PERSPECTIVE

Helicobacter pylori and Micronutrients

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Helicobacter pylori (HP) infection causes morbidity in several systems, especially in the gastrointestinal tract. The prevalence of disease is inversely related to social-economic and developmental status. It is more common in the developing than in developed countries. In the countries where social-economic status is low, not only HP infection, but also malnutrition and growth failure have a higher prevalence. According to these data, the relationship of nutrition and HP infection is still a question. Does HP infection affect nutritional status? On the contrary, does nutritional status affect HP infection? If so, how? This review was prepared after searching thoroughly almost all of the publications about relationship between HP infections and micronutrients, especially publications pertaining to childhood, from 1990 to 2009 in PubMed. Some valuable adult and experimental publications were also reviewed. These studies related *H.pylori* to iron, vitamin B_{12}, vitamin C, vitamin A, vitamin E, folate, and selenium. Published studies reveal some evidence that HP has a negative effect on iron, vitamin B_{12} and vitamin C metabolism, but its influence on others is not clear.

Key words: *Helicobacter pylori*, *Iron*, Micronutrients, Vitamin B_{12}, Vitamin C

The prevalence of *Helicobacter pylori* (HP) infection is stated to be as high as 80% in the developing countries. The overall seroprevalence of *H. pylori* in children of Texas is 12.2%, and 55.9% in the 11-16 age group in India(1,2). The infection penetrates especially during childhood and continues life-long. During its course, the disease can have several manifestations including acute gastritis, chronic atrophic gastritis, intestinal metaplasia, dysplasia, growth failure, malnutrition and finally cancer(3,4).

Trace minerals and vitamins are essential for life. They act as essential cofactors of enzymes and as organizers of the molecular structures of the cell. Deficiencies of micronutrients influence immune homeostasis and thus affect infection-related morbidity and mortality. Micronutrients like β-carotene, vitamin C, selenium, copper and others are powerful antioxidants and have a significant impact on infection related morbidity in humans. Subclinical deficiencies are known to impair biological and immune functions in the host(5). *H. pylori* can change the secretion and acidification functions of stomach, because it penetrates especially into the stomach. This situation can affect digestion and absorption of some components of the nutrients and micronutrients.

Although nutrient absorption does not take place in the stomach, this organ contributes to the process by means of secretion of hydrochloric acid and several enzymes. These substances help not only release the micronutrients from the food matrix, but also, in the case of the essential minerals, render them soluble during the digestive process. In the last few years, a number of studies have suggested that HP infection may affect the homeostasis of different micronutrients. Not many studies are available and only a few micronutrients with HP infection have been studied up to now. This review includes relation of iron, vitamin B_{12}, vitamin C, vitamin A, vitamin E, folate and selenium; with HP infection.

IRON

Many areas of the world with a high iron deficiency prevalence, have a high HP prevalence as well. Different epidemiological studies conducted all over the world have demonstrated an association between HP infection and iron deficiency anemia(6,7). A strong association was found between HP infection and iron deficiency in the recent studies(8-12). Serum ferritin concentrations were found decreased in 2794 Danish adults with elevated titers of anti-HP antibody(13). HP eradication was associated with the recovery of iron deficiency anemia even in patients who did not receive iron treatment(14). Several case reports and case series reported the reversion of unexplained iron deficiency anemia by efficacious eradication therapy in patients with HP non-atrophic gastritis. Kostaki, *et al*.(15) reported three children with chronic active HP gastritis and iron deficiency anemia; where iron supplementation therapy was effective only after the eradication of HP(15). In another recent study, at the beginning, there was no difference between the participants who have HP infection and those who did not have HP infection. After 8 weeks of iron supplementation, there was a significant difference between the groups, and the response of HP negative group was better(16). This data suggested that even asymptomatic HP infection can impair the iron absorption.

