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Chapter 6

Helicobacter pylori Infection and Diabetes Mellitus

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/63826

Abstract

Helicobacter pylori colonizes the stomach and causes chronic gastritis, which most often remains asymptomatic. However, in a small proportion of infected persons, it causes peptic ulcers and gastric cancer. We reviewed recent evidence of the association between *H. pylori* infection and diabetes mellitus (DM). Numerous studies have shown a positive association between *H. pylori* infection and DM, however, findings are still conflicting. Such a link is biologically plausible, given the importance of the stomach in the homeostasis of systems outside the digestive tract; however, the mechanisms by which *H. pylori* might affect the risk of DM are not clear. Current knowledge indicates that *H. pylori* infection can affect the regulation of ghrelin and leptin, two hormones that play central roles in energy homeostasis in humans. Yet, methodological limitations are present in studies that addressed the relationships of *H. pylori* infection with DM and with possible risk factors for DM, including inadequate control of confounders. The important question of whether *H. pylori* eradication might be beneficial for glycemic control in diabetic patients is still unresolved. Future well-designed studies are needed to address these research questions, which are of clinical and great public health significance.

Keywords: Helicobacter pylori, diabetes mellitus, epidemiology

1. Introduction

Helicobacter pylori is a gram-negative bacterium that colonizes the stomach and causes persistent infection. The infection is typically acquired in the first few years of life [1–3]. The associated risk factors of *H. pylori* infection include living in crowded households, low socioeconomic conditions and infected family members [4–6]. The infection is common worldwide with highest prevalence rates reaching 80–90% in developing countries and underprivileged communities [7], while a much lower prevalence of 20–50% is recorded in developed countries [7].

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H. pylori infection has two phases: an acute phase and a chronic course. Acute *H. pylori* infection is rarely diagnosed. Following establishment of the infection, chronic gastritis develops; however, most infected people remain asymptomatic and only 10–20% of them develop peptic disease during their lifetime [7]. *H. pylori* causes gastric and duodenal ulcers, and in rare occasions distal gastric cancer and mucosa-associated lymphoid tissue (MALT) lymphoma [7]. These diseases are the main indications to test and treat *H. pylori* infection [8], in addition to unexplained iron deficiency anemia (IDA) and idiopathic thrombocytopenic purpura [8]. Although *H. pylori* infection is acquired in childhood, peptic ulcer disease typically occurs in adulthood.

Following *H. pylori* colonization, rigorous local and systemic immune responses develop. However, these do not clear the infection but rather contribute to the damage of the gastric mucosa [7, 9, 10]. *H. pylori* simulates the innate immune response, as well as humoral and cell-mediated immune responses [9, 10]. The predominant human T cell response is the T-helper 1 mediated response, which is associated with releasing proinflammatory cytokines and activation of phagocytes [9, 10]. *H. pylori* also induces Th2 and T-regulatory (Tregs) responses [9, 10]. The importance of Treg response is in both controlling inflammation and promoting the persistence of the infection [9, 10].

H. pylori-associated gastric pathology develops over time in a progressive manner [11–13], and the damage to gastric mucosa can be observed even in asymptomatic persons [14]. Today it is clear that host (e.g., age, genetic susceptibility), agent (virulence antigens) and environment-related factors are important in the development of *H. pylori*-associated gastroduodenal diseases [9]. For example, host genetic polymorphisms that lead to increased release of proinflammatory cytokines are associated with increased gastric cancer risk [9]. Pathogenesis is dependent on a Th1-acquired immune response and on hormonal changes including hypergastrinemia [9]. Regarding pathogen virulence factors, most *H. pylori* strains carry the *cag* pathogenicity island that encodes for a type IV secretory apparatus, which allows translocation of cytotoxin-associated gene A (CagA) protein into the host cell. This, together with the vacuolating cytotoxin (VacA), plays a major role in the pathogenesis of gastroduodenal diseases [7, 9, 15–17]. Novel *H. pylori* antigens have been identified recently [18], some of which were found to be associated with atrophic gastritis and gastric cancer risk such as GroEL [18], Helicobacter cysteine-rich protein (HcpC) [19], outer membrane protein (Omp) and others [20, 21].

