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Effect of Helicobacter Pylori Eradication on Extent of Duodenal Gastric Metaplasia and Grade of Gastritis

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A B S T R A C T

The extent of the regression of duodenal gastric metaplasia (DGM) after the eradication of Helicobacter pylori infection is controversial. Therefore, we decided to assess the degree of DGM before, sex weeks and one year after H. pylori eradication. 105 consecutive Helicobacter pylori positive patients with endoscopically proven duodenal ulcer, with DGM and Helicobacter pylori infection were recruited for this study. The diagnosis of Helicobacter pylori infection was based on CLO-test and histology, and DGM was assessed on four bulb biopsies taken before, sex weeks and one year after Helicobacter pylori eradication. Histological assessment of Helicobacter pylori associated gastritis was performed according to the Sydney classification. Follow up study on 98 patients before, six weeks and one year after the eradication of Helicobacter pylori showed that the mean extent of DGM did not change significantly after eradication and did not differ when compared with 14 patients with persisting infection. Our results show that the inflammatory process related to Helicobacter pylori does not play the main role in the development of DGM.

Introduction

Helicobacter pylori (H. pylori) is a Gram-negative spiral organism that colonizes human gastric mucosa and is the major cause of gastritis. Duodenal gastric

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metaplasia (DGM) is the appearance of patches of gastric type mucous cells interspersed between the duodenal epithelial cells. It is assumed that DGM is the result of persistently high concentrations of acidity in the duodenal bulb and is commonly found in biopsy specimens from patients with duodenitis and duodenal ulcer disease. It is already known that H. pylori positive antral gastritis leads to increased output of gastric acid thus leading to increased exposure of duodenal mucosa to acid in some patients. In that context, DGM is an adaptive defense response on the duodenal bulb to high concentration of acidity[1,2]. However, DGM may also develop as a non-specific response to mucosal injury not associated with acid peptic damage[3].

As H. pylori colonization is restricted to gastric type epithelium, the presence of gastric metaplasia in the duodenum would allow H. pylori to colonize the mucosa and to produce active inflammation. This may ultimately lead to ulceration. Thus, both H. pylori infection and DGM are considered to be prerequisites for the development of H. pylori induced duodenitis[4].

It might be anticipated that the eradication of H. pylori infection and the consequent normalization on the acid secretion would induce regression of DGM.

However, the data on the regression of DGM after Helicobacter pylori eradication are controversial[5–7]. The aim of this study was to assess the extent of DGM and to assess five main histological features of gastritis in gastric mucosa before and after H. pylori eradication in a one year follow up period.

Material and Methods

Subjects

146 consecutive patients of either sex at least 18 years of age, with dyspeptic symptoms, referred to Endoscopic Services for diagnostic upper gastrointestinal endoscopy, and whose diagnosis was duodenal ulcer were considered for the study. Among these, 105 met all three inclusion criteria (H. pylori positive duodenal ulcer and duodenal gastric metaplasia).

Patients with a history of hemorrhagic diathesis or coagulation defects, malignancy of esophagus, stomach or duodenum as well as patients who underwent gastric surgery and those having insulin dependent diabetes mellitus were excluded from the study. Pregnant or lactating women were also excluded. No acid suppressants, antibiotics, nonsteroidal anti-inflammatory drugs or corticosteroids in the past month had been taken. The Ethics Committee approved the study and all patients gave written informed consent.

