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ORIGINAL RESEARCH

Relationship Between *Helicobacter pylori* Infection and Nonalcoholic Fatty Liver Disease (NAFLD) in a Developing Country: A Cross-Sectional Study

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Background: Non-alcoholic fatty liver disease (NAFLD) is a very common disease that affects 25–30% of the population in western countries. Many studies have observed the importance of *H. pylori* infection in the development of insulin resistance, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, and liver fibrosis and cirrhosis. However, the evidence from different studies was controversial. The present study aimed to investigate the relationship between *H. pylori* infection and NAFLD in a developing country.

Patients and Methods: This cross-sectional study included all the attending outpatient clinics at four Major University hospitals and two research and clinical institutes in a developing country in the period between June and October 2019. Patients were assessed for the diagnosis of *H. pylori* infection as detected by *H. pylori* antigen in stool; they were also assessed for the diagnosis of NAFLD by ultrasound, fibroscan, and CAP.

Results: The study was conducted on 646 patients; *H. pylori* infection was found to be present in 538 patients (83.3%). NAFLD (diagnosed by both U/S and Fibroscan with CAP), ALT, AST, hepatomegaly, hypertension, fasting blood sugar were significantly higher in *H. pylori* +ve group than *H. pylori* −ve group. After performing Linear regression of independent risk factors of NAFLD to prove or to refute the role of Helicobacter; *H. pylori* positivity, total cholesterol, degree of fatty liver by ultrasound, fasting blood sugar and diastolic blood pressure were independent risk factors for NAFLD.

Conclusion: *Helicobacter pylori* infection was independent risk factors for NAFLD and correlated with increased degree of steatosis.

Keywords: *Helicobacter pylori*, steatosis, fibrosis, NAFLD, prevalence, fibroscan

Introduction

Warren and Marshall discovered *Helicobacter pylori* (*H. pylori*) in 1983 and reported it in 1984 and in 2005, and they were awarded the Noble prize for this important discovery.[1] *H. pylori* is prevalent throughout the world but is specially more endemic in developing countries.[2–4] This infection is also present more in elderly persons than adolescents.[5,6]

H. pylori infection causes many gastric diseases, such as chronic gastritis, peptic ulcer disease, gastric cancer, and gastric mucosa-associated lymphoid tissue (MALT) lymphoma.[6,7]

Many studies have observed the importance of *H. pylori* infection in the development of insulin resistance, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, and autoimmune diseases in the liver and biliary tract, liver fibrosis, and cirrhosis.[8]

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Non-alcoholic fatty liver disease (NAFLD) is a very common disease that affects 25–30% of the population in western countries.[9] Non-alcoholic steatohepatitis (NASH), liver fibrosis and cirrhosis are the consequences of NAFLD and influence the prevalence of morbidity and mortality.[9] Fatty liver is significantly more often diagnosed in *H. pylori*-positive patients.[10] A study conducted in Japan demonstrated that *H. pylori* infection was one of the independent risk factors for the development of NAFLD.[11] In another study, *H. pylori* infection may be one of the hits that contributes to the pathogenesis of NAFLD, and the eradication of *H. pylori* may be significant in the treatment of this disease.[12] The pathogenic mechanism of this phenomenon is unclear. The effect of the gut microbiota, including *H. pylori*, on liver damage, has not been explored sufficiently. Helicobacter species may cause liver injury via specific toxins.[13] Moreover, invasion of Helicobacter in the small bowel mucosa might increase gut permeability and facilitate the passage of bacterial endotoxins via the portal vein to the liver.[14]

On the other hand, Polyzos et al[15] found that there were no significant differences regarding steatosis grade, fibrosis stage, lobular or portal inflammation, or ballooning. This study claimed the role of *H. pylori* infection in the early-stage NAFLD pathogenesis, which is described as simple steatosis; However, with no further contribution of *H. pylori* to the progression of NASH. It also remains to be determined if *H. pylori* are implicated in the natural course of NAFLD, or if it is just an incidental finding.

The present study aimed to determine the relationship between *H. pylori* infection and NAFLD in patients attending the outpatient clinics at four Major University hospitals and two research and clinical institutes in the period between June and October 2019.

Patients and Methods

The study protocol was performed according to the ethical guidelines of the Helsinki Declaration and was approved by the Tanta University Faculty of Medicine clinical research and ethics committee. A written informed consent was signed by all patients participating in the study.

