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ORIGINAL ARTICLE

Relationship between *Helicobacter Pylori* Infection and Gastric Dysplasia: Results from Histology of Gastric Samples in the South of Iran

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Background and Study Aims: Gastric dysplasia (GD) is a histologic premalignant lesion. Its significant lies in its strong association with the increased risk of developing gastric cancer. As there is no data about the frequency of *Helicobacter pylori* infection in histologic GD in the south of Iran, we designed the current study. **Patients and Methods:** In this cross-sectional study, we studied the frequency of *H. pylori* infection in consecutive cases with histologic diagnosis of GD; then, they were compared with a randomly selected group of age-matched participants whose histological diagnosis was normal or mild inflammation. The current study was conducted from November 2010 to January 2017 in Iran. **Results:** Of a total of 3521 patients, 126 cases with GD and 252 participants as the controls were enrolled. The mean age ± standard deviation of GD patients and controls was 50.25 ± 17.708 and 50.16 ± 17.388 years, respectively. Histologically, *H. pylori* infection was detected in 84.9% and 73.4% of the GD patients and controls, respectively. The frequency of *H. pylori* in the GD group was significantly higher than the comparison group ($P = 0.012$). On gastric endoscopic examination of patients with GD, 31 (24.6%) patients had normal endoscopy and others had abnormal endoscopic findings. **Conclusions:** In our study, the frequency of *H. pylori* in patients with GD was significantly higher than that of the comparison group. We recommend that further studies can be conducted to clarify the causal relationship of *H. pylori* infection and GD and also the impact of *H. pylori* eradication on the natural course of GD. We also recommend that further studies can be performed to determine the real association between endoscopic findings and GD.

Key words: *Helicobacter pylori*, dysplasia, chronic gastritis, intestinal metaplasia, gastric cancer

INTRODUCTION

Helicobacter pylori is an important cause of gastroduodenal disorders such as peptic ulcer diseases and gastric cancer. The most common routes of *H. pylori* transmission are oral-oral and fecal-oral.[1-4] The prevalence rate of this infection is different in various countries.[1,5-7] *H. pylori* is an important triggering factor in inducing gastric cancer by a cascade of events, i.e., atrophic gastritis, intestinal metaplasia, and gastric dysplasia (GD). Although chronic inflammation induced by *H. pylori* may progress to histologic premalignant lesions (PMLs) and finally gastric cancer,[8] gastric cancer is developed in only a very small number of people with *H. pylori* positivity.[9] Different mechanisms such as gastrin and other growth factors have been shown to be co-expressed in this carcinogenesis.[4,9,10]

Upper gastrointestinal endoscopy and histologic examination of the gastric sample is done for diagnosing the presence and extension of histologic PMLs in the stomach.[8,11,12] Although an optimal treatment of *H. pylori* has not been defined, many schemes with different efficacy rates have been introduced for the eradication of this infection. Typically, a combination of various antibiotics and proton pump inhibitors has been used.[13-15]

In many studies, the high prevalence of *H. pylori* infection in patients with histologic PMLs and cancer has been

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described,[16-18] but Farinati *et al*. showed that the *H. pylori* infection correlated inversely with the presence of histologic PMLs and cancer.[19] The risk of gastric cancer is related to the severity and extent of these histologic PMLs.[10,20] Male gender, older age, diabetes mellitus, obesity, and salty and/or spicy diet are other risk factors for the formation of PMLs and cancer.[8]

GD is one of the important PMLs because of its strong association with at least 10-fold increased risk of gastric cancer.[9,21,22] Dysplasia is characterized histologically by the increased mitotic activity, cellular pleomorphism, decreased cytoplasmic mucin, increased nuclear: cytoplasmic ratio, nuclear hyperchromatism, and glandular disarray. There is a difference in the prevalence of dysplasia in different countries. Variation in the prevalence of dysplasia can be due to the different uses of the term dysplasia, differences in histologic classification, and the different origins of the population. The prevalence of dysplasia is estimated to range from 0.5% to 3.75% in Western population and 9% to 20% in high-risk areas for gastric carcinoma.[21]

To the best of our knowledge, as there is no data about the frequency of *H. pylori* infection in patients with histologic diagnosis of GD in the south of Iran, we designed the current study.

MATERIALS AND METHODS

Population and study design

In this cross-sectional study, we studied the frequency of *H. pylori* infection in consecutive cases with histologic diagnosis of GD. In order to determine this frequency, we retrospectively studied the histologic documentation of 3521 consecutive histological diagnosis of gastric samples from November 2010 to January 2017 in Fars Province, South Iran.

These samples were obtained to evaluate the dyspeptic patients. Endoscopic biopsies of abnormal gastric mucosa and also random biopsies in participants with normal mucosa had been performed for all patients. After obtaining the approval of the university ethical committee and institutional review board (93-01-13-8141), we included all histologic documentation with histologic GD report by the pathologist. GD was defined as increased mitotic activity, cellular pleomorphism, decreased cytoplasmic mucin, increased nuclear: cytoplasmic ratio, nuclear hyperchromatism, and glandular disarray.[21] In order to compare GD patients with controls, we randomly selected a group consisting of age-matched participants whose histological diagnosis was normal or mild inflammation. The comparison group was randomly selected from the same histologic documentation [Figure 1].

