Helicobacter Pylori infection and non-alcoholic fatty liver disease. Is there a relationship?

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Abstract

The most prevalent infection that causes chronic gastritis, gastric ulcers, and gastric cancer is *Helicobacter pylori* infection. Recent research has implicated *H. pylori* in the pathogenesis of non-gastrointestinal diseases such as cardiovascular, autoimmune, and metabolic disorders. In addition, since *H. pylori* is believed to be implicated in insulin resistance, numerous studies have been conducted to determine the relationship between *H. pylori* infection and nonalcoholic fatty liver diseases (NAFLD), but the results have been contested. The purpose of this study is to determine the relationship between *H. Pylori* infection and nonalcoholic fatty liver diseases. One hundred patients were examined via urea breath test for the presence of *H. pylori* infection and vibration-controlled transient elastography for the diagnosis of non-alcoholic fatty liver disease. After adjusting for other variables, age, body mass index (BMI), and *H. pylori* infection were associated with elastography 248dB/m. Infection with *H. pylori* contributes to the development of NAFLD, and its eradication may influence prognosis.

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Introduction

Helicobacter pylori infection is a prevalent condition worldwide, particularly in developing countries. It is considered the most common cause of gastric mucosa causing chronic gastritis, gastric ulcers, and gastric cancer.[1] Recently, *H. Pylori* was found to be involved in the pathogenesis of other non-gastric diseases, and involved in the pathogenesis of insulin resistance and several metabolic and autoimmune diseases that affects the liver.[2]

Nonalcoholic fatty liver disease (NAFLD) is a group of metabolic diseases caused mainly by insulin resistance with hereditary susceptibility. It is considered a manifestation of metabolic syndrome in the liver, in the absence of alcohol consumption, and includes nonalcoholic fatty liver, nonalcoholic steatohepatitis, liver fibrosis, and cirrhosis.[3] NAFLD is a common disease condition affecting 25% of the population worldwide, with higher prevalence rates observed in the Middle East (32%), and in Latin America (31%).[4]

Hepatic lipid homeostasis is controlled by signaling/transcriptional pathways mediated by hormones, transcription factors, and nuclear receptors. Triglyceride accumulation mostly is considered the first step in the development of NAFLD and results from a disturbed balance between TG production and utilization and unregulated insulin signaling at the level of the adipose tissue.[5] In obese and diabetic patients with insulin resistance there is increased lipolysis with increased formation of nonesterified fatty acids directed to the liver where they are taken up by hepatocytes.[6] CD36 also facilitates their uptake and accumulation in other cell types (macrophages, adipocytes, enterocytes, and myocytes). CD36 has been shown to rise in animal models with hepatic steatosis. In humans, morbidly obese patients with NAFLD showed a correlation between messenger RNA levels of CD36 and liver fat content.[7] It has been shown that there are other two factors contributing to fat accumulation in the liver, these factors are dietary fat and de novo lipogenesis. Two enzymes catalyze hepatic

fatty acid synthesis which is acetyl-CoA carboxylase and fatty acid synthase and are controlled by insulin and by glucose through liver X receptors which directly induce acetyl-CoA carboxylase and fatty acid synthase. De novo lipogenesis is markedly increased in NAFLD mainly due to the coexistent hyperinsulinemia and increased intake of simple sugars.[6]

The mechanism claimed to be involved in the development of NAFLD is the "second hit hypothesis" which is the oxidative stress, as the "first hit" usually is the fat accumulation in hepatocytes, and the "second hit" is the oxidation that causes hepatic injury.[8] Recently, the "multiple hits" hypothesis is more reliable and accepted, as proposed by Takaki *et al.*,[9] and Buzzetti *et al.*,[10] they found that multiple factors work together on genetically predisposed subjects that lead to the development of NAFLD; these factors include insulin resistance, adipose tissue hormones, nutrition, and gut microbiota.

