Infection with *Helicobacter Pylori*, Coronary Heart Disease, Cardiovascular Risk Factors, and Systemic Inflammation: The Third National Health and Nutrition Examination Survey

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Background: Few data have been published on the association of variables of the metabolic syndrome and infection with *Helicobacter pylori*, a putative risk factor for cardiovascular morbidity, in large, representative samples of total populations.

The null hypothesis was no association of prevalent infection with *H. pylori* with prevalent coronary heart disease (CHD), systemic inflammation, and variables associated with the metabolic syndrome in American men.

Design: Cross-sectional survey of a large national sample, the Third National Health and Nutrition Examination Survey.

Methods: Among men aged 40–74 years, the survey measured history of CHD, glycated hemoglobin percent, and concentrations of fasting serum glucose, insulin, triglycerides, HDL cholesterol, and C-reactive protein (CRP).

Results: Prevalence of infection with *H. pylori* increased with age. *H. pylori* infection was not correlated with serum CRP, prevalence of diagnosed diabetes mellitus, glycated hemoglobin percent, or other risk factors other than age. In diabetic men but not in all men, seropositivity was significantly associated with CHD prevalence.

Conclusions: No consistent associations of *H. pylori* infection with diabetes prevalence or variables of the insulin resistance syndrome were found in American men aged 40–74 years. In diabetic men, *H. pylori* infection was associated with CHD prevalence.

Key words: *Helicobacter pylori* ■ coronary disease ■ health surveys ■ glucose tolerance ■ insulin ■ serum ■ diabetes mellitus ■ obesity

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INTRODUCTION

Few studies have examined the relationship of infection with *Helicobacter pylori* and prevalence of diabetes, increased serum insulin concentration, or insulin resistance, despite the relationship postulated for all these variables with coronary heart disease (CHD), and atherosclerosis.[1-4] Some studies report higher prevalence of infection with *H. pylori* in persons with type-2 or type-1 diabetes than in nondiabetics,[1] while others do not.[2-5] No study was found of the association of infection with *H. pylori* and glucose utilization measured using a hyperinsulinemic euglycemic clamp, the best indicator of insulin resistance.[3] The existence of an independent association of *H. pylori* infection status with future risk of myocardial infarction (MI) has been reported in a few studies but not in others,[6-9] an association in unadjusted analysis often being greatly or completely diminished after adjusting for confounders. One study found a strong association of *H. pylori* status with prevalence of coronary disease, stroke, and HDL and triglyceride concentration in a series of diabetics.[2] Studies of infection with *H. pylori* and obesity or other risk factors failed to find a consistent association.[3,5,6] Well-established are associations of metabolic risk factor clustering with insulin sensitivity and hyperinsulinemia, the metabolic syndrome.[10-21]

In order to test the null hypothesis that prevalences of MI, type-2 diabetes, and some of the variables comprising the metabolic syndrome are not significantly associated with exposure to *H. pylori* infection independent of gender, age, or ethnicity, data from the Third National Health and Nutrition Examination Survey (NHANES III) were examined.

METHODS

NHANES III was conducted in 1988–1994 on a nationwide multistage probability sample of approximately 40,000 persons from the civilian, noninstitutionalized population of the United States aged two months and over excluding reservation lands of

American Indians.[22-28] Of these, 31,311 were examined. The analysis was restricted to men to eliminate confounding by gender, pregnancy, menopause, parity, or female hormone use. IgG antibodies to *H. pylori* were measured only in the first half of the survey (Phase I), itself a representative sample of the U.S. population. The analyses in this report are limited to examined men aged 40–74 years for whom a valid serum *H. pylori* antibody measure and data on history of doctor diagnosed diabetes and glycated hemoglobin measured in the survey were available. The study was restricted to men older than 40 and younger than 75 years because that was the age range of the subsample, which received an oral glucose tolerance test in NHANES III. The analyses of serum antibody and fasting serum glucose, insulin, and triglycerides are restricted to men examined in the morning after fasting nine-to-24 hours with valid serum antibody and insulin data, no history of diabetes, and not taking insulin or oral hypoglycemic agents. Numbers of persons in various regression analyses that follow may vary slightly due to differing numbers with missing values on selected other variables. Details of the plan, sampling, operation, and response have been published as have procedures used to obtain informed consent and to maintain confidentiality of information obtained.[22-30]