Clinical methods

At each endoscopy, four corpus and three antrum biopsy specimens were obtained with standard biopsy forceps for histopathological examination. In addition one antrum and one corpus biopsy specimens were processed according to standard procedures for H. pylori culture. At the inclusion endoscopy, a CLO test (Delta West, Bentley, Australia) was also performed using one antrum and one corpus biopsy. To grade the extent of DGM, four duodenal bulb biopsy specimens were obtained at the margin of the ulcer and at least 1 cm away from the pylorus. Specimens were placed in buffered formal saline and processed for histological examination. All patients were treated with pantoprazole 40 mg, metronidazole 500 mg, amoxycillin a 1000 mg. All drugs were administered together, twice daily after breakfast and dinner during the seven days and pantoprazole 40 mg o.d. was continued during the three more weeks. Re-endoscopy was performed six weeks and one year after the triple ther-

apy. Gastric biopsies were repeated, taken from sites similar to those in the initial endoscopy, and four duodenal biopsy specimens were obtained from the center of the scar. The patients were considered H. pylori positive if two of the tests performed were positive and successfully eradicated if all tests were negative.

Histological methods

Biopsy specimen sections were stained with hematoxylin and eosin to detect H. pylori and gastritis. Sections from duodenal biopsy specimens were stained with alcan blue periodic acid-Shiff (pH 2.5) to evaluate gastric metaplasia. Duodenal gastric metaplasia was defined as the occurrence of foci of gastric epithelial cells containing apical periodic acid-Schiff-positive mucin together with the absence of a brush border. The extent of DGM was scored according to Patrick et al.[8] as follows: grade 0 (none), no gastric metaplasia; grade 1 (focal type), wherein mucus-containing cells replaced normal epithelial cells in a localized area; grade 2 (multifocal type), when two or more involved areas were separated by normal epithelium; grade 3 (diffuse type), when diffuse involvement was present. The histological features of pre- and post- treatment gastric mucosa were reviewed and categorized according to the Sydney system[9], i.e. severity of a) chronic and b) acute inflammation, c) atrophy of the mucosa, d) presence of intestinal metaplasia and e) density of H. pylori by Giemsa staining, and graded on scale from 0 to 3.

Statistical methods

The changes of grade of duodenal gastric metaplasia in cure patients were evaluated with Friedman ^{2} test.

The sign test was used to calculate the statistical difference in extent of duodenal gastric metaplasia in cured patients.

All statistical analysis was performed in SAS6.12.

The changes of grade of gastritis before and one year after Helicobacter pylori eradication were evaluated with chi-square test.

Results

We recruited 146 patients but 105 patients meet the inclusion criteria (H. pylori positive patients with duodenal ulcer and DGM). H. pylori infection was confirmed in 122 out of 146 duodenal ulcer patients (84%), and DGM was present in 128 patients (88%). The results were similar to our previous study[10]. All of 105 H. pylori positive patients with duodenal ulcer and DGM have no active ulcer at the time of re-endoscopy. H. pylori was successfully eradicated in 91 patients (87%). There was no significant difference between eradicated and no eradicated group with respect to age, sex, and smoking (Table 1). 7 of patient were lost during the one year follow-up period. 98 patients underwent the third endoscopy at one year. 7 patients (7%) dropped out from the study for the following reasons: lost to follow up (n=4), adverse events (n=2), refused endoscopy (n=1). Two of five patients that required an additional endoscopy because of dyspeptical symptoms have relapse of ulcer and were excluded from the study (Table 2).

TABLE 1
CHARACTERISTICS OF PATIENTS INCLUDED IN THE STUDY

Number of patients	146
Median age	53.2 (29–74)
Gender (M/F)	85 / 61
Smokers/nonsmokers	69 / 77
HP+/HP–	122 (84%) / 24 (16%)
DGM+/DGM–	128 (88%) / 18 (16%)
DGM+and HP+	105 (72%)

DGM = duodenal gastric metaplasia;
HP = Helicobacter pylori

TABLE 2
CHANGES OF EXTENT OF DGM ACCORDING TO THE NUMBER OF PATIENTS BEFORE AND AFTER THE THERAPY

Follow up	No. of patients	DGM gr. I	DGM gr. II	DGM gr. III	Lost	Without DGM
0	105	51	40	14	/	/
6 weeks	97	50	33	14	2	6
1 year	90	45	34	11	5	2

DGM = duodenal gastric metaplasia

Changes of extent of DGM

There was no statistical significant difference in the grade of DGM (Friedman test: df = 2, Q= 3.767, p=0.152) in the cure group of patients after the six weeks and one year period. Looking separately each of the patients in the cure group (n=91), the grade of DGM was not changed in 61/91 (67%), improved in 20/91 (22%) and worsened in 10/91 (11%).