However, the mechanisms by which HP infection causes iron deficiency are not been well established; but following are the possibilities:

(*a*) The development of iron deficiency in HP–infected subjects might be the result of the pattern of gastritis and related effects on gastric physiology, affecting the normal process of iron absorption(17);

(*b*) HP may cause iron deficiency through a competition with the host for iron absorption, as iron is an essential growth factor for this bacteria. HP has external membrane proteins playing a role in bacterial iron absorption as well as intracellular storage proteins with similar characteristics as ferritin(18); and,

(*c*) HP has been associated with a lower bioavailability and low gastric juice content of vitamin C, which may also decrease iron absorption in human(19).

VITAMIN B_{12}

The most common malabsorptive condition leading to vitamin B_{12} deficiency is the body's inability to extract cobalamin from food. Food-bound cobalamin malabsorption results from conditions that impair the secretion of gastric acid and pepsin required for the release of cobalamin from proteins in food(20). One of two pediatric studies investigating the relation between HP infection and vitamin B_{12} deficiency revealed no direct strong association between vitamin B_{12} deficiency and HP infection(21). In another study performed by us, we found a statistically significant relation between HP infection and serum vitamin B_{12} levels that was independent of gastric atrophy. Although prevalence of vitamin B_{12} deficiency was 28% and 11% in HP–positive and –negative groups, respectively, there was no statistically significant difference between the groups.

However, it should also be noted that one may expect to find a stronger relation in large-scale studies(8). We speculated that because vitamin B_{12} stores are adequate for a long time, severe deficiencies might not be detected during childhood. Untreated HP infection persists throughout lifespan and may cause more severe vitamin B_{12} deficiency in the elderly. In addition, hyperhomocysteinemia secondary to vitamin B_{12} deficiency may constitute a risk for severe cardiovascular and cerebrovascular diseases. The mechanisms of vitamin B_{12} malabsorption caused by HP infection are unclear but following are the possibilities; (*a*) Diminished acid secretion in HP induced gastritis may lead to a failure of critical splitting of vitamin B_{12} from food binders and its subsequent transfer to R binder in the stomach; (*b*) A secretory dysfunction of the intrinsic factor; and, (*c*) decreased secretion of ascorbic acid from the gastric mucosa and increased gastric pH(22). Annibale, *et al*.(23), demonstrated that almost two thirds of pernicious anemia patients had evidence of HP but only those with an active HP infection had distinct functional and histological features(23)

These findings support the hypothesis that HP infection could play a triggering role in a subgroup of patient with pernicious anemia, and suggest the possibility that HP is involved in the early stages of PA that lead to severe corpus atrophy. The later progress of gastritis seems to be dependent on factors other than HP, most likely "autoimmune" mechanisms(24). HP may also be involved in the pathogenesis of pernicious anemia via antigenic mimicry as antibodies directed against the H+, K+-adenosine triphosphate protein that has been found in high numbers of patients with HP infection(25). Food cobalamin malabsorption may occur without gastric atrophy or achlorhydria. Malabsorption can respond to antibiotics, but only in some patients(26).

VITAMIN C

Ascorbic acid (AA) is the reduced form of the vitamin and can act as a potent antioxidant, and is able to scavenge reactive oxygen species (ROS) in the gastric mucosa. This has been proposed as one means by which it exerts an anti-carcinogenic effect. HP infection leads to increases of ROS generations in the mucosa. It has been demonstrated that eradication of HP could lead to a reduction in ROS activity in the gastric mucosa(27). Banerjee, *et al*.(28) showed that HP causes considerable but reversible lowering of concentrations of vitamin C in gastric juice. This situation could be important in the association of HP infection, gastric cancer and ulcers(28). Kim, *et al.*(29) reported that HP seropositivity is a significant risk factor for gastric cancer in the low vitamin C intake group, but not in the high vitamin C intake group. Vitamin C intake was found to modify the relation between HP and gastric cancer(29). A number of studies have demonstrated that gastric juice but not gastric mucosal ascorbic acid (AA) levels were reduced in the presence of HP gastritis and that successful eradication restored the juice/plasma AA ratio. The studies support two mechanisms for this association: increased oxidation and a decreased secretion of ascorbic acid(30). The lower plasma vitamin C concentration in HP positive subjects could be due to reduced bioavailability, active secretion from plasma to gastric juice in attempts to restore the positive gastric juice/plasma ratio or both(31). In some studies, no difference was found in the gastric juice AA concentration between patients with antral-limited gastritis and HP negative healthy controls, while lower AA levels were observed in patients with gastric body involvement and increased pH(32). These observations suggest that AA, which is very unstable in the presence of increased pH, is converted to the less active form of dehydroascorbic acid, in the presence of gastric damage extending to the corporal mucosa with consequent hypochlydria(33). Intragastric pH is the key factor for the observed depletion of gastric juice AA levels, which are notably decreased in patients with corporal atrophy, and to lower extent in those with non-atrophic HP gastritis(34). HP infection associated low gastric juice-ascorbic acid levels return to normal after successful eradication of the infection(35). A study of antibiotic treatment failure showed that compliant patients in whom HP infection did not clear had lower baseline plasma and gastric juice vitamin C concentrations than patients whose infection was cleared(30).

