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ORIGINAL ARTICLE

Helicobacter pylori infection is associated with liver fibrosis in patients with obesity undergoing bariatric surgery

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Abstract

Background: Obesity is a significant risk factor for metabolic-associated steatotic liver disease (MASLD). The association between Helicobacter pylori (HP) infection and liver fibrosis has not been fully elucidated in patients with obesity and MASLD.
Methods: This observational retrospective study included clinical and biochemical parameters of patients with obesity undergoing bariatric surgery. HP infection was confirmed by gastric endoscopy, and liver biopsies were performed during surgery. Bivariate and logistic regression analyses were employed to evaluate independent associations with liver fibrosis and steatosis by biopsy.
Results: The mean age of the subjects was 42 ± 10 years, with 84.7% being women, and they had a mean BMI of 42.97 ± 7.56 kg/m2. Overall, 41.7% of patients had an HP infection. Multiple logistic regression models were conducted to assess the association between HP infection, liver steatosis, and fibrosis by biopsy. HP infection was independently associated with liver fibrosis [OR = 3.164 (95% CI 1.011–9.900)].
Conclusion: Biopsy findings associated HP infection with increased liver fibrosis.

Introduction

Obesity has become a public health problem, with 1.9 billion people living with overweight and 650 million with obesity (30% of the worldwide adult population) in 2016.[1] One of the main complications of obesity is metabolic-associated fatty steatotic disease (MASLD). MASLD, previously known as Nonalcoholic Fatty Liver Disease (NAFLD), is recognized as the most common cause of chronic liver disease worldwide, and its prevalence continues to increase.[2] MASLD is acknowledged as a global health issue affecting 20 to 30% of the general population, but its risk is 4.6 times higher in patients with obesity. It is expected that the prevalence of obesity will continue to grow

exponentially in the coming years, in conjunction with the global epidemics of obesity and type 2 diabetes.[3] Therefore, prompt recognition and prevention of liver fibrosis in patients with obesity could reduce the overwhelming costs of chronic liver disease and its complications on global health economies.

The diagnosis of MASLD relies on identifying hepatic steatosis by imaging or biopsy, along with at least one of the following criteria: a body mass index (BMI) >25 kg/m^2, fasting plasma glucose >100 mg/dL or type 2 diabetes, hypertension, or metabolic syndrome.[4] MASLD encompasses a spectrum ranging from simple steatosis to the inflammatory condition known as metabolic steatohepatitis. Its progression may culminate in cirrhosis, contributing to a mortality rate of 25.56 per 1000 person-years.[5]

Although advanced liver fibrosis in patients with obesity has a multifactorial etiology, including obstructive sleep apnea (OSA), diabetes, and hypertension,[6–9] several reports have shown that Helicobacter pylori (HP) infection is a potential trigger of inflammation. Moreover, eradicating HP improves insulin sensitivity, with no difference between weight loss.[10,11] Nonetheless, contradictory data have shown that HP infection could promote the progression of MASLD, particularly in women patients with dyslipidemia.[12,13] While most of these data come from observational studies of patients with MASLD across different BMI, the association of HP infection in patients with obesity who underwent bariatric surgery has not been thoroughly studied. Hence, the objective of the present study is to determine whether HP is associated with advanced liver fibrosis in patients with obesity undergoing Bariatric Surgery.

Methods

Patients. A retrospective observational study was performed using medical files from the bariatric surgery clinic of the Hospital General Dr. Manuel Gea Gonzalez (HGDMGG). We report our findings to the STROBE guidelines for observational studies. The inclusion criteria were patients with obesity aged over 18 years who underwent bariatric surgery and had undergone trans-surgical liver biopsy from December 2017 to February 2020. A flow diagram of the patient selection process is presented in Figure 1. The present study was approved by the HGDMGG Research Committee and Research Ethics Committee (REF 04-26-2022), and patient anonymity was guaranteed according to the 1975 Declaration of Helsinki. Upon medical admission, the patient or a family member signed an informed consent permitting the use of their medical file information for didactic, research, and publication purposes for each patient's anthropometric, clinical, radiological, biological, or biochemical, and endoscopic parameters which were recorded before bariatric surgery. HP infection was diagnosed by gastric antral biopsy. Liver biopsies were taken during the surgical procedure, and the histopathological results were recorded in the clinical chart. To our knowledge, none of the patients in the HP-negative group had previously been treated for HP infection. This information was derived from a thorough review of their medical histories and clinical records available at our institution. Consequently, it can be affirmed that the HP-negative cohort was comprised of individuals who had not undergone treatment for HP infection. Each liver biopsy was staged according to the NAFLD activity