Several studies have shown associations between *H. pylori* infection and various extragastric diseases [22]. *H. pylori* infection was positively linked with adulthood chronic diseases such as cardiovascular disease [23–25], dementia [26–28], insulin resistance and diabetes mellitus (DM) [22, 29, 30]. The mechanisms of such associations are not fully understood, and it is not clear whether such associations are causal or not. This chapter will focus on the association between *H. pylori* infection and DM.

2. *H. pylori* infection, changes in gastric physiology and metabolic hemostasis

Although the role of *H. pylori* infection in the pathogenesis of gastroduodenal diseases [7, 9, 17, 31] is well established, its impeding effects on metabolic homeostasis and DM are not clear.

http://dx.doi.org/10.5772/63826

The stomach plays a major role in the homeostasis of systems outside the digestive tract. Therefore, the link between *H. pylori*-chronic gastritis and metabolic homeostasis and DM seems biologically plausible.

H. pylori-induced inflammation and its severity affect gastric physiology. For example, *H. pylori* leads to hormonal changes in the stomach, such as reduced production of somatostatin and hypergastrinemia [9]. *H. pylori*-gastritis also alters the secretion of gastric acid [32, 33]; increased secretion of gastric acid is associated with antral-predominant phenotype and increased risk of duodenal ulcers [9, 10]. *H. pylori* infection can reduce gastric acid production, and this is typically associated with corpus-predominant gastritis and increased likelihood of gastric ulcer and gastric adenocarcinoma [9, 10]. Moreover, *H. pylori* infection is associated with reduced gastric ascorbic acid levels [34]. *H. pylori* affects the levels of pepsinogen (PG) I and PGII; proenzymes of the digestive enzyme pepsin. PGI is secreted from cells in the corpus and PGII is also secreted from cells in the antrum and duodenum [35, 36]. About 1% of PGs can be found in the serum. Serum PGI and PGII are increased in *H. pylori* infected vs. uninfected individuals, and higher levels are found in more severe gastritis. As the severity of gastritis progresses and corpus atrophic lesions appear, the PGI level decreases, while the PGII level remains stable; the result is a decrease in the PGI:PGII ratio [37, 38]. These markers have clinical significance, and they predict various gastric pathologies [16, 37–40].

In addition, *H. pylori* infection can affect the regulation of ghrelin and leptin [41–47], two hormones that play central roles in energy homeostasis [48]. Ghrelin reduces energy expenditure and promotes weight gain [48–50], while leptin decreases appetite and increases energy expenditure [48]. Both hormones are secreted by the epithelial cells in the stomach [48, 51]. The relationship between *H. pylori* and these hormones appears to be complex. While several studies reported no association between *H. pylori* infection and circulating leptin [43, 45, 46, 52–54] and ghrelin levels [45, 52, 54], others found lower levels of one or the two hormones in *H. pylori* infected vs. uninfected individuals [41, 42, 44]. There also appears to be differences in gastric mucosa levels of these hormones, according to *H. pylori* infection [41, 42, 47, 52–54]. Moreover, *H. pylori* eradication seems to affect these hormones as well [41, 43, 45, 47, 52] (Table 1).

Study	Exposure	Ghrelin		Leptin	
		Circulating levels	Gastric mucosa levels	Circulating levels	Gastric mucosa levels
Isomoto et al. [44]	*H. pylori* infection	↓	↓	ND	ND
	H. pylori eradication	NS	NS	ND	ND
Chuang et al. [46]	*H. pylori* infection	Males: ↓ Females: NS	ND	NS	ND
Jun et al. [52]	*H. pylori* infection	NS	NS	NS	↑
Nishi et al. [53]	*H. pylori* infection	ND	ND	NS	↑

