

Association of *Helicobacter pylori* infection with elevated serum lipids

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Abstract

Helicobacter pylori causes a chronic gastric infection, which has been associated with coronary heart disease. To evaluate the mechanisms of this association, we studied whether the infection affects serum lipid levels as previously shown in acute infections. We analysed the serum samples of 880 males who participated in a reindeer herders' health survey in Northern Finland in 1989. *H. pylori* IgG and IgA antibodies were measured by enzyme-linked immunosorbent assay and triglyceride, total cholesterol and high-density lipoprotein cholesterol concentrations by routine enzymatic methods. A total of 52% of the subjects were positive for both *H. pylori* specific IgG and IgA and 31% were antibody-negative. The serum triglyceride and total cholesterol concentrations were significantly higher in the males with positive IgG and IgA antibody titres for *H. pylori* than in the males with no signs of infection (1.20 vs. 1.03 mmol/l, $P < 0.001$ and 6.59 vs. 6.11 mmol/l, $P < 0.001$, respectively). The associations remained statistically significant in non-smokers after the adjustment for age, body mass index (BMI) and social class. The finding supports the hypothesis that chronic infections may modify the serum lipid profile in a way that increases the risk of atherosclerosis. © 1999 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

Helicobacter pylori is a Gram-negative bacterium, which commonly causes chronic infection of the gastric mucosa [1]. Recent studies have suggested that chronic infections with *H. pylori* and *Chlamydia pneumoniae*, a common respiratory pathogen, may be associated with the risk of coronary heart disease [2–5].

Acute infections are known to interfere with lipid metabolism. Elevation of triglycerides has been detected especially in infections caused by Gram-negative bacteria [6]. Several studies have also shown that high density lipoprotein decreases in both bacterial and viral

infections [7–10]. We have earlier shown that the presence of *C. pneumoniae* antibodies is associated with an altered serum lipid profile considered as a risk factor for atherosclerosis [11]. We now wanted to study whether *H. pylori* infection is also associated with changes in lipid metabolism.

2. Methods

2.1. Study population

The study population consisted of the men who participated in the reindeer herders' health survey carried out from 1985 to 1989 [12]. The all-male basic population consisted of men engaged in reindeer herding in Finland in 1985. In 1986, a postal inquiry about social background, work, smoking, disease symptoms,

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etc., was sent out to 3720 males, of whom 2705 responded. Two years later, a second inquiry was addressed on the 3466 males who were still alive and active in reindeer herding, and 2081 responded. The study group was then randomly divided into three parts. A medical examination was performed on one group, a dietary interview was conducted in another group (the intervention group), and the third group served as controls. Blood samples were collected in 1989 from all members of the medical examination group and from every second member of the intervention group, totalling 1053 men.

The blood samples were taken at 08.00 to 11.00 after 12 h of fasting. The blood was allowed to clot for 30 min and centrifuged, and the serum was frozen at -20°C .

2.2. Measurement of serum lipids

The triglyceride, total cholesterol and high-density lipoprotein cholesterol concentration measurements were performed in the laboratory of the University Hospital of Oulu by routine enzymatic methods.

2.3. Serological studies

H. pylori-specific serum IgG and IgA antibodies were determined from serum samples by an enzyme-linked immunosorbent assay (Pyloriset, Orion Diagnostica, Espoo, Finland). According to the manufacturer's instructions, titres ≥ 300 for IgG and ≥ 250 for IgA were regarded as positive.

2.4. Statistical analyses

Analysis of covariance with age, body mass index (BMI) and the socio-economic status as covariates was used to test the serum triglyceride, cholesterol and high density lipoprotein cholesterol concentrations and the high density lipoprotein cholesterol:total cholesterol ratios between antibody-positive and -negative cases in two smoking groups. Student *t*-test was used in comparison of continuous variables and χ -square test of categorical variables between the groups. The statistical analyses were performed with the SPSS statistical software.

3. Results

The study group consisted of 880 males, aged between 20 and 85 years (mean 47, S.D. 13 years). The principal occupation of 510 men (58%) was in agriculture, reindeer herding or comparable. A total of 13% (118) were unskilled labourers and 23% (203) trained workers. Only 6% (49) of the men were professionals.

