Original Article

Precancerous Conditions after *H. pylori* Eradication: A Randomized Double Blind Study in First Degree Relatives of Gastric Cancer Patients

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Abstract

Background: Regression of precancerous lesions after *H. pylori* eradication remains controversial. This study evaluates the change and topography in first degree relatives (FDR) of gastric cancer (GC) patients following *H. pylori* eradication.

Methods: Participants underwent endoscopy with antrum and corpus histological examinations. Subjects with pangastritis were randomly allocated to placebo or eradication therapy and followed over 4½ years.

Results: Among 989 evaluated FDR, we excluded 468 patients as follows: 108 had macroscopic lesions, 243 had no evidence of any *H. pylori* infection, and 117 were excluded for other reasons. The remaining subjects (n = 521) were allocated to therapy (group A, n = 261) or placebo (group B, n = 260) groups. Interim analysis of 403 subjects (201 placebo, 202 therapy) showed regression of atrophy (60 out of 97 in the antrum and 37 out of 104 in the corpus) in *H.pylori*-eradicated versus regression of atrophy (57 out of 184 in the antrum and 23 out of 173 in the corpus) in non-*H.pylori*-eradicated cases over 2½ years ($P < 0.0001$). No regression of intestinal metaplasia (IM) occurred in the antrum and corpus of treated subjects over 4½ years. However, progression of IM occurred in the antrum in 17 out of 90 patients in the non-*H. pylori*-eradicated versus 4 out of 68 *H. pylori*-eradicated subjects after 4½ years ($P < 0.05$).

Conclusion: Eradication of *H. pylori* is associated with regression of gastric atrophy but not IM, even in its early stages. Gastric atrophy and IM in the antrum have shown more rapid progression in cases not treated for *H. pylori* infection (over 4½ years follow-up) compared to *H. pylori*-eradicated cases.

Keywords: *H. pylori*-eradication, precancerous lesions, randomized trial

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Introduction

Gastric cancer (GC) is currently the most common cause of death among Asian males and the second culprit worldwide.[1] A meta-analysis with follow-up of the patients over four to ten years has suggested a reduction in GC in *H. pylori*-eradicated compared to non-eradicated patients.[2] The evidence based on the reversibility of precancerous conditions after eradication remains inconclusive in many randomized studies, which have been mainly conducted in China. This controversy exists particularly regarding the reversibility of intestinal metaplasia (IM).[3–19] According to a recently published meta-analysis, atrophy was found to regress only in the corpus after *H. pylori*-eradication. No regression of IM was noted in the antrum or corpus.[20] However, in 6 out of total 12 studies the follow-up period was for one-year, 5 of them had inadequate numbers of patients, and 9 out of 12 total studies were observational studies. Therefore, in these studies, the inclusion criteria were not homogenous. In two recently published studies, regression of gastric atrophy but not IM after *H. pylori* eradication were observed,[21, 22] however one was a non-randomized study.[21] In most of the published studies, progression of precancerous lesions following *H. pylori* eradication has not been assessed.

The first degree relatives (FDR) of GC patients are more prone to GC than the general population.[23,24] The current study has attempted to examine the effects of *H. pylori*-eradication on gastritis and precancerous conditions and their topographic changes in a double-blind, randomized controlled trial conducted over two and four years in FDR of GC patients.

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Materials and Methods

Sample size determination

The sample size was determined on the assumption that progression of atrophic gastritis (one additional score) over the follow-up period might occur in 20% of the patients in the non-eradicated group (placebo; P0 = 20%) and 10% of patients in the eradicated group (treatment; PI = 10%), by a power of 0.9 and loss of 15% of

patients. Thus, each arm needed 315 subjects. An interim analysis at second endoscopy was planned.

