

WJG 20th Anniversary Special Issues (6): *Helicobacter pylori***Role of *Helicobacter pylori* infection on nutrition and metabolism**

Francesco Franceschi, Annalisa Tortora, Teresa Di Rienzo, Giovanna D'Angelo, Gianluca Ianiro, Franco Scaldaferri, Viviana Gerardi, Valentina Tesori, Loris Riccardo Lopetuso, Antonio Gasbarrini

Francesco Franceschi, Department of Emergency, Internal Medicine Institute, Catholic University of Sacred Heart, 00168 Rome, Italy

Annalisa Tortora, Teresa Di Rienzo, Giovanna D'Angelo, Gianluca Ianiro, Franco Scaldaferri, Viviana Gerardi, Valentina Tesori, Loris Riccardo Lopetuso, Antonio Gasbarrini, Department of Medicine, Internal Medicine and Gastroenterology, Catholic University of Sacred Heart, 00168 Rome, Italy

Author contributions: All authors had contributed to the realization of this manuscript; Francesco F and Tortora A contributed to writing it; D'Angelo G, Ianiro G and Scaldaferri F contributed to performing PubMed search of articles published on nutrition; Gerardi V, Tesori V and Lopetuso LR contributed to performing PubMed search of articles published on metabolism; and Gasbarrini A contributed to editing the final version.

Correspondence to: Francesco Franceschi, MD, Professor, Department of Emergency, Internal Medicine Institute, Catholic University of Sacred Heart, Largo A. Gemelli, 8, 00168 Rome, Italy. francesco.franceschi@rm.unicatt.it

Telephone: +39-6-30157271 Fax: +39-6-35502775

Received: January 16, 2014 Revised: March 12, 2014

Accepted: May 23, 2014

Published online: September 28, 2014

Abstract

Helicobacter pylori (*H. pylori*) is a gram-negative pathogen that is widespread all over the world, infecting more than 50% of the world's population. It is etiologically associated with non-atrophic and atrophic gastritis, peptic ulcer and shows a deep association with primary gastric B-cell lymphoma and gastric adenocarcinoma. Recently, the medical research focused on the modification of the gastric environment induced by *H. pylori* infection, possibly affecting the absorption of nutrients and drugs as well as the production of hormones strongly implicated in the regulation of appetite and growth. Interestingly, the absorption of

iron and vitamin B12 is impaired by *H. pylori* infection, while infected subjects have lower basal and fasting serum levels of ghrelin and higher concentration of leptin compared to controls. Since leptin is an anorexigenic hormone, and ghrelin stimulates powerfully the release of growth hormone in humans, *H. pylori* infection may finally induce growth retardation if acquired very early in the childhood and in malnourished children. This review is focused on the nutritional effects of *H. pylori* infection, such as the reduced bioavailability or the malabsorption of essential nutrients, and of gastrointestinal hormones, as well as on the relationship between *H. pylori* and the metabolic syndrome.

© 2014 Baishideng Publishing Group Inc. All rights reserved.

Key words: *Helicobacter pylori*; Malabsorption; Metabolic syndrome; Gastrointestinal hormones

Core tip: This review analyzes in a very comprehensive way all aspects related to nutrition and metabolism induced by *Helicobacter pylori* (*H. pylori*). Interestingly, this bacterium is able to produce different biological effects on hormones controlling both appetite and growth, mostly depending on the time of acquisition of the infection and of eradication. On the other hand, *H. pylori* is able to induce malabsorption of several nutrients, with a strong effect on nutrition.

Franceschi F, Tortora A, Di Rienzo T, D'Angelo T, Ianiro G, Scaldaferri F, Gerardi V, Tesori V, Lopetuso LR, Gasbarrini A. Role of *Helicobacter pylori* infection on nutrition and metabolism. *World J Gastroenterol* 2014; 20(36): 12809-12817 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v20/i36/12809.htm> DOI: <http://dx.doi.org/10.3748/wjg.v20.i36.12809>

INTRODUCTION

***Helicobacter pylori* pathophysiology and related diseases**

Helicobacter pylori (*H. pylori*) is a gram-negative pathogen that is widespread all over the world, infecting more than 50% of the world's population, with a predominant distribution in developing countries (up to 80%) compared to industrialized ones (20%-80%). The essential way of transmission is the inter-human contact. Poor socio-economic condition is an important risk factor. Although the infection is largely diffused, only 10%-20% of patients develop clinical manifestations^[1-3].

H. pylori colonizes the entire gastric epithelium, and has an important urease activity, that leads to the ammonia production in order to protect itself from gastric acidity. It produces also other enzymes, such as phospholipase A2 and C, and glycosulfatase, which play a role in the development of the gastric mucosal damage^[1]. Indeed, *H. pylori* induces an inflammatory response through the gastric epithelium, with production of pro-inflammatory cytokines, such as interleukin 1 β and interleukin 8. Some *H. pylori* genotypes, especially those vacuolating toxin A (Vac-A) and cytotoxin-associated gene A (Cag-A) positive, are associated with greater pathogenicity and more severe disease. Cag-A positive strains induce a stronger inflammatory response of gastric mucosa, with increased production of pro-inflammatory cytokines. The *VacA* gene, which leads to vacuolization and apoptosis of gastric epithelial cells, is genetically expressed in every *H. pylori* strain, even if is phenotypically present in only 60% of them^[4]. *H. pylori* is etiologically associated with non-atrophic and atrophic gastritis and peptic ulcer (especially duodenal ulcer). Moreover, there is a deep association between *H. pylori* and primary gastric B-cell lymphoma (mucosa-associated-lymphatic-tissue or MALT-lymphoma) and gastric adenocarcinoma. *H. pylori* has been therefore classified by IARC/WHO as "group 1 carcinogen"^[5]. Finally, over the last years, many authors investigated the relationship between *H. pylori* infection and extra-digestive diseases, following the rationale that it may act as an immunological trigger. The strongest association has been found with idiopathic thrombocytopenic purpura, while other studies seems to connect *H. pylori* infection with autoimmune diseases (Schonlein-Henoch purpura, Sjogren syndrome, autoimmune thrombocytopenia), skin diseases (urticaria, rosacea, and alopecia areata), and cardiovascular diseases (chronic ischemic heart disease and chronic ischemic cerebrovascular disease)^[6,7]. Recently, the medical research focused on the modification of gastric environment induced by *H. pylori* infection. For example, it can affect the absorption of nutrients and drugs. In fact, idiopathic sideropenic anemia is strongly related to *H. pylori* infection^[8,9]. The aim of this review is to evaluate the nutritional effects of *H. pylori* infection, such as the reduced bioavailability or the malabsorption of essential nutrients, and of gastrointestinal (GI) hormones, and, moreover, the relationship between *H. pylori* and metabol-

ic imbalance conditions, such as the metabolic syndrome.

