

A Case-Control Study of Association of *Helicobacter pylori* Infection With Morbid Obesity in Taiwan

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Background: Obesity is an increasing health problem in developed countries, where the prevalence of *Helicobacter pylori* infection is decreasing. Recent studies suggested colonization of the stomach by *H pylori* might affect gastric expression of appetite- and satiety-related hormone and patients cured of *H pylori* infection gained weight. It was hypothesized that *H pylori* could be a contributing pathogenic factor in childhood and adult obesity.

Methods: To determine whether *H pylori* infection is linked to obesity, a case-control study composed of 414 patients with morbid obesity (a body mass index [calculated as weight in kilograms divided by the square of height in meters] of ≥ 35 with serious comorbidity or a body mass index of ≥ 40) and 683 control subjects (a body mass index of < 25) with a comparable socioeconomic status was conducted. Immunoglobulin G antibodies against *H pylori* were measured from frozen serum samples by an enzyme-linked immunosorbent assay. Logistic regression was used to calculate the odds ratio (OR) and 95% confidence interval (CI).

Results: The overall seropositivity was significantly lower in obese patients (181 [43.7%] of 414) than controls (410 [60.0%] of 683) (OR, 0.50; 95% CI, 0.39-0.65; $P < .001$). Differences in the estimated risk of the presence of *H pylori* were more pronounced in younger age groups, with ORs of 0.32 (95% CI, 0.10-1.00; $P = .05$) in those aged 10 to 19 years, 0.55 (95% CI, 0.34-0.89; $P = .01$) in those aged 20 to 29 years, 0.49 (95% CI, 0.30-0.80; $P = .007$) in those aged 30 to 39 years, and 0.58 (95% CI, 0.33-1.00; $P = .05$) in those aged 40 years or older.

Conclusions: Our data indicated an inverse relationship between morbid obesity and *H pylori* seropositivity. These findings raise the hypothesis that a lack of *H pylori* infection, especially during childhood, might enhance the risk of the development of morbid obesity.

Arch Intern Med. 2005;165:1552-1555

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Financial Disclosure: None.

OBESITY HAS BECOME A MAJOR public health problem of global significance. Health conditions caused or exacerbated by obesity include hypertension, diabetes mellitus, sleep apnea, obesity-related hypoventilation, back and joint problems, cardiovascular disease, and gastroesophageal reflux disease. The body mass index (BMI) (calculated as weight in kilograms divided by the square of height in meters) is the most commonly accepted measurement for obesity. A BMI exceeding 25 is considered overweight, while obesity is defined as a BMI of 30 or more. A BMI of 35 or more with serious comorbidity or a BMI of 40 or more is considered morbid obesity.¹ The incidence of obesity has increased rapidly during the past 2 decades. This increase had been most dramatic in affluent countries. The factors underlying this increase are largely unknown. Although

multiple studies show that the genetic contribution is significant, our genes have not changed appreciably during this period. An increasing obesigenic lifestyle of excessive caloric intake and decreased physical activity are assumed to play a central role in this epidemiologic trend.² Whether there are other environmental factors likely to explain the epidemic of obesity remains to be elucidated.

Helicobacter pylori is a gram-negative bacillus. It was estimated that half of the world's adult population harbors *H pylori* in their stomach. In developing countries, the infectious process occurs early and reaches 60% to 80% in adulthood. The annual incidence of *H pylori* acquisition by adults is much lower in developed countries. The increase by age largely reflects a birth cohort phenomenon.³ *Helicobacter pylori* is the main causative factor of chronic gastritis. Epidemiologic studies have consistently linked *H pylori* infection to peptic

ulcer and gastric malignancies.⁴ The diverse outcomes of *H pylori* infection are ascribed to the difference in extent and severity of gastritis, which leads to variation in the amount of gastric secretion and creates a permissive luminal milieu for disease to develop.⁵ Recently, the spectrum of *H pylori*-related diseases has expanded to include gastroesophageal reflux disease and obesity. The parallel epidemic of gastroesophageal reflux disease and obesity combined with decreasing *H pylori* infection in western countries suggests *H pylori* might play a protective role in the development of obesity and gastroesophageal reflux disease.^{6,7} Based on the findings that eradication of *H pylori* could influence the dynamic of ghrelin and increase body weight,⁸⁻¹¹ Blaser and Atherton¹² proposed that *H pylori* infection might influence food intake and calorie homeostasis through defective signaling of appetite-related hormone in the stomach. A possible inverse relationship between exposure to *H pylori* and the occurrence of obesity has been further addressed in studies of morbid obesity.¹³⁻¹⁵ Preliminary data by histological examinations have shown that the infection rate of *H pylori* in these patients ranged from 24% to 38%.¹³⁻¹⁵ However, controversial results existed, and whether *H pylori* infection plays a role in childhood and adult adiposity remains to be determined.¹²⁻¹⁸

