Online Submissions: wjg.wjgnet.com
wjg@wjgnet.com
doi:10.3748/wjg.15.2701

World J Gastroenterol 2009 June 14; 15(22): 2701-2707
World Journal of Gastroenterology ISSN 1007-9327

REVIEW

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

Konstantinos X Papamichael, Garyphallia Papaioannou, Helen Karga, Anastasios Roussos, Gerassimos J Mantzaris

Konstantinos X Papamichael, Anastasios Roussos, Gerassimos J Mantzaris, First Department of Gastroenterology, Evaggelismos Hospital, Kolonaki-10676 Athens, Greece
Garyphallia Papaioannou, Helen Karga, B' Department of Endocrinology, Alexandra Hospital, Vas. Sofias & Lourou-115 28 Athens, Greece
Author contributions: Papamichael KX, Mantzaris GJ and Karga H wrote the paper; Papaioannou G and Roussos A undertook the acquisition, analysis and interpretation of the data.
Correspondence to: Konstantinos X Papamichael, MD, PhD, First Department of Gastroenterology, Evaggelismos Hospital, 45-47 Ypsilantou street, Kolonaki-10676 Athens, Greece. kpapamdoc@yahoo.gr
Telephone: +30-210-7201609 Fax: +30-210-7239716
Received: March 23, 2009 Revised: May 13, 2009
Accepted: May 20, 2009
Published online: June 14, 2009

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 extra-intestinal 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.

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

Peer reviewer: Dr. Katsunori lijima, Division of Gastroenterology, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aobaku., Sendai 980-8574, Japan

Papamichael KX, Papaioannou G, Karga H, Roussos A, Mantzaris GJ. *Helicobacter pylori* infection and endocrine disorders: Is there a link? *World J Gastroenterol* 2009; 15(22): 2701-2707 Available from: URL: http://www.wjgnet.com/1007-9327/15/2701.asp DOI: http://dx.doi.org/10.3748/wjg.15.2701

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[5]. 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[7,9], the presence of dyspeptic symptoms[13,14] and cardiovascular autonomic neuropathy[13,15], age[6,8], gender[16], body mass index (BMI)[16], blood pressure[16], fasting glucose[16] and the HbA1c levels[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[6-9,13-16]. This could be related to a reduced gastric motility and peristaltic activity[10], various chemical changes in gastric mucosa following non-enzymatic glycosylation processes[10] 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[17], regardless of the type[8,17-22] and duration of DM[18,19,22] 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[23], while another showed a significantly lower incidence of *H pylori* infection in diabetics with active duodenal ulceration, as compared with non-diabetics[24].

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[17]. Moreover, *H pylori* infection was not associated with either delayed gastric emptying[9,25] or upper gastrointestinal symptoms in DM[19,21,25]. On the other hand, a high 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[26] 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], retinopathy[13], and/or micro-angiopathy[16] while other data shows that virulent strains of *H pylori*, such as cytotoxin-associated gene $CagA^+$, are associated with macro-angiopathy[16], neuropathy[16] 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[28]. 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[20,30-32] whereas re-infection rates seem to be higher, especially in patients with type Ⅱ DM compared to the general population[20,31]. 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[30,32]. 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[20,31,32], and higher re-infection rates one year after eradication of *H pylori* compared with control subjects[33]. 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[20,31]. These data suggest that vaccine development seems to be the only effective long term treatment for patients with DM[20].

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[34]. 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 was 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[37]. Also, a case report described an association of PHPT with duodenal ulcer and *H pylori* infection[38]. 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[40] and *H pylori* seropositivity or CagA antibody status are not associated with the BMI[41,42] or fasting serum leptin levels[41]. 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[10] and/or an elevation of the BMI[44] may be associated with an increased incidence of *H pylori* colonization, probably as a result of reduced gastric motility[10]. 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[45].

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[44,49,51-53], 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[49,55,56]. Since ghrelin exerts orexigenic and adipogenic effects in contrast to leptin which exerts anorexigenic effects[52], 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[50]. 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[57] and that successful eradication of *H pylori* had no effect on plasma ghrelin levels[44,57].

