

Editorial / Editöryal Yorum

Infection and atherosclerosis hypothesis: Is it alive or already buried?

Enfeksiyon ve ateroskleroz hipotezi: Yaşıyor mu, çoktan gömüldü mü?

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Atherosclerosis is a global problem causing significant morbidity and mortality. The 2013 Turkish Adult Risk Factor Study Survey revealed that coronary mortality between the ages of 45-74 years was 7.5 per 1000 person-years in men, and 3.7 per 1000 person-years in women in a cumulative 23-year evaluation of participants.^[1] These mortality rates are very high compared to those seen in many European countries.

Development of atherosclerosis is multifactorial. However, it is believed that low-grade inflammation is the common denominator of atherogenesis and its complications. The inflammatory process and immune response are possibly a “mechanistic link” between traditional risk factors and development, progression and complication of atherosclerosis.^[2]

Although the history of a relationship between infection and atherosclerosis dates back to the end of the 19th century, it was paid no considerable attention until the last quarter of the 20th century. As inflammation is an important factor in the pathophysiology of atherosclerosis, one might not be surprised by a relationship between atherosclerosis and infection, one of the well-known stimuli for inflammatory reaction, especially if infections are repetitive or chronic. Demonstration of acute infection-induced endothelial dysfunction has also fueled this idea.^[3,4] Several micro-

biological agents including *Chlamydia pneumoniae*, *Cytomegalovirus*, *Helicobacter pylori*, *Porphyromonas gingivalis* and others have been blamed for the development of atherosclerosis.

Even if the possible mechanism is increased inflammatory reaction caused by infection, the intermediary mechanisms are still not clear. Moreover, negative results in recent studies targeting certain infectious agents or inflammation have made the relationship between infection and atherosclerosis debatable. Then, it has been suggested that “pathogen burden” caused by multiple microorganisms, or synergism between microorganisms might be more important in the development of atherosclerosis and its complications.^[5,6]

Several mechanisms may be proposed for the possible relationship between infection and atherosclerosis (Figure 1): 1) Direct effect of infectious agent(s), which places certain microorganisms at the center of pathophysiology, and 2) Indirect effect, in which an infectious agent leads to endothelial dysfunction and atherosclerosis by virtue of activating several pathways and changing vascular biology.

The first mechanism (direct effect) makes atherosclerosis, to some extent, an infectious disease. Koch’s postulates have been proposed (and also criticized) to assess whether a microorganism (especially



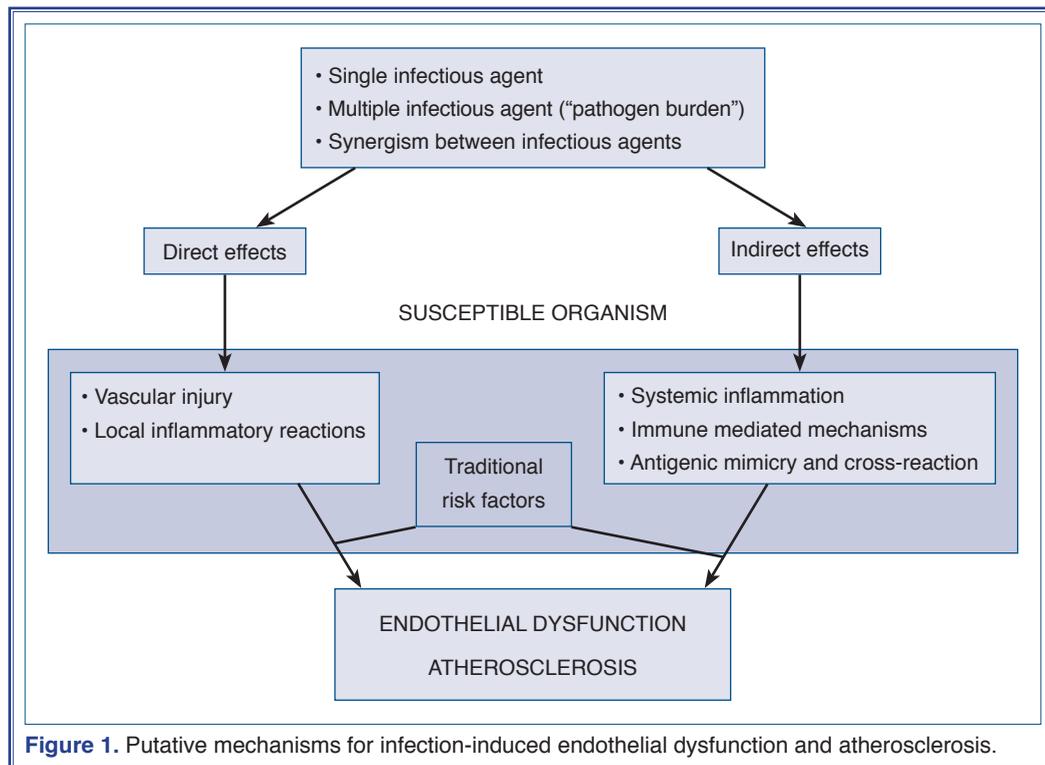


Figure 1. Putative mechanisms for infection-induced endothelial dysfunction and atherosclerosis.

a bacteria) is responsible for an infection. Although it may not be appropriate to apply these criteria to the pathophysiology of atherosclerosis, of the microorganisms studied, *Chlamydia pneumoniae* seems to be more related to development of atherosclerosis, as it has been identified in, and isolated from, human vascular plaque and increased atherosclerotic plaque in experimental settings. On the other hand, negative results obtained from antibiotic trials targeting *Chlamydia pneumoniae* have downgraded the infection hypothesis, but because of study limitations, it cannot be ruled out completely.

