

The effect of *Helicobacter pylori* eradication on liver enzymes in patients referring with unexplained hypertransaminasemia

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Abstract

Background: Evidence has shown an association of *Helicobacter pylori* infection with liver dysfunction and damage. We investigated if *H. pylori* eradication affects liver enzymes in patients referring with unexplained hypertransaminasemia.

Materials and Methods: Patients with mild unexplained hypertransaminasemia accompanied with dyspepsia and confirmed *H. pylori* infection were studied. Viral, metabolic, autoimmune, and drug/toxin induced hepatitis as well as fatty liver were all ruled-out by appropriate tests. Patients received bismuth-containing quadruple-therapy for 2 weeks. Serum levels of liver enzymes (alanine transaminase (ALT) and aspartate transaminase (AST)) and successful eradication (with stool antigen test) were evaluated 4 weeks after the medication.

Results: A total number of 107 patients (55 males, mean age = 35.0 ± 8.4 years) were studied. Eradication was successful in 93 patients (86.9%). Serum levels of AST (6.3 ± 19.6 IU/L, $P = 0.002$) and ALT (7.8 ± 24.9 IU/L, $P = 0.001$) were significantly decreased after eradication. Levels of AST and ALT decreased to normal range respectively in 46.6% and 45.7% of the cases who had baseline levels above the normal range.

Conclusion: This study showed a decrease in liver enzymes after receiving eradication regimen of *H. pylori*, suggesting a role for *H. pylori* infection in at least some of patients with mild unexplained hypertransaminasemia. Further studies are warranted to find the underlying mechanisms by which *H. pylori* infection affects the liver and clinical importance of such effects.

Key Words: *Helicobacter pylori*, liver diseases, transaminases

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INTRODUCTION

Helicobacter pylori is a pathogenic bacterium colonizing in the mucosal surface of the human stomach. Infection with *H. pylori* is highly prevalent worldwide; up to 90% of the adult populations in developing countries are affected by the bacteria.^[1] Consequences of the infection range from a mild chronic gastritis to peptic

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ulcer and gastric cancers.^[1] Besides gastric problems, association of *H. pylori* infection with other diseases such as cardiovascular, pulmonary, hematologic, ophthalmologic, dermatologic, neurologic, and hepatobiliary diseases are shown by several recent studies.^[2]

Liver is one of the organs that, according to some evidences, may be affected by *H. pylori* infection; however, the exact effects of the infection on the liver and the underlying mechanisms are still unclear.^[2] Some studies have suggested that *H. pylori* infection could be a risk factor for chronic diseases of the liver and biliary tract, such as chronic cholecystitis, primary sclerosing cholangitis, primary biliary cirrhosis, and even hepatocellular carcinoma.^[3-8] Animal studies have shown that *H. pylori* can exist in the liver and gallbladder cells.^[9,10] and can cause mild to moderate the multifocal hepatitis and hepatic fibrosis.^[11] Regarding human studies, an association between *H. pylori* presence in the liver and disease progression in those with viral chronic hepatitis and cirrhosis is reported.^[7,12] Furthermore, associations between *H. pylori* infection and cirrhosis in patients with hepatitis C virus,^[13] and between hypertransaminasemia and infection with Cag-A positive *H. pylori* in patients with peptic ulcer disease are presented.^[14]

Due to the uncertainty about the exact impacts of *H. pylori* on the liver and lack of studies in this regard, we investigated if liver enzymes are changed by *H. pylori* eradication in patients referring with hypertransaminasemia of unexplained origin and concomitant *H. pylori* infection.

MATERIALS AND METHODS

Patients and settings

This prospective observational study was conducted on patients with mild unexplained hypertransaminasemia who were referred for liver work-ups to the out-patient clinic of gastroenterology in Alzahra University Hospital, in Isfahan city (Central Iran), between 2011 and 2012. Patients who fulfilled the following inclusion criteria were consecutively included; (1) adult patients with double-checked (with about 2 weeks interval) alanine transaminase (ALT) or aspartate transaminase (AST) of more than 40 IU/L, but not three times above the normal; (2) no presence of fatty liver disease (investigated by ultrasonography) or viral, metabolic, autoimmune, and drug or toxin induced hepatitis as the causes of hypertransaminasemia; and (3) having dyspepsia and *H. pylori* infection approved by rapid urease test or stool antigen test. Patients who had recent antibiotic treatment for *H. pylori* eradication

and pregnant and lactating women were not included into the study. With regard to the type I error (α) = 0.05, study power = 80%, and an expected decrease of at least 5 IU/L in liver enzymes after eradication, sample size was calculated as 100 patients. The study was approved by the Ethics Committee of the Isfahan University of Medical Sciences and all patients signed a written inform consent before entering the study.