Study population and endoscopic examination

The Tehran Cancer Institute provided addresses of the FDRs of GC patients admitted to Tehran hospitals during 2002-2005. There were 989 FDRs (brothers, sisters, children or parents), of ages 40 to 65 years who accepted our invitation for an upper GI endoscopy screening. We excluded 108 patients with significant gastric lesions, such as GC (n = 2), esophageal cancer (n = 1), gastric ulcer (n = 32), combined gastric and duodenal ulcers (n = 4), duodenal ulcer disease (n = 58) and diffuse erosive duodenitis (n = 11). Biopsy specimens were taken from the remaining 881 patients (Flow Chart 1).

Specimens were obtained from five areas: two from the antrum (one just below the incisura angularis from the lesser curvature and one from the greater curvature) and three from the corpus (one from the lesser curvature in the mid-area between the cardia and incisura; one from the opposite side in the greater curvature; and one from the fornix). An additional specimen was taken from the area below the incisura angularis for the rapid urease test (RUT). All specimens were H&E and/or giemsa stained and evaluated according to the updated Sydney Classification.

During the first two years of the study, two pathologists (NR and MSh), who were blinded to all clinical and endoscopic data evaluated the biopsy specimens. During the follow-up period one pathologist (NR) evaluated the specimens. At the end of the study, a gastric pathologist (MS) evaluated the specimens. Observers' agreement between the two pathologists (NR and MSh) and then between MSh and MS was calculated.

The severity of cell infiltration, atrophy and IM was categorized in four grades: none = 1; slight = 2; moderate = 3, and severe = 4. We compared the mean score (MS) of the changes in the two specimens from the antrum and three specimens from the corpus with the histology scores obtained at the follow-up endoscopy. One grade above or below the MS of atrophy or IM was considered progression or regression in the antrum or corpus, respectively.

H. pylori infection was considered absent by both negative RUT and negative histology for *H. pylori* in at least four out of five specimens, or by positive RUT and negative *H. pylori* in all five specimens. *H. pylori* infection was considered positive when RUT was positive and it was detected histologically in at least one of five specimens, or a negative RUT result and *H. pylori* was detected in at least two out of five specimens. We enrolled subjects that tested positive for *H. pylori* infection but not antrum-restricted gastritis who consented to a follow-up study with two additional control gastroscopies at two and four years.

Therapy regimens

Through block randomization, participants were allocated to two groups. Patients in the treatment group (group A) received a regimen for two weeks that contained bismuth subcitrate (240 mg bid), metronidazole (500 mg bid) and furazolidone (200 mg bid). Group B received placebo medications of the same shape and color, which were provided by the same companies that produced the verum drug (Arya, Kharazmi, Tehran Daru and Darupakhsh Pharmaceutical Companies, Tehran, Iran). The placebo for omeprazole, planned initially according to the protocol for therapeutic treatment, was not available. Therefore, we substituted ranitidine (300 mg bid) and its placebo (Darupakhsh Company, Tehran, Iran).

Statistical analysis and clinical trial registration

Statistical analysis was performed with SPSS program version 15. T- and chi-square t-tests were for analyses. The difference was considered significant if $P < 0.05$.

The Ethics Committee of Shariati Hospital, affiliated with Tehran University of Medical Sciences, approved this protocol in 2001 according to the Declaration of Helsinki. The study protocol was registered in the WHO-approved Committee of Iranian Registry of Clinical Trials (http://www.irct.ir/index.php) with registration number: IRCT138802071852N1.

