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Helicobacter pylori infection as a risk factor for serum bilirubin change and less favourable lipid profiles: a hospital-based health examination survey

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Abstract

Background: *Helicobacter pylori* infection is associated with several extragastric conditions including dyslipidemia and metabolic syndrome. This study aimed to investigate additional metabolic parameters associated with *H. pylori* infection in a Chinese population.

Methods: Using a case-control approach we studied 617 subjects with ^{13}C-urea breath test (^{13}C-UBT) values ≥10‰ who were defined as being positive for *H. pylori* (cases), while 617 sex and age- matched subjects with ^{13}C-UBT values ≤1‰ were defined as *H. pylori* negative (controls) in Beijing Tongren Hospital from March 2016 to May 2017. Biochemical parameters including serum bilirubin and lipids were tested.

Results: A total of 1982 subjects participated in this study. The *H. pylori* infected subjects had significantly lower serum direct bilirubin concentrations (2.34 ± 0.38 vs. 2.47 ± 0.90 μmol/L, $P = 0.008$). *H. pylori* infection was independently associated with lower direct bilirubin levels (OR = 1.497, 95% CI =1.121–1.999, $P = 0.006$) or total bilirubin levels (OR = 1.322, 95% CI =1.005–1.738, $P = 0.046$) after adjustment for age, sex, body mass index (BMI), alanine aminotransferase (ALT), aspartate aminotransferase (AST), high-density lipoprotein cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), total cholesterol (TC) and triglycerides(TG). In addition, the *H. pylori* infected subjects had higher LDL-C levels (2.98 ± 0.76 vs. 2.89 ± 0.75 mmol/L, $P = 0.033$) and lower HDL-C levels (1.39 ± 0.37 vs. 1.44 ± 0.41 mmol/L, $P = 0.044$). LDL-C was negatively correlated with direct bilirubin concentration ($R = -0.260$, $P < 0.0001$).

Conclusions: Bilirubin has been found to be a potent endogenous antioxidant and negatively associated with metabolic syndrome. Our results suggest that *H. pylori* infection is an independent risk factor for serum bilirubin reduction and less favorable lipid profiles.

Keywords: *Helicobacter pylori*, Serum bilirubin, Metabolic disorders, Lipid metabolism

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Background

Helicobacter pylori infection affects ∼ 50% of the world's population and has been recognized as one of the most common chronic infections in human. [1] The overall prevalence is high in developing countries. *H. pylori* infection cause upper gastrointestinal diseases including gastritis, peptic ulcer disease and also increase the risk of gastric cancer. Interestingly, several studies suggest that *H. pylori* infection may influence the gut microbiome [2–4]. Further, diverse extragastric diseases have been linked to *H. pylori* infection, including dyslipidemia [5], type 2 diabetes [6], insulin resistance [7] and metabolic syndrome [8]. The correlation of *H. pylori* infection and bilirubin levels has not been reported. Nevertheless, *H. pylori* infection appears to play an important role in the development of metabolic disorders in which require further investigations.

In the current study, we aimed to investigate additional metabolic parameters and their clinical impact with regard to *H. pylori* infection in a Chinese population.

Methods

Study design and population

We performed a case-control study by selecting subjects who were overtly positive for *H. pylori* as cases and overtly negative controls matched by sex and age. We screened subjects aged 18–79 years who were receiving annual health examinations including ^{13}C –urea breath test (UBT) in Beijing Tongren Hospital from March 2016 to May 2017. Subjects with ^{13}C-UBT values≥10‰ or ≤ 1‰ were defined as overtly positive (cases) or overtly negative (controls) for *H. pylori*, respectively. Subjects with ^{13}C-UBT results between 1‰ and 10‰ were excluded from the study. Subjects in the *H. pylori* positive group were matched 1:1 with age and sex to *H. pylori* negative individuals. After the primary assessment of the baseline characters for all subjects, we further excluded participants with liver and gall bladder diseases (hepatitis, jaundice, cholecystitis, biliary calculus), abnormal liver function (alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 1.5 times upper normal limit, or bilirubin > twice upper normal limit), abnormal kidney function (Cr > upper normal limit) to better eliminate the potential biases caused by diseases.