Taiwan is a newly industrialized country where the incidence of obesity is accelerating and *H pylori* infection is prevalent.^{19,20} A recent mass screening program even showed the increase of childhood diabetes mellitus on this island is due to obesity.²¹ To clarify the relationship between obesity and *H pylori* infection, we investigated, in a case-control study, the seroprevalences of *H pylori* among patients with morbid obesity and control subjects with a normal weight.

METHODS

STUDY SUBJECTS

Studied concomitantly in a random order,²² we selected consecutive patients affected by morbid obesity between January 1, 2001, and December 31, 2003. A case was defined as a patient with a BMI of 35 or more with a serious comorbidity or with a BMI of 40 or more who was admitted to En-Chu Kong Hospital for evaluation of the possibility of weight reduction surgery. Blood samples for a prospective investigation of the effect of surgery on these patients were collected. Finally, 414 eligible patients (115 men and 299 women; mean \pm SD age, 31.9 \pm 9.2 years) were enrolled. In the same period, we also enrolled controls from healthy subjects with a BMI of less than 25 who underwent a health checkup at the same center. A total of 683 controls (337 men and 346 women; mean \pm SD age, 32.3 \pm 9.5 years) fulfilling the criteria were selected. Cases and controls were from the geographical area of northern Taiwan and had a similar socioeconomic status, judged by work type and level of instruction. Written informed consent was obtained from each participant, and the ethical committee of the hospital approved the study.

LABORATORY ASSESSMENT

Venous blood samples were obtained from the patients and controls after an overnight fast. Serum was separated in a cold centrifuge at 2000 rpm for 10 minutes and was stored in a deep

freezer at -20°C until studied concomitantly in a random order. The fasting glucose concentration was determined using an enzymatic colorimetric method (Sigma Chemical, St Louis, Mo). Serum insulin levels were measured by an immune luminescence assay (Access; Beckman Coulter, Brea, Calif). Insulin resistance was estimated by the homeostasis model of assessment based on the following formula: [fasting insulin level (measured in micro-international units per milliliter) \times fasting glucose level (measured in milligrams per milliliter)]/22.5. High-sensitivity C-reactive protein was measured using immunonephelometry (Nephelometer Analyzer II; Dade Behring, Deerfield, Ill). A commercially available enzyme-linked immunosorbent assay kit (IBL, Hamburg, Germany) with reported sensitivity and specificity of more than 95% was used to investigate the prevalence of *H pylori* infection. All assays were performed in duplicate and interpreted by a single laboratory investigator (M.-S.W.) unaware of sample status to avoid the possibility of interobserver variability.

STATISTICAL ANALYSIS

All data for cases and controls were computerized, and statistical analysis was performed using a commercially available software program (SPSS, version 11.0; SPSS Inc, Chicago, Ill). χ^2 and *t* tests were used for categorical and continuous data, respectively. Nonparametric tests (Kruskal-Wallis) have been used for cases of nonnormality. The strength of association between *H pylori* and sex or age was measured by binary logistic regression to estimate the odds ratio and 95% confidence interval (CI).

RESULTS

The seroprevalence of *H pylori* was 43.7% (181/414) for cases of morbid obesity and 60.0% (410/683) for controls (odds ratio, 0.50; 95% CI, 0.39-0.65; $P < .001$). The distributions of seropositivity of *H pylori* with respect to age and sex in cases and controls are summarized in **Table 1**. Differences in the estimated risk of the presence of *H pylori* were more pronounced in younger age groups, with odds ratios of 0.32 (95% CI, 0.10-1.00; $P = .05$) in those aged 10 to 19 years, 0.55 (95% CI, 0.34-0.89; $P = .01$) in those aged 20 to 29 years, 0.49 (95% CI, 0.30-0.80; $P = .007$) in those aged 30 to 39 years, and 0.58 (95% CI, 0.33-1.00; $P = .05$) in those aged 40 years or older. On the other hand, sex has no effect on the distribution of *H pylori* seropositivity. The clinical, demographic, and metabolic variables were further compared between *H pylori*-positive and *H pylori*-negative patients with morbid obesity. No difference in BMI, age, sex, white blood cell count, hemoglobin concentration, high-sensitivity C-reactive protein level, glycosylated hemoglobin level, and homeostasis model of assessment value was observed between these 2 groups (**Table 2**).

