ABSTRACT

Objective Conflicting results have been reported by numerous epidemiological studies investigating the association between Helicobacter pylori (H. pylori) infection and inflammatory bowel disease (IBD). We aimed in this study to assess the possible association between H. pylori infection and IBD and its effects on disease progression.

Design Prospective observational study.

Setting Specialised IBD care clinics at Alexandria University Student Hospital in northern Egypt, between March and June 2019.

Participants 182 patients with IBD.

Analysis and outcome measures Participants with IBD were screened for H. pylori infection and clinically evaluated at the initial visit and bimonthly for 3 months to record any potential improvement/flare of the IBD condition.

Results Overall, 90 (49.5%) patients with IBD had evidence of H. pylori infection. The course of IBD did not significantly differ in association with H. pylori infection or IBD treatment strategy. Cox regression analysis revealed that patients aged 20–35 years (HR=6.20 (95% CI: 1.74 to 22.12)) and 35–55 years (557.9 (17.4–17 922.8)), high socioeconomic status (2.9 (1.11–7.8)), daily consumption of fibre-rich food (5.1 (1.32–19.5)), occasional consumption of snacks between meals (2.8 (2.5–70.5)) and eating four meals per day (13.3 (1.0–7.7)) were predictive of IBD flare. By contrast, eating fruits and vegetables showed a strongly protective association (HR=0.001 (95% CI: 0.0002 to 0.02)). The probabilities of improvement of IBD symptoms after 12 weeks of follow-up were comparable in assessments based on H. pylori infection status (0.793 for H. pylori negative vs 0.778 for H. pylori positive) and IBD treatment option (0.811 for conventional therapy vs 0.750 for biological therapy).

Conclusion The association between IBD and H. pylori infection is unresolved and should be further investigated in the context of specific environmental exposures that can influence the development or relapse of IBD.

INTRODUCTION

Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn’s disease (CD), comprises chronic, disabling and progressive disorders characterised by lifelong treatment that imposes a significant globally increasing threat to human health. Numerous economically low-income countries have experienced a dramatic increase in the incidence of IBD. Improved access to a more hygienic environment and the resulting decreased incidence of common childhood infections may represent a contributing factor through altering susceptibility to diseases with an autoimmune component, such as IBD. Accordingly, microbial infections during childhood may protect against IBD. This rise may partially be accounted for by the implementation of improved diagnostic methods and heightened awareness of IBD.

Although the pathogenesis of IBD is unknown, evidence indicates that it involves complex and unidentified interactions between environmental factors (such as infections, medicines, tobacco, food components) as well as host genetic factors that induce abnormal or inappropriate immunological reactions, or both, to components of the intestinal flora.

Evidence indicates that Helicobacter pylori (H. pylori) resides in the upper gastrointestinal tract of approximately 50% of the world’s population, among which >80% of people lack symptoms. In Egypt, the prevalence is...
approximately 80%. \(^8\) *H. pylori* can elicit a chronic systemic inflammatory response, which may trigger autoimmune reactions that may contribute to the pathogenesis of autoimmune diseases. The inflammatory response of the gastric mucosa mainly involves stimulation of the host’s immune system in response to *H. pylori*, which induces a cell-mediated immune response characterised by elevated levels of cytokines. Consequently, products of local immune reactions may migrate to extragastric sites, which may account for the association between *H. pylori* infection and extragastric diseases, including autoimmune disorders.\(^9\)

Although numerous, diverse studies analysed the association between *H. pylori* infection and IBD,\(^9,10\) a causal association between *H. pylori* and IBD remains to be established; and the are contradictory data related to the potential causative and the protective roles of *H. pylori* infection associated with IBD.\(^11-19\)

Assuming a potential protective role of *H. pylori* infection against IBD, *H. pylori* eradication treatment may influence the progression of IBD course and thus should be carefully administered, considering the findings of future prospective studies.\(^16,20\)

IBD occurs more frequently in regions with lower rates of *H. pylori* colonisation. The steady increase in the incidence of IBD in *H. pylori*-endemic regions may reflect the advent of initiating anti-*H. pylori* therapy to treat peptic ulcers.\(^13\) Furthermore, meta-analyses show that the prevalence of *H. pylori* infection is lower in patients with IBD compared with controls.\(^9,10,13,19,21\) For example, long-term treatment with sulphasalazine contributes to the eradication of *H. pylori* infection.\(^22\) Although unconfirmed, most studies indicate a protective role for *H. pylori* infection against the development of IBD.\(^9,21\)

With advances in identifying the pathological mechanisms underlying IBD, new therapies have been proposed, particularly those involving biological response modifiers. These include antitumour necrosis factor antibodies (anti-TNF-α, anti-tumour necrosis factor alpha), interleukin-1 (IL-1)/IL-6 receptor antagonists and an anti-CD20 antibody. These therapies are generally well tolerated, although they may be associated with adverse effects, including increased susceptibility to infection and increased risk of malignancies.\(^23\)

These considerations inspired us to conduct a prospective, longitudinal study to further analyse the association between *H. pylori* infection and the flare of IBD and to investigate possible effects of *H. pylori* infection on the response to conventional versus biological treatment of IBD.

**METHODS**

**Study population and sampling**

We conducted a prospective observational study at Alexandria University Student Hospital (AUSH) that is affiliated with Alexandria University, Egypt and serves students, faculty and staff members. AUSH comprises outpatient clinics and inpatient and emergency departments with a bed capacity of 1000. We enrolled patients aged ≥18 years with confirmed IBD (triphasic CT abdomen, endoscopy/colonoscopy and faecal calprotectin) and commenced IBD treatment (conventional or biological). Patients with irritable bowel syndrome were excluded according to the Rome III criteria.\(^24\)

Clinicians on the staff of the Internal Medicine Department of the AUSH selected the treatment (standard vs biological). The prescribed treatment is the standard of care adopted by the AUSH for treating patients with IBD. Details of the treatment regimens and the parameters employed to select standard or biological treatment are described in online supplemental file S1.

