Association of *Helicobacter pylori* Infection With Cardiovascular and Cerebrovascular Disease in Diabetic Patients

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OBJECTIVE — Infection by *Helicobacter pylori* has been epidemiologically linked to some extradigestive conditions, including ischemic heart disease. Diabetic patients are an at-risk population for cardiovascular and thrombo-occlusive cerebral disease. The aim of the study was to examine a possible relationship between *H. pylori* infection and cardiovascular or cerebrovascular disease in diabetic patients.

RESEARCH DESIGN AND METHODS — This was a cross-sectional case-control study with 127 diabetic patients (both IDDM and NIDDM). Special emphasis was placed on the detection of clinical macro- and microvascular complications, cardiovascular risk factors, acute phase reactants, and serological markers of increased cardiovascular disease risk. *H. pylori* infection was assessed through the determination of specific Ig-G titers, measured by a commercial enzyme-linked immunosorbent assay.

RESULTS — Coronary heart disease was more prevalent in diabetic patients with than without *H. pylori* (odds ratio [OR] 4.07; 95% CI 1.21–13.6; $P < 0.05$). A history of thrombo-occlusive cerebral disease was also more frequent in *H. pylori*–positive diabetic patients (OR 4.8; 95% CI 1.24–18.51; $P < 0.05$). Other complications such as peripheral arteriopathy, advanced nephropathy, neuropathy, or retinopathy were no differently distributed according to serological status. Alterations in the levels of the following acute-phase reactants and blood chemistry determinations were significantly more profound in *H. pylori*–positive diabetic patients: high fibrinogen ($P < 0.05$), high erythrocyte sedimentation rate ($P < 0.001$), high triglycerides ($P < 0.001$), and low HDL cholesterol ($P < 0.001$). These values were also more deeply altered in *H. pylori*–positive diabetic patients with a history of coronary heart disease, thrombo-occlusive cerebral disease, or both, when compared with *H. pylori*–positive diabetic patients without those complications.

CONCLUSIONS — Our data indicate a possible association of *H. pylori* infection and the development of coronary heart disease, thrombo-occlusive cerebral disease, or both, in diabetic patients. The importance of this link is highlighted by the possibility of an effective intervention against *H. pylori* infection.

Recent studies have suggested a possible epidemiological association between some chronic infections (*Helicobacter pylori, Chlamydia pneumoniae)* and the presence of coronary heart disease (1–6). In a case-control study, Mendall et al. (1) found that being seropositive for *H. pylori* conferred a twofold risk of suffering coronary heart disease.

The mechanisms by which *H. pylori* might influence cardiovascular risk are unknown. One hypothesis is that this chronic infection might contribute by increasing the concentration of acute phase reactants, such as sialic acid (7), fibrinogen (8,9), lipoproteins (10), and C-reactive protein (11). Some authors have described an independent association between fibrinogen concentration and *H. pylori* infection (12).

Diabetic patients are an at-risk population for coronary heart and cerebrovascular diseases. The clarification of the influence of any factor on the development of these diseases could add to their control and prevention.

We performed a cross-sectional case-control study to investigate a possible association between cardiovascular disease, its risk factors, and infection by *H. pylori* in a population of diabetic patients. Recent data suggest that obesity, NIDDM, and IDDM might be associated with an increased incidence of *H. pylori* infection (13,14).

RESEARCH DESIGN AND METHODS

Subjects

A population of 127 diabetic outpatients (contacted during their periodic checkup between January 1996 and June 1997), with both IDDM ($n = 64$) and NIDDM ($n = 63$), was analyzed through clinical records review and personal interview. The distribution of IDDM and NIDDM was similar in the *H. pylori*–positive and *H. pylori*–negative groups.

The following variables were specifically recorded: general demographic details, years of diabetes duration, history of angina, myocardial infarct or cerebrovascular accident, smoking habits, and social circumstances (Elley-Irving criteria) (15). These patients were followed in a diabetes clinic and managed with hypoglycemic drugs or insulin in a standard way.

Outcome data

Coronary heart disease was clinically assessed. In addition, a 12-lead resting electrocardiogram was recorded with the patient in the supine position (Mac PC Electrocardiograph, Marquette Electronics) and

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Abbreviations: ESR, erythrocyte sedimentation rate; OR, odds ratio.