In the second mechanism (indirect effect), an infectious agent is associated with atherosclerosis or its complication by triggering some pathways involved in plaque formation or in complication of already developed plaques. These are systemic inflammation, sitokin-related changes in vascular biology, immune-mediated mechanisms in susceptible individuals, or cross-reaction due to antigenic mimicry.^[5]

Be it either mechanism, data regarding the causal association between infection and atherosclerosis are still conflicting, and it is still not clear whether these organisms really are a causal factor or “innocent bystanders” in the development and progression of ath-

erosclerosis. Associations are sometimes (or usually) puzzling in medicine, as it has been said “everything can be related to some extent with everything else”.^[7] Any association between two things is not necessarily causal, and it might be difficult to decide whether causality exists between those things. Cross-sectional studies, which are dominant among studies evaluating infection-atherosclerosis relationship, cannot give a reliable answer about causality. Even randomized controlled clinical trials in this field may have confounding factors. Sir Austin Bradford Hill has proposed several criteria to apply in assessing whether an association is causal or not.^[8] When Hill’s criteria are applied, one can see that a causal relationship between infection and atherosclerosis may exist (Table 1). However, before drawing any concrete conclusions, Hill’s own point of view on his nine criteria should be kept in mind.^[8]

“None of my nine viewpoints can bring indisputable evidence for or against the cause and-effect hypothesis and none can be required as a sine qua non”. Sir Austin Bradford Hill

In this volume of Archives of the Turkish Society of Cardiology, two studies evaluate the relationship between infection/inflammation and endothelial dys-

Table 1. Application of Bradford Hill criteria to the causal association between infection and atherosclerosis: an empirical grading

Criteria	Explanation	Grade
1) Strength of association	Spectrum of the strength of association varies from no association to strong association. It is relatively stronger for <i>Chlamydia pneumoniae</i> .	-/+
2) Consistency	The results of the studies are inconsistent.	-
3) Specificity	Infection is not specific for atherosclerosis. In other words, atherosclerosis cannot be predicted reliably by any infection	-
4) Temporality	Many of the pathogens possibly cause infection in young ages before atherosclerosis develops.	++
5) Biological gradient (dose-response relationship)	Some data exist.	+
6) Theoretical plausibility	Theoretical plausibility exists. It is relatively more plausible for <i>Chlamydia pneumoniae</i> . Reverse causality cannot be ruled out.	++/+++
7) Coherence	Cause-effect relationship is not seriously conflict with the generally known facts of the natural history and biology of the disease.	++
8) Experimental evidence	Moderate to strong	++/+++
9) Analogy	Chronic inflammatory disease increase atherosclerotic heart disease.	+

function/atherosclerosis. Çakıcı et al. evaluate the association between chronic sinusitis and carotid intima-media thickness in 50 patients and 50 controls.^[9] The study group is carefully selected to reduce the effects of potential confounding. Although several microorganisms may play a role in the development of chronic sinusitis, inflammation, rather than infection, seems to be a major factor. Therefore, this study assesses the relationship between chronic inflammation (possibly, rather than infection) and atherosclerosis, and shows that carotid intima-media thickness is significantly greater in patients compared to controls (adjusted mean difference 0.12 mm). Although intraobserver and interobserver variabilities have not been given, the difference might be important in a young study group with a mean age of around 25 years. It would be more interesting to see the difference in an older group, which would be important in terms of seeing the effect of longstanding chronic inflammation. An interesting finding of this study is that correlation between hs-CRP and carotid intima-media thickness is abolished in the multivariate analysis. A similar finding has been observed in other studies, and explained by the fact that CRP is not a good enough marker in reflecting ongoing process.^[4,10] In the second study, Gürsoy et al. compare flow-mediated vasodilatation (FMD) in patients with acute, subacute and chronic

Brucellosis, and in healthy controls.^[11] Brucellosis might be a good model for assessing effects of chronicity of inflammatory reaction on vascular biology, as it can be an acute, subacute or chronic infection. They found that FMD was significantly impaired in patients with chronic brucellosis, but they did not find any significant difference among the other groups. Neither did they find significant correlation between erythrocyte sedimentation rate (ESR), CRP, antibody levels and FMD. However, interestingly, ESR and CRP levels are not so high, even in the acute infection group, which makes the credibility of this correlation doubtful. One important finding of the two studies is that both underline the importance of chronicity, which is possibly very important in terms of ongoing inflammatory stimulus. Another common feature is that both studies are cross-sectional and give no reliable causal information.

As summarized above, the infection hypothesis still merits evaluation. Future trials will give us more information regarding the exact role of infection and inflammation on the development and complication of atherosclerosis.

Conflict-of-interest issues regarding the authorship or article: None declared.

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