Iron and *H. pylori*

Several epidemiological studies have revealed an association between *H. pylori* infection and iron deficiency anemia^[8,9]. According to a recent meta-analysis^[10], iron deficiency anemia is significantly more prevalent in paediatric subjects with *H. pylori* than negative controls, although the correlation is less marked in adult. *H. pylori*-related gastritis and its effects on gastric physiology, affecting the normal process of iron absorption, may possibly explain this phenomenon^[11]; however, *H. pylori* is probably responsible of iron deficiency anemia through several mechanisms. Hypochlorhydria might induce the conversion of ascorbic acid to dehydroascorbic acid - a less active form hampering the promotion of iron absorption; moreover, the reduction of the ferric to ferrous form, which is fundamental for the absorption of non-heme iron, might be impaired by *H. pylori* infection, that cause an increase of gastric pH through the atrophy of gastric glands and fundic mucosa and the consequent decreases in gastric acid secretion^[12,13]. Since iron is an essential growth factor for *H. pylori*, it also competes with the host for iron absorption: *H. pylori* possesses some proteins of the outer membrane that play a role in bacterial iron absorption as well as intracellular storage proteins with similar characteristics as ferritin^[14]. The association between iron deficiency anemia and *H. pylori* infection is so strong that a test and treat strategy for *H. pylori* infection is strongly recommended by Maastricht III European guidelines in patients with unexplained sideropenic anemia^[15].

Micronutrients and *H. pylori*

H. pylori infection can cause a deficiency of vitamins (such as vitamin C, vitamin A, α -tocopherol, vitamin B12 and folic acid) and essential minerals.

Vitamin B12: *H. pylori* infection might impair the absorption of vitamin B12 from food, leading to pernicious anemia^[16,17]. Dietary cobalamin is bound to other proteins, and its release is closely related to the gastric pH status^[18]. Food-cobalamin malabsorption is characterized by the inability to absorb food-bound or protein-bound cobalamin by patients normally capable of absorbing free cobalamin. Probably, antacid drugs^[19] used by infected symptomatic subjects and the modification of the intragastric pH^[20] caused by *H. pylori* are the principal factors of malabsorption of vitamin B12. Annibale *et al*^[18] described the presence of *H. pylori*-related gastritis as the unique pathological finding in 57.1% of patients with macrocytic anemia caused by B12 deficiency; the majority (76%) of the patients reported a classic pernicious anemia due to atrophy of the gastric body, with associated hypergastrinemia and hypo-achlorhydria. *H. pylori* may also act as a molecular mimicker, as antibodies directed against the H⁺, K⁺-adenosine triphosphate protein may be evoked by a similar antigen expressed by *H. pylori*^[21].

Hyperhomocysteinemia related to vitamin B12 deficiency may constitute a risk for ischemic heart disease and cerebrovascular diseases. This phenomenon would therefore be the link between *H. pylori* infection and vascular diseases.

β -carotene: β -carotene is the most abundant form of pro-vitamin A, being widely present in fruit and vegetables. It is able, together with its metabolites, to neutralize reactive oxygen compounds produced by oxidative stress. The bioavailability of β -carotenes depends on several factors such as the processing and cooking of foods, the composition of the nutritional matrix, and the GI health status^[22]. Hypo/achlorhydria significantly decreases bioavailability of β -carotene. β -carotene gastric mucosal concentration has been found to be markedly decreased in patients with gastric atrophy and intestinal metaplasia^[23]. In *H. pylori* positive subjects, the concentration of β -carotene in gastric juice is decreased, even if plasma levels are similar to controls^[24]. Probably, *H. pylori* reduces β -carotene bioavailability as a consequence of the slow movement of the micelle containing the vitamin through the membrane of the enterocytes due to its extreme negative charge derived from a non-acid medium.

Vitamin C: Vitamin C is actively absorbed from the small intestine *via* SVCTs and GLUTs transporters. Ascorbic acid is a water-soluble antioxidant that neutralizes nitrite-derived mutagens, with consequent protection against carcinogenesis^[25]. In a large study (more than 1100 patients), vitamin C plasma concentration was 20% lower in *H. pylori* infected subjects than in negative controls, even after correction for confounding factors, such as smoking and dietary habits^[26]. Probably, *H. pylori* infection may cause an irreversible inactivation of the ingested vitamin C in the intestinal lumen prior to its absorption. When hypochlorhydria occurs, such as in the case of gastric atrophy, intragastric pH levels increase, and ascorbic acid is converted to the less active form of dehydroascorbic acid^[27]. Intragastric pH is then the key factor for the observed depletion of gastric juice vitamin C levels, in patients with gastric atrophy^[28].

Vitamin E: Vitamin E includes tocopherols and tocotrienols, two classes of compounds with different biological activities. α -tocopherol is the most common alimentary form of vitamin E, representing the most important liposoluble antioxidant of the biological membranes. It is able to increase natural killer cell activity, playing an important immunologic role. In patients suffering from *H. pylori* infection, the mucosal concentration of α -tocopherol of the corpus is lower than that of the antrum or duodenum^[29]; probably, this phenomenon reflects a mobilization of antioxidant defenses to the sites of greatest gastric inflammation^[30]. Moreover, the presence of intestinal metaplasia and gastric atrophy is significantly associated with reduced mucosal concentration of α -tocopherol^[24]. Furthermore, mucosal concentrations

of α -tocopherol in the gastric antrum decreases progressively when antral mucosal histology changes from normal to chronic gastritis alone and finally to atrophy and intestinal metaplasia.

Folate: Few studies have investigated the relationship between folates and *H. pylori* infection. Some authors reported a negative relationship between *H. pylori* infection and folate metabolism in adults. A decrease in folate absorption may take place as a consequence of decreased concentration of vitamin C in gastric juice and/or an increased level of intragastric pH, as frequently occurs in *H. pylori* infection^[29].

Zinc: Even if available data are few, they do not demonstrate a correlation between *H. pylori* infection and serum zinc levels^[9,31].

Selenium: Selenium is a co-factor of glutathione peroxidase, which protects membranes from oxidative damage. Selenium deficiency exposes most tissues to oxidative damage. Plasma selenium levels have been shown to be similar in patients with *H. pylori*-related gastritis and healthy controls, even if in the first group selenium levels in the gastric tissue were significantly higher, probably because of the presence of elevated reactive oxygen species (ROS) associated with the infection^[32]. A similar behavior in gastric selenium levels may also occur as a reaction to any damage that leads to increase of ROS in the gastric mucosa. On the other side, selenium concentration is markedly decreased in the antral mucosa of patients with atrophic gastritis.