Table 1—*Clinical and epidemiological characteristics of the study population*

Characteristics	*H. pylori*–positive	*H. pylori*–negative
Number (n = 127)	53 (41.7)	74 (58.3)
Age (years)	59.2 ± 29	60.9 ± 31
Sex (M/W)	26/27	38/36
Diabetic duration (years)	16.3 ± 2.1	15.9 ± 3.1
BMI (kg/cm^{-2})	28.3 ± 2.3	29.1 ± 3.8
Urban/rural area	50/3	70/4
Smoking habit	56.6%	60.8%
Systolic blood pressure (mmHg)	128.5 ± 19	129.1 ± 21
Diastolic blood pressure (mmHg)	85.4 ± 9	84.6 ± 8.9

Data are means ± SD, n, or n (%). P = NS for all characteristics. Individuals in the study population had similar socioeconomic statuses.

evaluated by a cardiologist. The presence of any of the following was considered suggestive of coronary heart disease: T wave inversion, ST segment depression, or Q waves. Blood pressure was measured twice (average) after a 10-min rest with a random zero mercury sphygmomanometer in the same arm and with the patient lying down.

In patients with indicative signs or symptoms, the presence of cerebrovascular disease (thrombo/occlusive) was documented with a central nervous system computed tomography. The final diagnosis was reviewed by a neurologist.

Peripheral vascular disease was clinically defined by the presence of intermittent claudication, absent or weakened peripheral pulses, or both.

Retinopathy was documented by standard fundus examination, and diagnosed on the observation of microaneurysms, venous dilation, cotton-wool spots, neovascularization, or hemorrhages. The degree of retinopathy was determined with the Early Treatment Diabetic Retinopathy Study (ETDRS) interim scale (16).

Clinical neuropathy was defined by an abnormal neurological examination, consistent with the presence of peripheral sensorimotor neuropathy (altered vibration threshold and altered tendinous reflexes), plus abnormal nerve conduction in at least two peripheral nerves with temperature controlled and the patient lying down (Neuromatic 2000; Dantec, Skoulunde, Denmark).

Advanced nephropathy was defined by the presence of urinary albumin excretion ≥300 mg per 24 h (SSR-XT; Miles, Tarrytown, NY) and a rate of creatinine clearance <70 ml · min^{-1} · 1.73 m^{-2}.

Assays

Fasting blood samples were drawn for *H. pylori* serological tests and for measurement of plasma fibrinogen by quantitative assay (Boehringer-Mannheim, Mannheim, Germany) and glucose by the glucose oxidase method. Serum cholesterol and triglyceride concentrations were determined by enzymatic colorimetric assay (Technicon, Tarryton, NY), and HDL cholesterol was determined enzymatically in the supernatant after precipitation of other lipoproteins with dextran sulfate-magnesium. LDL cholesterol was calculated using the Friedewald formula. Total leukocytes and platelets and the erythrocyte sedimentation rate (ESR) were measured with Technicon H-2 (Technicon), and HbA_{1c} was measured by high-performance liquid chromatography (Hi-AutoA_{1c}, Daiichi, Kyoto, Japan).

H. pylori–negative specific IgG titers were measured by a commercial enzyme-linked immunosorbent assay (VARELISA elias, Osceola, WI). The manufacturer's recommended cut-off point (10 U/ml) provides, in a white population, a sensitivity of 92% and a specificity of 94% for the diagnosis of *H. pylori* infection, with intra-assay variability of 6.2% and interassay variability of 8.1%. Patients with results <10 U/ml were classified as *H. pylori*–negative (controls).

Statistical analysis

Data are averages ± SD. The distribution of variables was analyzed with the Kolmogorov-Smirnov test. Quantitative variables with normal distribution were analyzed with a two-tailed, unpaired Student's t test. Nonparametric variables were analyzed with the Mann-Whitney U test. Qualitative variables were analyzed with the χ^2 test, with Yates correction as necessary, and Fisher's test. $P < 0.05$ was considered statistically significant. The statistical package used was obtained from SPSS.

RESULTS — The presence of *H. pylori* infection was detected in 53 of 127 diabetic patients (41.7%). *H. pylori*–positive and *H. pylori*–negative subpopulations were comparable according to clinical and epidemiological characteristics (Table 1) as well as to socioeconomic status. There were no differences in the *H. pylori* titers between IDDM and NIDDM patients (data not shown). The dosage of insulin (41.2 ± 13 vs. 39.8 ± 12.9 U; NS) and the sulfonylurea, glibenclamide (10.5 ± 5 vs. 12.3 ± 2.5 mg; NS), was similar in both groups, with no statistical differences.