H. pylori infection was detected from the same histologic documentation of the GD and comparison groups based on

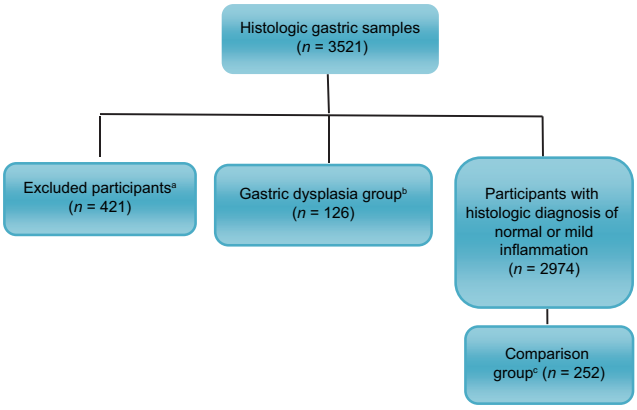

Figure 1: Flow diagram for the participants' selection process. [a]Participants with histologic diagnosis of premalignant lesion (except gastric dysplasia) or malignancy or no well-defined diagnosis were excluded, [b]Participants with histologic diagnosis of gastric dysplasia, [c]Age- matched randomly selected participants as comparison group

Giemsa stain and haematoxylin and eosin stain. Finally, the GD group was compared with the age-matched comparison group. The endoscopic findings of patients with GD were also demonstrated.

Statistical analysis

Comparisons between the two groups were analyzed by using the Chi-square test for categorical variables and by *t*-test for continuous variables. $P < 0.05$ was considered statistically significant. Odds of *H. pylori* features were analyzed by using logistic regression with adjustment by sex and age. Statistical analyses were performed SPSS software, version 16.0, Chicago, USA.

RESULTS

Overall, 126 participants with GD and 252 participants as controls were enrolled [Figure 1]. The mean age ± SD of the GD and comparison groups was 50.25 ± 17.708 and 50.16 ± 17.388 years, respectively [Table 1]. Age distribution of the GD and comparison groups is shown in Table 2. Of the 126 cases with GD, 28 (22.20%) were in the age range of 51–60 years.

Histologically, *H. pylori* infection was detected in 107 patients of GD group, whereas 185 controls of the comparison group were positive for *H. pylori* infection. The frequency of *H. pylori* in GD group was significantly higher than that of the comparison group (odds ratio [OR], 1.973; 95% confidence interval [CI], 1.107–3.516; $P = 0.012$) [Table 1].

A total of 123 cases (97.62%) with GD had low-grade dysplasia and only 3 (2.38%) cases had high-grade dysplasia. All the patients with high-grade dysplasia were male (ages:

64-63-48 years) and two of them (age: 64 and 63 years) had *H. pylori* infection.

On gastric endoscopic examination of patients with GD, 31 (24.6%) patients had normal endoscopy and others had abnormal endoscopic findings. The association between endoscopic and histopathologic findings in patients with GD is shown in Table 3.

DISCUSSION

Gastric cancer is an important cause of cancer-related mortality.[4] Atrophic gastritis, intestinal metaplasia, and GD are components of a cascade of morphological events for the development of gastric cancer.[8,23-25] Chronic inflammation induced by *H. pylori* may progress to histologic PMLs and finally gastric cancer. *H. pylori* is an important triggering factor in the induction of this cascade of events.[4,8,10]

Table 1: Clinical features of the group with gastric dysplasia versus comparison group

	GD group 126 (%)	Comparison group 252 (%)	*P*
Age (years)	50.25±17.708	50.16±17.388	-
Sex (male/female)	56/70 (44.4/55.6)	37/47 (44/56)	-
Comorbid illness			
Hypertension	6 (4.76)	10 (3.97)	0.7191
Diabetes mellitus	5 (3.97)	9 (3.57)	0.8461
Cirrhosis of liver	0	0	-
Chronic kidney disease (eGFR<60 mL/min/1.73m^2)	0	0	-
Medication			
Antiplatelet drugs	1 (0.79)	1 (0.40)	0.6225
Nonsteroidal anti-inflammatory drugs	2 (1.59)	3 (1.19)	0.7483
Anticoagulant drugs	0	0	-
Cigarette smoking	12 (9.52)	21 (8.33)	0.6992
Heavy drinking	0	0	-
Helicobacter pylori infection (%)	107 (84.9)	185 (73.4)	0.012

eGFR=Estimated glomerular filtration rate; GD=Gastric dysplasia

Table 2: Age distribution of the group with gastric dysplasia versus comparison group

