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Helicobacter Pylori and Non-Alcoholic Fatty Liver Disease: Is There a Relationship?

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Abstract

Background and Aim: researchers proposed a connection between *H pylori* and obesity, diabetes, and improper lipid metabolism. The studies have discovered that H pylori infection is one of the elements for Non-Alcoholic Fatty liver Disease (NAFLD) to progress and that getting rid of *Helicobacter pylori* (*H pylori*) can partially stop the evolution of NAFLD. Other research, however, argues that there is no definitive link between H pylori infection and NAFLD. We aimed to investigate the prevalence of *H pylori* infection in NAFLD.

Materials and Methods: This study was conducted on 110 patients diagnosed with NAFLD by ultrasound and fibroscan. They were assessed for the diagnosis of *H. pylori* infection by *H. pylori* antigen in stool.

Results: The patients were classified into *H pylori* +ve group and *H pylori* -ve group. There was a significant difference between both groups regarding sex (p = 0.01) and diabetes mellitus (p = 0.000) and no significant difference between both groups as regard smoking, hypertension, and BMI**.** There was significant difference between both groups regarding steatosis (p = 0.0001) and fibrosis grade (p = 0.0001)

Conclusion: the prevalence of *H. Pylori* has increased in NAFLD; also**,** *H. pylori* may be an independent risk factor for NAFLD.

Keywords: *H.pylori*, PPI, BMI, HDL, LDL.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is distinguished by liver injury due to metabolic stress, identified by diffuse hepatocyte macrovascular fatty lesions **[1].**

The prevalence of NAFLD is rising yearly, with a worldwide incidence rate between 20% and 30% **[2].** Complex hereditary variables, improper lipid metabolism, and insulin resistance are the key characteristics of the etiology of NAFLD **[3].**

The research has revealed that aberrant lipid metabolism in the liver can result in dysbacteriosis in the intestinal flora; abnormality of the flora eventually encourages lipid deposition in the liver. Additionally, there is mounting proof that NALFD is linked to abnormalities in the gut flora, particularly Helicobacter pylori (H, pylori) **[4].**

Gram-negative bacillus, termed *H pylori*, has colonized the deep layers of the gastric mucosa. **[5].** The global infection rate for H pylori is about 50% or higher **[6].**

According to research, H pylori causes gastric cancer, gastrointestinal lymphoma, peptic ulcers, and chronic gastritis **[7].** Additionally, some researchers indicate a connection between H pylori and liver cancers, diabetes, and improper lipid metabolism [8].

Some studies have discovered that infection by *H pylori* is one of the elements for NAFLD to progress and that getting rid of *H pylori* can partially stop the evolution of NAFLD **[9]**.

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Another research, however, argues that there is no definitive link between *H pylori* infection and NAFLD and that treating the infection does not stop the disease's progression **[10].**

As a result, this study further investigated the precise connection between NAFLD and H pylori infection.

Patients and Methods

The study included 110 patients over or equal to 18 who attended Tanta tropical medicine outpatient clinic between October 2021, and the cases were collected. They had evidence of NAFLD in the US and fibroscan, however patients aged < 18 years, pregnant women unwilling to participate in our study, and patients with a history of dyslipidemia or previous history of drugs (e.g., corticosteroids, PPI, antibiotics, contraceptive pills) or prior history of alcohol consumption(more than 40g of alcohol (or four units) per day)or a previous history of viral hepatitis or with a history of gastrectomy, or history of auto-immune 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. Are excluded from this study.

These patients were categorized into two groups, *H pylori* +ve and *H pylori* -ve, according to the *H pylori* antigen test in the stool.

All the patients were subjected to:

- Full history taking
- Anthropometric measures: weight, length, BMI,
- There are many diagnostic tests of *H. pylori* as (*H. pylori* antigen in the stool after stoppage of PPI and antibiotics two weeks before the test, urea breath test, serology, biopsy urease testing, histopathology, bacterial culture, and sensitivity testing). Our study uses *H. pylori* antigen in the stool as it is cheap and easy.
- Lipid profile (triglycerides, HDL, LDH, cholesterol level).
- Fasting Blood glucose level and or HbA1C.
- PCR for HCV to exclude viral hepatitis.
- Liver enzymes.