Demographic information; medical history, including doctor-diagnosed diabetes mellitus and coronary heart disease; and behavioral information were collected by household interview prior to the examination. Race and Mexican-American ethnicity were determined by self-report.[22] Examinations were carried out in a mobile examination center. Blood samples were obtained at the examination center. Blood in a redtop Vacutainer tube was allowed to stand for 45 min. at room temperature to allow complete clotting and clot retraction. Samples were centrifuged at 1,500 x g for 30 min at 4°C and were frozen at -20°C. *H. pylori* serologic testing was done using a commercial IgG ELISA (Wampole Laboratories, Cranbury, NJ). Immune status ratio (ISR) was calculated as the quotient of specimen optical density and the mean optical density of three cutoff controls (negative, high positive, and low positive).[29,30] For this analysis, negative specimens had ISR 0-1.09, and positive >1.09. Retesting in a sample of 900 specimens indicated a 97% reproducibility.[29] Previous validation studies indicated a test sensitivity of 91% and specificity of 96%.[29] Overall seroprevalence of *H. pylori* in this survey was 32.5% in adults aged 20 and over.[29] Quality-control methods are described elsewhere.[24,29]

Frozen serum was sent to the Missouri Diabetes Diagnostic Laboratory and stored at -70°C until analysis for serum insulin concentration. Insulin radioimmunoassay (RIA) was performed using the Pharmacia Insulin RIA kit (Pharmacia Diagnostics AB, Uppsala, Sweden) for the majority of samples. (Prior to November 1990, RIA kits purchased from Cambridge Laboratories, Cambridge, MA and its successor, Ventrex, Inc., Cambridge, MA were used. Based on simultaneous analyses using all three assays, results from these kits were converted to Pharmacia equivalence.) Quality control procedures included the reanalysis of 5% of specimens randomly selected either within-assay or between-assay, and the analysis of batch specimens consisting of four levels of control pools before and after all survey specimens. The internal reference range for fasting serum insulin in nonobese, nondiabetic adults (mean age 28.1 years) was 3.08–11.92 uIU/mL.[24] The cross-reactivity of Pharmacia insulin antibody with proinsulin is approximately 40%. Concentration of C-peptide in serum was determined by RIA in a three-day, batch, sequential-saturation method with two incubations.[24] The internal reference range for fasting serum C-peptide was 0.266–1.079 pmol/mL. Frozen plasma was sent to the Missouri Diabetes Diagnostic Laboratory for determination of plasma glucose using a modified hexokinase enzymatic method on the Cobas Mira Chemistry System (Roche Diagnostic Systems, Inc., Montclair, NJ). Within- and between-assay quality-control procedures were used. During the six years of the survey, the coefficient of variation of the method was 1.6–3.7%.[24] Glycated hemoglobin (HbA_{IC}) in whole blood was determined using a high-performance liquid chromatographic assay on the Diamat automated HPLC system, model 723 (Bio-Rad Laboratories, Hercules, CA). The upper limit of normal for HbA_{IC} in this system has been defined as 6.1%.[24-26]

Technicians measured height to the nearest 0.1 cm; weight to the nearest 0.01 kg; triceps, subscapular, suprailiac, and mid-thigh skinfold thickness to the nearest 0.1 mm; and waist and buttocks circumference to the nearest 0.1 cm, as described in detail elsewhere.[22,27,28] With the sample person standing at minimal respiration,

Table 1. Prevalence (Percent) of *H. pylori* Seropositivity by History of Myocardial Infarction and Age in Diabetic Men: Third National Health and Nutrition Examination Survey, 1988–1994 (NHANES III)