H. pylori eradication regimen

All patients received bismuth-containing quadruple-therapy for 2 weeks contained omeprazole 20 mg/bid, bismuth subcitrate 240 mg/bid, amoxicillin 1000 mg/bid, and clarithromycin 500 mg/bid. This regimen is used in our center based on the recent Iranian Association of Gastroenterology guideline^[15] and a systematic review on the treatment of *H. pylori* infection in Iran,^[16] and expected to have eradication rate as about 85-90%.

Assessments

A gastroenterologist visited all patients and viral, metabolic, autoimmune, and drug/toxin induced hepatitis as well as fatty liver disease were investigated by appropriate tests. One month after the end of the eradication, patients were visited again and the eradication of *H. pylori* was assessed by stool antigen test (rapid immunoassay method, generic assays GmbH, Germany) with sensitivity, specificity, positive predictive value, negative predictive value of 96%, 83%, 98%, and 96% respectively.^[17] Furthermore, a blood sample was taken and serum levels of the liver enzymes were re-checked. Almost all of the patients had tested in the same laboratory.

Statistical analysis

Data were analyzed using the SPSS software for windows (version 16.0). Quantitative and qualitative variables are presented as mean \pm SD and number (%), respectively. Wilcoxon Test was used for comparing liver enzyme levels before and after eradication (considering not-normal distribution of liver enzymes' levels after eradication). Furthermore, Mann-Whitney Test was used for comparing changes in liver enzymes between those with successful and unsuccessful eradication. A $P < 0.05$ was considered significant in all analyses.

RESULTS

During the study period, a total number of 107 patients including 55 males and 52 females with a mean age of 35.0 ± 8.4 (18-56) years were included into the study. Baseline ALT and AST levels ranged from 44 IU/L to 79 IU/L (61.2 ± 9.6) and from 27 IU/L to 70 IU/L (47.8 ± 10.5), respectively. None of the patients has AST/ALT > 2 before or after the study. Among the studied population, 93 patients (86.9%) had successful

H. pylori eradication. Liver enzymes were decreased significantly by 7.8 ± 24.9 IU/L for ALT ($P = 0.001$) and by 6.3 ± 19.6 IU/L for AST ($P = 0.002$). However, there was no difference between those with successful eradication and those with failed eradication in changes in liver enzymes' levels ($P = 0.657$ and 0.821 respectively for ALT and AST), Table 1.

Regarding ALT, all patients were above the normal range before eradication. After eradication, ALT levels decreased to normal range in 45.7% (49/107) of the cases by 30.7 ± 10.2 IU/L. In those who has no decrease in ALT levels after eradication (48 cases), ALT levels changed by 16.4 ± 11.3 IU/L. Additional analyses also showed that in patients with baseline AST levels above the normal range (75 cases), AST levels decreased to normal range in 46.6% (35/75) of the cases by 28.5 ± 8.3 IU/L. However, in patients who had been in the normal range before eradication (32 cases), AST levels changed to above the normal in 25% (8/35) of the cases by 13.3 ± 8.6 IU/L.

DISCUSSION

Mild unexplained hypertransaminasemia is an especial concern when is found accidentally in routine laboratory tests or in tests with other indications in individuals without specific liver disease or complaints. For example, a population-based study in the United States estimated an abnormal liver function test (LFT) in up to 9% of the healthy population who had a single screening test.^[18] Another study showed that, if retested with about 2 weeks interval, more than 30% of abnormal cases would be reclassified as normal and only 5% of normal cases at the first test would have elevated enzymes at the second test.^[19] Considering high prevalence of *H. pylori* infection in the general population and some evidence indicating an association between *H. pylori* infection with some degrees of liver damage, we evaluated if *H. pylori* eradication has any effects on liver enzymes in those with unexplained hypertransaminasemia. The results showed that the mean level of liver enzymes significantly reduced after receiving eradication regimen. Liver enzyme levels were also decreased in those with unsuccessful eradication, which could be due to reduction in bacterial load by

eradication regimen. However, liver enzymes decreased to normal range only in about half of the patients and even increased in about 25% of the cases after eradication. These results suggest a role for *H. pylori* infection in the pathophysiology of unexplained hypertransaminasemia, of course not in all of the cases.

