ORIGINAL ARTICLE

Association between *Helicobacter pylori* Infection and Nonalcoholic Fatty Liver Disease

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Abstract

Background: The role of *Helicobacter pylori* in extragastrointestinal diseases, though not clearly established, is of great importance.

Objectives: The study aims to evaluate the role of *H. pylori* infection in nonalcoholic fatty liver disease (NAFLD) and its association with NAFLD severity.

Materials and methods: Thirty-six patients with biopsy-proven NAFLD (17 patients with simple nonalcoholic fatty liver and 19 patients with nonalcoholic steatohepatitis—NASH) and 23 healthy blood donors (control group) were included in the study. Serum samples were tested for *H. pylori* antibodies IgG, IgM, and IgA using enzyme-linked immunosorbent assay (ELISA). Parameters associated with metabolic syndrome were compared between *H. pylori* seropositive and seronegative patients in the NAFLD group. Seroprevalence and antibody titers of *H. pylori* in the NAFLD group were compared with the control group.

Results: Anti-*H. pylori* IgG was positive in 22 (61%) cases of the NAFLD group and 13 (56%) cases of the control group. Anti-*H. pylori* IgM was positive in 4 (11%) cases of the NAFLD group and 2 (8%) cases of the control group. Anti-*H. pylori* IgA seroprevalence in the NAFLD group ($n = 11$; 31%) was higher than the control group ($n = 4$; 17%; $p = 0.03$). The NAFLD group had a higher anti-*H. pylori* IgA titer than the control group ($p = 0.03$). There were similar rates of anti-*H. pylori* IgG/IgM/IgA titers between NAFLD and NASH patients with no significant correlation between *H. pylori* infection and metabolic syndrome.

Conclusion: An association of *H. pylori* infection was seen in NAFLD cases which might have a role in the pathogenesis of fatty liver diseases. This can be further explored for its exact role in the causation of fatty liver disease.

Keywords: ELISA, *Helicobacter pylori*, IgA, IgG, IgM, NAFLD, NAS, NASH.

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is a condition defined by excessive fat accumulation in the form of triglycerides (steatosis) in the liver. The earliest stage is simple steatosis. It can progress to nonalcoholic steatohepatitis (NASH) with liver cell injury and inflammation in addition to excessive fat (steatohepatitis).[1–3] NASH, in turn, may progress to cirrhosis and ultimately liver cancer in some patients.[4] Cirrhosis due to NASH is an increasingly frequent reason for liver transplantation. NASH is widely considered to be the liver expression of the metabolic syndrome diseases related to hyperlipidemia (low high-density lipoprotein cholesterol (CHOL), hypertriglyceridemia), and hypertension.[5,6] Epidemiological studies suggest the prevalence of NAFLD to be around 9–32% in general Indian population.[7]

Recent reports have emerged on the effect of gut microbiota on the development and progression of liver cell damage. In this regard, *Helicobacter pylori* deoxyribonucleic acid (DNA) was detected in patients with various etiologies of chronic liver disease including NAFLD.[8–11] There are proposed mechanisms for the development of NAFLD in patients with *H. pylori* infection. The earlier theory expressed that *H. pylori* species would produce a liver-specific toxin that causes liver cell damage.[12] Afterwards, it was found that *H. pylori* invasion to intestinal mucosa might increase gut permeability and facilitate the bacterial endotoxin passage via the portal vein to the liver.[13] *H. pylori* infection may also inhibit white adipose tissue to release leptin, and then promote liver stearoyl-CoA desaturase, thus, accelerating fatty deposits in the liver tissue. Insulin resistance (IR) has also been implicated as an important link between *H. pylori* infection and NAFLD. *Helicobacter pylori*-induced IR may be mediated through fetuin-A and IR favors the accumulation of free fatty acids in the liver.[14]

Helicobacter pylori is a gram-negative and microaerophilic bacterium[15] that colonizes the stomach in childhood and persists throughout life, causing diseases mainly in adults, including chronic gastritis, peptic ulcer disease, gastric mucosa-associated lymphoid tissue lymphoma, and gastric cancer.[16,17]

Since *H. pylori* treatment is not difficult and comparatively not expensive in most cases, discovering its role in diseases apart from the stomach could be of great importance for public health. However, only limited clinical data suggest that *H. pylori* infection might be a risk factor for the development of NAFLD.[18–20]