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- The diagnosis of NAFLD requires (1) evidence of hepatic steatosis (HS) by imaging or histology, (2) no significant alcohol consumption, (3) no competing causes of HS, and (4) no coexisting causes of chronic liver disease [11].

Fibroscan was used to assess the stages of fibrosis and steatosis using Dimensional ultrasound TE (transient elastography). Liver fibrosis and steatosis can be staged using Dimensional ultrasound TE (transient elastography) (Fibroscan), 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 tissue density, assumed to be constant). The stiffer the tissue, the faster the shear wave propagates.

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

The CAP score (Controlled attenuation parameter)
is measured in decibels per meter (dB/m) and ranges from 100-400

Grade of Steatosis	CAP (db/m)
S0	<237.7
S1	237.7-259.4
S2	259.4-292.3
S3 (severe steatosis)	>292.3

The stiffness of the liver is measured by the fibrosis score, which indicates scarring.

- A fibrosis score of F0 to F1 (2 to 7 kPa) means the liver has little or no scarring.
- A fibrosis score of F2 (7.5 to 10 kPa) indicates moderate scarring that has spread outside the liver.
- A fibrosis score of F3 (10 to 14 kPa) indicates severe scarring, which has spread and disrupts normal blood flow.
- A fibrosis score of F4 (14 kPa or higher) means late-stage scarring or cirrhosis, where the scarring is permanent and the damage is irreversible

- Ultrasound on abdomen and pelvis for evaluation of liver condition.

All patients signed written informed consent. The Ethical Committee of the Faculty of Medicine at Tanta University approved the study with approval code **35012/11/21**.

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Statistical analysis:

The organization, tabulation, presentation, and data analysis were performed using SPSS IBM Chicago, version 23. Qualitative data were divided into categories and presented as frequency number and percentage, with the chi-square test used to determine the relationship between groups. Quantitative data were presented as mean ± SD, and the relationship between groups was done using an independent student t-test. The level of significance adopted was $p < 0.05$.

Results

The study population comprised 110 subjects, including 41(37.3%) men and 69 (62.7%) women. There were 74 (67.3%) patients with diabetes mellitus and 70 (63.3%) patients were hypertension, Table [1].

Table 1. shows the general characteristics of the studied patients.

Character	No. (%)
Age in years	44.4±9.9
Gender	
Male	41 (37.3%)
Female	69 (62.7%)
Diabetes mellitus	
Yes	74(67.3%)
No	36(32.7%)
Hypertension	70 (63.3%)
Smoking	
Yes	16(14.5%).
No	93(84.5%).
Stop smoking	1(0.9)

Test: Mean ±SD

Patients were classified into *H pylori* +ve group and *H pylori* -ve group. Both groups had a significant difference regarding sex, diabetes mellitus, and weight but no significant differences regarding hypertension, height, waist circumference, and BMI (Table 2).

Table [2] Sociodemographic and anthropometric measurements in *H. pylori* -ve and *H. pylori* +ve

Table 2. Sociodemographic and anthropometric measurements in H. pylori -ve and H. pylori +ve

	***H pylori* -ve N=47**	***H pylori* +ve N=63**	**P value**
Sex:			

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Male	24(51.1%)	17(27%)	0.01*
female	23(48.9%)	46(73%)	
DM:			
Yes	41(87.2%)	33(52.4%)	0.000*
No	6(12.8%)	30(47.6%)	
Hypertension:			
Yes	32(68.1%)	38(60.3%)	0.4
No	15(31.9%)	25(39.7%)	
Weight	97.7±11.4	108.6±13.3	0.0001*
Height	166.2±8.9	163.3±6.7	0.06
Waist circumference	102.4±11.5	104.5±9.5	0.3
BMI	35.5±5	36.1±3.9	0.4

H. Pylori: *helicobacter pylori* ***DM:*** *diabetes mellitus,* ***BMI:*** *body mass index,* ******* *significant difference,* ***Tests used****: Chi-square, T-test.*

There were variations between both groups regarding triglyceride, LDL, and HDL but not statistically significant. Both groups had a substantial difference regarding cholesterol, ALT, AST, FBS, and HA1C (Table 3).

