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• REVIEW •

Helicobacter pylori infection and micronutrient deficiencies

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Abstract

It is known that deficiencies of micronutrients due to infections increase morbidity and mortality. This phenomenon depicts itself conspicuously in developing countries. Deficiencies of iron, vitamins A, E, C, B12, *etc* are widely prevalent among populations living in the third world countries. *Helicobacter pylori* (*H pylori*) infection has a high prevalence throughout the world. Deficiencies of several micronutrients due to *H pylori* infection may be concomitantly present and vary from subtle sub-clinical states to severe clinical disorders. These essential trace elements/ micronutrients are involved in host defense mechanisms, maintaining epithelial cell integrity, glycoprotein synthesis, transport mechanisms, myocardial contractility, brain development, cholesterol and glucose metabolism. In this paper *H pylori* infection in associaed with various micronutrients deficiencies is briefly reviewed.

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INTRODUCTION

Helicobacter pylori (*H pylori*) is a gram negative, microaerophilic human pathogen which colonizes the gastric mucosa. Infection with *H pylori* leads to gastritis and is associated with the development of peptic ulcer disease, gastric carcinoma and lymphoma[1]. *H pylori* may be acquired at any age, and the infection persists for years once acquired. The age specific prevalence of *H pylori* infection is higher in developing countries and particularly in lower socioeconomic group[2]. In developing countries *H pylori* infection occurs early in life, and hypochlorhydria commonly seen in the malnourished predisposes them to repeated gastrointestinal infection, persistent diarrhea and malnutrition[3]. *H pylori* infection usually causes both acute and chronic inflammatory cell infiltration, leading to an increase in reactive oxygen species (ROS) which have been shown to accumulate in *H pylori* gastritis[4]. Excessive production of reactive oxygen metabolites (ROMs) by phagocytic cells is thought to contribute to mucosal lesions produced by *H pylori* infection. These are highly reactive compounds capable of combining with DNA in a number of potentially genotoxic ways[5]. Reactive oxygen species can react with the lipid-bilayers releasing peroxidation products such as malondialdehyde. These processes could lead to alterations in the structure of DNA facilitating mutations and carcinogenesis.

Nutrition is a critical determinant of the outcome of host microbe interactions through a modulation of the immune response. "Micronutrient" or "trace elements" are generally defined as constituting less than 0.01 % of body mass and are needed in much smaller amounts. Trace minerals and vitamins are essential for life and include iron (Fe), zinc (Zn), copper (Cu), nickel (Ni), *etc*. They act as essential cofactors of enzymes and as organizers of the molecular structures of the cell, e.g. mitochondria and its membrane. 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. Antioxidants play a part in gastric mucosal defense by protecting against damage caused by excessive oxygen derived free radicals. β-carotene and α-tocopherol are lipophilic and have been shown to suppress the oxidation induced by either lipophilic or hydrophilic radical species[6]. In addition, they could act as anti-carcinogens through their ability to prevent the formation of N-nitrosamines which are important in the development of gastric carcinoma[7]. These vitamins are the major oxidant scavengers in biomembranes in contrast to vitamin C, which is mainly responsible for scavenging free radicals in the aqueous phase. However, compensatory mechanisms may become defective while gastric inflammation develops from normal to chronic gastritis and finally to gastric atrophy/intestinal metaplasia, perhaps due to reduced infiltration of inflammatory cells, loss of gastric gland cells and increased ROM production.

IRON

Iron deficiency anemia affects all groups of the under privileged population in most developing countries. Iron is an essential growth factor for *H pylori*, which contains Fe in their outer membrane protein and a system for intracellular storage of iron, consisting of ferritin like molecules pfr and napA[8]. Patients with *H pylori* associated iron deficiency anemia (IDA) would have involvement of both antral and corporal mucosa when compared with controls (90 % *vs* 42.7 %; P=0.0001)[9]. Iron deficiency anemia associated with *H pylori* gastritis is characterized by a concomitant increase in median intragastric pH value >3 and lowering of intragastric concentrations of ascorbic acid. A significant percentage (43 %) of *H pylori* positive IDA patients presented atrophic changes in the gastric body, and the remaining had a superficial gastritis extended to the fundic mucosa, in contrast with *H pylori* positive controls[10]. *H pylori* eradication has also been shown to improve the absorption of other nutrients besides iron, and produce more rapid and complete clinical responses in patients with iron deficiency anemia[11].

COPPER

Copper is involved in the function of several enzymes. It is required for infant growth, host defense mechanisms, bone strength, red and white cell maturation, iron transport, *etc*. Acquired deficiency is mainly seen in infants. However, it has been diagnosed also in malnourished children and adults[12]. A

gene, copA, associated with copper transport, has been isolated from *H pylori* UA802. The adenosine triphosphatase-derived copper-transporting mechanism is employed by various *H pylori* strains[13]. As a cofactor in various redox enzymes and an essential trace metal required for the synthesis of metalloproteins, copper plays a role in the pathogenesis of *H pylori*. *H pylori* has a differential effect on some gastric mucosal scavenger enzymes of ROMs, namely mitochondrial and cytoplasmic superoxide dismutases reflected by a large increase in the cytokine inducible manganese superoxide dismutase and a decrease in the constitutive copper/zinc superoxide dismutase[14].