Anthropometric and laboratory measurements

Each subject had anthropometric measurements. Presence of systematic or previous diseases, such as diabetes mellitus (DM), hypertension, hepatitis, jaundice, cholecystitis or biliary calculus were noted. Body mass index (BMI) was measured as weight (kg) divided by height (meters) squared (kg/m^2). Waist circumference (WC) was measured at the level of the umbilicus in cm.

Blood pressure (BP) was measured three times when participants were seated, and the average of the last two measurements was recorded. Blood samples were collected after an overnight fasting for the determination of plasma glucose, glycosylated hemoglobin A1c (HbA1c), total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), direct bilirubin, total bilirubin, total bile acids, alkaline phosphatase (ALP), ALT, AST [9], γ-glutamyl transpeptidase (γ-GT), blood urea nitrogen [10], serum creatinine (SCr) and uric acids (UA) concentrations.

Statistical analysis

Data are presented as the mean ± SD. The baseline characteristics of subjects were compared using the chi-squared test for categorical variables and the Student *t*-test for continuous variables. Distribution of discrete/ qualitative variables was compared by trend chi-square test. Binary logistic regression analysis was used to estimate crude and adjusted odds ratios (ORs) (95% CIs) to assess the risk of bilirubin change associated with *H. pylori* infection. When data were not normally distributed, the correlations of bilirubin and cholesterol were determined by the Spearman correlation coefficient analysis. Calculations were performed using SPSS 24.0 statistical software (SPSS Inc., Chicago, IL, USA), and significance was established at a two-tailed $P < 0.05$.

Results

Clinical characteristics of the study population

A total of 1982 subjects participated in the health examination including ^{13}C -UBT, physical examination and blood tests. Based on selection criteria, 623 subjects were initially defined as cases, 1010 were defined as controls, and 349 were excluded from the study. The primary baseline characters of the two groups are shown in Additional file 1: Table S1. Unexpectedly, our results unveiled an intriguing association between bilirubin decrease and *H. pylori* infection (direct bilirubin 2.50 ± 0.99 vs. 2.37 ± 0.90 μmol/L, $P = 0.015$, total bilirubin 14.49 ± 5.66 vs. 13.87 ± 5.32 μmol/L, $P = 0.049$). We doubted if other disorders may influence the bilirubin levels and caused the inauthentic results, hence, we excluded participants with diseases which could affect bilirubin levels pathologically. According to the specified criteria, 29 patients were excluded from the study. Of the remaining 1953 subjects, 617 (31.6%) overtly positive for *H. pylori* were matched 1:1 with age and sex to 988 (50.6%) overtly negative for *H. pylori*, 348 subjects with ^{13}C-UBT results between 1‰ and 10‰ were excluded from the study. Thus, 617 overtly positive *H. pylori* individuals (case group) and 617 sex and age- matched

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overtly negative *H. pylori* subjects (control group) comprised the case-control study (Fig. 1).

The demographic and biochemical parameters of the cases and the controls are shown in Table 1. The case group had significantly less favourable lipid profiles than controls: LDL-C 2.98 ± 0.76 vs. 2.89 ± 0.75 mmol/L ($P = 0.033$), HDL-C 1.39 ± 0.37 vs. 1.44 ± 0.41 mmol/L ($P = 0.044$). Unsurprisingly, the case group also had lower bilirubin levels compared with the control group: direct bilirubin 2.34 ± 0.38 vs. 2.47 ± 0.90 μmol/L ($P = 0.008$), total bilirubin 13.65 ± 4.84 vs. 14.28 ± 5.01 μmol/L ($P = 0.026$). There was no significant difference in other demographic and clinical characteristics.