To the best of our knowledge, this is the first study that has investigated if *H. pylori* eradication affects liver enzymes in patients with hypertransaminasemia. One other study by Karahalil *et al.* found no change in alpha-glutathione S-transferase (a marker of hepatocellular damage better than transaminases in toxic and autoimmune hepatitis)^[20] or other LFTs after eradicating *H. pylori*; however, included patients in this study had normal LFTs at enrolment.^[21] In another study, Graham *et al.* evaluated LFTs of patients with peptic ulcer and *H. pylori* before and 3 months after *H. pylori* eradication. Authors found higher AST levels with Cag-A positive *H. pylori* infection, but found no change in liver enzymes after eradication. Again, included patients in the mentioned study had normal LFTs at enrolment.^[14] Considering no association of *H. pylori* with ALT level, which is more specific than AST, and no change in liver enzymes after eradication, these authors introduced two hypotheses; that there is an extra-hepatic source for increased AST level; and/or there is a host genetic susceptibility to both *H. pylori* infection and increased levels of liver enzymes.^[14] However, our results are against these studies and suggest that *H. pylori* infection plays a role in at least some patients with hypertransaminasemia, and liver enzymes would decrease after eradication.

The underlying mechanisms of liver damage by *H. pylori* infection are still unclear. In an *in-vitro* study, Le Roux-Goglin *et al.* showed that *H. pylori* can stimulate podosome formation and collagen accumulation in cultured mouse hepatocytes that can lead to liver fibrosis and possibly cancer *in-vivo*.^[22] Another animal study by Goo *et al.* showed that inoculation of *H. pylori* in hepatic fibrosis-induced mice accelerates the fibrosis. This finding suggests a role for *H. pylori* infection in the development/progression of liver cirrhosis.^[11] A similar study by Ki *et al.* indicated pro-inflammatory signaling pathways as the underlying mechanisms of accelerated hepatic fibrosis by *H. pylori* infection.^[23] Human studies also have shown an association between *H. pylori* presence in the liver (genetically similar to those isolated from the stomach) and disease progression in patients with viral chronic hepatitis and cirrhosis.^[7,12] Furthermore, associations between *H. pylori* infection and cirrhosis in patients with hepatitis C virus,^[13] and between hypertransaminasemia and infection with Cag-A positive *H. pylori* in patients with peptic ulcer disease

Table 1: Levels and changes of liver transaminases before and after *Helicobacter pylori* eradication

Liver aminotransferases	ALT (IU/L)	AST (IU/L)
Before eradication	61.2±9.6	47.8±10.5
After eradication	53.3±25.8	41.5±21.5
Change	7.8±24.9	6.3±19.6
Change with the successful eradication, n=93	7.2±25.7	6.1±20.2
Change with failed eradication, n= 14	11.2±18.8	7.5±15.0

Data are presented as mean±SD; ALT: Alanine transaminase, AST: Aspartate transaminase

are presented.^[14] It is suggested that *H. pylori* can reach to and colonized in the liver via the blood or the biliary system as a result of structural changes in the hepatobiliary system.^[7,10] Furthermore, concomitant infection with *H. pylori* and other *helicobacter* species such as *H. hepaticus* are possible. Studies showed that *H. hepaticus* could progress the liver disease.^[24] It must be noted that infection with such species also responds to current *H. pylori* eradication regimens.^[25,26]

There are some limitations to our study. First of all, it was better to conduct a controlled trial with an arm for which no eradication was carried out. Then, we could evaluate the exact effects of eradication on liver enzymes changes. Furthermore, if we had more workups to discover the exact reasons of enzymes elevation (e.g., by liver biopsy), we could have more judicable data to conclude an association between *H. pylori* and liver damage. However, it is not possible and not recommended to do a liver biopsy in all patients with mild hypertransaminasemia. We did not investigate celiac disease in our study population and according to some reports from our society about 10% of patients presenting with hypertransaminasemia are celiac disease cases.^[27] Furthermore, evaluation of Cag-A positive strain of *H. pylori* would have provided information on the possible association of specific *H. pylori* strains and liver damage. We focused our study on patients with less than threefold abnormal enzyme elevation, and thus we cannot generalize our results to more severe cases. Furthermore, the sample size of our study was not large enough for comparison of those with and without successful eradication, and the follow-up was not long enough to monitor the long-term effects of *H. pylori* eradication on liver enzymes.

In summary, the results of the present study suggest a role for *H. pylori* infection in some of the patients referring with mild unexplained hypertransaminasemia, and reduction in liver enzyme levels after receiving eradication regimen in these patients. According to limitations, the results of our study should be interpreted cautiously. We recommend conducting a controlled trial with enough sample size and follow-up period to investigate the exact effects of *H. pylori* eradication on liver enzymes changes in patients referring with unexplained hypertransaminasemia. Further, studies are also required regarding the association of specific *H. pylori* strains with liver dysfunction and the underlying mechanisms, and long-term clinical consequences of such association.

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