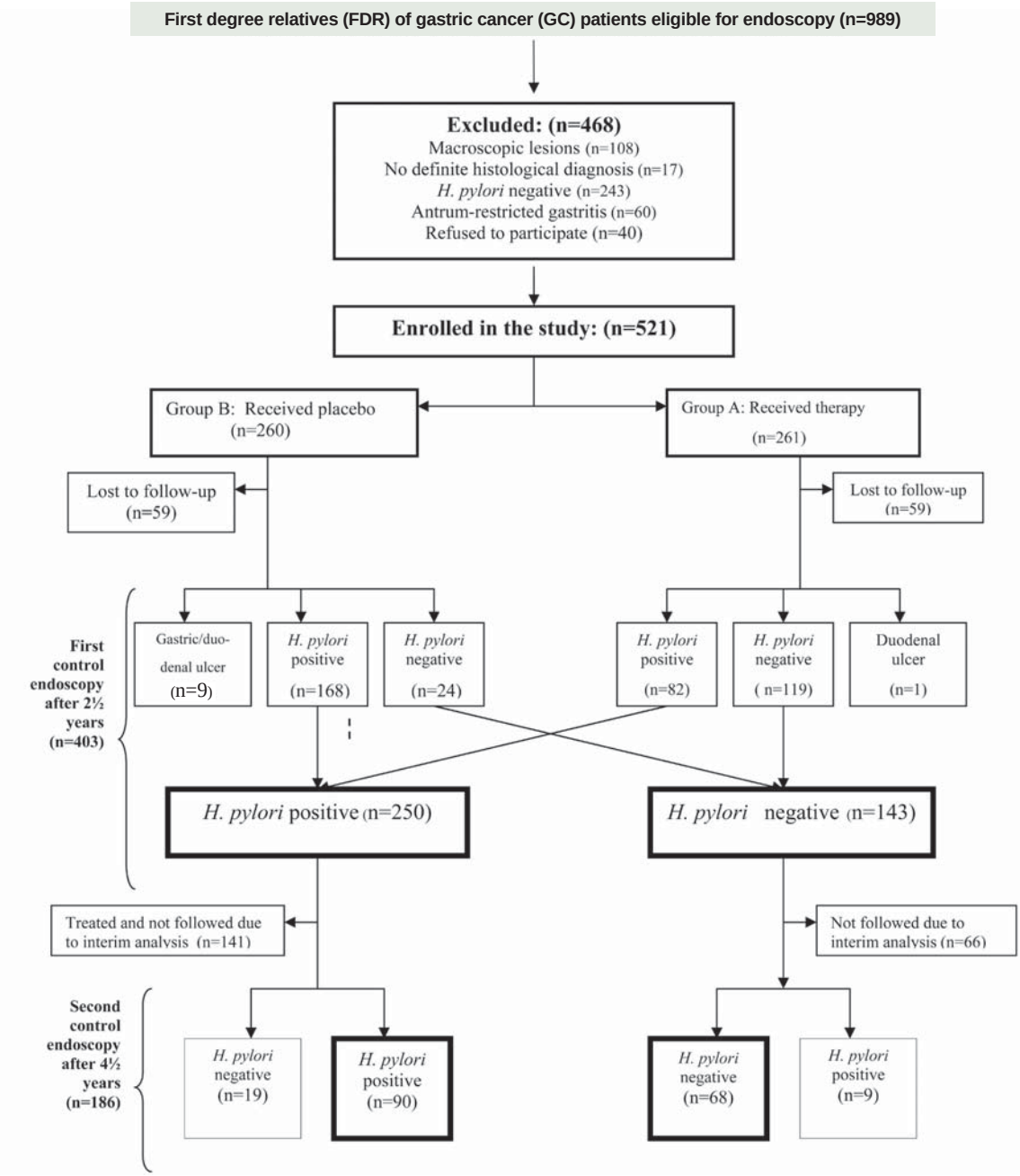
Results

Among the 881 patients with no macroscopic findings (Flow Chart 1), 360 patients were further excluded for the following: absence of *H. pylori* infection (243), inadequate histological findings (17), antrum-restricted gastritis (60) and refusal to participate (40). We enrolled 521 patients with antrum- or corpus- predominant pangastritis. Patients' mean age was 47.8 ± 6.7 years, (range: 38 – 70 years) and there were 256 males and 265 females. Subjects were allocated to either the eradication regimen (group A, n = 261) or placebo (group B, n = 260) by block randomization. A total of 403 patients attended the first endoscopic follow-up (201 after 32 ± 8 months in group A; 202 after 33 ± 9 months in group B). The flow chart shows the course of patients' follow-ups during the study. We performed an interim analysis at the end of 2006. Due to low eradication rate of *H. pylori* in group A, the number of eradicated patients in this group was remarkably different from those in the non-eradicated group B. This likely explained why we could not show a statistical difference in regression of corpus atrophy or IM between the two arms of the blinded study by intent-to-treat analysis.