Gastrointestinal hormones and *H. pylori*

Ghrelin, a 28-amino-acid peptide produced in the gastric oxyntic gland of the fundic mucosa, is an endogenous ligand of the growth hormone (GH) secretagogue receptor, and stimulates powerfully the release of GH in humans. Other properties are the increase of appetite, facilitation of fat storage, modulation of energy homeostasis^[33-35]. The effect of ghrelin on appetite and food intake is believed to be primarily mediated by peripheral input at the arcuate nucleus and further spread to the nucleus tracti solitari. Ghrelin is involved in the hypothalamic regulation of metabolic control and energy balance. Since the structure of ghrelin resembles motilin, its secretion may be associated with gastric motility and acid secretion in addition to appetite regulation^[36-38]. Leptin, is an anorexigenic hormone, with opposite effect of ghrelin, inhibiting both gastric ghrelin secretion and ghrelin-dependent feeding stimulation^[39]. Secretion of ghrelin is inhibited also by insulin, growth hormone, insulin-like growth factor- I, and a high-fat diet, while both a low protein diet and fasting result in an increased secretion of ghrelin^[37,38,40]. Also *H. pylori* infection has been hypothesized to play a role in ghrelin levels' modulation. A recent systematic review^[41] evaluated the studies investigating this relationship. Interestingly, circulating ghrelin

levels were lower in *H. pylori* positive patients compared to negative controls in the majority of the trials analyzed.

The effect of *H. pylori* on ghrelin production has been related also to *H. pylori* virulence. Patients with type I strain *H. pylori*, expressing CagA and VacA, have lower circulating ghrelin levels than those with the less virulent type II strain^[42]. Probably, the extent of gastric damage and the duration of the infection play a key role in modulation of ghrelin levels by *H. pylori*^[43]. Similar data have been reported also in patients with autoimmune gastritis^[44]. However, we have to consider that ghrelin production may also be replaced by other sources^[45].

The effect of *H. pylori* infection has been studied also in relationship with the production of other gastric hormones^[38]. Serum gastrin concentrations were significantly increased in both *H. pylori* positive children and adults. Dyspeptic symptoms, including upper GI symptoms accompanied by lost or reduced appetite, were reported by the majority of *H. pylori*-positive children (65%), but only by 15% of *H. pylori* negative children^[46]. Subjects with *H. pylori* infection have lower basal and fasting serum levels of ghrelin and higher concentration of leptin than controls. Briefly, the gastric mucosal damage due to *H. pylori* provokes a marked increase of leptin and gastrin levels, and a reduction in ghrelin plasma levels, and this phenomenon may contribute to the occurrence of dyspeptic symptoms and appetite alteration.

Many studies investigated on the possible association between *H. pylori* infection and metabolic syndrome and atherosclerotic cardiovascular disease.

***H. pylori* and insulin resistance**

Insulin-resistance (IR) and subsequent hyperinsulinemia are the main pathogenic factors in metabolic syndrome. IR is characterized by a complex clinic scenario which includes type 2 diabetes mellitus, central obesity, dyslipidemia, hypertension, non-alcoholic fatty liver disease (NAFLD), hypertension and endothelial dysfunction. Two parameters can be used to quantify IR: body mass index (BMI) calculated as weight (kg)/[height (m)]², and HOMA-IR (homeostasis model assessment estimates steady state beta cell function and insulin sensitivity calculated as [fasting insulin (mU/L) × fasting glucose (mmol/L)]/22.5). There is no currently widely accepted normal range for HOMA-IR, but the upper cut-off value has been proposed to be between 2.0 and 3.0^[47]. Many studies showed that *H. pylori* infection is linked with a higher serum oxidative stress and lower serum total antioxidant capacity^[48] and could be an independent predictor for HOMA-IR^[49]. Contrasting results emerge by studies on the effect of eradication therapy on HOMA-IR^[50,51]. A case report of an 84-year-old Japanese man with IR and immune thrombocytopenic purpura showed improvement of both conditions after *H. pylori* eradication, with no longer need of diabetes treatment^[52]. The link between *H. pylori* and IR is not already clarified, but many pathogenic mechanisms have been suggested^[47]: (1) pro-inflammatory and vasoactive substances, such as

cytokines [tumor necrosis factor (TNF)- α , interferon- γ , interleukin (IL)-1, IL-6, IL-8, IL-10, IL-12], eicosanoids (leukotrienes, prostaglandins), and acute phase proteins (fibrinogen, C-reactive protein) are released in infection and involved in the pathogenesis of IR; (2) enhanced platelet activation and platelet-leukocyte aggregation^[53]; (3) alteration of apoptotic process^[54]; (4) oxidative stress. *H. pylori* infection causes inflammation, accumulation of ROS, and oxidative DNA damage. Enhanced ROS levels due to neutrophil infiltration and increased oxidative DNA damage have been reported in gastric mucosa of *H. pylori*-infected patients^[48]; (5) reduction of vitamin B12 and folate concentrations, due to the chronic atrophic gastritis, and the consequent increase of homocysteine^[55]; and (6) *H. pylori* infection has been associated with lower ghrelin^[56] and increased leptin^[57] levels, which are associated with impaired energy homeostasis, lipid metabolism, elevated fasting insulin levels and insulin sensitivity.

Moreover, fetuin A, another acute-phase glycoprotein, can be associated to *H. pylori* infection and insulin resistance^[58]. This molecule is involved in mineralization and insulin signaling regulation. Its dysregulation results in an excessive inhibition of insulin signaling in the liver and skeletal muscle^[59]. Kebapcilar *et al*^[60] reported lower baseline serum fetuin-A levels in *H. pylori*-positive patients *vs* negative. Furthermore, fetuin-A levels appear significantly increased after successful *H. pylori* eradication treatment.

***H. pylori* and lipid profile**

Several studies have demonstrated that *H. pylori* might be implicated in the change in serum lipid concentration, increasing the risk of atherosclerosis^[61-64], but these data are not confirmed by other studies^[65,66].

Kim *et al*^[67] conducted a study on 454 elderly Koreans, showing that *H. pylori* was independently associated with increase of low-density lipoprotein (LDL) cholesterol, with a correlation between LDL levels and infection severity.

Satoh *et al*^[68], instead, showed a difference based on gender: studying 6289 Japanese subjects, it has been revealed that LDL and high-density lipoprotein (HDL) cholesterol were significantly higher and lower in *H. pylori* seropositive male subjects, while this association was not significant in female subjects. C-reactive protein values did not differ between *H. pylori*-positive and *H. pylori*-negative subjects. Another study tried to investigate circulating and gastric mucosal levels of IL1-alpha, IL-6, IL-8 and TNF- α in patients with ischemic heart disease (IHD) and matched controls, according to the presence or absence of active *H. pylori* infection. The results of the present study provide evidence that active *H. pylori* infection may play a role as a trigger factor in the pathophysiology of IHD by inducing an inflammatory cascade concentrated on gastric mucosa^[69].

In an Italian study, infected subjects showed increased levels of cholesterol, LDL-cholesterol, and cholesterol/

HDL-cholesterol atherogenic index and significant difference between infected and uninfected subjects was found in lipoprotein(a) levels.