Age (Years)	MI History	
	Negative	Positive
40–59	40.1	68.8
60–69	45.0	96.0
70–74	45.9	83.5
N	154	33

waist circumference was measured in a horizontal plane at the level of the high point of the iliac crest to the nearest 0.1 cm. Hip circumference was measured in a horizontal plane at the maximum extension of the buttocks. The following were computed: waist-to-hip circumference ratio (WHR) and body mass index (BMI=weight /height^2, kg/m^2). Extensive descriptive data on prevalence of *H. pylori* infection, diabetes, glucose tolerance, height, weight, BMI, and obesity prevalence in the NHANES III population have been published elsewhere and will not be duplicated here.[23,25,26,28-30]

Statistical Analysis

The plan of the present analyses was as follows. *H. pylori* infection was considered the exposure variable for all analyses. Detailed descriptive statistics and measures of association were computed using the Statistical Analysis System (SAS).[32] Analysis of covariance was used to assess the association of the mean levels of continuous risk variables in persons with and without infection controlling for age.[32] Multivariate logistic regression analysis was used to develop models for controlling for confounding of the association of infection status with history of doctor-diagnosed acute myocardial infarction, stroke, or diabetes mellitus.[32] Linear multivariate regression analysis was used to develop models for controlling for confounding of the association of infection status with concentrations of glycated hemoglobin, fasting serum insulin, and other continuous variables.[32] Only variables with prespecified hypotheses were entered into the regression models. Population estimates for means and percentiles of variables were produced using weighted SAS or SUDAAN (statistical software packages) procedures.[34] Age-adjusted means were performed using SAS weighted analysis, and all statistical testing and variance estimation were performed using the PROC LOGISTIC and PROC REGRESS procedure for regression models in the SUDAAN system.[32-34] These weighted analyses used techniques that incorporated sampling weights and design features of the survey.[32,33]

RESULTS

Prevalence

Figure 1 shows the prevalence of infection with *H. pylori* by age in American men aged 40–74. The prevalence generally rose in each decade of life from the fifth through seventh decades.

Table 2. Linear Regression Coefficients for *H. pylori* in Models with Fasting Serum Concentrations of Risk Factors of the Insulin Resistance Syndrome

Variable	Beta	SE beta	p
Insulin	1.25	3.18	0.70
Glucose*	1.41	1.57	0.38
Triglyceride	-0.84	9.65	0.93

Myocardial Infarction

Age-specific exposure prevalence by MI history is shown in Table 1. At age 40–74 combined, among 118 men with a history of doctor-diagnosed MI prevalence of *H. pylori* infection was no greater than in 1,483 men with no such history (age-adjusted OR=1.07, 95% CI 0.60–1.90). Similarly, in 39 men with a history of doctor-diagnosed stroke and in 1,588 men with no such history, prevalence of infection did not differ (age-adjusted OR=0.98, 95% CI 0.51–1.89). Thus, no overall association was evident in men without a history of diabetes.

However, in the subgroup of 183 diabetic men, infection was significantly associated with a history of MI (n=33, age-, ethnicity-adjusted OR=5.56, 95% CI 1.28–24.12, p=0.024). Too few prevalent stroke cases (n=13) were reported for analysis in the diabetic subgroup.

Noninsulin-Dependent Diabetes

In men aged 40–74, 52.7% (n=193) of men with a history of doctor-diagnosed diabetes and 38.6% (n=1,628) of men with no such history had evidence of *H. pylori* infection. In logistic regression models, the positive relationship between *H. pylori* infection (yes, no) and diabetic status (dependent variable) after adjusting for age or age and race/ethnicity did not attain statistical significance (age-adjusted OR 1.47, 95% CI 0.92–2.36, p=0.10).

In all men aged 40–74, infection status was not significantly associated with glycated hemoglobin (HbA_{IC}) concentration (%) (age-, ethnicity-adjusted beta -0.11, se 0.08, p=0.21). Nor was there a significant association between infection and HbA_{IC} in men with a history of diabetes (age-, ethnicity-adjusted beta -0.19, se 0.49, p=0.69), or in those without such a history (age-, ethnicity-adjusted beta -0.05, se 0.05, P=0.33).

