Research Article

Demographics and Clinical and Endoscopic Characteristics of Patients with Helicobacter pylori Infection and Gastroesophageal Reflux Disease: A Case-Control Study

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Background. The correlation between Helicobacter pylori (H. pylori) and gastroesophageal reflux disease (GERD) is complex. Some studies showed a protective role of H. pylori infection against GERD. This study was aimed at assessing the role of H. pylori infection in GERD utilizing a large cohort of patients diagnosed with GERD.

Methods and Materials. All patients who underwent gastroscopy for an indication of GERD during the study period between 2015 and 2017 at the EMMS Nazareth Hospital were considered eligible for the study and therefore were included. H. pylori infection was determined by the rapid urease test or histology. Severity of esophagitis was assessed using the Los Angeles classification. Univariate analysis was performed to figure out differences between patients according to H. pylori infection status. Multivariate regression analysis was conducted to illustrate the predictors of positivity for H. pylori infection. Results. 2,508 GERD patients were included with a median age of 49.42 ± 17.96 years. H. pylori infection was detected in 299 (11.9%) patients. GERD patients with H. pylori infection were found to be younger (48.83 ± 17.42 years versus 44.57 ± 17.69 years, p < 0.001), have the tendency to smoke more (1406 (63.6%) versus 266 (89.0%), p < 0.001), and use more proton pump inhibitors or PPIs (1314 (59.5%) versus 242 (80.9%), p < 0.001). In multivariate regression analysis, age (OR 0.987, p < 0.001), smoking status (OR 0.190, p < 0.001), use of ASA/NSAIDs (OR 1.652, p = 0.004), and use of statins (OR 0.499 (95%CI 0.295-0.846), p = 0.010) were found significant among H. pylori-positive individuals. H. pylori-positive subjects have less severe esophagitis and more hiatus hernia.

Conclusion. Patients with GERD and H. pylori infection were significantly younger, tended to smoke more, and used more PPIs and had significantly lower grades of esophagitis compared to noninfected ones.

1. Introduction

The association between infectious agents and gastritis has been known for centuries. However, this relation was not strongly implicated until the discovery of Helicobacter pylori (H. pylori) in the early 1980s [1]. Since then, and in addition to gastritis, strong evidences have been accumulated regarding the role of H. pylori in multiple gastric disorders including peptic ulcer disease [2, 3], gastric cancer, and lymphoma [4, 5]. H. pylori is spiral-shape slow-growing gram-negative bacteria characterized by urease, catalase, and oxidase positivity [6]. Urease activity is crucial for bacterial survival, as
well as constituting the basis of \textit{H. pylori} diagnostic testing [7]. In developed countries, the \textit{H. pylori} infection rate is low in childhood; however, it increases with age reaching 10 percent in adulthood and raising up to 50 percent in individuals older than 60 years [8, 9]. Low socioeconomic status, overcrowding, smoking, family member with \textit{H. pylori}, and unfiltered drinking water were all shown to be directly associated with increased prevalence rates [10, 11]. The isolation of \textit{H. pylori} from gastric secretions as well as stool culture explains transmissibility among family members [12]. Diagnostic tests of infection are classified as invasive and noninvasive and are based mainly on urease activity. Invasive tests include the urease test, culture, histology, and polymerase chain reaction (PCR) in which gastroscopy is required to obtain stomach tissue [7, 13, 14]. \textit{H. pylori} infection, if not properly treated, leads to the insurgence of many digestive disorders, such as chronic gastritis, peptic ulcer, upper gastrointestinal bleeding, MALToma, chronic atrophic gastritis, intestinal metaplasia, and distal gastric adenocarcinoma, among others. Triple or quadruple antibiotic-based regimens are the mainstay of therapy. Detailed guidelines for the treatment of \textit{H. pylori} infection were released by the American College of Gastroenterology (ACG) and the Maastricht Group [15, 16]. \textit{H. pylori} and GERD are common gastrointestinal conditions in the general population and may coexist. The relationship between \textit{H. pylori} and GERD symptoms and esophagitis is still controversial. Despite the fact that numerous papers showed a protective role of \textit{H. pylori} against GERD and esophagitis [17, 18], one landmark study reported consistent results [19]. The suggestive protective role has been related to decreased gastric acid secretion due to atrophic gastritis in patients infected with \textit{H. pylori} [18]. Moreover, reports showed that eradication of \textit{H. pylori} by restoring gastric acid secretion could exacerbate GERD symptoms [20]. Taking these controversies into consideration, we aimed in our study to characterize demographic and endoscopic findings in patients with GERD according to their \textit{H. pylori} infection status.

