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Association between Helicobacter Pylori Infection and Risk of Non-Alcoholic Fatty Liver Disease

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ABSTRACT

Background: About 25% of the general population suffers from the epidemic liver condition known as nonalcoholic fatty liver disease (NAFLD). Clinical phenotyping ranges widely including liver cirrhosis, advanced fibrosis, non-alcoholic steatohepatitis (NASH), and hepatic steatosis.

Objective: We aimed to find out the link between H. Pylori infection and the risk of NAFLD.

Patients and methods: This cross-sectional study was conducted on 80 patients presented with H-Pylori in Ain Shams University Hospitals during the period from September 2020 to June 2021. Patients were divided into 2 groups: Risky group according to one or more of the following (dyslipidemia, BMI>24.9, SBP>140, DBP>90) and non-risky group with no metabolic risk factors.

Results: Our findings demonstrated a statistically significant link between H. pylori and the development of NAFLD. We also discovered that gender has no effect on the prevalence of NAFLD. Furthermore, we discovered that NAFLD is related with higher TG levels. High SBP and DBP were shown to be related with an elevated risk of NAFLD in our research. In our investigation, the levels of AST and ALT were considerably higher in the risky group patients than in the non-risky group patients. In terms of the degree of fibrosis in patients with NAFLD, we discovered that riskier patients had a higher risk of fibrosis.

Conclusion: Our findings showed that H. pylori infection may play a role in the development of NAFLD. Taking into account the limitations of the case control research and the limited size of the population covered. Other metabolic risk variables such as dyslipidemia and obesity may have a substantial role in the development and progression of NAFLD.

Key words: H. pylori infection, NAFLD, NASH.

INTRODUCTION

NAFLD is a liver disease pandemic that affects around 25% of people in general. Clinical phenotyping ranges widely, encompassing liver cirrhosis, advanced fibrosis, NASH, and hepatic steatosis. NAFLD is often associated with obesity and is a risk factor for several metabolic illnesses, including type 2 diabetes (T2D). NAFLD affects up to 90% of people with Type 2 DM. It has also been connected to a number of extrahepatic conditions, including chronic renal disease and cardiovascular problems. The pathophysiology of NAFLD is intricate and little understood. It involves inflammation of adipose tissue, insulin resistance, and gut microbiota, which, in addition to other environmental, dietary, and genetic variables, is a key component in the development of NAFLD. The gold standard for diagnosing NAFLD is a liver biopsy. Its invasive nature and associated morbidity concerns, such as bleeding and infection, restrict its usage, albeit [(1)].

The spiral-shaped, gram-negative bacteria Helicobacter pylori, or H. pylori, is a coloniser of the stomach epithelium. Over half of the world's population is impacted by it. According to recent research, H. pylori infection may be linked to increased intestinal permeability and insulin resistance, both of which may hasten the onset of NAFLD [(1-3)].

This study was designed to find out the link between H. Pylori infection and the risk of NAFLD.

PATIENTS AND METHODS

This cross sectional-study was conducted on 80 patients presented with H-Pylori in Ain Shams University Hospitals during the period from September 2020 to June 2021.

The patients included in our study were divided into two groups as follows: Risky Group: According to one or more of (Dyslipidemia, BMI > 24.9, SBP > 140, DBP> 90) included 40 patients. **Non-Risky group:** (40 patients in number) who had no metabolic risk factors.

Inclusion Criteria: Adult patients (18–60 years old, both genders) who agreed to participate in our study and provided informed consent, patients who were diagnosed with a positive H pylori infection through either an invasive endoscopic gastric biopsy or a non-invasive stool Ag test, and patients whose ultrasound criteria showed the presence of NAFLD. Hepatic echoes that are bright, increased hepato-renal echogenicity, and vascular blurring of the portal or hepatic vein. NAFLD is defined as two out of three.