This cross-sectional study included all the attending outpatient clinics above 18 years at four Major University hospitals and two research and clinical institutes in a developing country in the period between June and October 2019 and who approved to be enrolled in this study. However, patients with history of Diabetes or hypertension or Dyslipidemia or previous history of steatotic drugs (eg, corticosteroids, contraceptive pills) or previous history of alcohol consumption or a previous history of viral hepatitis or with a history of gastrectomy, or history of autoimmune hepatitis or any other forms of chronic liver disease were excluded from the study. Patients with a previous history of respiratory, heart failure, or renal diseases were also excluded from the study.

All patients enrolled in the study were assessed by anthropometric and biochemical measurements. All subjects were assessed after overnight fasting for at least 12–14 hrs. Bodyweight, height, systolic, and diastolic blood pressure (SBP, DBP) were measured by an experienced physician. Body Mass Index (BMI) was calculated as body weight in kilograms divided by body height squared in meters. The guidelines of the United States National Institutes of Health (NIH) stratified the degrees of obesity as follows: BMI below 18.5 kg/m2 as underweight; BMI 18.5 to 24.9 kg/m2 as normal weight; BMI 25.0 to 29.9 kg/m2 as overweight; BMI 30.0 to 34.9kg/m2 as obesity class I; BMI 35.0 to 39.9 kg/m2 as obesity class II and BMI 40.0 kg/m2 or more as obesity class III.[15]

Blood samples were collected from the cubital vein by one experienced nurse. Fasting serum triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and serum creatinine (Scr) were measured using Chemistry autoanalyzer Cobas c 311 (Roche diagnostics, Germany). Patients were assessed for the diagnosis of *H. pylori* infection as detected by *H. pylori* antigen in stool; they were also assessed for the diagnosis of NAFLD by ultrasound, fibroscan, and CAP.

Helicobacter pylori Infection Test: The diagnosis of *H. pylori* infection was done by ELISA technique using IBL International Kit (Flughafenstrasse, Hamburg, Germany), and Tecan Spectra ELISA reader (supplied by Tecan Group Ltd., Switzerland).

Fibroscan: Liver fibrosis and steatosis can be staged using Dimensional ultrasound TE (transient elastography) (FibroScan®, Echosens, Paris, France), which measures the velocity of a low-frequency (50 Hz) elastic shear wave propagating through the liver. This velocity is directly related to tissue stiffness, called the elastic modules (expressed as E=3qv2, where v is the shear velocity and q is the density of tissue, assumed to be constant). The stiffer the tissue, the faster the shear wave propagates. Transient elastography was performed on a patient lying supine, with the right arm elevated to facilitate access to the

right liver lobe. The tip of the probe is contacted to the intercostal skin with coupling gel in the 9th to 11th intercostal space at the level where a liver biopsy would be performed. The operator, assisted by a time-motion image, located a liver portion at least 6 cm deep and free of large vascular structures. The operator then pressed the probe button to start the measurements (shots). TE measures LS in a volume that approximates a cylinder 1 cm wide and 4 cm long, between 25 mm and 65 mm below the skin surface. The software determines whether each measurement is successful or not. When a shot is unsuccessful, the machine does not return a value. The final result of a TE session can be regarded as valid if the following criteria are fulfilled: 1) a number of valid shots of a least 10; 2) a success rate (the ratio of valid shots to the total number of shots) above 60%; and 3) an interquartile range (IQR, reflecting the variability of measurements) less than 30% of the median LS measurements (M) value (IQR/M 60.30%).

The results are expressed in Kilopascals (KPa) and range from 1.5 to 75 KPa with normal values around 5 KPa, higher in men and in patients with low or high body mass index (BMI) (U-shaped distribution). Machine model is 502.

The metabolic syndrome was defined according to the definitions of the American Heart Association and the National Heart, Lung, and Blood Institute, and the International Diabetes Federation as ≥ 3 of the following: (1) waist circumference ≥ 90 cm in men and ≥ 80 cm in women, which are the modified criteria for the Asian population; (2) triglyceride concentration ≥ 150 mg/dL or use of triglyceride-lowering medication; (3) low HDL-C concentration (<40 mg/dL in men and <50 mg/dL in women); (4) systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 85 mmHg, or use of antihypertensive medication; or (5) fasting glucose level ≥ 100 mg/dL or use of antidiabetic medication or previously diagnosed type 2 diabetes.

