Helicobacter Pylori Eradication May Increase Body Mass Index, But the Effect May Not Last Long. A 10-year Observational Study in Male Patients

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ABSTRACT

Background/Aims: We retrospectively investigated the long-term change in body mass index (BMI) in our Japanese cohort of patients to elucidate whether *Helicobacter pylori* eradication results in weight gain.

Methodology: Four hundred and thirty-five patients who had received eradication therapy and 167 who were *H. pylori*-positive but declined treatment were followed for 10 years or longer, and their BMIs were recorded.

Results: After 10 years, BMI significantly increased from baseline values in both the eradication and the no-eradication groups. However, the increase was significantly more in the eradication group than in the no-eradication group. The greater weight gain in the eradication group could largely be accounted for by gain above a lower baseline value, and occurred only within the first year after eradication. The lower baseline BMI of the eradication group correlated with their higher prevalence of peptic ulcers. From the one-year time point onward, gradual weight gain occurred at a similar rate in both groups. At the 10-year point, the BMIs of the two groups were not significantly different.

Conclusions: Eradication of *H. pylori* resulted in a short-term weight gain that likely was related to the eradication and their ulcer healing, but the effect did not last thereafter.

Key words: *Helicobacter pylori*, eradication therapy, body mass index, obesity

INTRODUCTION

More than ten years have passed since *Helicobacter pylori* eradication therapy was approved for health insurance coverage in Japan, in 2000. Now, eradication treatment widely employed in daily practice, and the population of people who have achieved cure of *H. pylori* infection is increasing. Eradication of

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H. pylori cures certain peptic ulcers (1-3) and reduces the risk of gastric cancer (4-7). However, several concerns regarding possible adverse effects of eradicating *H. pylori* have been raised. The development or worsening of reflux esophagitis is one of the concerns (8), but we have found this risk to be minimal or nonexistent (9,10). The possibility of promoting or exacerbating obesity also has raised concern (11-16), but data regarding this issue, especially of long-term observation, are inconclusive.

We have been examining the effects of *H. pylori* eradication therapy on several medical issues in a large cohort of Japanese patients (4, 9, 10, 17-24), including the prevention of gastric cancer (4, 22, 23), factors associated with failure of eradication therapy (17, 20, 21), and the re-infection rate after cure of *H. pylori* infection (18, 24). In the present study, we retrospectively investigated the change of body mass index (BMI) in this cohort of patients who had been followed up for 10 years or longer to determine whether *H. pylori* eradication resulted in weight gain or obesity.

PATIENTS AND METHODS

We studied 602 male patients aged 60 years or younger who had visited the outpatient clinic of Nippon Kokan Fukuyama Hospital for esophagogastroduodenoscopy and *H. pylori* examination, and had been followed up for 10 years or more. Indications for esophagogastroduodenoscopy were health-check in 494 patients, dyspeptic symptoms in 86, and upper gastrointestinal bleeding in 22. At the endoscopy, we evaluated for peptic ulcers, gastric mucosal histology and *H. pylori* infection, and confirmed that there was no gastric cancer or other malignancies. One hundred forty-one patients had gastric ulcer, 223 had duodenal ulcer, 152 had both diseases, and 86 had no ulcer. The subjects consisted of two groups: 1) 435 patients who had received eradication therapy from May 1995 and December 2001 and achieved cure of *H. pylori* infection (eradication group), and 2) 167 who had tested positive for *H. pylori* infection but declined eradication therapy (no-eradication, control group). Both groups were followed for 10 years or more after the completion of eradication therapy or the initial examination. Endoscopic examination was performed annually in each subject, and BMI was recorded at the time of endoscopy. Females were not included in this study because pregnancy or menopause may have affected their weight. Also, most patients were male factory workers at the JFE Steel Corporation. Patients with a history of surgery on the gastrointestinal tract, cancer, or

taking corticosteroids were excluded from the study.