Association between serum bilirubin levels and *H. pylori* infection

To further investigate the correlation between *H. pylori* infection and bilirubin levels, subjects from both groups were assigned to 4 grades based on quartiles of serum bilirubin concentrations and the proportions of each grade in case and control groups are shown in Fig. 2. In the *H. pylori* positive group, the proportion of subjects with direct bilirubin levels in the highest quart (> 2.8 μmol/L) was smaller than that of the *H. pylori* negative group (21.1% vs 28.4%) (Trend $\chi^2 = 4.119$, $P = 0.042$). The same trend was also observed in subjects assigned by total bilirubin level (Trend $\chi^2 = 6.256$, $P = 0.012$). This suggests that *H. pylori* infection is associated with both direct and total bilirubin reduction.

Similar trend was observed when subjects were grouped according to quartiles of LDL-C level (Trend $\chi^2 = 4.577$, $P = 0.032$, data not shown), but was not seen when subjects grouped according to quartiles of HDL-C level (Trend $\chi^2 = 1.185$, $P = 0.288$, data not shown) although the mean of HDL-C was significant different in *H. pylori* overtly positive and negative groups (Table 1).

The risk of bilirubin changes according to the infection of *H. pylori*

Given the association between increased serum bilirubin levels within the reference range and better health outcomes (or conversely lower bilirubin concentrations with higher morbidities) [11–16], we assigned subjects into two groups with direct bilirubin (2.8) and total bilirubin (16.4) in the upper distribution quartile. Bilirubin levels below the upper quartile were defined as "bilirubin not increase". Logistic regression analysis was performed to determine the independence of the association between *H. pylori* infection and risk for "bilirubin not increase". As shown in Table 2, *H. pylori* infection was associated
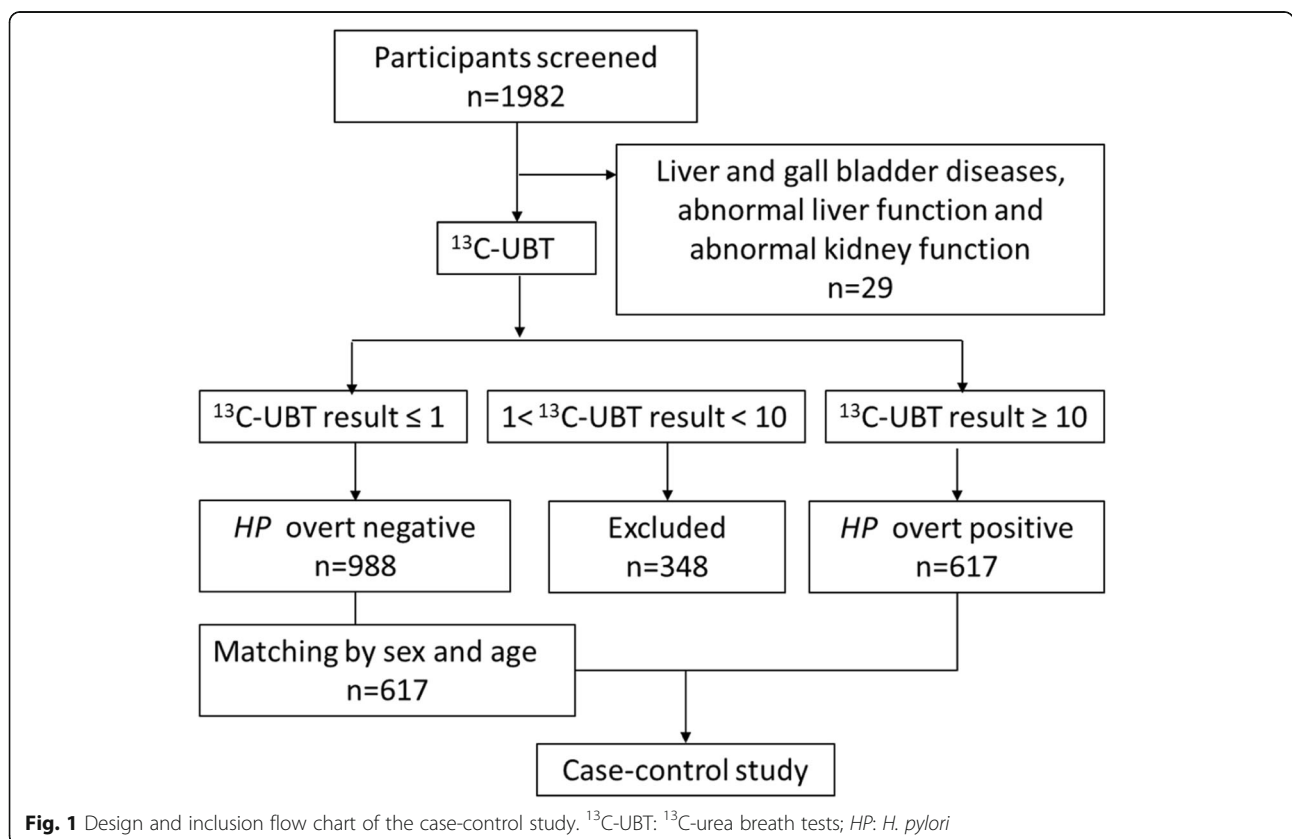