Exclusion Criteria:

Patients who consumed alcohol, had a history of gastrectomy, diabetics, infections with HBV and HCV, cirrhotic or other chronic liver illnesses, younger than 18 or older than 60, patients on antihypertensive, on anti-cholesterol, or on corticosteroid medications.

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Methods:

Pre-enrollment assessment and work up: All patients presented with H-Pylori infection were subjected to the following: Full history taking including history of diabetes mellitus, viral infection, medication history, drinking alcohol or history of surgical operation (gastrectomy) and full clinical examination (general and local abdominal examination), weight, height and BMI calculation.

Initial laboratory assessment including: Liver profile: ALT, AST, s. albumin, s. T. bilirubin, CBC, HCV antibodies and HBsAg by ELISA, FBS or HbA1c and lipid profile (s. cholesterol, TG, HDL and LDL).

Abdominal ultrasonography (abdominal US):

This method was employed in our study to report the existence of fatty or bright liver since it is thought to be a low-cost, non-invasive process that can be carried out with ease and has a good sensitivity and specificity for identifying hepatic steatosis. At Ain Shams University Hospital, it was carried out by a lone, skilled radiologist using a Toshiba I-style machine. Regarding the clinical and analytical data of the patient, the examiner was blind. The procedure was carried out in a supine position with the patient having fasted for seven hours. The focal fat sparing echoes were present, the liver's echogenicity was greater than that of the renal cortex, the hepatic vasculature (portal or hepatic vein) was vascularly blurred, and the ability to see the diaphragm and deeper liver parenchyma was diminished.

Grading of NAFLD was done as follows:

- **Grade 1 steatosis:** Hepatic echogenicity is more than the renal cortex.
- **Grade 2 steatosis:** Liver echogenicity obscures echogenic wall of portal venous branches.
- **Grade 3 steatosis:** Diaphragmatic wall and portal venous walls are not visible due to increased hepatic echogenicity.

Analytical methods: Liver function tests: serum liver enzymes (ALT, AST) and serum albumin were measured on Synchron CX-9 autoanalyzer.

Complete blood count (CBC) was done on coulter LH 750 hematology analyzer. **Fasting blood glucose (FBS)** was performed on Synchron CX-9 auto-analyzer. Following these tests, the NAFLD fibrosis score was computed, which is based on patient age, BMI, FBS, platelet count, and AST/ALT ratio and has a negative predictive value of 88% to 93% and a positive predictive value of 82% to 90% [(4)]. -1.455 NAFLD cutoff value, there was a low likelihood of fibrosis or there was no major fibrosis. Cutoff value for NAFLD (-1.455 - 0.676), the likelihood of fibrosis was moderate. NAFLD cutoff value greater than 0.676, there was a high likelihood of fibrosis or severe stenosis.

Ethical approval: Ain Shams Faculty of Medicine Ethics Committee gave its approval to this study. All participants gave written consents after receiving all information. The Helsinki Declaration was followed throughout the study's conduct.

Statistical Analysis

IBM SPSS V. 18.0 was used to code, tabulate, and statistically analyse the collected data. For quantitative data that was normally distributed, descriptive statistics were calculated as the minimum and maximum of the range and mean ± SD. Qualitative data were represented as number and percentage.

Shapiro-Wilk test and independent t-tests were used for two independent groups with normally distributed data. ANOVA test with post hoc Tukey test were used for more than two independent groups with normally distributed data in inferential research for qualitative variables. The Fishers Extract test was used for variables with small predicted numbers and the Chi Square test for fluctuations in proportions while conducting inferential research for independent variables in qualitative data. P values ≤ 0.050 were considered significant.

RESULTS

There was highly statistically significant difference between risky and non-risky groups regarding age (p-value= 0.000). While there was no statistically significant difference between both groups regarding gender. There was highly statistically significant difference between risky and non-risky groups regarding BMI (p-value= 0.000), SBP (p-value= 0.000, and DBP (p-value= 0.002). There was high statistical significance between risky & non-risky groups regarding lipid profile (cholesterol with p- value 0.000, HDL with p- value 0.008, LDL with p- value 0.000 and TG with p- value 0.498). There was statistical significance between both groups regarding liver enzymes (AST with p- value 0.017 and ALT with p-value 0.014), while there was no statistical significance regarding T. Bilirubin. There was no statistical significance between both groups regarding s. albumin, uric acid & platelets (Table 1).