The frequency of *H. pylori* infection among patients with IBD is as high as 10.0%.\(^21\) Using a margin of error=5.0%, an alpha error=0.05 and a 95% CI level, the minimum required sample size was 158.\(^8\) However, we ultimately enrolled 182 patients with IBD, because we expected that the prevalence of *H. pylori* infection might be higher because of the endemicity of *H. pylori* infection in Egypt,\(^8\) and to compensate for possible dropouts during the follow-up. The sample size was calculated using Epi info V.7 software. Patients with confirmed IBD who agreed to participate in the study were consecutively enrolled. According to their characteristics (figure 1), the patients were assigned into groups according to the prescribed treatment regimen (online supplemental file S1) as follows: Group 1 comprised patients administered conventional IBD treatment, and Group 2 included patients undergoing biological IBD treatment.

Stool samples were used to detect *H. pylori* antigen using a commercially available enzyme immunoassay (EIA) kit (Foresight EIA test kit for qualitative and quantitative detection of *H. pylori* in the stool; ACON Laboratories, Inc, San Diego, California, USA). Each assigned group included patients with IBD with or without *H. pylori* infection, and patients who were *H. pylori*-positive were shown their laboratory findings. We did not commence *H. pylori* eradication therapy during the study period. After a 3-month follow-up, patients who were *H. pylori*-positive were referred to a specialist for further evaluation and case management according to the adopted standard of care.
Patient and public involvement

We informed the patients about the aims and concerns of the study and how it will add to better understanding of their disease aetiology and triggering factors, which was highly appreciated by the patients, and motivated them to be a part of the cohort intended for the long-term follow-up by the clinicians. However, it was not appropriate or possible to involve patients or the public in the design, conduct, reporting or dissemination plans of our research. All the laboratory and clinical data were reported to the study participants, where we discussed the study findings in a simple language.

Assessments

Baseline evaluation included the patient’s history, full clinical examination and laboratory tests. A data collection form (online supplemental file S2) was used to collect baseline data as follows: sociodemographic characteristics, personal habits, lifestyle, physical activity and exercise, dietary habits and restrictions, family history, medical history, comorbidities and medications. Clinical data collected from each patient during the initial visit are as follows: disease onset, history of present complaints, frequency and duration of IBD attacks, past and current IBD medications, history of changing therapy, surgical intervention and complications. History of *H. pylori* infection and undergoing *H. pylori* eradication therapy during the past 12 months were recorded during each follow-up visit. All patients were followed bimonthly for 3 months (six visits) during IBD treatment. Patients were contacted weekly via telephone and asked about the frequency and severity of symptoms and if adverse effects associated with treatment occurred during the previous week.

Blood pressure (BP) and anthropometric measurements were measured according to standard techniques.25–27 Body mass index (BMI) was calculated according to the Quetelet’s index: BMI = (weight (kg)/height² (m²)). At each follow-up visit, laboratory tests were performed as follows: complete blood count, C reactive protein (CRP), erythrocyte sedimentation rate (ESR), fasting blood glucose (FBG) and faecal calprotectin.28 Imaging techniques included triphasic CT and endoscopy/colonoscopy when indicated. All patients underwent full-length colonoscopy (Pentax colonoscopies). Colonoscopic biopsies were acquired from the rectum and sigmoid; descending, transverse, ascending colon; as well as the cecal mucosa. Histological analyses of the degree of inflammation associated with CD and UC were evaluated according to the European consensus on the histopathology of IBD.29

The socioeconomic status of the enrolled patients with IBD was calculated and categorised as high, middle, low and very low; according to a modified social scoring system.30

Outcomes

Patients in each group were clinically evaluated every 2 weeks for 3 months to record potential improvement/flare of IBD. The primary outcome of the study was the number of patients with IBD who achieved remission (improvement of IBD symptoms and normalisation of the laboratory tests) at the end of the follow-up period.

Statistical analysis

Data were reviewed for accuracy and integrity and analysed using SPSS Statistics for Windows, V.21.0 (IBM Corp, Armonk, New York, USA). Continuous variables are presented as the mean±SD, and categorical variables are expressed as numbers with proportion, n (%). Variables relevant to laboratory data were dichotomised according to prefixed cut-offs, considering the normal reference values. The Student’s t-test was performed to compare quantitative variables between two groups of normally distributed data. The χ² test was performed to evaluate the association between qualitative variables. Fisher’s exact test with Yates correction was used when cell count was <5. Responses that have non-applicable values were coded with ‘−1’ and we use the SPSS programme strategy for handling missing values in the analysis. Repeated-measures analysis of variance (ANOVA) was used to test the significance of differences in the means of quantitative variables measured at different times. Multivariate logistic regression analyses were conducted to identify independent risk factors for *H. pylori* infection among patients with IBD. Cox regression analysis (or proportional hazards regression) was used to evaluate the effects of several variables at the time of occurrence of a specified event. Hazard rate ratios (HR) with 95% confidence intervals (CIs) were calculated, and factors associated with IBD flare/remission were thus identified when testing variables with significant differences (significance levels <0.05) in the simple logistic regression analyses. Kaplan-Meier analysis was used to estimate the probability of recovery (remission of IBD as the event-of-interest) considering *H. pylori* infection status and treatment option. Recovery-defined remission/improvement in IBD status was based on clinical and laboratory data, whereas censored data defined lack of improvement or flare of the inflammatory condition. Statistical analyses were conducted using two-tailed tests (level of significance <0.05).

