Association between Helicobacter pylori infection and the risk of type 2 diabetes mellitus based on a middle-aged and elderly Chinese population

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Abstract. Evidence about the relationship between Helicobacter pylori (Hp) infection and type 2 diabetes mellitus (T2DM) is inconsistent and contradictory. This study attempted to investigate this association in the middle-aged and elderly Chinese population and analyze the joint effects of Hp infection and some risk factors on T2DM. Following a cross-sectional design, participants were recruited from the First Affiliated Hospital of Anhui Medical University in Hefei City, China. Hp status was measured using a ¹⁴C urea breath test. A total of 1,288 participants, including 90 diabetic patients and 1,198 non-diabetic subjects, were recruited in the current study. The participants with T2DM had a greater prevalence of Hp infection than participants without T2DM (26.67% versus 18.11%, p = 0.045). Furthermore, we found that Hp infection was closely associated with an incremental risk of T2DM [odds ratio (OR) = 1.77, 95% confidence intervals (CI): 1.04–3.00] after adjustment for potential confounders. In addition, we observed that the participants who were Hp-positive and ≥60 years old (OR = 9.16, 95% CI: 3.29–25.52), Hp-positive and obese (OR = 3.35, 95% CI: 1.57–7.14) or Hp-positive and hypertensive (OR = 6.10, 95% CI: 3.10–12.01) had a significantly higher risk for T2DM than those who were Hp-negative and ≤50 years old, Hp-negative and nonobese or Hp-negative and nonhypertensive. These findings imply that Hp infection is associated with an increased risk of T2DM in the middle-aged and elderly Chinese population. The association could be further elevated by the combination of Hp infection and some traditional risk factors.

Key words: Helicobacter pylori (Hp), Type 2 diabetes mellitus (T2DM), Joint effects

DIABETES MELLITUS is a multifactorial metabolic disorder characterized by persistent hyperglycemia that affects a large part of the population [1-4]. Type 2 diabetes mellitus (T2DM), as the most common form of the disease, accounts for approximately 90% of diabetic people [5, 6]. It is a multisystem disease associated with both microvascular and macrovascular complications [7], such as diabetic retinopathy, neuropathy, nephropathy and atherosclerosis [8, 9], hence posing a serious threat to human health. The etiology of T2DM seems to be relatively complex, and the interaction between environmental and genetic factors usually plays a pivotal role [10, 11]. Recently, accumulating evidence suggests that Helicobacter pylori (Hp) infection may be associated with an increased risk of T2DM [12, 13].

Hp is a gram-negative bacterium that colonizes the human stomach, mainly causing chronic gastritis, gastric malignancy and peptic ulcer disease [14]. Based on a systematic worldwide study conducted in 2015, nearly 4.4 billion individuals were documented to be positive for Hp infection [15]. Moreover, the prevalence remains high in most developing regions [16]. For instance, a meta-analysis indicated that the pooled prevalence is 79.1% in Africa, 54.7% in Asia and 55.8% in China [16]. In addition to causing several gastric diseases, Hp infection was discovered to be tightly linked with metabolic syndrome and cardiovascular diseases [17, 18], such as nonalcoholic fatty liver disease (NAFLD) [19], hypertension [20] and atherosclerosis [21].

The positive relationship between Hp infection and the risk of T2DM has been reported by several investigations [12, 13], but other studies have reported conflicting and inconsistent results [22, 23]. Therefore, the association between Hp infection and the risk of T2DM remains unclearly defined. The joint effects of Hp infection and other traditional risk factors on T2DM are seemingly elusive. In this cross-sectional study that included 1,288 participants, the possible associations between Hp infection...
and T2DM and the joint effects of Hp infection and traditional risk factors on T2DM were identified.