Statistical Analysis: All statistical analyses were performed using SPSS 25. Continuous variables were presented as mean ± SD or median (interquartile range), and categorical variables were displayed as percentages (%). Non-normally distributed data were logarithmically transformed before analysis. Differences between two groups were tested by χ^2 test and Monte Carlo for categorical variables. Linear regression was also used to evaluate the association between *H. pylori* infection and NAFLD. $P < 0.05$ was considered statistically significant.

Results

The study was conducted on 646 patients, males were 327 (50.6%) and females were 319 (49.4%). The mean age, weight, height, BMI, ALT, AST, cholesterol, HDL, LDL, triglycerides, liver span, systolic BP, diastolic BP and fasting blood sugar were (36.65 ±11.15, 80.58±14.48, 159.77±32.10, 50.54±22.31, 41.59±14.74, 200.50±40.21, 46.92±6.46, 121.51 ±33.86, 161.69±60.42, 16.68±1.97, 125.82±13.46, 80.97 ±8.29, and 107.33±18.32), respectively. Demographic data of all the patients are demonstrated in Table 1.

H. pylori infection was found to be present in 538 patients (83.3%) and it was higher in females than males. NAFLD (diagnosed by both U/S and Fibroscan with CAP), ALT, AST, hepatomegaly, hypertension, fasting blood sugar were significantly higher in *H. pylori* +ve group than *H. pylori* –ve group. However, BMI was higher in *H. pylori* +ve group than *H. pylori* –ve group but did not reach the statistical significance. However, there were no significant differences between both groups regarding LDL, metabolic syndrome, and fibrosis stage. HDL level was lower in *H. Pylori* +ve group than *H. Pylori* −ve groups. The difference in sociodemographic, anthropometric, and biochemical measurements between *H. Pylori* +ve and *H. Pylori* –ve patients are demonstrated in Table 2.

After performing binary logistic regression BMI, triglycerides (TAG), liver span were negative independent risk factors for NAFLD. However, ALT, degree of fatty liver (By U/S), systolic blood pressure, HDL and LDL were positive independent risk factors for NAFLD. This is demonstrated in Table 3.

Table 1 Demographic Data Among All Patients in the Study

	Mean±SD
Age (years)	36.65±11.146
Weight (kg)	80.584±14.4816
Height (cm)	159.7690±32.10094
BMI (kg/cm)	29.213±5.0612
ALT (IU/L)	50.538±22.3057
AST (IU/L)	41.591±14.7357
Cholesterol (mg/dL)	200.50±40.211
Triglycerides (mg/dL)	161.685±60.4182
Liver span (cm)	16.680±1.9695
Systolic BP (mmHg)	125.82±13.461
Diastolic BP (mmHg)	80.97±8.285
Fasting blood sugar (mg/dL)	107.33±18.321
HDL (mg/dL)	46.92±6.457
LDL (mg/dL)	121.51±33.860

Abbreviations: BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate transaminase; BP, blood pressure; HDL, high-density lipoproteins; LDL, low-density Lipoproteins.

Table 2 Comparison Between Sociodemographic, Anthropometric and Biochemical Measurements Between *H. pylori* +ve and *H. pylori* −ve