***H. pylori* and obesity**

The relationship between obesity and *H. pylori* infection is controversial. Obesity can alter innate and adaptive immunity, with relation between grade of obesity and immunity deterioration. Morbidly obese subjects have lower maturation of monocytes into macrophages and reduced polymorphonuclear bactericidal capacity. Severely obese patients have a significant decrease in NK cells activity in comparison to normal individuals matched for age and gender^[70].

According to some studies, the risk of *H. pylori* infection does not increase in overweight young persons and *H. pylori* positivity or CagA antibody status are not associated with the BMI or fasting serum leptin levels^[71-73].

However, there are data demonstrating that the eradication of *H. pylori* significantly increases the incidence of obesity in patients with peptic ulcer disease, since it increases the level of BMI, and/or enhances the appetite of asymptomatic patients, due to an elevation of plasma ghrelin and a reduction of leptin levels^[38,74-77].

A potential relationship between insulin-resistance, NAFLD and *H. pylori* appears to exist based on the following points: (1) NAFLD is the hepatic component of metabolic syndrome and insulin-resistance regarded as its key pathogenic hallmark; (2) patients with NAFLD present a significant increase in gut permeability, and this data is positively related with liver fat accumulation; and (3) *H. pylori* infection has been implicated in the pathogenesis of IR by many mechanisms, in particular: increased level of pro-inflammatory cytokines, eicosanoids, acute phase proteins, reactive oxygen species production, and cytokine serum changes (*i.e.*, low adiponectin, ghrelin and leptin levels; high TNF- α)^[78].

In conclusion in *H. pylori* negative patients, obesity and metabolic syndrome mostly depend on genetic and lifestyle habits. If *H. pylori* is acquired very early in the childhood (as in developing countries) it may lead to malnutrition and growth retardation especially when either food intake or variety is poor.

***H. pylori* and malnutrition**

According to some authors^[79] *H. pylori* can play a role on the balance of nutritional status. The incidence of *H. pylori* infection in childhood in developing countries is high^[79-81] and in some studies *H. pylori* has been correlated with malnutrition and growth retardation^[82,83]. Contracting *H. pylori* infection in childhood may result in a series of events that influence morbidity and mortality^[84]. *H. pylori* is associated with hypochlorhydria both in adults and in children^[85-87] hypochlorhydria impairs the absorption of several nutrients and increases susceptibility to enteric infections^[87] such as giardiasis, cholera, typhoid and non-typhoidal salmonellosis^[88-91] and other microorganisms, particularly in areas where they are endemic. The resul-

tant diarrhea^[85-91] may lead to malnutrition and growth retardation in children^[92-94]. In conclusion, *H. pylori* could be associated with childhood malnutrition in developing countries both because of increased susceptibility to enteric infections caused by hypochlorhydria and because of malabsorption of nutrients.

Improvement of nutritional aspects after *H. pylori* eradication

In a recent meta-analysis^[95] of randomized controlled trials comparing *H. pylori* eradication therapy plus oral iron supplementation to oral iron supplementation alone in subjects with *H. pylori* infection and iron deficiency anemia, the combination therapy showed a statistically significant increase of serum iron, serum ferritin and hemoglobin, than iron supplementation alone; those results were strongest in patients with hemoglobin levels lower than 9 g/dL. Moreover, eradication of *H. pylori* was significantly associated with healing of iron deficiency anemia even in patients not receiving iron supplementation therapy^[96,97].

Furthermore, *H. pylori* eradication has been showed to improve not only iron absorption but also vitamin B12 absorption^[17], and the successful eradication of *H. pylori* restored the juice/plasma ascorbic acid ratio^[98].

On the other hand, the eradication of *H. pylori* has not shown efficacy on the modulation of vitamin A or vitamin E levels in serum or gastric juice^[99].

The role of *H. pylori* eradication on ghrelin levels has been recently evaluated by systematic review^[41] of literature, without conclusive statements. However, a recent study^[42] showed that ghrelin did not change during the first 4 wk after *H. pylori* eradication, but gradually increased after 6 mo of follow-up.

Finally, in a trial by Furuta *et al*^[100], body mass index and fasting blood glucose levels were not significantly modified by *H. pylori* eradication, while serum levels of total protein and albumin and serum total cholesterol levels significantly increased only in subjects with successful eradication; according to authors, the restoring of gastric pH that follows eradication is probably responsible for this phenomenon.

CONCLUSION

Overall, *H. pylori* has an exceptional impact on GI system. It is able to influence all the vital pathways of human system. Increasing evidences are focusing on its role also in pathological aspects not immediately related to the GI tract, such as metabolic syndrome and gynecological diseases. This new approach in studying *H. pylori* has obvious therapeutic implications and could lead to the screening of *H. pylori* in these diseases, especially in metabolic syndrome. Finally *H. pylori*, the most studied bacteria in GI tract, represents a model to follow for studying the gut microbiota properties. This could open the discussion on new diagnostic and therapeutical approaches of GI and extra-intestinal diseases.

