

# Could *Helicobacter pylori* infection increase the risk of coronary heart disease by modifying serum lipid concentrations?

Seppo Niemelä, Tuomo Karttunen, Taina Korhonen, Esa Läärä, Riitta Karttunen, Markku Ikäheimo, Y Antero Kesäniemi

## Abstract

**Objective**—To investigate the relation between *Helicobacter pylori* infection and coronary heart disease (CHD).

**Design**—A case-control study.

**Setting**—Northern Finland (about 650 000 inhabitants).

**Patients**—116 patients with angiographically documented CHD and 116 controls matched for age and gender randomly recruited from the register of the Finnish Social Insurance Institute.

**Main outcome measures**—The odds ratio (OR) estimates for the association of *H pylori* infection with CHD.

**Results**—64% of the CHD patients and 53% of the controls were seropositive for *H pylori*; the OR adjusted for age and gender was 1.5 (95% confidence interval (CI) 0.9 to 2.5). An additional adjustment for the common risk factors of CHD, including lipid concentrations, in a logistic regression analysis produced an OR estimate of 1.1 (95% CI 0.6 to 2.1). Among the controls, those who were *H pylori* positive had significantly ( $P = 0.03$ ) higher concentrations of serum triglycerides than those who were *H pylori* negative; the trend among the cases was similar, but non-significant. The concentrations of HDL cholesterol tended to be lower in those who were *H pylori* positive than in those who were *H pylori* negative, among both the cases and the controls.

**Conclusions**—The impact of *H pylori* infection as an independent risk factor for CHD seems to be minor. On the other hand the results are consistent with the hypothesis that *H pylori* infection might modify the serum lipid concentrations in a way that could increase the risk of CHD.

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**Keywords:** coronary heart disease, *Helicobacter pylori*, serum lipids

*Helicobacter pylori* infection and coronary heart disease (CHD) are common conditions in late middle and old age. *H pylori* usually causes a lifelong infection of the gastric mucosa.<sup>1</sup> In addition, *H pylori* has been shown to cause systemic responses related to CHD.<sup>2-5</sup> *H pylori* is a major cause of gastric ulcer disease, which coincides with CHD more frequently than expected.<sup>6</sup> Recently, *H pylori* infection turned out to be associated with CHD in cross sec-

tional studies.<sup>4,7</sup> The prevalence of *H pylori* infection is dependent on the population studied,<sup>1</sup> and the results of the studies may be confounded by other risk factors for CHD and *H pylori* infection.<sup>1,8</sup> We investigated the association of *H pylori* infection with CHD in a case-control study by comparing a group of patients with angiographically documented CHD and a group of controls with a similar age and gender distribution.

## Patients and methods

The case series originally consisted of 138 consecutive patients referred to the Department of Internal Medicine, Oulu University Hospital, Finland, for elective coronary angiography because of suspected CHD. The catchment area comprised Northern Finland, which has about 650 000 inhabitants. We excluded one patient without a serum sample for serological determination of *H pylori* and 21 on lipid-lowering medication. We studied 116 patients (96 men, 20 women, aged 35-65 years, median 54 years) with angiographically documented coronary artery disease and 116 people (aged 40-59 years, median 52 years) randomly recruited from the register of the Finnish Social Insurance Institute covering the population of Oulu, the biggest city in the area, and matched for age and gender with the cases. The controls had not needed medical treatment for hypertension.

The frozen sera of the patients and the controls were simultaneously investigated for IgG antibodies to *H pylori* by an enzyme linked immunosorbent assay (Pyloriset, Orion Diagnostica, Espoo, Finland) by one of the authors (RK) who was blind to the disease status. Titres  $\geq 500$  were regarded as positive (a specificity and sensitivity of 95%). Fasting serum total cholesterol, HDL cholesterol, and total triglycerides were also measured. The patients and the controls were interviewed about their history of diabetes and smoking habits. The controls were also asked about their possible history of CHD. Selective coronary angiography was performed on the patients using the Judkins method and analysed according to the clinical routine of the hospital. A narrowing of the luminal dimensions of 50% or more was defined as a significant lesion. The patients were defined as having one, two, or three vessel disease, according to the number of arteries affected.