Fig. 1 Design and inclusion flow chart of the case-control study. ^{13}C-UBT: ^{13}C-urea breath tests; *HP*: *H. pylori*

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Table 1 Comparison of various clinical characteristics classified by *H. pylori* infection

	H. pylori obvious negative ($n = 617$)	*H. pylori* obvious positive ($n = 617$)	*P* value
Age (years)	41.2 ± 11.7	41.3 ± 11.3	0.910
Female (%)	54.3	54.3	matching
Waist circumference (cm)	80.72 ± 11.33	80.37 ± 11.64	0.601
BMI (kg/m^2)	24.32 ± 3.78	24.34 ± 3.89	0.943
SBP (mmHg)	118.0 ± 13.4	116.8 ± 12.9	0.103
DBP (mmHg)	75.2 ± 9.1	74.9 ± 9.0	0.465
Hypertension (%)	15.9	13.8	0.334
Fasting blood glucose (mmol/l)	5.37 ± 1.54	5.34 ± 1.13	0.705
Diabetes (%)	5.0	6.2	0.389
Total cholesterol (mmol/l)	4.90 ± 0.88	4.98 ± 0.89	0.142
Triglycerides (mmol/l)	1.40 ± 0.99	1.43 ± 1.22	0.651
HDL-C (mmol/l)	1.44 ± 0.41	1.39 ± 0.37	**0.044**
LDL-C (mmol/l)	2.89 ± 0.75	2.98 ± 0.76	**0.033**
Direct bilirubin (μmol/l)	2.47 ± 0.90	2.34 ± 0.83	**0.008**
Total bilirubin (μmol/l)	14.28 ± 5.01	13.65 ± 4.84	**0.026**
Total bile acids (μmol/L)	3.27 ± 2.20	3.21 ± 2.35	0.657
Alkaline phosphatase (U/L)	73.68 ± 20.93	74.14 ± 21.62	0.706
ALT (U/L)	22.19 ± 16.37	22.33 ± 18.18	0.883
AST (U/L)	22.14 ± 10.23	22.09 ± 11.04	0.932
γ-GT (U/L)	28.55 ± 23.05	28.31 ± 25.81	0.864
BUN (mmol/L)	4.73 ± 1.22	4.68 ± 1.15	0.442
Serum creatinine (μmol/L)	65.88 ± 13.61	66.56 ± 14.35	0.391
Uric acid (μmol/L)	331.87 ± 86.34	330.67 ± 88.87	0.809

SBP systolic blood pressure, *DBP* diastolic blood pressure
Data are mean ± SD; Student *t*-test

with higher risk of both direct bilirubin (OR = 1.483, 95% CI =1.143–1.925, *P* = 0.003) and total bilirubin (OR = 1.336, 95% CI =1.030–1.733, *P* = 0.029) "not increase" in univariate analysis. After adjustment for age and sex (model 2), further adjustment for BMI, ALT and AST (model 3), and then additional adjustment for HDL-C, LDL-C, TC and TG (model 4), the ORs remained significant.