REFERENCES

- 1 **Dzierzanowska-Fangrat K**, Dzierzanowska D. Helicobacter pylori: microbiology and interactions with gastrointestinal microflora. *J Physiol Pharmacol* 2006; **57** Suppl 3: 5-14 [PMID: 17033102]
- 2 **Malfertheiner P**, Chan FK, McColl KE. Peptic ulcer disease. *Lancet* 2009; **374**: 1449-1461 [PMID: 19683340 DOI: 10.1016/S0140-6736(09)60938-7]
- 3 **Gaetano C**, Aldo B, editors. Infezione gastrica da Helicobacter pylori. Trattato di Medicina Interna: Piccin Edizioni, 2009
- 4 **Yamaoka Y**. Mechanisms of disease: Helicobacter pylori virulence factors. *Nat Rev Gastroenterol Hepatol* 2010; **7**: 629-641 [PMID: 20938460 DOI: 10.1038/nrgastro.2010.154]
- 5 **Pandey R**, Misra V, Misra SP, Dwivedi M, Kumar A, Tiwari BK. Helicobacter pylori and gastric cancer. *Asian Pac J Cancer Prev* 2010; **11**: 583-588 [PMID: 21039020]
- 6 **Gasbarrini A**, Franceschi F, Armuzzi A, Ojetti V, Candelli M, Torre ES, De Lorenzo A, Anti M, Pretolani S, Gasbarrini G. Extradigestive manifestations of Helicobacter pylori gastric infection. *Gut* 1999; **45** Suppl 1: I9-I12 [PMID: 10457029 DOI: 10.1136/gut.45.2008.i9]
- 7 **Solnick JV**, Franceschi F, Roccarina D, Gasbarrini A. Extra-gastric manifestations of Helicobacter pylori infection--other Helicobacter species. *Helicobacter* 2006; **11** Suppl 1: 46-51 [PMID: 16925612 DOI: 10.1111/j.1478-405X.2006.00430.x]
- 8 **Capurso G**, Marignani M, Delle Fave G, Annibale B. Iron-deficiency anemia in premenopausal women: why not consider atrophic body gastritis and Helicobacter pylori role? *Am J Gastroenterol* 1999; **94**: 3084-3085 [PMID: 10520890 DOI: 10.1111/j.1572-0241.1999.03084.x]
- 9 **Akcam M**, Ozdem S, Yilmaz A, Gultekin M, Artan R. Serum ferritin, vitamin B(12), folate, and zinc levels in children infected with Helicobacter pylori. *Dig Dis Sci* 2007; **52**: 405-410 [PMID: 17211708 DOI: 10.1007/s10620-006-9422-8]
- 10 **Qu XH**, Huang XL, Xiong P, Zhu CY, Huang YL, Lu LG, Sun X, Rong L, Zhong L, Sun DY, Lin H, Cai MC, Chen ZW, Hu B, Wu LM, Jiang YB, Yan WL. Does Helicobacter pylori infection play a role in iron deficiency anemia? A meta-analysis. *World J Gastroenterol* 2010; **16**: 886-896 [PMID: 20143469]
- 11 **Annibale B**, Capurso G, Martino G, Grossi C, Delle Fave G. Iron deficiency anaemia and Helicobacter pylori infection. *Int J Antimicrob Agents* 2000; **16**: 515-519 [PMID: 11118871 DOI: 10.1016/S0924-8579(00)00288-0]
- 12 **Capurso G**, Lahner E, Marcheggiano A, Caruana P, Carnuccio A, Bordi C, Delle Fave G, Annibale B. Involvement of the corporal mucosa and related changes in gastric acid secretion characterize patients with iron deficiency anaemia associated with Helicobacter pylori infection. *Aliment Pharmacol Ther* 2001; **15**: 1753-1761 [PMID: 11683689 DOI: 10.1046/j.1365-2036.2001.01101.x]
- 13 **Annibale B**, Capurso G, Lahner E, Passi S, Ricci R, Maggio F, Delle Fave G. Concomitant alterations in intragastric pH and ascorbic acid concentration in patients with Helicobacter pylori gastritis and associated iron deficiency anaemia. *Gut* 2003; **52**: 496-501 [PMID: 12631657 DOI: 10.1136/gut.52.4.496]
- 14 **Pérez-Pérez GI**, Israel DA. Role of iron in Helicobacter pylori: its influence in outer membrane protein expression and in pathogenicity. *Eur J Gastroenterol Hepatol* 2000; **12**: 1263-1265 [PMID: 11192313 DOI: 10.1097/00042737-200012120-00001]
- 15 **Malfertheiner P**, Megraud F, O'Morain C, Bazzoli F, El-Omar E, Graham D, Hunt R, Rokkas T, Vakil N, Kuipers EJ. Current concepts in the management of Helicobacter pylori infection: the Maastricht III Consensus Report. *Gut* 2007; **56**: 772-781 [PMID: 17170018 DOI: 10.1136/gut.2006.101634]
- 16 **Stopeck A**. Links between Helicobacter pylori infection, cobalamin deficiency, and pernicious anemia. *Arch Intern Med* 2000; **160**: 1229-1230 [PMID: 10809024 DOI: 10.1001/archinte.160.9.1229]