Between the patients with improved and worsened DGM was not statistical significant difference according to the sign test (p=0,18).

After the one year 30/81 (37%) cured patients have not changed DGM, 35/81 (43%) improved and 15/81 (19%) worsened.

One year after the Helicobacter pylori eradication there was not statistical significant difference between the patients with the improved the DGM and those with worsened (p=0.23) (Tables 3–5).

Changes of gastritis

H. pylori density, acute and chronic inflammation showed statistically significant differences between pre- and post-

TABLE 3
CHANGES OF GRADE I OF DGM

Changes of gr. of DGM	6 weeks after therapy		1 year after therapy
	HP–	HP+	HP–
0	3	1	4
I	38	4	35
II	2	1	2
III	1	0	1
lost	1	0	2

DGM = duodenal gastric metaplasia;
HP– = Helicobacter pylori eradicated;
HP+ = Helicobacter pylori non-eradicated

TABLE 4
CHANGES OF GRADE II OF DGM

Changes of gr. of DGM	6 weeks after therapy		1 year after therapy
	HP–	HP+	HP–
0	1	0	1
I	5	3	2
II	25	2	24
III	3	1	4
lost	0	0	2

DGM = duodenal gastric metaplasia;
HP– = Helicobacter pylori eradicated;
HP+ = Helicobacter pylori non-eradicated

TABLE 5
CHANGES OF GRADE III OF DGM

Changes of gr. of DGM	6 weeks after therapy		1 year after therapy
	HP–	HP+	HP–
0	1	0	0
I	0	0	3
II	2	1	2
III	8	1	6
lost	1	0	0

DGM = duodenal gastric metaplasia;
HP– = Helicobacter pylori eradicated;
HP+ = Helicobacter pylori non-eradicated

TABLE 6
EXTENT OF THE GRADE OF GASTRITIS BEFORE AND AFTER H. PYLORI ERADICATION

path. parameter	No. of patients								
	0		1		2		3		
	before	after	before	after	before	after	before	after	p
Chronic inflammation	1	10	22	57	53	20	12	3	<0.05
Acute inflammation	15	57	43	25	25	6	7	2	<0.05
H. pylori density	0	59	29	24	36	6	25	1	<0.05
Atrophy	54	50	22	30	12	8	2	2	>0.05
Intestinal metaplasia	71	71	12	13	6	5	1	1	>0.05

^{2} test

treatment biopsy specimens ($p<0.001$), and not statistically significant change were observed for the degree of atrophy and presence of intestinal metaplasia ($p>0.05$) (Table 6).

Discussion

DGM is almost constant finding in patients with duodenal ulcer. It s considered to be an acquired condition to high acid exposure[11].

While up to date reports about influence of H. pylori eradication on DGM are still conflicting we tried to investigate changes of grades of DGM in every patients with duodenal ulcer, separately during the six weeks and one year after the H. pylori eradication.

Assess of even minimal change in DGM in every patient separately after the Helicobacter pylori eradication was the primary goal of our study.

Our results show that there was no statistical significant difference in the grade of DGM after six weeks and one year in the group of Helicobacter pylori eradicated patients. Even more, statistical significant difference was not reached in the patients with improved and worsened extent of DGM.

Kim et al.[12] find that initial prevalence and initial extent of DGM in duodenal ulcer patients one year after the Helicobacter pylori eradication did not change. Four years after the Helicobacter pylori eradication, in the former study there was not statistical significant difference in the extent of DGM. It has been observed that patients with duodenal ulcer followed for five years after the Helicobacter pylori eradication have not decrease in DGM.

