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Atrophic gastritis, but not antibody to *Helicobacter pylori*, is associated with body mass index in a Japanese population

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Background. The relationship between *Helicobacter pylori* (HP) infection and body mass index (BMI) is controversial. Several reports have indicated that eradication of HP infection induces an increase in BMI. In contrast, epidemiological case–control studies have failed to show an association between HP infection and BMI. Therefore, we investigated whether HP and atrophic gastritis (AG) were associated with BMI. ***Methods.*** A total of 617 individuals were recruited for the measurements of BMI, serum leptin, pepsinogens (PGs) I and II, and IgG antibody to HP (HP-IgG). BMI and leptin of the subjects were compared when the subjects were stratified by HP-IgG and PGs. ***Results.*** The subjects were divided into AG-positive and AG-negative groups according to PGs (AG-positive: PG I ≤ 70 ng/ml and PG I/II ratio ≤3.0). BMI after adjusting for sex and age was significantly lower in the AG-positive group than in the AG-negative group (23.47 ± 3.05 vs. 24.18 ± 3.25, $P = 0.010$). When the subjects were divided into two groups according to HP-IgG, BMI tended to be lower in the HP-IgG-positive group, though the difference was not large. When the subjects were divided into four groups for different combinations of AG and HP-IgG, BMI was the lowest in the AG-positive and HP-IgG-negative group. ***Conclusions.*** BMI was associated with AG, as diagnosed by PGs, but not with HP infection status. These results mean that HP infection affects BMI via atrophic gastritis.

Key words: *Helicobacter pylori*, atrophic gastritis, pepsinogen, body mass index, leptin

Introduction

The relationship between *Helicobacter pylori* (HP) infection and body mass index (BMI) is controversial. Several reports have indicated that eradication of HP infection induces an increase in BMI. Patients with duodenal ulcer gain weight after eradication of HP.[1] Eradication of HP infection induces an increase in BMI in patients with chronic gastritis,[2] peptic ulcer,[3,4] and atrophic gastritis.[5,6] The reason for the increased BMI appears to be increased food intake, because the upper gastrointestinal symptoms are cured after the eradication of HP. Recently, other mechanisms have been reported, and both leptin and ghrelin have been shown to be potential factors associated with this phenomenon. Leptin is an adipocyte-derived hormone that is also present in the gastric mucosa. Leptin decreases body weight by regulating food intake and energy expenditure. HP infection causes upregulation of leptin levels in the stomach and may reduce body weight, although HP infection does not increase systemic leptin levels.[7]

On the other hand, epidemiological studies have failed to show an association between HP infection and reduced BMI. A meta-analysis of 18 studies has shown that BMI is slightly higher in HP-seropositive persons.[8] Subjects in the upper one-fourth of BMI distribution are more likely to have immunoglobulin G (IgG) antibody to HP (HP-IgG).[9] HP-IgG and antibody to cytotoxin-associated gene product A (CagA) status are not associated with obesity or being overweight.[10] There are discrepancies between intervention studies by HP eradication and case–control studies. HP-IgG is useful in epidemiological studies, but appears to be insufficient because patients with severe atrophic gastritis or intestinal metaplasia after long-term HP infection, especially elderly patients, are negative for HP-IgG.[11]

There are two pepsinogen (PG) isozymogens, PG I and PG II, which are precursors of pepsin. Very low serum PG I levels and a low PG I/II ratio are markers

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of atrophic gastritis (AG) and are predictors of gastric cancer. The cutoff levels for PGs have been established by previously described criteria (PG I ≤70 ng/ml and PG I/II ratio ≤3.0).[12] In this study, 617 individuals were measured with regard to BMI, leptin, and PG I and PG II. After exclusion of 67 subjects who had been treated with HP eradication therapy, HP-IgG, BMI, and leptin of the study subjects were compared after classifying them according to the two factors HP-IgG and PG.

Methods

In 2005, 617 individuals residing in or around Kitakyushu City, Fukuoka Prefecture, Japan, were invited to undergo health checkups and agreed to participate in the present study. The study complied with the ethical rules for human experimentation stated in the Declaration of Helsinki, and was approved by the Human Investigations Committee of Kyushu Dental College. Informed consent to participate in this study was obtained from all patients.

The 617 subjects were 60–81 years old, with 290 men and 327 women. After exclusion of 67 persons who had received HP eradication treatment, because eradication of HP affects BMI, 550 individuals (255 men and 295 women) were analyzed. The measurement of serum PG concentrations was carried out by chemiluminescent enzyme immunoassay (PG I/II Lumipulse; Fujirebio, Tokyo, Japan). AG was diagnosed on the basis of previously described criteria (PG I ≤70 ng/ml and PG I/II ratio ≤3.0).[12] The serum IgG to HP ratio was measured by enzyme-linked immunosorbent assay (ELISA) (Eiken, Tokyo, Japan). BMI was calculated from height and weight [BMI = weight (kg)/height^2 (m)]. Leptin was measured by radioimmunoassay (Human leptin RIA kit; Linco, St Charles, MO, USA).

