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Improved fold width and increased acid secretion after eradication of the organism in *Helicobacter pylori* associated enlarged fold gastritis

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Abstract

This study examined the effects of eradication of *Helicobacter pylori* (*H pylori*) infection on gastric mucosal morphology and acid secretion. Sixteen *H pylori* positive patients with enlarged gastric body folds were divided into two groups: (a) patients with moderate enlargement (fold width: 6 to 10 mm, n=8) and (b) patients with severe enlargement (>10 mm, n=8). After successful treatment, gastric body fold width was reduced in both groups ($p<0·01$) with an associated decrease in inflammatory infiltrates in the body mucosa ($p<0·01$ and $p<0·05$). Basal acid output and tetragastrin stimulated maximal acid output (mean (SEM)) in all 16 patients significantly increased from 1·1 (0·5) to 2·9 (0·9) mmol/h ($p<0·05$) and from 5·4 (1·3) to 18·7 (2·3) mmol/h ($p<0·01$), respectively, with a significant decrease in fasting serum gastrin concentrations, from 127·1 (16·1) to 59·6 (3·8) pg/ml ($p<0·01$). The increase in acid secretion after eradication of *H pylori* was more noticeable in the severe group, who had shown lower acid secretion and higher serum gastrin concentrations ($p<0·05$) before eradication, than the increase seen in the moderate group. The decreases in ammonia nitrogen content seen after eradication were significant in basal (from 0·91 (0·17) to 0·37 (0·08) mmol/h, $p<0·05$) and stimulated gastric secretions (from 1·57 (0·19) to 0·37 (0·13) mmol/h, $p<0·01$), although these changes were too small to explain the increases in basal acid output and maximal acid output. These results suggest that inflammation of the gastric body mucosa caused by *H pylori* infection is associated with enlarged gastric body folds and inhibition of acid secretion in *H pylori* positive patients with enlarged gastric body folds.

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Enlarged gastric folds are a common finding in the body of the stomach, during radiographic or endoscopic examination of adults. Enlarged gastric folds may be associated with a variety of diseases, including so called 'hypertrophic gastritis', Ménétrier's disease, Zollinger-Ellison syndrome, primary gastrin cell hyperplasia, carcinoma, and lymphoma.[1 2] It is critical to determine the cause of this fold enlargement, especially to exclude the diagnosis of scirrhous carcinoma ('hard' cancer). Recently, it has been suggested that *Helicobacter pylori* (*H pylori*) associated gastritis may be one of the causes of enlarged gastric folds.[3–6] Stolte *et al*[6] reported that patients with fold width >10 mm had more severe inflammation and *H pylori* colonisation of the gastric body mucosa. Although *H pylori* infection and inflammation of the body mucosa may affect acid secretion, this association has not been clearly shown in *H pylori* positive patients with enlarged gastric body folds. In this study, we have investigated the effects of eradication of *H pylori* on gastric morphology and acid secretion in patients with *H pylori* positivity and enlarged gastric body folds. Additionally, we have examined changes in gastric ammonia content, which may be increased by ammonia production from urea by *H pylori* urease.

Methods

We identified 16 *H pylori* positive patients with enlarged gastric body folds who had successful eradication of *H pylori* infection. Initially, 19 *H pylori* positive patients with enlarged gastric body folds were enrolled in the study, but three patients failed treatment and were excluded from further study. All patients had undergone endoscopic examination after the finding of crowded, tortuous, and enlarged gastric body folds by barium study as part of a mass screening for gastric carcinoma. The barium study was performed in each patient using the same equipment and agents by experienced radiologists. The width of the gastric fold was measured on double contrast radiographs of the appropriately distended stomach in the supine position. We had known by experience and also confirmed in some patients in this study that this method of measurement of the gastric fold had good reproducibility. Gastric body folds were considered to be enlarged when the widest fold was greater than 5 mm.[7 8] The mean (SEM) of the widest fold was 9·3 (0·5) mm (range 6–12 mm). Endoscopic examination in all 16 patients showed enlarged gastric body folds with and without mucosal erythema or erosions. There were no peptic ulcers or carcinomas found. *H pylori* infection was determined by positive culture or urease test, or both using biopsy specimens from the antrum and body. In 15 of 16 patients, *H pylori* was positive in both the antrum and the body; in one patient, it was positive only in the body. Patients were divided into two groups: those

TABLE I *Inflammatory infiltrates and fold width before and after eradication of* Helicobacter pylori

