**Helicobacter pylori** infection and endocrine disorders: Is there a link?

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**Abstract**

*Helicobacter pylori* (H. pylori) infection is a leading world-wide infectious disease as it affects more than half of the world population and causes chronic gastritis, peptic ulcer disease and gastric malignancies. The infection elicits a chronic cellular inflammatory response in the gastric mucosa. However, the effects of this local inflammation may not be confined solely to the digestive tract but may spread to involve extraintestinal tissues and/or organs. Indeed, *H. pylori* infection has been epidemiologically linked to extra-digestive conditions and diseases. In this context, it has been speculated that *H. pylori* infection may be responsible for various endocrine disorders, such as autoimmune thyroid diseases, diabetes mellitus, dyslipidemia, obesity, osteoporosis and primary hyperparathyroidism. This is a review of the relationship between *H. pylori* infection and these endocrine disorders.

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**Key words:** *Helicobacter pylori*; Hormones; Thyroid; Osteoporosis; Diabetes; Dyslipidemia

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**INTRODUCTION**

*Helicobacter pylori* (H. pylori) is a gram-negative, spiral-shaped pathogenic bacterium that specifically colonizes the gastric epithelium and causes chronic gastritis, peptic ulcer disease and/or gastric malignancies[1,2]. The infection induces an acute polymorphonuclear infiltration in the gastric mucosa. If the infection is not effectively cleared, this acute cellular infiltrate is gradually replaced by an immunologically-mediated, chronic, predominantly mononuclear cellular infiltrate[3]. The latter is characterized by the local production and systemic diffusion of pro-inflammatory cytokines[4], which may exert their effect in remote tissues and organic systems[6]. As a result, *H. pylori* infection has been epidemiologically linked to some extra-digestive conditions, including endocrine disorders (Table 1), although there are contradictory data regarding the relationship between *H. pylori* infection and these diseases.

**H pylori AND DIABETES MELLITUS**

The relationship between diabetes mellitus (DM) and *H. pylori* infection is controversial. According to some studies there is a high prevalence of *H. pylori* infection in patients with either type I[6-9] or type II DM[10-13] which is correlated with the duration of DM[10], the presence of dyspeptic symptoms[14,15] and cardiovascular autonomic neuropathy[15,16], age[8], gender[16], body mass index (BMI)[16], blood pressure[14], fasting glucose levels[16] and the HbA1c levels[10,16]. In particular, the prevalence of *H. pylori* infection was found to be higher in obese, female, middle-aged patients with a long standing DM, dyspeptic symptoms, cardiovascular autonomic neuropathy and increased blood pressure, fasting glucose levels and HbA1c values[8,11,13,16]. This could be related to a reduced gastric motility and peristaltic activity[16], various chemical changes in gastric mucosa following non-enzymatic glycosylation processes[14] and an impaired non-specific immunity observed in diabetic patients[11].

In contrast, other studies showed that *H. pylori* infection is not associated with DM, as there is no
difference in the prevalence of *H. pylori* infection between diabetics and non-diabetics[7,17,23], regardless of the type[8,17,23] and duration of DM[8,9,22] and/or severity of dyspeptic symptoms in patients with DM[22]. The presence of micro-angiopathy in patients with DM may be a negative factor for colonization by *H. pylori*, because micro-vascular changes in the gastric mucosa may create an unfavourable environment for the establishment or survival of *H. pylori*[16]. Interestingly, one study even showed a lower sero-prevalence of *H. pylori* in patients with DM, in comparison with the healthy population[13], while another showed a significantly lower incidence of *H. pylori* infection in diabetics with active duodenal ulceration, as compared with non-diabetics[14].

The relationship between gastrointestinal symptoms in DM and *H. pylori* infection is also controversial. According to some studies, there is no difference between diabetics and non-diabetics concerning the prevalence of *H. pylori*-related gastro-duodenal disorders[7]. Moreover, *H. pylori* infection was not associated with either delayed gastric emptying[9,24] or upper gastrointestinal symptoms in DM[19,21,25]. On the other hand, a higher prevalence of esophagitis and peptic ulcer was found in *H. pylori*-ve patients with DM, with or without dyspepsia, especially those with cardiovascular autonomic neuropathy[13,15], suggesting that this population should be considered as “high risk” for *H. pylori* infection and suitable candidates for treatment[12]. In addition, some data demonstrated a higher prevalence of *H. pylori* infection in diabetic patients with dyspepsia[14,26], reactive gastritis[27] and chronic gastritis[29] compared to those with no signs or symptoms of gastrointestinal disease.