Study	Exposure	Ghrelin		Leptin	
		Circulating levels	Gastric mucosa levels	Circulating levels	Gastric mucosa levels
	H. pylori eradication	ND	ND	NS	
Francois et al. [45]	*H. pylori* infection	NS	ND	NS	ND
	H. pylori eradication	Pre-meal: NS Post meal: ↑	ND	↑	ND
Azuma et al. [47]	*H. pylori* infection	ND	ND		↑
	H. pylori eradication	ND	ND	NS	↓
Jang et al. [54]	*H. pylori* eradication	NS	↑	NS	ND
Roper et al. [41]	*H. pylori* infection	NS	Fundic: NS Antral: NS Gastric juice:↑	↓	Fundic: NS Antral:↓
Breidert et al. [43]	*H. pylori* infection	ND	ND	NS	Antrum: NS Corpus:↑

NS, no significant difference; ND, not determined;, ↑ increase;, ↓ decrease.

Table 1. Selected studies that addressed associations of *H. pylori* infection and *H. pylori* eradication with ghrelin and leptin levels

Altogether, these studies suggest that *H. pylori* can alter gastric physiology, which can in turn affect metabolic homeostasis and the risk of DM.

3. *H. pylori* infection and diabetes mellitus

DM refers to a group of metabolic disorders that manifest with hyperglycemia. DM is classified based on the pathogenic course that results in hyperglycemia, with two broad categories designated as type 1 DM (T1DM) and type 2 DM (T2DM). T1DM is the result of interaction among genetic, environmental and immunological factors that eventually leads to destruction of beta cells in the pancreas and complete or near-complete insulin deficiency. T2DM consists of various disorders with variable levels of insulin resistance, impaired insulin secretion and increased glucose production. T1DM usually occurs in childhood and adolescence, and comprises 5–10% of all DM cases [55]. T2DM typically develops in adulthood and is responsible for the majority (90–95%) of DM cases [55].

DM is a major public health problem [56–60], causing an enormous burden to patients and their families, as well as to health care systems. The prevalence of T2DM is increasing globally

[56–60] due to increases in life expectancy and obesity [56, 58]. It is estimated that 240 million people have T2DM, and that in 2025 about 380 million will have the disease, while 418 million will have impaired glucose tolerance (IGT) [56]. The burden of DM is amplified given its significant macro and microvascular complications (such as cardiovascular disease, kidney disease), in addition to peripheral neuropathy [55].

There are well-established risk factors for T2DM [61–67], including sociodemographic factors [64, 68, 69], lifestyle factors (e.g., obesity, physical inactivity, poor diet [61–67]) and high glucose levels reflecting IGT [65, 66]. Changes in diet (i.e., higher consumption of whole grain products and exchanging unsaturated fat for saturated fat), and in particular physical activity and avoidance of obesity, can prevent T2DM through changes in body fat and other mechanisms [61, 67, 70–72]. These may reduce the incidence of DM by 28–59% [72]. Such interventions are also important for better control of diabetes [70, 73]. Current evidence suggests that there must be additional factors besides lifestyle that contribute to the occurrence of DM.

In addition to the association mentioned above, between *H. pylori* infection and ghrelin and leptin [41, 45, 74–80], associations have been reported of *H. pylori* infection with glycated hemoglobin levels (Hb1Ac) [81], as well as with disturbances in metabolic homeostasis including insulin resistance; the latter according to a recent literature review and a systematic review [22, 82]. These findings support the postulation that *H. pylori* infection may be involved in the etiology of the emerging pandemic of obesity and DM, and in diabetes-related complications.