COMMENT

Increasing attention has recently been paid to the role of *H pylori* in the pathogenesis of nutritional problems and obesity.⁸⁻¹⁸ The results of this case-control study show a statistically significant inverse relationship between morbid obesity and *H pylori* seropositivity. Of special interest is that the younger the age, the greater the influence

Table 1. Seroprevalences of *Helicobacter pylori* in Patients With Morbid Obesity and Control Subjects With Respect to Age and Sex*

Age, y	Patients With Morbid Obesity			Controls		
	Male	Female	All	Male	Female	All
10-19	0/6	4/16 (25.0)	4/22 (18.2)	33/77 (42.9)	30/77 (39.0)	63/154 (40.9)
20-29	21/63 (33.3)	50/130 (38.5)	71/193 (36.8)	35/58 (60.3)	22/53 (41.5)	57/111 (51.4)
30-39	14/33 (42.4)	42/85 (49.4)	56/118 (47.5)	42/66 (63.6)	47/74 (63.5)	89/140 (63.6)
≥40	9/13 (69.2)	41/68 (60.3)	50/81 (61.7)	94/136 (69.1)	107/142 (75.4)	201/278 (72.3)
All	44/115 (38.3)	137/299 (45.8)	181/414 (43.7)	204/337 (60.5)	206/346 (59.5)	410/683 (60.0)

*Data are given as number/total (percentage) of each group.

Table 2. Demographic and Clinical Data Between *Helicobacter pylori*-Positive and *H pylori*-Negative Patients With Morbid Obesity*

Variable	<i>H pylori</i> -Positive Patients (n = 181)	<i>H pylori</i> -Negative Patients (n = 233)	All Patients (N = 414)	P Value†
Male-female ratio	44:137	71:162	115:299	.18
Age, y	34.3 ± 9.3	30.0 ± 8.6	31.9 ± 9.2	.13
BMI	40.1 ± 7.8	40.5 ± 7.7	40.3 ± 7.7	.69
WBC count, ×10 ³ /μL	8.5 ± 2.3	8.6 ± 2.4	8.5 ± 2.4	.74
Hb level, g/dL	13.6 ± 1.6	13.7 ± 1.4	13.6 ± 1.5	.63
hsCRP level, mg/L	0.8 ± 1.5	0.8 ± 1.2	0.8 ± 1.3	>.99
Glycosylated hemoglobin level, %	5.8 ± 1.0	5.9 ± 1.1	5.8 ± 1.1	.51
HOMA value‡	95.5 ± 279.8	79.5 ± 212.9	86.5 ± 244.2	.64

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); Hb, hemoglobin; HOMA, homeostasis model of assessment; hsCRP, high-sensitivity C-reactive protein; WBC, white blood cell.

*Data are given as mean ± SD unless otherwise indicated.

†Data given for the comparison between *H pylori*-positive and *H pylori*-negative groups.

‡The formula for this value is given in the "Laboratory Assessment" subsection of the "Methods" section.

of *H pylori*. These findings raise the hypothesis that a lack of *H pylori* infection, particularly during childhood, might favor the development of obesity.

The prevalence of *H pylori* infection is related to several confounding factors, such as age and socioeconomic status.²⁰ There is evidence of a decreased seroprevalence of *H pylori* in developed countries during recent decades.^{3,4} The decrease in *H pylori* seroprevalence seems to coincide with the increase in the incidence of obesity. Previous studies^{19,20} in Taiwan indicated that the seropositivity of *H pylori* in the general population varied from 54% to 63% and the incidence of obesity has increased to the level of developed countries. In the present study, the seroprevalence of *H pylori* in the control group was within the reported range.²⁰ Furthermore, the marked decrease in seroprevalence of *H pylori* with decreasing age in morbidly obese patients supports the notion that populations with a low prevalence of *H pylori* have more obese individuals.¹² However, certain limitations were noted in interpreting our observations. Although both groups were said to be of the same socioeconomic status, it is likely that a more sensitive assessment would have found among the controls more individuals from larger sibships, who had grown up in more crowded homes. Effectively, thin people are more likely to be of lower socioeconomic status than age-matched obese people.²³ In addition, we had no data regarding exposure to antibiotics between the 2 groups.