H. pylori infection was diagnosed by at least one test: gastric histology, tissue culture of gastric biopsies, a ¹³C-urea breath test (UBIT, Otsuka Pharmaceutical Co., LTD, Tokyo, Japan), or a rapid urease test (MR UREA S; Institute of Immunology Co., LTD, Tokyo, Japan). Patients in the eradication group received *H. pylori* eradication therapy as described (4). One hundred and seventy-one patients from June 1995 to August 1999 received two weeks of dual therapy consisting of amoxicillin 750 mg b.i.d. and proton pump inhibitor (omeprazole 20 mg b.i.d. or lansoprazole 30 mg b.i.d.), and 264 patients from February 1997 to December 2001 received one week of triple therapy consisting of amoxicillin 750 mg b.i.d., clarithromycin 200 mg or 400 mg b.i.d., and proton pump inhibitor (omeprazole 20 mg b.i.d., lansoprazole 30 mg b.i.d. or rabeprazole 10 mg b.i.d.), or triple therapy consisting of amoxicillin 750 mg b.i.d., metronidazole 500 mg b.i.d., and proton pump inhibitor. Before the Japanese government approved the national health insurance coverage of the eradication therapy of *H. pylori* in November 2000, we mostly used the dual therapy on the basis of reports on this therapy. After the approval, we used the triple therapy regimens according to the Japanese government's notice. One to two months after the completion of therapy, including the cessation of acid-secretion inhibitors, the ¹³C-urea breath test and endoscopy were carried out in each patient to determine the *H. pylori* status. *H. pylori* infection was considered cured when the bacterial culture, rapid urease test and urea breath test (cut-off value, 3.5 per mil)(19) were all negative. Re-positive test was observed in one patient one year after the eradication therapy, and an additional therapy was performed.

The study was conducted according to the guidelines of the Declaration of Helsinki. A local ethics committee approved the study protocol. The objective of the study was explained to all patients, and written informed consent was obtained from each patient.

Statistical differences were calculated using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. A *p* value <0.05 was considered to be statistically significant.

RESULTS

The patients' baseline characteristics are provided in *table 1*. There was no significant difference between the two groups with respect to age, the percentage of obese patients, or alcohol consumption or detection of gastric cancer during the follow-up period. BMI at

Table 1 - Patient characteristics

	eradication group n=435	no-eradication group n=167	P value
Age (years, mean±SE)	47.2±0.3	47.9±0.5	0.18
BMI (kg/m ² , mean±SE)	22.9±0.1	23.5±0.2	0.006
Obesity	90 (20.7%)	45 (26.9%)	0.10
Symptoms*	105 (24.1%)	3 (1.8%)	<0.0001
Peptic ulcer	429 (98.6%)	87 (52.1%)	<0.0001
Smoking	345 (79.3%)	96 (57.5%)	<0.0001
Drinking	320 (73.6%)	121 (72.5%)	0.84
Gastric cancer†	7 (1.6%)	4 (2.4%)	0.36

SE, standard error. *, dyspeptic symptoms or upper gastrointestinal bleeding.

†, gastric cancer detected during 10 years follow-up.

baseline in the eradication group (22.9±0.1 kg/m², mean ± standard error) was significantly lower than in the no-eradication group (23.5±0.2 kg/m²) (p = 0.006). Peptic ulcers were more prevalent in the eradication group (98.6%; gastric ulcer, n=107; duodenal ulcer, n=181; gastro-duodenal ulcer, n=141; and no ulcer, n=6) than in the no-eradication group (52.1%; n=34, 42, 11, 80, respectively) (p<0.0001). More smokers were included in the eradication group than in the no-eradication group (p<0.0001).

During the 10-year interval, BMI significantly increased from the baseline values in both the eradication group (23.5 ± 0.1 kg/m², p < 0.0001) and in the no-eradication group (23.8 ± 0.2 kg/m², p < 0.05) (table 2), but the increase in BMI was significantly more in the eradication group (0.65 ± 0.09 kg/m²) than in the no-eradication group (0.25 ± 0.12 kg/m²). The difference in the BMI between the two groups became smaller from 0.67 kg/m² at baseline to 0.27 kg/m² at 10 years later, when the difference was not statistically significant.

BMI data at one - and five-years follow-up were available in 433 of the 602 patients (the eradication group, n=314; the no-eradication group, n=119). In the no-eradication group, BMI gradually increased throughout the 10-year period almost at a steady rate. The increase from the baseline was not statistically significant at one- and five-year follow-up, but reached statistical significance after 10 years. In contrast, in the eradication group, BMI rapidly and significantly increased from the baseline value at one year (0.47 ± 0.07 kg/m²) (p<0.0001), then gradually increased at about the same rate as that observed in the no-eradication group (fig. 1). These findings indicate that

Table 2 - BMI at baseline and after 10 years

	eradication group n=435	no-eradication group n=167
BMI at baseline (kg/m ²)	22.9±0.1	23.5±0.2
BMI at 10 years (kg/m ²)	23.5±0.1*	23.8±0.2 [#]

mean±standard error. *, P<0.0001 vs. baseline; [#], P<0.05, vs. baseline

the change in BMI in the eradication group during the 10-year interval mostly occurred within one year after eradication of *H. pylori*.