RESULTS

Sociodemographic and clinical characteristics

Patients with IBD (n=182) (n=96 (52.7%) UC and n=86 (47.3%) CD) included 51.7% males, 58.2% married, 51.6% resided in urban areas, 76.9% highly literate, and 82.4% non-smokers. The average age was 27.0±7.3 years, with the majority ranging from 20 to 35 years. Normal BMI was a predominant feature (59.3%), and 31.9% were overweight. Patients’ other sociodemographic characteristics are shown in table 1.

The physical activity scores were comparable between the study participants. However, those without *H. pylori* infection were judged to have a favourable food-habit
## Table 1  Characteristics of the study population

|                          | Patients with IBD Total (n=182) | H. Pylori infection in patients with IBD Negative (n=92) | Positive (n=90) |
|--------------------------|---------------------------------|--------------------------------------------------------|-----------------|
|                          | No  | %    | No  | %    | No  | %    |
| **Type of IBD diagnosed**|      |      |      |      |      |      |
| Crohn's disease          | 86  | 47.3 | 44  | 47.8 | 42  | 46.7 |
| Ulcerative colitis       | 96  | 52.7 | 48  | 52.2 | 48  | 53.3 |
| **Onset of H. pylori infection** |      |      |      |      |      |      |
| None                     | 92  | 50.5 | 92  | 100  | 0   | 0    |
| Few weeks ago            | 7   | 3.8  | 0   | 0    | 7   | 7.8  |
| 3–6 months               | 10  | 5.5  | 0   | 0    | 10  | 11.1 |
| 6 months–1 year          | 35  | 19.2 | 0   | 0    | 35  | 38.9 |
| >1 year                  | 38  | 20.9 | 0   | 0    | 38  | 42.2 |
| **History of receiving H. pylori eradication therapy in the past 12 months prior to the study** |      |      |      |      |      |      |
| No                       | 89  | 48.9 | 76  | 82.6 | 13  | 14.4 |
| Yes                      | 93  | 51.1 | 16  | 17.4 | 77  | 85.6 |
| **Treatment option given** |      |      |      |      |      |      |
| Conventional             | 106 | 58.2 | 47  | 51.1 | 59  | 65.6 |
| Biological               | 76  | 41.8 | 45  | 48.9 | 31  | 34.4 |
| **Sex**                  |      |      |      |      |      |      |
| Male                     | 94  | 51.6 | 46  | 50   | 48  | 53.3 |
| Female                   | 88  | 48.4 | 46  | 50   | 42  | 46.7 |
| **Age (years)**          |      |      |      |      |      |      |
| 16–<20                   | 20  | 11   | 15  | 16.3 | 5   | 5.6  |
| 20–<35                   | 136 | 74.7 | 62  | 67.4 | 74  | 82.2 |
| 35–55                    | 26  | 14.3 | 15  | 16.3 | 11  | 12.2 |
| Mean±SD                  | 27.0±7.3 | 27.6±8.0 | 26.3±6.5    |      |
| **Age at IBD diagnosis** |      |      |      |      |      |      |
| 10–>19                   | 69  | 37.9 | 35  | 38   | 34  | 37.8 |
| 20–<30                   | 83  | 45.6 | 46  | 50   | 37  | 41.1 |
| 30–45                    | 30  | 16.5 | 11  | 12   | 19  | 21.1 |
| Mean±SD                  | 21.6±6.4 | 21.4±6.3 | 22.0±6.5    |      |
| **Residence**            |      |      |      |      |      |      |
| Rural                    | 88  | 48.4 | 51  | 55.4 | 37  | 41.1 |
| Urban                    | 94  | 51.6 | 41  | 44.6 | 53  | 58.9 |
| **Education**            |      |      |      |      |      |      |
| Illiterate               | 2   | 1.1  | 0   | 0    | 2   | 2.2  |
| Read and write           | 23  | 12.6 | 12  | 13   | 11  | 12.2 |
| Primary                  | 4   | 2.2  | 4   | 4.3  | 0   | 0    |
| Preparatory              | 13  | 7.1  | 9   | 9.8  | 4   | 4.4  |
| Secondary                | 44  | 24.2 | 24  | 26.1 | 20  | 22.2 |
| University education     | 96  | 52.7 | 43  | 46.7 | 53  | 58.9 |
| **Working status**       |      |      |      |      |      |      |
| No                       | 88  | 48.4 | 39  | 42.4 | 49  | 54.4 |
| Yes                      | 94  | 51.6 | 53  | 57.6 | 41  | 45.6 |
| **Occupation**           |      |      |      |      |      |      |