Associations of *H. pylori* infection with DM incidence [30, 83, 85] have been reported. Recent meta-analyses showed a significant 1.7 to 2-fold higher prevalence of *H. pylori* infection in persons with T2DM vs. non-diabetic individuals [84, 85]. In some of the studies that reported a positive association between *H. pylori* infection and DM [30, 86–88], the association became non-statistically significant after adjustment for potential confounders such as age and socioeconomic status [87, 88]. Other studies reported no significant association between *H. pylori* and DM [89–92], or a significant association only in persons with BMI>25 [81] (Table 2). Several studies did not control adequately for socioeconomic status and for traditional risk factors of DM, such as obesity and physical inactivity. Furthermore, most of the evidence is based on small-scale hospital-based case–control studies, in which the source population, selection of control population and representativeness of the sample were not fully described. For these reasons, inference and generalizability of findings from such studies should be done with caution. On the other hand, recent well-designed studies show convincing evidence of the potential involvement of *H. pylori* infection in the occurrence of DM, and possibly in IGT. A large population-based follow-up investigation of elderly persons has demonstrated a significant two-fold increased risk of DM in *H. pylori* infected vs. uninfected persons, even after controlling for possible confounders, while such an association was not observed for other pathogens [30]. A large well-designed and thoroughly analyzed survey that utilized nationwide data (N~13,000) from the United States indicated no significant association between *H. pylori* infection and self-reported diabetes. However, among individuals with BMI>25 kg/m^2 who were assessed in the 1999–2000 National Health & Nutrition Examination Survey (NHANES), DM was more prevalent among those who were *H. pylori* seropositive than those

who were *H. pylori*-seronegative[81] (Table 2). Moreover, that study showed that *H. pylori* infected persons, especially those infected with CagA strains, had significantly elevated mean HbA1c levels compared with those who were *H. pylori* seronegative [81].

Study	**Study population**	**Study design**	***Hp detection***	**Outcome**	**Findings**	**Adjusting for confounders**
Jeon et al. [30] California	*N*=782 diabetes free individuals at baseline Age >60 years	Prospective cohort	Serum IgG by ELISA	DM	Adjusted HR 2.69 (95% CI: 1.10–6.60)	Sex, education, smoking, cholesterol, DBP, HSV-1
Hsieh et al. [86] Taiwan	*N*=903 *Hp* infected patients aged 57.16±11.64 years *N*=1167 uninfected patients aged 56.57±13.34 years	Cross-sectional	Gastric biopsy: culture, histology and rapid urease test	T2DM	OR 1.67 (95% CI: 1.19–2.35)	
Chen and Blaser [81] USA	Data from NHANES III *N*=7417 age ≥18 years NHANES 1999–2000 *N*=6072 age ≥3 years	Cross-sectional	Serum IgG by ELISA	DM	NHANES 1999–2000: Adjusted OR: 1.30 (95% CI: 0.94–1.80) BMI>25 OR (1.43; 95% CI: 1.00–2.03) NHANES III: Adjusted OR: 0.99 (95% CI: 0.80–1.23)	Age, sex, race, BMI, smoking, education
El-Eshmawy et al. [111] Egypt	*N*=162 T1DM patients aged 19.35±2.6 years *N*=80 healthy subjects aged 19.76±2.76 years	Case-control	Serum IgG and IgA by ELISA	T1DM	OR 3.67 (95% CI: 2.07–6.55)	Matching by age, sex, SES
Longo-Mbenza et al. [91] Democratic Republic of the Congo	*N*=128 patients with *Hp* infection aged 53.4±12.9 years *N*=77 uninfected patients aged 52.5±16.6 years	Prospective cohort Follow-up 9.6±0.8 years	Serum IgG by ELISA	DM	OR: 0.97 (95% CI: 0.35–2.86)	
Xia et al. [89] Australia	*N*=49 T1DM and *N*=380 T2DM (aged 60.7±13.3 years) *N*=170 non-diabetic controls aged 60.4± 11.3 years	Case-control	Serum IgG by ELISA	T1DM T2DM	Overall 0.94 (95% CI: 0.65–1.39) T2DM: OR: 1.03 (95% CI: 0.71–1.52) T1DM: OR: 0.40 (95% CI: 0.15–0.94)	