2. Material and Methods

2.1. Ethical Clearance. The current study received ethical approval from the local hospital ethical committee and was conducted according to the 1964 Helsinki declaration and its subsequent amendments. The data was coded in order to preserve the anonymity of the patients. Informed consent was waived because of the noninterventional design of the study.

2.2. Patient Selection. All patients referred to the endoscopy unit at the EMMS Nazareth Hospital (a district university-affiliated hospital, Nazareth, Israel) for esophagogastroduodenoscopy (EGD) due to GERD symptoms such as heartburn and/or regurgitations or refractory GERD, typical symptoms, or the presence of alarm symptoms between the years 2015 and 2017 were considered potentially eligible and enrolled in the study. Patients were allocated retrospectively, through electronic medical reports at our unit software. All EGD procedures were performed at the single endoscopic unit, at the Nazareth Hospital, by five different senior gastroenterologists. Severity of esophagitis was assessed using the Los Angeles classification [21]. \textit{H. pylori} infection was determined either by histological examination through a biopsy taken during the EGD or by the rapid urease test using commercially available kits in the unit (PyloriPlis+ manufactured by Gulf Coast Medical Inc., Oldsmar, FL 34677, USA).

2.3. Statistical Analysis. Before proceeding with any statistical handling and processing, data were visually inspected for potential outliers. The assumption of normal distribution of data was checked conducting the D’Agostino-Pearson omnibus test. Continuous data were expressed as means and standard deviations, whereas categorical parameters were computed as percentages, where appropriate.

Univariate analysis (chi-squared test, Student’s t-test, and Kruskal-Wallis test) was performed to capture the main differences between subjects seronegative and seropositive for \textit{H. pylori}.

Multivariate logistic or Poisson’s regression analysis was conducted to shed light on the predictors of positivity for \textit{H. pylori}, adjusting for potential confounders.

All statistical analyses were performed with the commercial software “Statistical Package for the Social Sciences” (SPSS version 24.0, IBM, Chicago, IL, USA). A \( p \) value of less than 0.05 was considered statistically significant.

3. Results

A sample of 2,508 subjects with classical clinical GERD symptoms of heartburn and regurgitations, aged 49.42 ± 17.96 years, was included in the study: most were Arabs (83.7%), 52.4% were females, 66.7% were current smokers, and 10.3% had comorbidities. Concerning pharmacological
### Table 2: Values broken down according to *Helicobacter pylori* infection status (univariate analysis).

