

Original Article

ZJU index is associated with prevalence of *Helicobacter pylori* infection in a Chinese population

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Received July 26, 2016; Accepted September 18, 2016; Epub November 15, 2016; Published November 30, 2016

Abstract: Background/Aim: The association between fatty liver and *H. pylori* infection is controversial in the literature. This study aimed to investigate the association of ZJU index, a novel indicator of fatty liver, with the prevalence of *H. pylori* infection in a Chinese population. Methods: The adults who underwent their health checkups at the First Affiliated Hospital, College of Medicine, Zhejiang University between July 1, 2014 and December 31, 2014, were enrolled in this study. *H. pylori* infection status was determined by ¹³C urea breath test, and the association of ZJU index with the prevalence of *H. pylori* infection was analyzed. Results: Of 8308 participants enrolled, 3732 (44.92%) were positive for *H. pylori* infection. *H. pylori*-positive participants had higher ZJU index and more unfavorable metabolic profile than *H. pylori*-negative controls. ZJU index was positively associated with the prevalence of *H. pylori* infection. Both univariate and multivariate logistic analysis showed that ZJU index was significantly associated with risk factors of *H. pylori* infection. Conclusions: *H. pylori* infection affects 44.92% of the study population, and ZJU index was positively associated with the prevalence of the infection.

Keywords: *Helicobacter pylori*, fatty liver, ZJU index

Introduction

Helicobacter pylori (*H. pylori*) infection is one of the most common chronic infections worldwide [1]. The infection significantly increases the risk of gastropathy including chronic gastritis, peptic ulcer, gastric cancer, and gastric mucosa-associated lymphoid tissue (MALT) lymphoma [2]. *H. pylori* infection may also cause extragastric diseases such as idiopathic thrombocytopenic purpura, chronic bronchitis, and neurological disorders [3]. The contribution of *H. pylori* infection on obesity, insulin resistance, and cardiovascular diseases has also been reported [4-6].

Fatty liver disease is the most common liver disease in Western countries, affecting 20%-30% of general adults [7]. The association of *H. pylori* infection with fatty liver disease has been paid much attention to during recent decade. Cindoruk and colleagues firstly detected *H. pylori* DNA in the liver biopsy sample

from a nonalcoholic steatohepatitis patient [8]. Pirouz *et al.* reported that 45.5% (5/11) of paraffin-embedded liver specimens from patients with nonalcoholic fatty liver disease (NAFLD) were positive for *H. pylori* DNA [9]. Further studies observed that fatty liver patients had higher rates of anti-*H. pylori* IgG compared with controls [10, 11], and *H. pylori*-positive individuals had lower liver-to-spleen ratio, an indicator of fatty liver, than *H. pylori*-negative controls [12]. The observations that *H. pylori* eradication significantly improved the metabolic profile, liver function and fatty liver further support a significant association of *H. pylori* infection with fatty liver disease [13, 14]. On the contrary, a recent study reported that the prevalence of *H. pylori* infection was not associated with fatty liver disease determined by hepatic steatosis index or NAFLD liver fat score [15]. The inconsistency may rise from relatively small sample size, differences in study population, methodologies for detecting *H. pylori* infection and fatty liver.

ZJU index is a novel model developed recently by our group for screening fatty liver in the Chinese population [16]. The index is based on body mass index, fasting plasma glucose, triglycerides and serum alanine aminotransferase-to-aspartate transaminase ratio, and is proved to be an effective parameter for screening fatty liver with high sensitivity and specificity [16]. A recent study by Ji *et al.* also found that ZJU index is a useful indicator for recognizing insulin resistance in the Chinese general population [17]. Whether ZJU index, instead of ultrasonography-diagnosed fatty liver, is associated with *H. pylori* infection is unclear.

In this study, we performed a cross-sectional study to investigate the association of ZJU index with the prevalence of *H. pylori* infection in a Chinese population.

Materials and methods

Study population

This was a cross-sectional study population of asymptomatic Chinese adults who underwent their health examinations at the First Affiliated Hospital, College of Medicine, Zhejiang University between July 1, 2014 and December 31, 2014. The analyses were limited to those who had full records of anthropometric, biochemical data, and had results of *H. pylori* tests. Those who took proton pump inhibitors, anti-dyslipidemia or antidiabetic drugs were excluded. Participants who had a history of *H. pylori* eradication were also excluded from this study. A total of 8308 participants (4928 men and 3380 women) with a mean (standard deviation) age of 47.0 (11.2) years were enrolled in the final analysis.

All participants voluntarily consented to entry into this study. The participants' information was anonymized at collection and analysis. The study procedures were approved by the Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University.