Correlation between direct bilirubin and cholesterol
We found that lipid profiles improved with increasing direct bilirubin levels regardless of *H. pylori* status. LDL-C was negatively correlated with direct bilirubin concentration (R = − 0.260, *P* < 0.0001) (Fig. 3a), while HDL-C was positively correlated with direct bilirubin level. (R = 0.063, *P* = 0.028) (Fig. 3b).

Discussion
With the sensitivity and specificity exceeding 90%, UBT is often considered as the gold standard test in the diagnosis of *H. pylori* infection [17–19]. However, there is a "grey zone" of uncertainty when UBT values range from

2.0 to 5.0‰ [20, 21]. Fortunately, positive and negative UBT results tend to cluster outside this range [22]. We performed this study by selecting subjects at the extreme ends of the range of ^{13}C-UBT values to comprise the study groups. We selected subjects with ^{13}C-UBT values ≤1 ‰ and ≥10 ‰ to avoid false-positive and false-negative results.

In this case-control study, we found that subjects with high ^{13}C-UBT values had lower bilirubin concentrations and less favourable lipid profiles compared those with low ^{13}C-UBT values. In addition to being a breakdown product of heme, serum bilirubin is also a powerful anti-oxidant [23, 24]. High normal concentrations of serum bilirubin correlate with better health outcomes [11–16]. Bilirubin concentrations have been reported as being inversely associated with risk for cardiovascular disease [15, 25], metabolic syndrome [16], diabetes [11], inflammatory disease [13] and some cancers [14]. However, little is known of determinants of bilirubin levels within the reference range. To our knowledge, this study indicates for the first time that *H. pylori* infection may be associated with decreased bilirubin concentrations
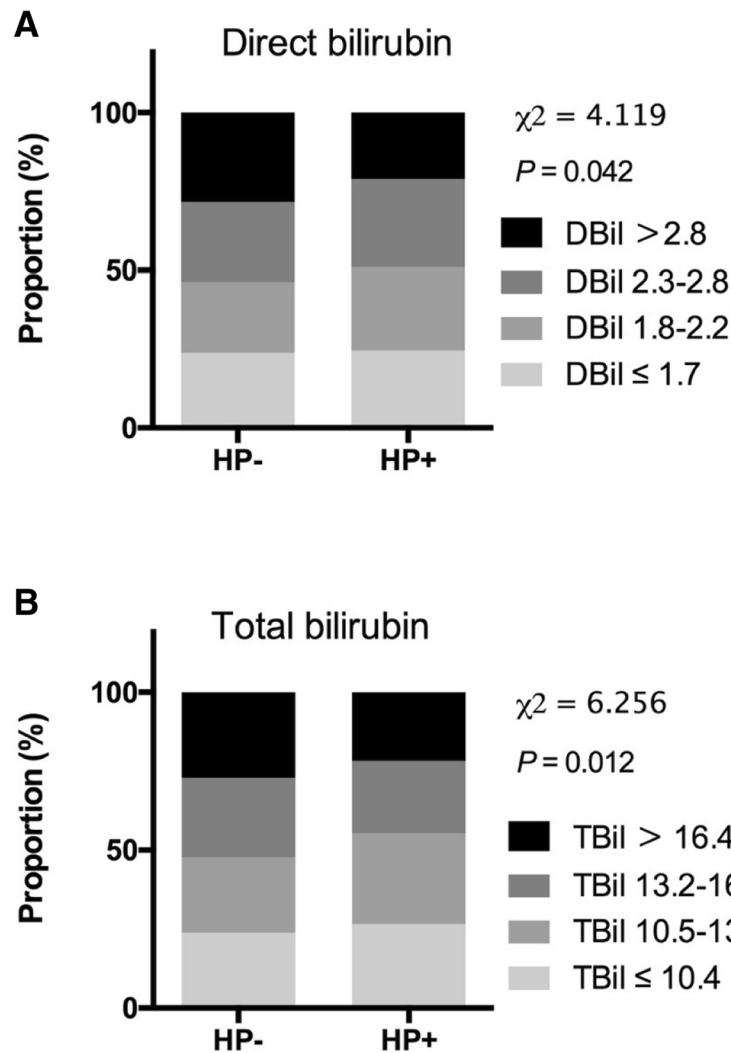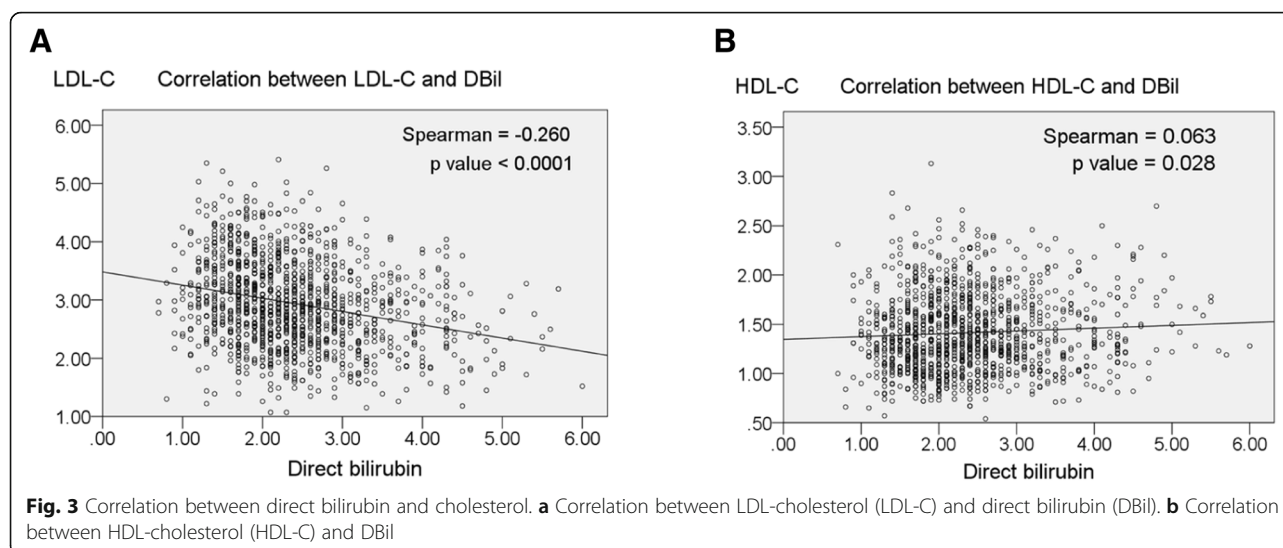
Fig. 2 The association between serum bilirubin levels and *H. pylori* infection. **a** Proportion of subjects according to the quartiles of direct bilirubin. The percentages of each grade from higher to lower direct bilirubin levels were 28.4, 25.4, 22.4, 23.8% respectively in *H. pylori* overt negative group and 21.1, 27.9, 26.5, 24.5% respectively in *H. pylori* overt positive group. **b** Proportion of subjects according to the quartiles of total bilirubin. The percentages of each grade from higher to lower total bilirubin levels were 27.2, 25.1, 24.0, 23.7% respectively in *H. pylori* overt negative group and 21.8, 22.9, 28.7, 26.6% respectively in *H. pylori* overt positive group. HP, *H. pylori*

Table 2 The risk of bilirubin decreases according to the infection of *H. pylori*

	Direct bilirubin			Total bilirubin		
	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
Model 1	1.483	1.143–1.925	0.003	1.336	1.030–1.733	0.029
Model 2	1.500	1.151–1.955	0.003	1.352	1.036–1.764	0.026
Model 3	1.503	1.146–1.972	0.003	1.328	1.014–1.739	0.039
Model 4	1.497	1.121–1.999	0.006	1.322	1.005–1.738	0.046