In the statistical analysis, the current socio-economic status was adjusted by grouping the study subjects into three categories according to the principal occupation so that trained workers and professionals were combined. A total of 242 (28%) men were current smokers, but in the statistical analysis also those who smoked occasionally or had quit smoking < 10 years ago were classified as smokers. The mean age of the smokers and the non-smokers differed only slightly (46.8 vs. 47.1 years, respectively). The mean BMI of the whole study group was 25.7 (range 17.7–39.7, S.D. 3.2), being the same in both smokers and non-smokers.

The distributions of age and *H. pylori* specific IgG and IgA antibodies of the whole study group are shown in Table 1. Both the IgG and IgA antibody prevalence and the geometric mean titres increased steadily with age. A total of 52% (460/880) of the cases were positive for both IgG and IgA; 13% (113/880) were positive for only IgG and 4% (38/880) for IgA, and 31% (269/880) were antibody-negative. No significant difference in the antibody prevalence was found between the smoking groups; 64% of the smokers versus 66% of the non-smokers were positive for IgG ($P = 0.464$) and 55 versus 58% for IgA, respectively ($P = 0.416$).

The geometric mean triglyceride concentration of the whole study group was 1.13 mmol/l (95% C.I. 1.09–1.17), the mean total cholesterol concentration 6.40 mmol/l (95% C.I. 6.32–6.48) and the mean high-density lipoprotein cholesterol concentration 1.26 mmol/l (95% C.I. 1.23–1.28). The geometric mean ratio of high-density lipoprotein cholesterol to total cholesterol was 0.194 (95% C.I. 0.190–0.198). Triglyceride and total cholesterol concentrations were higher and high-density lipoprotein concentrations lower in smokers than in non-smokers. Fig. 1 shows geometric mean serum triglyceride, mean total cholesterol and high density lipoprotein cholesterol concentrations and geometric mean high density lipoprotein cholesterol: total cholesterol ratios after the adjustment by age, BMI and socio-economic status in terms of the presence of *H.*

Table 1

Age distribution and *H. pylori* specific IgG and IgA antibody frequencies (%) and geometric mean titres (GMT) in different age groups

Age (years)	<i>n</i>	IgG		IgA	
		% ≥ 300	GMT	% ≥ 250	GMT
≤ 25	51	24	221	22	164
26–35	133	49	368	28	183
36–45	220	57	582	51	251
46–55	216	75	1073	67	357
56–65	199	78	1116	72	385
≥ 66	61	85	1221	82	504
Total	880	65	728	57	294