Continued
Table 1 Continued

|                                | Patients with IBD Total (n=182) | H. Pylori infection in patients with IBD Negative (n=92) | Positive (n=90) |
|--------------------------------|---------------------------------|----------------------------------------------------------|-----------------|
|                                | No     | %   | No     | %   | No    | %    | No     | %   | No    | %    | No    | %    |
| Unemployed                     | 37     | 20.3| 21     | 22.8| 16    | 17.8|        |      |        |      |        |      |
| Student                        | 45     | 24.7| 16     | 17.4| 29    | 32.2|        |      |        |      |        |      |
| Clerical                       | 2      | 1.1 | 2      | 2.2 | 0     | 0    |        |      |        |      |        |      |
| Professional                   | 39     | 21.4| 17     | 18.5| 22    | 24.4|        |      |        |      |        |      |
| Housewife                      | 21     | 11.5| 10     | 10.9| 11    | 12.2|        |      |        |      |        |      |
| Auxiliary worker               | 22     | 12.1| 12     | 13  | 10    | 11.1|        |      |        |      |        |      |
| Farmer                         | 16     | 8.8 | 14     | 15.2| 2     | 2.2 |        |      |        |      |        |      |
| Marital status                 |        |     |        |      |        |      |        |      |        |      |        |      |
| Single                         | 73     | 40.1| 37     | 40.2| 36    | 40  |        |      |        |      |        |      |
| Married                        | 106    | 58.2| 55     | 59.8| 51    | 56.7|        |      |        |      |        |      |
| Widowed                        | 2      | 1.1 | 0      | 0   | 2     | 2.2 |        |      |        |      |        |      |
| Divorced                       | 1      | 0.5 | 0      | 0   | 1     | 1.1 |        |      |        |      |        |      |
| Socioeconomic standard         |        |     |        |      |        |      |        |      |        |      |        |      |
| High                           | 58     | 31.9| 24     | 26.1| 34    | 37.8|        |      |        |      |        |      |
| Middle                         | 52     | 28.6| 30     | 32.6| 22    | 24.4|        |      |        |      |        |      |
| Low                            | 72     | 39.6| 38     | 41.3| 34    | 37.8|        |      |        |      |        |      |
| Consanguinity                  |        |     |        |      |        |      |        |      |        |      |        |      |
| No                             | 144    | 79.1| 70     | 76.1| 74    | 82.2|        |      |        |      |        |      |
| Yes                            | 38     | 20.9| 22     | 23.9| 16    | 17.8|        |      |        |      |        |      |
| History of being breastfed     |        |     |        |      |        |      |        |      |        |      |        |      |
| No                             | 26     | 14.3| 14     | 15.2| 12    | 13.3|        |      |        |      |        |      |
| Yes                            | 156    | 85.7| 78     | 84.8| 78    | 86.7|        |      |        |      |        |      |
| Smoking                        |        |     |        |      |        |      |        |      |        |      |        |      |
| Never                          | 150    | 82.4| 75     | 81.5| 75    | 83.3|        |      |        |      |        |      |
| Current smoker                 | 26     | 14.3| 13     | 14.1| 13    | 14.4|        |      |        |      |        |      |
| Ex-smoker                      | 6      | 3.3 | 4      | 4.3 | 2     | 2.2 |        |      |        |      |        |      |
| Age of starting smoking        |        |     |        |      |        |      |        |      |        |      |        |      |
| Non-smoker                     | 153    | 84.1| 77     | 83.7| 76    | 84.4|        |      |        |      |        |      |
| <20 years                      | 17     | 9.3 | 10     | 10.9| 7     | 7.8 |        |      |        |      |        |      |
| 20–30 years                    | 12     | 6.6 | 5      | 5.4 | 7     | 7.8 |        |      |        |      |        |      |
| >30 years                      | 0      | 0   | 0      | 0   | 0     | 0   |        |      |        |      |        |      |
| Smoking other than cigarette   |        |     |        |      |        |      |        |      |        |      |        |      |
| Never                          | 180    | 98.9| 90     | 97.8| 90    | 100 |        |      |        |      |        |      |
| Shisha                         | 2      | 1.1 | 2      | 2.2 | 0     | 0   |        |      |        |      |        |      |
| BMI categories                 |        |     |        |      |        |      |        |      |        |      |        |      |
| <18.5 (underweight)            | 3      | 1.6 | 2      | 2.2 | 1     | 1.1 |        |      |        |      |        |      |
| 18.5–24.99 (normal weight)     | 108    | 59.3| 58     | 63  | 50    | 55.6|        |      |        |      |        |      |
| 25–29.99 (overweight)          | 58     | 31.9| 24     | 26.1| 34    | 37.8|        |      |        |      |        |      |
| 30–39.99 (obese)               | 13     | 7.1 | 8      | 8.7 | 5     | 5.6 |        |      |        |      |        |      |
| Comorbidities                  |        |     |        |      |        |      |        |      |        |      |        |      |
| No                             | 82     | 45.1| 43     | 46.7| 39    | 43.3|        |      |        |      |        |      |
| Yes                            | 100    | 54.9| 49     | 53.3| 51    | 56.7|        |      |        |      |        |      |
| Diabetes mellitus              | 10     | 5.5 | 4      | 4.3 | 6     | 6.7 |        |      |        |      |        |      |

Continued
score compared with those with *H. pylori* infection (12.2±5.0 vs 10.7±3.8) (online supplemental table S1).

Patients’ baseline clinical and laboratory findings are presented in online supplemental table S2. Compared with patients without *H. pylori* infection, infected patients had higher rates of abdominal cramps (91.1% vs 84.8%), abdominal pain (85.6% vs 81.5%), bloating/indigestion (98.9% vs 95.7%), diarrhoea (98.9% vs 96.7%), fatigue/lack of energy (98.9% vs 96.7%), fever (33.3% vs 26.1%), chills (23.3% vs 14.1%), infection (23.3% vs 14.1%), rectal bleeding (88.9% vs 68.5%), skin poikiloderma (88.9% vs 68.5%), fever (33.3% vs 26.1%), and higher mean CRP (33.0±23.0 vs 28.2±23.9) and ESR (34.6±13.2 vs 33.6±14.1) levels. Gastrointestinal (GIT) endoscopy and colonoscopy revealed features of CD and UC, indicated by superficial ulcerations and mild infiltration.