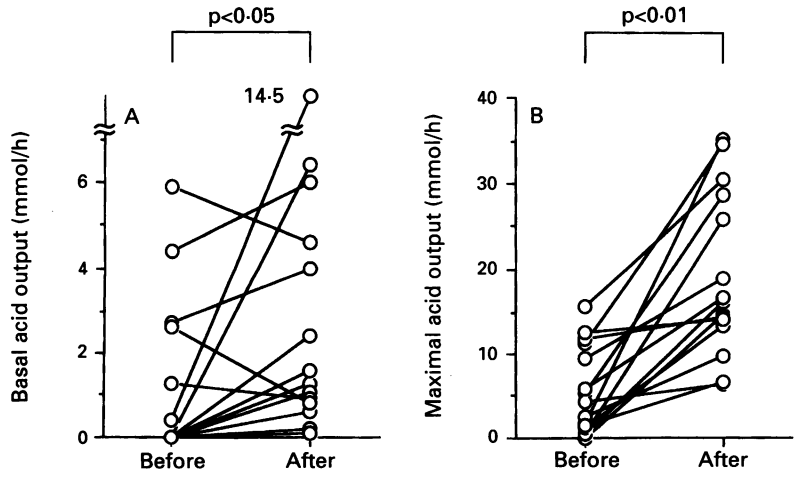
		Mononuclear infiltrates (grade)*		*Polymorphonuclear infiltrates (grade*)*		*Fold width (mm)*
		Antrum	*Body*	*Antrum*	*Body*	
Total	Before	2·6 (0·1)	2·3 (0·2)	0·9 (0·2)	1·6 (0·2)‡	9·3 (0·5)
(n=16)	After	1·0 (0·1)§	0·9 (0·1)§	0·1 (0·1)§	0·1 (0·1)§	6·1 (0·4)§
Moderate group	Before	2·8 (0·2)	2·1 (0·1)	1·0 (0·3)	1·4 (0·2)	7·4 (0·4)
(n=8)†	After	1·0 (0·2)¶	0·8 (0·2)§	0·1 (0·1)¶	0·0 (0·0)§	5·0 (0·3)§
Severe group	Before	2·5 (0·2)	2·5 (0·3)	0·9 (0·3)	1·9 (0·2)‡	11·3 (0·2)
(n=8)†	After	1·0 (0·0)§	1·0 (0·0)¶	0·0 (0·0)¶	0·1 (0·1)§	7·3 (0·6)§

All results were expressed as mean (SEM). *Four grades; 0=none, 1=mild, 2=moderate, and 3=severe. †Moderate group; the widest fold=6 to 10 mm. Severe group; the widest fold >10 mm. ‡p<0·05 *v* antrum. §p<0·01 and ¶p<0·05 *v* before.

with moderate fold enlargement (widest fold ≤10 mm, seven males and one female, mean (SEM) age 47·9 (2·9) years, range 30—60) and those with severe enlargement (widest fold >10 mm, six males and two females, mean age 46·9 (3·9) years, range 35–68).[7] No patients had severe clinical symptoms; serum protein and creatinine concentrations were within normal limits. All patients were free from any antisecretory drugs before and during this study. Informed consent was obtained from all patients.

Fasting serum gastrin concentrations were determined by radioimmunoassay[9] (Gastrin RIA Kit II; Dainabot, Tokyo, Japan). Biopsy specimens from the prepylorus and the greater curvature of the upper portion of the body were examined for the presence of *H pylori* by culture[10] (Department of Chemotherapy, Pharmacological Research Laboratory of Fujisawa Pharmaceutical Co, Osaka, Japan) or by urease test[11] (CLOtest, Delta West, Bentley, Australia), or both. Histological assessments of mononuclear infiltrates (for chronic inflammation) and polymorphonuclear infiltrates (for activity of inflammation) were examined by haematoxylin and eosin stain and graded as follows: 0=none, 1=mild, 2=moderate, and 3=severe.[7] Basal and stimulated (4 μg/kg tetragastrin) gastric secretions were collected for 30 and 60 minutes, respectively, for the determination of basal acid output and maximal acid output. Ammonia nitrogen concentrations in basal and stimulated gastric secretions were determined by a colorimetric method[12] (Ammonia Test Wako, Wako, Osaka, Japan).

