JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

Association between *Helicobacter pylori* infection, eradication and diabetes mellitus

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Keywords
Eradication, *Helicobacter pylori*, Inflammation

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J Diabetes Investig, 2019; 10: 1341–1346

doi: 10.1111/jdi.13011

ABSTRACT

Aims/Introduction: It is suspected that *Helicobacter pylori* is associated with extradigestive diseases including diabetes. So far, a number of studies have examined the association between *H. pylori* and diabetes, and the results were conflicting. The aim of the present study was to examine the association between *H. pylori* infection, eradication and diabetes.

Materials and Methods: The present cross-sectional study was carried out using data from annual health checkups carried out at the Toranomon Hospital Health Management Center. The status of *H. pylori* infection, determined by serum antibodies and history of eradication, was categorized into three groups as "never," "current" and "past." The association between *H. pylori* infection and diabetes was examined using logistic regression.

Results: Of 21,634 participants, 6,530 (30.2%) had a current or past history of *H. pylori* infection, and 1,184 (5.5%) were identified as having diabetes. Multivariate adjusted odds ratios for diabetes compared with the "never" group were 1.36 (95% confidence interval 1.10–1.67) for the "current" group and 0.92 (95% confidence interval 0.79–1.07) for the "past" group. The association between *H. pylori* infection and diabetes was also observed among participants without a history of eradication.

Conclusions: We found that current *H. pylori* infection was associated with an increased risk of diabetes, and the increased risk was not observed among participants after eradication. The results were concordant with the hypothesis that *H. pylori* infection increases the risk of diabetes. Further studies are necessary to validate the present results.

INTRODUCTION

Helicobacter pylori is a Gram-negative bacterium that colonizes the stomach, and causes chronic gastritis, peptic ulcers and gastric cancer. It is one of the most common chronic infections worldwide. *Helicobacter pylori* infection is more frequent in developing countries, and it was estimated that there were approximately 4.4 billion individuals with *H. pylori* infection worldwide in 2015[1]. Besides gastritis, gastroduodenal ulcer and gastric cancer, *H. pylori* is suspected to be associated with extradigestive diseases, including diabetes[2–5]. Today, diabetes is a major public health concern worldwide. In 2015, it was estimated that there were 415 million people with diabetes aged 20–79 years, 5 million deaths attributable to diabetes and the total global health expenditure due to diabetes was estimated at $673 billion[6]. The number of people with diabetes was predicted to rise to 642 million by 2040. If a causal relationship between *H. pylori* and diabetes becomes clear, it will lead to new preventive and therapeutic strategies for diabetes, and the impact will be large because of the large number of patients of both diseases.

Although a number of studies have examined the association between *H. pylori* and diabetes, the results were conflicting[7–13]. Furthermore, if there is a link between *H. pylori* infection and diabetes, it is natural to expect a change in diabetes state after eradication. However, few studies have examined the association between *H. pylori* eradication and diabetes.

The aim of the present study was to examine the association between *H. pylori* infection, eradication and diabetes in a relatively large-scale cross-sectional study.

METHODS

Study population

The present cross-sectional study was carried out using data from annual health checkups carried out at the Toranomon

Received 4 July 2018; revised 17 December 2018; accepted 17 January 2019

Hospital Health Management Center, Tokyo, Japan. Most of the study participants were apparently healthy Japanese government employees. The annual health checkup included a questionnaire about medical conditions, such as diabetes, liver disease and hypertension, and a questionnaire about lifestyle, such as alcohol intake, smoking, exercise and family history of diabetes. It also contained questions about *H. pylori* eradication.

Among 25,025 health checkup participants aged ≥20 years from April 2015 to June 2017, the following individuals were excluded from the study: those with liver disease, renal disease, hematological disorders, any cancer and pregnant women. Of the remaining 23,117 participants, 350 with missing information about *H. pylori* eradication were excluded. Of the remaining 22,767 participants, 1,133 individuals without a history of eradication and *H. pylori* immunoglobulin G (IgG) antibody titer of 3–9.9 U/mL were further excluded (see next section).