All data are reported as means ± standard deviation. Differences in mean values between groups were assessed by using Student's *t* test or the Mann-Whitney *U* test. BMI adjusted for age, sex, and smoking habits by using the covariance method is shown as BMIc. The relationships between BMIc and the PG I/II ratio and between BMI and HP-IgG were assessed by multiple linear regression analysis. All statistical analyses were performed using SPSS 15.0J for Windows (SPSS, Chicago, IL, USA).

Results

The subjects were divided into two groups according to serum PG levels, an AG-positive group (PG I <70 ng/ml and PG I/II ratio <3.0) and an AG-negative group. Table 1 displays the BMI and BMIc values. BMI and BMIc were significantly lower in the AG-positive group than in the AG-negative group (23.47 ± 3.05 vs. 24.18 ± 3.25, $P = 0.010$). In female subjects, BMI and BMIc were significant lower in the AG-positive group than in the AG-negative group (23.39 ± 3.18 vs. 24.45 ± 3.32, $P = 0.009$). In male subjects, BMI and BMIc tended to be lower in AG-positive group than in AG-negative group, but the difference did not reach statistical significance (23.49 ± 2.96 vs. 23.83 ± 3.11, $P = 0.372$). The relation between BMIc and the PG I/II ratio is shown in Fig. 1. These two factors were correlated ($r = 0.143$, $P < 0.001$). In male subjects, the relation was significant ($r = 0.174$, $P = 0.005$), whereas in female subjects the relation was not significant ($r = 0.097$, $P = 0.096$).

Table 1. Body mass index and atrophic gastritis

	AG-positive ($n = 211$)	AG-negative ($n = 339$)	*P*
BMIc	23.47 ± 3.05*	24.18 ± 3.25*	0.010
BMI	23.53 ± 3.08*	24.17 ± 3.25*	0.019
Leptin (ng/ml)	6.88 ± 4.80*	8.17 ± 5.46*	0.028
Age (years)	64.89 ± 5.21	64.21 ± 4.75	0.126
Sex (male/female)	113/98*	142/197*	0.008
Smoking (%)	8.06	9.73	0.498
HP-IgG (U/ml)	95.23 ± 77.22*	54.43 ± 75.83*	0.000

AG, atrophic gastritis; HP, *Helicobacter pylori*; BMI, body mass index; BMIc, BMI after adjusting for age, sex, and smoking habits; PG, pepsinogen
*$P < 0.05$

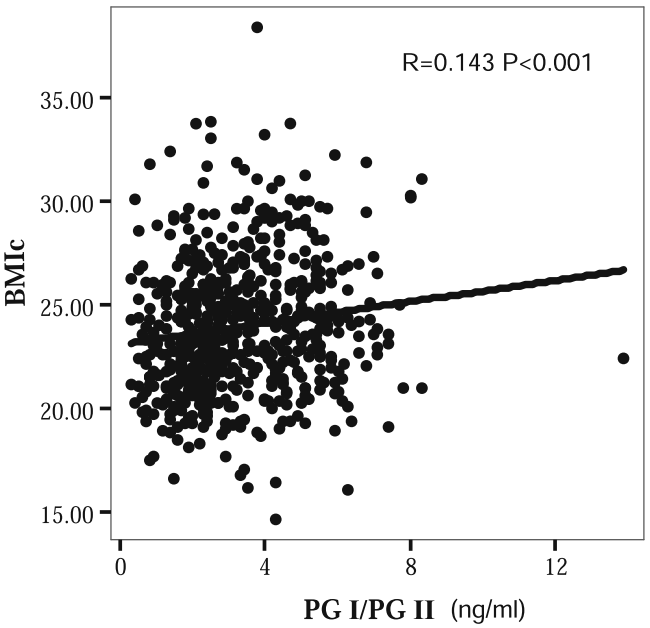

Fig. 1. Relation between atrophic gastritis and body mass index (BMI) adjusted for age, sex, and smoking habits (*BMIc*). The pepsinogen (*PG*) I/PG II ratio and BMI were significantly correlated ($r = 0.143$, $P < 0.001$)

When the subjects were divided into two groups according to whether they were HP-IgG positive or HP-IgG negative, BMIc values tended to be lower in the HP-IgG-positive group than in the HP-IgG-negative group, although the difference did not reach statistical significance (Table 2). HP-IgG-positive subjected tended to be AG-positive, but our results were different depending on whether the subjects were divided by their HP-IgG or AG status. Multiple linear regression analysis also showed a significant correlation between BMIc and PG I/II ($\beta = 0.124$, $P = 0.011$), but not between BMIc and HP-IgG ($\beta = -0.020$, $P = 0.683$).