| Parameter                  | Subjects without *H. pylori* infection | Subjects with *H. pylori* infection | p value |
|----------------------------|---------------------------------------|------------------------------------|---------|
| **Ethnicity**              |                                       |                                    |         |
| Arabs (n = 2,100)          | 1,841 (83.3% of *H. pylori* subjects, 87.7% of Arabs) | 259 (86.6% of *H. pylori* subjects, 12.3% of Arabs) | 0.157   |
| Jews (n = 408)             | 368 (16.7% of *H. pylori* subjects, 90.2% of Jews) | 40 (13.4% of *H. pylori* subjects, 9.8% of Jews) |         |
| BMI                       | 29.69 ± 7.67                          | 29.91 ± 6.29                      | 0.297   |
| **Sociodemographic status**|                                       |                                    | 0.256   |
| Rural (n = 1,524)          | 1,333 (60.3% of *H. pylori* subjects, 87.5% of rural subjects) | 191 (63.9% of *H. pylori* subjects, 12.5% of rural subjects) |         |
| Urban (n = 984)            | 876 (39.7% of *H. pylori* subjects, 89.0% of urban subjects) | 108 (36.1% of *H. pylori* subjects, 11.0% of urban subjects) |         |
| Age                       | 48.83 ± 17.42                         | 44.57 ± 17.69                     | p ≤ 0.001|
| **Gender**                 |                                       |                                    | 0.902   |
| Males (n = 1,194)          | 1,053 (47.7% of *H. pylori* subjects, 88.2% of males) | 141 (47.2% of *H. pylori* subjects, 11.8% of males) |         |
| Females (n = 1,314)        | 1,156 (52.3% of *H. pylori* subjects, 88.0% of females) | 158 (52.8% of *H. pylori* subjects, 12.0% of females) |         |
| Smoking status (n = 1,672) | 1,406 (63.6% of *H. pylori* subjects, 84.1% of smokers) | 266 (89.0% of *H. pylori* subjects, 15.9% of smokers) | p ≤ 0.001|
| Alcohol consumption (n = 96) | 82 (3.7% of *H. pylori* subjects, 85.4% of alcohol consumers) | 14 (4.7% of *H. pylori* subjects, 14.6% of alcohol consumers) | 0.421   |
| Comorbidities (n = 259)    | 222 (10.0% of *H. pylori* subjects, 85.7% of subjects with comorbidities) | 37 (12.4% of *H. pylori* subjects, 14.3% of subjects with comorbidities) | 0.224   |
| ASA/NSAID users (n = 680)  | 613 (27.8% of *H. pylori* subjects, 90.1% of ASA/NSAID users) | 67 (22.4% of *H. pylori* subjects, 9.9% of ASA/NSAID users) | 0.052   |
| Statin users (n = 190)     | 164 (7.4% of *H. pylori* subjects, 86.3% of statin users) | 26 (8.7% of *H. pylori* subjects, 13.7% of statin users) | 0.416   |
| PPI users (n = 1,556)      | 1,314 (59.5% of *H. pylori* subjects, 84.4% of PPI users) | 242 (80.9% of *H. pylori* subjects, 15.6% of PPI users) | p ≤ 0.001|

ASA: acetylsalicylic acid; BMI: body mass index; NSAIDs: nonsteroidal anti-inflammatory drugs; PPIs: proton pump inhibitors.

### Table 3: Predictors of *Helicobacter pylori* infection (multivariate logistic regression analysis).

| Parameter                  | OR   | 95%CI OR Lower bound | Upper bound | p value |
|----------------------------|------|----------------------|-------------|---------|
| Ethnicity (Arabs versus Jews) | 1.105 | 0.765                | 1.595 | 0.596   |
| BMI                        | 1.002 | 0.988                | 1.017 | 0.747   |
| Rural versus urban         | 1.144 | 0.883                | 1.481 | 0.308   |
| Age                        | 0.987 | 0.980                | 0.994 | 0.001   |
| Gender                     | 1.008 | 0.786                | 1.293 | 0.951   |
| Smoking status             | 0.190 | 0.112                | 0.324 | 0.001   |
| Alcohol consumption        | 0.773 | 0.425                | 1.406 | 0.398   |
| Comorbidities              | 0.781 | 0.534                | 1.143 | 0.203   |
| ASA/NSAID users            | 1.652 | 1.169                | 2.333 | 0.004   |
| Statin users               | 0.499 | 0.295                | 0.846 | 0.010   |
| PPI users                  | 1.116 | 0.716                | 1.741 | 0.627   |
| Constant                   | 0.567 |                      |         | 0.301   |

ASA: acetylsalicylic acid; BMI: body mass index; NSAIDs: nonsteroidal anti-inflammatory drugs; PPIs: proton pump inhibitors.
treatment, 62.0% consumed PPIs, whereas 7.6% used statins. 

