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The Effects of Helicobacter Pylori Infection on Nutrition Status and Metabolism

Helicobacter Pylori Enfeksiyonunun Beslenme Durumu ve Metabolizma Üzerine Etkileri

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ABSTRACT

H.pylori infection, which is common in the world as well as in our country and has been identified as a group 1 carcinogen by the World Health Organization (WHO) is a Gram negative pathogen. Low socio-economic level, low consumption of fruits and fresh vegetables, increased consumption of fast food, tobacco use and poor oral hygiene are reported risk factors for *H.pylori* infection. It is considered that disruption of the absorption of some micronutrients affected the appetite and food intake because of due to changing ghrelin and leptin hormone levels in the presence of *H.pylori*. Also, some studies showed that *H.pylori* infection is effective in the development or progression of gastrointestinal diseases, metabolic syndrome, insulin resistance, diabetes and diabetes complications. Some foodstuffs and nutrients are thought to have infection-protective and/or having preventive effects and recent studies have focused on these subject. It is mentioned that especially fresh fruits, vegetables and some probiotic formulation can play an important role in the treatment of *H.pylori* infection. The relationship between nutrition and *H.pylori* infection and its metabolic effects of *H.pylori* will be discussed in this review.

Key words: *Helicobacter pylori*; ghrelin; appetite; nutrition; nutrients

ÖZET

H.pylori ülkemizde ve dünyada yaygın olarak görülen ve Dünya Sağlık Örgütü (DSÖ) tarafından 1. sınıf karsinogen olarak tanımlanan Gram negatif bir patojendir. Düşük sosyo ekonomik düzey, taze sebze, meyve tüketiminin az ve fast food tüketiminin fazla olması, yetersiz ağız hijyeni ve sigara kullanımının *H.pylori* enfeksiyonuna yakalanma riskini artırdığı bildirilmektedir. *H.pylori* varlığında ghrelin ve leptin hormonlarının seviyelerindeki değişiklik nedeniyle iştah ve besin alımını etkilemekte, bazı mikro besin öğelerinin emilimini bozmaktadır. Ayrıca yapılan çalışmalarda gastrointestinal sistem hastalıkları, metabolik sendrom, insülin direnci, diyabet ve diyabetin komplikasyonlarının gelişimi veya ilerlemesinde *H.pylori* enfeksiyonunun etkili olduğu gösterilmektedir. *H.pylori* enfeksiyonunda bazı besinlerin ve besin öğelerinin koruyucu ve/veya önleyici etki gösterdiği düşünülmekte ve bu konuda yapılan çalışmaların sayısı her geçen gün artmaktadır.

Özellikle taze meyve, sebzeler ve bazı probiyotik formülaların *H.pylori* enfeksiyonu tedavisinde önemli rol oynadığından bahsedilmektedir. Bu derlemede de *H.pylori* enfeksiyonunun beslenme durumu ile ilişkisi ve metabolizma üzerine etkileri irdelenecektir.

Anahtar kelimeler: *Helicobacter pylori*; ghrelin; iştah; beslenme; besin öğesi

Introduction

Known as a Gram negative pathogen, *H.pylori*, which is common in the world as well as in our country, affects more than about 50% of population¹. More than 80% of the population in developing countries and 20–80% in developed countries suffers from this bacteria and its effects². In Turkey, the frequency of *H.pylori* infection have reported to be approximately 70–80% according to the recent studies^{3,4}. Urea breath test, stool antigen scanning and endoscopic evaluation is used in the diagnosis of *H.pylori* infection⁵. The incidence of infection has been increasing with age since the early years and those who have lived under poor socioeconomic conditions especially in childhood are at a more risk of *H.pylori* infection in the following years⁶. Low socio-economic status, low consumption of fresh vegetables and fruits, increased fast food consumption, poor oral hygiene and tobacco use are known as risk factors for *H.pylori* infection^{3,4,7–10} as well as alcohol use but, present data are contradictory^{9,11}.

H.pylori, identified as a group 1 carcinogen by the WHO plays an important role especially in the development of gastric cancer and mucosal-associated lymphoid tissue lymphoma⁵. *H.pylori* colonize in the epithelial cell lining of the stomach by affecting the human gastric flora that disrupts the gastric mucosal integrity. The presence of bacteria affect the levels of ghrelin and leptin hormones results in negative effects on appetite and food intake¹². Some micronutrient malabsorptions, especially folate,

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homocysteine and iron deficiency can develop in the presence of *H.pylori* infection².

Specific foods and nutrients have protective and/or preventive effects in the development or progression of the infection. Especially fresh vegetables and fruits can play an important role in the treatment of *H.pylori* infection⁵. Honey and green/black tea consumption has also been shown to be associated with reduced prevalence of *H.pylori* infection¹³.