When we conducted a separate analysis of the *H. pylori*-eradicated subjects from the non-eradicated ones in both arms and calculated the change in corpus atrophy, we found a statistically significant decrease in *H. pylori*-eradicated subjects compared to non-eradicated subjects. Therefore we stopped the study. At this time, 521 patients were enrolled, 403 had completed the 2½ year follow-up and 186 patients had completed 4½ years of follow-up.

In group A, *H. pylori* infection was eradicated in 119 out of 201 (59%) patients. Twenty-four became *H. pylori*-negative in group B (placebo), which was most likely due to spontaneous clearance or intake of antibiotics. In group B, 168 had stable *H. pylori* infection with no macroscopic lesions. Therefore, after 2½ years of follow-up, there were 143 patients with no infection (119 from group A; 24 from group B) and 250 patients with persistent *H. pylori* infection (82 from group A; 168 from group B). Among 186 patients who underwent endoscopy at the 4½ year follow-up, 68 remained *H. pylori*-negative and 90 had persistent *H. pylori* infection (14 from group A; 76 from group B).

The measure of agreement (Kappa value) between the two pathologists (MSh and NR) who evaluated the five areas of gastric mucosa in 147 participants, was 0.49 for normal mucosa, 0.55 for antral predominant gastritis, 0.51 for corpus predominant gastritis, 0.37 for any atrophy and 0.47 for any IM in the corpus ($P < 0.001$). The Kappa values of agreement between pathologist



Flow Chart 1. Follow-up of study subjects

NR, who examined the majority of specimens (58%), which were mostly from the follow-up endoscopies and gastric pathologist MS, who examined 27 specimens from the corpus area were 0.53 for grade of neutrophilic cell infiltration, 0.84 for mononuclear infiltration, 0.72 for atrophy and 0.61 for IM ($P < 0.01$).

Table 1 lists the MS of the severity of inflammatory cells during 2½ and 4½ years of follow-up for the antrum and corpus. Neutrophilic cell infiltration decreased completely, whereas there was a moderate decrease in mononuclear cell infiltration in eradicated cases. Some decrease in neutrophilic cell infiltration also occurred in the non-eradicated participants in the antrum and corpus ($P < 0.001$). However, mononuclear cell infiltration in non-eradicated individuals remained unchanged in the corpus and progressed in the antrum over 2½ years of follow-up ($P < 0.001$).

The regression or progression of atrophy and IM of more than one score separated for antrum and corpus are demonstrated after 2½ years (Table 2) and after 4½ years (Table 3) of follow-up. Although the regression or the progression of atrophy or IM of more than one score occurred in both groups, the numbers of patients with regression of atrophy was higher in the antrum and corpus of eradicated cases compared to non-eradicated cases during the first follow-up ($P < 0.0001$; Table 2). There was no regression of IM in the antrum or corpus of *H. pylori*-eradicated cases when compared with non-eradicated cases, although the majority of cases in the *H. pylori*-eradicated group initially had slight-to-moderate IM in the corpus (18 out of 23, which was similar to the group assigned to non-eradication with 17 out 20). However, progression of atrophy ($P < 0.02$) and IM ($P < 0.05$) occurred only in

Table 1. Mean score (MS) of histological findings in the antrum and corpus during 2½ and 4½ years follow-up of *H. Pylori*-eradicated and non–eradicated subjects.