To clarify the relation between AG and HP-IgG with regard to BMIc, the subjects were divided into four groups according to their combined AG and HP-IgG status: group A, AG negative and HP-IgG negative; group B, AG negative and HP-IgG positive; group C, AG positive and HP-IgG positive; and group D, AG positive and HP-IgG negative (Table 3). BMIc was the lowest in group D, followed by groups C, B, and A. Although a statistically significant difference was found between groups C and A (23.51 ± 3.00 vs. 24.37 ± 3.49, $P = 0.012$), BMIc of group D was not significantly different from those of the other groups, probably because of the small sample size ($n = 24$).

Table 2. Body mass index and HP-IgG

	HP-positive ($n = 206$)	HP-negative ($n = 344$)	P
BMIc	23.72 ± 2.98	24.22 ± 3.50	0.076
BMI	23.75 ± 2.99	24.23 ± 3.51	0.083
Leptin (ng/ml)	7.56 ± 5.27	7.92 ± 5.25	0.531
Age (year)	64.67 ± 5.03	64.14 ± 4.77	0.132
Sex (male/female)	86/120	169/175	0.094
Smoking (%)	10.19	8.43	0.496
PG I (ng/m)	62.52 ± 33.26*	46.32 ± 21.89*	0.000
PG I/PG II	2.33 ± 0.97*	4.64 ± 1.54*	0.000

*$P < 0.05$

Leptin, however, was found to be an important factor leading to a reduced BMI with HP infection. Serum leptin levels were decreased in subjects who were AG positive (Table 1), and leptin was the lowest in group D, followed by groups, C, A, and B (Table 3). After adjustment for BMI, age, and sex, leptin levels did not differ between AG-positive and AG-negative subjects (7.641 ± 0.307 ng/ml vs. 7.768 ± 0.238 ng/ml, $P = 0.745$) and also in any groups divided according to their combined AG and HP-IgG status. BMI and serum leptin levels were positively correlated ($r = 0.562$, $P < 0.001$; Pearson's correlation). The regression coefficient of BMI on leptin did not differ significantly between the AG-positive and -negative groups (0.41 vs. 0.38, $P = 0.334$), or between HP-IgG-positive and HP-IgG-negative groups (0.42 vs. 0.35, $P = 0.143$). Therefore, the difference in BMI between the AG-positive and AG-negative groups was not a consequence of the serum leptin level.

Discussion

The present data indicate that BMI was associated with AG, as diagnosed by PGs, but not with HP-IgG. In clinical studies, serum PGs are known to be a marker of gastric mucosal status, namely, mucosal atrophy. Very low serum PG I levels and a low PG I/II ratio are markers of AG and are predictors of gastric cancer.[11] In our study, BMI and BMIc were significantly reduced in the AG-positive group compared with the AG-negative group (Table 1), and BMI and BMIc were correlated with PG I/PG II (Fig. 1). These results suggested that AG affects BMI.

Atrophic gastritis is caused primarily by HP infection. However, long-term HP infection can result in the development of intestinal metaplasia, causing the HP load to be reduced in the stomach.[13] This ultimately resulted in the HP-IgG-negative and AG-positive status (group D) in our study.[14,15] The natural course of the status of the

Table 3. Body mass index and combination of atrophic gastritis and HP-IgG

	Group A AG-negative HP-negative ($n = 182$)	Group B AG-negative HP-positive ($n = 157$)	Group C AG-positive HP-positive ($n = 187$)	Group D AG-positive HP-negative ($n = 24$)
BMIc	24.37 ± 3.49*	23.97 ± 2.96	23.51 ± 3.00*	23.11 ± 3.48
BMI	24.36 ± 3.51*	23.96 ± 2.91	23.56 ± 3.05*	23.26 ± 3.40
Leptin (ng/ml)	8.04 ± 5.24	8.32 ± 5.75	6.90 ± 4.75	6.79 ± 5.47
Age (years)	63.97 ± 4.64	64.48 ± 4.88	64.82 ± 5.17	65.38 ± 5.62
Sex (male/female)	72/110	70/87	99/88	14/10
Smoking (%)	9.34	10.19	6.95	16.67
PG I (ng/ml)	49.98 ± 19.84*	86.17 ± 30.75*	42.66 ± 19.45*	18.58 ± 16.26*
PG I/PG II	5.05 ± 1.06*	2.97 ± 0.90*	1.79 ± 0.65*	1.51 ± 0.87*
HP-IgG (U/ml)	3.24 ± 1.94*	113.78 ± 76.51*	106.81 ± 74.48*	5.04 ± 2.85*