Inflammation

In American men aged 40–74 after adjusting for age and ethnicity, infection with *H. pylori* was not significantly associated with serum C-reactive protein concentration (p=0.31), white blood cell count (p=0.14), or plasma fibrinogen concentration (p=0.74), markers of inflammation. However, a positive association of infection with serum ferritin concentration was seen (beta 28.20, 11.87, p=0.03). In those with and without infection, age-, ethnicity-adjusted means were CRP 0.42 versus 0.37 mg/dL, white blood cell count 7.49 versus 7.17 x 103 cell/mm^3, plasma fibrinogen 294 versus 299 mg/dL,

respectively. Serum ferritin was significantly higher in those with infection (mean 200 versus 178 μg/dL).

Insulin Resistance Syndrome

Regression coefficients were computed for *H. pylori* infection status with dependent variables associated with the insulin resistance syndrome adjusting for age and ethnicity. In men with no history of diabetes, *H. pylori* infection was not significantly associated with HDL cholesterol, systolic blood pressure, waist-to-hip ratio, or body mass index, risk variables associated with the insulin resistance syndrome.

In the subset of 764 fasting men aged 40–74 with no history of diabetes, weighted regression coefficients adjusted for age, ethnicity, and body mass index were computed for *H. pylori* infection status with fasting serum insulin and plasma glucose, blood measurements of insulin resistance, and glucose tolerance (Table 2). Infection status was not associated with fasting serum insulin (p=0.70), the best measure in this survey of insulin resistance, plasma glucose (p=0.38), nor with fasting serum triglycerides (p=0.93).

DISCUSSION

This study of a national sample of American men aged 40–74 years confirmed that seropositivity for *H. pylori* is associated with MI prevalence in men with diabetes but not in men without diabetes. Seropositivity for *H. pylori* was not significantly associated with prevalent diabetes mellitus or certain variables of the metabolic syndrome. For example, fasting serum insulin and glucose concentrations showed no significant associations with seropositivity for *H. pylori* in nondiabetic men. Serum or blood markers of inflammation were not associated with seropositivity for *H. pylori*, with the exception of serum ferritin.

Mechanisms

The microbiology, transmission, and immunology of *H. pylori* have been described.[35-41] Since its initial isolation in 1982, serologic tests for IgG (and IgA) antibodies against *H. pylori* have been developed. Such tests have made possible the population-based study of the epidemiology of infection and its sequelae.[36] Studies to date have indicated an equivocal association of seropositivity for *H. pylori* with CHD.[6-9] Mechanisms for putative associations of seropositivity for *H. pylori* with CHD have not been elucidated. Although atherogenic mechanisms in humans are unproven, mechanisms for vascular damage postulated based on experimental results include promoting atherogenesis, along with other bacteria, such as *Chlamydia pneumonia* or viruses, by facilitation of a synergistic inflammatory response that could cause oxidative arterial injury and augmentation of smooth muscle proliferation.[7-9,42,43] Infection-induced molecular mimicry is another postulated mechanism.[9] Increased plaque vulnerability may result from an enhanced immune response. Prothrombotic effects may also occur. Early trials of antibiotic therapy for secondary prevention of coronary events have not supported such therapy, but larger trials are needed.[42,43] Seropositivity for *H. pylori* may be more important as a contributor to infectious burden, i.e. infections with multiple pathogens.[8,9,42,43] Although one cross-sectional study reported independent associations of infectious burden with cardiovascular death and extent of atherosclerosis,[9] a prospective study failed to find an association.[7,42]

There is a need for research on the biological plausibility of the association of *H. pylori* infection and MI in men with diabetes. A clue in this study may be in the serum ferritin. Serum ferritin levels are higher with *H. pylori* infection and though ferritin is an acute phase reactant, ferritin levels probably represent total-body iron stores. High ferritin/total-body iron has been linked to increased formation of highly reactive forms of oxygen free radicals that can modify lipoproteins in an atherogenic way and perhaps diminish nitric oxide effects.