Table (1): Comparison between risky and non-risky groups regarding risk factors

		Risky group	Non-risky group	Test value	P- value	Sig.
		No. = 40	No. = 40			
Age (Years)	**Mean ± SD** **Range**	**41.43 ± 6.74** **28 – 54**	**29.38 ± 6.64** **19 – 42**	**8.055•**	**0.001**	**HS**
Gender	**Female** **Male**	**15 (37.5%)** **25 (62.5%)**	**10 (25.0%)** **30 (75.0%)**	**1.455***	**0.228**	**NS**
BMI (kg/m^2)	**Mean ± SD** **Range**	**28.58 ± 2.41** **25.1 – 33.6**	**23.06 ± 1.25** **20.4 – 24.8**	**12.849**	**0.001**	**HS**
SBP (mmHg)	**Mean ± SD** **Range**	**123.85 ± 14.24** **100 – 154**	**111.00 ± 9.00** **90 – 130**	**4.823**	**0.001**	**HS**
DBP (mmHg)	**Mean ± SD** **Range**	**78.88 ± 9.71** **60 – 95**	**72.25 ± 9.20** **60 – 90**	**3.134**	**0.002**	**HS**
T. Choles. (mg/dl)	**Mean ± SD**	**225.60 ± 39.22**	**170.45 ± 19.67**	**7.950**	**0.001**	**HS**
HDL (mg/dl)	**Mean ± SD**	**47.73 ± 9.76**	**54.35 ± 11.73**	**-2.740**	**0.008**	**HS**
LDL (mg/dl)	**Mean ± SD**	**138.22 ± 36.26**	**89.44 ± 9.01**	**8.258**	**0.001**	**HS**
TG (mg/dl)	**Mean ± SD**	**179.45 ± 43.77**	**130.30 ± 31.79**	**4.495**	**0.001**	**HS**
AST (U/l)	**Mean ± SD**	**52.10 ± 12.64**	**38.25 ± 9.51**	**2.443**	**0.017**	**S**
ALT (U/l)	**Mean ± SD**	**46.15 ± 11.31**	**35.55 ± 7.96**	**2.502**	**0.014**	**S**
T. Bilirubin (µmol/L)	**Mean ± SD**	**0.74 ± 0.16**	**0.77 ± 0.18**	**-0.493**	**0.623**	**NS**
S. Alb (g/dL)	**Mean ± SD**	**4.26 ± 0.52**	**4.26 ± 0.46**	**-0.045**	**0.964**	**NS**
Uric acid (mg/dL)	**Mean ± SD**	**6.02 ± 1.17**	**5.72 ± 1.03**	**1.196**	**0.235**	**NS**
PLT (mcL)	**Mean ± SD**	**232.48 ± 43.04**	**243.18 ± 43.03**	**-1.112**	**0.270**	**NS**

P-value >0.05: Non significant (NS); P-value ≤0.05: Significant (S); P-value≤ 0.01: highly significant (HS), *: Chi-square test; •: Independent t-test

Table (2) showed that 55% of cases (44 cases) included in the study who had H-pylori positive infection had fatty liver in ultrasound, while 36 cases (45%) had normal ultrasound.

Table (2): Descriptive data regarding U/S results in all cases

US	No.	%
Normal	**36**	**45.0%**
Fatty liver	**44**	**55.0%**
Total	**80**	**100**

Table (3) showed that 29 of cases (72.5%) had fatty liver in risky group while 15 of cases (37.5%) had fatty liver in non-risk group. This showed high statistical significance between both groups (p-value 0.002). As regards grade of hepatic steatosis (HS), 24.1% (7 patients) of risky-group patients had grade 1 HS, 34.5% (10 patients) had grade 2 HS, 41.4% (12 patients) had grade 3 HS. In non-risky group, 33.3% (5 patients) had grade 1 HS, 66.7% (10 patients) had grade 2 HS. There was significant difference between both groups as regards grade of HS.