Age (years)	GD group (%)	Comparison group (%)
<20	5 (4.0)	10 (8.0)
20-30	14 (11.1)	28 (12.2)
31-40	23 (18.3)	46 (36.6)
41-50	19 (15.1)	38 (30.2)
51-60	28 (22.2)	56 (44.4)
61-70	19 (15.1)	38 (30.2)
71-80	12 (9.5)	24 (19.0)
>80	6 (4.8)	12 (9.6)
Total	126 (100)	252 (100)

GD=Gastric dysplasia

GD is one of the important PMLs.[9] The average age of the cases with GD has been reported to be from the fifth to seventh decades of life.[21] Some studies have shown that patients with high-grade GD are older than those with low-grade GD.[22,26]

In a population-based study, You *et al*. showed that GD was seen in 20% of cases and it increased significantly with age. GD was more common (1.6-fold) among men.[27] Bearzi *et al*.[28] in a follow-up study on GD of 125 patients showed that 81 and 44 cases had low- and high-grade dysplasia, respectively. Cases with low-grade dysplasia were younger than those with high-grade dysplasia.

Di Gregorio *et al*.[22] in a study on GD of 99 dyspeptic patients showed that the degree of GD was mild in 73 (58 men, 15 women, aged 57 years), moderate in 16 (10 men, 6 women, aged 55 years), and severe in 10 (7 men, 3 women, aged 61 years) cases. GD was predominantly seen among males (ratio: 3:1). Only in the severe type of GD, males were predominantly younger than females (mean age. 57 vs. 72.35 years).

On review of forty patients with a diagnosis of GD, Lansdown *et al*.[29] showed that only twenty (12 men, 8 women, median age: 72 years with a range of 55–86 years) of them had true dysplasia. Seven and 13 cases had low- and high-grade dysplasia, respectively.

In our research, the frequency of *H. pylori* infection was significantly higher in GD group than that in the comparison group (OR, 1.973; 95% CI, 1.107–3.516; $P = 0.012$). Although this result, similar to some other published reports,[10,21-25] suggest that *H. pylori* infection may be considered as a possible risk factor for the formation of GD, well designed prospective studies need to determine the causal relationship of *H. pylori* infection and GD. In this study, similar to some other published reports,[20] the mean age of the patients with GD was the sixth decade of life. Nearly 22.20% of our GD cases were in the age group of 51–60 years. These results suggest that older age may be considered as a possible risk factor for the formation of GD.[27] Although only three of our cases had high-grade dysplasia, all of them were male. These results suggest that male gender may be considered as a risk factor for the formation of severe type of GD. Some other published reports[8,27] also suggest that male gender and older age are statistically significant risk factors for the formation of PMLs.

The association between endoscopic findings and GD is not clear based on previous studies. A study by Aste *et al*. revealed that 29 of 694 patients with endoscopic localized gastric

Table 3: Comparison of endoscopic findings between the group of gastric dysplasia with *Helicobacter pylori* infection and the comparison group with *Helicobacter pylori* infection

	GD group (107 patients) (%)	Comparison group (185 controls) (%)	*P*
Normal mucosa	30 (28.04)	142 (76.76)	0.000
Erythematous mucosa	16 (14.95)	10 (5.40)	0.0058
Nodularity	24 (22.43)	6 (3.24)	0.000
Erosion	28 (26.17)	23 (12.43)	0.0029
Ulcer	6 (5.61)	4 (2.16)	0.1183
Concurrent erosion and ulcer	3 (2.80)	0	0.0222

GD=Gastric dysplasia

lesions and 1 out of 123 patients with normal endoscopy had GD. They concluded that GD was significantly associated with endoscopic prominent or depressed lesions.[30] Although different endoscopic findings including ulcers, erosions, polyps, and atrophic mucosa have been associated with GD, 7%–60% of GD patients have unremarkable mucosa on endoscopy.[21] In our research, 31 (24.6%) of 126 patients with GD had normal endoscopy based on random mucosal biopsies for dyspeptic patients. The endoscopic findings of other GD patients in our study were erosions, nodularity, erythematous mucosa, ulcer, and polyp [Table 3]. These discrepancies of endoscopic findings in different studies may be due to different endoscopic techniques and histological diagnostic criteria of GD.[21] Well-designed studies can be done to determine the real association between endoscopic findings and GD.

Our study had some important limitations and confounding factors. Our research was retrospective which was conducted in a single center and there was no enough evidence of medication use including proton pump inhibitors as a confounding factor in *H. pylori* infection diagnosis. The gastric samples were examined by different pathologists; furthermore, it is difficult for pathologists to differentiate GD from normal tissue in the presence of inflammation. These facts can create interobserver bias as an important confounding factor. There was no evidence of other possible risk factors that predispose patients to the formation of PMLs including diet status.[8] The confirmation of *H. pylori* infection was done with only one method. Multicentric and well-designed prospective research with consideration of the above limitations and confounding factors can be used to highlight the importance of these results.

CONCLUSIONS

We suggest that well-designed prospective studies can be done to determine the causal relationship of *H. pylori* infection and GD and also the impact of *H. pylori* eradication on the natural course of GD. We also recommend that further studies can be performed to determine the true association between endoscopic findings and GD.

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Conflicts of interest

There are no conflicts of interest.

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