H. pylori infection was found positive in 299 patients (11.9%). For further details, the reader is referred to Table 1.

In the univariate analysis (Table 2), H. pylori-negative and H. pylori-positive patients differed for age (48.83 ± 17.42 years versus 44.57 ± 17.69 years, p ≤ 0.001), smoking status (1406 (63.6%) versus 266 (89.0%), p > 0.001), and use of PPI (1314 (59.5%) versus 242 (80.9%), p ≤ 0.001), respectively. 70.6% of the H. pylori-non-infected group had no signs of esophagitis in endoscopy. 29.4% had esophagitis in the following LA classification severity order (17.2% had esophagitis LA A, 9.8% had esophagitis LA B, and 1.9% had LA D). In turn, 54.1% of the H. pylori-infected group had signs of esophagitis in endoscopy, in the following LA classification severity order (33.1% had esophagitis LA A, 9.7% had esophagitis LA B, 1.9% and 1.3% had LA C, and 0% had LA D). H. pylori-infected patients had less hiatus hernias (21.7%), compared to noninfected patients (30.7%).

In the multivariate logistic regression analysis (Table 3), age (OR 0.987 (95%CI 0.980-0.994), p < 0.001), smoking status (OR 0.190 (95%CI 0.112-0.324), p < 0.001), use of aspirin/nonsteroidal anti-inflammatory drugs (ASA/NSAIDs) (OR 1.652 (95%CI 1.169-2.333), p = 0.004), and use of statins (OR 0.499 (95%CI 0.295-0.846), p = 0.010) were assessed.

Concerning the outcomes, H. pylori-infected and noninfected subjects differed in terms of insurgence (p < 0.001) and severity (p = 0.003) of esophagitis (Table 4(a)) and insurgence of hiatal hernia (p = 0.001, Table 4(b)). No differences could be found in terms of prevalence of Barrett’s esophagus.

Confirming the univariate analysis, the multivariate logistic regression shows that with respect to H. pylori-positive GERD patients, H. pylori-negative GERD individuals have a

### Table 4

(a) Endoscopic findings of GERD (insurgence and severity of esophagitis) subjects stratified according to the Helicobacter pylori (H. pylori) infection status

| H. pylori status (n = 2,508) | No esophagitis (n = 1,726) | Esophagitis (n = 782) |
|-----------------------------|-----------------------------|-----------------------|
| Grade A (n = 478)           | Grade B (n = 245)           | Grade C (n = 47)      | Grade D (n = 12) |
| H. pylori negative (n = 2,209) | 1,559 (70.6%)               | 379 (17.2%)           | 216 (9.8%)       | 43 (1.9%)       | 12 (0.5%)     |
| H. pylori positive (n = 299) | 167 (55.9%)                 | 99 (33.1%)            | 29 (9.7%)        | 4 (1.3%)        | 0 (0.0%)      |

(b) Outcomes of subjects with GERD symptoms (insurgence of hiatal hernia) stratified according to their Helicobacter pylori infection status

| H. pylori status (n = 2,508) | No hiatal hernia (n = 1,764) | Hiatal hernia (n = 744) |
|-----------------------------|-----------------------------|-------------------------|
| H. pylori negative (n = 2,209) | 1,530 (69.3% of H. pylori-negative subjects, 86.7% of subjects without hiatal hernia) | 679 (30.7% of H. pylori-negative subjects, 91.3% of subjects with hiatal hernia) |
| H. pylori positive (n = 299) | 234 (78.3% of H. pylori-positive subjects, 13.3% of subjects without hiatal hernia) | 65 (21.7% of H. pylori-positive subjects, 8.7% of subjects with hiatal hernia) |