Prior studies¹³⁻¹⁸ have not uniformly demonstrated a clear association of *H pylori* with obesity. Scapa et al¹³ first recognized that the incidence of *H pylori* in stom-

achs of morbidly obese patients was low: 26.7% in 15 obese patients by culture and biopsy urease test results. Renshaw et al¹⁴ and Ramaswamy et al¹⁵ have documented that 38% and 24% of patients undergoing surgery for morbid obesity have evidence of *H pylori* by histological examination result, respectively. Consistent with these earlier studies, the seroprevalence of *H pylori* in our large cohort of morbidly obese patients was relatively lower (43.7%) compared with our controls. On the other hand, several studies¹⁶⁻¹⁸ with a non-case-control design have described the lack of any difference in prevalence of *H pylori* with respect to body weight. Kawano et al¹⁶ reported that *H pylori* infection was not related to BMI in asymptomatic subjects. Kyriazanos et al¹⁷ found that the incidence of *H pylori* is not increased in obese people. Perdichizzi et al¹⁸ even showed *H pylori* infection tended to increase in hyperglycemic obese subjects. Collectively, the major controversy from different studies seemed to arise from method. Small sample sizes, different definition of obesity and selection of patients, various detecting methods of *H pylori* infection, no control group, and lack of consideration of confounding factors are among the reasons to explain the discrepant results. Further large-scale prospective studies of comparable subjects with full consideration of the confounding factors are warranted to definitely establish the protective role of *H pylori* in morbidly obese patients.

It is not possible to deduce from our study the causal relationship between *H pylori* infection and obesity. The mechanisms underlying the inverse association have remained obscure, but several potential interactions are op-

erative between *H pylori* and obesity. Blaser and Atherton¹² proposed a fascinating pathogenic role of *H pylori* in obesity in a recent review. They assumed that *H pylori*-induced persistent and uncontrolled gastric inflammation would lead to dysregulation of appetite and calorie homeostasis through its effect on the expression of gut hormones such as ghrelin.⁸⁻¹¹ Therefore, individuals exposed to *H pylori* in early childhood are prone to have a decreased appetite and food intake due to defective signaling of appetite- and satiety-related hormone in the stomach. Moreover, the coexisting dyspepsia would exaggerate the poor nutritional status in *H pylori*-positive subjects and they, thus, tended to be thinner than their *H pylori*-negative counterparts in adulthood. Our data, as far as the greater difference of *H pylori* seropositivity in younger age groups, comply with this hypothesis. In our study, we did not investigate ghrelin levels. This issue has recently been addressed in animal and human studies.⁸⁻¹¹ Experimental work by Suzuki et al⁹ demonstrated that expression of ghrelin levels in the stomach was significantly decreased in Mongolian gerbils colonized by *H pylori*. Nwokolo et al⁸ reported that plasma ghrelin increased profoundly following eradication of *H pylori*. Tatsuguchi et al¹¹ have also shown gastric tissue ghrelin concentration increased significantly after *H pylori* eradication. Furthermore, Furuta et al¹⁰ have documented that patients cured of *H pylori* gained weight. Taken together, these studies have provided evidence that nutritional status and gastric and plasma ghrelin dynamics are altered in response to *H pylori* infection. However, evidence conflicts as to whether metabolic variables and levels of ghrelin were influenced by *H pylori* infection.²⁴⁻²⁶ Candelli et al²⁵ showed that *H pylori* infection and cytotoxin-associated gene A-positive strains do not affect metabolic control in patients with type 1 diabetes mellitus. Gokcel et al²⁶ also reported that *H pylori* has no effect on plasma ghrelin concentration. Both of these studies were cross-sectional. *Helicobacter pylori* infection in early childhood may be a key issue, and a long induction time seems to be required because ghrelin is a long-term regulator of body weight rather than a short-term meal-related orexigenic signal in humans.²⁴ Therefore, further in-depth studies in this field are mandatory to clarify the relationship and mechanisms between *H pylori* and the development of obesity.

In conclusion, our data indicated an inverse relationship between morbid obesity and *H pylori* seropositivity. These findings raise the hypothesis that a lack of *H pylori* infection, especially during childhood, might favor the development of morbid obesity. Further large-scale, prospective, epidemiologic studies with full consideration of confounding factors and in-depth mechanistic investigations are warranted to elucidate whether *H pylori* infection could be a contributing pathogenic factor in childhood and adult obesity.

Accepted for Publication: February 20, 2005.

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Funding/Support: This study was supported by grants

NSC2314-B002-122, NSC2314-B002-123, and NSC2314-B002-124 from the National Science Council, Taipei, Taiwan.

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