Table 3. Comparison between biochemical measurements between H. pylori -ve and H. pylori +ve

	H. pylori-ve	***H. pylori +ve***	**P Value**
TG (Mean ± SD)	188.1±35.2	202.9±44.2	0.06
HDL (Mean ± SD)	41.2±7.7	40.7±5.5	0.7
LDL (Mean ± SD)	123.8±20	126.8±24.6	0.5
Cholesterol (Mean ± SD)	205.6±14.6	232.9±30.6	0.0001*
FBS (Mean ± SD)	120.6±8.2	124.8±10.5	0.02*
HBA1C (Mean ± SD)	6.0±1.0	6.4±1.1	0.03*
ALT Median (Min.-Max)	33.02(12-60)	39.4(6-125)	0.03*
AST Median (Min.-Max)	34.7(17-70)	41.8(13-95)	0.004*

TG*: triglyceride,* ***HDL:*** *high-density lipoprotein,* ***LDL:*** *low-density lipoprotein,* ***FBS:*** *fasting blood sugar,*

HBA1C: *haemoglobin A1c,* ***ALT****: alanine transaminases,* ***AST:*** *alanine transaminases.*

Means significant difference,* ***SD**: standard deviation,* ***Min:*** *minimum,* ***Max:*** *maximum,* ***Test used****: T-test*

There was a significant difference between the two groups regarding steatosis and fibrosis grade, which are determined by fibroscan (Table 4).

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Table 4. Steatosis grade, Fibrosis grade between H. pylori -ve group and H. pylori +ve group.

	H. pylori-ve	***H. pylori +ve***	**P Value**
Steatosis grade			
1	42(89.4%)	10(15.9%)	0.0001*
2	5(10.6%)	28(44.4%)	
3	0(0%)	22(34.9%)	
4	0(0%)	3(4.8%)	
Fibrosis grade			
0	9(19.1%)	1(1.6%)	0.0001*
1	29(61.7%)	23(36.5%)	
2	9(19.1%)	29(46%)	
3	0(0%)	7(11.1%)	
4	0(0%)	3(4.8%)	

**chi-square test.*

Discussion

The prevalence of H. Pylori changed among countries generally. The prevalence is about 30% in developed countries and about 80% in developing countries **[12].**

Some studies discussed the relationship between H. pylori infection and NAFLD. A meta-analysis showed a significant increase in the risk of NAFLD in the patients infected with *H. pylori* **[13].** However, different results were presented **[14].**

In our study, the prevalence of NAFLD was significantly higher in the *H. pylori* (+ve) group than in the *H. pylori* (−ve) group. This agrees with **Dogan Z et al. 2013 and Polyzos S et al.**, **2011** who discovered that fatty liver is more significantly diagnosed in *H. pylori*-positive patients **[15],[16].**

Sumida Y et al., 2015, found that NASH prevalence was significantly increased in the *H. pylori*-positive patients (80.8%) than in the *H. pylori*-negative subjects (50.7%, p = 0.008) **[17].**

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On the other hand, no relation between *H. pylori* infection and NAFLD was found in two clinical trials **[18], [19].**

In our study, *H. Pylori* infection in females was significantly higher than in males. On the other hand, **Fan N. et al. 2018** found that males were more infected with *H. pylori* than females **[10].**

But our result agreed with **Esam-Eldin Y et al., 2020** who found that *H. Pylori* infection was significantly higher in females **[20]**

There was a significant increase in ALT and AST in the *H. pylori* +ve group than in the *H. pylori* −ve group. Sumida Y et al., 2015) also found a significant difference between both groups regarding AST and ALT **[17].**

Regarding BMI, there were no significant differences between both groups, but some studies discovered an association between *H. pylori* infection and BMI and a more unfavorable metabolic profile **[21].**

There were no significant differences between both groups as regard triglyceride, LDL, and HDL; this agrees with **Akbas et al. 2010** who found that there were no significant differences as regard serum levels of HDL-C, LDL-C, or TC between *H. pylori*-seropositive and *H. pylori*-seronegative individuals **[22].**

Kim., et al. 2017 found higher blood pressure, BMI, total cholesterol, LD-C, triglycerides, and HOMA-IR, and lower levels of HDL-C in *H. pylori*-infected patients than in people without *H.pylori* infection **[23].**