The relationship between DM complications and *H. pylori* infection is another issue which is contentious and deserves further investigation, as only few data are available. According to some data there is no relationship between *H. pylori* infection and diabetic complications, such as nephropathy[13,16], retinopathy[17,18], and/or micro-angiopathy[10] whereas other data show that virulent strains of *H. pylori*, such as cytotoxin-associated gene CagA+, are associated with macro-angiopathy[10], neuropathy[10] and micro-albuminuria in type II diabetic patients, maybe due to an immuno-mediated injury at the level of the endothelium, caused by a systemic immune response to the infection, leading to albumin leakage[10]. Additionally, some data indicate a possible association of *H. pylori* infection and the development of coronary heart disease, thrombo-occlusive cerebral disease, or both, in diabetic patients[29].

One point on which all studies seem to converge is that the effectiveness of eradication regimens for *H. pylori* infection is significantly lower in diabetics than in non-diabetics[20,28,32] whereas re-infection rates seem to be higher, especially in patients with type II DM compared to the general population[32]. This may be due to changes in the gastric microvasculature leading to reduced absorption of antibiotics. Alternatively, frequent antibiotic use in diabetics may result in the development of resistant *H. pylori* strains[20,30]. Moreover, type I diabetic patients achieve lower *H. pylori* eradication rates on standard triple therapy than non-insulin-dependent diabetic subjects, regardless of the dosage and/or the duration of therapy[28,30,32], and higher re-infection rates one year after eradication of *H. pylori* compared with control subjects[18]. Quadruple therapies seem to cure a large percentage of patients who fail first-line therapy, although this is accompanied by a greater incidence of minor side effects[28,30]. These data suggest that vaccine development seems to be the only effective long term treatment for patients with DM[28].

Noteworthy is the observation that children with type I DM and *H. pylori* infection had an increased daily insulin requirement compared with their uninfected peers[14]. Finally, several issues, such as the role of *H. pylori* in etiopathogenesis of DM and the influence of *H. pylori* eradication on the control of DM, remain to be elucidated.

### Table 1  Endocrine disorders in relationship with *H. pylori* infection

| Endocrine disorders                        |
|-------------------------------------------|
| Autoimmune thyroid diseases               |
| Autoimmune atrophic thyroiditis           |
| Hashimoto’s thyroiditis                   |
| Thyroid mucosal associated lymphocyte tissue (MALT) lymphoma |
| Diabetes mellitus                         |
| Dyslipidemia                              |
| Obesity                                   |
| Osteoporosis                              |
| Primary hyperparathyroidism               |

#### H pylori AND OSTEOPOROSIS

There are limited data regarding the association between *H. pylori* infection and osteoporosis. According to one study, *H. pylori* infection was not accompanied by significant changes in levels of markers of bone metabolism in children, such as estradiol, parathyroid hormone (PTH), cross-linked collagen I carboxy terminal telopeptide, total alkaline phosphatase (ALP), bone-specific ALP, N-terminal cross-links of human pro-collagen type I, osteocalcin, calcium and phosphate[35]. In another study, infection by CagA+ *H. pylori* strains were more prevalent in men with osteoporosis compared to the general population, who showed reduced systemic levels of estrogens and increased bone turnover[36]. *H. pylori* infection by CagA+ strains may therefore be considered a risk factor for osteoporosis in men[36]. Further studies are required to clarify the relationship between *H. pylori* infection and osteoporosis and whether *H. pylori* infection causes time-dependent changes in bone turnover markers during the long course of this chronic inflammatory disease.

### H pylori AND HYPERPARATHYROIDISM

There are only a few studies attempting to clarify the association between *H. pylori* infection and hyperparathyroidism. In fact, only one study showed that *H. pylori* infection was more prevalent amongst patients with primary hyperparathyroidism (PHPT) than in the
general population, suggesting that patients with PHPT, and especially those with dyspeptic symptoms, should be evaluated for *H pylori* infection and treated appropriately if positive[47]. Also, a case report described an association of PHPT with duodenal ulcer and *H pylori* infection[58]. On the other hand, another study claimed no significant relationship between parathyroid abnormalities and *H pylori* infection in haemodialysis patients and this study found that a longer period of dialysis therapy was related to a decreased ability of these patients to produce antibodies against *H pylori*[39].