Table (3): Percentage of fatty liver in Ultrasound between both risky and non-risky groups

		Risky group		Non-risky group		Test value	P-Value	Sig.
		No.	%	No.	%			
u/s	Normal Fatty liver	11 29	27.5% 72.5%	25 15	62.5% 37.5%	9.899	0.002	HS
Grade 1 HS Grade 2 HS Grade 3 HS		7 10 12	24.1% 34.5% 41.4%	5 10 0	33.3% 66.7% 0.0%	8.766	0.012	S

There was high statistical significance between liver enzymes (AST & ALT) and calculated NFS (Table 4).

Table (4): The degree of steatosis associated with increased risk of elevation of both liver enzymes & NAFLD fibrosis score (NFS)

		Grade of steatosis			Test value	P- value	Sig
		Grade 1	Grade 2	Grade 3			
		No. = 12	No. = 20	No. = 12			
AST (U/L)	Mean ± SD	29.25 ± 6.87	50.80 ± 12.51	82.67 ± 19.92	23.928	0.001	HS
ALT (U/L)	Mean ± SD	34.67 ± 8.58	42.30 ± 10.54	68.17 ± 16.67	15.312	0.001	HS
NFS (CALC.	Median (IQR) Range	-3.14 (-3.88 – -2.12) -5.08 – -1.82	-2.4 (-3.18 – -1.96) -4.14 – 0.58	-1.44 (-2 – -1.14) -2.94 – -0.16	15.429	0.001	HS
F0-F2 (<-1.455) Intermediate score (-1.455 - 0.675)		12 (100.0%) 0 (0.0%)	18 (90.0%) 2 (10.0%)	6 (50.0%) 6 (50.0%)	11.733	0.003	HS

Median, IQR and range: Non-parametric test.
*: Chi-square test; One Way ANOVA test; ‡: Kruskall Wallis test.

There was statistical significance between both groups (p- value 0.025) regarding NFS. 21 of cases (72.4%) in risky group had NFS F0-F2, while 8 cases (27.6%) had indeterminist score. While, in non-risky group 100% of cases had F0-F2 NFS score (Table 5).

Table (5): Comparison between risky and non-risky groups regarding NFS

		Risky group	Non-risky group	Test value	P-value	Sig.
		No. = 40	No. = 40			
NFS (CALC.	Median (IQR) Range	-1.98 (-2.33 - -1.42) -5.08 – 0.58	-3.06 (-3.63 - 2.48) -3.84 – -1.93	-3.281	0.001	HS
NFS (CALC.	F0-F2 (<-1.455)	21 (72.4%)	15 (100.0%)	5.057	0.025	S
	Intermediate score (-1.455 - 0.675)	8 (27.6%)	0 (0.0%)			

Median, IQR and range: Non-parametric test.

There was statistically significant relation found between fatty liver and **Age (p-value=0.020).** While, there was no statistically significant relation found between fatty liver and **gender** (Table 6)**.**

Table (6): Demographic data in risky group

		Risky group		Test value	P- value	Sig.
		Normal	Fatty liver			
		No. = 11	No. = 29			
Age (Years)	Mean ± SD	37.45 ± 6.76 28 – 47	42.93 ± 6.20 30 – 54	-2.434	0.020	S
Gender	Female Male	4 (36.4%) 7 (63.6%)	11 (37.9%) 18 (62.1%)	0.008	0.927	NS

There was highly statistical significance between BMI and fatty liver cases in risky group (p- value 0.000), while there was statistical significance between SBP and fatty liver cases in risky group (p- value 0.028). There was no statistical significance between DBP and fatty liver (Table 7).