A significant increase in BMI, blood pressure, TG, LDL-C, and UA levels in the *H. pylori* group than the control group was also reported by **Fan N et al**., **2018 [10].**

Ultrasonography examination of the liver is not sensitive enough to detect mild liver steatosis in diagnosing NAFLD **[10].**

In lower degrees of fatty infiltration, the sensitivity of ultrasound decreases, the sensitivity of ultrasound is 80% in the presence of ≥30% fatty infiltration, compared with a sensitivity of 55% when the fat content in the liver is 10% to 19% **[24].**

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In our study, there was a significant difference between both groups regarding the ultrasonography examination of the liver; the more echogenic liver was present in *H. pylori*-positive patients than in *H. pylori*-negative patients.

Steatosis is detected in ultrasonography when more than 20% of hepatocytes contain histologically visible fat droplets **[25].**

There was a statistically significant difference between both groups as regard liver fibrosis in this study, and this is the same results of **Sumida Y et al., 2015** who found that the hepatic fibrosis grades were higher in *H. pylori* seropositive patients [**17**]

On the other hand, Polyzos **S et al**., **2013** found no significant difference in fibrosis stages in both groups, with and without infection [**26].**

Polyzos S et al., 2013 found no significant difference between both groups regarding steatosis grades, which is different from our results, as we reported that patients with *H. Pylori* infection had more steatosis [**26**].

The small number of patients limited this study, so we need large-scale research. Also, our analysis depends on imaging and Fibroscan assessment to diagnose NAFLD and not on liver biopsy, which is the gold standard for evaluating the stages of fibrosis and necroinflammatory grades.

In conclusion, the prevalence of *H. Pylori* has increased in NAFLD. Also**,** H. pylori may be an independent risk factor for NAFLD.

Footnotes.

Peer-Reviewers: Ahmed Agrodey (assistant professor of internal medicine), Samah Soliman (assistant professor of tropical medicine), Bassam Mansour (lecturer of tropical medicine), and Amany Mohamed Abdallah (lecturer of community medicine).

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Data availability

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All the data obtained and analyzed are included in this manuscript.

Conflicts of interest

The authors declare that they have no competing interests.

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Authors' contributions

Eslam Ahmed Habba and Fatma Ali Elgebaly conceived and supervised the work. Ahmed Abdel-Hafiz, Doaa Elwy, and Shimaa Moustafa Mansour planned and conducted the experiments. All authors analyzed the data. All authors wrote the manuscript. All authors read and approved the final manuscript.

References

[1] Jian-Gao F. Guidelines for management of nonalcoholic fatty liver disease: an updated and revised edition. Zhonghua Gan Zang Bing Za Zhi 2010; 18:163–6.

[2] Younossi Z, Tacke F, Arrese M, Sharma B, Mostafa I, Bugianesi E, et al. Global perspectives on non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. Hepatology 2019; 69:2672–82.

[3] Buzzetti E, Pinzani M, Tsochatzis EA. The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). Metabolism 2016; 65:1038–48.

[4] Cheng DD, He C, Ai HH, Huang Y, and Lu N. The possible role of helicobacter pylori infection in non-alcoholic fatty liver disease. Front Microbiol 2017; 8:743.

[5] Dunn BE, Cohen H, Blaser MJ. Helicobacter pylori. Clin Microbiol Rev 1997; 10:720–41.

[6] Mentis A, Lehours P, Megraud F. Epidemiology and diagnosis of helicobacter pylori infection. Helicobacter 2015; 20(Suppl 1):1–7.

[7] Jonaitis L, Pellicano R. Helicobacter pylori and nonmalignant upper gastrointestinal diseases. Helicobacter 2018; 23(Suppl 1): e12522.

[8] Gravina AG, Zagari RM, De Musis C, Romano L, Loguercio C and Romano M. Helicobacter pylori and extragastric diseases: a review. World J Gastroenterol 2018; 24:3204–21.

[9] Sumida Y, Kanemasa K, Imai S, Mori K, Tanaka S, Shimokobe H, et al. Helicobacter pylori infection might have a potential role in hepatocyte ballooning in nonalcoholic fatty liver disease. J Gastroenterol 2015; 50:996–1004.