Participants were assigned to two groups according to upper quartile of direct bilirubin (2.8) and total bilirubin (16.4) respectively. Participants with *H. pylori* overt negative were defined as 0 and those with *H. pylori* overt positive were defined as 1. Model 1 is unadjusted. Model 2 is adjusted for age, sex. Model 3 is further adjusted for BMI, ALT and AST. Model 4 is further adjusted for TG, TC, LDL-C, HDL-C

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Fig. 3 Correlation between direct bilirubin and cholesterol. **a** Correlation between LDL-cholesterol (LDL-C) and direct bilirubin (DBil). **b** Correlation between HDL-cholesterol (HDL-C) and DBil

within the reference range. *H. pylori* infection has been shown to result in chronic inflammation and influence of bile reflux [9, 26], which may at least in part explain the bilirubin changes, but further research relating to possible mechanisms is required.

Our study also found an association between *H. pylori* infection and lipid profiles. Serum LDL-C level was significantly higher and HDL-C significantly lower in *H. pylori* infected subjects. This association was first observed in 1996 in Finnish subjects [27]. Since then, several studies have been performed in different populations. However, the results are still equivocal. Most studies have supported the significant correlation between *H. pylori* infection and elevated lipids levels [5, 10, 28–33]. However Elizalde et al. found that *H. pylori* infection had no influence on blood lipids in 686 *H. pylori*-positive patients before and 3 months after eradication therapy with a low treatment rate (53.6%) [9]. It should be noted that cases and controls were not matched for sex and age which are key influence determinants of serum lipids. Furthermore *H. pylori* infection is associated with a long-term effect on human health [34] and 3 months may not be long enough to observe changes resulting from eradication of *H. pylori.* In our relatively large study, we selected individuals with extreme ^{13}C-UBT values to better distinguish the differences associated with *H. pylori* infection and matched the subjects by sex and age. We found that *H. pylori* infected subjects had significantly higher LDL-C and lower HDL-C levels.

Our study also found that decreased direct bilirubin was correlated with adverse lipid profiles, an important cause of cardiovascular disease and a feature of clusters of metabolic disease risk factors. Recent in vivo and in vitro studies suggest that this may due to bilirubin regulation of the fat burning nuclear receptor, PPAR-α and γ levels and thus inhibited lipid accumulation [35, 36]. Given that *H. pylori* infection may influence lipid profiles and that we could not prove a causal relationship between bilirubin and cholesterol levels. It is conceivable that the elevated cholesterol levels may be a result of both *H. pylori* infection and decreased bilirubin concentrations.

Limitations of our study should be acknowledged. First, our study was not a prospective study, so we could not examine the effects of eradication therapy. Comparing bilirubin and lipid levels before and after eradication of *H. pylori* would enable more definitive conclusions. Second, our study was a cross-sectional study. Despite of statistical significance in lipid profiles between groups, we could not assure a real difference in clinical practice. Larger sample size prospective study is still required in the future.

Conclusion

Our data suggest that *H. pylori* infection may be an independent risk factor for serum bilirubin reduction and adverse lipid profiles. If confirmed, this would provide further evidence for the importance of diagnosis and eradication of *H. pylori* infection.

Additional files

Additional file 1: Table S1. Primary baseline characteristics classified by *H. pylori* infection. SBP, systolic blood pressure; DBP, diastolic blood pressure. Data are mean ± SD; Student *t*-test. (DOCX 365 kb)

Additional file 2: Database. Primary database of this study. (SAV 181 kb)

Abbreviations

ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; BP: Blood pressure; DM: Diabetes mellitus; HbA1c: Glycosylated hemoglobin A1c; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low density lipoprotein-cholesterol; OR: Odds ratio; SCr: Serum creatinine; TC: Total cholesterol; TG: Triglycerides; UA: Uric acids; UBT: Urea breath test; WC: Waist circumference; γ-GT: γ-glutamyl transpeptidase

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