Materials and Methods

Study population

This cross-sectional study was conducted at the First Affiliated Hospital of Anhui Medical University in Hefei city, Anhui Province, from March 2014 to September 2014. A total of 1,288 middle-aged and elderly participants were recruited at the Medical Center of the First Affiliated Hospital of Anhui Medical University for a health examination, which included anthropometric parameters, serum biochemical indices, and 14C-urea breath tests. Meanwhile, sociodemographic characteristics and self-reported lifestyle habits were collected using a structured questionnaire during the physical examination. The study has been approved by the Medical Ethics Committee of Anhui Medical University. All participants provided written informed consent.

Data collection

Baseline data were collected by trained interviewers using a structured questionnaire. Information on sociodemographic factors (name, sex, date of birth and education level, etc.), health status and lifestyle (smoking status and alcohol consumption) was included in the questionnaire. Smoking status was categorized as (i) nonsmoker and (ii) smoker, and alcohol consumption was categorized as (i) none and (ii) drinker. The physical examination included measurements for height, weight and blood pressure. Height and weight were measured twice, and the average value of the two measurements was used. Body mass index (BMI) was calculated as weight in kilograms divided by height in square meters. Blood pressure was measured twice by a trained nurse using a mercury sphygmomanometer. As a rule, the measurements were taken with the subjects in a sitting position after a minimum 10-min rest. Thereafter, the mean of the two measurements was identified as the blood pressure level of the participant.

Blood samples were collected in the morning after overnight fasting, and the levels of serum total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), fasting plasma glucose (FPG), glycated hemoglobin A1c [HbA1c (%)], aspartate aminotransferase (AST), alanine aminotransferase (ALT) and uric acid (UA) were measured by a Hitachi 7180 automatic biochemical analyzer.

Hp status was determined using a 14C-urea breath test, a noninvasive test regarded as ‘the gold standard’ for Hp infection [24]. The results are expressed as disintegrations per minute (dpm). Only subjects with dpm greater than 100 were deemed to be infected with Hp.

Definitions of variables

BMI (kg/m²) was classified into 4 categories based on the criteria recommended for Chinese adults (below 18.5 as underweight, 18.5–23.9 as normal weight, 24.0–27.9 as overweight and 28 or above as obese) [25]. Hypertension was defined as a systolic blood pressure ≥140 mmHg and/or a diastolic blood pressure ≥90 mmHg or taking oral medical treatment [26].

Subjects were confirmed as having hypertriglyceridemia if they had TG levels ≥2.26 mmol/L and as having hypercholesterolemia if they had TC levels ≥6.22 mmol/L [27]. Hyperuricemia was identified as serum UA levels ≥420 μmol/L in men and ≥360 μmol/L in women [28]. The T2DM was diagnosed according to the following American Diabetes Association criteria [29]: a fasting blood glucose level ≥7.0 mmol/L, self-reported diabetes or the use of antidiabetic medication.

Statistical analysis

Characteristics of the participants are described as the mean ± standard deviation (SD) for continuous variables with a normal distribution and as percentages for categorical variables. Student’s *t* test was used to examine mean differences for continuous variables, and the $\chi^2$ test was applied to compare the differences for categorical variables. To assess the effect of risk factors on T2DM and the joint effects of Hp infection and traditional risk factors on T2DM, binary logistic regression analysis was used to estimate adjusted odds ratios (ORs) and 95% confidence intervals (CIs). All statistical analyses were performed by using SPSS 22.0 software (IBM Corp., Armonk, NY, USA). A *p* < 0.05 was considered to be statistically significant.

Results

Sociodemographic characteristics of subjects with Hp infection and those without Hp infection

A total of 1,288 individuals (465 men and 823 women) were included in this study. The prevalence of Hp infection in the total sample was 18.7% (241/1,288). The characteristics of the included population according to the status of Hp infection are summarized in Table 1. There were significant differences among the statuses of Hp infection for HbA1c (%) ($t = 2.967$, *p* = 0.003), fasting blood glucose levels ($t = 2.017$, *p* = 0.044), ALT levels ($t = 4.685$, *p* = 0.031) and the prevalence of T2DM ($\chi^2 = 4.026$, *p* = 0.045). Moreover, subjects who had Hp infection were more likely to have higher levels of HbA1c (%) and fasting blood glucose and a higher
prevalence of T2DM, but lower levels of ALT. However, no significant difference in the prevalence of \(Hp\) infection in subjects was found for sex, age, smoking status, alcohol consumption, BMI, systolic and diastolic blood pressures, TC levels, TG levels, HDL-C levels, AST levels, uric acid levels, antidiabetic and antihypertensive medication (all \(p > 0.05\)).

