

***Helicobacter pylori* infection and the risk for coronary artery disease**

To the Editor

We have read with interest the paper by Prof. Al-Nozha and colleagues, who found no association of coronary artery disease (CAD) with *Helicobacter pylori* (*H. pylori*) infection.¹ The authors advocated that "our patients, presented in this study, being of younger age group strengthens our negative finding of a causal relation of *H. pylori* as an independent risk factor for CAD". Indeed, they included patients as young as 16 years of age (mean 37.8 years), which makes it very unlikely for these patients to have an established CAD. Atherosclerosis is a gradual process being more frequent at older ages, and is associated with various factors. For instance, fibrinogen is a plasma protein that is converted into fibrin in the common pathway of coagulation. It remains significantly associated with the severity of coronary atherosclerosis in a progressive manner, even when adjustment is made for the age, hypertension, dyslipidemia, cigarette smoking, and body mass index.² Accumulating data shows that the increase in fibrinogen level during *H. pylori* infection and the high incidence of *H. pylori* seropositivity in patients with CAD represent a link between chronic *H. pylori* infection and CAD.^{3,4} However, few studies show a lack of association between *H. pylori* infection and angiographically documented CAD. The observed discrepancy could be explained, at least in part, by the differences in various parameters of the population. Our study demonstrated that increased fibrinogen levels (an independent risk factor for CAD²) are associated with *H. pylori* infection and can be significantly reduced by *H. pylori* eradication.³ Similar findings have also been reported in a few other studies that included CAD patients with anti *H. pylori* antibodies but without any clinical evidence of peptic ulcer disease and active *H. pylori* infection, as anti *H. pylori* antibodies themselves do not indicate whether a person is actively infected or not.⁵

Apart from its effect on fibrinogen levels, *H. pylori* could influence the development of CAD through the following mechanisms: 1. *H. pylori* can coagulate blood by stimulating mononuclear cells. Under bacterial stimulation mononuclear leukocytes produce a tissue factor like procoagulant activity, which, through the extrinsic pathway of blood coagulation, converts fibrinogen into fibrin. Thus, *H. pylori* has another activity (blood clotting) potentially contributing to CAD pathogenesis.³ 2. Von Willebrand factor antigen is strongly associated

with *H. pylori* infection, providing solid evidence that *H. pylori* positive patients have increased risk of CAD.³ 3. *H. pylori* infection promotes formation of L - and P - selectin dependent platelet leukocyte aggregates in murine gastric microvessels and human *H. pylori* infection also induces platelet activation and aggregation. This phenomenon may be a contributory factor to the proposed relationship between *H. pylori* and CAD.³ 4. *H. pylori* infection is associated with the increased serum levels of tumor necrosis factor α , a circulating cytokine able to exert its effects at distance. This finding sheds some light on the pathogenesis of some "extra-gastric" diseases (including CAD), which are significantly associated with *H. pylori* infection.³ 5. Anticardiolipin antibodies, linked to CAD, have also been detected in *H. pylori* positive patients with CAD.³ 6. Circulating concentrations of lipid peroxides also associated with cardiovascular risk, are raised in patients with *H. pylori* infection. Regarding the latter mechanism, the combination of an antioxidant with classic triple *H. pylori* eradication therapy might improve the rate of *H. pylori* eradication. Indeed, our study indicates that vitamin E improves the rate of *H. pylori* elimination without concomitant side effects.³ Taken together, Prof. Al-Nozha could have included many of the above mentioned parameters to investigate the influence of *H. pylori* infection in the development of coronary atherosclerotic process. We believe that the lack of abnormal electrocardiogram (ECG) findings is not sufficient to support a marginal association between CAD and *H. pylori* infection in these young patients.

Moreover, the authors avoid referring to the limitations of their study in the discussion. These include: 1. Absence of a control group. 2. Absence of stratification of data according to various age groups. 3. Not clear inclusion and exclusion criteria (for example were the patients receiving antibiotics or proton pump inhibitors excluded from their study?). 4. Histology, the actual gold standard for the detection of *H. pylori* infection, did not seem to have a high accuracy in this paper. What were the stains used, and what was the accuracy of each method? Could it be that the elevated anti *H. pylori* antibodies referred to a past infection and not an active one? and 5. The cut off values that the authors used for the immunoglobulin G readings were: 155-230 u/ml positive and <135 u/ml negative. How were these values established? In our own experiments, the manufacturer's cut off value (enzyme link immunosorbent assay kit) was 10 u/ml. Were these values established in the authors' own lab and what about the values between 135 and 155 or over 230 u/ml?

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Reply from the Author

We thank Dr. Kountouras and his colleagues for the interest and we appreciate his comments on our study.¹

Dr. Kountouras' argument for a possible relation between *H. pylori* infection and CAD, through increasing fibrinogen level as well as other mechanisms, is not supported by a reduction in CAD after eradication of *H. pylori*.² A recent study showed a relationship between C-reactive protein, interleukin-6, fibrinogen, plasminogen-activator inhibitor 1 activity, D-dimer, Von Willebrand factor, plasma viscosity (collectively referred to as inflammatory markers) and seropositivity to *H. pylori*, *Chlamydia*, cytomegalovirus, as well as herpes simplex virus. However, odds for the presence of angiographically confirmed stable CAD were not increased after controlling for a variety of potential confounders.⁶

Moreover, several other investigators showed no association of CAD with *H. pylori* infection based on the following evidence that there was no relationship found between seropositivity of *H. pylori* and unstable angina or association between chronic infection with *H. pylori* and endothelial function.^{7,8} Furthermore, eradication of *H. pylori* infection does not change coronary risk factors and no benefit was observed in high risk patients with CAD after treatment with antibiotics.⁹ Interestingly, seropositivity for *H. pylori* was not increased in patients with acute myocardial infarction and those who tested positive for *H. pylori* were not at increased risk of atherosclerosis as indicated by measuring the mean intima media thickness of the carotid artery.^{10,11}

Our study demonstrated absence of CAD in patients with proven *H. pylori* infection.¹ We agree with Dr. Kountouras that normal ECG is not sufficient to exclude CAD, however, our study was based on obtaining symptoms of CAD as well as ECG together with echocardiography, stress test, and coronary angiography. Our study, like any other retrospective study, has the limitations of absence of control group as well as lack of ability to obtain specific variables. We examined a group of patients

with confirmed diagnosis of *H. pylori* for the presence of CAD that was found to be absent. The result of 0% has made no difference in stratifying patients to various groups or comparing to a control group. None of the patients included in the study was receiving antibiotics, proton pump inhibitor, or H2 blockers for at least one month prior to endoscopy. The values for serology are provided by the manufacturer and values from 135-155 u/ml are called equivocal that can be considered negative, but none of our patients had values in the equivocal range.

Recently, the finding of *H. pylori* DNA in the atherosclerotic plaques of patients with CAD has added heat to the debate of a causal relation, nonetheless, it is perhaps co-linear but not an association. Further evidences are awaited in this regard.

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