Mechanisms for an association of seropositivity for *H. pylori* with diabetes mellitus or insulin resistance are unclear. Clinical diabetes might promote infection by lowering immunocompetence or altering gastric motility with autonomic neuropathy.[33-39] Alternatively, infection by *H. pylori* since childhood might induce beta-cell damage by molecular mimicry or systemic inflammation.[9,40,41] Cross-sectional studies have linked insulin resistance and diabetes to low-grade inflammation and alterations in the innate immune system.[42] Follow-up studies have linked baseline inflammation (elevated CRP and interleukin-6) to the subsequent onset of type-2 diabetes.[42] Statins, which reduce CRP as well as LDL cholesterol, reduce the risk of new diabetes.[42] An association of diabetes with serum ferritin may reflect altered iron absorption with chronic gastritis.[36] Serum ferritin is also an acute phase reactant as well as an iron transport protein, perhaps explaining its association with *H. pylori* status in this study. Serum ferritin has been reported to be higher in CHD cases than controls in some studies but not in NHANES II.[44]

The metabolic syndrome, also termed insulin resistance syndrome, is usually defined as associated insulin resistance or hyperinsulinemia, glucose intolerance, dyslipoproteinemia (low HDL, elevated triglycerides), and hypertension.[10-21] It may also include central obesity, hyperuricemia, hypercoagulability, and is a risk factor for atherosclerotic vascular

disease and related disorders.[10-21] Insulin resistance may be defined as "a state in which greater-than-normal amounts of insulin are required to elicit a quantitatively normal response."[10] In large epidemiologic studies, fasting serum insulin concentration is used as the best measure of insulin resistance, since it is not feasible to measure it more directly using the euglycemic hyperinsulinemic clamp technique. Insulin resistance and/or hyperinsulinemia is postulated to cause the metabolic components of the narrowly defined metabolic syndrome, but its role in arteriosclerotic vascular disease is in question. Inflammation has been described as a possible component of the metabolic syndrome, with mechanisms for the association not established but perhaps include the aforementioned. Infectious burden, including *H. pylori*, might be hypothesized to be linked to the syndrome through resulting inflammation.

Comparisons with Previous Reports

In agreement with these results from NHANES III, one study reported a strong association of infection with *H. pylori* with prior MI in diabetic patients,[2] while several studies reported equivocal associations in various large samples unselected for diabetes.[42] The pooled odds ratio for seropositivity for *H. pylori* in 10 prospective studies was 1.15 (95% CI, 0.96 to 1.37).[7] Seropositivity for *H. pylori* may be more important as a contributor to infectious burden, i.e., infections with multiple pathogens.[9,42] Although one cross-sectional study reported independent associations of infectious burden with cardiovascular death and extent of atherosclerosis,[9] a prospective study failed to find an association.[7,42]

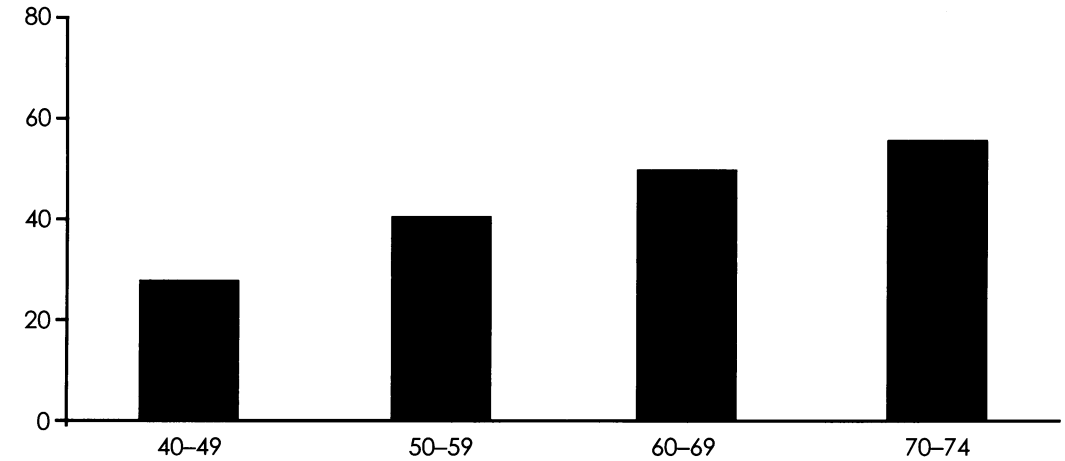
NHANES III was the first study to provide population-based data on distributions of seropositivity for *H. pylori* in a national survey of the U.S. Prevalence of seropositivity for *H. pylori* was higher in Mexican Americans than in non-Hispanic whites or blacks. Prevalence of seropositivity for *H. pylori* increased with age and was higher in men than women. A meta-analysis of data on associations of seropositivity for *H. pylori* and cardiovascular risk factors of the insulin resistance syndrome showed no significant associations except for slightly higher BMI and slightly lower HDL cholesterol in seropositive persons.[5] In the total NHANES III sample, seropositivity for *H. pylori* was not associated with risk factors of the insulin resistance syndrome, consistent with these negative findings.

