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Frequency and risk factors of non-alcoholic fatty liver disease in *Helicobacter pylori*-infected dyspeptic patients: A cross-sectional study

Basit Siddiqui[1], Muhammad Kamran[1], Shiyam Sunder Tikmani[2], Rabeea Azmat[1], Zain Mushtaq[1], Saad Bin Zafar[1], Muhammad Tahir Khan[3], Javed Yakoob[1] and Zaigham Abbas[1]

Abstract

Background: In dyspeptic patients with *Helicobacter pylori* contributes to non-alcoholic fatty liver disease. However, little evidence available from Pakistan.

Objective: The study aims to determine the frequency and risk factors of non-alcoholic fatty liver disease in dyspeptic patients with *Helicobacter pylori*.

Methods: This cross-sectional study was conducted between 22 November 2016 and 30 June 2018. Adults of age between 18 and 90 years who attended the out-patient department due to abdominal discomfort, pain, fullness, and bloating who underwent upper gastrointestinal tract endoscopy were enrolled after taking informed consent. Patients with celiac disease, inflammatory bowel disease, taking alcohol, pregnant women and lactating mothers, known cases of hepatitis B and C, and history of recent antibiotic use were excluded. Data on age, gender, smoking, alcohol use, dyslipidemia, hypertension, type 2 diabetes mellitus, and ischemic heart disease were collected. Non-alcoholic fatty liver disease was diagnosed through ultrasonography. *Helicobacter pylori* infection was detected using a carbon urea breath test.

Results: A total of 698 patients were screened for eligibility, and 399 (57.2%) had *Helicobacter pylori* infection and were enrolled in the study after consent. The median age was 50.1 (interquartile range = 14.5) years and 209 (52.4%) were males. Frequency of non-alcoholic fatty liver disease in patients with *Helicobacter pylori* dyspeptic patients was 153 (38.3%). Factors associated with non-alcoholic fatty liver disease in the presence of *Helicobacter pylori* were dyslipidemia 7.38 (95% confidence interval = 2.4–22.71), type 2 diabetes mellitus 5.96 (95% confidence interval = 1.86–19.07), hypertension 3.0 (95% confidence interval = 1.21–7.45), and moderate gastritis 2.81 (95% confidence interval = 1.2–6.59).

Conclusion: The frequency of non-alcoholic fatty liver disease in *Helicobacter Pylori* dyspeptic patients was 38.3%. Male gender, dyslipidemia, hypertension, ischemic heart disease, and moderate gastritis were associated with non-alcoholic fatty liver disease.

Keywords

Helicobacter pylori, non-alcoholic fatty liver disease, type 2 diabetes mellitus, dyslipidemia, ischemic heart disease, gastritis

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Introduction

Dyspepsia is the most common condition described as epigastric pain or burning, post-meal discomfort, bloating, burping, and a sensation of abdominal fullness.[1] In addition, dyspepsia, without evidence of organic pathology in the upper gastrointestinal (GI) tract endoscopy or imaging is called functional dyspepsia.[2] The prevalence of dyspepsia in the general population is 21%.[3] Moreover, the prevalence is

[1]Department of Medicine, Aga Khan University Hospital, Karachi, Pakistan
[2]Department of Community Health Sciences, Aga Khan University, Karachi, Pakistan
[3]School of Public Health, Dow University of Health Sciences, Karachi, Pakistan

Corresponding author:
Basit Siddiqui, Department of Medicine, Aga Khan University Hospital, PO Box 3500, Stadium Road, Karachi 74800, Sindh, Pakistan.
Email: dr.basit.siddiqui@gmail.com

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high in females, individuals taking non-steroidal anti-inflammatory drugs (NSAIDs), smokers, and *Helicobacter pylori*-positive individuals.