- 17 **Kaptan K**, Beyan C, Ural AU, Cetin T, Avcu F, Gülşen M, Finci R, Yalçın A. Helicobacter pylori--is it a novel causative agent in Vitamin B12 deficiency? *Arch Intern Med* 2000; **160**: 1349-1353 [PMID: 10809040 DOI: 10.1001/archinte.160.9.1349]
- 18 **Annibale B**, Capurso G, Delle Fave G. Consequences of Helicobacter pylori infection on the absorption of micronutrients. *Dig Liver Dis* 2002; **34** Suppl 2: S72-S77 [PMID: 12408446]
- 19 **Howden CW**. Vitamin B12 levels during prolonged treatment with proton pump inhibitors. *J Clin Gastroenterol* 2000; **30**: 29-33 [PMID: 10636207 DOI: 10.1097/00004836-200001000-00006]
- 20 **Cohen H**, Weinstein WM, Carmel R. Heterogeneity of gastric histology and function in food cobalamin malabsorption: absence of atrophic gastritis and achlorhydria in some patients with severe malabsorption. *Gut* 2000; **47**: 638-645 [PMID: 11034579 DOI: 10.1136/gut.47.5.638]
- 21 **Claeys D**, Faller G, Appelmek BJ, Negrini R, Kirchner T. The gastric H⁺,K⁺-ATPase is a major autoantigen in chronic Helicobacter pylori gastritis with body mucosa atrophy. *Gastroenterology* 1998; **115**: 340-347 [PMID: 9679039 DOI: 10.1016/S0016-5085(98)70200-8]
- 22 **Tang G**, Serfaty-Lacrosniere C, Camilo ME, Russell RM. Gastric acidity influences the blood response to a beta-carotene dose in humans. *Am J Clin Nutr* 1996; **64**: 622-626 [PMID: 8839509]
- 23 **Sanderson MJ**, White KL, Drake IM, Schorah CJ. Vitamin E and carotenoids in gastric biopsies: the relation to plasma concentrations in patients with and without Helicobacter pylori gastritis. *Am J Clin Nutr* 1997; **65**: 101-106 [PMID: 8988920]
- 24 **Zhang ZW**, Patchett SE, Perrett D, Domizio P, Farthing MJ. Gastric alpha-tocopherol and beta-carotene concentrations in association with Helicobacter pylori infection. *Eur J Gastroenterol Hepatol* 2000; **12**: 497-503 [PMID: 10833091 DOI: 10.1097/00042737-200012050-00004]
- 25 **Ziegler EE**, Filer LJ. Present Knowledge in Nutrition. 6th ed. North America: International Life Sciences Institute, 1990
- 26 **Waring AJ**, Drake IM, Schorah CJ, White KL, Lynch DA, Axon AT, Dixon MF. Ascorbic acid and total vitamin C concentrations in plasma, gastric juice, and gastrointestinal mucosa: effects of gastritis and oral supplementation. *Gut* 1996; **38**: 171-176 [PMID: 8801192 DOI: 10.1136/gut.38.2.171]
- 27 **Woodward M**, Tunstall-Pedoe H, McColl K. Helicobacter pylori infection reduces systemic availability of dietary vitamin C. *Eur J Gastroenterol Hepatol* 2001; **13**: 233-237 [PMID: 11293441 DOI: 10.1097/00042737-200103000-00003]
- 28 **Capurso G**, Ricci R, Panzuto F, Baccini F, Passi S, Di Giulio E, Delle Fave G, Annibale B. Intragastric ascorbic but not uric acid is depleted in relation with the increased pH in patients with atrophic body gastritis and H. pylori gastritis. *Helicobacter* 2003; **8**: 300-306 [PMID: 12950602 DOI: 10.1046/j.1523-5378.2003.00157.x]
- 29 **Sies H**, Stahl W. Vitamins E and C, beta-carotene, and other carotenoids as antioxidants. *Am J Clin Nutr* 1995; **62**: 1315S-1321S [PMID: 7495226]
- 30 **Phull PS**, Price AB, Thorniley MS, Green CJ, Jacyna MR. Vitamin E concentrations in the human stomach and duodenum--correlation with Helicobacter pylori infection. *Gut* 1996; **39**: 31-35 [PMID: 8881804 DOI: 10.1136/gut.39.1.31]
- 31 **Zullo A**, Rinaldi V, Efrati C, Hassan C, Caroli S, Riggio O, Attili AF. Zinc, ammonia, and Helicobacter pylori infection in liver cirrhosis. *Dig Liver Dis* 2000; **32**: 836-838 [PMID: 11515492]
- 32 **Ustündag Y**, Boyacıoğlu S, Haberal A, Demirhan B, Bilezikçi B. Plasma and gastric tissue selenium levels in patients with Helicobacter pylori infection. *J Clin Gastroenterol* 2001; **32**: 405-408 [PMID: 11319311 DOI: 10.1097/00004836-200105000-00009]
- 33 **Kojima M**, Hosoda H, Date Y, Nakazato M, Matsuo H,

- Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. *Nature* 1999; **402**: 656-660 [PMID: 10604470 DOI: 10.1038/45230]
- 34 Murray CD, Kamm MA, Bloom SR, Emmanuel AV. Ghrelin for the gastroenterologist: history and potential. *Gastroenterology* 2003; **125**: 1492-1502 [PMID: 14598266]
- 35 Cummings DE. Helicobacter pylori and ghrelin: Interrelated players in body-weight regulation? *Am J Med* 2004; **117**: 436-439 [PMID: 15380502 DOI: 10.1016/j.amjmed.2004.07.034]
- 36 Masuda Y, Tanaka T, Inomata N, Ohnuma N, Tanaka S, Itoh Z, Hosoda H, Kojima M, Kangawa K. Ghrelin stimulates gastric acid secretion and motility in rats. *Biochem Biophys Res Commun* 2000; **276**: 905-908 [PMID: 11027567 DOI: 10.1006/bbrc.2000.3568]
- 37 Asakawa A, Inui A, Kaga T, Yuzuriha H, Nagata T, Ueno N, Makino S, Fujimiya M, Nijima A, Fujino MA, Kasuga M. Ghrelin is an appetite-stimulatory signal from stomach with structural resemblance to motilin. *Gastroenterology* 2001; **120**: 337-345 [PMID: 11159873]
- 38 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 [PMID: 17218760]
- 39 Kalra SP, Ueno N, Kalra PS. Stimulation of appetite by ghrelin is regulated by leptin restraint: peripheral and central sites of action. *J Nutr* 2005; **135**: 1331-1335 [PMID: 15867335]
- 40 Blaser MJ, Atherton JC. Helicobacter pylori persistence: biology and disease. *J Clin Invest* 2004; **113**: 321-333 [PMID: 14755326 DOI: 10.1172/JCI20925]
- 41 Nweneka CV, Prentice AM. Helicobacter pylori infection and circulating ghrelin levels - a systematic review. *BMC Gastroenterol* 2011; **11**: 7 [PMID: 21269467 DOI: 10.1186/1471-230X-11-7]
- 42 Isomoto H, Nishi Y, Ohnita K, Mizuta Y, Kohno S, Ueno H, Nakazato M. The Relationship between Plasma and Gastric Ghrelin Levels and Strain Diversity in Helicobacter pylori Virulence. *Am J Gastroenterol* 2005; **100**: 1425-1427 [PMID: 15929785 DOI: 10.1111/j.1572-0241.2005.41929_7.x]
- 43 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 [PMID: 16687031 DOI: 10.1381/096089206776945002]
- 44 Checchi S, Montanaro A, Pasqui L, Ciuoli C, Cevenini G, Sestini F, Fioravanti C, Pacini F. Serum ghrelin as a marker of atrophic body gastritis in patients with parietal cell antibodies. *J Clin Endocrinol Metab* 2007; **92**: 4346-4351 [PMID: 17711921 DOI: 10.1210/jc.2007-0988]
- 45 Abiko Y, Suzuki H, Masaoka T, Nomura S, Kurabayashi K, Hosoda H, Kangawa K, Hibi T. Enhanced plasma ghrelin levels in Helicobacter pylori-colonized, interleukin-1-receptor type 1-homozygous knockout (IL-1R1-/-) mice. *World J Gastroenterol* 2005; **11**: 4148-4153 [PMID: 16015681]
- 46 Talley NJ, Stanghellini V, Heading RC, Koch KL, Malagelada JR, Tytgat GN. Functional gastroduodenal disorders. *Gut* 1999; **45** Suppl 2: II37-II42 [PMID: 10457043]
- 47 Polyzos SA, Kountouras J, Zavos C, Deretzi G. The association between Helicobacter pylori infection and insulin resistance: a systematic review. *Helicobacter* 2011; **16**: 79-88 [PMID: 21435084 DOI: 10.1111/j.1523-5378.2011.00822.x]
- 48 Aslan M, Horoz M, Nazligul Y, Bolukbas C, Bolukbas FF, Selek S, Celik H, Erel O. Insulin resistance in H pylori infection and its association with oxidative stress. *World J Gastroenterol* 2006; **12**: 6865-6868 [PMID: 17106938]
- 49 Gunji T, Matsuhashi N, Sato H, Fujibayashi K, Okumura M, Sasabe N, Urabe A. Helicobacter pylori infection significantly increases insulin resistance in the asymptomatic Japanese population. *Helicobacter* 2009; **14**: 144-150 [PMID: 19751440 DOI: 10.1111/j.1523-5378.2009.00705.x]
- 50 Park SH, Jeon WK, Kim SH, Kim HJ, Park DI, Cho YK, Sung IK, Sohn CI, Kim BI, Keum DK. Helicobacter pylori eradication has no effect on metabolic and inflammatory parameters. *J Natl Med Assoc* 2005; **97**: 508-513 [PMID: 15868771]
- 51 Gen R, Demir M, Ataseven H. Effect of Helicobacter pylori eradication on insulin resistance, serum lipids and low-grade inflammation. *South Med J* 2010; **103**: 190-196 [PMID: 20134372 DOI: 10.1097/SMJ.0b013e3181cf373f]
- 52 Imai J, Yamada T, Saito T, Ishigaki Y, Hinokio Y, Kotake H, Oka Y, Katagiri H. Eradication of insulin resistance. *Lancet* 2009; **374**: 264 [PMID: 19616723 DOI: 10.1016/S0140-6736(09)60872-2]
- 53 Yeh JJ, Tsai S, Wu DC, Wu JY, Liu TC, Chen A. P-selectin-dependent platelet aggregation and apoptosis may explain the decrease in platelet count during Helicobacter pylori infection. *Blood* 2010; **115**: 4247-4253 [PMID: 20097880 DOI: 10.1182/blood-2009-09-241166]
- 54 Basso D, Plebani M, Kusters JG. Pathogenesis of Helicobacter pylori infection. *Helicobacter* 2010; **15** Suppl 1: 14-20 [PMID: 21054648 DOI: 10.1111/j.1523-5378.2010.00781.x]
- 55 Evrengul H, Tanriverdi H, Kuru O, Enli Y, Yuksel D, Kilic A, Kaftan A, Kirac S, Kilic M. Elevated homocysteine levels in patients with slow coronary flow: relationship with Helicobacter pylori infection. *Helicobacter* 2007; **12**: 298-305 [PMID: 17669101 DOI: 10.1111/j.1523-5378.2007.00505.x]
- 56 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 [PMID: 15483107 DOI: 10.1210/jc.2004-1330]
- 57 Roper J, Francois F, Shue PL, Mourad MS, Pei Z, Olivares de Perez AZ, Perez-Perez GI, Tseng CH, Blaser MJ. Leptin and ghrelin in relation to Helicobacter pylori status in adult males. *J Clin Endocrinol Metab* 2008; **93**: 2350-2357 [PMID: 18397989 DOI: 10.1210/jc.2007-2057]
- 58 Manolakis AC, Tiaka EK, Kapsoritakis AN, Georgoulas P, Tsiopoulos F, Valotassiou V, Potamianos SP. Increased fetuin A levels in Helicobacter pylori infection: a missing link between H. pylori and insulin resistance? *Diabetologia* 2011; **54**: 472-474 [PMID: 21116603 DOI: 10.1007/s00125-010-1995-2]
- 59 Polyzos SA, Kountouras J, Zavos C, Deretzi G. The potentially dual-faceted nature of fetuin-A in Helicobacter pylori infection and insulin resistance. *Clinics (Sao Paulo)* 2011; **66**: 911-912 [PMID: 21789399 DOI: 10.1590/S1807-59322011000500031]
- 60 Kebapcilar L, Bilgir O, Cetinkaya E, Akyol M, Bilgir F, Bozkaya G. The effect of Helicobacter pylori eradication on macrophage migration inhibitory factor, C-reactive protein and fetuin-a levels. *Clinics (Sao Paulo)* 2010; **65**: 799-802 [PMID: 20835558 DOI: 10.1590/S1807-59322010000800010]
- 61 Cullen P, Assmann G. High risk strategies for atherosclerosis. *Clin Chim Acta* 1999; **286**: 31-45 [PMID: 10511283]
- 62 Hoffmeister A, Rothenbacher D, Bode G, Persson K, März 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 [PMID: 11231924 DOI: 10.1161/01.ATV.21.3.427]
- 63 Laurila A, Bloigu A, Näyhä S, Hassi J, Leinonen M, Saikku P. Association of Helicobacter pylori infection with elevated serum lipids. *Atherosclerosis* 1999; **142**: 207-210 [PMID: 9920523 DOI: 10.1016/S0021-9150(98)00194-4]
- 64 Niemelä S, Karttunen T, Korhonen T, Läärä E, Karttunen R, Ikäheimo M, Kesäniemi YA. Could Helicobacter pylori infection increase the risk of coronary heart disease by modifying serum lipid concentrations? *Heart* 1996; **75**: 573-575 [PMID: 8697159]
- 65 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 [PMID: 9552950 DOI: 10.1136/bmj.316.7138.1130]
- 66 Zhu J, Quyyumi AA, Muhlestein JB, Nieto FJ, Horne BD, Zalles-Ganley A, Anderson JL, Epstein SE. Lack of associa-