Studies of *H. pylori* infection and diabetes or glucose intolerance have yielded conflicting results. For example, one Italian study of 385 diabetics and 506 controls found no excess prevalence of infection in diabetics at any age or social class.[1] Other studies have reported a higher prevalence in diabetics, postulating that impaired host defenses in diabetes may enhance susceptibility to infection.[4] A study of 59 hospital patients with antral gastritis suggested that both diabetes and obesity were associated with infection.[4] A population-based study of hypertensives and controls found combined positive serology for *H. pylori* and *C. pneumonia* to be related to higher BMI but not to fasting insulin after controlling for age and BMI.[3]

The lack of association of CRP or white blood cell count with seropositivity for *H. pylori* is consistent with studies indicating that cell-mediated immune response is responsible for the inflammatory response and for protective immunity.[37]

Limitations of the present study include possible bias arising from survey nonresponse and from missing values for some variables. Several special

Figure 1. Age-specific *Helicobacter pylori* seroprevalence (percent) in American men aged 40-74 years in the Third National Health and Nutrition Examination Survey, 1988-1994 (NHANES III).



studies of earlier NHANES and NHANES III data have indicated little bias due to nonresponse.[31,33] Adequate reliability has been demonstrated for serum IgG and IgA ELISA.[33] Day-to-day variability in serum IgG would tend to bias reported associations towards the null. Blood collection conditions in NHANES III were standardized with regard to body position and vein constriction. Although freshly collected plasma samples were not available for IgG determination in NHANES III, serum samples were promptly harvested and frozen in NHANES III and are suitable samples for IgG assay.[24,33,34] Type of drug therapy in diabetics was not considered in this analysis. Some of the drugs used to treat persons with diabetes, for example thiazolidinediones, may suppress inflammatory markers.[45] However, these were not in widespread use in 1988–1994 during NHANES III.

Unfortunately, no completely unbiased measure of insulin resistance is available for use in large population surveys.[10-21] As in the present study, fasting serum insulin concentration has been used in many studies. However, traditional insulin assays, such as the one used in NHANES III, measure proinsulin and several split products as well as specific insulin, leading to falsely high values, especially in prediabetes.[17] This could lead to biased estimates of the association of seroprevalence and serum insulin. However, this seems unlikely given the consistent lack of association will all variables of the insulin resistance syndrome. Insulin:glucose ratios were not used in this paper.

The lack of a single, generally accepted measurement protocol for insulin resistance or metabolic syndrome in epidemiologic studies remains a problem for interstudy comparisons, perhaps explaining in part inconsistencies among studies. Confounding by variables not controlled for cannot be excluded. However, given the uncertainty about the existence or nature of the association, it is unclear for which other variables should be controlled as confounders. Despite the large overall sample size in NHANES III, statistical power was limited for some subgroups, but such analyses were not reported here. The number of tests was restricted to those of weighted regression models. The representativeness of the sample and the use of sample weights provides wide generalizability of the results to U.S. men of the same ages but not necessarily to females or persons of other age groups.

Future research should include longitudinal studies of *H. pylori* infection and subsequent CHD in Mexican Americans and African Americans with and without diabetes. *H. pylori* infection and multiple risk factors should be assessed prospectively as risk factors for development of noninvasively measured atherosclerosis (e.g., carotid intima-medial thickness) in noninsulin dependent diabetes.

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