**General characteristics of subjects with diabetes mellitus and those without diabetes mellitus**

The general characteristics of the participants according to diabetic status are also presented (Table 2). The prevalence of T2DM was 7.0% (90/1288). The number of newly diagnosed T2DM patients by this health examination was 37, and the number of self-reported T2DM patients with/without medication was 53. Significant differences between diabetic and nondiabetic patients were observed for sex \((\chi^2 = 12.24, p < 0.001)\), age \((t = 6.169, p < 0.001)\), BMI levels \((t = 5.539, p < 0.001)\), systolic \((t = 6.987, p < 0.001)\) and diastolic \((t = 4.689, p < 0.001)\) blood pressures, TG levels \((t = 7.351, p < 0.001)\), LDL-C levels \((t = 1.511, p = 0.020)\), HbA1c (%) levels \((t = 22.34, p < 0.001)\), fasting blood glucose levels \((t = 36.61, p < 0.001)\), ALT levels \((t = 3.024, p = 0.0025)\), and \(Hp\) infection \((\chi^2 = 4.026, p = 0.045)\). Moreover, subjects who had diabetes were more likely to be female and older. They also had higher levels of BMI, systolic and diastolic blood pressures, TG levels, LDL-C levels, HbA1c (%) levels, fasting blood glucose levels, ALT levels, and \(Hp\) infection rates than those who were not diabetic. However, there were no significant differences between the diabetic and nondiabetic groups for smoking status, alcohol consumption or the levels of TC, AST and uric acid (all \(p > 0.05\)).

**Table 1** General characteristics of subjects with \(Helicobacter pylori\) infection and those without infection

| Variables               | \(Helicobacter pylori\) negative \((n = 1,047)\) | \(Helicobacter pylori\) positive \((n = 241)\) | \(\chi^2/t\) | \(p\) |
|-------------------------|-----------------------------------------------|-----------------------------------------------|--------------|------|
| Male (%)                | 382 (36)                                      | 83 (34)                                       | 0.355        | 0.551|
| Age (years)             | 61.74 ± 16.91                                | 61.80 ± 17.01                                | 0.002        | 0.965|
| Smoking (%)             | 190 (18.15)                                   | 42 (17.43)                                   | 0.069        | 0.793|
| Alcohol consumption (%) | 239 (22.83)                                   | 53 (22.41)                                   | 0.02         | 0.888|
| BMI (kg/m\(^2\))        | 23.42 ± 3.13                                 | 23.75 ± 2.68                                 | 2.217        | 0.137|
| Blood pressure (mmHg)   |                                               |                                               |              |      |
| Systolic                | 134.67 ± 19.99                                | 135.63 ± 20.64                               | 0.425        | 0.515|
| Diastolic               | 79.49 ± 11.54                                 | 79.74 ± 11.39                                | 0.095        | 0.758|
| TC (mmol/L)             | 4.95 ± 0.95                                   | 4.91 ± 0.93                                  | 0.404        | 0.525|
| TG (mmol/L)             | 1.57 ± 1.17                                   | 1.46 ± 1.19                                  | 1.815        | 0.178|
| HDL-C (mmol/L)          | 1.4 ± 0.44                                    | 1.43 ± 0.43                                  | 0.717        | 0.397|
| LDL-C (mmol/L)          | 3.11 ± 0.87                                   | 3.11 ± 0.89                                  | <0.001       | 0.995|
| HbA1c (%)               | 5.47 ± 1.33                                   | 5.75 ± 1.28                                  | 2.967        | 0.003|
| FPG (mmol/L)            | 5.69 ± 0.92                                   | 5.83 ± 1.17                                  | 2.017        | 0.044|
| AST (U/L)               | 22.89 ± 10.51                                 | 21.80 ± 6.54                                 | 2.376        | 0.123|
| ALT (U/L)               | 22.71 ± 18.33                                 | 20.05 ± 11.07                                | 2.163        | 0.031|
| Uric acid (μmol/L)      | 343.58 ± 92.46                                | 334.70 ± 87.38                               | 1.843        | 0.175|
| T2DM (%)                | 66 (6.30)                                     | 24 (9.96)                                    | 4.026        | 0.045|
| Antidiabetic drug use (%)| 42 (4.01)                                    | 11 (4.56)                                    | 0.147        | 0.701|
| Antihypertensive drug use (%)| 255 (24.35)                  | 58 (24.07)                                    | 0.009        | 0.925|

