THE POSSIBLE LINK BETWEEN INFECTIONS AND 
ATHEROSCLEROSIS

Inflammation is a main component of atherosclerosis. The inflammatory response in the arterial lesion has been described in numerous animal and human studies. T cells and monocytes adhere to the 'activated' and dysfunctional endothelium and are abundantly found in the arterial lesion. By the local secretion of cytokines and other mediators, such as extracellular matrix-digesting enzymes, the leukocytes are important directors in atherogenesis. Although the inflammatory pattern in atherosclerosis has been extensively studied during the last two decades, the trigger (or triggers) of the process is/are still not identified. Clonal expansions of T cells have been detected not only within lesions but also in peripheral blood of patients with acute coronary syndromes, indicating the presence of antigen-specific activity. Potential antigens are self-molecules, like oxidized low-density lipoprotein and related phospholipids; and also non-self-molecules, like viral and bacterial agents. A broad variety of bacterial DNA has been found in human coronary atherosclerotic lesions. On the other hand, several epidemiological studies investigating the link between infection and disease have
failed to demonstrate any association. One major limitation with most seroepidemiological studies is, however, that they rely only on the measurements of IgG antibodies to pathogens. Intracellular infections, like C. pneumoniae and cytomegalovirus, are characterized by alternating periods of latency and reactivation. Seropositivity, i.e., the presence of antibodies, indicates mainly the previous exposure to pathogens and cannot discriminate between latent or active infection.

Lately, clinical studies of cardiovascular disease have focused on the combined impact of inflammatory activity and seropositivity to pathogens, demonstrating that the predictive power of seropositivity may be dependent on the inflammatory response. In this issue of the Indian Journal of Medical Sciences, the article by Vahdat et al. confirms and extends these findings. In a population-based study, Vahdat and co-workers showed that seropositivity per se to C. pneumoniae, Herpes simplex virus type 1, H. pylori or cytomegalovirus did not have any association with ECG-defined coronary disease, neither did the increased burden of pathogens, i.e., the number of pathogens to which an individual had been exposed. Instead, Vahdat and co-workers demonstrated that the concurrent presence of elevated C-reactive protein levels (>10 mg/l) and seropositivity correlated with the prevalence of coronary disease. Furthermore, their study supports the hypothesis that the total burden of pathogens is more important than one single antigen. The prevalence of coronary artery disease gradually increased when elevated C-reactive protein was combined with seropositivity to three or four infectious agents.

The importance of several concurrent infections may be one explanation why large randomized antibiotic trials have failed to show benefit for antibiotics in the treatment of coronary artery disease.

Still, we cannot define the atherogenic role of intracellular infections, but the data obtained so far from experimental and epidemiological studies allow us to speculate. There may be several explanations for an important influence of pathogens in plaque development. The presence of microbial antigens in the lesions may represent a primary local infection or constitute the invasion of ‘innocent passengers’ since many of the recruited leukocytes harbor intracellular pathogens. In the pro-inflammatory milieu provided by the plaque, these ‘passengers’ may then easily reactivate. Another intriguing hypothesis is that the concurrent CRP elevation in a seropositive individual indicates the presence of an active infection. However, a latent intracellular infection may first need an activation of the immune system to trigger its own activation. Therefore, another possibility is that an elevated CRP, due to an already ongoing systemic inflammation, has the potential to reactivate latent infections. In addition, coronary artery disease has been associated with typical features of immunological aging/exhaustion. It is thus possible that the chronic immune stimulation associated with coronary disease makes the patients more susceptible to reactivation of intracellular infections.

To conclude, the clinical relevance of chronic infections in atherosclerosis calls for further investigations. The link between infection and atherosclerosis may be multifaceted but the result will be the same, i.e., increased inflammatory burden due to persistent or repeated infections, leading to an aggravation of the atherosclerotic process.

REFERENCES


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