[10] Fan N, Peng L, Xia Z, Zhang L, Wang Y, and Peng Y. Helicobacter pylori infection is not associated with non-alcoholic fatty liver disease: a cross-sectional study in China. Front Microbiol. 2018; 1(9):73.

[11] Chalasani N, Younossi Z, Lavine JE, Diehl AM, **Brunt EM**, **Cusi K**, et al**.** The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. *Hepatology* 2018; 67: 328- 357

[12] Salama RI, Emara MH, Mostafa HM, Abd-Elsalam S, Alnabawy SM, Elshweikh S, et al. Helicobacter pylori infection and risk of salmonella infection. Medicine (Baltimore). 2019; 98(6): e14335.

[13] Wijarnpreecha K, Thongprayoon C, Panjawatanan P, Wuttiporn Manatsathit W, Jaruvongvanich Vand Ungprasert P. Helicobacter pylori and Risk of Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-analysis. J Clin Gastroenterol. (2018) 52:386–91.

[14] Zhou B, Yang H, Xu W, Wang K, Guo P and Ai Y. Association between Helicobacter pylori infection and nonalcoholic fatty liver disease: A systematic review and meta-analysis of observational studies. Helicobacter. (2019) 24: e12576.

[15] Doğan Z, Filik L, Ergül B, Sarikaya M, and Akbal E. Association between Helicobacter pylori and liver-to-spleen ratio: a randomized-controlled single masked study. Eur J Gastroenterol Hepatol. 2013; 25:107–110.

[16] Polyzos S, Kountouras J, Zavos C, and Deretzi G. The association between Helicobacter pylori infection and insulin resistance: a systemic review. Helicobacter. 2011;16(2):79–88.

[17] Sumida Y, Kanemasa K, Imai S, Mori K, Tanaka S, Shimokobe H, et al. Helicobacter pylori infection might have a potential role in hepatocyte ballooning in nonalcoholic fatty liver disease. J Gastroenterol. 2015; 50:996–1004.

[18] Okushin K, Takahashi Y, Yamamichi N, Shimamoto T, Enooku K, Fujinaga H, et al. Helicobacter pylori infection is not associated with fatty liver disease, including nonalcoholic fatty liver disease: a large-scale cross-sectional study in Japan. BMC Gastroenterol. 2015; 15(1):25.

[19] Baeg M, Yoon S, Ko S, Noh Y, Lee I, and Choi M. Helicobacter pylori infection is not associated with nonalcoholic fatty liver disease. World J Gastroenterol. 2

[20] Esam-Eldin Y, Sabal A, Ahmed R, Hasan N, Refaie R, Mostafa S., et al. Relationship Between Helicobacter Pylori Infection and Nonalcoholic Fatty Liver Disease (NAFLD) in a Developing Country: A Cross-Sectional Study Diabetes Metab Syndr Obes. 2020; 13: 619–625.

[21] Xu C, Yan M, Sun Y, Joo J, Wan X, Yu C, et al. Prevalence of Helicobacter pylori infection and its relation with body mass index in a Chinese population. Helicobacter. 2014; 19:437–442.

[22] Akbas H, Basyigit S, Suleymanlar I, Kemaloglu D, Koc S, Davran F ,et al. The assessment of carotid intima media thickness and serum paraoxonase-1 activity in Helicobacter pylori positive subjects. Lipids Health Dis. 2010; 9:92.

[23] Kim T, Sinn D, Min Y, Son H, Kim J, Chang Y, et al. A cohort study on Helicobacter pylori infection associated with nonalcoholic fatty liver disease. J Gastroenterol. 2017; 52:1201–1210.

[24] Ryan CK, Johnson LA, Germin BI, and Marcos A. One hundred consecutive hepatic biopsies in the workup of living donors for right lobe liver transplantation. Liver Transpl. 2002; 8:1114–1122

[25] Shannon A, Alkhouri N, Carter-Kent C, Monti L, Devito R, Lopez R, et al. Ultrasonographic quantitative estimation of hepatic steatosis in children with NAFLD. J Pediatr Gastroenterol Nutr. 2011; 53:190–195.

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[26] Polyzos SA, Kountouras J, Papatheodorou A, Patsiaoura K, Katsiki E, Zafeiriadou E, et al. Helicobacter pylori infection in patients with nonalcoholic fatty liver disease. Metabolism. 2013; 62:121–126.