Each patient received triple therapy with bismuth subnitrate or subcarboxylate 1 g thrice daily, metronidazole 250 mg twice daily, and tetracycline hydrochloride 250 mg four times daily for three weeks. Four to 10 weeks after completion of this treatment schedule, fasting serum gastrins, endoscopic examination, and gastric secretion studies were repeated. At 7 to 29 weeks after completion of treatment, an upper gastrointestinal barium study was repeated for reassessment of the size of the folds. All results were expressed as mean (SEM). Statistical analysis was performed using the Wilcoxon signed rank test and the Mann-Whitney test. Statistical significance was assigned for any p value less than 0·05.



Basal (A) and 4 μg/kg tetragastrin stimulated maximal acid outputs (B) before and after eradication of the organism in 16 patients with Helicobacter pylori *associated enlarged fold gastritis.*

Results

Baseline histological examinations showed mononuclear and polymorphonuclear infiltrates in the body mucosa, as well as in the antral mucosa, in both the moderate and severe groups (Table I). In the severe group, polymorphonuclear infiltrates in the body mucosa were significantly more severe than those in the antral mucosa (p<0·05). When the severe group was compared with the moderate group, both mononuclear and polymorphonuclear infiltrates in the body mucosa were more extensive in the severe group. Polymorphonuclear infiltrates were nearly absent in the antral and body mucosa after eradication; although the mononuclear infiltrate was significantly decreased (p<0·05 and p<0·01), it persisted to a mild degree. The width of gastric body folds was significantly reduced in both groups after treatment (p<0·01). In the moderate group, the fold width of two patients was reduced to less than 5 mm; in the severe group, the fold width of none of the patients was reduced to less than 5 mm.

The Figure shows the basal acid output and maximal acid output before and after eradication of *H pylori* in each patient. Before eradication, both basal acid output and maximal acid output were lower in the severe group compared with the moderate group, although this difference was not statistically significant (Table II). After eradication, both basal acid output and maximal acid output increased significantly over pretreatment values in the severe group (p<0·05), whereas only maximal acid output increased significantly in the moderate group (p<0·05). Although the severe group's improvement in acid output was more pronounced than the moderate group, this difference was not statistically significant.

Baseline serum gastrin concentrations were significantly higher in the severe group than in the moderate group (p<0·05). After eradication, serum gastrin concentrations significantly decreased to within normal limits in both groups (p<0·05). Ammonia nitrogen content in both basal and stimulated gastric secretions

TABLE II *Fasting serum gastrin concentration, acid secretion, and gastric juice ammonia nitrogen before and after eradication of* Helicobacter pylori

		Serum gastrin (pg/ml)	*Basal acid output (mmol/h)*	*Maximal acid output (mmol/h)*	*Gastric juice ammonia nitrogen (mmol/h)*	
					Basal	*Stimulated*
Total	Before	127·1 (16·1)	1·1 (0·5)	5·4 (1·3)	0·91 (0·17)	1·57 (0·19)
(n=16)	After	59·6 (3·8)*	2·9 (0·9)†	18·7 (2·3)*	0·37 (0·08)†	0·37 (0·13)*
Moderate group	Before	92·1 (13·1)	1·6 (0·7)	6·9 (1·9)	1·23 (0·28)	1·99 (0·23)
(n=8)	After	55·3 (6·9)†	2·0 (0·5)	18·2 (2·8)†	0·38 (0·14)	0·21 (0·07)†
Severe group	Before	162·1 (24·3)‡	0·6 (0·5)	3·9 (1·7)	0·60 (0·14)	1·14 (0·22)
(n=8)	After	63·9 (3·0)†	3·7 (1·8)†	19·3 (3·9)†	0·36 (0·09)	0·53 (0·25)

*p<0·01 and †p<0·05 *v* before. ‡p<0·05 *v* moderate group.

were significantly decreased after eradication (p<0·05 and p<0·01), although the changes were too small to explain the respective increases in basal acid output and maximal acid output.

Discussion

This study has shown that gastric body fold width was decreased and that there was an associated improvement in mucosal inflammatory infiltrates, especially polymorphonuclear infiltrates, after eradication of *H pylori* in *H pylori* positive patients with enlarged gastric body folds. Moreover, the degree and activity of inflammation of the gastric body mucosa was more severe in the group with severely enlarged folds compared with the group with moderately enlarged folds. This result has shown that the enlargement of gastric body folds may be attributed to the inflammation of the body mucosa caused by *H pylori* infection. In agreement with our results, Stolte *et al*[6] reported an association between *H pylori* infection and comparatively severe chronic active inflammation of the body mucosa in patients with giant fold (fold width >10 mm) gastritis.