Because only anonymized data were used in the present study, individual informed consent was waived according to the Japanese ethical guidelines for medical and health research. The study protocol was approved by the institutional review board of Toranomon Hospital (IRB study number: 1582-K).

Status of *H. pylori* infection

The status of *H. pylori* infection was assessed using answers to the questions about *H. pylori* eradication and serum *H. pylori* IgG antibody concentration. The questions about *H. pylori* eradication consisted of three questions; that is, history (yes or no), results (succeeded or failed) and period (<1, 1–4.9 and ≥5 years ago). The serum *H. pylori* IgG antibody concentration was measured by enzyme immunoassay (E Plate Eiken *H. pylori* Antibody; Eiken Chemical Co., Ltd., Tokyo, Japan). The recommended cut-off point for this kit was 10 U/mL, and the minimum determination limit was 3 U/mL. Using the cut-off (10 U/mL) and stool antigen test as the gold standard, the sensitivity and specificity for this kit were reported as 91.2% and 97.4%, respectively[14]. However, it was also reported that this kit might yield false negative results in the range of 3–9.9 U/mL[14,15]. To avoid potential misclassification as far as possible, a titer of 10 U/mL was used as a cut-off point for *H. pylori* infection, and 3 U/mL was used as a cut-off point for non-infection in the present study. Therefore, participants without a history of eradication and IgG antibody 3–9.9 U/mL were excluded from the main analysis. The remaining participants were categorized into three groups according to the status of *H. pylori* infection as "never," "current" and "past." Participants without a history of eradication and IgG antibody <3 U/mL were classified as "never." Participants with a history of eradication and reported failed or without a history of eradication and IgG antibody ≥10 U/mL were classified as "current." Participants with a history of eradication and reported succeeded or IgG antibody <3 U/mL were classified as "past," and this group was subdivided into three groups according to the period after eradication (<1, 1–4.9 and ≥5 years) in some analysis.

Definition of diabetes mellitus

Participants were considered to have diabetes if they answered "under treatment" to the question regarding diabetes status or using antidiabetic medication or fasting plasma glucose ≥7 mmol/L (126 mg/dL) and hemoglobin A1c (HbA1c) level ≥6.5% (48 mmol/mol)[16–18]. It was reported that fasting plasma glucose, oral glucose tolerance test and HbA1c are equally appropriate for diagnostic testing. The HbA1c has several advantages compared with the oral glucose tolerance test, including convenience, stability and reproducibility. However, HbA1c values do not reflect the plasma glucose level of individuals with hemoglobinopathy or diseases that result in abnormal erythrocyte turnover. Therefore, we excluded individuals with liver disease, renal disease and hematological disorders, and defined diabetes not only by HbA1c levels, but also in combination of fasting plasma glucose and HbA1c.

Assessment of other variables

Alcohol consumption was assessed by the frequency of alcohol consumption and the quantity of alcohol consumed per occasion, and the weekly ethanol intake for each participant was calculated. Dyslipidemia was defined as taking lipid-lowering medication. Smoking status was categorized as never smoker, ex-smoker and current smoker. Physical activity was assessed by whether the participant was doing exercise regularly.

Statistical analysis

To examine the association between *H. pylori* infection and diabetes, we calculated the odds ratios using logistic regression analysis adjusted for age, sex, body mass index, history of hypertension, dyslipidemia, family history of diabetes, physical activity, alcohol intake (non-drinker, current drinker with weekly ethanol intake <150, 150–299, ≥300 g) and smoking status (never, ex-smoker and current smoker). Sensitivity analysis was carried out including 1,133 participants without a history of eradication and IgG antibody 3–9.9 U/mL (methods and results were shown in the Appendix S1).

RESULTS

The characteristics of the participants are shown in Table 1. Of 21,634 participants, 6,530 (30.2%) had a current or past history of *H. pylori* infection. Participants with current or past *H. pylori* infection were more likely to be male, older, ex- or current smokers, hypertensive and dyslipidemic compared with participants without *H. pylori* infection. Participants with C-reactive protein >0.1 mg/dL were more frequently among the "current" group ($P = 0.0003$ compared with the "never" group, and $P = 0.0001$ compared with the "past" group). When participants were restricted to C-reactive protein <1 mg/dL to exclude overt inflammation, these results were similar (9.1%, 11.7% and 8.6% among the "never," "current" and "past" groups, respectively, and *P*-values for the "current" group were 0.0006 and 0.0002 compared with the "never" and "past" group, respectively).