Clinical examinations

The examination including anthropometric measurements and biochemical analyses were conducted according to standard procedures as previously described [4, 18]. All participants

were instructed to fast overnight before the clinical examinations. Height and body weight were measured without shoes and with light clothing. Body mass index was calculated by dividing body weight in kilograms by the square of height in meters. Blood pressure was measured using an automated sphygmomanometer.

Peripheral venous blood samples were collected for the analysis of serum glucose, uric acid, liver enzymes including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ -glutamyltransferase, and serum lipids including triglyceride, total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol. The levels of thyroid stimulating hormone, and platelet count were also analyzed according to standard protocols. Regular intake of proton pump inhibitors, antidyslipidemia or antidiabetic drugs, and the history of *H. pylori* eradication were collected by self-reported questionnaire.

Detection of *H. pylori* infection

The *H. pylori* infection status was determined based on the results of fasting ^{13}C urea breath test (^{13}C -UBT). The test was carried out according to standard procedures described previously [4, 19]. In brief, a baseline breath sample was collected by blowing through a straw in to a 10-mL plastic container. A second breath sample was collected 30 min after taking a tablet containing 75 mg of ^{13}C -urea (Beijing Boran Pharmaceutical Co., Ltd., Beijing, China). Both the baseline and 30-min breath samples were analyzed by an infrared heterodyne radiometer (Beijing Huaheng Anbang Science and Technology Co., Ltd, Beijing, China). If the 30-min value showed a greater than 4.0‰ difference over the baseline value, the test was considered to be positive and the participant was considered to be *H. pylori* infected.

Statistics analysis

Statistical analyses were performed with SPSS version 13.0 (SPSS Inc., Chicago, IL). ZJU index was calculated according to the formula: ZJU index = body mass index (kg/m^2) + fasting blood sugar (mmol/L) + triglyceride (mmol/L) + $3 \times \text{ALT}/\text{AST}$ ratio (+2, if female). Continuous data for different groups were presented as

ZJU index and *H. pylori* infection

Table 1. Comparison of clinical characteristics according to *H. pylori* infection status

Variables	<i>H. pylori</i> (+)	<i>H. pylori</i> (-)	t value	P value
n (male/female)	3732 (2252/1480)	4576 (2676/1900)	2.959 ^a	0.088
Age (yr)	46.9 (10.8)	47.0 (11.6)	0.575	0.565
Body mass index (kg/m ²)	24.14 (3.20)	23.76 (3.19)	5.321	<0.001
Systolic blood pressure (mmHg)	127.4 (17.5)	126.5 (17.7)	2.337	0.019
Diastolic blood pressure (mmHg)	77.9 (11.4)	77.4 (11.5)	2.043	0.041
Alanine aminotransferase (U/L)	20.0 (14.0-30.0)	19.0 (13.0-28.0)	2.966 ^b	0.003
Aspartate aminotransferase (U/L)	21.0 (18.0-25.0)	20.0 (17.0-25.0)	1.620 ^b	0.105
γ-Glutamyltransferase (U/L)	23.0 (15.0-42.0)	23.0 (15.0-39.0)	3.139 ^b	0.002
Triglyceride (mmol/L)	1.30 (0.90-1.89)	1.25 (0.86-1.92)	2.058 ^b	0.040
Total cholesterol (mmol/L)	4.86 (0.92)	4.80 (0.93)	2.955	0.003
HDL cholesterol (mmol/L)	1.13 (0.28)	1.14 (0.29)	2.618	0.009
LDL cholesterol (mmol/L)	2.59 (0.64)	2.55 (0.63)	2.552	0.011
Fasting plasma glucose (mmol/L)	4.78 (4.48-5.13)	4.77 (4.47-5.11)	1.193 ^b	0.233
Serum uric acid level (μmol/L)	338.5 (92.1)	334.6 (89.6)	1.976	0.048
Thyroid stimulating hormone (mIU/L)	1.68 (1.21-2.31)	1.65 (1.17-2.33)	1.098	0.272
Platelet count (×10 ⁹ /L)	203.0 (172.0-238.0)	201.0 (170.0-235.0)	1.810 ^b	0.070
ZJU index	34.7 (4.5)	34.2 (4.5)	4.671	<0.001

Data are presented as mean (SD) or median (IQR). ^aχ² value; ^bZ value. HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 2. Association of ZJU index with prevalence of *H. pylori* infection

ZJU index quartiles	Total	<i>H. pylori</i> (+)	PR%	PR	χ ² value	P value
Quartile 1	2077	872	41.98	1.00	23.028	<0.001
Quartile 2	2077	886	42.66	1.02		
Quartile 3	2077	981	47.23	1.13		
Quartile 4	2077	993	47.81	1.14		

PR%, prevalence rate; PR, prevalence ratio.