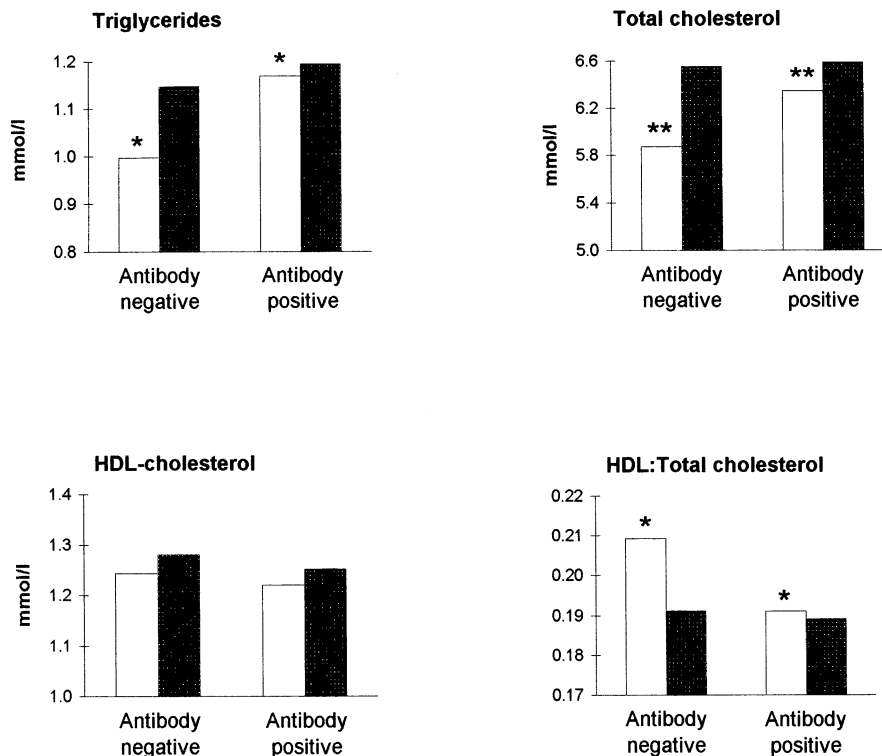


Fig. 1. Geometric mean concentrations of serum triglycerides, mean total cholesterol and high density lipoprotein cholesterol concentrations and geometric mean high density lipoprotein cholesterol: total cholesterol ratios adjusted by age, BMI and socio-economic status in relation to the presence of *H. pylori* antibodies and smoking (open columns, non-smokers; dark columns, smokers; * $P < 0.05$, ** $P < 0.01$).

pylori-specific IgG and IgA antibodies and smoking. In non-smokers, the triglyceride and cholesterol concentrations were higher in the cases positive for both IgG and IgA than in the antibody-negative cases (1.17 mmol/l vs. 1.00 mmol/l, $P = 0.014$ and 6.34 vs. 5.87 mmol/l, $P = 0.003$, respectively). The high-density lipoprotein cholesterol concentration was somewhat lower (1.22 vs. 1.24 mmol/l, respectively), but the difference was not statistically significant. However, the high-density lipoprotein cholesterol:total cholesterol ratio was significantly lower in the antibody-positive than in the antibody-negative cases (0.19 vs. 0.21, $P = 0.013$). In smokers, the differences in the lipid levels were parallel but statistically non-significant.

4. Discussion

We show in this study that *H. pylori*-seropositive males have higher serum triglyceride and total cholesterol and lower high-density lipoprotein cholesterol concentrations than seronegative subjects. Some earlier studies have suggested an association between *H. pylori* infection and cardiovascular diseases, which may be due to the effect of the infection on lipid metabolism [13–15]. However, a recent study suggested that the association might be indirect and related to social class [16]. Our study population consisted of males engaged

in reindeer herding in a relatively small area in Northern Finland. The social background of the population is very homogenous and thus, the odds of indirect association through social class differences in childhood are not probable. The adjustment for age, BMI and current socio-economic status did not weaken the association. Smoking, however, is a potent confounder, although no difference in antibody prevalence between the smokers and the non-smokers was found. To exclude the effect of smoking, the study group was divided into non-smokers and smokers, and in non-smokers, the infection was found to be significantly associated with altered serum lipid levels. Smoking seems to effect the lipid metabolism so strongly that it dilutes the effect of other factors.

Acute microbial infections are known to induce disturbances in lipid and lipoprotein metabolism [6–10]. Triglyceride levels usually rise and high density lipoprotein cholesterol levels decline. Total cholesterol levels respond more variably; both elevated and lowered values have been found in different studies. These changes are thought to be mediated by cytokines, especially by tumour necrosis factor- α , which inhibits lipoprotein lipase, leading to mobilisation of lipids from tissues and to elevated serum triglyceride and lowered high density lipoprotein cholesterol concentrations [17]. High triglyceride and low high-density lipoprotein cholesterol concentrations and especially low high-den-

sity lipoprotein cholesterol: total cholesterol ratios are known to be important risk factors for atherosclerotic diseases [18,19].

In our previous study, we found subjects with *C. pneumoniae* antibodies to have higher serum triglyceride and lower serum high-density lipoprotein cholesterol concentrations and high-density lipoprotein cholesterol: total cholesterol ratios than antibody-negative subjects [11]. *H. pylori* antibody-positivity seems to have a similar, but somewhat weaker effect on serum lipid values. Both bacteria are Gram-negative, thus carrying lipopolysaccharide, which stimulates the production of many cytokines, including tumour necrosis factor- α [20,21]. However, *C. pneumoniae* is an invasive, obligatory intracellular organism and may induce a different immune response and produce more vigorous cytokine expression.

Chronic infections, i.e. *C. pneumoniae* [1,22] and dental infections [23], along with *H. pylori* have been shown to relate with atherosclerosis, but the causality and possible mechanisms of this association are obscure. The *C. pneumoniae* organism has also been detected in atherosclerotic lesions by several different methods [24,25]. Now, we have shown that in addition to *C. pneumoniae*, also *H. pylori* infection is associated with altered serum lipid profile. The findings support the hypothesis that chronic infections may modify lipid metabolism in a way that could increase the risk of atherosclerosis.

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