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[58] 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[63] 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 anti-thyroperoxidase (anti-TPO) antibodies[58,61,62] resulting in abnormalities of gastric secretory function[58]. 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[61]. 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[64], 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-T_3 and Free-T_4 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[59,65] whereas *H pylori* infection seemed not to increase the risk of ATD in individuals with dyspeptic symptoms[65]. Taking these results into account, it was proposed that screening for ATD in patients with a positive urea breath test is not indicated[65]. Other studies have failed to show any correlation between *H pylori* infection and ATD in children[66]. 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[59]. 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[68], *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[60]. 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 an autoimmune disease[60]. 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[68].

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 T_4 than controls, suggesting that normal gastric acid secretion is necessary for effective absorption of oral T_4[69]. In addition, development of *H pylori* infection in patients treated with T_4 led to an increased serum level of thyrotropin (TSH), an effect that was nearly reversed after eradication of *H pylori* infection[69].

H pylori AND DYSLIPIDEMIA

H pylori infection may cause dyslipidemia, as it leads to elevated levels of total cholesterol[70,71], low-density lipoprotein cholesterol (LDL-c)[71,72], lipoprotein Lp(a)[71], apolipoprotein apo-B[73], triglyceride concentrations[72,74,75] and decreased levels of high-density lipoprotein cholesterol (HDL-c)[73-78] and apolipoprotein apoA-1 concentration in the blood[73,75]. 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[70]. It was postulated that chronic *H pylori* infection may shift lipid profiles towards 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 tumour 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[71,79]. 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[80,81], although other studies do not support this hypothesis[71,82,83].

According to other studies, *H pylori* infection did not cause any significant changes in plasma levels of total cholesterol[78,84], triglycerides[78,84], LDL-c[78,84] and Apo-B[78,85].

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, apo-AI and apo-AII levels was observed in the study by Scharnagl *et al*[86]. Moreover, eradication of *H pylori* in healthy subjects seems to increase HDL-c and decrease LDL-c levels[78]. 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*[46,47,87].

Table 2 Endocrine disorders and eradication of *H pylori*

Endocrine disorders	*H pylori* eradication
Autoimmune thyroid diseases	↓ of thyroid auto-antibodies[64] ↓ of thyrotropin in *H pylori*+ve patients treated with T4[69]
Diabetes mellitus	↓ in diabetics more than in non-diabetics[20,30-32] ↓ in type I diabetic patients on standard triple therapy more than non-insulin dependent diabetic subjects, regardless of the dosage and/or the duration of therapy[20,31,32]
Dyslipidemia	↑ of HDL-c, apo-AI and apo-AII levels in patients with duodenal ulcers, after 1 year[86] ↑ of HDL-c and ↓ LDL-c levels in healthy subjects[78] ↓ of total cholesterol and LDL-c after 6 mo in *H pylori*+ve controls and *H pylori*+ve patients with stroke[70] ↔ of lipids in patients submitted for endoscopy[84] ↑ of total cholesterol and triglycerides in patients with peptic ulcer disease[46,47] or without[87]
Obesity	↑ of BMI in patients with peptic ulcer disease[46,47] ↑ of the appetite of asymptomatic patients, due to ↑ of plasma ghrelin[48] and ↓ of leptin levels[49,50] ↔ of plasma ghrelin levels in subjects referred for upper gastrointestinal endoscopy[44,57]

BMI: Body mass index; HDL-c: High-density lipoprotein cholesterol; apo-AI: Apolipoprotein AI; apo-AII: Apolipoprotein AII; LDL-c: Low-density lipoprotein cholesterol; +ve: Positive.

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].