Table (7): Comparison between normal and fatty liver patients in risky group regarding BMI, SBP and DBP

		Risky group		Test value	P - value	Sig.
		Normal	Fatty liver			
		No. = 11	No. = 29			
BMI (kg/m^2)	Mean ± SD Range	26.42 ± 1.52 25.1 – 29.8	29.40 ± 2.18 26.1 – 33.6	-4.161	0.000	HS
SBP (mmHg)	Mean ± SD Range	115.91 ± 12.41 100 – 140	126.86 ± 13.91 100 – 154	-2.286	0.028	S
DBP (mmHg)	Mean ± SD Range	75.00 ± 11.18 60 – 90	80.34 ± 8.86 60 – 95	-1.585	0.121	NS

There was high statistical significance between fatty liver and ALT in risky group cases (p- value 0.009), and there was statistical significance between fatty liver and AST (p- value 0.009). There was no statistical significance between bilirubin and fatty liver (Table 8).

Table (8): Comparison between normal and fatty liver patients in risky group as regards liver enzymes and T. Bilirubin

		Risky group		Test value	P-value	Sig.
		Normal	Fatty liver			
		No. = 11	No. = 29			
AST (U/L)	Mean ± SD	33.00 ± 7.79	59.34 ± 3.92	-2.731	0.010	S
ALT (U/L)	Mean ± SD	31.55 ± 7.70	51.69 ± 12.62	-2.770	0.009	HS
T. Bilirubin (µmol/L)	Mean ± SD	0.76 ± 0.18	0.73 ± 0.16	0.322	0.750	NS

There was no statistical significance between fatty liver and lipid profile, S. albumin, uric acid & PLT within risky group cases (Table 9).

Table (9): Comparison between normal and fatty liver patients in risky group as regards lipid profile, S. Albumin, uric acid & platelets

		Risky group		Test value	P-value	Sig.
		Normal	Fatty liver			
		No. = 11	No. = 29			
T. Choles. (mg/dl)	Mean ± SD	219.09 ± 35.15	228.07 ± 40.97	-0.642•	0.525	NS
HDL (mg/dl)	Mean ± SD	48.48 ± 9.31	47.45 ± 10.07	0.296•	0.769	NS
LDL (mg/dl)	Mean ± SD	131.91 ± 31.90	140.62 ± 34.82	-0.673•	0.505	NS
TG (mg/dl)	Mean ± SD	169.73 ± 41.42	183.14 ± 44.61	-0.629•	0.533	NS
S. Alb (g/dL)	Mean ± SD	4.38 ± 0.61	4.21 ± 0.49	0.925	0.361	NS
Uric acid (mg/dl)	Mean ± SD	6.10 ± 0.93	5.98 ± 1.27	0.279	0.782	NS
PLT (mcL)	Mean ± SD	221.00 ± 17.18	236.83 ± 49.02	-1.040	0.305	NS

There was high statistical significance between age and fatty liver in non-risky group with p-value 0.000, while there was no statistical significance between gender and fatty liver (Table 10).

Table (10): Demographic data in non-risky group

		Non-risky group		Test value	P- value	Sig.
		Normal	Fatty liver			
		No. =25	No. = 15			
Age (years)	Mean ± SD Range	26.20 ± 5.72 19 – 39	34.67 ± 4.30 26 – 42	-4.943	0.000	HS
Gender	Female Male	7 (28.0%) 18 (72.0%)	3 (20.0%) 12 (80.0%)	0.320	0.572	NS

DISCUSSION

Up to 75% of obese people and 20%–45% of the general population suffer from NAFLD, a widespread condition. It is thought to be the metabolic syndrome's hepatic manifestation. Numerous variables, including genetic, metabolic, and environmental ones, affect the pathophysiology of NAFLD [(1)].