H. pylori is a gram-negative, microaerophilic bacterium that resides in the gastric mucosa, and it is one of the most common pathogens isolated in dyspeptic patients. Around 50% of the world's population is infected with *H. pylori*.[4] In a population-based study, it was found that the prevalence of *H. pylori* in dyspeptic patients was 70%.[5] In Pakistan, the frequency of *H. pylori* in dyspeptic patients was estimated to be around 45%.[6] Moreover, *H. pylori* is a major cause of chronic gastritis, peptic ulcer, gastric cancer, and GI lymphoma.[7] *H. pylori* infection is also closely related to obesity, type 2 diabetes mellitus (T2DM), and various abnormalities in lipid metabolism.[8]

Non-alcoholic fatty liver disease (NAFLD) is one of the most common causes of liver cirrhosis in the Western world. Globally, the prevalence of NAFLD in the general population ranges from 9% to 37%,[9] while it is 12%–24% among Asian countries.[10] In Pakistan, the frequency of NAFLD to be approximately 14%–15%.[11] NAFLD may increase the risk of developing T2DM, cardiovascular disease (CVD), and chronic kidney disease (CKD).[12] In addition, advancing age and male gender are more likely to develop fatty liver.[13]

H. pylori initiates a low-grade inflammatory response, which results in up-regulation of the expression of several inflammatory elements, for example, tumor necrosis factor (TNF), C-reactive protein (CRP), and other interleukins resulting in insulin resistance.[14] The decreased expression of adiponectin in the presence of *H. pylori* is another factor predisposing to NAFLD as adiponectin prevents the deposition of fatty acid in the hepatocytes and suppresses inflammation by inhibiting nuclear factor kappa B (NF-κB) pathway.[15] *H. pylori* plays an important role in lipid metabolism, and dyslipidemia is frequently seen in patients with NAFLD.[16]

Various studies have been conducted internationally to explore the association of NAFLD in patients with *H. pylori* infection.[17,18] However, insufficient data are available from Pakistan.[18] The existing studies conclude inconsistent results with regard to the association between the two clinical entities.[19] Moreover, there is a gap in knowledge regarding the relationship of NAFLD with *H. pylori* infection in a population of dyspeptic patients in Pakistan, who, because of their lifestyle and other factors, are also at a risk for obesity, T2DM, and CVDs.[20] The objectives of the study were to (1) determine the frequency of NAFLD in *H. pylori*-infected dyspeptic patients and (2) determine the risk factors of NAFLD in these patients.

Materials and methods

This cross-sectional study was conducted in the out-patient department (OPD) of Gastroenterology and Hepatology, Department of Medicine, Aga Khan University from 22 November 2016 to 30 June 2018. Adults of age between 18 and 90 years who attended the OPD due to dyspeptic symptoms such as abdominal discomfort or pain, fullness, and bloating who underwent upper GI tract endoscopy were included in the study. Patients with celiac disease, inflammatory bowel disease (IBD), pregnant and lactating females, taking alcohol, known cases of hepatitis B and C, history of recent antibiotic use, and not willing to participate in the study were excluded.

Eligible patients were enrolled in the study after taking written informed consent in the presence of a witness. A history, physical examination, height, and weight were taken to calculate body mass index (BMI). Urea breath test (UBT) was used for the diagnosis of *H. pylori.* Modified Criteria for South Asians were used to categorized BMI into healthy (BMI 18.5–<23) and overweight (BMI ⩾23). T2DM was defined as a fasting plasma glucose (FPG) level of 126 mg/dL (7.0 mmol/L) or higher, *OR* a 2-h plasma glucose level of 200 mg/dL (11.1 mmol/L) or higher during a 75-g oral glucose tolerance test (OGTT), *OR* a random plasma glucose of 200 mg/dL (11.1 mmol/L) or higher in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, *OR* a hemoglobin A1c (HbA1c) level of 6.5% (48 mmol/mol) or higher.[21] Hypertension was defined as a blood pressure >140/90 mm Hg on two occasions for new cases or person on antihypertensive medication. Dyslipidemia was defined as a disorder of lipid metabolism reflected if total cholesterol (TC) was >290 mg/dL and/or low-density lipoprotein cholesterol (LDL-C) was >190 mg/dL and/or non-high-density lipoprotein cholesterol (non-HDL-C) was >228 mg/dL.