Their observations show that one-year follow up of patients is probably enough and it is not to be expected that our results would be significant change after the three more years. In agreement with our results Noach et al.[5] showed that there was no statistical significant difference of DGM one-year after the Helicobacter pylori eradication. Harris et al.[6] excluded any significant changes in prevalence and the extent of DGM six months after the Helicobacter pylori eradication.

In the study by Savarino et al.[13] gastric acid output and DGM did not change significantly one year after the Helicobacter pylori eradication in patients with duodenal ulcer thus fail to confirm that DGM is an adoptive response to high concentration of acidity in duodenal bulb. Therefore the DGM was also unchanged.

By contrast, Khulusi et al.[7,14] showed reduction of DGM as the exclusive result of the Helicobacter pylori eradication.

An important problem in the DGM detection is its patchy distribution. In addition Wyatt et al.[3] could not find the significant difference between the extent of DGM at sites around the ulcer craters of scars and macroscopically normal appearing mucosa. To exclude possible biopsy sampling error we took four duodenal mucosa biopsy specimens at the margin of the ulcer and at least 1cm away from the pylorus at the beginning of the study. After the Helicobacter pylori eradication we took biopsies from a topographic sites similar to that in the initial endoscopy and four addition biopsy specimens from the center of the scar.

In opposite to acute inflammation, chronic inflammation and Helicobacter pylori density atrophy of gastric mucosa and intestinal metaplasia did not change significantly after the Helicobacter pylori eradication in one year follow up. Similarly results were observed by others[15].

In conclusion we failed to confirm the positive relationship between Helicobacter pylori infection and extent of DGM. This result may be explained by the fact the recurred patients have natural high acid output and that the decreased acid output caused by Helicobacter pylori eradication may not be enough to bring reversal change of DGM after one year.

Secondly, it is possible that the follow up interval was too short to detected significant decrease in the prevalence of the extent of DGM after the Helicobacter pylori eradication. Thirdly, after the Helicobacter pylori eradication fail in acid output may not have been sufficed to affect DGM.

Chronic mucosal inflammation caused by Helicobacter pylori infection which leads to gastric mucosa atrophy and intestinal mataplasia persist one year after the Helicobacter pylori eradication thus potentially lead to the gastric carcinoma.

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UČINAK ERADIKACIJE HELICOBACTER PYLORI NA VELIČINU DUODENALNE ŽELUČANE METAPLAZIJE I NA STUPANJ GASTRITISA

S A Ž E T A K

Opseg želučane duodenalne metaplazije (DŽM) i njezina regresija poslije eradikacije Helicobacter pylori je dvojbena. Stupanj DŽM pratili smo prije eradikacije, te šest tjedana i jednu godinu poslije eradikacije Helicobacter pylori. U studiju smo uključili 105 bolesnika s endoskopski verificiranim duodenalnim vrijedom, DŽM te infekcijom s Helicobacter pylori. Infekciju s Helicobacter pylori dokazivali smo s CLO-testom i histološki, a DŽM je određivana patohistološki u četiri bioptička materijala iz bulbusa dvanaesnika prije eradikacije, šest tjedana i jednu godinu nakon eradikacije Helicobacter pylori. Gastritis s Helicobacter pylori pozitivnim nalazom podijeljen je prema Sydneyskoj klasifikaciji. U 98 bolesnika prije eradikacije, šest tjedana i jednu godinu nakon eradikacije Helicobacter pylori, nije pronađena značajnija promjena u opsegu DŽM. Isto tako, nije bilo značajnije razlike u stupnju DŽM u usporedbi s 14 bolesnika kod kojih nije uspjela eradikacija Helicobacter pylori. Naši rezultati pokazuju da upalni proces izazvan s Helicobacter pylori nema presudnu ulogu u nastanku DŽM.