Study	Study population	Study design	*Hp detection*	Outcome	Findings	Adjusting for confounders
Demir et al. [90] Turkey	*N*=141 T2DM patients aged 52±8.2 years *N*=142 non-diabetic subjects aged 51±9.3 years	Case-control	Gastric biopsy: rapid urease test and histology	T2DM	OR: 1.15 (95% CI: 0.71–1.85)	
Colombo et al. [112] Italy	*N*=138 T1DM patients aged 12.0±3.4 years *N*=138 controls aged 12.2±2.0 years	Case-control	Serum IgG and IgA by ELISA	T1DM	OR: 0.87 (95% CI: 0.52–1.46)	Matching by age
Cenerelli et al. [92] Italy	*N*=30 T2DM patients aged 55.7±9.7 years *N*=43 controls aged 51.2±11.3 years	Case-control	UBT	T2DM	OR: 1.06 (95% CI: 0.41–2.76)	
Dore et al. [87]	*N*=145 T1DM and *N*=240 T2DM *N*=506 controls (ages 12–75 years)	Case-control	Serum IgG by ELISA	T1DM T2DM	T1DM: 0.59 (95%CI: 0.40–0.87) T2DM: 2.08 (95%CI: 1.52–2.85)	In stratified analysis by age group, SES, the differences were not significant
Lutsey et al. [88]	*N*= 1000 ages 45–84 years	Cross-sectional	Serum IgG by ELISA	DM	Crude OR: 1.65 (95%CI: 1.16–2.34) Adjusted OR: 1.12 (0.78–1.62)	Age, sex, rate, education and site

BMI, body mass index; CI, confidence intervals; DM, diabetes mellitus; DBP, diastolic blood pressure; ELISA, enzyme-linked immunosorbent assay; *Hp*, *Helicobacter pylori*; HR, hazard ratio; HSV-1, *Herpes simplex virus 1*; IgA, immunoglobulin A; IgG, immunoglobulin G; NHANES, National Health & Nutrition Examination Survey; OR, odd ratio: SES, socioeconomic status; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; UBT, urea breath test.

Table 2. Selected epidemiological studies that examined an association between *H. pylori* infection and diabetes mellitus

4. *H. pylori* infection and glycemic control among diabetic patients

Given the observed associations between *H. pylori* infection and various metabolic and glycemic measures, the question arises of whether *H. pylori* infection and/or *H. pylori* eradication can affect glycemic control in diabetic patients. If indeed *H. pylori* infection plays a role in glycemic control, *H. pylori* eradication might be beneficial to diabetic patients. A recent meta-analysis that included 14 observational studies involving 1781 diabetic patients (both T1DM and T2DM) showed no significant difference in mean HbA1c values among *H. pylori* infected individuals compared with those uninfected; mean difference 0.19% (95% CI: −0.18 to 0.46),

(Pv=0.16) [93]. In contrast, another meta-analysis involving 11 studies and 513 patients reported significantly higher HbA1c values among *H. pylori*-infected diabetic persons than among uninfected ones: weighted mean difference 0.43 (95% CI: 0.07–0.79), (Pv=0.02) [94]. The discrepancy in results between the two meta-analyses can be explained by differences in their criteria of study selection, which determined the number and quality of the studies analyzed.

Study	Study population	*H. pylori* infection	Intervention	Outcome	Findings	Adjusting for confounders
T2DM						
Zojaji et al. [95] Iran	*Hp* positive T2DM patients (*N*=85). Mean age 52.3 ±4.7 yrs, 31.8% males	Serum IgG antibodies by ELISA	OCA for 14 d.	HbA1c, FPG	Mean HbA1c levels before successful treatment were 8.7±1.1% and 3 m. after treatment were 8.3±0.9% (P<0.001) FPG before successful treatment were 145±22 mg/dl and 3 m. after treatment were 133±18 mg/dl (NS) No significant change in HbA1c was found before and after therapy among patients with no successful *Hp* eradication	None