Khosravi *et al.*,[11] found that *H. Pylori* infection was related to gut microbiota by using germ-free and specific pathogen-free mice and found that there is a strong relation between normal gut microbiota and infection with *H. Pylori* which alters the metabolism and induce gut inflammation considering *H. Pylori* as one of the mechanisms that cause NAFLD through gut microbiota dysbiosis. This was confirmed by Sumida *et al.*,[12] as they found that invasion of *H. Pylori* into intestinal mucosa may increase gut permeability and alter gut microbiota and subsequently increase the passage of bacterial endotoxin through the portal vein to the liver and initiate inflammation and considered as one of the multiple hits causing NAFLD. In this study, we are aiming at finding the relationship between H. Pylori infection and the development of NAFLD.

Materials and Methods

Study design and population

This study was conducted on 100 patients, 50 of whom were diagnosed with *H. Pylori* infection while the other 50 were not. The patients were examined for the presence of fatty liver in the absence of alcohol consumption. They were selected from either outpatient clinics or inpatient wards of the Medical Research Institute for any medical reason during the period from June 2022 to December 2022, in Alexandria, Egypt. Participants with DM, hypertension, alcohol consumption, and chronic liver disease were excluded from the study. Informed consent was obtained from all patients in a case-control study and approved by the Medical Research Institute Ethics Committee.

Clinical data

The clinical data collected included: i) thorough clinical examination including weight and height; ii) routine laboratory investigations include liver function tests, renal function tests, lipid profiles, electrolytes, complete blood pictures, and fasting blood sugar;[13] iii) the urea breath test was done for the diagnosis of *H. pylori* infection;[14] iv) NFLD was diagnosed using vibration-controlled transient elastography, the cut-off for steatosis is >248 dB/m.[15]

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Categorical data were represented as numbers and percentages. The chi-square test was applied to investigate the association between the categorical variables. For continuous data, they were tested for normality by the Shapiro-Wilk test. Quantitative data were expressed as a range (minimum and maximum), mean, standard deviation, and median. Student *t*-test was used to compare two groups for normally distributed quantitative variables. On the other hand, the Mann-Whitney test was used to compare two groups for not normally distributed quantitative variables. And Receiver operating characteristic curve (ROC) was used to determine the diagnostic performance of the markers, an area of more than 50% gives an acceptable performance, and an area of about 100% is the best performance for the test. The significance of the obtained results was judged at the 5% level.

Results

The effect of demographic data on NAFLD was tested, and we found that fatty liver is more common in females but not statistically significant. p=0.680, while age was significantly related to fatty liver where the mean age in patients with steatosis was 52.5±12.4 years, and the mean age of patients without steatosis was 38.2±14.3 (p<0.001). BMI also was a risk factor for steatosis, where the mean BMI in Patients with NAFLD was 32±3.9 kg/m^2, and in patients without NAFLD was 28.8±4.3kg/m^2, p<0.001 (Table 1).

Various biochemical markers were evaluated for their relationship to NAFLD, including liver enzymes such as alanine aminotransferase (ALT), Aspartate aminotransferase (AST), total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglyceride level (TG). However, none of these markers showed a significant relationship with NAFLD (Table 2).

Table 1. Relation between elastography and demographic data.

	Total n = 100	Elastography		Test of Sig.	p
		≤248 dB/m	>248 dB/m		
Gender					
Male (%)	38 (38.0)	18 (36.0)	20 (40.0	χ^2= 0.170	0.680
Female (%)	62 (62.0)	32 (64.0)	30 (60.0)		
Age (years)					
Mean±SD	45.4±15.1	38.2±14.3	52.5±12.4	U=566.0*	<0.001*
Median (Min-Max)	46 (19-68)	35 (19-66)	57 (29-68)		
BMI (kg/m^2)					
Mean±SD	30.4±4.37	28.8±4.3	32±3.9	t=3.963*	<0.001*
Median (Min-Max)	30.5 (18.5-38)	29.0 (18.5-37.0)	32 (26-38)		

SD, standard deviation; χ^2, chi-square test; *t*, student *t*-test; U, Mann-Whitney test. *Statistically significant at p≤0.05.

The relation between NAFLD and *H. Pylori* infection was examined, revealing a prevalence of *H. Pylori* infection in patients with NAFLD was 68% and in patients without NAFLD 32%. Additionally, we found that the mean elastography value in *H. Pylori* +ve patients was 250.4±33.59 dB/m, while the mean in *H. Pylori*-ve patients was 229.3±33.83 dB/m, p=0.002 (Table 3).