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Materials and Methods

Study Design and Subjects

This was a single-center, prospective study carried out in a tertiary liver-care institute. Determination of eligibility was based on medical history, and standard tests were performed during the screening visit. Institutional Ethics Committee of Institute of Liver and Biliary Sciences approved the study protocol. Serum samples were collected from patients ($n = 36$) of age ≥18 years and who were biopsy-proven NAFLD cases with increased liver function tests for at least 6 months before liver biopsy. Exclusion criteria for both NAFLD patients and controls were (i) liver cirrhosis; (ii) other liver diseases (viral hepatitis, autoimmune hepatitis, primary sclerosing cholangitis, primary biliary cirrhosis, and overlap syndromes); and (iii) patients of NAFLD who scored NAS between 0 and 2. Blood samples from donors ($n = 23$) were collected at the Blood Bank with normal body weight according to the age and body mass index of <25 kg/m^2 served as controls. Liver biopsy, being an invasive procedure, could not be performed in blood donors on account of ethical issues. Hence, NAFLD and the diseases mentioned in the exclusion criteria were subjectively ruled out in the blood donors via simple history taking. Blood samples were collected in plain vials; the serum was separated and kept frozen at −20°C until analyzed.

Samples were used for testing serum *H. pylori* IgG, serum *H. pylori* IgA, and serum *H. pylori* IgM with ELISA on a manual ELISA plate reader, by using the following commercial kits, respectively: serum *H. pylori* IgG, serum *H. pylori* IgM, and serum *H. pylori* IgA (DEMEDITECH, Germany). Alanine aminotransferase (ALT), aspartate aminotransferase (AST), fasting serum glucose (FSG), serum insulin (SI), C-reactive protein (CRP), tumor necrosis factor (TNF), TG, CHOL, high-density lipoprotein (HDL), low-density lipoprotein (LDL) values, and biopsy results were noted from the hospital information system.

Scoring System for NAFLD Activity Score

A wide variety of attempts have been made to develop scoring systems or imaging techniques that will allow non-invasive diagnosis of NASH and avoid the need for a liver biopsy. Currently, none has been tested rigorously enough in prospective, double-blind studies, nor has their ability to predict the prognosis or response to therapy been proven.

Liver Biopsy

Although it is invasive and has a potential for sampling errors and inconsistent interpretation of the histopathology, liver biopsy is required to establish the diagnosis and to stage NASH. Kleiner et al.[3] studied the histologic features of NAFLD and devised a NAFLD activity score (NAS). Staging of fatty liver disease and steatohepatitis is done by evaluating fibrosis score (Tables 1 and 2).

ELISA

Serum *H. pylori* antibodies IgG, IgM, and IgA were tested in the serum samples of the biopsy-proven NAFLD group using a quantitative ELISA method (DEMEDITEC, Germany). The Demeditec serum *H. pylori* IgG, IgM, and IgA antibody test kit is based on the principle of the indirect type of ELISA. Indirect ELISA is a two-step ELISA which involves two binding processes of the primary antibody and the labeled secondary antibody. The primary antibody is incubated with the antigen followed by incubation with the secondary antibody. The procedure was performed according to the manufacturer's instructions.

Statistical Analysis

Continuous data are presented as mean ± standard error (SE) of the mean. Qualitative data are presented as numbers (percentage). Numerical data are calculated using Microsoft excel and analyzed. Statistical analysis was done using the SPSS package program. Independent *t* test and Chi-square test were used for the comparison of two groups. The *p* value <0.05 was considered significant.

Results

Thirty-six patients with NAFLD (17 with nonalcoholic fatty liver—NAFL and 19 with NASH) and 23 controls with a mean age of 38.8 ± 1.7 years were included in the study.

As shown in Figure 1, the serum *H. pylori* IgG was positive in 22 (61%) cases of the NAFLD group and 13 (56%) cases of the control group. Serum *H. pylori* IgM was positive in 4 (11%) cases and 2 (8%) cases of the NAFLD group and the control group, respectively. Serum *H. pylori* IgA seroprevalence in the NAFLD group ($n = 11$; 31%) was higher ($p = 0.03$) than in the control group ($n = 4$; 17%).

Of 36 NAFLD cases, 22 (61%) cases were *H. pylori* IgG seropositive and 14 (39%) cases were *H. pylori* IgG seronegative. In Table 3, a

Table 2: Staging system devised by the pathology committee of the NASH Clinical Research Network (Kleiner DE, 2005)

NASH fibrosis stage	*Stage*
None	0
Mild, zone 3 perisinusoidal fibrosis	1a
Moderate, zone 3 perisinusoidal fibrosis	1b
Portal/periportal fibrosis only	1c
Zone 3 perisinusoidal and portal/periportal fibrosis	2
Bridging fibrosis	3
Cirrhosis	4

Table 1: NAFLD activity score (NAS) devised by the pathology committee of the NASH Clinical Research Network (Kleiner DE, 2005)

Steatosis (%)	*S score*	*Lobular inflammation*	*L score*	*Hepatocyte ballooning*	*B score*
<5	0	None	0	None	0
5–33	1	<2	1	Few ballooned cells	1
34–66	2	2–4	2	Many ballooned cells	2
>66	3	>4	3		