Table 3. Association of ZJU index category with prevalence of *H. pylori* infection

ZJU index category	Total	<i>H. pylori</i> (+)	PR%	PR	χ ² value	P value
<32.0	2698	1143	42.36	1.00	13.347	0.001
32.0-38.0	3964	1801	45.43	1.07		
>38.0	1646	788	47.87	1.13		

PR%, prevalence rate; PR, prevalence ratio.

mean and standard deviation or median and interquartile range. Student's *t*-test, Mann-Whitney *U* test, and Pearson's χ² test were used for comparisons between the groups. Univariate and multivariate logistic regression analyses were used to evaluate the odds ratio (OR) and 95% confidence interval (CI) for *H. pylori* infection using the related covariates.

P<0.05 (2-tailed) was considered to be statistically significant.

Results

Prevalence of *H. pylori* infection in the study population

Of 8308 participants enrolled in this study, 3732 (44.92%) were positive for ¹³C-UBT and considered to be *H. pylori*-infected. Compared with *H. pylori*-negative participants, *H. pylori*-positive participants had higher body mass index, systolic and diastolic blood pressure, serum alanine aminotransferase and γ-glutamyltransferase levels. *H. pylori*-positive participants also had higher serum triglyceride, total cholesterol, LDL cholesterol, and uric acid levels, while lower serum LDL cholesterol levels than *H. pylori*-negative participants (**Table 1**). These results showed that *H. pylori* infection is associated with unfavorable metabolic profile compared with *H. pylori*-negative individuals.

ZJU index and prevalence of *H. pylori* infection

A noticeable finding in **Table 1** is that ZJU index, a novel model for screening fatty liver, was sig-

ZJU index and *H. pylori* infection

Table 4. Univariate analysis for factors associated with *H. pylori* infection

Variables	χ^2 value	OR (95% CI)	P value
Age (yr)	0.331	0.999 (0.995-1.003)	0.565
Gender (male)	2.959	0.926 (0.848-1.011)	0.085
Body mass index (kg/m ²)	28.113	1.037 (1.023-1.052)	<0.001
Systolic blood pressure (mmHg)	5.456	1.003 (1.000-1.005)	0.019
Diastolic blood pressure (mmHg)	4.171	1.004 (1.000-1.008)	0.041
Alanine aminotransferase (U/L)	2.377	1.002 (1.000-1.004)	0.123
Aspartate aminotransferase (U/L)	1.838	1.002 (0.999-1.005)	0.175
γ -Glutamyltransferase (U/L)	2.238	1.001 (1.000-1.002)	0.135
Triglyceride (mmol/L)	2.249	1.026 (0.992-1.060)	0.134
Total cholesterol (mmol/L)	8.711	1.073 (1.024-1.124)	0.003
HDL cholesterol (mmol/L)	6.845	0.816 (0.701-0.950)	0.009
LDL cholesterol (mmol/L)	6.500	1.093 (1.021-1.170)	0.011
Fasting plasma glucose (mmol/L)	0.170	1.009 (0.996-1.055)	0.680
Serum uric acid level (μ mol/L)	3.903	1.000 (1.000-1.001)	0.048
Thyroid stimulating hormone (mIU/L)	4.269	0.970 (0.942-0.998)	0.039
Platelet count ($\times 10^9/L$)	4.269	0.970 (0.942-0.998)	0.039
ZJU index	21.693	1.023 (1.013-1.033)	<0.001

OR, odds ratio; CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 5. Multivariate analysis for factors associated with *H. pylori* infection

Variables	χ^2 value	OR (95% CI)	P value
Total cholesterol (mmol/L)	5.281	1.064 (1.009-1.122)	0.022
Thyroid stimulating hormone (mIU/L)	4.926	0.967 (0.939-0.996)	0.026
ZJU index	9.652	1.017 (1.006-1.028)	0.002

OR, odds ratio; CI, confidence interval.

nificantly higher among *H. pylori*-positive participants than *H. pylori*-negative controls. To further analyze the association of ZJU index with prevalence of *H. pylori* infection, we divided all the participants into quartiles according to their ZJU index: ZJU index <32.2, 31.2-33.9, 33.9-37.1, >37.1 for quartile 1, 2, 3, and 4, respectively. We found that ZJU index was positively associated with the prevalence of *H. pylori* infection. The prevalence was 41.98% among the participants with ZJU index in quartile 1, and increased to 42.66%, 47.23%, and 47.81% in quartile 2, 3, and 4, respectively (*P* for trend <0.001; **Table 2**). This finding suggests that individuals with higher ZJU index were more likely to be *H. pylori* infected.