**H. pylori infection among patients with IBD**

We detected *H. pylori* infection in 49.5% of patients, including those with UD (48.50.0%) and CD (42.48.8%) (OR=1.05 (95% CI: 0.59 to 1.88)), although 85.6% of them reported undergoing *H. pylori* eradication therapy in the past 12 months prior to the study. The infection rate was highest (74.82.2%) among the age group 20 to <35 years (table 1). Logistic regression analysis revealed that conventional treatment of IBD (OR=1.99 (95% CI: 1.03 to 3.85)), adults aged 20 or <35 years (6.20 (1.74–22.12)) and 35–55 years (11.1 (1.18–104.64)) and mixed food sources (3.12 (1.60–6.06)) predicted *H. pylori* infection (p<0.05) (table 2).

**Assessment of IBD improvement/flare in relation to *H. pylori* infection**

The total symptom scores of all patients, as well as the levels of ESR, CRP, haemoglobin and faecal calprotectin,
Table 2  Predictors of *H. pylori* infection in patients with IBD

| Backward stepwise (Wald) logistic regression | B         | SE       | Wald    | df | Sig. (p value) | Exp(B) | 95% CI for Exp(B) |
|---------------------------------------------|-----------|----------|---------|----|----------------|--------|------------------|
| Step 5                                      |           |          |         |    |                |        |                  |
| Treatment of IBD                            |           |          |         |    |                |        |                  |
| Biological treatment                        | -0.686    | 0.337    | 4.14    | 1  | 0.042          | 0.50   | 0.26             | 0.98 |
| Conventional treatment                      | 0.686     | 0.337    | 4.14    | 1  | 0.042          | 1.99   | 1.03             | 3.85 |
| Age group (years)                           |           |          |         |    |                |        |                  |
| 16–<20                                      |           |          |         |    |                |        |                  |
| 20–<35                                      | 1.825     | 0.649    | 7.92    | 1  | 0.005          | 6.20   | 1.74             | 22.12|
| 35–55                                       | 2.408     | 1.144    | 4.43    | 1  | 0.035          | 11.11  | 1.18             | 104.64|
| Food source                                 |           |          |         |    |                |        |                  |
| Homemade                                    |           |          |         |    |                |        |                  |
| Restaurant                                  | -0.024    | 0.915    | 0.00    | 1  | 0.979          | 0.98   | 0.16             | 5.87 |
| Mixed                                       | 1.137     | 0.339    | 11.25   | 1  | <0.001         | 3.12   | 1.60             | 6.06 |
| Constant                                    | 0.108     | 1.015    | 0.01    | 1  | 0.915          | 1.11   |                  |      |

P value significant at <0.05.

*H. pylori*, *Helicobacter pylori*; IBD, inflammatory bowel disease; Ref, reference category.

DISCUSSION

Recent improvements in hygienic conditions and socioeconomic status have reduced *H. pylori* infection rates, and this trend accompanies increased IBD incidence in most countries. However, the role of *H. pylori* in IBD is unknown.2 16 31 Numerous studies found lower *H. pylori* infection rates in patients with CD, UC or both, compared with non-IBD controls, although a few studies did not detect a significant association.9 10 13 21 31 Recent epidemiological studies, animal experiments, and meta-analyses reveal an inverse correlation between *H. pylori* infection and the onset of IBD onset, suggesting that colonisation by *H. pylori* confers a protective effect against autoimmune diseases.13 23 32

To further explain the negative association between *H. pylori* infection and IBD, we conducted a longitudinal study of patients with IBD, with or without *H. pylori* infection, to determine the influence of *H. pylori* infection on patients' responses to conventional versus biological treatment of IBD.