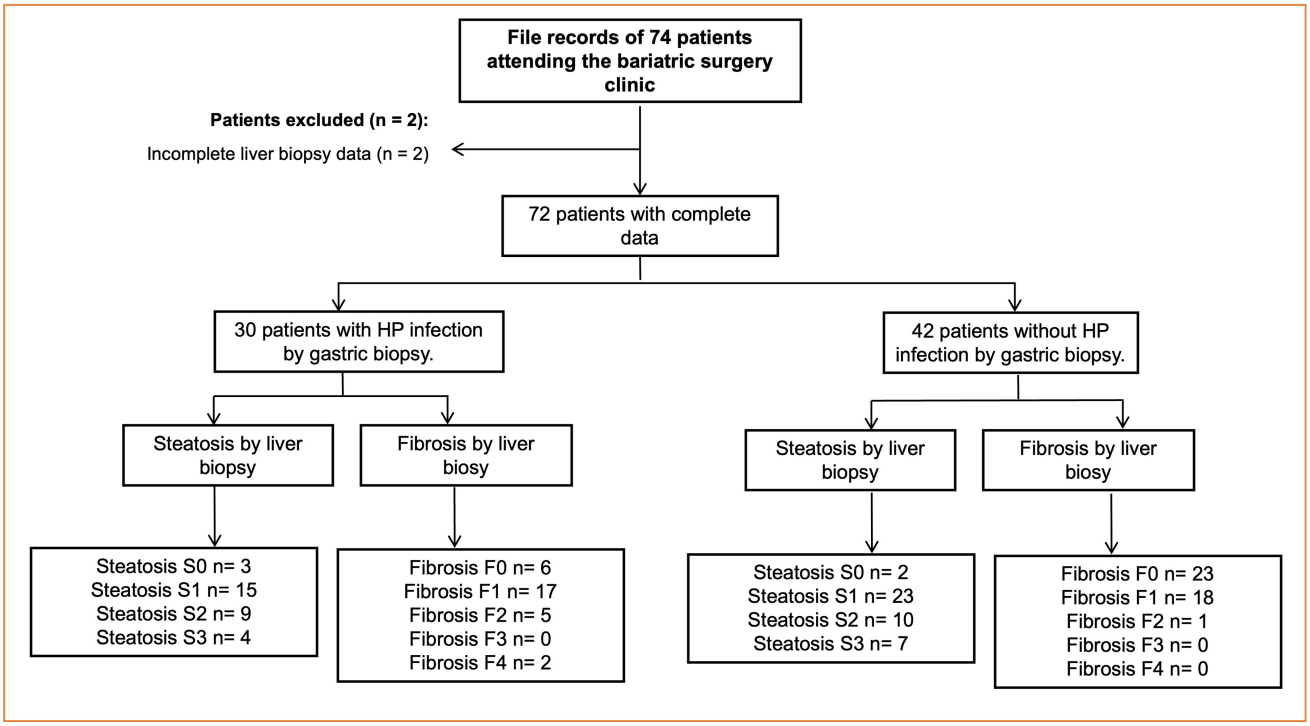

Figure 1 Patient selection flowchart.

score (NAS). Biochemical parameters were used to calculate noninvasive serological markers, including the FIB4 score, APRI score, NAFLD fibrosis score, and HEPAMET fibrosis score, for each patient pre-surgery. Trained staff obtained anthropometric measurements.

Biochemical analysis. Blood samples from the patients were collected after admission to the emergency department. The measurements were carried out with commercially available standardized methods. Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), glucose, glycosylated hemoglobin (HbA1c), lipids profile, and uric acid were measured using DxC 700 AU Chemistry Analyzer (Beckman Coulter, Fullerton CA). Plasma insulin, ferritin, and ferritin saturation were estimated using an enzyme-linked immunosorbent assay (Beckman Coulter DxC 600i, Fullerton, CA).