### Table 5: Determinants of insurgence of hiatal hernia in GERD patients (multivariate logistic regression analysis).

| Parameter                      | OR  | 95%CI OR   | p value |
|--------------------------------|-----|------------|---------|
| H. pylori status (negative versus positive) | 1.641 | 1.036 to 2.600 | 0.035   |
| Ethnicity (Arabs versus Jews)    | 0.993 | 0.685 to 1.441 | 0.972   |
| BMI                            | 1.000 | 0.982 to 1.018 | 0.968   |
| Rural versus urban             | 0.768 | 0.583 to 1.012 | 0.061   |
| Age                            | 1.014 | 1.006 to 1.022 | 0.001   |
| Gender                         | 0.950 | 0.724 to 1.248 | 0.713   |
| Smoking status                 | 0.916 | 0.539 to 1.555 | 0.745   |
| Alcohol consumption            | 0.955 | 0.480 to 1.903 | 0.897   |
| Comorbidities                  | 0.730 | 0.484 to 1.102 | 0.134   |
| ASA/NSAID users                | 0.001 | 0.001 to 0.002 | p ≤ 0.001 |
| Statin users                   | 253.885 | 89.148 to 723.041 | p ≤ 0.001 |
| PPI users                      | 0.591 | 0.346 to 1.007 | 0.053   |
| Constant                       | 0.334 |             | 0.074   |

ASA: acetylsalicylic acid; BMI: body mass index; NSAIDs: nonsteroidal anti-inflammatory drugs; PPIs: proton pump inhibitors.
Table 6: Determinants of insurgence of esophagitis in GERD patients (multivariate logistic regression analysis).

| Parameter                      | OR  | 95%CI OR       | Lower bound | Upper bound | p value |
|--------------------------------|-----|----------------|-------------|-------------|---------|
| H. pylori status (negative versus positive) | 0.611 | 0.474 | 0.787 | p ≤ 0.001 |
| Ethnicity (Arabs versus Jews) | 0.786 | 0.622 | 0.995 | 0.045 |
| BMI                           | 0.995 | 0.982 | 1.007 | 0.395 |
| Rural versus urban            | 0.957 | 0.801 | 1.143 | 0.629 |
| Age                           | 0.997 | 0.992 | 1.002 | 0.242 |
| Gender                        | 1.199 | 1.007 | 1.426 | 0.041 |
| Smoking status                | 0.370 | 0.265 | 0.519 | p ≤ 0.001 |
| Alcohol consumption           | 0.859 | 0.551 | 1.339 | 0.503 |
| Comorbidities                 | 0.768 | 0.584 | 1.011 | 0.060 |
| ASA/NSAID users               | 0.779 | 0.629 | 0.965 | 0.022 |
| Statin users                  | 1.209 | 0.831 | 1.761 | 0.321 |
| PPI users                     | 1.359 | 0.990 | 1.866 | 0.058 |
| Constant                      | 1.913 |             |            | 0.120 |

ASA: acetylsalicylic acid; BMI: body mass index; NSAIDs: nonsteroidal anti-inflammatory drugs; PPIs: proton pump inhibitors.

crude odds ratio (OR) of 1.598 (95%CI 1.196-2.134, p = 0.002) and a crude OR of 1.641 (95%CI 1.036-2.600, p = 0.035) of developing hiatal hernia (Table 5). Conversely, they had a crude OR of 0.527 (95%CI 0.412-0.675, p < 0.001) and an adjusted OR of 0.611 (95%CI 0.474-0.787, p < 0.001) of developing esophagitis (Table 6). Positivity for H. pylori impacted also on the severity of esophagitis (p = 0.047, Table 7).