*H. pylori* was detected in approximately 50% of the patients, which is low compared with the prevalence among the population of Egypt, where disease is endemic.33–36 These findings support the results of studies
| Parameter                  | Measur es ANOVA of clinical and laboratory findings among patients with IBD during follow-up |
|---------------------------|-------------------------------------------------------------------------------------------|
|                           | Follow-up period (3 Months)                                                                 |
|                           | Visit 1 | Visit 2 | Visit 3 | Visit 4 | Visit 5 | Visit 6 | Visit 7 | Visit 8 | Visit 9 | Visit 10 | Visit 11 | Visit 12 |
|                           | Mean±SD | Mean±SD | Mean±SD | Mean±SD | Mean±SD | Mean±SD | Mean±SD | Mean±SD | Mean±SD | Mean±SD | Mean±SD | Mean±SD |
| ESR (mm/hr)               | Positive | 34.4±0.5 | 13.2±0.1 | 10.9±0.2 | 27.0±0.4 | 24.5±0.3 | 20.4±0.3 | 17.3±0.3 | 14.0±0.3 | 5.3     | T       | 96.93   | <0.001  |
|                           | Negative | 33.6±0.1 | 29.1±0.1 | 25.2±0.4 | 21.4±0.2 | 19.2±0.2 | 15.9±0.2 | 13.0±0.2 | 5.3     | T       | 1.156   | 0.322   | 0.038   | 0.448   |
| CRP (mg/dL)               | Positive | 33.0±0.6 | 26.4±0.8 | 18.6±1.6 | 13.0±1.6 | 15.4±1.3 | 10.5±1.3 | 9.4     | T       | 3.174   | <0.001  | 0.531   | 1.000   |
|                           | Negative | 28.2±0.1 | 22.2±0.1 | 19.0±0.2 | 15.9±1.2 | 13.0±1.2 | 10.6±1.2 | 8.2±1.0 | T       | 0.708   | 0.644   | 0.024   | 0.276   |
| FBG (mg/dL)               | Positive | 15.4±0.5 | 16.3±0.5 | 19.4±0.5 | 14.1±0.5 | 13.8±0.5 | 12.9±0.5 | 9.7     | T       | 3.52±0.3 | 0.003   | 0.108   | 0.945   |
|                           | Negative | 11.6±0.5 | 10.6±0.5 | 9.1±0.5  | 9.0      | 9.1±0.5  | 9.1±0.5  | 9.1±0.5 | T       | 1.8±0.6  | 0.447   | 0.056   | 0.087   |
| Calprotectin (µg/g)       | Positive | 515.0±0.5 | 154.6±0.5 | 154.6±0.5 | 154.6±0.5 | 154.6±0.5 | 154.6±0.5 | 154.6±0.5 | T       | 25.30±0.5 | 0.001   | 0.810   | 1.000   |
|                           | Negative | 517.4±0.5 | 214.4±0.5 | 139.4±0.5 | 172.0±0.5 | 88.1±0.5  | 86.5±0.5  | 69.5±0.5 | T       | 0.15±0.5 | 0.925   | 0.003   | 0.078   |
| Hb (g/dL)                 | Positive | 11.0±0.5 | 11.7±0.5 | 11.2±0.5 | 11.6±0.5 | 11.8±0.5 | 12.0±0.5 | 12.2±0.5 | T       | 49.7±0.5 | <0.001  | 0.63     | 1.1     |
|                           | Negative | 10.8±0.4 | 11.0±0.4 | 11.3±0.4 | 11.6±0.4 | 11.7±0.4 | 12.3±0.4 | 12.5±0.4 | T       | 3.1±0.7  | 0.006   | 0.098   | 0.91    |
| WBCs (×10³/µl)            | Positive | 6791.1±0.5 | 1505.9±0.5 | 16160.1±0.5 | 2717.1±0.5 | 6852.4±0.5 | 6497.2±0.5 | 10255.0±0.5 | T       | 4.21±0.7 | 0.012   | 0.126   | 0.97    |
|                           | Negative | 6620.8±0.5 | 1530.5±0.5 | 16279.3±0.5 | 1086.4±0.5 | 979.3±0.5 | 989.5±0.5 | 1033.1±0.5 | T       | 1.05±0.7 | 0.394   | 0.035   | 0.409   |
| Platelets (×10³/µl)       | Positive | 296.2±0.5 | 61.7±0.5  | 66.3±0.5  | 267.1±0.5 | 57.9±0.5  | 28.0±0.5  | 51.1±0.5 | 52.0±0.5 | T       | 0.3±0.5  | 0.006   | 0.038   |
|                           | Negative | 304.8±0.5 | 283.0±0.5 | 30.4±0.5  | 279.2±0.5 | 44.3±0.5  | 280.0±0.5 | 48.5±0.5 | 46.5±0.5 | T       | 1.02±0.6 | 0.415   | 0.034   |
| Total symptom score       | Positive | 20.9±0.5 | 30.6±0.5 | 3.2±0.5  | 14.2±0.5 | 5.8±0.5  | 3.9±0.5  | 3.0±0.5  | 2.8±0.5  | T       | 75.4±0.5 | <0.001  | 0.964   | 1.000   |
|                           | Negative | 20.6±0.5 | 30.4±0.5 | 3.7±0.5  | 13.8±0.5 | 5.4±0.5  | 3.0±0.5  | 3.0±0.5  | 2.8±0.5  | T       | 0.30±0.5 | 0.496   | 0.031   |
| Body weight (kg)          | Positive | 68.3±0.5 | 68.3±0.5 | 69.1±0.5  | 69.4±0.5 | 69.4±0.5 | 69.5±0.5 | 69.3±0.5 | T       | 20.34±0.5 | 0.001   | 0.411   | 1.000   |
|                           | Negative | 67.6±0.5 | 67.6±0.5 | 68.3±0.5 | 69.4±0.5 | 68.9±0.5 | 69.4±0.5 | 69.3±0.5 | T       | 2.08±0.5 | 0.008   | 0.077   |
| Pulse (bpm)               | Positive | 50.5±0.5 | 79.3±0.5 | 4.3±0.5  | 78.3±0.5 | 4.0±0.5  | 77.8±0.5 | 4.0±0.5  | T       | 5.36±0.5 | <0.001  | 0.155   | 0.995   |
|                           | Negative | 90.5±0.5 | 95.5±0.5 | 5.8±0.5  | 80.3±0.5 | 5.0±0.5  | 78.3±0.5 | 5.0±0.5  | T       | 2.67±0.5 | 0.017   | 0.084   |
| Pulse pressure (mmHg)     | Positive | 39.5±0.5 | 41.7±0.5 | 4.1±0.5  | 40.7±0.5 | 4.1±0.5  | 41.8±0.5 | 4.1±0.5  | T       | 0.729±0.5 | 0.687   | 0.024   |
|                           | Negative | 41.5±0.5 | 40.2±0.5 | 6.8±0.5  | 39.7±0.5 | 8.9±0.5  | 40.7±0.5 | 8.6±0.5  | T       | 0.759±0.5 | 0.593   | 0.004   |

*rolate significance at *<0.05.
†Wilks’ lambda F* P
‡Partial eta squared
§Effect size (partial eta squared)

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showing that lower rates \( H. \) pylori infection of patients with IBD, suggesting an association between \( H. \) pylori and IBD. The rate of \( H. \) pylori infection is significantly higher among patients with IBD who undergo conventional treatment, which conflicts with studies suggesting that 5-aminosalicylates or sulphasalazine interfere with the adhesion of \( H. \) pylori to the mucosa and block its proliferation. For example, the results of multiple studies do not support the conclusion that treatment with sulfasalazine or other drugs such as 5-aminosalicylic acid, thiopurines, steroids and antibiotics influence the colonisation rate of \( H. \) pylori. It is therefore possible that such patients with IBD were treated for \( H. \) pylori infection before enrolment, culminating in an incorrectly low rate of \( H. \) pylori infection.