Furthermore, *H. Pylori* was found to have a significant prognostic performance of *H. Pylori* infection with elastography values ≥248 dB/m, (95% CI 0.582-0.794, p=0.001, sensitivity 68% and specificity 68%; Table 4, Figure 1).

Assessment of various biochemical markers, demographic data, and H. Pylori infection in patients with and without NAFLD in a univariate analysis showed that age, BMI, and H. Pylori infection were associated with elastography ≥ 248 dB/m after adjustment with other variables. Multivariate analysis showed that these factors were independent risk factors for NAFLD (Table 5).

Discussion

Non-alcoholic fatty liver disease is a common metabolic health problem that has become a public health concern. The peak of fatty liver incidence is between 40-50 years of age in males and 60-69 years in females, with minimal reduction in older (>70 yrs) cohorts.[16] In a retrospective cohort study conducted on 351 patients with NAFLD diagnosed by biopsy, the patients were divided into (≥60 yrs), (≥50 to <60 yrs), and a younger (<50 yrs) group.

The study found that NAFLD was more prevalent in the middle-aged and the elderly.[17] In our study, we found that the mean age of patients with NAFLD was 52.5±12.4 years and in patients without NAFLD it was 38.2±14.3 years. Hence, confirming that the incidence increases with age and it is an independent risk factor for NAFLD. This is probably due to an increase in all risk factors for fatty liver in older age groups such as hypertension, diabetes, hyperlipidemia, and obesity.

According to previous longitudinal studies, NAFLD is more common in males as compared to females.[18] However, a study specifically investigating NAFLD in females found that the incidence is higher in menopausal females (7.5%) and postmenopausal females (6.1%) than in premenopausal females (3.5%). The study also reported that postmenopausal women had an increased risk of NAFLD at univariate but not at multivariate analysis after adjustment for age, metabolic syndrome, and BMI.[19] In our study, we found that the incidence of NAFLD is more common in females but was not statistically significant, this may be due to the increased age of patients with NAFLD in our study, and the fact that most of the females studied were postmenopausal. Female sex hormones are known to protect against dysmetabolism and promote the division of fatty acids into ketone bodies rather than into very low-density lipoprotein-triacylglycerol. The senescence of the

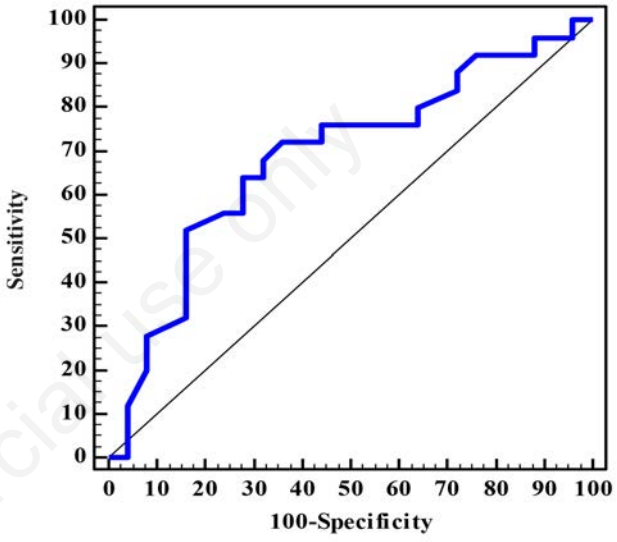

Figure 1. ROC curve for Elastography to prognoses positive *H. Pylori* patients.

Table 2. Relation between elastography and different parameters.