### H pylori AND OBESITY

The relationship between obesity and *H pylori* infection is controversial. According to some studies, the risk of *H pylori* infection does not increase in overweight young persons[46] and *H pylori* seropositivity or CagA antibody status are not associated with the BMI[41,42] or fasting serum leptin levels[40]. Furthermore, one study indicated an inverse relationship between morbid obesity and *H pylori* seropositivity, leading to the hypothesis that the absence of *H pylori* infection during childhood may enhance the risk of the development of morbid obesity[43]. In contrast, other studies showed that obesity[44] and/or an elevation of the BMI[45] may be associated with an increased incidence of *H pylori* colonization, probably as a result of reduced gastric motility[44]. In addition, the incidence of *H pylori* infection in patients undergoing Roux-en-Y gastric bypass surgery for morbid obesity was higher than that found in all patients undergoing endoscopies and biopsy, even though the incidence of infection was not higher in controls matched for age[44].

The relationship between obesity and *H pylori* eradication is also controversial. There are data which demonstrate that eradication of *H pylori* significantly increases the incidence of obesity in patients with peptic ulcer disease, since it increases the level of BMI[46,47], and/or enhances the appetite of asymptomatic patients, due to an elevation of plasma ghrelin[48] and a reduction of leptin levels[49,50]. In fact, *H pylori* infection caused a marked reduction in plasma levels of ghrelin[44-46,51,53], as a result of a negative effect of this infection on the density of gastric ghrelin-positive cells[51,54] and an increase in plasma levels of leptin and gastrin[49,53,50]. Since ghrelin exerts orexigenic and adipogenic effects in contrast to leptin which exerts anorexigenic effects[42], alterations in plasma levels of gastric originated appetite-controlling hormones in children and adults infected by *H pylori* may contribute to chronic dyspepsia and loss of appetite[49]. Consequently, *H pylori* can be a “protective” factor against the development of becoming overweight[48]. In contrast, other studies showed that there are no differences in plasma ghrelin levels between *H pylori*+ve and *H pylori* -ve patients matched for age and BMI[47] and that successful eradication of *H pylori* had no effect on plasma ghrelin levels[44,51].

### H pylori AND THYROID DISEASES

There have been controversial reports linking *H pylori* infection to thyroid disorders including autoimmune thyroid disorders (ATD) such as autoimmune atrophic thyroiditis[56] and Hashimoto’s thyroiditis[59], or thyroid mucosal associated lymphocyte tissue (MALT) lymphoma[60].

Thus, some studies have reported an increased prevalence of *H pylori* infection in adults[58,61,62] and children[59] with ATD and a relationship between *H pylori* infection and the presence of high titers of thyroid auto-antibodies, such as anti-thyroglobulin (anti-Tg) and antithyroxperoxidase (anti-TPO) antibodies[58,61,62] resulting in abnormalities of gastric secretory function[42]. It has also been suggested that CagA *H pylori* strains increase the risk for ATD, especially in women, and that they are involved in the pathogenesis of Hashimoto’s thyroiditis. This is based on the detection of monoclonal antibodies against Cag-A *H pylori* strains which cross-react with follicular cells of the thyroid gland and also on the fact that *H pylori* strains possessing the Cag-A pathogenicity island carry a gene encoding for an endogenous peroxidase[60]. Moreover, the strong correlation between IgG anti-*H pylori* antibodies and thyroid auto-antibodies, as well as the observation that eradication of *H pylori* infection is followed by a gradual decrease in the levels of thyroid auto-antibodies[61], suggest that *H pylori* antigens might be involved in the development of autoimmune atrophic thyroiditis or that autoimmune function in this disease may increase the likelihood of *H pylori* infection[58]. One study showed a significant decrease of Free-T4 and Free-T3 in *H pylori*+ve subjects compared to *H pylori*-ve controls[62].

On the contrary, other studies showed no differences in the serum levels of thyroid hormones or thyroid auto-antibodies in patients with and without *H pylori* infection[59,63] whereas *H pylori* infection seemed not to increase the risk of ATD in individuals with dyspeptic symptoms[63]. Taking these results into account, it was proposed that screening for ATD in patients with a positive urea breath test is not indicated[59]. Other studies have failed to show any correlation between *H pylori* infection and ATD in children[64]. Moreover, the similar prevalence of *H pylori* infection, with or without CagA strains, in patients with Hashimoto’s thyroiditis and controls argues against a true association between *H pylori* infection and Hashimoto’s thyroiditis[65]. To further explore the relationship between ATD and *H pylori* infection more clinical trials are required.