Table 1 | Characteristics of participants

	Status of *Helicobacter pylori* infection		
	Never (n = 15,104)	Current (n = 1,739)	Past (n = 4,791)
Male	9,321 (61.7)	1,119 (64.3)	3,356 (70.0)
Age (years)	50.6 (10.4)	54.4 (12.2)	58.8 (10.4)
Body mass index (kg/m^2)	22.9 (3.5)	23.6 (3.6)	23.1 (3.2)
Non-drinker	6,057 (40.1)	675 (38.8)	1,835 (38.3)
Current drinker <150 g/week	5,051 (33.4)	522 (30.0)	1,559 (32.5)
Current drinker 150–299 g/week	2,984 (19.8)	365 (21.0)	1,055 (22.0)
Current drinker ≥300 g/week	1,012 (6.7)	177 (10.2)	342 (7.1)
Never smoker	9,087 (60.2)	905 (52.0)	2,566 (53.6)
Ex-smoker	4,316 (28.6)	571 (32.8)	1,784 (37.2)
Current smoker	1,701 (11.3)	263 (15.1)	441 (9.2)
Family history of diabetes	3,402 (22.5)	406 (23.3)	1,079 (22.5)
Physical activity	7,823 (51.8)	838 (48.2)	2,921 (61.0)
History of hypertension	1,911 (12.7)	308 (17.7)	1,071 (22.4)
Dyslipidemia	1,357 (9.0)	215 (12.4)	815 (17.0)
CRP >0.1 mg/dL	1,578 (10.4)	231 (13.3)	469 (9.8)

Age and body mass index are represented as the mean (standard deviation), and the other characteristics are represented as numbers (proportions). CRP, C-reactive protein.

A total of 1,184 participants (5.5%) were identified as having diabetes. Tables 2 and 3 show the odds ratios for diabetes mellitus according to the status of *H. pylori* infection. The proportions of participants with diabetes mellitus were larger in the "current" or "past" group; however, the odds ratios were statistically significant only in the "current" group after adjustment (Table 2). The odds ratios were similar among three "past" groups, although there was a tendency (not statistically significant) that the odds ratios decreased according to the period after eradication (Table 3).

To avoid recall bias about the results of eradication (succeeded or failed) and highlight the association between *H. pylori* infection and diabetes, we carried out a similar analysis only among participants without a history of eradication. In this analysis, groups were defined based only on the value of IgG antibody; that is, "never" and "current" groups were defined with IgG <3 and ≥10 U/mL, respectively. The results are shown in Table 4. The proportion of participants and the odds ratios for diabetes compared with the "never" group were larger in the "current" group.

Results of the sensitivity analysis are shown in Appendix S1. The percentage of misclassification (false negative) was reported to be approximately 7%[14], and the results showed that the odds ratios were statistically significant and stable within a relatively wide range of the percentage of misclassification.

DISCUSSION

In the present study, we examined the association between *H. pylori* infection, eradication and diabetes mellitus. Our results showed that current *H. pylori* infection was associated with an increased risk of diabetes; however, the increased risk was observed only among participants with current infection, and was not observed among participants after eradication. To highlight the association between *H. pylori* infection and diabetes, we carried out a similar analysis only among participants without a history of eradication, and the increased risk was also observed for the current infection group. This study was a cross-sectional study and generally assessing a temporal association is impossible. However, *H. pylori* infection is mainly acquired in childhood[19] and the onset of type 2 diabetes is

Table 2 | Odds ratios for diabetes mellitus according to status of *Helicobacter pylori* infection

H. Pylori status	n	Cases	Proportion (%)	Age and sex adjusted OR (95% CI)	Multivariate adjusted OR (95% CI)[†]
Never	15,104	696	4.61	1 (Reference)	1 (Reference)
Current	1,739	150	8.63	1.48 (1.22–1.79)	1.36 (1.10–1.67)
Past	4,791	338	7.05	0.94 (0.81–1.08)	0.92 (0.79–1.07)

[†]Adjusted for age, sex, body mass index, history of hypertension, dyslipidemia, family history of diabetes, alcohol intake (non-drinker, current drinker ethanol intake <150, 150–299 and ≥300 g/week), smoking status (never smoker, ex-smoker and current smoker) and physical activity. CI, confidence interval; OR, odds ratio.