This study has further shown that basal acid output and maximal acid output increased significantly after eradication of *H pylori* in these patients with enlarged gastric body folds. Miki *et al*[13] have reported that basal acid output and 4 μg/kg tetragastrin stimulated maximal acid output were 4·0 (0·7) and 21·6 (1·4) mmol/h respectively, in Japanese subjects in whom there was no atrophy of fundic glands (estimated by means of the Congo red test). Thus, basal acid output and maximal acid output values after eradication were nearly as high as those in Japanese subjects without atrophy of fundic glands, showing that acid secretion was abnormally low before eradication. This study also suggests that diminished neutralisation of gastric acid by ammonia, which is produced in gastric juice from urea by *H pylori* urease,[14] cannot completely explain these increases in basal acid output and maximal acid output after treatment. These findings imply that acid secretion is inhibited by *H pylori* infection. In this respect, *H pylori* positive patients with enlarged gastric body folds are different from previously reported patients with chronic *H pylori* infection.[15–19] Transient hypochlorhydria has been reported to occur with acute *H pylori* infection,[14] and proteins produced by *H pylori* have been shown to inhibit acid secretion by parietalcells in in vitro studies.[20] Therefore, it is possible that chronic *H pylori* infection has some persistent inhibitory effect upon acid secretion.[14]

Another possibility is that cytokines, which are released by inflammatory infiltrates, may inhibit acid secretion. Although León-Barúa *et al*[21] have reported that gastric juice pH was significantly decreased after eradication of *H pylori* in dyspeptic hypochlorhydric patients, the distribution of *H pylori* or inflammation in the stomach, as well as the details of acid secretion were not shown. In patients with duodenal ulcer, eradication of *H pylori* seems to have little, if any, effect upon acid secretion.[15–19] Duodenal ulcer is usually accompanied by *H pylori* associated chronic active gastritis of the antrum rather than of the body,[14] whereas *H pylori* infected patients with enlarged gastric body folds have comparatively severe, chronic active gastritis of the body. This suggests that an inhibitory effect of *H pylori* infection upon acid secretion in *H pylori* infected patients with enlarged gastric body folds may be caused by specific distribution of *H pylori* infection or its associated inflammation, or both within the body. Differences in the distribution of *H pylori* infection or its associated inflammation, or both may result from differences in either strains of *H pylori* or immune responses of the host. Moreover, our finding of comparatively severe inflammation of the body mucosa and more noticeable inhibition of acid secretion in the severe group compared with the moderate group suggests that inflammation of the body mucosa is associated with both enlargement of gastric body folds and inhibition of acid secretion in *H pylori* positive patients with enlarged gastric body folds.

This study has shown that fasting serum gastrin concentrations decreased after eradication of *H pylori* in these patients. The lower fasting serum gastrin concentrations may result from the increase in acid secretion after eradication of *H pylori*. It has been reported that circulating gastrin concentrations decrease despite no evident change in acid secretion after eradication of *H pylori* in patients with duodenal ulcer. We have previously reported that eradication of *H pylori* normalises both serum gastrin concentration and antral gastrin cell number in a patient with primary gastrin cell hyperplasia characterised by hypergastrinaemia and hyperchlorhydria.[5] This patient also showed an improvement in inflammatory infiltrates in the antral mucosa and unchanged acid secretion. *H pylori* infection and its associated inflammation of the antral mucosa has now been reported in patients with enlarged gastric body folds as well as patients with duodenal ulcer or our patient with primary gastrin cell hyperplasia. Therefore, the decrease in fasting serum gastrin concentrations after eradication may be related to not only the concomitant increase in acid secretion but also the improvement in the inflammation caused by *H pylori* infection in the antral mucosa.

The prevalence of enlarged gastric body folds in a barium study as part of a mass screening for gastric carcinoma in our institute has been about 15%. We believe, therefore, that enlarged fold gastritis is not an uncommon type of chronic gastritis, and must be associated with *H pylori* infection because of the high prevalence of *H pylori* infection in chronic gastritis.[14] Accordingly, we think that *H pylori* associated enlarged fold gastritis may not be an uncommon subgroup of the population with *H pylori* infection, at least in Japan. The histological characterisation of *H pylori* associated enlarged fold gastritis, as well as the effects of eradication of *H pylori* on gastric folds and acid secretion, may be useful in the differential diagnosis of enlarged gastric folds. Moreover, this study has introduced interesting questions, that is, whether or not comparatively severe chronic inflammation of the gastric body mucosa may lead to the atrophy of fundic glands, and longstanding inhibition of acid secretion may participate in gastric carcinogenesis through increasing intragastric formation of *N*-nitroso compounds.[14]

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