	H. pylori +ve (538) (83.3%)	H. pylori –ve (108)(16.7%)	P-value
Sex			
• Male	242(45%)	85(78.7%)	0.000*
• Female	296(55%)	23(21.3%)	
ALT (IU/L)			
• Normal	136(25.3%)	85(78.7%)	0.000*
• Elevated	402(74.7%)	23(21.3%)	
AST (IU/L)			
• Normal	266(49.4%)	72(66.7%)	0.001*
• Elevated	272(50.6%)	36(33.3%)	
TAG (mg/dL)			
• Normal	280(52%)	46(42.6%)	0.074
• Elevated	258(48%)	62(57.4%)	
Cholesterol (mg/dL)			
• Normal	312(58%)	62(57.4%)	0.915
• Elevated	226(42%)	46(42.6%)	
Liver span (cm)			
• <15 cm	104(19.3%)	49(45.4%)	0.000*
• >15 cm	434(80.7%)	59(54.6%)	
Systolic BP (mmHg)			
• Normal	468(87%)	78(72.2%)	0.002*
• Elevated	70(13%)	30(27.8%)	
Diastolic BP (mmHg)			
• Normal	468(87%)	78(72.2%)	0.002*
• Elevated	70(13%)	30(27.8%)	
Fasting bl. Sugar(mg/dL)			
• Normal	176(32.7%)	82(75.9%)	0.004*
• Elevated	362(67.3%)	26(24.1%)	
HDL (mg/dL)			
• Normal	284(52.8%)	39(36.1%)	0.002*
• Elevated	254(47.2%)	69(63.9%)	
LDL (mg/dL)			
• Normal	346(64.3%)	69(63.9%)	1.000
• Elevated	192(35.7%)	39(36.1%)	
BMI (kg/m^2)			
• Underweight	0(0%)	0(0%)	0.050
• Normal	96(17.8%)	13(12%)	
• Overweight	184(34.2)	52(48.1%)	
• Obesity grade I	170(31.6%)	33(30.6)	
• Obesity grade II	76(14.2%)	10(9.2%)	
• Morbid obesity	12(2.2%)	0(0%)	
Degree of fatty liver (by ultrasound)			
• 0	96(17.8%)	26(24%)	0.000*
• 1	80(14.9%)	49(45.4%)	
• 2	202(37.6%)	10(9.3%)	
• 3	160(29.7%)	23(21.3%)	
Steatosis			
• S0	210(39%)	40(37%)	0.000*
• S1	64(11.9%)	39(36.1%)	
• S1-2	8(1.5%)	0(0%)	
• S2	120(22.3%)	19(17.6%)	
• S2-3	8(1.5%)	0(0%)	
• S3	128(23.8%)	10(9.3%)	
Metabolic Syndrome			
• Negative	301(56%)	67(62%)	0.203
• Positive	237(44%)	41(38%)	
Fibrosis			
• 0	446(82.9%)	93(86.1%)	0.413
• 1	77(14.3%)	14(12.9%)	
• 2	15(2.8%)	1(1%)	

Note: *Means significant difference.

Discussion

H. pylori prevalence varies among countries; generally, the prevalence is about 30% in developed and up to 80% in developing countries.[16–18] This was similar to our results, as we found that *H. pylori* prevalence was 83.3% among the participants in the study.

NAFLD was significantly higher in *H. pylori* (+ve) group than *H. pylori* (−ve) group. This is in accordance with Dogan et al[10] and Polyzos et al[15] who found that fatty liver is significantly more often diagnosed in *H. pylori*-positive patients. The prevalence of NASH was significantly higher in the *H. pylori*-positive patients (80.8%) than in the *H. pylori* negative subjects (50.7%, p = 0.008).[19] On the other hand, no association between *H. pylori* infection and NAFLD was found in two recent large clinical trials.[20,21]

In the current study, *H. Pylori* infection was more significantly higher in females. This disagrees with Fan et al[22] who found that males were more infected with *H. pylori* positive. *H. pylori* infection was associated with male gender.

Table 3 Binary Logistic Regression of Independent Risk Factors of NAFLD

	B	S.E.	Wald	df	Sig.	Exp(B)
Age	0.01	0.011	1.221	1	0.269	1.012
BMI	−0.66	0.136	23.311	1	0.000*	0.519
ALT	1.10	0.349	9.965	1	0.002*	3.010
AST	0.13	0.269	0.228	1	0.633	1.137
Cholesterol	0.32	0.258	1.575	1	0.210	1.383
TAG	−0.75	0.257	8.474	1	0.004*	0.474
Liver span	−1.49	0.430	12.057	1	0.001*	0.225
Degree of fatty liver (By U/S)	1.13	0.158	50.947	1	0.000*	3.092
Systolic BP	0.80	0.282	8.016	1	0.005*	2.224
Diastolic BP	0.40	0.236	2.805	1	0.094	1.484
Fasting blood sugar	−0.13	0.218	0.341	1	0.559	0.880
HDL	0.74	0.213	12.190	1	0.000*	2.101
LDL	2.70	0.287	88.045	1	0.000*	14.735
Metabolic syndrome	−0.23	0.214	1.117	1	0.291	0.798
Fibrosis	−0.04	0.229	0.029	1	0.865	0.962
H. pylori	0.03	0.221	0.017	1	0.897	1.029
Constant	−1.27	0.433	8.615	1	0.003*	0.281

Note: *Means significant difference.
Abbreviations: BMI, body mass index, ALT, alanine aminotransferase, AST, aspartate transaminase; BP, blood pressure; HDL, high-density lipoproteins; LDL, low-density lipoproteins; TAG, triglycerides.