H. pylori infection was diagnosed using a carbon urea breath test (14C-UBT). Patients were asked to fast for 6 h and rinse their mouth before UBT. Patients were then asked to swallow a capsule containing 14C-urea (Helicap, Noster System AB Stockholm, Sweden) with water in a sitting position, followed by the collection of breath samples in a cartridge system (Heliprobe Breath Card, Noster System AB Stockholm) after 10 min. The patients exhaled breath into the cartridge system which changed color to yellow from orange. The breath card was inserted into a β-scintillation counter (Heliprobe-analyzer, Noster System AB Stockholm) and activity was measured for 250 s. Results were expressed both as counts per minute (CPM) and graded as (0: not infected, CPM <25; 1: equivocal, CPM 25–50; 2: infected, CPM >50).[21] UBT was considered *H. pylori*-positive when the grade was 2.

Abdominal ultrasonography was used for diagnosing NAFLD. It routinely evaluates, liver, gallbladder, pancreas, kidneys, spleen, and abdominal aorta. Main determinants of NAFLD were described as (1) an increase in the brightness of the liver, (2) an increase in the hepato-renal echo contrast pattern, (3) existence of vascular blurring in the hepatic parenchyma, (4) deep attenuation of hepatic echo, (5) borderline blurring existing between liver and gallbladder, or right kidney, and (6) existence of focal hypoechoic lesion.

For labeling a liver as fatty liver, ultrasonographic findings had to satisfy both (1) and (2) in addition to at least one of the findings between (3) and (6).[22,23] The diagnosis was double-checked by the ultrasonographer and gastroenterologists.

For grading the gastritis, patients with dyspeptic symptoms undergone gastroscopy with biopsy sent for histopathology. Formalin-fixed and paraffin-embedded gastric biopsy specimens obtained at upper GI endoscopy were stained with hematoxylin and eosin for histological examination. The degree of acute and chronic inflammation was scored according to the updated Sydney system.[22]

Statistical analysis was performed with SPSS 17.0 for Windows (SPSS, Chicago, IL, USA). Numeric variable such as age was presented as the median interquartile range (IQR). Categorical variables such as gender, BMI, dyslipidemia, T2DM, hypertension, ischemic heart disease (IHD), gastritis, and grades of gastritis were presented as frequencies and percentages. Mann–Whitney test was used for the comparison of numeric variable, and chi-square test was used to compare categorical variables. Multiple logistic regression was done to determine the risk factors of NAFLD in dyspeptic patients with *H. pylori*. The odds ratio with a 95% confidence interval (CI) was reported.

The study was approved by the ethical review committee of Aga Khan University Hospital (4532-Med-ERC-16). Informed consent was taken from all enrolled participants.

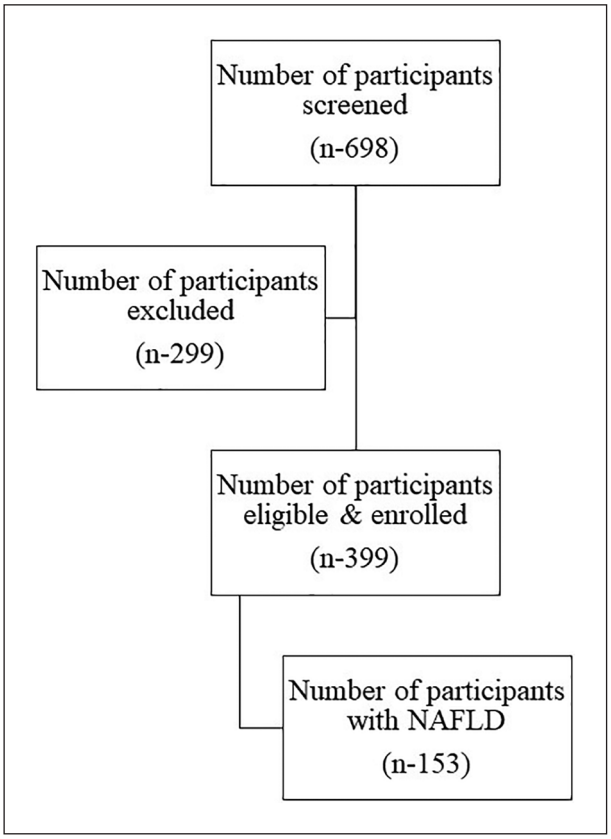

Figure 1. Study flow diagram.