In a study performed in Korea, vitamin C levels in whole blood, plasma, and gastric juice and the gastric juice pH were closely related to the severity of HP infection and the histological changes in the stomach. These authors reported that vitamin C can have a role in initiation and progression of HP infection, so vitamin C supplementation can act on HP infection treatment approach(36). However, in the studies about HP eradication, it was thought that the antioxidants like vitamin C could have a potential effect like an antimicrobial agent against HP(37). HP infection may impair the protective role of vitamin C in the stomach. Colonization of the gastric mucosa with HP reduces the vitamin C concentration of gastric juice.

VITAMIN A

The xerotic surfaces form potential sites for increased bacterial adherence thus leading to bacterial colonization. The antimicrobial enzyme lysozyme depends on vitamin A for its synthesis. A decrease in T cell number with no change in proliferative activity has been demonstrated in children suffering from mild xerophthalmia due to vitamin A deficiency. HP infection and low

β-carotene in plasma contribute to the increased risk of gastric atrophy, indicating that HP infection might be associated with low plasma β–carotene(38).

There are not many studies that examine the association of vitamin A and HP. In a study, gastric juice beta-carotene concentration was markedly lower in patients infected with HP than uninfected controls, but there was no significant difference in serum or gastric mucosal beta-carotene concentrations between the two patient groups. The presence of gastric atrophy and intestinal metaplasia was significantly associated with reduced mucosal beta-carotene concentrations. Authors reported that beta-carotene concentrations are affected by HP-associated gastric histological changes, and these findings suggest that HP infection may impair the protective role of beta-carotene, like vitamin C and alpha-tocopherol in the stomach(39). Colonization of the gastric mucosa with HP does not reduce the vitamin A content of gastric juice. Eradication of HP within four weeks after completed treatment does not exert a significant effect on changes in the concentration of vitamins A in gastric juice or serum(40).

VITAMIN E

Álpha-tocopherol is the major active form of vitamin E in the human body, accounting for 95% of vitamin E and is the most effective lipid soluble anti-oxidant in biomembranes. It plays an immune modulatory part and is capable of increasing natural killer cell activity. Concentrations of α-tocopherol in HP negative subjects were higher in the corpus than in the antrum or duodenum(41). This distribution of α-tocopherol is reversed in the presence of antral HP infection. These findings may reflect a mobilization of antioxidant defenses to the sites of maximal inflammation in the stomach.

In another study, vitamin E had no effect on HP growth compared to controls(42). In an experimental study performed on SD rats, oxidative stress was found to play a critical role in the augmented mucosal damage provoked by water immersion restraint stress in HP infection and that an antioxidant, μ-tocopherol, could ameliorate the aggravation of stress-associated gastric mucosal damage(43).