*$P < 0.05$

gastric mucosa after HP infection varies significantly. However, in most cases of HP infection, acute gastritis progresses to chronic gastritis, intestinal metaplasia, and occasionally gastric cancer, a pathway known as the Correa pathway. In the present study, group A tended to reflect normal gastric mucosa, group B acute and chronic gastritis, group C atrophic gastritis, and group D intestinal metaplasia status. BMIc was lowest in group D, followed by groups C, B, and A (Table 3). This result means that progression of gastric mucosal atrophy was associated with reduced BMI. When subjects were divided according to HP-IgG status, the HP-IgG-negative group had the most atrophic status (group D). Therefore, no difference in BMI was observed in our study. This may also have been the case in previous epidemiological studies in which the subjects were stratified according to HP-IgG status.[7,9,10] The subjects were older in our study than those in other studies. It thus seems possible that the effects of long-term HP infection were enhanced in the present investigation. Atrophic gastritis was found to be caused not only by HP but also by autoimmune or environmental factors. Many group D subjects reflected the end result of past HP infection, but some had not had HP infection. Therefore, it was difficult to classify group D by origin.

When the subjects were divided by sex, the relation between AG and BMI was not significant, probably because the statistical power of this study was weak. The correlation of BMIc and PG I/PG II was significant in men, and the difference in BMIc between the AG-positive and the AG-negative groups was significant in women. Therefore, AG is related to a reduced BMI in both sexes, although the association of AG and BMI was rather weak in men. In our study, there were fewer men ($n = 255$) than women ($n = 295$), which may provisionally explain the low correlation between AG and BMI in men. As in our study, other studies have reported no difference in PG I and PG II between men and women.[16–18] In our study, however, PG I tended to be lower and the prevalence of AG tended to be higher in men than in women. Furthermore, mean age was higher in men than in women. These differences are presumed to be the causes of the discordant results between male and female subjects. Because our sample size was small, further studies are needed to confirm the correlation between AG and BMI.

Leptin was found to be an important factor causing reduced BMI in the presence of HP infection. A previous eradication study also showed that local gastric leptin levels changed after eradication, but not serum leptin. Although the serum leptin level was lower in the AG-positive than in the AG-negative group, the difference became insignificant after adjusting for BMI, age, and sex. Therefore, serum leptin levels were affected by BMI, but BMI was not affected by serum leptin. Gastric leptin was not investigated in our study. Further studies are recommended to investigate the relation between local leptin, HP, and BMI. Several other factors can be considered as possible mechanisms by which AG reduces BMI. HP and gastritis influence life style and change food tolerance.[19] Atrophic gastritis causes low gastric acid, low pepsin, and hypergastrinemia.[20,21] Low gastric acid and low pepsin cause poor digestion, especially protein digestion. Hypergastrinemia may be related to the leanness of AG subjects, because gastrin-deficient mice develop obesity.[22]

In Japan, morbidity associated with HP infection is high and almost all HP strains have CagA.[23] Because of differences in HP strain and host genetics, symptomatic outcomes are different between Asian and Western countries.[24,25] Many patients suffer from intestinal metaplasia and AG in Japan, whereas there are few AG and many duodenal ulcer patients in Western countries.[26] Therefore, the effect of HP infection on BMI by way of AG was enhanced in our study, because many subjects suffered from AG. In Japan, there are few cases of obesity, and the elderly in particular tend to ingest a low-calorie diet. In Western countries, there are many obese subjects, so the influence of HP is not generally observed because the influence of diet on BMI is much larger (World Health Statistics, 2007; http://www.who.int/whosis/whostat2007/en/). Differences such as HP strain, host genetics, and host food intake habits influenced the results in our study and those of previous case–control studies. Atrophic gastritis caused by HP infection results in lean rather than obese subjects. In other studies, HP-IgG-positive subjects were lean, and they became normalized after HP eradication.[2,6] Previous case–control studies utilized BMI categories such as normal weight, overweight, and obese.[9,10] In subjects classified as lean, the association between BMI and HP can be observed more clearly.

In conclusion, the present data indicate that BMI is associated with AG, as diagnosed by PGs, but not with HP infection status, as diagnosed by HP-IgG, probably because subjects with severe atrophic gastritis or intestinal metaplasia after long-term HP infection were found to be negative for HP-IgG. These results mean that HP infection, including past infection, affects BMI via atrophic gastritis.

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