Abdominal ultrasound (US). A certified and experienced technician performed a pre-surgery abdominal US using a Siemens ACUSON Sequoia (Siemens Healthineers, Germany). The images were digitally stored and reevaluated by our institution's imaging specialist.

Statistical analysis. Statistical analysis was performed using SPSS 26 (SPSS Inc., Chicago, IL). Data were screened for outliers and normality assumptions. The normality of continuous variables was assessed with the Shapiro–Wilk normality test and visually using histograms and Q-Q plots. Values are expressed as mean ± standard deviation, median (interquartile range), or frequencies (%). Means and medians were compared using the Student *t*-test or Mann–Whitney *U* test when needed and frequencies with a chi-squared test. Binary Logistic regression models were used to determine the association between HP infection and liver fibrosis. Odds ratios (ORs) with 95% confidence intervals (95%CI) were reported, and a statistical significance $P \leq 0.005$.

Results

This study included 72 patients with obesity who underwent bariatric surgery. The mean age of the subjects was 42 ± 10 years, with 84.7% ($n = 61$) being women, having a mean BMI of 42.97 ± 7.56 kg/m^2 (BMI 30–34.99 kg/m^2 15.3% [$n = 11$], BMI 35–39.99 kg/m^2 26.4% [n = 19], and BMI >40 kg/m^2 58.3% [$n = 42$]), and having a mean WC of 126 ± 18 cm. Only 6.9% ($n = 5$) of patients reported alcohol ingestion >20 g/day, 23.6% ($n = 17$) were active smokers, 19.4% ($n = 14$) had type 2 diabetes, 26.4% ($n = 19$) had hypertension, and 25.0% ($n = 18$) had OSA. Figure 2 shows the distribution of liver enzymes in the population. Overall, 41.7% ($n = 30$) of patients had an infection with HP, and 58.3% ($n = 42$) did not have an HP infection.