NAFLD activity score = total score: S + L + B (range 0–8)
NAS = 0–2; not diagnostic of NASH
NAS = 3–4; borderline, or positive for NASH
NAS = 5–8; largely considered diagnostic of NASH

comparison of several parameters of NAFLD patients between *H. pylori* IgG seropositive and *H. pylori* IgG seronegative group is shown. Both the groups had high LDLs and low HDLs. Triglycerides and serum insulin (SI) were higher in anti-*H. pylori* IgG seropositive patients than IgG seronegative patients but with no significant difference. C-Reactive protein (CRP) was higher in IgG seronegative NAFLD patients than IgG seropositive patients but the difference was not significant, and values of CHOL, FSG, and TNF-alpha (TNF-α) were within normal range in both the groups (Table 3).

Mean values of serum *H. pylori* antibodies IgG, IgM, and IgA were compared in the NAFLD group and the control group as shown in Table 4. In the NAFLD group, serum *H. pylori* IgG and serum *H. pylori* IgM levels were higher than in the control group but statistically no difference was found. However, the NAFLD group had statistically higher serum *H. pylori* IgA titer than the control group ($p = 0.03$).

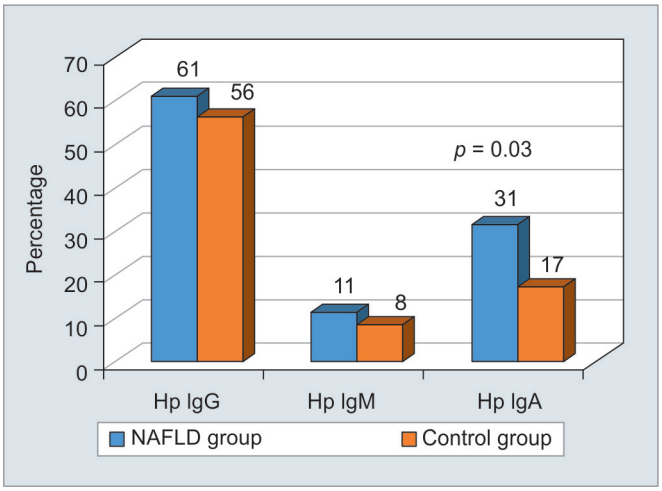

Fig. 1: Comparative analysis of *H. pylori* seroprevalence in NAFLD and control groups

The NAFLD group was divided into two subgroups on the basis of their NAS score obtained by liver biopsy. Patients with NAS between 3 and 4 constituted simple NAFLD, and those with NAS between 5 and 8 constituted NASH. Serum *H. pylori* IgG/IgM/IgA levels in these two groups did not show a statistically significant difference (Table 5).

Discussion

A growing body of evidence has implicated *H. pylori* infection in extra gastrointestinal diseases such as cardiovascular, liver, and biliary diseases. Recent reports have emerged on the relationship between *H. pylori* and NAFLD. This study was done with the aim to evaluate the role of *H. pylori* in NAFLD patients and in the progression of NAFLD to NASH. To our knowledge, this is the first report for the comparison of serum *H. pylori* IgG/IgA/IgM titer levels in the NAFLD and the control groups.

Helicobacter pylori infection elicits a local mucosal and a systemic antibody response in patients, and measurement of specific antibodies in serum has been used as a noninvasive method to detect *H. pylori* infection. Crabtree et al.[21] and Alem et al.[22] showed that specific IgM antibodies can be detected shortly after the infection is acquired, but IgA and IgG titers indicate chronic infection while Serrano et al.[23] and Cherian et al.[24] found IgM to have little diagnostic utility to indicate recent acquisition.

The primary aim of this study is to evaluate the role of serum *H. pylori* IgG/IgM/IgA in NAFLD patients. IgA indicates a mucosal infection so its diagnostic value increases in *H. pylori* infection since it mainly colonizes the mucosal surfaces. A significant difference was found in this study between the NAFLD and the control group for IgA seroprevalence and serum *H. pylori*-IgA titer. Although the diagnostic utility of IgA antibodies is less well documented than IgG antibodies in *H. pylori* infection, certain studies have shown the presence of IgA positive and IgG negative *H. pylori* infection in a subset of cases, thus, making the evaluation of IgA titers the

Table 3: Comparison of parameters of NAFLD patients between *H. pylori* IgG seropositive and *H. pylori* IgG seronegative group