BMI, body mass index; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c (%), glycated hemoglobin A1c; FPG, fasting plasma glucose; AST, aspartate aminotransferase; ALT, alanine aminotransferase; T2DM, type 2 diabetes mellitus.
Respective effects of Hp infection and traditional risk factors on participants with diabetes

To assess the effects of Hp and traditional risk factors on subjects with T2DM, binary logistic regression was used (Table 3). Compared with those who were age ≤50 years, participants aged ≥60 years had a significantly higher risk for T2DM (OR = 4.25, 95% CI: 1.75–10.32). Obesity (OR = 1.72, 95% CI: 1.08–2.75), hypertension (OR = 2.49, 95% CI: 1.50–4.12) and hypertriglyceridemia (OR = 2.52, 95% CI: 1.49–4.29) were found to be dramatically associated with an increased risk of T2DM. Interestingly, participants who were positive for Hp infection had a significantly higher risk for T2DM than those who were negative for Hp infection (OR = 1.77, 95% CI: 1.04–3.00). However, a substantially increased risk for T2DM was not discovered in subjects by sex, smoking, alcohol consumption, hypercholesterolemia or hyperuricemia (all p > 0.05).

Joint effects of Hp infection and traditional risk factors on participants with diabetes

To elevate the synergy of Hp infection and traditional risk factors on T2DM, the joint effects based on logistic regression were analyzed (Table 4). Compared with subjects who were negative for Hp infection and aged ≤50 years, the subjects who were positive for Hp infection and aged ≥60 years had a remarkably higher risk of T2DM (OR = 9.16, 95% CI: 3.29–25.52, p for trend <0.001). Compared with the nonobese subjects who were negative for Hp infection, the obese subjects who were positive for Hp infection had a significantly greater risk for T2DM (OR = 3.35, 95% CI: 1.57–7.14, p for trend <0.001). Moreover, the increased risk for T2DM was also discerned in the subjects by the joint effects of positive infection and hypertension (OR = 6.10, 95% CI: 3.10–12.01, p for trend <0.001), but not in those by the joint effects of positive infection and hypertriglyceridemia (OR = 1.50, 95% CI: 0.34–6.56, p for trend = 0.126).

Discussion

In the present study, we observed a positive link between Hp infection and the risk of T2DM. More importantly, our current study demonstrated the combined effects of Hp infection and traditional risks (age,
obesity or hypertension) on T2DM. Therefore, Hp infection may be a susceptibility factor for the prevalence of T2DM, which is consistent with published studies [12, 13]. The present study may provide useful information for the primary prevention of T2DM. However, some studies have suggested no significant difference in Hp infection between T2DM patients and controls [22, 23, 30, 31]. The discrepancies are likely due to the inconsistencies in the methods used in the studies, including the definition of Hp positivity, diabetic status, the limited sample sizes and the adjustments for potential confounders such as age and socioeconomic status, as shown in He C et al. [32].