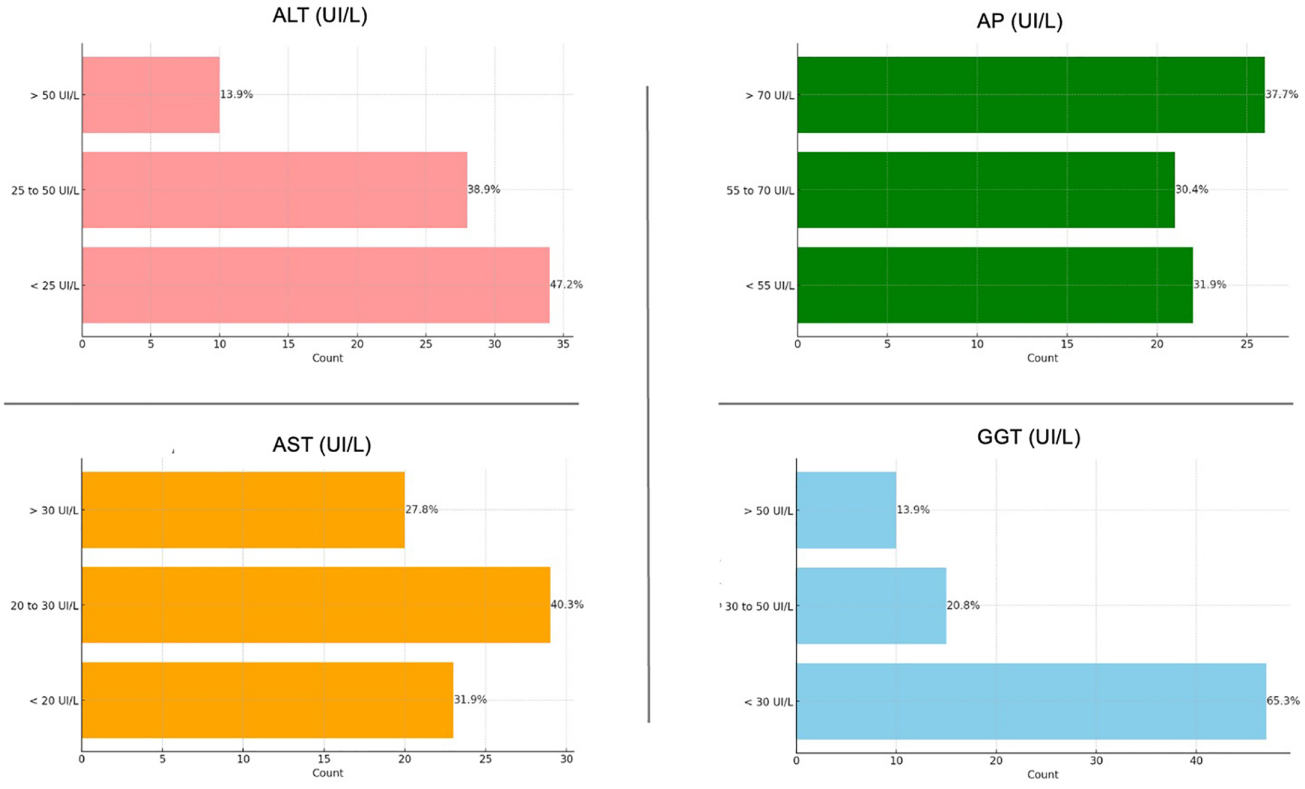

Figure 2 Distribution of liver enzymes and alkaline phosphatase levels among patients with obesity undergoing bariatric surgery. The bar charts show the percentage and count of patients within specific ranges for each biochemical marker. ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase.

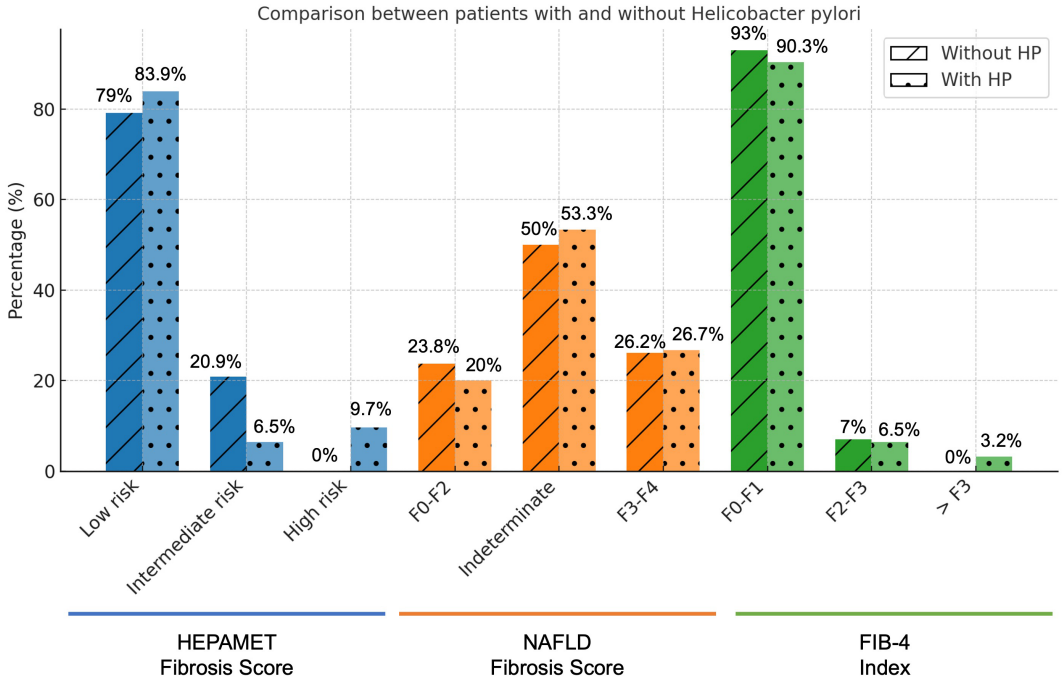

Figure 3 Comparison of noninvasive fibrosis risk calculators between patients with and without Helicobacter pylori (HP) infection. Categorized by HEPAMET Fibrosis Score, NAFLD Fibrosis Score, and FIB-4 Index. Bars represent the percentage of patients in each category. "Without HP" (black-striped) and "With HP" (black-dotted) groups are shown for each risk level and score.