Accumulating evidence suggests that \( H. \) pylori, through its ability to regulate the immune response, protects human from diseases with an autoimmune component. It is worth noting that although the treatment of patients with IBD with anti-TNF-\( \alpha \) agents, immunosuppressant and/ or corticosteroid increases the risk of infections, there is no direct evidence that novel therapeutic strategies such as anti-TNF-\( \alpha \) and immunosuppressants result in exacerbating or influence the prevalence of \( H. \) pylori infection. Similar findings were reported by a study of novel therapeutic strategies such as anti-TNF-\( \alpha \) treatment.

Here we show that the majority of patients who were \( H. \) pylori positive with IBD admitted undergoing \( H. \) pylori eradication therapy during the previous 12 months, which raises questions about the efficacy of eradication therapy or reveals reinfection among this group of patients. Notably, most studies do not report subjects' history of treatment of \( H. \) pylori infection. It is therefore possible that such patients with IBD were treated for \( H. \) pylori infection before enrolment, culminating in an incorrectly low rate of \( H. \) pylori infection.

### Table 4: Cox regression analysis of factors associated with IBD flare during follow-up

| Backward stepwise (Wald) logistic regression | B   | SE  | Wald | df | Sig. (p value) | Exp(B) | 95% CI for Exp(B) |
|---------------------------------------------|-----|-----|------|----|----------------|--------|-------------------|
|                                            |     |     |      |    |                |        | Lower limit       |
| **Step 6** Age (years)                      |     |     |      |    |                |        | Upper limit       |
| 16–<20                                      | 13.83 | 2 | <0.001 | Ref |                |        |                  |
| 20–<35                                      | 4.41 | 1  | 0.036 | 4.49 | 1.11           |        | 18.21             |
| 35–55                                       | 12.76 | 1 | <0.001 | 557.92 | 17.37 |        | 17 922.78        |
| Socioeconomic standard                      |     |     |      |    |                |        |                  |
| High                                        | 1.08 | 0.50 | 4.71 | 1  | 0.030          | 2.94   | 7.79              |
| Middle                                      | 0.68 | 0.48 | 1.97 | 1  | 0.160          | 1.97   | 5.10              |
| Low                                         | 4.71 | 2   | 0.095 |    |                |        |                  |
| Food rich in insoluble fibre                |     |     |      |    |                |        |                  |
| Once per week                               | 8.75 | 2   | 0.013 | Ref |    |        |                  |
| 2–4 times per week                          | 0.02 | 0.58 | 0.00 | 1  | 0.973          | 1.02   | 3.18              |
| Daily                                       | 1.62 | 0.69 | 5.61 | 1  | 0.018          | 5.08   | 19.49             |
| Fruits and vegetables                       |     |     |      |    |                |        |                  |
| Never                                       | 22.20 | 3 | <0.001 | Ref |    |        |                  |
| Once per week                               | −7.07 | 1.63 | 18.74 | 1 | 0.001          | 0.0003 | 0.02              |
| 2–4 times per week                          | −7.61 | 1.62 | 22.06 | 1 | 0.001          | 0.0002 | 0.01              |
| Daily                                       | −7.47 | 1.68 | 19.76 | 1 | <0.001          | 0.0002 | 0.02              |
| Number of meals per day                     |     |     |      |    |                |        |                  |
| Two                                         | 10.25 | 2 | 0.006 | Ref |    |        |                  |
| Three                                       | −0.11 | 0.38 | 0.08 | 1  | 0.780          | 0.90   | 1.89              |
| Four                                        | 2.59 | 0.85 | 9.30 | 1  | 0.002          | 13.33  | 70.46             |
| Snacks between meals                        |     |     |      |    |                |        |                  |
| Never                                       | 11.43 | 2  | 0.003 | Ref |    |        |                  |
| Occasionally                                | 1.04 | 0.51 | 4.07 | 1  | 0.044          | 2.82   | 7.72              |
| Daily                                       | −3.89 | 2 | 0.055 | 0.02 | 0.00 |        | 1.08              |

\( \text{P value signficant at } <0.05. \)