Table 3 | Odds ratios for diabetes mellitus according to status of *Helicobacter pylori* infection

H. Pylori status	*n*	Cases	Proportion (%)	Age and sex adjusted OR (95% CI)	Multivariate adjusted OR (95% CI)†
Never	15,104	696	4.61	1 (Reference)	1 (Reference)
Current	1,739	150	8.63	1.48 (1.22–1.79)	1.35 (1.10–1.67)
Past (<1 year)	666	47	7.06	1.15 (0.84–1.58)	1.08 (0.77–1.51)
Past (1–4.9 years)	2,375	162	6.82	0.92 (0.76–1.10)	0.91 (0.75–1.11)
Past (≥5 years)	1,750	129	7.37	0.89 (0.73–1.09)	0.87 (0.70–1.08)

†Adjusted for age, sex, body mass index, history of hypertension, dyslipidemia, family history of diabetes, alcohol intake (non-drinker, current drinker ethanol intake <150, 150–299 and ≥300 g/week), smoking status (never smoker, ex-smoker and current smoker) and physical activity. "Past" was subdivided according to the period after eradication. CI, confidence interval; OR, odds ratio.

Table 4 | Odds ratios for diabetes mellitus according to status of *Helicobacter pylori* infection among participants without a history of eradication.

H. Pylori status	*n*	Cases	Proportion (%)	Age and sex adjusted OR (95% CI)	Multivariate adjusted OR (95% CI)†
Never	15,104	696	4.59	1 (Reference)	1 (Reference)
Current	1,457	132	9.09	1.53 (1.25–1.88)	1.44 (1.16–1.80)

†Adjusted for age, sex, body mass index, history of hypertension, dyslipidemia, family history of diabetes, alcohol intake (non-drinker, current drinker ethanol intake <150, 150–299 and ≥300 g/week), smoking status (never smoker, ex-smoker and current smoker) and physical activity. CI, confidence interval; OR, odds ratio.

usually after middle age, so it is probable that *H. pylori* infection preceded the onset of diabetes. Taking this temporal relationship together, the present result was concordant with the hypothesis that *H. pylori* infection increases the risk of diabetes.

Although the mechanism of *H. pylori* infection increasing the risk of diabetes is not clear, it is biologically plausible. *H. pylori* infection induces inflammation, and inflammation is suspected to cause diabetes[20–22]. In the present study, the number of participants with elevated C-reactive protein was higher in the current infected group than in the never or past infected groups. Participants with more longstanding *H. pylori* infection might have greater mucosal/systemic inflammation, and the duration of *H. pylori* infection might be important for the risk of diabetes. However, we could not estimate the duration of *H. pylori* infection in the present study, and it is not clear whether the duration of infection is important or not.

Besides the inflammatory pathway, it was suggested that *H. pylori* infection can affect the regulation of ghrelin and leptin, which play central roles in energy homeostasis. However, the results of the effect of *H. pylori* infection on ghrelin and leptin were conflicting[23,24]. In epidemiological studies, a potential association between *H. pylori* infection and insulin resistance was suggested[25]. Recently, it was reported that *H. pylori* infection induces hepatic insulin resistance by the c-Jun/miR-203/SOCS3 signaling pathway[26]. Few studies have examined the association between *H. pylori* eradication and diabetes. It was reported that *H. pylori* eradication improved the mean glycated hemoglobin in patients with type 2 diabetes[27], however, whether *H. pylori* eradication improves glycemic control is also controversial[28,29]. Recent randomized trial showed that *H. pylori* eradication improves glucose homeostasis in patients with type 2 diabetes through a decrease in pro-inflammatory factors[30].