	Total n=100	Elastography ≤248 dB/m	Elastography >248 dB/m	Test of Sig.	p
ALT					
Mean±SD	28.7±23.1	24.2±12.8	33.3±29.6	U=1014.0	0.103
Median (Min-Max)	23 (10-153)	20 (11-72)	23 (10-153)		
AST					
Mean±SD	25.6±16.5	22.9±8.49	28.3±21.5	U=1046.0	0.159
Median (Min-Max)	22 (11-125)	22 (13-49)	26 (11-125)		
Total cholesterol					
Mean±SD.	183.7±30	181.6±26.0	185.8±33.6	t 0.692	0.490
Median (Min.-Max.)	181 (105-254)	180 (137-245)	182 (105-254)		
LDL					
Mean±SD	100.7±22.5	98.5±22	102.9±23.1	t=0.985	0.327
Median (Min-Max)	95 (59-157)	93 (68-155)	100 (59-157)		
HDL					
Mean±SD	49.96±8.80	50.5±8.84	49.4±8.83	t=0.589	0.557
Median (Min-Max)	49 (29-74)	53 (29-67)	46 (38-74)		
Triglyceride					
Mean±SD	114.8±46.49	112.4±44.52	117.2±48.72	U=1250.0	1.000
Median (Min-Max)	96.5 (51-246)	98 (51-246)	94 (60-225)		
H. pylori (%)	50	16	34	χ^2=12.96*	<0.001*

SD, standard deviation; *t,* student *t*-test; U, Mann-Whitney test; χ^2, chi-square test. *Statistically significant at p≤0.05

ovaries also increases the formation of hepatic steatosis and progression to fibrosis.[20]

Obesity has been linked to fatty liver disease in all stages, starting from simple steatosis to steatohepatitis and fibrosis. Obesity causes the accumulation of fat inside liver cells through increasing insulin resistance and leads to progression to non-alcoholic steatohepatitis and its related cirrhosis.[21] In a cross-sectional study conducted on 3202 individuals to investigate the association of BMI with fatty liver found that a dose-response analysis with adjustment of other factors like age, gender, hypertension, total cholesterol, triglycerides, glucose, high-density lipoprotein, low-density lipoprotein, uric acid, homocysteine, creatinine, aspartate aminotransferase, and alanine transaminase showed that overweight and obesity were significantly related to fatty liver risk (p=0.004 or lower). They reported that high BMI (overweight/obesity) is an independent, dose-dependent risk factor for fatty liver.[22] In a study conducted on the Sudanese population to assess the risk factors for non-alcoholic fatty liver disease, they found that increasing age and obesity were the most prominent predisposing factors in developing NAFLD[23] In our study, we found that the mean BMI in patients with NAFLD was 32±3.9 kg/m^2, and in patients without NFLD it was 28.8±4.3 kg/m^2, and increased BMI was highly significantly related to fatty liver p<0.001 and was an independent risk factor for NAFLD p≤0.009

NAFLD occurs when there is an imbalance between the rate of uptake of fatty acids and triglycerides from circulation, increased lipogenesis, and a decreased ability to oxidize fatty acids and export very low-density lipoprotein-TG. Therefore, changes in liver and serum lipid parameters can be a predictor of disease development.[24]

Kantartzis *et al*.[25] in their study on 16 patients with fatty liver and 24 control subjects found that fatty liver was associated with decreased levels of high-density lipoprotein 2 (HDL_2) which is potent antiatherogenic. Moreover, in patients with NAFLD, abnormal serum ALT and AST are usually present when the disease progress to steatohepatitis or hepatic fibrosis.[26] However, in a study done by Ma *et al*.[27] they found the prevalence of normal ALT in patients with NAFLD reached over 90%. In our study, we found that in patients with NAFLD, total cholesterol, LDL, and TG, as well as ALT and AST were higher than in patients without NAFLD. However, none of these were statistically significant. This may be attributed to the low number of patients with dyslipidemia involved in the study and the early stage of NAFLD in those patients.

Several studies have been conducted to demonstrate the relationship between *H. pylori* infection and NAFLD. This is because the main pathogenic mechanism in NAFLD is insulin resistance which makes hepatocytes more susceptible to oxidative stress and lipid peroxidation. At the same time, *H. Pylori* was implicated in the development of insulin resistance through increasing pro-inflammatory cytokines and reactive oxygen species production. Numerous studies aimed to find out whether there is a relationship between them or not.[28] In a study done by Polyzos *et al*.[29] on 28 patients with biopsy-proven NAFLD and 25 healthy controls, they

Table 3. Relation between *H. pylori* and elastography.

	Total n=100	*H. pylori*		Test of Sig.	p
		Negative (n=50)	Positive (n=50)		
Mean±SD	239.8±35.18	229.3±33.83	250.4±33.59	3.133*	0.002*
Median (Min-Max)	248.5 (150-296)	230 (150-296)	259 (170-294)		

SD, standard deviation; *t*, student *t*-test; U. *Statistically significant at p≤0.05.