REFERENCES

1 **Wotherspoon AC**, Ortiz-Hidalgo C, Falzon MR, Isaacson PG. Helicobacter pylori-associated gastritis and primary B-cell gastric lymphoma. *Lancet* 1991; **338**: 1175-1176
2 **Parsonnet J**. Helicobacter pylori and gastric cancer. *Gastroenterol Clin North Am* 1993; **22**: 89-104
3 **Graham DY**, Osato MS, Olson CA, Zhang J, Figura N. Effect of H. pylori infection and CagA status on leukocyte counts and liver function tests: extra-gastric manifestations of H. pylori infection. *Helicobacter* 1998; **3**: 174-178
4 **Perri F**, Clemente R, Festa V, De Ambrosio CC, Quitadamo M, Fusillo M, Grossi E, Andriulli A. Serum tumour necrosis factor-alpha is increased in patients with Helicobacter pylori infection and CagA antibodies. *Ital J Gastroenterol Hepatol* 1999; **31**: 290-294
5 **Patel P**, Mendall MA, Khulusi S, Northfield TC, Strachan DP. Helicobacter pylori infection in childhood: risk factors and effect on growth. *BMJ* 1994; **309**: 1119-1123
6 **Oldenburg B**, Diepersloot RJ, Hoekstra JB. High seroprevalence of Helicobacter pylori in diabetes mellitus patients. *Dig Dis Sci* 1996; **41**: 458-461
7 **Gasbarrini A**, Ojetti V, Pitocco D, De Luca A, Franceschi F, Candelli M, Sanz Torre E, Pola P, Ghirlanda G, Gasbarrini G. Helicobacter pylori infection in patients affected by insulin-dependent diabetes mellitus. *Eur J Gastroenterol Hepatol* 1998; **10**: 469-472
8 **Salardi S**, Cacciari E, Menegatti M, Landi F, Mazzanti L, Stella FA, Pirazzoli P, Vaira D. Helicobacter pylori and type 1 diabetes mellitus in children. *J Pediatr Gastroenterol Nutr* 1999; **28**: 307-309
9 **Arslan D**, Kendirci M, Kurtoglu S, Kula M. Helicobacter pylori infection in children with insulin dependent diabetes mellitus. *J Pediatr Endocrinol Metab* 2000; **13**: 553-556
10 **Perdichizzi G**, Bottari M, Pallio S, Fera MT, Carbone M, Barresi G. Gastric infection by Helicobacter pylori and antral gastritis in hyperglycemic obese and in diabetic subjects. *New Microbiol* 1996; **19**: 149-154
11 **Senturk O**, Canturk Z, Cetinarslan B, Ercin C, Hulagu S, Canturk NZ. Prevalence and comparisons of five different diagnostic methods for Helicobacter pylori in diabetic patients. *Endocr Res* 2001; **27**: 179-189
12 **Quatrini M**, Boarino V, Ghidoni A, Baldassarri AR, Bianchi PA, Bardella MT. Helicobacter pylori prevalence in patients with diabetes and its relationship to dyspeptic symptoms. *J Clin Gastroenterol* 2001; **32**: 215-217
13 **Gulcelik NE**, Kaya E, Demirbas B, Culha C, Koc G, Ozkaya M, Cakal E, Serter R, Aral Y. Helicobacter pylori prevalence in diabetic patients and its relationship with dyspepsia and autonomic neuropathy. *J Endocrinol Invest* 2005; **28**: 214-217
14 **Gentile S**, Turco S, Oliviero B, Torella R. The role of autonomic neuropathy as a risk factor of Helicobacter pylori infection in dyspeptic patients with type 2 diabetes mellitus. *Diabetes Res Clin Pract* 1998; **42**: 41-48
15 **Persico M**, Suozzo R, De Seta M, Montella F, Torella R, Gentile S. Non-ulcer dyspepsia and Helicobacter pylori in type 2 diabetic patients: association with autonomic neuropathy. *Diabetes Res Clin Pract* 1996; **31**: 87-92
16 **Quadri R**, Rossi C, Catalfamo E, Masoero G, Lombardo L, Della Monica P, Rovera L, Pera A, Cavello Perin P. Helicobacter pylori infection in type 2 diabetic patients. *Nutr Metab Cardiovasc Dis* 2000; **10**: 263-266
17 **Anastasios R**, Goritsas C, Papamihail C, Trigidou R, Garzonis P, Ferti A. Helicobacter pylori infection in diabetic patients: prevalence and endoscopic findings. *Eur J Intern Med* 2002; **13**: 376
18 **Kozak R**, Juhasz E, Horvat G, Harcsa E, Lovei L, Sike R, Szele K. [Helicobacter pylori infection in diabetic patients] *Orv Hetil* 1999; **140**: 993-995
19 **Ko GT**, Chan FK, Chan WB, Sung JJ, Tsoi CL, To KF, Lai CW, Cockram CS. Helicobacter pylori infection in Chinese subjects with type 2 diabetes. *Endocr Res* 2001; **27**: 171-177