Moreover, patients had a median HEPMAET fibrosis score of 0.04 (0.02–0.09), a median APRI score of 0.19 (0.15–0.33), a median NAFLD fibrosis score of −0.43 (−1.36–0.78), and a median FIB-4 index of 0.65 (0.48–0.88). Moreover, Figure 3 shows the comparison of noninvasive serological markers for fibrosis according to HP infection.

Table 1 presents the patients' baseline clinical and biochemical characteristics before undergoing bariatric surgery. Patients who did have an HP infection had higher triglyceride levels, a higher frequency of steatosis grade 2 and 3 by ultrasound, fibrosis >F1 by liver biopsy, and increased hepatocellular ballooning. Figure 1 shows the categorical distribution of ALT, AST, GGT, and alkaline phosphatase.

Multiple logistic regression models were performed to assess the association between HP infection, liver steatosis (S1–S4), and fibrosis (F1–F4) by biopsy (Table 2). HP infection did not show a significant association with liver steatosis by biopsy. However, the unadjusted model for liver fibrosis shows that HP infection had a significant association. Interestingly, both model 1 and model 2 demonstrated that HP infection maintained a significant association with liver fibrosis. Moreover, we analyzed the association of HP infection with hepatocellular ballooning. The crude model showed that HP infection was associated with increased ballooning ($\chi^2 = 4.906$; OR = 3.00 [95% CI 1.135–7.931]). After adjusting for sex, age, BMI, OH, hypertension, OSA, type 2 diabetes, and triglycerides, HP remained associated with hepatocellular ballooning ($\chi^2 = 4.351$; OR = 2.833 [95% CI 1.065–7.539]). Likewise, Table 3 shows the binary regression models of HP infection and the odds for liver steatosis (>S2) and fibrosis (>F2) in our population. In line with the last regression, no association with liver steatosis was found. The crude analysis and model 1 showed that HP infection was significantly associated with liver fibrosis >F2.

Discussion

The results from the present study demonstrate an association between liver fibrosis and HP infection in patients with obesity undergoing bariatric surgery. However, does HP infection play a role in increased liver fibrosis?

Due to its fecal-oral transmission, HP is a gram-negative bacterium prevalent in underdeveloped or developing countries.[10] HP infection prevalence is greater in developing countries, such as Latin America, where it affects 50–65% of the population. While HP infection often remains asymptomatic in most patients, it predisposes individuals to conditions such as peptic ulcers, gastric adenocarcinomas, and lymphoma.[10–12] Recently, attention has been drawn to the possible association between HP infection and the development and progression of MASLD, especially in populations with a high prevalence of both diseases, such as in Latin America.[14] Some meta-analyses have suggested that HP infection may slightly increase the prevalence of MASLD,[14] while others have confirmed this association, particularly in patients with HP strains expressing cytotoxin-associated gene A (CagA) and vacuolization cytotoxin A (VacA) cytotoxins.[12,15]

In the stomach, this bacterium triggers inflammation by expressing harmful factors like Duodenal ulcer promoting gene A and Alp A/B, boosting IL-6 and IL-8 production, causing

Table 1 Baseline clinical and biochemical characteristics of the patients stratified by helicobacter pylori (HP) infection before undergoing bariatric surgery