Vafaeimanes et al. [97] Iran	*N*=191 *Hp* positive patients aged 55.6±9.8 yrs, 53.9% males T2DM patients non-insulin users (*N*=93) and non-diabetic patients (*N*=98) with upper GI symptoms	Gastroscopy and biopsy: histology	Quadruple therapy for 14 d. (*N*= 96; 47 diabetic and 49 non-diabetic patients): OMAB Triple therapy for 14 d. (*N*=95; 46 diabetic and 49 non-diabetic patients): OCA	HbA1c, FPG	*Hp* eradication was successful in 63% of T2DM patients vs. 87.7% in non-diabetic patients who received OCA therapy (*P*=0.017) and 38.2 vs. 55.1%, respectively (*P*< 0.001) in those who received OMAB Decrease in HbA1c level 3 and 6 m after treatment was 0.23±0.91% vs. 0.25±0.85% and 0.19±0.85% vs. 0.20±0.91% in T2DM patients who had successful *Hp* eradication vs. no eradication, respectively (NS)	Age and sex-matching between diabetic and non-diabetic patients

http://dx.doi.org/10.5772/63826

					Decrease in FPG level 3 and 6 m. after treatment was 10.9±12.1 mg/dl vs. 9.5±14.3 mg/dl and 8.9±16.8 mg/dl vs. 9.4±15.6 mg/dl in T2DM patients who had successful *Hp* eradication vs. no eradication, respectively (NS)
Wada et al. [96] Japan	T2DM patients (*N*=72) who received *Hp* eradication therapy. Mean age 63.7 ±1.1 yrs, 76.4% males	Gastric biopsy	AC plus lansoprazole (*N*=65) or Omeprazole (*N*=2), or rabeprazole (*N*=5) for 7 d.	HbA1c	HbA1c levels did not show significant change after therapy 6.9% ±0.1% 3 m. before to 7.0 ±0.1% 3 m. after (*P*=0.3), 7.0 ±0.1% after 6 m. (*P*=0.3)
Akanuma et al. [98] Japan	T2DM *Hp* infected patients (*N*=174) aged 65±7 yrs, 83.9% males without GI complications who had successful *Hp* eradication therapy	Gastroscopy biopsy: Culture, histology,, rapid urease test serum IgG antibodies UBT	First-line treatment: LR or OCA (*N*=119) Patients with penicillin allergy: LCM (*N*=3) Quadruple therapy: LACM (*N*=24) Second-line therapy: lansoprazole or	HbA1c	Overall, no significant changes in mean HbA1c values were observed 1 year before and after *Hp* eradication (*P*=0.07) Among patients with uncontrolled diabetes (*N*=76), HbA1c levels decreased

			RAM (*N*=28) Regimens were given for 7 d.		significantly between baseline and post *Hp* eradication (*P*=0.08): 8.22±0.92% at baseline 8.08 ±1.1% 3 m. 7.95 ±1.2% 6 m. 8.06 ±1.1% 9 m. 7.99 ±0.99% 12 m. Among patients with controlled diabetes (*N*=98), HbA1c levels increased between baseline and post-*Hp* eradication (*P*=0.41): 6.77±0.4% at baseline6 .88 ±0.6% 3 m. 6.97 ±0.6% 6 m. 7.00 ±0.6% 9 m. 7.01 ±0.6% 12 m.	
T1DM						
Candelli et al. [99] Italy	T1DM patients aged 13.6±4.6 yrs, 51.7% males infected with *Hp*	UBT	ACR for 7 d.	HbA1c	No difference in HbA1c level was observed between *Hp* infected and	Sex, age, family income, BMI

http://dx.doi.org/10.5772/63826

	(*N*=29) and uninfected T1DM patients aged 13.1±4.2 yrs, 51.7% males (*N*=29)				uninfected patients. 8.25±1.06% vs. 8.4±1.7% (NS) No difference in HbA1c level was observed in patients before and 6 m. after eradication 8.2±1% vs. 8.3±1% (NS) nor between *Hp* infected patients and uninfected ones 6 m after the evaluation of *Hp* status	
Begue et al. [100] Louisiana	T1DM patients aged 7–17 yrs with asymptomatic *Hp* infection (*N*=8) and uninfected T1DM patients aged 6–18 (*N*=16)	Serum IgG antibodies, UBT	OCM for 14 d.	HbA1c	HbA1c values were higher among T1DM *Hp* infected patients than T1DM uninfected patients at the beginning of the study (median, 13.6% and 11.0%, respectively; *P*=0.07) After treatment, T1DM *Hp*-infected patients had a steady decrease in HbA1c level (slope = −0.10), whereas uninfected T1DM patients had a slightly increasing trend (slope= +0.03) (*P*= 0.05)	Age, race, BMI, diabetes duration and compliance with clinical appointments