20 **Ojetti V**, Pitocco D, Ghirlanda G, Gasbarrini G, Gasbarrini A. [Role of Helicobacter pylori infection in insulin-dependent diabetes mellitus] *Minerva Med* 2001; **92**: 137-144
21 **Xia HH**, Talley NJ, Kam EP, Young LJ, Hammer J, Horowitz M. Helicobacter pylori infection is not associated with diabetes mellitus, nor with upper gastrointestinal symptoms in diabetes mellitus. *Am J Gastroenterol* 2001; **96**: 1039-1046
22 **Stanciu OG**, Trifan A, Sfarti C, Cojocariu C, Stanciu C. Helicobacter pylori infection in patients with diabetes mellitus. *Rev Med Chir Soc Med Nat Iasi* 2003; **107**: 59-65
23 **Zelenkova J**, Souckova A, Kvapil M, Soucek A, Vejvalka J, Segethova J. [Helicobacter pylori and diabetes mellitus] *Cas Lek Cesk* 2002; **141**: 575-577
24 **Kojecky V**, Roubalik J, Bartonikova N. [Helicobacter pylori in patients with diabetes mellitus] *Vnitr Lek* 1993; **39**: 581-584
25 **Jones KL**, Wishart JM, Berry M, Russo A, Xia HH, Talley NJ, Horowitz M. Helicobacter pylori infection is not associated with delayed gastric emptying or upper gastrointestinal symptoms in diabetes mellitus. *Dig Dis Sci* 2002; **47**: 704-709
26 **Marrollo M**, Latella G, Melideo D, Storelli E, Iannarelli R, Stornelli P, Valenti M, Caprilli R. Increased prevalence of Helicobacter pylori in patients with diabetes mellitus. *Dig Liver Dis* 2001; **33**: 21-29
27 **Malecki M**, Bien AI, Galicka-Latala D, Klupa T, Stachura J, Sieradzki J. [Reactive gastritis in patients with diabetics with dyspeptic symptoms] *Przegl Lek* 1996; **53**: 540-543
28 **Pietroiusti A**, Giuliano M, Magrini A, Bergamaschi A, Galante A. Cytotoxin-associated gene A strains of Helicobacter pylori represent a risk factor for the development of microalbuminuria in type 2 diabetes. *Diabetes Care* 2006; **29**: 1399-1401
29 **de Luis DA**, Lahera M, Canton R, Boixeda D, San Roman AL, Aller R, de La Calle H. Association of Helicobacter pylori infection with cardiovascular and cerebrovascular disease in diabetic patients. *Diabetes Care* 1998; **21**: 1129-1132
30 **Gasbarrini A**, Ojetti V, Pitocco D, Franceschi F, Candelli M, Torre ES, Gabrielli M, Cammarota G, Armuzzi A, Pola R, Pola P, Ghirlanda G, Gasbarrini G. Insulin-dependent diabetes mellitus affects eradication rate of Helicobacter pylori infection. *Eur J Gastroenterol Hepatol* 1999; **11**: 713-716
31 **Gasbarrini A**, Ojetti V, Pitocco D, Armuzzi A, Silveri NG, Pola P, Ghirlanda G, Gasbarrini G. Efficacy of different Helicobacter pylori eradication regimens in patients affected by insulin-dependent diabetes mellitus. *Scand J Gastroenterol* 2000; **35**: 260-263
32 **Sargyn M**, Uygur-Bayramicli O, Sargyn H, Orbay E, Yavuzer D, Yayla A. Type 2 diabetes mellitus affects eradication rate of Helicobacter pylori. *World J Gastroenterol* 2003; **9**: 1126-1128
33 **Ojetti V**, Pitocco D, Bartolozzi F, Danese S, Migneco A, Lupascu A, Pola P, Ghirlanda G, Gasbarrini G, Gasbarrini A. High rate of helicobacter pylori re-infection in patients affected by type 1 diabetes. *Diabetes Care* 2002; **25**: 1485
34 **Begue RE**, Mirza A, Compton T, Gomez R, Vargas A. Helicobacter pylori infection and insulin requirement among children with type 1 diabetes mellitus. *Pediatrics* 1999; **103**: e83
35 **Ozdem S**, Akcam M, Yilmaz A, Gultekin M, Artan R. Biochemical markers of bone metabolism in children with Helicobacter pylori infection. *Dig Dis Sci* 2007; **52**: 967-972
36 **Figura N**, Gennari L, Merlotti D, Lenzi C, Campagna S, Franci B, Lucani B, Trabalzini L, Bianciardi L, Gonnelli C, Santucci A, Nut A. Prevalence of Helicobacter pylori infection in male patients with osteoporosis and controls. *Dig Dis Sci* 2005; **50**: 847-852
37 **Dokmetas HS**, Turkay C, Aydin C, Arici S. Prevalence of Helicobacter pylori in patients with primary hyperparathyroidism. *J Bone Miner Metab* 2001; **19**: 373-377
38 **Sato H**, Abe K, Oshima N, Kawashima K, Hamamoto N, Moritani M, Mak R, Ishihara S, Adachi K, Kawauchi H, Kinoshita Y. Primary hyperparathyroidism with duodenal ulcer and H. pylori infection. *Intern Med* 2002; **41**: 377-380