Variables	All patients ($n = 72$)	Helicobacter Pylori negative ($n = 42$)	Helicobacter Pylori positive ($n = 30$)	*P* value
Age (years)	42 ± 10	41 ± 10	43 ± 11	0.425
Female sex (%)	84.7	85.7	83.3	0.517
Body Mass Index (kg/m^2)	42.97 ± 7.56	42.52 ± 7.08	43.60 ± 8.26	0.553
30–34.9 kg/m^2 (%)	15.3	14.3	16.7	0.873
35–39.9 kg/m^2 (%)	26.4	28.6	23.3	
≥40 kg/m^2 (%)	58.3	57.1	60.0	
Waist circumference (cm)	126 ± 18	126 ± 16	128 ± 20	0.582
Alcohol >20 g/day (%)	6.9	9.5	3.3	0.393
Active smoking (%)	23.6	26.2	20.0	0.587
Diabetes (%)	19.4	19.0	20.0	0.999
Hypertension (%)	26.4	23.8	30.0	0.596
OSA (%)	25.0	23.8	26.7	0.790
Leucocyte count (X10^3/μl)	7.74 ± 1.81	7.82 ± 1.73	7.63 ± 1.95	0.658
Hemoglobin (g/dL)	14.67 ± 1.83	14.60 ± 1.43	14.76 ± 2.30	0.726
Platelet count (X10^3/μL)	271 ± 62	269 ± 54	273 ± 73	0.823
Serum creatinine (mg/dL)	0.66 ± 0.28	0.69 ± 0.25	0.62 ± 0.32	0.300
Fasting insulin (mIU/L)	21 (12–29)	19 (12–27)	23 (15–31)	0.319
Fasting plasma glucose (mg/dL)	108 ± 32	107 ± 35	110 ± 29	0.725
HOMA-IR	5.01 (3.14–7.05)	5.01 (3.06–6.69)	5.25 (3.84–8.40)	0.338
Hemoglobin A1c (%)	6.01 ± 1.10	6.03 ± 1.21	5.98 ± 0.95	0.851
Serum uric acid (mg/dL)	5.85 ± 1.52	5.91 ± 1.45	5.75 ± 1.66	0.680
AST (UI/L)	21 (18–32)	21 (18–33)	22 (18–31)	0.977
ALT (UI/L)	26 (19–42)	26 (19–46)	25 (20–41)	0.995
Alkaline phosphatase (UI/L)	76 (63–93)	70 (58–84)	79 (65–105)	0.068
GGT (UI/L)	24 (18–37)	25 (17–37)	20 (18–36)	0.748
Total Bilirubin (mg/dL)	0.58 (0.44–0.79)	0.58 (0.45–0.75)	0.60 (0.44–0.79)	0.939
Albumin (g/dL)	4.03 ± 0.48	3.99 ± 0.49	4.09 ± 0.48	0.424
Cholesterol (mg/dL)				
Total	182 ± 32	182 ± 30	182 ± 35	0.916
Low-density lipoprotein	115 ± 48	117 ± 59	112 ± 28	0.686
High-density lipoprotein	42 ± 12	44 ± 13	38 ± 8	0.059
Triglycerides (mg/dL)	158 (128–334)	148 (121–196)	211 (145–967)	0.018
Steatosis by US (%)				
Without steatosis	12.7	7.3	20.0	
Steatosis grade 1	35.2	48.8	16.7	0.023
Steatosis grade 2	36.6	34.1	40.0	
Steatosis grade 3	15.5	9.8	23.3	
Steatosis by biopsy (%)				
Without steatosis	5.6	4.7	9.7	
Steatosis grade 1	52.8	55.8	48.4	0.395
Steatosis grade 2	26.4	23.3	29.0	
Steatosis grade 3	15.3	16.3	12.9	
Fibrosis by biopsy (%)				
F0	40.3	55.8	19.4	
F1	48.6	41.9	58.1	0.002
F2	8.3	2.3	16.1	
F3	0.0	0.0	0.0	
F4	2.8	0.0	6.5	
Hepatocellular ballooning (%)	44.4	33.3	60.0	0.032
Portal inflammation (%)	84.7	88.1	80.0	0.508
Lobular inflammation (%)	81.9	78.6	86.7	0.537

Variables are mean ± standard deviation, median (interquartile range), or percentages—p-value: *T*-student test, *U* Mann–Whitney, or chi^2.
ALT, alanine Transaminase; AST, aspartate Transaminase; GGT, gamma-glutamyl transferase.

Table 2 Binary logistic regression models of Helicobacter pylori (HP) infection and the odds for liver steatosis (S1–S4) and fibrosis (F1–F4) by biopsy in patients with obesity undergoing bariatric surgery

	Liver steatosis		Liver fibrosis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Unadjusted				
HP negative	1	0.199	1	0.004
HP positive	0.220 (0.022–2.222)		4.842 (1.642–14.279)	
Model 1				
HP negative	1	0.188	1	0.005
HP positive	0.211 (0.021–2.142)		4.851 (1.602–14.692)	
Model 2				
HP negative	1	0.172	1	0.048
HP positive	0.195 (0.019–2.031)		3.164 (1.011–9.900)	

Model 1 was adjusted by sex, age, BMI, OH, hypertension, OSA, type 2 diabetes, and triglycerides.
Model 2 was adjusted by sex, age, BMI, OH, hypertension, OSA, HOMA, and triglycerides.