DISCUSSION

In this study, we investigated the change of BMI in our Japanese cohort of patients who had been cured of *H. pylori* infection and had been followed up for 10 years or longer. Control subjects were those who had not received eradication therapy. We found that BMI after 10 years follow-up had significantly increased from the baseline values in both the eradication and the no-eradication groups. However, the BMI increased significantly more in the eradication group than in the no-eradication group. The greater weight gain in the eradication group was due to gain above a lower baseline value, and occurred only during the first year after eradication. The time course of the BMI increase was strikingly different in the two populations: In the eradication group, the BMI increased dramatically during the first year after eradication, but thereafter it increased only gradually. In contrast, BMI in the

Figure 1 - Body mass index at one, 5 and 10 years follow-up ○, eradication group (n=314); ●, no eradication group (n=119); bars, standard error of the mean. *, P<0.0001, vs. baseline. \$, P<0.05 eradication vs. no-eradication group. ns, not significant

no-eradication group increased gradually throughout the 10 years follow-up.

Thus, the influence of *H. pylori* eradication on BMI seemed to be substantial only during the first year. Others have reported similar findings (11,13-15). Lane JA et al. (16) reported that BMI significantly increased during the first six months after *H. pylori* eradication, and Kamada et al. (14) found that the early weight-gain effect of eradication had disappeared three years after eradication. Importantly, we found that a similar trend continues for as long as 10 years after *H. pylori* eradication.

According to the Japanese Ministry of Health, Labor and Welfare (25), the average BMI in males in their 40s was 23.7 kg/m², in 1998, and 23.9 kg/m² in their 50s, in 2008. Compared with these data, the BMI in our no-eradication group was comparable to that of the general population, whereas the BMI in the eradication group was lower. The explanation for this observation is not definitely known. However, it may be relevant that the eradication group included significantly more patients with peptic ulcer disease than did the no-eradication group. We speculate that the symptoms of peptic ulcer had resulted in reduced dietary intake in the eradication-group subjects, which improved when *H. pylori* were killed and the ulcers healed. Smoking was more common among the subjects who received eradication therapy, but we doubt that factor alone accounted for their lower BMIs. Detection of gastric cancer during the follow-up period was not different between the two groups. Because more patients with peptic ulcer and smoking habit were included in the eradication group, the preventive effect of *H. pylori* eradication against gastric cancer could be obscured; but this is not likely to influence the main outcomes of this study.

In addition to the ulcer healing, *H. pylori* eradication may have influenced hormones, such as ghrelin and leptin, in the gastric wall that regulate appetite and food intake. Ghrelin increases appetite (26), acid secretion (27), gastrointestinal motility (28), and gastric mucosal protection (29). Circulating ghrelin levels were low in *H. pylori*-infected patients (30) and increased after cure of infection (31). A recent meta-analysis confirmed lower circulating ghrelin levels in *H. pylori* infected people compared to those not infected, but the effect of eradication of *H. pylori* on the circulating ghrelin level is controversial (32). Leptin, in contrast to ghrelin, suppresses appetite and enhances energy consumption (33). Leptin mRNA level in the gastric mucosa significantly decreased three months after eradication of *H. pylori* (34). Taken together, effects

of *H. pylori* eradication on these hormones, the ulcer healing, and other unidentified factors may have contributed the restoration of the lower BMI at one year after the eradication. Thereafter, BMI seemed to increase in both the eradication and the non-eradication groups as much as in the general population without *H. pylori* infection.

In summary, BMI increased after *H. pylori* eradication, mostly within one year after eradication therapy, but the effect did not seem to last thereafter in our patients-group. BMI increase up to one year after *H. pylori* eradication may be due to the effect of *H. pylori* eradication, whereas BMI increase thereafter was not likely to be relevant to the eradication; rather it seemed to be the natural change of BMI due to aging, as in the general population. Thus, the long-term change of BMI after *H. pylori* eradication should be regarded as a general health issue and not a deterrent to eradication therapy.

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