ZJU index could rule out fatty liver at a value of <32.0 with a sensitivity of 92.2%, and could detect fatty liver at a value of >38.0 with a

specificity of 93.4%. To analysis potential association of fatty liver with *H. pylori* infection, we classified all the participants into three groups according to their ZJU index category: without fatty liver (ZJU index <32.0), uncertain (ZJU index between 32.0 and 38.0), and with fatty liver (ZJU index >38.0). As illustrated in **Table 3**, the prevalence of *H. pylori* infection was significantly higher among individuals with fatty liver (ZJU index >38.0) than those without fatty liver (ZJU index <32.0). This finding suggests a close association between fatty liver and *H. pylori* infection among the study population.

ZJU index and risk of *H. pylori* infection

The factors associated with *H. pylori* infection were analyzed by both univariate and multivariate binary logistic analysis. Our univariate analysis found

that ten variables, including body mass index, systolic and diastolic blood pressure, total cholesterol, HDL and LDL cholesterol, uric acid, thyroid stimulating hormone, platelet count, and ZJU index were associated with risk factors for *H. pylori* infection (**Table 4**). We further performed multivariate stepwise logistic analysis by adjusting the variables that significantly associated with *H. pylori* infection in **Table 4**. We found that ZJU index (OR = 1.017; 95% CI: 1.006-1.028) remained to be statistically significantly associated with risk factors for *H. pylori* infection (**Table 5**). This finding further supported a significant association between ZJU index and *H. pylori* infection.

Discussion

In this study, we provided evidence that ZJU index, an indicator of fatty liver, is closely asso-

ciated with *H. pylori* infection in a Chinese population. First, ZJU index was significantly higher among *H. pylori*-positive individuals than that among *H. pylori*-negative controls. Second, ZJU index was linear and positively related with prevalence of *H. pylori* infection. Third, our univariate and multivariate logistic analysis both found that ZJU index was significantly associated with risk factors for *H. pylori* infection.

The extragastric consequences of *H. pylori* infection has attracted a lot of attention [3, 20]. *H. pylori* infection may deteriorate metabolic profile, and thereby induce obesity and obesity related metabolic diseases [21, 22]. Our results were in line with previous reports that *H. pylori*-positive participants had unfavorable metabolic profile compared with *H. pylori*-negative controls. Our results also showed that *H. pylori*-positive participants had higher ZJU index than *H. pylori*-negative controls. ZJU index is a novel model developed recently by our group for predicting fatty liver disease [16]. ZJU index could rule out fatty liver at a value of <32.0, and detect fatty liver at a value of >38.0 with high sensitivity and specificity. Pathology results confirmed that this model can be used for the detection of steatosis [16]. In this study, we found that for participants with fatty liver (ZJU index >38.0) had significantly higher prevalence of *H. pylori* infection than those without fatty liver (ZJU index <32.0). This finding suggested a significant link between fatty liver and *H. pylori* infection.

The mechanism by which *H. pylori* infection is associated with fatty liver remains unclear. *H. pylori* colonizes the stomach in childhood and persists throughout life, and this persistent infection elicits local and systemic chronic inflammatory responses [23]. Recent study found that *H. pylori* infection induced activation of NLRP3 inflammasome [24, 25], which is an important trigger for obesity, insulin resistance, and fatty liver [26]. Fatty liver in turn may impact the susceptibility of *H. pylori* infection. Morbidly obese individuals with fatty liver had reduced polymorphonuclear bactericidal capacity [27], and decreased maturation of monocytes into macrophages [28]. These alterations may induce a more favorable immune environment for *H. pylori* infection. Further studies are needed to find out the the

mechanistic explanation for the link between fatty liver and *H. pylori* infection.

Our study had some limitations. First, the cause-and-consequence relationship between fatty liver and *H. pylori* infection could not be answered by this cross-sectional study. Second, whether *H. pylori* eradication decreases ZJU index and reduces the risk for fatty liver remains uncertain. Further prospective studies are needed to clarify these issues.

In conclusion, our results showed that *H. pylori* infection affects 44.92% of the study population, and ZJU index was positively associated with the prevalence of the infection. Our results suggested a significant association of fatty liver with *H. pylori* infection. Further clarifying the cause-and-consequence relationship and underlying mechanism may have significant clinical importance for the disease prevention and management.

Acknowledgements

This work was supported by National Natural Science Foundation of China (Nos. 81100278 and 81470838 to C.X., 81170378 and 8123-0012 to Y.L.), International Science and Technology Cooperation Projects of Zhejiang Province (No. 2013C24010 to C.X.), and Science Foundation of Health Bureau of Zhejiang Province (Nos. 2015DTA020 to H.L., and 2012RCA026 to C.X.). The funders did not play any role in the study design, data collection and analysis, decisions regarding data release or manuscript preparation.

Disclosure of conflict of interest

None.

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