IBD, inflammatory bowel disease; Ref, reference category.
| Variable                  | Group                      | Case summary | No of events N (%) | Censored N (%) | Event time (bimonthly visit) | No of events (recovery*) | No of relapse | No at risk (to recovery*) | Probability of recovering* | Test of equality of recovery* |
|---------------------------|----------------------------|--------------|--------------------|---------------|------------------------------|--------------------------|---------------|--------------------------|----------------------------|-------------------------------|
|                          | Negative                   | n=92         | 73 (79.3)          | 19 (20.7)     | 1                            | 0                        | 2             | 92                       | 0.000                      | 0.969 0.708 0.833             |
| H. pylori infection       |                            |              |                    |               | 2                            | 1                        | 4             | 91                       | 0.011                      |                               |
| in patients with IBD     |                            |              |                    |               | 3                            | 0                        | 5             | 91                       | 0.011                      |                               |
|                          |                            |              |                    |               | 4                            | 14                       | 3             | 77                       | 0.163                      |                               |
|                          |                            |              |                    |               | 5                            | 17                       | 1             | 60                       | 0.348                      |                               |
|                          |                            |              |                    |               | 6                            | 41                       | 4             | 19                       | 0.793                      |                               |
|                          | Positive                   | n=90         | 70 (77.8)          | 20 (22.2)     | 1                            | 0                        | 0             | 90                       | 0.000                      | 0.011 0.000 0.013             |
| Treatment of IBD         | Conventional               | n=106        | 86 (81.1)          | 20 (18.9)     | 1                            | 0                        | 0             | 106                      | 0.000                      | 0.893 0.867 0.880             |
|                          |                            |              |                    |               | 2                            | 0                        | 3             | 106                      | 0.000                      |                               |
|                          |                            |              |                    |               | 3                            | 2                        | 1             | 104                      | 0.019                      |                               |
|                          |                            |              |                    |               | 4                            | 21                       | 5             | 83                       | 0.217                      |                               |
|                          |                            |              |                    |               | 5                            | 16                       | 6             | 67                       | 0.368                      |                               |
|                          |                            |              |                    |               | 6                            | 47                       | 5             | 20                       | 0.811                      |                               |
|                          | Biological                 | n=76         | 57 (75.0)          | 19 (25.0)     | 1                            | 0                        | 2             | 76                       | 0.000                      | 0.013 0.013 0.211             |
|                          |                            |              |                    |               | 2                            | 1                        | 4             | 75                       | 0.013                      |                               |
|                          |                            |              |                    |               | 3                            | 0                        | 5             | 75                       | 0.013                      |                               |
|                          |                            |              |                    |               | 4                            | 15                       | 4             | 60                       | 0.211                      |                               |
|                          |                            |              |                    |               | 5                            | 9                        | 1             | 51                       | 0.329                      |                               |
|                          |                            |              |                    |               | 6                            | 32                       | 3             | 19                       | 0.750                      |                               |

*Recovery reflects a state of remission of IBD condition.

H. pylori, Helicobacter pylori; IBD, inflammatory bowel disease.
and improving the microbiota. In our present cohort, patients who were *H. pylori* negative with IBD and those experiencing less flare had a more favourable overall dietary habit score. Consistent with Kakodkar and Mutlu’s recommendations, which encourage the consumption of all vegetables and fruits in an IBD diet, we observed a strong protective role on IBD flare of daily and two to three times weekly consumption of vegetables and fruits. Moreover, a recent meta-analysis shows that the beneficial effect of *H. pylori* experienced by Mediterranean populations with IBD is lower compared with residents of East Asian and European regions. Nevertheless, the analysis did not explicitly incorporate dietary information or study the putative beneficial effect of diet as a confounder. Moreover, this positive effect may be attributed to the relative abundance of CagA *H. pylori* in these populations, a strain that produces specific constituents that modulate host immune defences.

Fibre may serve as an anti-inflammatory component of IBD treatment, although a converse effect can occur. Our Cox regression analysis revealed that daily consumption of foods rich in insoluble fibre, such as whole bread, cereals, beans, peas, wheat, oat, artichoke, cabbage, cauliflower, broccoli, dried herbs and spices, significantly increased the risk of IBD flare, particularly in patients who consume four daily meals interspersed with occasional snacks.

In agreement with Gentschew et al, trans-fat consumption was associated with a higher probability of IBD flare, although this was not a variable included in our final model. Although our findings suggest a role for diet in IBD flare, its effect is questionable because of the limitations of recall bias and multifactorial exposures. Moreover, patients with IBD may alter their dietary habits in response to symptoms that vary with disease activity, which requires further direct research into the role of diet in IBD.

Variations in the protective effects of *H. pylori* on IBD may be explained by socioeconomic factors. For example, here we show that patients with IBD with higher socioeconomic status and mainly urban residents had a higher chance of disease flares. Moreover, the frequency of *H. pylori* infection did not significantly vary in association with socioeconomic status. These findings support the argument that factors associated with an urban lifestyle and industrialisation influence risk of IBD. Furthermore, the rate of gastric colonisation by *H. pylori* was significantly higher in adults aged >20 years, although there was no significant difference in the average age of IBD onset between *H. pylori*-positive and *H. pylori*-negative groups. This age group experienced a higher frequency of disease flares. These findings may be explained by patients’ histories of comorbidities or lifestyle, which affect the occurrence of IBD. Demographic variables other than age did not exert detectable effects.

The findings of this study must be interpreted in view of its limitations. First, we did not test gastric biopsies for *H. pylori*, which may have decreased the disease prevalence.
rate. However, this would incur the burdens of an ethically questionable invasive procedure. A urea breath test may serve as a better alternative, although we did not have access to this test in our centres. Second, the small sample size was a major limitation and may have influenced the estimation of effect size. Third, the trend of decreased \textit{H. pylori} infection in patients administered biological therapy coincided with increased severity of IBD, which should be investigated by a larger, statistically robust randomised controlled trial. Moreover, our results merit reassessment in a cohort of patients from a background population with a low prevalence of \textit{H. pylori} that includes detailed information about eradication treatment and administration of other antibiotics. Fourth, a causal relationship between \textit{H. pylori} infection and IBD cannot be established through an uncontrolled study (control group without IBD), and further large-scale prospective studies are required. Thus, studies are warranted to investigate the effects of eradication of \textit{H. pylori} on the development of IBD combined with analyses of environmental exposures, hygiene diet, physical activity and intestinal microbiota as significant confounders. An ideal study would be prospective and initiated when IBD is diagnosed.

**CONCLUSIONS**

Together, the findings of our present analysis of the association between IBD and \textit{H. pylori} infection are inconclusive, and further studies are required. Thus, much remains to be learnt about the causes of IBD and whether specific environmental exposures influence the development of disease and its course.

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