39 **Bednarek-Skublewska A**, Schabowski J, Majdan M, Baranowicz-Gaszczyk I, Ksiazek A. [Relationships between hyperparathyroidism and Helicobacter pylori infection in long-term hemodialysis patients] *Pol Arch Med Wewn* 2001; **105**: 191-196

40 **Kyriazanos ID**, Sfiniadakis I, Gizaris V, Hountis P, Hatziveis K, Dafnopoulou A, Datsakis K. The incidence of Helicobacter pylori infection is not increased among obese young individuals in Greece. *J Clin Gastroenterol* 2002; **34**: 541-546

41 **Ioannou GN**, Weiss NS, Kearney DJ. Is Helicobacter pylori seropositivity related to body mass index in the United States? *Aliment Pharmacol Ther* 2005; **21**: 765-772

42 **Cho I**, Blaser MJ, Francois F, Mathew JP, Ye XY, Goldberg JD, Bini EJ. Helicobacter pylori and overweight status in the United States: data from the Third National Health and Nutrition Examination Survey. *Am J Epidemiol* 2005; **162**: 579-584

43 **Wu MS**, Lee WJ, Wang HH, Huang SP, Lin JT. A case-control study of association of Helicobacter pylori infection with morbid obesity in Taiwan. *Arch Intern Med* 2005; **165**: 1552-1555

44 **Isomoto H**, Ueno H, Nishi Y, Wen CY, Nakazato M, Kohno S. Impact of Helicobacter pylori infection on ghrelin and various neuroendocrine hormones in plasma. *World J Gastroenterol* 2005; **11**: 1644-1648

45 **Renshaw AA**, Rabaza JR, Gonzalez AM, Verdeja JC. Helicobacter pylori infection in patients undergoing gastric bypass surgery for morbid obesity. *Obes Surg* 2001; **11**: 281-283

46 **Fujiwara Y**, Higuchi K, Arafa UA, Uchida T, Tominaga K, Watanabe T, Arakawa T. Long-term effect of Helicobacter pylori eradication on quality of life, body mass index, and newly developed diseases in Japanese patients with peptic ulcer disease. *Hepatogastroenterology* 2002; **49**: 1298-1302