4. Discussion

During the last decade, there has been a decrease in the prevalence of H. pylori infection; the prevalence of GERD, Barrett’s esophagus, and esophageal adenocarcinoma has increased [22]. In our study, the prevalence of H. pylori infection among patients with symptoms suggestive of GERD was approximately 12%, which goes in parallel with the assumed inverse correlation between these two conditions. Chung et al. [23] showed in a Korean cohort of matched age and sex individuals lower prevalence of GERD was approximately 12%, which goes in parallel with the assumed inverse correlation between these two conditions. Chung et al. [23] showed in a Korean cohort of matched age and sex individuals lower prevalence of GERD enrolled in our study differed among H. pylori-infected and noninfected individuals. H. pylori-infected patients were much younger than noninfected persons indicating an earlier acquisition of infection. Our findings suggest closer pictures to developing world. In terms of ethnicity, in contrast to the findings of Everhart et al. [25] that Blacks and Hispanics were found to have a higher prevalence of H. pylori infection, we found no difference in both groups analyzed. The authors concluded this ethnic variation to be probably explained by differences in socioeconomic status. Relationship between smoking status and H. pylori infection has given contrasting findings in the literature [26]. Ogihara and collaborators found that current smokers had a 0.82- (95%CI 0.74-0.91) fold greater risk of H. pylori infection than those who had never smoked, with current cigarette consumption exhibiting a dose-dependently negative association with H. pylori [27]. This association was strong in younger subjects. Authors postulated that smoking-induced increased gastric acidity could play a major role in leading to H. pylori infection. Furthermore, polymorphisms could explain the relationship between smoking status and H. pylori [28]. On the other hand, Zhang and coauthors failed to find a statistically significant relationship between smoking status and H. pylori infection. Our data showed significantly higher smoking rates among H. pylori-positive individuals compared to negative persons [29]. In our study, alcohol drinking was not associated with H. pylori infection. In other studies, such as that by Ogihara and coworkers, current drinkers had a 0.88- (95%CI 0.79-0.98) fold greater risk of H. pylori infection than those who had never consumed alcohol [28]. Giral et al. [23] showed that PPI use in patients infected with H. pylori was associated with greater inhibition of gastric acid secretion when compared to uninfected individuals. Similar findings were demonstrated by Verdu et al.; by this manner, our data showed that H. pylori-infected patients have significantly greater proportion of PPI use. These findings have two main implications. First, while PPI is a guideline-recommended part of therapy, when it is used on top of H. pylori infection, it leads to substantially higher degrees of acid secretion inhibition. Second, while inhibition of gastric acid secretion seems to explain the protective role
of \textit{H. pylori} infection against GERD and higher degrees of esophagitis, this explains the lower prevalence rate of advanced grades of esophagitis in \textit{H. pylori}-infected individuals. As shown in this, we saw our findings as going consistent with previous studies in medical literature.

While infection of \textit{H. pylori} is assumed to be protective against GERD, the presence of hiatal hernia after eradication of \textit{H. pylori} contributes to the development of GERD [30]. In our study, most of the patients enrolled had no hiatal hernia. Taking into consideration the presence of symptoms of GERD in all patients enrolled, hiatal hernia was more common in \textit{H. pylori}-negative patients. This sheds light on the pathogenetic correlation between GERD and \textit{H. pylori} in the presence of hiatal hernia.

Our study, when compared to similar studies in the literature, has several strong points: a large cohort of patients with well-defined characteristics, as well as a quite uniform ethnic homogeneity, as this prevents possible bias. Another point is that patients were screened endoscopically due to GERD symptoms including not only those with esophagitis but also those who were previously diagnosed with GERD as this permitted a larger cohort to be included.

The retrospective manner of the study and operator-dependent endoscopy and the clinical diagnosis of GERD without having PH monitoring to confirm acid reflux are all part of our limitations.

In conclusion, patients with GERD who tested positive for \textit{H. pylori} were younger, tend to smoke more, and use more PPI than those who tested negative. In addition, patients infected with \textit{H. pylori} had more esophagitis; however, they had less severe esophagitis compared to noninfected patients.

**Data Availability**

The data used to support the findings of this study are available from the corresponding author upon request. Data was collected retrospectively by authorized researchers.

**Ethical Approval**

Our institutional ethics committee approved this study.

**Conflicts of Interest**

The authors declare that they have no conflicts of interest.

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