Table 3 Binary logistic regression models of Helicobacter pylori (HP) infection and the odds for liver steatosis (>S2) and fibrosis (>F2) by biopsy in patients with obesity undergoing bariatric surgery

	Liver steatosis >S2		Liver fibrosis >F2	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Unadjusted				
HP negative	1	0.808	1	0.022
HP positive	1.125 (0.435–2.906)		12.478 (1.444–107.834)	
Model 1				
HP negative	1	0.826	1	0.041
HP positive	0.891 (0.318–2.495)		11.292 (1.109–114.985)	
Model 2				
HP negative	1	0.885	1	0.101
HP positive	0.923 (0.311–2.739)		7.762 (0.672–89.680)	

Model 1 was adjusted by sex, age, BMI, OH, hypertension, OSA, type 2 diabetes, and triglycerides.
Model 2 was adjusted by sex, age, BMI, OH, hypertension, OSA, HOMA, and triglycerides.
OSA, obstructive sleep apnea.

tissue inflammation and cell infiltration. Another factor, OipA, worsens inflammation by damaging cells and reducing junctions. HP also increases ROS production, activates immune responses via lipopolysaccharide secretion and Toll-like receptors like TLR4, triggering pro-inflammatory pathways like NFkB and c-jun N-terminal kinase activation. Moreover, HP secretes pathogen-associated patterns through CagA protein.[16]

The phosphorylation of CagA, as mentioned above, activates signaling pathways that perpetuate cytokine release.[17] This inflammatory environment promotes the recruitment of PMN and mononuclear cells. It also activates the adaptive immune response of CD4 and CD8+ T cells, with a Th1 response increasing levels of interferon-gamma, tumor necrosis factor, IL-1β, IL-6, IL-7, IL-8, IL-10, and IL-18.[16] Additionally, it activates Major histocompatibility complex II and expression of B7-1 and B7-2, leading to consecutive Th2 cell activation.[17]

In vitro studies suggest HP infection in obesity and T2DM triggers inflammation via NFkB activation, leading to pro-inflammatory cytokine secretion. HP also accumulates catabolic intermediates, hindering fatty acid oxidation and causing mitochondrial stress by downregulating SOD 1, promoting ROS production.[18] In a recent meta-analysis published in Chinese patients, an association between HP infection and obesity was found. Chen et al. also concluded that HP infection, coupled with age less than 50 years, increases the risk of obesity in their population compared with patients without HP infection.[19] The explanation for this phenomenon remains debated. It has been proposed that the secretion of ghrelin, an orexigenic hormone primarily secreted in the stomach and duodenum, which is involved in hunger and the long-term regulation of body weight, plays a role in body weight reduction. Studies have shown that consistent infusion of exogenous ghrelin increases body weight and decreases the metabolic rate and fat catabolism. Blocking ghrelin signaling into the brain leads to reduced food intake. This suggests that the continuous decrease in ghrelin levels in patients after RYGB (Roux-en-Y gastric bypass) might contribute to weight reduction, confirming that ghrelin suppression might contribute to weight loss.[20] It has been described that patients with HP gastritis have lower plasma active ghrelin levels than those with peptic ulcers. Kasai et al. suggest that plasma active ghrelin levels decrease after HP eradication; this seems contradictory because it would be expected that after the recovery of oxyntic

cells, ghrelin-producing cells (GPC) should be restored. Hence, this might be partially due to the time required to recover GPC.[21] Conversely, other data suggest that ghrelin, obestatin, and leptin levels are not affected by the presence of HP in patients with obesity,[22] probably demonstrating that alterations in hunger hormones are not the only factors associated with HP infection and metabolic features in patients living with obesity.

Thirdly, all the previously presented data might suggest that HP infection in patients with obesity and weight gain may not be directly related to active ghrelin levels but could instead result from a combination of factors associated with HP, such as the alteration of the gut microbiota.[23] HP infection has been associated with lipid and glucose disorders. Studies have shown that HP infection is associated with higher HbA1c levels and that hepatic insulin resistance is higher in HP-positive patients due to the c-Jun/miR-203/SOCS3 signaling pathway.[24] Hence, these findings suggest that HP eradication does not affect glucose control. These findings are supported by cohort studies such as one published by Kim et al.,[25] which found that HP infection increases the risk of MASLD development, insulin resistance, diabetes, dyslipidemia, and metabolic syndrome.