Concentrations of serum lipids (log transformed values) in the *H pylori* positive and

Department of Internal Medicine, University of Oulu, Finland

S Niemelä  
T Korhonen  
M Ikäheimo  
Y A Kesäniemi

Department of Pathology, University of Oulu, Finland  
T Karttunen

Public Health Science and General Practice, University of Oulu, Finland  
E Läärä

Medical Microbiology, University of Oulu, Finland  
R Karttunen

Biocenter Oulu, University of Oulu, Finland  
Y A Kesäniemi

Correspondence to: Dr S Niemelä, Department of Internal Medicine, University Hospital of Oulu, 90220 Oulu, Finland.

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Table 1 Distribution of some determinants of coronary heart disease in patients with CHD and their controls who were seropositive or seronegative for *Helicobacter pylori*

	CHD patients		Controls	
	Positive (n = 74)	Negative (n = 42)	Positive (n = 62)	Negative (n = 54)
Cholesterol (mmol/l) (median and quartiles)	6.26 (5.6, 7.1)	6.46 (5.5, 7.2)	5.71 (4.9, 6.7)	5.64 (5.2, 6.2)
HDL cholesterol (mmol/l) (median and quartiles)	0.97 (0.9, 1.2)	1.06 (0.8, 1.3)	1.18 (1.0, 1.4)	1.32 (1.1, 1.5)
Triglycerides (mmol/l) (median and quartiles)	1.87 (1.4, 2.5)	1.75 (1.1, 2.3)	1.50 (1.1, 1.9)	1.17 (0.9, 1.5)*
Number with diabetes	4	4	2	1
Number ever smokers	58	31	41	28

\*P = 0.03 for comparison between seropositive and seronegative individuals for log triglyceride concentrations adjusted for age, gender, and history of smoking in non-diabetic subjects.

negative individuals were compared in the control group, excluding those with a history of diabetes or some evidence of CHD and adjusting for age, gender, and history of smoking (current *v* ex- and never-smokers) by the analysis of covariance. A similar analysis was performed on the CHD patients. The odds ratio (OR) for the relative risk of CHD associated with the *H pylori* infection was estimated by the logistic regression model, adjusting by forward steps for age and gender; the history of smoking and diabetes; and total cholesterol, triglycerides and HDL cholesterol. Each lipid variable was divided into tertiles according to the distribution of values in the whole study group. We also analysed the data by comparing the patients with two or three vessel disease with the control group and by excluding the subjects with some evidence of CHD from the control group. The statistical analyses were performed using the SAS program (SAS Institute, Cary, NC, USA).

### Results

Compared with the control group, the CHD patients had higher serum concentrations of total cholesterol and total triglycerides and lower serum concentrations of HDL cholesterol and were more often diabetic and ever-smokers (table 1). In the control group, after adjustment for the effect of age, gender, and smoking by the analysis of covariance, those who were *H pylori* positive had higher serum concentrations of triglycerides (P = 0.03) and lower HDL cholesterol (P = 0.19) than those who were not. Findings in the CHD patients were similar (P = 0.18 and P = 0.18, respectively).

Seventy four (64%) cases and 62 (53%) controls were *H pylori* positive. The proportion of *H pylori*-positive individuals was higher among the cases with two or three vessel disease (51/74, 69%) than in the other CHD patients (23/42, 55%). The results of logistic

regression modelling (table 2) indicated that the CHD status was associated, though not significantly, with *H pylori* positivity when adjusted for age and gender only (OR = 1.5). However, when further adjustments were made for diabetes, smoking, total cholesterol and triglycerides, the association became weaker (OR = 1.3) and almost disappeared after adjustment for HDL cholesterol (OR = 1.1). The relative risks were higher when the patients with two or three vessel disease were compared with the control group, but even then the association was fairly weak after adjustment for all of the above determinants and the confidence interval was wide. The results were similar when the analyses were performed by excluding the subjects with any evidence of CHD from the control group.