H.pylori infection has an important role in terms of public health because of its worldwide distribution and high level of prevalence and the importance of associated pathologies according with gastroduodenal diseases¹⁴. Besides the gastrointestinal diseases, *H.pylori* can be associated with diabetes and development of diabetic complications, metabolic syndrome and insulin resistance also¹⁵. So, this paper aims to discuss the relationship between nutrition and *H.pylori* infection and its metabolic effects of *H.pylori*.

Pathophysiology of H.pylori and Its Effect on Appetite

H.pylori colonizes in the gastric epithelium and has an important urease activity that leads to the production of ammonia in order to protect itself from gastric acidity. It also produces enzymes such as glucosulfatase, phospholipase A2 and C, which play an important role in the development of gastric mucosal damage. *H.pylori* leads to an inflammatory response through the gastric epithelium with the production of proinflammatory cytokines such as interleukin 8 and interleukin 1 β ². *H.pylori* has various virulence factors that play an important role in the pathogenesis of infection. Especially vacuolating toxin A (Vac-A) and cytotoxin-associated gene A (Cag-A) positive are associated with greater pathogenicity and more severe disease^{2,14}. CagA positive strains cause a stronger inflammatory response of gastric mucosa with increasing of proinflammatory cytokines. On the other hand, the VacA gene is responsible for vacuolization and apoptosis of gastric epithelial cells. *H.pylori* infection reduces the gastrointestinal hormones and the absorption or bioavailability of essential nutrients and *H.pylori* is associated with metabolic balance also. Additionally, *H.pylori* infection plays a role in changing ghrelin and leptin levels².

Ghrelin peptide is constituted of 28 amino acids with a fatty acid chain modification (octanoyl group) on the third amino acid. Ghrelin peptide was originally isolated from the stomach, but ghrelin protein has also been

identified in other peripheral tissues. The acylated forms of ghrelin have been recognised as the major active orexigenic molecules regulating energy balance. When studying the effects of ghrelin on energy balance, differential influences of the acylated and non-acylated forms of the peptide must be considered^{16,17}. While active form of ghrelin regulates growth hormone-releasing and food intake, inactive form of ghrelin is effective on cell proliferation and adipogenesis. Acylated ghrelin increases the food intake and involves in positive energy balance. On the other hand, des-acylated ghrelin decreases food intake and devoid of any endocrine activities^{18,19}.

The presence of *H.pylori* on the gastric mucosa affect the levels of ghrelin and leptin hormones results in negative effects on appetite and food intake. Leptin concentrations were higher, ghrelin concentrations and ghrelin/obestatin ratios were lower in the *H.pylori*-positive group than in the *H.pylori*-negative group. Additionally, appetite was decreased in *H.pylori* positive group^{12,20}. After the eradication of *H.pylori*, ghrelin levels and appetite was increased that results in body weight gain^{21,22}. Ghrelin levels and body mass index (BMI) was lower in *H.pylori* positive group than *H.pylori* negative group in older ages and *H.pylori* infection may be one of the underlying causes of malnutrition in the elderly²³.

The relationship between *H.pylori* infection and gastric hormones has also been investigated. The effect of *H.pylori* on ghrelin production has been associated with *H.pylori* virulence. The extent of gastric damage and level of the infection has been thought to play a key role in the modulation of ghrelin levels. Increased leptin and gastrin levels, decreased plasma ghrelin levels and a negative effect on appetite and dyspeptic symptoms were found to be the consequences of gastric mucosal damage due to *H.pylori*².

H. Pylori and Absorption Disorders

H.pylori in the gastric mucosa can cause a malabsorption of certain vitamins and minerals. In several studies, vitamin B₁₂ and folate deficiency was found in *H.pylori* positive patients compared with healthy individuals^{2,24,25}. Reduction of gastric acid secretion, deficiency of ascorbic acid and blocking of iron binding protein lead to iron deficiency in patients with *H.pylori*²⁶. Iron deficiency and anemia were seen more frequently especially in children^{27,28}. Hypochlorhydria (reduction of HCL production in stomach) decreases iron absorption by reducing the availability of ascorbic acid. So that, it decreases the absorption of non-heme

iron leading to the reduction in the transformation of ferric to ferrous form and using iron by *H.pylori* strains as a growth factor in patients with *H.pylori*. It may be the main reason for iron deficiency². Absorption can be decreased due to the change in gastric physiology²⁹. Also, the increase in gastric pH reduces the iron solubility and iron absorption will be affected by reducing the bioavailability of vitamin B₁₂ and folic acid³⁰.