Electrocardiographic and clinical evidence of coronary heart disease was present in 10 of 53 *H. pylori*–positive patients (18.8%). A history of angina was present in 6 of 53 (11.3%), and a history of myocardial infarct was noted in 4 of 53 patients (7.5%) (Table 2). Among *H. pylori*–negative patients, 4 of 74 (5.4%) had electrocardiographic and clinical evidence of coronary heart disease, 3 of 74 (4.1%) had a history of angina, and 1 of 74 (1.35%) had a history

Table 2—*Macro- and microvascular complications in diabetic patients with* H. pylori *infection*

Characteristics	*H. pylori*–positive	*H. pylori*–negative
n	53	74
Coronary heart disease	18.8*	5.4
Myocardial infarction	7.5	1.35
Angina	11.3	4.1
Cerebrovascular disease	16.9†	4.1
Peripheral vascular disease	28.3	27.02
Retinopathy	26.4	27.0
Nephropathy	32	29.72
Neuropathy	22.6	20.27

Data are % unless otherwise indicated. *OR 4.07, 95% CI 1.21–13.6, P = 0.035; †OR 4.8, 95% CI 1.24–18.51, P = 0.034. No statistically significant differences were found in the other complications.

Table 3—*Acute-phase reactants and lipid levels*

Factors	*H. pylori*–positive	*H. pylori*–negative
n	53	74
Leukocyte count ($\times 10^{12}$/l)	4.12 ± 2.38	4.05 ± 1.09
Platelet count ($\times 10^{12}$/l)	153 ± 9.6	150.9 ± 9.3
ESR (mm/h)	57.8 ± 9*	41.2 ± 7.3
Fibrinogen (g/l)	0.547 ± 0.122†	0.498 ± 0.101
HDL cholesterol (mmol/l)	0.61 ± 0.31*	1.04 ± 0.24
LDL cholesterol (mmol/l)	3.17 ± 0.51	3.01 ± 0.82
Triglycerides (g/l)	2.01 ± 0.13*	1.9 ± 0.11
HbA_{1c} (%)	7.1 ± 1.8	7.2 ± 1.9
Fasting glucose (mmol/l)	9.26 ± 3	9.39 ± 2.38

Data are *n* or means ± SD. *$P < 0.001$; †$P < 0.05$.

of myocardial infarct. The prevalence of coronary heart disease was significantly different when comparing *H. pylori*–positive and *H. pylori*–negative patients (odds ratio [OR]) 4.07; 95% CI 1.21–13.6; $P < 0.05$).

A history of cerebrovascular accident, as shown by clinical examination, imaging techniques, or both, was present in 9 of 53 (16.9%) *H. pylori*–positive patients and 3 of 74 *H. pylori*–negative patients (4.1%). This prevalence was again significantly higher in the former (OR 4.8; 95% CI 1.24–18.51; $P < 0.05$). Titers of anti–*H. pylori* IgG were similar in patients with and without coronary heart disease, and in patients with and without cerebrovascular disease.

Other diabetic complications (peripheral vascular disease, nephropathy, neuropathy, and retinopathy) were similarly distributed in both groups (Table 2).

The prevalence of risk factors for cardiovascular disease, according to the presence of *H. pylori* infection, is shown in Table 3. High ESR, high triglyceride, low HDL cholesterol ($P < 0.001$), and high fibrinogen levels ($P < 0.05$) were significantly more prevalent in *H. pylori*–positive patients than in *H. pylori*–negative patients. Other parameters, such as hematometric values, indicators of diabetes control (fasting glucose, HbA_{1c}), age, and diabetes duration were similar in both groups (data not shown).

The distribution of other analytical parameters (HDL cholesterol, triglycerides, fibrinogen, ESR) in the subgroups of *H. pylori*–positive patients with and without coronary heart disease and cerebrovascular disease are shown in Table 4. These data show significant high ESR, high triglycerides, high fibrinogen, and low HDL cholesterol in *H. pylori*–positive diabetic patients with coronary heart disease and/or cerebrovascular disease. Other classical risk parameters such as glucose control, BMI, smoking habits, and blood pressure were similar in the two groups (data not shown).

CONCLUSIONS — The prevalence of ischemic heart disease and cerebrovascular disease was higher in patients with than without *H. pylori*. We are the first to describe this relationship in a diabetic population. The prevalence of infection in diabetic patients (41.7%) was similar to the prevalence rate in a nondiabetic population in Madrid (53%) (17).

In other clinical settings, a possible relationship between *H. pylori* infection and cardiovascular risk has been detected by epidemiological data in the general population, as exemplified by the high incidence (84.1–85.7%) of *H. pylori* seropositivity in patients with coronary heart disease (3,4,18). Although the number of patients in our study was relatively small and the possibility of a βII error should be noted, our study adds to this intriguing association by confirming this observation in a population of diabetic patients. Furthermore, in this subgroup, there seemed to be an additional relationship of *H. pylori* infection and cerebrovascular disease.

