosclerotic than in non-atherosclerotic tissue [38]. In another autopsy study, Kotronias et al. [39] compared coronary artery autopsy samples from 42 patients who died from acute myocardial infarction with 28 samples from controls. Herpes simplex virus was detected [using nested polymerase chain reaction (nPCR) and the highly sensitive in situ hybridization with tyramide signal amplification (ISH-TSA)] and was more commonly found in patients who died from an acute myocardial infarction (43% vs. 25%). HSV-DNA was found in more than one third of cases in the myocardial infarction group, with the hybridization signal being located in the nuclei of endothelial and smooth muscle cells and in the macrophages around the atheroma. This study provided an important insight into vascular damage caused by herpes simplex virus.

More recently, Kaklikaya et al. [40] investigated the presence of human herpesvirus 6 (HHV-6), human herpesvirus 7 (HHV-7), and human herpesvirus 8 (HHV-8) DNA in various arterial tissues of cadavers including carotid, iliac, and coronary artery specimens. The study showed the presence of HHV-6 but not that of HHV-7 and HHV-8 in atherosclerotic tissues.

There have been a few clinical studies addressing the relationship between herpesvirus infections and atherosclerotic coronary artery disease. In 1984, Gyorkey et al. [41] observed virions of the herpesviridae family in 10 of 60 patients' punch biopsy specimens taken from aortic tissue during cardiac surgery. More recently, Horvath et al. [42] performed a large study to reveal whether viral DNA is more commonly found in aortic or venous walls of atherosclerotic patients compared to those without confirmed coronary artery disease in angiography. The authors reported that DNAs of HCMV, Ebstein-Barr virus, and HHV-6 were more frequently found in the arterial walls of patients with atherosclerosis when compared to those without atherosclerosis.

In a recent larger volume study of 105 consecutive patients undergoing coronary artery bypass grafting, the association between cytomegalovirus infection and acute coronary syndrome was investigated. CMV-PCR test results were positive for 28 (26.7%) of the patients with coronary atherosclerosis. The study showed that patients with a history of acute coronary syndrome were more likely to have a positive CMV-PCR test, indicating the potential role of this microorganism in development acute coronary syndromes [43].

Conclusion

Despite experimental and autopsy studies regarding the association between infection with certain microorganisms and atherosclerosis, it is still unclear whether infectious etiology plays a crucial role in the development of coronary artery disease. Current data particularly indicate the causal relationship of C. pneumoniae with atherosclerosis. There has also been convincing evidence that H. pylori and herpesviruses may also be responsible for disease progression or severity. Further experimental studies are needed to clarify whether infectious etiology constitutes an important target for the treatment of cardiovascular diseases.

Competing interests

The authors declare that they have no competing interests.

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