	2½ year follow-up				4½ year follow-up					
	H. pylori-eradicated subjects (n=143)		*H. pylori* non-eradicated subjects (n=250)		*H. pylori*-eradicated subjects (n=68)			*H. pylori* non-eradicated subjects (n=90)		
	Before	After 2½ years	Before	After 2½ years	Before	After 2½ years	After 4½ years	Before	After 2½ years	After 4½ years
Neutrophilic infiltration										
in antrum	2.30±0.70	1.03±0.15*	2.41±0.7	1.65±0.65*	2.46±0.71	1.0±0.06*	1.03±0.15*	2.54±0.58	1.76±0.7*	1.57±0.58**
in corpus	2.03±0.69	1.05±0.25*	1.96±0.61	1.36±0.46*	2.14±0.62	1.03±0.05*	1.03±0.15*	2.16±0.6	1.45±0.53*	1.36±0.49*
Mononuclear cell infiltration										
in antrum	2.9±0.65	1.85±0.63*	2.95±0.55	3.1±0.7*	2.87±0.57	1.69±0.51*	1.86±0.56*	2.9±0.45	3.2±0.64*	3.2±0.65*
in corpus	2.6±0.51	1.7±0.62*	2.49±0.55	2.45±0.68	2.50±0.43	1.68±0.60*	1.63±0.52*	2.56±0.47	2.52±0.69	2.6±0.7

*P<0.001 compared with initial values; **P<0.005 compared with 2½ year values.

Table 2. Progression or regression of atrophy and intestinal metaplasia (IM) by at least one score in eradicated and non-eradicated patients at the 2½-year follow-up.

	H. pylori-eradicated subjects (n=143)			*H. pylori* non–eradicated subjects (n=250)		
	Before N	Regression N(%)95% CI	Progression N(%)95% CI	Before N	Regression N(%) 95% CI	Progression N(%) 95% CI
Atrophy in antrum	97	60* (61.8%) (51–71)	9 (6.3%) (3–12)	184	57 (31%) (25–39)	28 (11.2%.) (22–34)
Atrophy in corpus	104	37* (35.6%) (26–45)	2 (1.4%) (0.23–6.7)	173	23 (13.3%) (17–30)	10 (4%) (6–14)
IM in antrum	23	8 (34.8%) (16–57)	5 (3.5%) (1–8)	32	9 (28.1%) (13–46)	19 (7.6%) (14–24)
IM in corpus	23	2 (8.7%) (1–28)	2 (1.4%) (0–5)	20	2 (10%) (1–31)	9 (3.6%) (6–13)

*P<0.0001 compared with non-eradicated group.

the antrum of the non-eradicated group when compared with the eradicated group.

Discussion

Although the reduction of GC through eradication of *H. pylori* has been verified by meta-analysis studies, [2] regression of precancerous conditions remains a subject of debate in many studies. Most short- and long-term follow-up studies show significant regression of gastric atrophy; however, the controversy remains regarding the reversibility of IM. The majority of authors have not reported IM regression[3,5–12] while some randomized studies with longer follow-up periods of over two years have shown evidence of IM regression.[13–18] In a non-randomized study, regression of atrophic gastritis both in the antrum and corpus and IM in the corpus, but not in the antrum was observed after 8.6 years.[25] In one non-randomized, non-controlled study, mass eradication of *H. Pylori* in Taiwan led to regression of gastric atrophy in 78% over four years. No change in IM was noted.[21] The incidence of GC declined compared to the time period before start of eradication.

In another randomized controlled trial in patients with advanced atrophic gastritis, *H. pylori* eradication or continuous celecoxib therapy over a two year period resulted in regression of gastric atrophy, but not IM.[22] Progression of precancerous conditions could not be studied in any of the treatment or placebo groups due to exclusion of patients with mild atrophic gastritis. In this study, no definite data were given about the topography of histological changes.

We observed progression of atrophic gastritis or IM in some *H. pylori*-eradicated cases and regression in some non-eradicated cases over a long follow-up period. This observation revealed that in addition to *H. pylori* infection, other environmental factors such as smoking habits,[26–28] salt intake[29,30] and dietary habits [27] might have promoted the development of precancerous conditions.