These data could suggest that infection by this microorganism might be an additional risk factor for these conditions. Our study was performed with a serological test that indicates that the patient has had an infection with *H. pylori*, but does not necessarily imply that the infection was present at the time the serological test was taken. The mechanism by which such an infection could have this effect is unclear. Our results showed a relationship among *H. pylori* infection in diabetic patients; high levels of tryglicerides, fibrinogen, and ESR; and low levels of HDL cholesterol.

No relationship was found between macrovascular complications of diabetes and glucose control, BMI, diabetes duration, and sex. It has been hypothesized that chronic inflammation could contribute to the risk of vascular disease by increasing some acute-phase reactants and inflammation mediators, damaging endothelial cells, altering lipid levels and oxidation, and changing blood coagulation.

Systemic effects of *H. pylori* infection are not clinically apparent. However, *H. pylori* has been shown to influence fibrinogen concentration and total leukocyte count (19), as happens in chronic dental infection (19), which has also been linked to coronary heart disease (20). This effect of *H. pylori* on markers of inflammation such as fibrinogen, GSR, and leukocyte count may be mediated via certain cytokines, including interleukin-6 and tumor necrosis factor-α (TNF-α). Concentrations of this cytokine are increased in the gastric mucosa of *H. pylori*–positive infected patients (21). Interleukin-6 can increase hepatic gluconeogenesis and triglyceride synthesis. TNF-α also inhibits

Table 4—*Acute-phase reactants and lipid levels in* H. pylori*–positive patients*

Factors	Coronary heart disease		Cerebrovascular disease	
	Yes	No	Yes	No
Leukocyte count ($\times 10^{12}$/l)	4.1 ± 2.37	4.08 ± 2	4.23 ± 2.4	4.1 ± 1
Platelet count ($\times 10^{12}$/l)	154.2 ± 10.2	150.9 ± 9.97	158.9 ± 11	156 ± 8
ESR (mm/h)	56.9 ± 4.5‡	40.2 ± 2.1	57.3 ± 3.8‡	41.9 ± 3
Fibrinogen (mg/l)	563.2 ± 100*	473.7 ± 101	561 ± 90†	469.2 ± 93
HDL cholesterol (mmol/l)	0.62 ± 0.31*	1.08 ± 0.2	0.59 ± 0.25‡	1.08 ± 0.19
LDL cholesterol (mmol/l)	3.17 ± 0.51	3.03 ± 0.77	3.22 ± 0.54	3.05 ± 0.77
Triglycerides (g/l)	2.03 ± 0.1‡	1.82 ± 0.09	204.7 ± 9.3‡	181.2 ± 8.9
HbA_{1c} (%)	7 ± 0.8	7.1 ± 1.2	7.2 ± 1	7.1 ± 0.9
Fasting glucose (mmol/l)	9.29 ± 2.5	9.39 ± 4.05	9.33 ± 2.66	9.41 ± 3.5

Data are means ± SD. *$P < 0.01$; †$P < 0.05$; ‡$P < 0.001$.

lipoprotein-lipase activity and stimulates hepatic lipogenesis, altering the lipid levels.

On the other hand, gram-negative bacilli produce lipopolysaccharides, which act as a potent immunogen agent, stimulating an inflammatory reaction that could ultimately lead to the destruction of endothelial cells (22,23).

Systemic effects of gram-negative bacilli have been described in animals and humans, particularly in lipoprotein levels. The most frequent alterations are an increase in triglyceride and VLDL levels and a decrease in HDL cholesterol levels (24–28). These are related to the acute and chronic phases of infection, respectively.

Another possible mechanism involving *H. pylori* in atherogenesis is the promotion of LDL oxidation mediated by the release of superoxide anion induced by bacterial lipopolysaccharides (30,31). Oxidation enhances the atherogenic capacity of those molecules (32).

Another hypothesis is direct cytokine-mediated endothelialitis and alteration of lipid levels toward a high cardiovascular risk profile, which could explain how *H. pylori* infection would lead to a vascular damage.

More recently, Miragliotta et al. (5) showed that *H. pylori* is able to induce blood coagulation through the stimulation of leukocyte production of tissular-like factor, which in turn promotes the conversion of fibrinogen into fibrin (4).

In summary, *H. pylori* infection seems to be epidemiologically linked to the presence of cardiovascular and cerebrovascular diseases in diabetic patients. This effect could be explained by the ability of *H. pylori* to alter lipid profiles and promote the synthesis and release of acute phase reactants. The fact that *H. pylori* infection can be effectively treated opens intriguing possibilities of lowering vascular disease risk of diabetic patients already burdened by this important complication.

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