Results

A total of 698 patients were screened for eligibility. Of 698 screened patients, 399 (57.2%) had *H. pylori* infection and were enrolled in the study after informed consent (Figure 1).

The median age of enrolled participants was 50.1 (IQR = 14.5) years and 209 (52.4%) were males. Overall, 319 (843%) has BMI of >23, 74 (30.7%) each were dyslipidemic and T2DM, 65 (23.5%) hypertensive, 52 (21.4%) IHD, 220 (51.3%) moderate gastritis, and 262 (67.4%) have chronic active gastritis. The frequency of NAFLD in patients with *H. pylori* dyspeptic patients was 153 (38.3%). Comparison of baseline factors by non-alcoholic fatty liver is summarized in Table 1.

Male patients were 2.7 (95% CI = 1.02–7.06) time more likely to develop NAFLD compared to female, while patients with dyslipidemia 7.38 (95% CI = 2.4–22.71), T2DM 5.96 (95% CI = 0.86–19.07), hypertension 3.0 (95% CI = 1.21–7.45), IHD 75.7 (95% CI = 2.67–139.84), and patients with moderate gastritis 2.81 (95% CI = 1.2–6.59) were more likely to develop NAFLD (Table 2).

Discussion

In this study, the frequency of NAFLD in *H. pylori*-positive dyspeptic patients was found to be 38.3%. The presence of NAFLD is well known for exacerbating upper GI tract symptoms in obese patients due to high intra-abdominal pressure, and most of them consume a diet rich in fat.[24] In addition, NAFLD is one of the major factors causing persistent dyspeptic symptoms, even after eradication of *H. pylori* infection (confirmed by negative stool antigen testing).[25]

This study recognized some factors that are associated with patients with NAFLD. Male patients, patients with dyslipidemia T2DM, hypertension, IHD, and patients with moderate gastritis were more likely to develop non-alcoholic fatty liver compared to patients with mild gastritis.

The results of two large studies were found different from the findings of this study. The first study was conducted in Japan to analyze the relationship between *H. pylori* and NAFLD. This study used the same diagnostic modality for NAFLD. But in contrast, they diagnosed *H. pylori* based on antibody testing, which, in most cases, indicates prior exposure and cannot differentiate accurately between previous and ongoing infection. Multivariate regression analysis did not find an association between *H. pylori* infection with NAFLD in either gender (*p*-values of 0.7 in females and 0.4 in males).[26] The second study was performed in South Korea to assess the relationship between *H. pylori* and NAFLD. The diagnostic modality utilized was similar to this study that is, UBT. However, NAFLD was diagnosed based on hepatic steatosis index and NAFLD liver fat score.[27] This study did not find a significant relationship between *H. pylori* and NAFLD based on regression analysis. Another

Table 1. Comparison of patient's characteristics by non-alcoholic fatty liver.

		Non-alcoholic fatty liver		Total
		No	Yes	
Median age (IQR)		48.7 (15)	51.5 (14)	50.1 (14.5)
Gender	Female	143	47	190
		46.0%	53.4%	49.7%
	Male	168	41	209
		54.0%	46.6%	50.3%
Body mass index	23 or more	238	81	319
		76.5%	92.0%	84.3%
	up to 23	73	7	80
		23.5%	8.0%	15.8%
Dyslipidemia		29	45	74
		9.3%	51.1%	30.2%
Type 2 DM		28	46	74
		9.0%	52.3%	30.7%
Hypertension		33	32	65
		10.6%	36.4%	23.5%
Ischemic heart disease		20	32	52
		6.4%	36.4%	21.4%
Gastritis	Mild	130	49	179
		41.8%	55.7%	48.8%
	Moderate	181	39	220
		58.2%	44.3%	51.3%
Grade	Chronic inflammation	111	26	137
		35.7%	29.5%	32.6%
	Chronic active gastritis	200	62	262
		64.3%	70.5%	67.4%

IQR: interquartile range; DM: diabetes mellitus.