In another study, alpha-tocopherol was affected by HP-associated gastric histological changes, and these findings suggest that HP infection may not only impair the protective role of vitamin C, but also of alpha-tocopherol in the stomach. The presence of gastric atrophy and intestinal metaplasia was significantly associated with reduced mucosal alpha-tocopherol. Furthermore, antral mucosal alpha-tocopherol concentrations decreased progressively as antral mucosal histology changed from normal to chronic gastritis alone and finally to atrophy and intestinal metaplasia(39). Eradication of HP within four weeks after completed treatment does not exert a significant effect on changes in the concentration of vitamins E in gastric juice or serum. Despite this, it was recorded that, after eradication, vitamin E level starts to rise in gastric juice. Substitution of vitamin C and E in gastritis associated with colonization with HP has a favorable effect and may reduce the risk of malignant transformation (40).

As for the effect of vitamin E on gastric mucosal injury induced by HP infection, it is suggested that vitamin E has a protective effect on gastric mucosal injury induced by HP infection in gerbils, through the inhibition of accumulation of activated neutrophils(44).

FOLATE

A few studies have associated folate with HP infection. Some studies report a negative relation between HP infection and folate metabolism in adults. In the only study that was performed by us in children, on the contrary, we found no significant difference in folate levels between HP–positive and negative patients. Furthermore, none of our patients had a significant reduction in serum folate level(8). A decrease in folate absorption may take place as a consequence of an increment in pH and/or decrement in vitamin C concentration in gastric juice, a situation frequently observed in HP–infected patients(41).

ZINC

Relation between HP infection and zinc is not adequately researched. A protein that strongly binds to zinc has been identified on the membrane and in the cytosol of HP(45). Because zinc is absorbed

mainly in the small intestine, by binding dietary zinc in the stomach, HP may possibly contribute to serum zinc deficiency.

The only study in humans investigating relation of HP infection with serum zinc levels in adults suffering from liver cirrhosis concluded that there was no relation between HP infection and serum zinc levels(46). In a study that we performed in children, although the number of the participants was limited, we found no significant difference between the serum zinc levels of HP–positive and negative patients(8).

SELENIUM

Selenium is an essential micronutrient required by most of the organ systems in the body. The best-known function of selenium is its role as a cofactor of glutathione peroxidase, which protects membranes from oxidative damage. Selenium deficiency exposes most tissues to peroxidative damage.

Low selenium status in the plasma and gastric tissue biopsies of patients with gastric cancer been reported in the literature(47,48). In the current study, the higher concentrations of selenium in the infected gastric mucosa may be a protective response to increased oxidative stress in association with HP infection. A similar comment was made with regard to the gastric tissue of patients with mild, chronic, and erosive gastritis(47). In that case, nonspecific increase in selenium content was related to the severity of the inflammation process, and the authors proposed that the organism gives priority to tissue in which selenium is needed the most; however, the presence or absence of HP infection in these patients was not investigated. In another study(49), it was demonstrated that plasma selenium levels were similar between HP (+) gastritis and healthy controls, but in the gastric tissue selenium levels were significantly higher in HP (+) gastitis. There was statistically significant decrease in mucosal selenium levels in patients after successful HP eradication therapy(49). Authors believe that increased gastric mucosal selenium levels can be explained on the basis of elevated ROS in association with HP infection. It follows that a similar response in gastric mucosal selenium levels may occur in response to any insult that leads to increased ROS generation in the gastric mucosa. In another study, it was observed that high intake of selenium reduces growth of HP in the guinea pig(50).

CONCLUSION

HP infection might cause iron, vitamin B_{12}, and vitamin C deficiencies; however, the number of studies that examine other micronutrients are scarce. Therefore, it is a strong possibility that this bacterium causes serious or moderate micronutrient deficiencies. Especially in the developing countries, the addition of micronutrient deficiencies facilitated by HP infection to already present macronutrient problem is a great clinical and public health problem. Thus, this important public health problem could be partly resolved by the supplementation of the micronutrients, until this infection is prevented (if a vaccine is manufactured) especially in the developing world. Regular eradication of asymptomatic HP infection by current treatment regimens does not seem realistic and cost effective. However, in patients unresponsive to supplementation therapy, eradication treatment could be considered.

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