Lymphoid follicles in the gastric mucosa are common in ATD, and *H pylori* infection plays a causative role[67]. When an autoimmune disease such as ATD coexists with *H pylori* infection[46], *H pylori* may be involved in the pathogenesis of extra-gastric MALT lymphomas, such as thyroid MALT lymphoma, as shown by a case report describing a primary thyroid MALT lymphoma which occurred in an *H pylori*+ve patient with gastric cancer and Hashimoto’s thyroiditis[66,67]. In this case, after subtotal gastrectomy, the thyroid lymphoma became smaller transiently and when the patient was treated with *H pylori* eradication therapy, the lymphoma completely disappeared. Nevertheless, *H pylori* organisms were not detected in the thyroid lymphoma tissue by polymerase
chain reaction (PCR), questioning the role of *H. pylori* in the development of extra-gastric MALT lymphoma in patients with autoimmune disease[^30]. In addition, one study suggested that patients with an autoimmune disease might not be optimal candidates for *H. pylori* eradication, even in the case of an early stage gastric MALT lymphoma, since very few of these patients responded to an *H. pylori* eradication therapy[^49].

On the other hand, it is important to realize that patients with *H. pylori*-related gastritis, atrophic gastritis, or both conditions required increased daily doses of Ti than controls, suggesting that normal gastric acid secretion is necessary for effective absorption of oral Ti[^49]. In addition, development of *H. pylori* infection in patients treated with Ti led to an increased serum level of thyrotropin (TSH), an effect that was nearly reversed after eradication of *H. pylori* infection[^49].

### H. pylori AND DYSLIPIDEMIA

*H. pylori* infection may cause dyslipidemia, as it leads to elevated levels of total cholesterol[^50,51], low-density lipoprotein cholesterol (LDL-c)[^52,53], lipoprotein Lp(a)[^51], apolipoprotein apo-B[^73], triglyceride concentrations[^54,55,56] and decreased levels of high-density lipoprotein cholesterol (HDL-c)[^57-59] and apolipoprotein apo-A1 concentration in the blood[^57,58]. In addition, plasma levels of cholesterol and LDL-c were significantly higher in *H. pylori*-ve patients with ischemic stroke compared to *H. pylori*-ve patients[^55]. It was postulated that chronic *H. pylori* infection may shift lipid profiles toward an atherogenic direction via the action of pro-inflammatory cytokines, such as interleukins 1 and 6 (IL-1 and IL-6), interferon-α (INF-α) and tumor necrosis factor-α (TNF-α). These cytokines are capable of affecting lipid metabolism in different ways, including activation of adipose tissue lipoprotein lipase, stimulation of hepatic fatty acid synthesis and influencing lipolysis[^1,50]. This atherogenic modified lipid profile created by *H. pylori* infection may increase the risk for cardiovascular and cerebrovascular diseases, by participating in the process of atherogenesis, especially when Cag-A+ cytotoxic strains of *H. pylori* are present[^60,61], although other studies do not support this hypothesis[^1,52,82,83].

According to other studies, *H. pylori* infection did not cause any significant changes in plasma levels of total cholesterol[^53,54], triglycerides[^53,54], LDL-c[^57,58] and Apo-B[^58,59].

The relationship between dyslipidemia and *H. pylori* eradication is also controversial. After one year of eradication of *H. pylori* in patients with duodenal ulcers, a significant increase of HDL-c and decrease of LDL-c levels[^59]. Also, 6 mo following successful eradication of *H. pylori* infection the plasma levels of total cholesterol and LDL-c were found to be significantly lower than those in *H. pylori*-ve controls and *H. pylori*-ve patients with stroke[^70].

In contrast, one study showed that eradication of *H. pylori* is associated with minor lipid changes[^84], while others showed a significant increase in the incidence of hyperlipidemia in patients with peptic ulcer disease, as serum total cholesterol and triglycerides were elevated in these patients after eradication of *H. pylori*[^44,47,87].

### CONCLUSION

Since the discovery of *H. pylori*, a variety of studies, essentially epidemiological or therapeutic trials, case reports and others, have evaluated the potential direct or indirect involvement of this bacterium in the pathogenesis of various extra-gastric diseases or disorders, amongst them disorders of the endocrine system. A critical review of data published on these proposed associations suggests a strong link between dyslipidemia and *H. pylori* infection, whereas increasing evidence emerges on the role of *H. pylori* infection in thyroid autoimmune diseases. On the contrary, the association between *H. pylori* infection and obesity, PHPT, DM and osteoporosis remains controversial, as evidence is hindered by the small numbers and methodological problems. Therefore, these associations should be interpreted cautiously. Although some evidence suggests that eradication of *H. pylori* may lead to an improvement of many endocrine disorders, such as DM, dyslipidemia and autoimmune thyroid disease, excluding obesity (Table 2), more clinical trials are needed in order to confirm this beneficial effect. In conclusion, the causal association between *H. pylori* infection and endocrine disorders is still controversial but worthy of further investigation since these diseases affect many people and have a great impact on human health and health economics[^88].
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