Table 2. Crude and adjusted odds ratio with 95% CI of risk factors of non-alcoholic fatty liver disease in *H. pylori* dyspeptic patients.

		Crude OR	95% CI	Adjusted OR	95% CI
Median age (IQR)		1.01	0.99–1.03	1.02	0.995–105
Gender	Female	1		1	
	Male	1.34	0.83–2.16	2.7	1.02–7.06*
Body mass index	23 or more	3.55	1.57–8.02	2.8	0.72–10.80
	up to 23	1		1	
Dyslipidemia		10.17	5.77–17.93	7.38	2.40–22.71*
Type 2 DM		11.07	6.25–19.58	5.96	1.86–19.07*
Hypertension		4.81	2.73–8.47	3	1.21–7.45*
Ischemic heart disease		8.31	4.43–15.57	75.7	2.67–139.85*
Gastritis	Mild	1		1	
	Moderate	1.74	1.08–2.82	2.81	1.2–6.59*
Grade	Chronic inflammation	1.32	0.79–2.21		
	Chronic active gastritis	1			

CI: confidence interval; OR: odds ratio; IQR: interquartile range; DM: diabetes mellitus.
*p-value $\leqslant 0.05$.

study failed to show any improvement in the overall fat content of the liver, liver function tests, and other metabolic parameters in NAFLD patients with dyspepsia, after successful eradication of *H. Pylori*.[28] Hence, the association of NAFLD with *H. pylori* especially in the dyspeptic population of patients is still debatable.

This was the first study from Pakistan which observed the frequency of NAFLD in *H. pylori*-infected individuals with

underlying dyspepsia. Our diagnostic criteria for *H. pylori* infection was based on the non-invasive UBT, which has high sensitivity and specificity for detecting active *H. pylori* infection. However, this study had some limitations. First, the diagnosis of NAFLD was solely based on ultrasonography which is the common modality of diagnosing NAFLD. Percutaneous liver biopsy is still considered the "Gold standard."[29] However, the invasive nature of the procedure limits its utility in current practice. Moreover, the results of liver ultrasonography are almost comparable to any other non-invasive investigation about the diagnosis of hepatic steatosis, same is true for other non-invasive parameters such as hepatic steatosis index and NAFLD liver fat score.[30] Second, we did not evaluate the role of inflammatory markers and pro-inflammatory cytokines in the development of NAFLD in *H. pylori*-infected dyspeptic individuals, as has been elucidated in a recent work.[31] Finally, the sample size was not adequate for establishing the association of different factors and NAFLD; however, multiple logistic regression analyses provided reasonable estimates.

In conclusion, although the association of NAFLD with *H. pylori* infection could not be established in our population, yet there was a strong association seen in the 30–50 years age group which is an early onset of NAFLD in *H. pylori*-infected dyspeptic patients. In addition, a BMI >23, dyslipidemia, and T2DM in the context of *H. pylori* infection had a greater predisposition to the development of NAFLD. Since *H. pylori* bring about an intense milieu of pro-inflammatory cytokines and it is supposed to be having a close interaction with gut microbiota (as shown in other studies), further prospective studies in this regard need to be carried out to fully comprehend the pathophysiology and association between these two commonly occurring conditions.

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Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Ethical approval for this study was obtained from the ethical review committee of Aga Khan University Hospital (4532-Med-ERC-16).

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Informed consent

Written informed consent was obtained from all subjects before the study.

ORCID iD

Shiyam Sunder Tikmani https://orcid.org/0000-0001-8828-8325

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