Table 3. *Helicobacter pylori* eradication and glycemic control in diabetic patients

					After 2 yrs, HbA1c values were similar in *Hp* infected and uninfected patients (median: 11.7 and 11.4%, respectively; *P*= 0.69)
de Luis et al. [101] Spain	*Hp*-infected T1DM patients (*N*=13) aged 44.9±15.5 yrs, 30.77% males	Serum IgG antibodies, UBT, gastric biopsy	First-line therapy OCA for 10 d. In persistent infection: retreatment adding bismuth for 10 d.	HbA1c	HbA1c levels before and 6 m after *Hp* eradication were 7.%±1.7%vs. 7.5±0.6% in patients free of gastritis (*N*=9) and 7.1±1.1% vs. 6.8±1.4% in patients with gastritis (*N*=4). All NS

A, amoxicillin; B**,** bismuth; BMI, body mass index; C, clarithromycin; d**,** days; ELISA**,** enzyme linked immunosorbent assay; FPG**,** fasting plasma glucose; GI, gastrointestinal; HbA1c, glycosylated hemoglobin; *Hp*, *Helicobacter pylori*; IgG, immunoglobulin G; L, lansoprazole; m, months; NS, not significant; O, omeprazole; OCA, omeprazole 20 mg and clarithromycin 500 mg and amoxicillin 1 g each twice a day; OMAB, omeprazole 20 mg and metronidazole 500 mg and amoxicillin 1 g and bismuth subcitrate 240 mg, each twice a day; PU, peptic ulcer; R, rabeprazole; SES, socioeconomic status; T1DM, type 1 diabetes mellitus; T2DM**,** type 2 diabetes mellitus; UBT**,** urea breath test; yrs, years.

The question of whether *H. pylori* eradication can improve glycemic control was assessed in a limited number of observational studies, most of them were small scale [95–101] (Table 3). Findings from these studies were conflicting, ranging from no difference, to small non-significant or borderline improvements from baseline to up to 2-years after eradication [95–101] and to a significant decrease from baseline, in HbA1c at 3 months after *H. pylori* eradication [95]. A pooled analysis of two studies that compared mean differences in HbA1c between diabetic individuals who had undergone successful *H. pylori* eradication and those whose *H. pylori* eradication therapy had failed, showed no significant difference between the groups [94]. The optimal study design to examine the effect of *H. pylori* eradication therapy on glycemic control is a randomized controlled trial with intention-to-treat analysis, in which diabetic patients are assigned to either an *H. pylori* eradication group or a placebo control group. However, to-date such trials are lacking, and the current evidence is based on observational studies, which are evidently prone to biases and confounders. Therefore, the question of whether *H. pylori* infection affects glycemic control in diabetic patients remains unresolved.

5. *H. pylori* infection and metabolic syndrome

Metabolic syndrome is a cluster of metabolic risk factors that are associated with increased risk for atherosclerotic cardiovascular disease, T2DM and their complications. These factors include atherogenic dyslipidemia (elevated triglycerides and apolipoprotein B, increases small low-density lipoproteins [LDL], and low concentration of high-density lipoproteins [HDL]), elevated blood pressure and elevated fasting glucose levels known as impaired fasting glucose (IFG) or prediabetes [102, 103], which lead to a prothrombotic and proinflammatory state. The main risk factors for metabolic syndrome include obesity, mainly abdominal obesity and insulin resistance [103], as well as aging, physical inactivity and diet rich with saturated fat and cholesterol [103].

Recent studies have tested the hypothesis of a positive association between *H. pylori* and metabolic syndrome [22, 104–106]. While the underlying mechanisms remain to be determined, the inflammatory response to infection and secretion of cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin-1 (IL-1), IL-6 and IL-8 likely play a role in the postulated association. Additionally, *H. pylori*-induced atrophic gastritis, which develops with aging, reduces the levels of vitamin B12 and folate, which increase homocysteine levels, a known risk factor for insulin resistance [104].