Fourthly, another important point to discuss is the effect of HP infection on gut microbiota. It has been widely discussed that the crosstalk between microbiota and the host modulates metabolic pathways. HP infection has been associated with metabolic-related diseases.[26,27] Studies have shown that HP affects ghrelin and leptin levels and influences gut microbiota. In murine models with HP infection, Yin et al. demonstrated a reduction in Lactobacillus spp. in the stomach and an increase in Enterococcus spp. and Staphylococcus aureus in the stomach and duodenum,[26] while Heimesaat et al. showed an increase in E. coli, enterococci, and Bacteroides/Prevotella spp. in the colon.[27] Similar changes in gut microbiota have been described in patients living with MASLD and obesity.

HP infection causes gastric atrophy, reduces acid, and leads to small intestinal bacterial overgrowth. This increases intestinal permeability and portal endotoxins, potentially advancing MASLD to metabolic steatohepatitis and fibrosis. Kounburas et al.[28] found HP eradication improves metabolic parameters, lowering C-reactive protein and fibrinogen, decreasing HOMA-IR, and boosting HDL cholesterol. They suggest HP infection is a risk factor for MASLD and metabolic comorbidities, warranting more research.[28]

Fifthly, several studies have confirmed the association between HP infection and the development and progression of MASLD. A study by Liu et al. concluded that HP infection was one of the risk factors associated with MASLD progression.[12] Another study by Doulberis et al.[29] found that active HP infection was independently associated with nonalcoholic steatohepatitis and fibrosis. Ning et al.[30] conducted a meta-analysis showing an increased MASLD risk in HP-positive patients. Several risk factors for the progression of MASLD have been proposed.

The present study has several strengths. To the best of our knowledge, this was the first study to investigate the association between HP infection and liver fibrosis and activity in patients with obesity undergoing bariatric surgery. Other reports based their observations on noninvasive markers, such as FIB-4. While we did not identify an independent association between liver steatosis and HP infection by biopsy, reporting these negative results is valuable for future research. Another strength is that the study population exclusively comprised patients with a BMI over 30 kg/m^2, allowing us to analyze a population at very high risk for metabolic-associated liver fibrosis.

On the other hand, our study has some significant limitations. The most important limitation is that the diagnosis of HP infection was based solely on endoscopic biopsy with Giemsa staining, as our institution did not have access to rapid urease tests, serological antibody tests, or HP stool antigen tests during the study period. We acknowledge that a combination of diagnostic methods could have increased the sensitivity and accuracy of the diagnosis.

Additionally, while we evaluated all surgery patients for viral infections such as hepatitis B and C, ensuring they had negative serology for these viruses, we did not assess for other potential causes of liver fibrosis, such as primary biliary cholangitis or autoimmune hepatitis. However, the liver enzyme levels and clinical characteristics of our patients did not suggest the presence of these diseases.

As a single-center retrospective study conducted in Mexico, the results may be challenging to generalize, and further studies are needed to confirm our findings. Moreover, our sample size was smaller than ideal due to the limited number of liver samples obtained for histological analysis. Lastly, we could not determine the duration of HP infection exposure and its direct association with liver fibrosis.

In summary, HP infection was independently associated with liver fibrosis and hepatocellular ballooning in patients with obesity undergoing bariatric surgery. Screening for and eradicating HP infection could reduce the growing prevalence of liver fibrosis. Further studies are needed to expand upon this observation.

Acknowledgments

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Ethics statement

The study was approved by the HGDMGG Research Committee and Research Ethics Committee (REF 04-26-2022) and conducted according to the 1975 Declaration of Helsinki. Upon medical admission, the patient or a family member signed an informed consent form permitting the use of their medical file information for didactic, research, and publication purposes. Ethics approval was taken from: Comité de Investigación y Comité de Ética en Investigación (Research Committee and Research Ethics Committee) del Hospital General Dr. Manuel Gea González, Office number: CI y CEI-068-2022. Reference number: 04-26-2022.

Data availability statement. All data and materials are available from the corresponding author and will be made available on reasonable request.

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