In our current study, the prevalence of Hp infection might be underreported, but an increased risk for T2DM was still discerned by Hp infection. Although the mechanism underlying Hp infection and the occurrence of T2DM has been unclear thus far, several potential assumptions have been proposed. First, the Hp infection could enhance the impairment of cellular and humoral immunity, which may induce diabetes [33]. Second, pathogen colonization and infection rates in the gut may be strengthened because of the diabetes-induced reduction of gastrointestinal motility and acid secretion [34]. Third, preceding studies indicated that Hp infection was positively related to the levels of c-reaction protein [35].

| Table 3 | Respective effect of *Helicobacter pylori* infection and traditional risk factors on participants with diabetes |
|---------|---------------------------------------------------------------|
| Variables | N (%) | OR (95% CI) | p  |
| Sex | | | |
| Women | 809 (62.81) | 1 | |
| Men | 479 (37.19) | 0.61 (0.34–1.08) | 0.087 |
| Age | | | |
| ≤50 | 397 (30.82) | 1 | |
| 50–60 | 388 (30.12) | 1.77 (0.66–4.73) | 0.254 |
| ≥60 | 503 (39.05) | 4.25 (1.75–10.32) | 0.001 |
| Smoking | | | |
| No | 1,069 (83.00) | 1 | |
| Yes | 219 (17.00) | 1.45 (0.67–2.33) | 0.563 |
| Alcohol consumption | | | |
| No | 1,110 (86.18) | 1 | |
| Yes | 178 (13.82) | 1.43 (0.64–2.30) | 0.429 |
| Obesity | | | |
| No | 893 (69.33) | 1 | |
| Yes | 395 (30.67) | 1.72 (1.08–2.75) | 0.023 |
| Hypertension | | | |
| No | 819 (63.59) | 1 | |
| Yes | 469 (36.41) | 2.49 (1.50–4.12) | <0.001 |
| Hypercholesterolemia | | | |
| No | 1,168 (90.68) | 1 | |
| Yes | 120 (9.32) | 1.14 (0.60–2.30) | 0.727 |
| Hypertriglyceridemia | | | |
| No | 1,073 (83.31) | 1 | |
| Yes | 215 (16.69) | 2.52 (1.49–4.29) | 0.001 |
| Hyperuricemia | | | |
| No | 959 (74.46) | 1 | |
| Yes | 329 (25.54) | 0.693 (0.58–1.08) | 0.089 |
| Helicobacter pylori infection | | | |
| Negative | 1,047 (81.29) | 1 | |
| Positive | 241 (18.71) | 1.77 (1.04–3.00) | 0.035 |

OR, odds ratio; 95% CI, confidence intervals.
interleukin-6 and tumor necrosis factor-α [36], the key inflammatory cytokines causing insulin resistance and the pathogenesis of diabetes [37].

We found that an age ≥60 years was positively associated with the risk of T2DM. Subjects with *Hp* infection and aged ≥60 years had a higher risk for T2DM than those who were negative for *Hp* infection and aged ≤50 years. Previous evidence suggests that the joint effects in our current study are biologically plausible. Substantial preceding evidence has shown that T2DM, an age-related disease, is highly prevalent in older adults and generally manifests after the age of 40 [38, 39]. Moreover, we observed that obesity could increase the risk of T2DM, which might be further elevated by the combination of *Hp* infection and obesity. Besides, previous publications implied that obesity could play a vital role in development of insulin resistance and inflammation [40, 41]. Additionally, we noticed that hypertension was associated with the risk of T2DM, which is consistent with a large number of studies [42, 43]. Interestingly, our current data revealed that the risk was enhanced by the combination of *Hp* infection and hypertension. T2DM is usually accompanied by hypertriglyceridemia-based lipid dysregulation [44, 45], which was affirmed in our current study. However, an elevated risk of T2DM was not observed in the participants with the combination of *Hp* infection and hypertriglyceridemia, which could be attributed to the small sample size in our current study. The coexistence of *Hp* infection and hypertriglyceridemia only accounts for a small proportion, resulting in a wide CI estimate. This might explain why the joint effect was not statistically significant. Given these results, a large number of participants are needed in future studies.

