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TOPIC HIGHLIGHT

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Role of *Helicobacter pylori* infection on nutrition and metabolism

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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 malabsorbption of essential nutrients, and of gastrointestinal hormones, as well as on the relationship between *H. pylori* and the metabolic syndrome.

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.

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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 1β 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 metabolic 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 it 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 depend 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 hypochlorydria 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 showed 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 resultant 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 metanalysis[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.

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