Helicobacter pylori and ischemic heart disease. *Which potential pathogenic mechanisms?*

To the Editor

In a recent paper, Adiloglu et al[1] have explored one aspect of the intriguing issue of ischemic heart diseases (IHD) and bacterial infections. The authors reported their results regarding the detection of *Chlamydia pneumoniae* and *Helicobacter pylori* (*H. pylori*) DNA in atherosclerotic plaques of 14 coronary endarterectomy specimens. As control, 15 left internal mammarian artery samples without any plaques were chosen. Some serological parameters indicating inflammation or the lipid profile were analyzed. Focusing on *H. pylori*, the DNA was detected in 3 out of 14 specimens (21.4%) versus one out of 15 (6.7%) in the control group. The difference was not statistically significant. Regarding the level of C-reactive protein, apolipoprotein B and interleukin-6, no significant difference was shown between *H. pylori* DNA positive and negative subjects. However, both C-reactive protein and interleukin-6 levels were higher in the case of positivity.

After the first report, in 1994,[2] on the association between *H. pylori* infection and IHD, a series of studies has investigated on a possible link, obtaining conflicting results.[3] Although, currently available data do not prove the role of the bacterium in the pathogenesis of IHD, any potential relationship cannot be ruled out. Indeed, the heterogeneity of past studies does not allow to draw an unquestionable conclusion.[3]

A crucial matter deals with possible pathogenic mechanisms through which *H. pylori* infection could be the source or involved in the development of IHD. *Helicobacter pylori* DNA has been detected in the plaque only on sporadic occasions[4] and the attempt to cultivate the bacterium as the ultimate test to prove the viability has failed.[3] These events give room for some essential questions. Do these findings represent a true colonisation or only an evidence of *H. pylori* DNA circulation? Alternatively, the bacterial load may be too low to allow the growth of the microorganism? Hitherto, there is no answer. Moreover, it is well known in the microbiological setting that the presence of the agent is not indispensable in a site to induce a pathogenic cascade. Thus, the involvement of the bacterium in IHD might be via an indirect pathway. Several mechanisms of damage have been proposed. Indeed, the long-term inflammation generated by *H. pylori* might raise cytokine levels in the bloodstream, and consequently, activate fibroblast and smooth muscle cell proliferation.[3] Experimental evidence from the animal studies supports the concept that the role of *H. pylori* could be even more important in the acute phase of myocardial infarction. Elizalde et al[5] demonstrated that *H. pylori* infection in mice induces the formation of platelet aggregates. By damaging the mesenteric arteriole endothelium by laser pulses, another group was able to show a significant increase in the number of platelet emboli and in the duration of embolization in mice chronically infected with *H. pylori* as compared with non-infected mice.[6] Such results can be explained by the binding of some strains of the microorganism with von Willebrand Factor and interaction with the platelet glycoprotein Ib.[7] Hence, the speculation that the infection might induce the platelet and immune activation mediated by cytokines, such as IL-1, IL-6 and TNF-alpha.[3] Alternatively, an autoimmune mechanism could be involved in extra-gastrointestinal manifestations associated with the infection. It has been shown that *H. pylori* eradication leads to an important decrease in the level of the heat shock protein 60/65, a marker of severity and extension of coronary atherosclerosis.[3] The finding of anti-CagA cross-reaction with antigens of both normal and atherosclerotic blood vessels could consent to speculate that their binding to those antigens in injured arteries could influence the progression of atherosclerosis.[8] In addition, *H. pylori* infection causes an increase in gastric pH and a decrease in ascorbic acid. These events lead to a reduction in folate absorption and an elevation in concentration of blood homocysteine, known to be toxic to endothelial cells and as risk factor for atherosclerosis.[3]

In conclusion, whether *H. pylori* is culprit or simply an opportunistic agent in the initiation or in the progression of IHD, cannot yet be answered. The presence of bacterial DNA in atherosclerotic plaque is not a direct proof of causality. However, IHD is a multifaceted disease, the mechanism of which cannot be explained by only one cause. Hence to date, defining *H. pylori* as a target for the therapy of IHD remains a topic with much controversy but of essence, as any relationship would have a relevant impact on the leading cause of mortality worldwide.[9] Finally, on a statistical point of view, concording with Adiloglu et al,[1] these data should be reproduced in larger cohort. The sample size is small, and may limit and influence the results due to potential B errors.

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Reply from the Authors

I read the correspondence of Pellicano et al and I agree with them that 'these data should be reproduced in a larger cohort', which I had already mentioned both in the abstract and the conclusion part of my article as 'The increased titers of inflammation markers in DNA positive patients support inflammation in atherosclerosis, however, the results should be reproduced in a larger cohort'.

For the comment on statistics, the authors concern regarding the B errors. The statistical results do not give sharp conclusions when the groups are small or when the *p* values are not very small. Indeed, I am also worried regarding the B errors that I did not state that the 'inflammation markers were not related with bacterial DNA positivity', but I rather stated that 'inflammation markers were increased in DNA positive patients, which support inflammation in atherosclerosis, but the increase was not statistically significant'.

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