### Discussion

Our CHD patients, especially those with two or three vessel diseases, were more often *H pylori* seropositive than the non-diseased controls. Apart from the large random variation, the estimated odds ratios may be biased by the selection of the controls and the cross sectional study design. Our controls were representative of the source population of the cases, but the exclusion of the patients with obvious hypertensive disease reduced their risk of CHD. We found that 53% of our controls were seropositive for *H pylori*, which accords with the previously reported seroprevalences of 39–60% among the Finnish blood donors aged 36–65 years.<sup>10</sup> Some misclassification of infection status is likely. This will affect all the groups and hence tend to reduce the relative risk estimates towards 1.

In the present study, the adjustment for the conventional risk factors, especially the serum HDL cholesterol concentration, reduced the estimated relative risk of CHD associated with *H pylori* positivity. In a recent study of 47 subjects with electrocardiographic evidence of myocardial ischaemia or infarction and 341 controls, *H pylori* infection was significantly associated with CHD, and the relation could not be explained by the risk factors of CHD including history of hyperlipidaemia.<sup>4</sup> However, the data also suggest a negative, although not statistically significant, effect of *H pylori* positivity on plasma apolipoprotein A concentration (reflecting HDL cholesterol concentration) and a positive effect on triglyceride concentration.<sup>4</sup> Another recent study reported a weak negative association between *H pylori* infection and HDL-cholesterol.<sup>11</sup> In addition,

Table 2 Estimated relative odds ratio (OR) with 95% confidence interval (CI) of *H pylori* positivity among all the patients with CHD and those with two or three vessel disease compared with controls and adjusted in a forward manner for certain determinants of CHD in a logistic regression models

	All CHD		2 and 3 vessel disease	
	OR	(CI)	OR	(CI)
(1) Age and gender	1.48	(0.9, 2.5)	1.86	(1.0, 3.5)
(2) 1 + diabetes and smoking	1.37	(0.8, 2.4)	1.71	(0.9, 3.3)
(3) 2 + total cholesterol	1.40	(0.8, 2.5)	1.62	(0.8, 3.2)
(4) 3 + triglycerides	1.31	(0.7, 2.4)	1.55	(0.8, 3.2)
(5) 4 + HDL cholesterol	1.10	(0.6, 2.1)	1.40	(0.6, 3.0)

acute infections have been shown to reduce the serum HDL cholesterol concentration and increase the serum triglyceride concentration.<sup>12</sup> In our study the similar trend observed both in the CHD patients and in the controls suggests that *H pylori* may modify serum lipid concentrations. If this is true and the effect of *H pylori* infection on the risk of CHD is mediated by HDL cholesterol and triglyceride concentrations, then these lipid variables should not be adjusted when the effect of *H pylori* on the disease is assessed. If, however, *H pylori* infection does not affect serum HDL cholesterol or triglyceride concentrations, these variables would be ordinary confounders and should be adjusted for. We analysed the data both without and with these adjustments and present the appropriate results for the alternative theories about the role of HDL cholesterol and triglycerides.

*H pylori* infection and CHD may have shared risk factors, because low socioeconomic status in childhood may predispose to both conditions.<sup>18</sup> We did not have this information for those in our study. In the British study, adjustment for the features of current and childhood socioeconomic conditions only slightly reduced the effect of *H pylori* seropositivity on the risk of CHD<sup>7</sup> and a recent study concluded that the social class was associated with CHD independently of *H pylori* infection.<sup>11</sup>

The present results indicate that after adjustment for some known key determinants of CHD, *H pylori* infection has little impact as an independent risk factor for CHD. However, the confidence intervals were wide leaving room for the possibility that *H pylori* could

have a moderate effect on the risk of CHD. Also the data are consistent with the hypothesis that *H pylori* may modify serum lipid concentrations in a way that may increase the risk of CHD. A longitudinal study with treatment intervention and with more expected cases would be needed to examine the causal relations between these associations.

Orion Diagnostica, Espoo, Finland, provided the Pyloriset kits free of charge.

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