Parameters	*NAFLD patients with H. pylori IgG seropositivity*	*NAFLD patients with H. pylori IgG seronegativity*	*p value*
ALT (IU/L)	82.7 ± 52.6	96.54 ± 56.02	0.42
AST (IU/L)	67.2 ± 57	62.38 ± 50.42	0.99
TG (mg/dL)	189.8 ± 80.8	140.8 ± 50.6	0.1
CHOL (mg/dL)	193 ± 27.3	170.4 ± 53.3	0.16
HDL (mg/dL)	40.5 ± 11.6	35.5 ± 9.57	0.16
LDL (mg/dL)	111.3 ± 35.2	111.1 ± 43.9	0.37
FSG (mg/dL)	96.2 ± 17	102.3 ± 14.7	0.26
SI (μIU/mL)	31.7 ± 55.01	10.6 ± 7.9	0.27
CRP (mg/L)	3.41 ± 2.61	6 ± 3	0.72
TNF-α (ng/L)	7.03 ± 10.62	2.1 ± 1.3	0.17

Table 4: *Helicobacter pylori* related comparative data in NAFLD and control group

	NAFLD group (n = 36)	*Control group (n = 23)*	*p value*
Serum *H. pylori* IgG	42.53 ± 52.49	35.78 ± 45.55	0.62
Serum *H. Pylori* IgM	9.42 ± 3.69	8.65 ± 8.29	0.68
Serum *H. pylori* IgA	13 ± 10.13	9 ± 3.58	0.035

Table 5: *Helicobacter pylori* related comparative data in NAFL and NASH groups

	NAFL (n = 17)	*NASH (n = 19)*	*p value*
Serum *H. pylori* IgG	39.47 ± 55.54	45.26 ± 50.98	0.75
Serum *H. pylori* IgM	9.06 ± 3.76	9.74 ± 3.71	0.59
Serum *H. pylori* IgA	11.12 ± 9.56	14.68 ± 10.58	0.29

only serological marker for the diagnosis of *H. pylori* infection.[25–28] This proves that the presence of significant IgA antibody titers is an important evidence of *H. pylori* infection irrespective of the presence of IgG titers.

Serum *H. pylori* IgM and IgG titers were also higher in the NAFLD group as compared with the control group, although they were not statistically significant showing that *H. pylori* has some role in the pathogenesis of fatty liver diseases which has not yet been properly defined. Our study results correlate well with another study which also showed higher serum *H. pylori* IgG titers in NAFLD than control groups.[29,30] But the association being still unclear, certain studies show no association of *H. pylori* with NAFLD.[31–33]

As per the existing literature, *H. pylori* exposure occurs to most of us early in life and, therefore, a seroprevalence of approximately 60% is seen in our study which is in agreement with the other published studies.[34–39]

The second goal of this study is to evaluate the role of *H. pylori* in the progression of NAFLD to NASH. Serum *H. pylori* IgG and serum *H. pylori* IgA are not statistically higher in NASH patients as compared to NAFLD patients. The level of serum *H. pylori* IgM is the same in both the groups. It shows that both current and past *H. pylori* infection did not cause any progression of the fatty liver disease. This finding is in contrast to another study which states that *H. pylori* infection may act as a contributing factor in the progression of NAFLD to NASH.[30]

In this study, all patients of NAFLD irrespective of their serum *H. pylori* IgG seropositivity or seronegativity had high serum LDL and low HDL. TG and SI were higher in serum *H. pylori* IgG seropositive NAFLD patients than seronegative patients but the difference was not significant. This finding correlates well with a study by Akbas et al.[40] showing that there is no significant correlation between *H. pylori* infection and metabolic syndrome and eradication of *H. pylori* will probably have no effect on the lipid profile.[41] Our study results are in contrast with a few studies which have shown that *H. pylori* infection is associated with an unfavorable metabolic profile in NAFLD patients.[42]

Limitations of This Study

(i) The controls were not subjected to liver biopsy, due to ethical considerations; (ii) serum *H. pylori* IgG cannot distinguish current from old *H. pylori* infection; (iii) the diagnosis of *H. pylori* infection was not established by culture or histology that represent the practical diagnostic gold standard of *H. pylori* infection.

Conclusion

IgA antibodies that are representative of mucosal immunity were found to be at a higher prevalence in the NAFLD group as compared to the control group indicating that *H. pylori* infection does have some role in the pathogenesis of fatty liver diseases, although its exact role is not defined. Since there were similar rates of *H. pylori* infection between NAFLD and NASH so it may not contribute to the progression of disease. Both *H. pylori* seropositive and *H. pylori* seronegative NAFLD patients had deranged lipid profile, thereby showing no positive correlation between *H. pylori* infection and metabolic syndrome.

Eradication of *H. pylori* is easy and relatively inexpensive, hence, further studies need to be conducted to confirm this particular association between *H. pylori* and NAFLD, which, once established, will drastically change our perception of pathophysiology and treatment of NAFLD.

Ethical Statement

Institutional Ethics Committee of ILBS approved the study protocol.

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