The evidence from epidemiological studies on the association between *H. pylori* infection and metabolic syndrome has been evolving over the past few years.

A recent large cross-sectional study conducted among 3578 persons aged 18–64 years from Taiwan has demonstrated that *H. pylori* infected persons (according to urea breath test [UBT]) had a significantly increased prevalence of metabolic syndrome than uninfected persons; 12.4 vs. 7.4% (Pv<0.001) in men and 7.4 vs. 2.5% in women (Pv<0.001) [105]. In this study, metabolic syndrome was defined based on National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III Criteria, which were adjusted to the Taiwanese population [105].

http://dx.doi.org/10.5772/63826

The observed positive associations between *H. pylori* infection and metabolic syndrome were attenuated in multivariable analyses, while adjusting for confounders such as age, smoking and alcohol drinking; adjusted odds ratio (OR) 1.91 (95% CI: 1.03–3.53) in women, while in men the association was not statistically significant: adjusted OR: 1.38 (95% CI: 0.97–1.95) [105].

A population-based study conducted among adults aged 25 years or over in Iran also reported a 1.5-fold significantly increased prevalence of metabolic syndrome (according to NCEP-ATP-III criteria) among *H. pylori* (based on serum IgG detection) infected men and women compared with uninfected ones [107]. The same study reported positive associations in relation to exposure to other infectious agents as well such as *Chlamydia pneumoniae*, *Herpes simplex virus 1* (HSV-1) and *Cytomegalovirus* (CMV) [107]. From this study, it is not clear whether the results were adjusted for confounders, and which ones [107].

Gunji et al. [106], in a well-designed study carried out among 5488 Japanese men (mean age 47± 5 years) and 1906 women (mean age 46±4 years), demonstrated a significant positive relationship between *H. pylori* seropositivity (according to the presence of IgG antibodies) and metabolic syndrome (based on the Japanese diagnostic criteria); adjusted OR: 1.39 (95% CI: 1.18–1.62) Pv<0.001 [106]. This association was independent of known risk factors for metabolic syndrome namely age, sex, diet and smoking [106].

While there is a growing compelling evidence from large epidemiological studies supporting the existence of a positive association between *H. pylori* infection and metabolic syndrome, other studies reported no signification association [108] or reported small magnitude association measures [109]. Therefore, the question of whether *H. pylori* infection is associated with metabolic syndrome, although biologically plausible, remains to be determined, as well as the source of variation among the studies in their findings. Multi-national studies employing similar clinical, epidemiological and diagnostic protocols and methods will be needed to assess true population-to-population variations.

6. Conclusions and future directions

Current evidence is conflicting regarding the question of whether *H. pylori* may be associated with an increased risk of DM, metabolic syndrome and poor glycemic control. Although an association between *H. pylori* infection and DM is biologically plausible [110], the nature of such an association is not yet understood. This is due, in part, to important methodological limitations apparent in studies that addressed the relationship between *H. pylori* infection and DM, including inadequate control for socioeconomic status and for known DM risk factors. Moreover, most studies focused on DM, and less on the reversible conditions of IGT, and IFG. Understanding the role in this association of pathogen-related factors, i.e., virulence antigens such as CagA and VacA is still limited. In addition, it is not clear which biological mechanisms may contribute to the postulated excess risk of DM and/or metabolic syndrome in *H. pylori* infected persons compared with uninfected ones. Importantly, it is not yet clear whether *H. pylori* eradication may be beneficial for glycemic control in diabetic patients. Randomized placebo-controlled trials assessing such research questions are lacking.

Addressing these research questions is of great public health and clinical significance given the high prevalence of *H. pylori* infection and significant burden of DM. If *H. pylori* infection is truly involved in the etiology of DM, even to a small magnitude (i.e., small relative risks), the public health impact is expected to be great, given the high prevalence of the infection.

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