47 **Kamada T**, Hata J, Kusunoki H, Ito M, Tanaka S, Kawamura Y, Chayama K, Haruma K. Eradication of Helicobacter pylori increases the incidence of hyperlipidaemia and obesity in peptic ulcer patients. *Dig Liver Dis* 2005; **37**: 39-43

48 **Nwokolo CU**, Freshwater DA, O'Hare P, Randeva HS. Plasma ghrelin following cure of Helicobacter pylori. *Gut* 2003; **52**: 637-640

49 **Konturek PC**, Cześnikiewicz-Guzik M, Bielanski W, Konturek SJ. Involvement of Helicobacter pylori infection in neuro-hormonal control of food intake. *J Physiol Pharmacol* 2006; **57** Suppl 5: 67-81

50 **Loffeld RJ**. Helicobacter pylori, obesity and gastro-oesophageal reflux disease. Is there a relation? A personal view. *Neth J Med* 2005; **63**: 344-347

51 **Tatsuguchi A**, Miyake K, Gudis K, Futagami S, Tsukui T, Wada K, Kishida T, Fukuda Y, Sugisaki Y, Sakamoto C. Effect of Helicobacter pylori infection on ghrelin expression in human gastric mucosa. *Am J Gastroenterol* 2004; **99**: 2121-2127

52 **Shiotani A**, Miyanishi T, Uedo N, Iishi H. Helicobacter pylori infection is associated with reduced circulating ghrelin levels independent of body mass index. *Helicobacter* 2005; **10**: 373-378

53 **Osawa H**, Nakazato M, Date Y, Kita H, Ohnishi H, Ueno H, Shiiya T, Satoh K, Ishino Y, Sugano K. Impaired production of gastric ghrelin in chronic gastritis associated with Helicobacter pylori. *J Clin Endocrinol Metab* 2005; **90**: 10-16

54 **Liew PL**, Lee WJ, Lee YC, Chen WY. Gastric ghrelin expression associated with Helicobacter pylori infection and chronic gastritis in obese patients. *Obes Surg* 2006; **16**: 612-619

55 **Azuma T**, Suto H, Ito Y, Ohtani M, Dojo M, Kuriyama M, Kato T. Gastric leptin and Helicobacter pylori infection. *Gut* 2001; **49**: 324-329

56 **Nishi Y**, Isomoto H, Uotani S, Wen CY, Shikuwa S, Ohnita K, Mizuta Y, Kawaguchi A, Inoue K, Kohno S. Enhanced production of leptin in gastric fundic mucosa with Helicobacter pylori infection. *World J Gastroenterol* 2005; **11**: 695-699

57 **Gokcel A**, Gumurdulu Y, Kayaselcuk F, Serin E, Ozer B, Ozsahin AK, Guvener N. Helicobacter pylori has no effect on plasma ghrelin levels. *Eur J Endocrinol* 2003; **148**: 423-426

58 **de Luis DA**, Varela C, de La Calle H, Canton R, de Argila CM, San Roman AL, Boixeda D. Helicobacter pylori infection is markedly increased in patients with autoimmune atrophic thyroiditis. *J Clin Gastroenterol* 1998; **26**: 259-263

59 **Franceschi F**, Satta MA, Mentella MC, Penland R, Candelli M, Grillo RL, Leo D, Fini L, Nista EC, Cazzato IA, Lupascu A, Pola P, Pontecorvi A, Gasbarrini G, Genta RM, Gasbarrini A. Helicobacter pylori infection in patients with Hashimoto's thyroiditis. *Helicobacter* 2004; **9**: 369

60 **Arima N**, Tsudo M. Extragastric mucosa-associated lymphoid tissue lymphoma showing the regression by Helicobacter pylori eradication therapy. *Br J Haematol* 2003; **120**: 790-792

61 **Figura N**, Di Cairano G, Lore F, Guarino E, Gragnoli A, Cataldo D, Giannace R, Vaira D, Bianciardi L, Kristodhullu S, Lenzi C, Torricelli V, Orlandini G, Gennari C. The infection by Helicobacter pylori strains expressing CagA is highly prevalent in women with autoimmune thyroid disorders. *J Physiol Pharmacol* 1999; **50**: 817-826