VITAMIN B12

The mechanisms of vitamin B12 malabsorption caused by *H pylori* infection are unclear but following are the possibilities: a) The diminished acid secretion in *H pylori* induced gastritis may lead to a failure of critical splitting of vitamin B12 from food binders and its subsequent transfer to R binder in the stomach. b) A secretory dysfunction of the intrinsic factor. c) Decreased secretion of ascorbic acid from the gastric mucosa and increased gastric pH[15,16]. Annibale *et al*, studied the prevalence of *H pylori* infection in pernicious anemia patients and have demonstrated that almost two thirds of pernicious anemia patients had evidence of *H pylori* but only those with an active *H pylori* infection had distinctively functional and histological features[17]. These findings support the hypothesis that *H pylori* infection could play a triggering role in a subgroup of pernicious anemia patients, and suggest the possibility that *H pylori* 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 *H pylori*, most likely "autoimmune" mechanisms[18]. *H pylori* 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 *H pylori* infection[19]. Food cobalamin malabsorption may occur without gastric atrophy or achlorhydria. Malabsorption can respond to antibiotics, but only in some patients[20].

VITAMIN A

Vitamin A has effects on important determinants of immune function and epithelial cell integrity such as gene expression, cellular proliferation and differentiation and also glycoprotein synthesis. Loss of integrity of the epithelial lining of mucus membranes in a vitamin A deficient state could explain its close association with increased susceptibility to infections particularly of gastrointestinal, respiratory and genitourinary tracts especially in children and pregnant women[21]. Even mild or subclinical vitamin A deficiency could induce keratinizing metaplasia of the epithelium and depletes goblet cells from mucosal linings thus causing xerosis of the membrane[22]. 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. *H pylori* infection and low β-carotene in plasma contribute to the increased risk of gastric atrophy, indicating that *H pylori* infection might be associated with low plasma β-carotene[23].

VITAMIN E

Vitamin E is composed of a group of compounds termed tocopherols and tocotrienols. α-tocopherol is the major active form in the human body, accounting for 95 % of vitamin E and is the most effective lipid soluble anti-oxidant in biomembranes. It acts as the major chain breaking antioxidant and is able to interfere with the propagation of lipid peroxidation. It plays an immune modulatory part and is capable of increasing natural killer cell activity. Concentrations of α-tocopherol in *H pylori* negative subjects were higher in the corpus than in the antrum or duodenum[6]. This distribution of α-tocopherol is reversed in the presence of antral *H pylori* infection. These findings may reflect a mobilization of antioxidant defenses to the sites of maximal inflammation in the stomach.

VITAMIN C

Vitamin C exists as ascorbic acid (AA) or dehydroascorbic acid. The stomach secretes ascorbic acid across the gastric mucosa into the gastric juice against a concentration gradient. Ascorbic acid is the reduced form of the vitamin and can act as a potent antioxidant, and is able to scavenge ROS in gastric mucosa. This has been proposed as one means by which it exerts an anti-carcinogenic effect. Ascorbic acid may also prevent formation of N-nitroso compounds in gastric juice by scavenging nitrite. It has been observed that diets poor in foods containing AA were associated with an increased risk of gastric cancer[24]. Wei-cheng *et al* showed that presence of *H pylori* infection at the baseline and smoking were strongly associated with progression to dysplasia or gastric cancer, whereas the risk of progression was decreased by 80 % among subjects with baseline ascorbic acid levels in the highest tertile compared with those in the lowest tertile[25]. A number of studies have demonstrated that gastric juice but not gastric mucosal AA levels were reduced in the presence of *H pylori* gastritis and that successful eradication restored the juice/plasma AA ratio[23, 26]. The lower plasma AA concentration in *H pylori* 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[27]. In some studies no difference was found in the gastric juice AA concentration between patients with antral-limited gastritis and *H pylori* negative healthy controls, while lower AA levels were observed in patients with gastric body involvement and increased pH[28]. 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 hypochlorhydria[29,30]. It has been demonstrated that eradication of *H pylori* could lead to a reduction in ROS activity in gastric mucosa[31]. Ascorbic acid has also been shown to inhibit *H pylori* urease activity and growth *in vitro*[32]. *H pylori* infection associated low gastric juice-ascorbic acid levels return to normal after successful eradication of the infection[33]. A study of antibiotic treatment failure showed that compliant patients in whom *H pylori* infection did not clear had lower baseline plasma and gastric juice vitamin C concentrations than patients whose infection was cleared[26].

In developing countries micronutrient deficiencies facilitated by *H pylori* infection are a clinical and public health problem. It is essential to define the precise extent of the problem. Several micro and macronutrient deficiencies could be concomitantly present in the population with several other deficits. They will require correction to achieve significant effects on the over all health of the population.

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