ALT, AST, hepatomegaly, hypertension, and fasting blood sugar were significantly higher in *H. pylori* +ve group than *H. pylori* −ve group. However, BMI was higher in *H. pylori* +ve group than *H. pylori* −ve group but did not reach the statistical significance. There were no significant differences between both groups regarding LDL, metabolic syndrome, and fibrosis stage. HDL level was lower in *H. Pylori* +ve group than *H. Pylori* -ve groups.

Some studies had shown an association between *H. pylori* infection and obesity and a more unfavorable metabolic profile.[23] Also, Kim et al[24] reported higher blood pressure, BMI, total cholesterol, LD-C, triglycerides and HOMA-IR, and lower levels of HDL-C in *H. pylori* infected patients than those without *H. pylori* infection. Significantly higher BMI, blood pressure, TG, LDL-C and UA levels in *H. pylori* group than the control group, also found by Fan et al.[22] Consistent to these previous studies, our present study showed higher BMI, hypertension, fasting blood sugar, lower HDL higher in *H. pylori* +ve group than *H. pylori* −ve group. However, the prevalence of obesity and T2DM was similar between the subjects with and without *H. pylori* according to a recent study.[19]

Also, Akbas et al[25] reported that there were no significant differences regarding serum HDL-C, LDL-C, or TC levels between *H. pylori*-seropositive and *H. pylori*-seronegative individuals, whereas the serum TG level was higher in the *H. pylori*-positive group.

The levels of AST and ALT were significantly higher in *H. pylori* infected patients than those without infection. This agrees with that found by Sumida et al[19] who reported that there was significant difference between both groups regarding AST and ALT between those with or without *H. pylori* infection.

Ultrasonic examination, which was applied in the present study for diagnosis of NAFLD, is not sensitive enough to detect mild liver steatosis.[22] The sensitivity and specificity of ultrasound for detecting hepatic steatosis vary from 60% to 94% and 88% to 95%, respectively. However, the sensitivity of ultrasound decreases with lower degrees of fatty infiltration. In the presence of ≥30% fatty infiltration, the sensitivity of ultrasound is 80% compared with a sensitivity of 55% when hepatic fat content is 10% to 19%.[26]

Steatosis is reported to be detectable by US when more than 20% of hepatocytes contain histologically visible fat droplets, with a reported sensitivity of 79.7% and specificity of 86.2%.[27]

We found that there was no statistically significant difference between both groups as regards liver fibrosis. This is in agreement with Polyzos et al[12] who found no significant difference in fibrosis stage between both groups, with or without infection. But, this is in disagreement with Sumida et al[19] who reported that the hepatic fibrosis grades were higher in *H. pylori* seropositive patients.

On the other hand, Polyzos et al[12] reported that there was no significant difference between both groups regarding steatosis grade, which in contrary to our results, as we found that *H. pylori* positive group had more steatosis.

The present study showed that BMI, triglycerides (TAG), liver span were negative independent risk factors for NAFLD. However, ALT, degree of fatty liver (By U/S), systolic BP, HDL, and LDL were positive independent risk factors for NAFLD. This is in agreement with, Sumida et al[19] who reported that univariate analysis revealed that hypertension was significantly correlated with NASH.

In agreement to our results, a recent study showed that the risk factors for NAFLD were age, male gender, BMI, smoking, and CRP concentration.[21] However, multivariate logistic analysis showed no independent association between *H. pylori* infection and NAFLD.[22] Meta-analysis of data from longitudinal studies showed that *H. pylori* infection was also associated with increased NAFLD incidence.[28] The pooled results from 12 studies indicated

a higher risk of NAFLD in patients infected with *H. pylori*.[29] *Helicobacter pylori* infection may be an independent risk factor in NAFLD progress.[30]

The main limitations of the study are the relatively small-sized population. So, large-scale studies are needed. Also, our study relied on imaging and Fibroscan assessment for NAFLD and not on liver biopsy which is the gold standard for evaluation of fibrosis stage and necroinflammatory grade as many of patients refuse doing liver biopsy.

In conclusion, *H. pylori* was an independent risk factor for NAFLD and correlated with increased degree of steatosis.

Disclosure

The authors report no conflicts of interest in this work.

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