62 **Triantafillidis JK**, Georgakopoulos D, Gikas A, Merikas E, Peros G, Sofroniadou K, Cheracakis P, Sklavaina M, Tzanidis G, Konstantellou E. Relation between Helicobacter pylori infection, thyroid hormone levels and cardiovascular risk factors on blood donors. *Hepatogastroenterology* 2003; **50** Suppl 2: cccxviii-ccccccxx

63 **Larizza D**, Calcaterra V, Martinetti M, Negrini R, De Silvestri A, Cisternino M, Iannone AM, Solcia E. Helicobacter pylori infection and autoimmune thyroid disease in young patients: the disadvantage of carrying the human leukocyte antigen-DRB1*0301 allele. *J Clin Endocrinol Metab* 2006; **91**: 176-179

64 **Bertalot G**, Montresor G, Tampieri M, Spasiano A, Pedroni M, Milanesi B, Favret M, Manca N, Negrini R. Decrease in thyroid autoantibodies after eradication of Helicobacter pylori infection. *Clin Endocrinol* (Oxf) 2004; **61**: 650-652

65 **Tomasi PA**, Dore MP, Fanciulli G, Sanciu F, Realdi G, Delitala G. Is there anything to the reported association between Helicobacter pylori infection and autoimmune thyroiditis? *Dig Dis Sci* 2005; **50**: 385-388

66 **Novikova VP**, Iur'ev VV, Tkachenko EI, Strukov EL, Liubimov IuA, Antonov PV. [Chronic gastritis in children with concomitant diseases of the thyroid gland] *Eksp Klin Gastroenterol* 2003; 40-43, 114

67 **Cammarota G**, De Marinis AT, Papa A, Valle D, Cuoco L, Cianci R, Fedeli G, Gasbarrini G. Gastric mucosa-associated lymphoid tissue in autoimmune thyroid diseases. *Scand J Gastroenterol* 1997; **32**: 869-872

68 **Raderer M**, Osterreicher C, Machold K, Formanek M, Fiebiger W, Penz M, Dragosics B, Chott A. Impaired response of gastric MALT-lymphoma to Helicobacter pylori eradication in patients with autoimmune disease. *Ann Oncol* 2001; **12**: 937-939

69 **Centanni M**, Gargano L, Canettieri G, Viceconti N, Franchi A, Delle Fave G, Annibale B. Thyroxine in goiter, Helicobacter pylori infection, and chronic gastritis. *N Engl J Med* 2006; **354**: 1787-1795

70 **Majka J**, Rog T, Konturek PC, Konturek SJ, Bielanski W, Kowalsky M, Szczudlik A. Influence of chronic Helicobacter pylori infection on ischemic cerebral stroke risk factors. *Med Sci Monit* 2002; **8**: CR675-CR684

71 **Chimienti G**, Russo F, Lamanuzzi BL, Nardulli M, Messa C, Di Leo A, Correale M, Giannuzzi V, Pepe G. Helicobacter pylori is associated with modified lipid profile: impact on Lipoprotein(a). *Clin Biochem* 2003; **36**: 359-365

72 **Laurila A**, Bloigu A, Nayha S, Hassi J, Leinonen M, Saikku P. Association of Helicobacter pylori infection with elevated serum lipids. *Atherosclerosis* 1999; **142**: 207-210

73 **Hoffmeister A**, Rothenbacher D, Bode G, Persson K, Marz W, Nauck MA, Brenner H, Hombach V, Koenig W. Current infection with Helicobacter pylori, but not seropositivity to Chlamydia pneumoniae or cytomegalovirus, is associated with an atherogenic, modified lipid profile. *Arterioscler Thromb Vasc Biol* 2001; **21**: 427-432