The presence of *H.pylori* on the gastric mucosa affect the levels of vitamin C. Induced by *H.pylori*, chronic gastritis may be associated with hypochlorhydria and accompanied by low levels of vitamin C in plasma and gastric juice both in adults and children. Vitamin C levels in whole blood, plasma and the gastric juice pH in Korean children are closely related to the severity of *H.pylori* infection and the histologic changes in the stomach³¹. High concentration of vitamin C in gastric juice might inactivate *H.pylori* urease, the key enzyme for the pathogen's survival and colonization into acidic stomach. Moreover higher prevalence of *H.pylori* infection is related with low serum Vitamin C levels and gastric juice^{29,32}.

Vitamin B₁₂ deficiency due to food-cobalamin malabsorption is associated with gastritis originating from *H.pylori*. Decreased secretion of intrinsic factor by parietal cells may be the probable cause of cobalamin malabsorption and atrophic gastritis secondary to *H. Pylori* infection is one explanation for vitamin B₁₂ malabsorption. Low acid-pepsin secretion results in decreased release of free vitamin B₁₂ from food proteins and/or promotes overgrowth of bacteria that bind vitamin B₁₂ for their own use in the hypochlorhydric stomach and small intestine^{33,34}. In a study, *H.pylori* was detected in 56% of 138 patients with vitamin B₁₂ deficiency and eradication of *H.pylori* infection successfully improved anemia and serum vitamin B₁₂ levels in 40% of 77 infected patients³⁵.

There is a concern about the relationship between β -carotene bioavailability and *H.pylori* infection. In the presence of *H.pylori*, hypochlorhydria and achlorhydria significantly decreased β -carotene bioavailability³⁶. *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 -carotene³⁷.

Effects of Nutrition on the Prevention and Eradication of *H. Pylori* Infection

Some nutritional regimens may reduce the virulence of *H.pylori* infection. Some food items like fruits and

vegetables, special spices, bee products (e.g. honey and propolis) and probiotics are supposed to have positive health impacts⁵. Fruits and vegetables have been mentioned as anti *H.pylori* agents according to their content of antioxidant compounds like bioflavonoids, phytochemicals and ascorbic acid as well as honey, which is known to have antimicrobial activity due to its hydrogen peroxide and non-peroxide components. Also, green tea has positive effects on the prevention of *H.pylori* due to its polyphenolic catechins content⁵. Additionally, tea catechins may have antibacterial effects against *H.pylori* and therapeutic effects against gastric mucosal injury³⁸. Foods/drinks containing polyphenols such as red wine and green tea have an inhibiting effect on the urease activity of *H.pylori* and thus being effective on mitigating the related symptoms³⁹. There was a positive correlation between daily consumption of sausage, mayonnaise, soft drinks and burgers with the incidence of *H.pylori* infection. Lower consumption of fresh fruits and vegetables are an important risk factor for the development of *H.pylori* infection. In addition, fish, honey, olive oil, peans and beans are suggested to have negatively correlation with *H.pylori* infection⁸.

Increased salt consumption is a risk factor for gastric cancer and associated with *H.pylori*. *H.pylori* infected individuals with a higher salt consumption had a risk of early gastric cancer 10 fold more than *H.pylori* negative individuals with a low salt consumption, and the consumption of fruits and vegetables reduced the risk of gastric cancer⁴⁰.

Milk and dairy products are another food items supposed to have protective effects against *H.pylori* infection and may support the treatment. Especially fermented milk-based probiotics, bovine lactoferrin, immunoglobulin-enriched α -lactalbumin and whey protein have been shown to have beneficial effects on the treatment of *H.pylori*^{5,41}. Because of limited data on the benefits of milk and dairy products on *H.pylori*, further studies should be performed to determine the optimal dose and duration of these food items providing clinically useful effects.

Recent studies have focused on broccoli sprouts, manuka honey, blackcurrant oil and omega-3 oil. Isothiocyanate-rich broccoli sprout was found the most effective food against *H.pylori*. Additionally, the broccoli sprouts are most effective when used alone it has sinergetic effect with omega-3 or manuka honey^{42,43}. Also, these nutrients may decrease inflammation related to *H.pylori* by blocking the release of IL-8 from gastric epithelial cells⁴³. The

bacteriostatic effects of isothiocyanate sulforaphane (SF), an abundant compound in broccoli sprouts, have been explained by two probable mechanisms, a direct effect on *H.pylori* and an indirect effect by triggering the cytoprotective response³⁹.