The GUT microbiota and its potential role in the development of NAFLD are the subject of recent research. The gram-negative bacteria H. pylori is responsible for a number of gastrointestinal disorders and is also suspected to be the cause of NAFLD due to its propensity to increase intestinal permeability, induce the production of proinflammatory cytokines, and increase insulin resistance [(1-3)].

According to **Angulo *et al.* [(4)],** the NAFLD fibrosis score (NFS) was determined for all patients with NAFLD, who separated the patients in our research into two categories: no or low likelihood of fibrosis (F0-F2) and intermediate probability of fibrosis (F2-F3). In our study, the overall prevalence of NAFLD was 55%, with the risky group having 72.5% of cases.

The prevalence of NAFLD was 37.5% in patients who were not at risk and did not have any metabolic risk factors. This suggests that the presence of an active H. pylori infection may contribute to the development of NAFLD. The findings are consistent with those of **Abo-Amer *et al.* [(5)]** who demonstrated that H. pylori was an independent risk factor for NAFLD and was correlated with an increased degree of steatosis. Additionally, **Xu *et al.* [(6)]** found a correlation between H-Pylori infection and NAFLD through a retrospective investigation. **Jiang *et al.* [(7)]** found a correlation between H. Pylori infection and NAFLD in females. Furthermore, a different cohort research by **Kim *et al.* [(8)]** comprised 17,028 participants and showed that H-Pylori was substantially linked to NAFLD regardless of inflammatory and metabolic risk variables.

On the other hand, a number of investigations, like the one presented by **Baeg *et al.* [(9)]** with 3600 participants, found no correlation between H-pylori infection and NAFLD. This is also in line with the findings of **Okushin *et al.* [(10)]** who studied 13,737 Japanese patients. **Fan *et al.* [(11)]** conducted a multivariate logistic analysis that revealed no connection between H. pylori infection and non-NAFLD.

The degree of hepatic steatosis was found to be correlated with the level of liver enzymes, with the level of liver enzymes increasing as the degree of steatosis increased. This finding is consistent with **Briseño-Bass *et al.* [(12)]** who observed that there is a strong correlation between the degrees of steatosis and increased liver enzyme levels.

In line with other research done by **Ogden *et al.* [(13)]**, we discovered a statistically significant correlation between greater BMI and the occurrence of NAFLD based on the clinical features of the patients in our study.

The results of our study support the findings of **Golabi *et al.* [(14)]** that there is a statistically significant correlation between the presence of NAFLD and age.

In contrast to other studies that found that NAFLD is more common in women, such as **Summart *et al.* [(15)]**, our research demonstrated that gender had no bearing on the prevalence of NAFLD, which is consistent with **Bedogni *et al.* [(16)]**.

Furthermore, we discovered that high levels of TG, cholesterol, and LDL are linked to NAFLD. This aligns with the findings of **Katsiki *et al.* [(17)]**.

Our research showed that a higher risk of NAFLD is linked to elevated SBP and DBP. This is consistent with the findings of **Bedogni *et al.* [(16)]** who found that higher incidence of NAFLD was linked to systolic hypertension.

In line with **Sumida *et al.* [(18)]**, the levels of AST and ALT in our research were considerably higher in patients in the risky group than in patients in the non-risky group.

Using NFS to measure the degree of fibrosis in NAFLD patients, we discovered that riskier individuals had a higher chance of developing fibrosis, which is consistent with **Angulo *et al.* [(4)]**.

It is evident from our discussion that H-Pylori infection may contribute to the development of NAFLD. Our study is not without limitations.

Though, first, the population in this cross-sectional research was tiny. Second, rather of doing a liver biopsy, which is the gold standard for diagnosing steatohepatitis and NAFLD, we chose to employ ultrasonography.

CONCLUSION

Our findings showed that H-Pylori infection may play a role in the development of NAFLD. Taking into account the limitations of the case-control research and the limited size of the population covered, other metabolic risk variables such as dyslipidemia and obesity may have a substantial role in the development and progression of NAFLD.

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