74 **Solcia E**, Fiocca R, Luinetti O, Villani L, Padovan L, Calistri D, Ranzani GN, Chiaravalli A, Capella C. Intestinal and diffuse gastric cancers arise in a different background of Helicobacter pylori gastritis through different gene involvement. *Am J Surg Pathol* 1996; **20** Suppl 1: S8-S22

75 **Niemela S**, Karttunen T, Korhonen T, Laara E, Karttunen R, Ikaheimo M, Kesaniemi YA. Could Helicobacter pylori infection increase the risk of coronary heart disease by modifying serum lipid concentrations? *Heart* 1996; **75**: 573-575

76 **Danesh J**, Peto R. Risk factors for coronary heart disease and infection with Helicobacter pylori: meta-analysis of 18 studies. *BMJ* 1998; **316**: 1130-1132

77 **Takashima T**, Adachi K, Kawamura A, Yuki M, Fujishiro H, Rumi MA, Ishihara S, Watanabe M, Kinoshita Y. Cardiovascular risk factors in subjects with Helicobacter pylori infection. *Helicobacter* 2002; **7**: 86-90

78 **Ando T**, Minami M, Ishiguro K, Maeda O, Watanabe O, Mizuno T, Fujita T, Takahashi H, Noshiro M, Goto H. Changes in biochemical parameters related to atherosclerosis after Helicobacter pylori eradication. *Aliment Pharmacol Ther* 2006; **24** Suppl 4: 58-64

79 **Feingold KR**, Grunfeld C. Role of cytokines in inducing hyperlipidemia. *Diabetes* 1992; **41** Suppl 2: 97-101

80 **Pieniazek P**, Karczewska E, Duda A, Tracz W, Pasowicz M, Konturek SJ. Association of Helicobacter pylori infection with coronary heart disease. *J Physiol Pharmacol* 1999; **50**: 743-751

81 **Kowalski M**. Helicobacter pylori (H. pylori) infection in coronary artery disease: influence of H. pylori eradication on coronary artery lumen after percutaneous transluminal coronary angioplasty. The detection of H. pylori specific DNA in human coronary atherosclerotic plaque. *J Physiol Pharmacol* 2001; **52**: 3-31

82 **Fraser AG**, Scragg RK, Cox B, Jackson RT. Helicobacter pylori, Chlamydia pneumoniae and myocardial infarction. *Intern Med J* 2003; **33**: 267-272

83 **Al-Nozha MM**, Khalil MZ, Al-Mofleh IA, Al-Ghamdi AS. Lack of association of coronary artery disease with H.pylori infection. *Saudi Med J* 2003; **24**: 1370-1373

84 **Elizalde JI**, Pique JM, Moreno V, Morillas JD, Elizalde I, Bujanda L, De Argila CM, Cosme A, Castiella A, Ros E. Influence of Helicobacter pylori infection and eradication on blood lipids and fibrinogen. *Aliment Pharmacol Ther* 2002; **16**: 577-586

85 **Adiloglu AK**, Can R, Kinay O, Aridogan BC. Infection with Chlamydia pneumoniae but not Helicobacter pylori is related to elevated apolipoprotein B levels. *Acta Cardiol* 2005; **60**: 599-604

86 **Scharnagl H**, Kist M, Grawitz AB, Koenig W, Wieland H, Marz W. Effect of Helicobacter pylori eradication on high-density lipoprotein cholesterol. *Am J Cardiol* 2004; **93**: 219-220

87 **Furuta T**, Shirai N, Xiao F, Takashima M, Hanai H. Effect of Helicobacter pylori infection and its eradication on nutrition. *Aliment Pharmacol Ther* 2002; **16**: 799-806

88 **Figura N**, Piomboni P, Ponzetto A, Gambera L, Lenzi C, Vaira D, Peris C, Lotano MR, Gennari L, Bianciardi L, Renieri T, Valensin PE, Capitani S, Moretti E, Colapinto R, Baccetti B, Gennari C. Helicobacter pylori infection and infertility. *Eur J Gastroenterol Hepatol* 2002; **14**: 663-669

S- Editor Tian L **L- Editor** Logan S **E- Editor** Ma WH