Although possible risk factors of diabetes were considered in the present study, there still remains a possibility of confounding. One possible confounding is a difference in eradication failure among individuals with and without diabetes. Indeed, it was reported that the risk of *H. pylori* eradication failure is higher in individuals with diabetes[31,32], and this might cause an (spurious) association between *H. pylori* and diabetes. To clarify this point, we compared the proportion of participants who reported eradication failure between participants with diabetes and without diabetes. The proportion of participants who reported eradication failure was 3.7% among participants with diabetes, and 2.5% among participants without diabetes. Although the proportion of eradication failure was higher in participants with diabetes, the difference (1.2%, 95% confidence interval −0.8% to 3.2%) was not statistically significant. Further excluding the effect of eradication, we also calculated the odds ratio of diabetes only among participants without a history of eradication. As shown in Table 4, the proportion of participants and the odds ratios for diabetes compared with the never infected group were also larger and significant in the current infected group. These results suggested that the association between *H. pylori* and diabetes was not a consequence of higher eradication failure in individuals with diabetes. It is suspected that there is an association between polycystic ovary syndrome (PCOS) and type 2 diabetes mellitus[33,34]. It is also reported that there might be an association between PCOS and *H. pylori* infection[35]. Therefore, PCOS is a potential confounding factor between *H. pylori* and diabetes. Unfortunately, we

have no data about PCOS, and the effect of PCOS on the present results was unclear. However, the number of participants with ovarian disorder was not large (233 participants, 3.0% of the female participants), and we can expect that the effect of PCOS on our results was not large.

So far, although a number of studies have examined an association between *H. pylori* infection and diabetes, the results were conflicting[7–13]. Part of the reason for the conflicting results could be due to small sample size and inappropriate adjustment of risk factors. Although the present study had a relatively large sample size and adjusted possible risk factors of diabetes, there still remain several limitations. In the present study, socioeconomic status, which has a relationship with the risk of diabetes, was not adjusted for[36]. However, our study participants were mainly Japanese government employees, and it is unlikely that there existed a large difference in socioeconomic status among the participants. In contrast, this introduced another limitation about the generalizability of our results to the general population. Furthermore, all of the study participants were Japanese, and the generalizability of the present results to other ethnicities was not clear. The present study was carried out in Japan, and most *H. pylori* strains in Japan are cytotoxin-associated gene A (CagA)-positive[37], which cause a greater inflammatory reaction than CagA-negative strains[38], and this was another limitation about the generalizability of the present result to regions where CagA-negative strains are dominant. In the present study, the status of *H. pylori* infection was assessed using serum IgG antibody concentration, and a serological test is unable to accurately distinguish between current and past infection[39]. However, the present analysis among individuals without a history of eradication showed increased risk among participants with current infection. Therefore, misclassification among participants with current and past infection was expected to distort the results of the current infection group toward null and our conclusion was unchanged. Unfortunately, we did not have any information about the type of diabetes, and were not able to distinguish type 1 and type 2 diabetes. The onset of type 1 diabetes is typically during childhood, and might precede *H. pylori* infection. However, type 2 diabetes is more common than type 1 diabetes, and approximately 90–95% of people with diabetes have type 2 diabetes. Therefore, it is unlikely that a small number of participants with type 1 diabetes distorted the results. In addition, the present study was a cross-sectional study, and although *H. pylori* infection was thought to precede the onset of diabetes, the actual temporal relationship between *H. pylori* infection, especially eradication, and diabetes was unclear.

Besides these limitations, the present study examined and clearly showed the association between *H. pylori* infection, eradication and the risk of diabetes in a relatively large-scale study, and the results were concordant with the hypothesis that *H. pylori* infection increases the risk of diabetes. Although our study suggested that *H. pylori* infection increases the risk of diabetes, traditional risk factors (obesity, lack of physical activity and so on) are likely more important and contributory towards the risk of diabetes. This can be seen from the fact that *H. pylori* infection is more prevalent in developing countries, whereas diabetes is more prevalent in developed countries. However, the present study suggested that eradication of *H. pylori* might be useful not only to prevent gastric disease, but also, to a certain extent, to reduce the risk of diabetes.

Further studies, especially longitudinal studies, are necessary to validate the present results.

ACKNOWLEDGMENT

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1 | Methods and results of the sensitivity analysis.