In contrast to our expectations, in our population there were not many FDRs of GC patients with IM in their gastric mucosa. When present, in the majority of patients, IM was in a non-advanced stage. Nevertheless, the eradication of *H. pylori* did not result in regression of IM in its mild stage in neither the antrum, nor corpus mucosa even with longer follow-up periods. This confirmed the results obtained in the recently published meta-analysis.[20] However, the *H. pylori*-eradicated individuals showed less progression, more regression of atrophy, and no progression of IM in the antrum and corpus in general, compared to non-eradicated cases. Progression of IM in the antrum in non-*H. pylori*-eradicated patients and regression of antral atrophy in eradicated subjects was not observed in a published meta-analysis study,[20] which was probably due to the lack of a longer follow-up.

Eradication of *H. pylori* may prevent progression of both atrophy and IM. Thus, the process of precancerous lesions might not advance to a state where conditions for neoplastic cell production exist.

It seems that the antrum is more prone to the progression of IM under the presence of *H. pylori* infection than the corpus. In other words, persistence of the *H. pylori* infection may promote the de-

Table 3. Progression or regression of atrophy and intestinal metaplasia (IM) by at least one score in eradicated and non-eradicated patients at 4½ years of follow-up.

	H. pylori-eradicated subjects (n=68)			*H. pylori* non–eradicated subjects (n=90)		
	Before N	Regression N (%) 95% CI	Progression N (%) 95% CI	Before N	Regression N (%) 95% CI	Progression N (%) 95% CI
Atrophy in antrum	42	21 (50%) (31–65)	0 (0%) (0–5)	66	20 (30.3%) (19–42)	14** (15.6%) (8–24)
Atrophy in corpus	53	23* (43.4%) (29–57)	1 (1.5%) (0–8)	61	13 (21.3%) (12–33)	5 (5.6%) (2–12)
IM in antrum	8	3 (37.5%) (8–75)	4 (5.9%) (1–12)	14	3 (21.4%) (4–50)	17*** (18.9%) (12–28)
IM in corpus	10	2 (20%) (2–55)	0 (0%) (0–30)	7	2 (28.6%) (3–71)	3 (3.3%) (1–9)

*P<0.02 compared with non-eradicated group; **P<0.02 compared with eradicated group; ***P<0.05 compared with eradicated group.

velopment of precancerous conditions in the antrum over a shorter time period when compared to the corpus. Therefore, individuals at risk of IM in the upper stomach would not benefit from *H. pylori* eradication. Eradication of *H. pylori* might decrease GC located in the distal, rather than in the upper stomach.

We have observed regression of atrophy in the eradicated group. Diagnosis of atrophy is difficult and the agreement between pathologists is low[31,32] as with our study, particularly when large numbers of inflammatory cells are present in the mucosa and its regression can be incorrectly interpreted as an improvement of atrophy. In our study, the follow-up specimens were mostly evaluated by one pathologist. Thus, the remarkable regression of atrophy in eradicated compared to non-eradicated cases was evident. By measuring the concentration of serum biomarkers, pepsinogen I, II and its ratio, we observed a remarkable decrease in the pepsinogen I to pepsinogen II ratio only in the *H. pylori*-eradicated group, which confirmed the histological regression of atrophic gastritis (manuscript in preparation).

The decrease of neutrophilic cell infiltration in non-eradicated patients was due to intake of antibiotics administered to a high number of subjects who failed *H. pylori* eradication in the treatment arm and were subsequently included in the non-eradicated group.

The cause for the low eradication rate of *H. pylori* in the treatment arm could be in the choice of the H2-receptor blocker, ranitidine as an acid suppressant. Ranitidine cannot provide an optimal increase of pH that is necessary for enhanced antibiotic effectiveness.[33] Another potential contributing factor leading to the lower eradication rate could have been lower compliance of the subjects to the eradication regimen. We were unable to assess this since most of the study population resided in remote areas of the country.

In conclusion, we noted that once IM developed in gastric mucosa, eradication of *H. pylori* in this area did not cause regression in IM even in its mild stage with longer follow-up periods. However, eradication of *H. pylori* prevented further progression of atrophy in the stomach and IM in the antrum, rather than in the corpus compared to non-eradicated individuals.

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