- tion of *Helicobacter pylori* infection with coronary artery disease and frequency of acute myocardial infarction or death. *Am J Cardiol* 2002; **89**: 155-158 [PMID: 11792334 DOI: 10.1016/S0002-9149(01)02192-0]
- 67 **Kim HL**, Jeon HH, Park IY, Choi JM, Kang JS, Min KW. *Helicobacter pylori* infection is associated with elevated low density lipoprotein cholesterol levels in elderly Koreans. *J Korean Med Sci* 2011; **26**: 654-658 [PMID: 21532857 DOI: 10.3346/jkms.2011.26.5.654]
- 68 **Satoh H**, Saijo Y, Yoshioka E, Tsutsui H. *Helicobacter Pylori* infection is a significant risk for modified lipid profile in Japanese male subjects. *J Atheroscler Thromb* 2010; **17**: 1041-1048 [PMID: 20610892 DOI: 10.5551/jat.5157]
- 69 **Di Bonaventura G**, Piccolomini R, Pompilio A, Zappacosta R, Piccolomini M, Neri M. Serum and mucosal cytokine profiles in patients with active *Helicobacter pylori* and ischemic heart disease: is there a relationship? *Int J Immunopathol Pharmacol* 2007; **20**: 163-172 [PMID: 17346440]
- 70 **Arslan E**, Atilgan H, Yavaşoğlu I. The prevalence of *Helicobacter pylori* in obese subjects. *Eur J Intern Med* 2009; **20**: 695-697 [PMID: 19818289 DOI: 10.1016/j.ejim.2009.07.013]
- 71 **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 [PMID: 11960066 DOI: 10.1097/00004836-200205000-00012]
- 72 **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 [PMID: 15771763 DOI: 10.1111/j.1365-2036.2005.02369.x]
- 73 **Cho I**, Blaser MJ, François 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 [PMID: 16093294 DOI: 10.1093/aje/kwi237]
- 74 **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 [PMID: 12239930]
- 75 **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 [PMID: 15702858 DOI: 10.1016/j.dld.2004.07.017]
- 76 **Nwokolo CU**, Freshwater DA, O'Hare P, Randeve HS. Plasma ghrelin following cure of *Helicobacter pylori*. *Gut* 2003; **52**: 637-640 [PMID: 12692045 DOI: 10.1136/gut.52.5.637]
- 77 **Loffeld RJ**. *Helicobacter pylori*, obesity and gastro-oesophageal reflux disease. Is there a relation? A personal view. *Neth J Med* 2005; **63**: 344-347 [PMID: 16244381]
- 78 **Abenavoli L**, Milic N, Masarone M, Persico M. Association between non-alcoholic fatty liver disease, insulin resistance and *Helicobacter pylori*. *Med Hypotheses* 2013; **81**: 913-915 [PMID: 24011768 DOI: 10.1016/j.mehy.2013.08.011]
- 79 **Mégraud F**, Brassens-Rabbé MP, Denis F, Belbouri A, Hoa DQ. Seroepidemiology of *Campylobacter pylori* infection in various populations. *J Clin Microbiol* 1989; **27**: 1870-1873 [PMID: 2549098]
- 80 **Kehrt R**, Becker M, Brösicke H, Krüger N, Helge H. Prevalence of *Helicobacter pylori* infection in Nicaraguan children with persistent diarrhea, diagnosed by the 13C-urea breath test. *J Pediatr Gastroenterol Nutr* 1997; **25**: 84-88 [PMID: 9226533 DOI: 10.1097/00005176-199707000-00014]
- 81 **Goodman KJ**, Correa P, Tenganá Aux HJ, Ramírez H, DeLany JP, Guerrero Pepinosa O, López Quiñones M, Collazos Parra T. *Helicobacter pylori* infection in the Colombian Andes: a population-based study of transmission pathways. *Am J Epidemiol* 1996; **144**: 290-299 [PMID: 8686698 DOI: 10.1093/oxfordjournals.aje.a008924]
- 82 **Thomas JE**, Dale A, Bunn JE, Harding M, Coward WA, Cole TJ, Weaver LT. Early *Helicobacter pylori* colonisation: the association with growth faltering in The Gambia. *Arch Dis Child* 2004; **89**: 1149-1154 [PMID: 15557054 DOI: 10.1136/adc.2002.015313]
- 83 **Mera RM**, Correa P, Fontham EE, Reina JC, Pradilla A, Alzate A, Bravo LE. Effects of a new *Helicobacter pylori* infection on height and weight in Colombian children. *Ann Epidemiol* 2006; **16**: 347-351 [PMID: 16246582 DOI: 10.1016/j.annepidem.2005.08.002]
- 84 **Windle HJ**, Kelleher D, Crabtree JE. Childhood *Helicobacter pylori* infection and growth impairment in developing countries: a vicious cycle? *Pediatrics* 2007; **119**: e754-e759 [PMID: 17325213 DOI: 10.1542/peds.2006-2196]
- 85 **Dale A**, Thomas JE, Darboe MK, Coward WA, Harding M, Weaver LT. *Helicobacter pylori* infection, gastric acid secretion, and infant growth. *J Pediatr Gastroenterol Nutr* 1998; **26**: 393-397 [PMID: 9552134 DOI: 10.1097/00005176-199804000-00006]
- 86 **Weaver LT**. Royal Society of Tropical Medicine and Hygiene Meeting at Manson House, London, 16 February 1995. Aspects of *Helicobacter pylori* infection in the developing and developed world. *Helicobacter pylori* infection, nutrition and growth of West African infants. *Trans R Soc Trop Med Hyg* 1995; **89**: 347-350 [PMID: 7570858 DOI: 10.1016/0035-9203(95)90002-0]
- 87 **Howden CW**, Hunt RH. Relationship between gastric secretion and infection. *Gut* 1987; **28**: 96-107 [PMID: 3546004 DOI: 10.1136/gut.28.1.96]
- 88 **Khosla SN**, Jain N, Khosla A. Gastric acid secretion in typhoid fever. *Postgrad Med J* 1993; **69**: 121-123 [PMID: 8506192 DOI: 10.1136/pgmj.69.808.121]
- 89 **Giannella RA**, Broitman SA, Zamcheck N. Salmonella enteritis. I. Role of reduced gastric secretion in pathogenesis. *Am J Dig Dis* 1971; **16**: 1000-1006 [PMID: 4942816 DOI: 10.1007/BF02235012]
- 90 **Nalin DR**, Levine RJ, Levine MM, Hoover D, Bergquist E, McLaughlin J, Libonati J, Alam J, Hornick RB. Cholera, non-vibrio cholera, and stomach acid. *Lancet* 1978; **2**: 856-859 [PMID: 81410 DOI: 10.1016/S0140-6736(78)91568-4]
- 91 **Cook GC**. Infective gastroenteritis and its relationship to reduced gastric acidity. *Scand J Gastroenterol Suppl* 1985; **111**: 17-23 [PMID: 3925541 DOI: 10.3109/00365528509093751]
- 92 **Passaro DJ**, Taylor DN, Meza R, Cabrera L, Gilman RH, Parsonnet J. Acute *Helicobacter pylori* infection is followed by an increase in diarrheal disease among Peruvian children. *Pediatrics* 2001; **108**: E87 [PMID: 11694671 DOI: 10.1542/peds.108.5.e87]
- 93 **Bravo LE**, Mera R, Reina JC, Pradilla A, Alzate A, Fontham E, Correa P. Impact of *Helicobacter pylori* infection on growth of children: a prospective cohort study. *J Pediatr Gastroenterol Nutr* 2003; **37**: 614-619 [PMID: 14581807 DOI: 10.1097/00005176-200311000-00021]
- 94 **Choe YH**, Kim SK, Hong YC. *Helicobacter pylori* infection with iron deficiency anaemia and subnormal growth at puberty. *Arch Dis Child* 2000; **82**: 136-140 [PMID: 10648367 DOI: 10.1136/adc.82.2.136]
- 95 **Yuan W**, Li Yumin D, Yang L. Iron deficiency anemia in *Helicobacter pylori* infection: meta-analysis of randomized controlled trials. *Scand J Gastroenterol* 2010; **45**: 665-676 [PMID: 20201716 DOI: 10.3109/00365521003663670]
- 96 **Barabino A**, Dufour C, Marino CE, Claudiani F, De Alessandri A. Unexplained refractory iron-deficiency anemia associated with *Helicobacter pylori* gastric infection in children: further clinical evidence. *J Pediatr Gastroenterol Nutr* 1999; **28**: 116-119 [PMID: 9890483 DOI: 10.1097/00005176-199901000-00027]
- 97 **Kostaki M**, Fessatou S, Karpathios T. Refractory iron-deficiency anaemia due to silent *Helicobacter pylori* gastritis

- in children. *Eur J Pediatr* 2003; **162**: 177-179 [PMID: 12655422
DOI: 10.1007/s00431-002-1139-x]
- 98 **Ruiz B**, Rood JC, Fontham ET, Malcom GT, Hunter FM, Sobhan M, Johnson WD, Correa P. Vitamin C concentration in gastric juice before and after anti-*Helicobacter pylori* treatment. *Am J Gastroenterol* 1994; **89**: 533-539 [PMID: 8147356]
- 99 **Hep A**, Pospíšilová J, Dolina J, Prásek J, Dítě P. [Levels of vitamins A, E and C in serum and gastric juice in relation to gastric mucosa and occurrence of *Helicobacter pylori*]. *Vnitř Lek* 1998; **44**: 396-399 [PMID: 9748875]
- 100 **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 [PMID: 11929399
DOI: 10.1046/j.1365-2036.2002.01222.x]

P- Reviewer: Abenavoli L, Green JT, Guandalini S, Naser SA
S- Editor: Ma YJ **L- Editor:** A **E- Editor:** Zhang DN





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>



ISSN 1007-9327