This study has several strengths and limitations. To our knowledge, the current study is the first to report the joint effects of *Hp* infection and traditional risk factors on T2DM. As such, our findings may have implications in the prevention and management of T2DM. Second, the diagnosis of *Hp* infection in our current study was based on the 14C-urea breath test rather than serological testing, which made the results more reliable and convincing. Despite the strengths, there are still some limitations in our present study. First, the cross-sectional design only allowed us to evaluate the associations, and the underlying cause-effect relationship cannot be determined. Second, potential confounders, such as dietary

### Table 4 Joint effect of *Helicobacter pylori* infection and traditional risk factors on participants with diabetes

|          | Variables | n (%)   | OR (95% CI) | p-trend |
|----------|-----------|---------|-------------|---------|
| *Helicobacter pylori* infection | Age       |         |             |         |
| Negative | ≤50       | 261 (20.28) | 1           | <0.001  |
| Negative | 50–60     | 291 (22.61) | 2.20 (0.77–6.34) |         |
| Negative | ≥60       | 494 (38.38) | 6.55 (2.59–16.55) |         |
| Positive | ≤50       | 62 (4.82)   | 1.71 (0.32–9.010) |         |
| Positive | 50–60     | 67 (5.21)   | 4.13 (1.16–14.71) |         |
| Positive | ≥60       | 112 (8.7)   | 9.16 (3.29–25.52) |         |
| *Helicobacter pylori* infection | Obesity   |         |             | <0.001  |
| Negative | No        | 697 (56.85) | 1           |         |
| Negative | Yes       | 156 (12.72) | 2.05 (1.07–3.94) |         |
| Positive | No        | 301 (24.55) | 2.82 (1.72–4.64) |         |
| Positive | Yes       | 72 (5.88)   | 3.35 (1.57–7.14) |         |
| *Helicobacter pylori* infection | Hypertension |         |             | <0.001  |
| Negative | No        | 598 (49.63) | 1           |         |
| Negative | Yes       | 139 (11.54) | 1.18 (0.47–2.97) |         |
| Positive | No        | 378 (31.37) | 3.81 (2.26–6.42) |         |
| Positive | Yes       | 90 (7.46)   | 6.10 (3.10–12.01) |         |
| *Helicobacter pylori* infection | Hypertriglyceridemia |         |             | 0.126   |
| Negative | No        | 858 (67.99) | 1           |         |
| Negative | Yes       | 209 (16.56) | 2.03 (1.19–3.45) |         |
| Positive | No        | 170 (13.47) | 3.12 (1.87–5.19) |         |
| Positive | Yes       | 25 (1.98)   | 1.50 (0.34–6.56) |         |

OR, odds ratio; 95% CI, confidence intervals.
habits and physical activity levels, could not be adjusted in the analysis because they were not precisely measured in our current investigation. Third, the sample size was small; hence, the results are subject to type II error and they cannot be generalized. Therefore, a well-designed large population-based cohort studies are indispensable. Fourth, due to a lack of follow-up data, the effect of the eradication of Hp infection on the risk of T2DM is not available so far. Finally, a specific mechanism needs to be explored in animal studies in the future.

Conclusion

In summary, we found that Hp infection is positively associated with the risk of T2DM, which may be further exacerbated under the coexistence of Hp infection and some traditional risk factors. To clarify the relationship, large-scale, well-designed prospective studies are needed to investigate whether Hp plays an etiological role in the initiation and development of diabetes.

Disclosure

J.Z. and X.W. designed the study and collected data.

J.Z. and K.L. conducted data analysis. J.Z and K.C. wrote the manuscript. K.C. provided the funding and edited/revised the manuscript. All authors read and approved the final draft.

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Competing Interests

The authors declare no competing interests.

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