Table 4. Prognostic performance for Elastography to prognoses positive *H. Pylori* patients (n = 50) from negative *H. Pylori* patients (n = 50).

	AUC	p	95% C.I	Cut off	Sensitivity	Specificity	PPV	NPV
Elastography	0.688	0.001*	0.582-0.794	>248	68.0	68.0	68.0	68.0

AUC, area under a curve; CI, confidence intervals; NPV, negative predictive value; PPV, positive predictive value. *Statistically significant at p≤0.05.

Table 5. Univariate and multivariate Logistic regression analysis for the parameters affecting Elastography >248dB/m.

	Univariate		Multivariate	
	p	OR (LL–UL 95%C.I)	p	OR (LL–UL 95%C.I)
Male	0.680	1.185 (0.528-2.660)		
Age (years)	<0.001*	1.075 (1.041-1.110)	<0.001*	1.082 (1.039-1.127)
BMI (kg/m^2)	0.001*	1.227 (1.091-1.380)	0.009*	1.225 (1.052-1.427)
ALT	0.077	1.023 (0.998-1.049)		
AST	0.151	1.028 (0.990-1.067)		
Total cholesterol	0.487	1.005 (0.991-1.018)		
LDL	0.324	1.009 (0.991-1.027)		
HDL	0.553	0.986 (0.943-1.032)		
Triglyceride	0.607	1.002 (0.994-1.011)		
H. pylori	<0.001*	4.516 (1.949-10.463)	0.001*	5.632 (1.967-16.130)

OR, odd's ratio; CI, confidence interval; LL, lower limit; UL, upper limit. *Statistically significant at p≤0.05.

found that H. Pylori diagnosed by serology were found in 82% of NAFLD patients and 56% of healthy controls. Meta-analysis of data from cross-sectional and case-control studies involving 91,958 individuals concluded that *H. Pylori* infection was also associated with increased NAFLD incidence.[30] In addition, another study found a remarkable effect of *H. Pylori* infection on NAFLD after ruling out many confounding factors like age, dyslipidemia, diabetes, hypertension, and liver enzymes, *H. Pylori* infection was found to be an independent risk factor for NAFLD (95% CI 1.02-1.79, OR 1.35, p=0.036).[31] Yan *et al*.[32] conducted a wide-scale study on 1185 patients. Abdominal color Doppler ultrasound was used to assess nonalcoholic fatty liver disease and[13] C-urea breath test was used to diagnose *H. Pylori* infection, NAFLD was found in 44.6% (n=529), distributed in 362 males and 167 females. The study concluded that *H. pylori* is a significant and independent risk factor for NAFLD (95% CI 1.02-1.79, p=0.036, OR=1.35). On the other hand, a similar study was conducted using abdominal color Doppler ultrasonography as well as transient elastography, fat attenuation parameter, and liver stiffness for diagnosis of NAFLD,[13] C-urea breath was the method for diagnosis of *H. pylori* infection. The study found no association between *H. pylori* infection and NAFLD or elevated liver steatosis, but it could be a risk of increased liver stiffness in males.[33]

Other studies intended to demonstrate the effect of H. Pylori eradication on hepatic fat contents. One of these studies performed by Jamali *et al*.[34] on 100 patients diagnosed H. Pylori positive and given slandered treatment and re-tested again to confirm eradication, found no effect of eradication on hepatic fat content checked by NAFLD liver fat score.

In our study, *H. Pylori* infection was significantly associated with NAFLD, where it existed in 68% of patients with elastography > 248 dB/m (95% CI 0.582-0.794, p=0.001, sensitivity 68% and specificity 68%). Univariate analysis showed that age, BMI, and *H. Pylori* infection were associated with NAFLD after adjustment with ALT, AST, total cholesterol, LDL, HDL, and TG,

Multivariate analysis showed that they were still independent risk factors for NAFLD.

Conclusions

Increasing age, weight, and *H. Pylori* infection are independent risk factors for the development of NAFLD. Therefore, weight reduction and treatment of *H. Pylori* infection may help to reduce the incidence of fatty liver.

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