Probiotics are defined as 'live microorganisms, which, when administered in adequate amounts, confer a health benefit on the host'. Using probiotics in the treatment of *H.pylori* can reduce the side effects and using probiotics more than two weeks and including lactobacillus significantly enhanced the efficacy of the eradication⁴⁴. Probiotics have shown their positive effects via maintaining gastric mucosal barrier and acidity and providing protection against the harmful effects of *H.pylori* infection. In addition, probiotics provide a better compliance to the treatment as a result of reduced side effects to the intestines⁴⁵. Mechanisms explaining the effects of probiotics on *H.pylori* are described as; competing against *H.pylori* on the gastric mucosal epithelium, providing the production of anti *H.pylori* substances such as acetic acid, propionic acid and butyric acid, supporting the regulation of immune functions and immunoglobulin-A secretion to improve mucosal defensive ability and strengthening the bonds between epithelial cells⁴⁴. Although probiotics have beneficial effects on *H.pylori*, the impacts on *H.pylori* eradication are still controversial due to insufficient data on the effective strain and dosage of probiotics⁴⁶.

Nutritional Status After the Eradication of H.pylori

There are some alterations in gastric hormone levels after the treatment of *H.pylori*. After the eradication therapy, appetite and body weight had increased due to the elevation of plasma ghrelin^{47,48}. Eradication therapy of *H.pylori* is associated with increased ghrelin levels and growth in children with *H.pylori* positive⁴⁹.

After the treatment of *H.pylori*, there are some changes in the blood lipid levels. After the treatment of *H.pylori* infection, body weight and serum levels of total cholesterol, total protein and albumin had significantly increased. Also reported that incidence of hyperlipidaemia significantly increased and pancreatic function significantly improved⁵⁰.

Some micronutrient malabsorptions improved after the eradication. Eradication therapy with iron supplementation has been found to be better than using only iron supplementation to provide a significant increase in serum iron, serum ferritin and hemoglobin levels in *H.pylori*

positive patients with iron deficiency anemia⁵¹. Also, eradication therapy with iron and folic acid supplementation resulted better than only iron and folic acid supplementation among *H.pylori* infected pregnant women with IDA⁵². Additionally, *H.pylori* infection is associated with IDA and after eradication of *H.pylori* is followed by increasing of serum ferritin and hemoglobin levels in adolescent girls⁵³. In a study, evaluated the effects in homocysteine and cobalamin levels after the eradication of *H.pylori*, was found that eradication therapy associated with increasing of cobalamin levels and decreasing of homocysteine blood levels in elderly patients with cobalamin deficiency⁵⁴. Eradication of *H.pylori* is effective also in the absorption of vitamin B₁₂⁵⁵.

Relationships With Other Diseases of H.Pylori Infection

H.pylori infection is related with chronic gastritis, peptic ulcer, development of gastric cancer. Also, complications of gastrointestinal diseases. *H.pylori* uses the enzyme urease to convert urea to carbon dioxide and ammonia in the stomach. Carbon dioxide and ammonia having toxic effect for gastric mucosal epithelial cells and elevating acidic pH of the gastric lumen and impairing gastric epithelial functions such as mucus secretion. *H.pylori* is an important risk factor in development of peptic ulcer disease and chronic gastritis due to damage in the gastric mucosa⁵.

H.pylori is effective in the etiology 95% of duodenal ulcer and 70–85% of stomach ulcer. Gastric cancer usually develops in atrophic gastritis and the risk of gastric cancer in patients with atrophic gastritis is 5–9 fold more than the normal population⁵⁶. The issue that the individuals infected with *H.pylori* develop chronic gastritis is well known, the risk of atrophic gastritis and malignancies is not clear in these patients. However, *H.pylori* induced stomach ulcers and intestinal metaplasia⁵⁷.

H.pylori is also associated with metabolic syndrome, insulin resistance, diabetes and the development of diabetic complications as well as gastrointestinal disease¹⁵. The presence of *H.pylori* infection in patients with diabetes, glucose and lipid absorption is affected by gastrointestinal inflammation induced by *H.pylori* that may be a risk factor for ensuring blood glucose regulation in diabetic patients⁵⁸. The presence of *H.pylori* infection in diabetic individuals is associated with microalbuminuria and albumin/creatinine ratio⁵⁹. Additionally, inflammation which is caused by *H.pylori* is a risk factor for cardiovascular diseases⁶⁰. Some mechanisms such as activation of proinflammatory and vasoactive components,

production of reactive oxygen species and changed ghrelin and leptin levels may explain the relationship between *H.pylori* and metabolic syndrome and insulin resistance¹⁵. *H.pylori* infection was significantly associated with metabolic syndrome, lower HDL, higher systolic blood pressure and higher LDL levels⁶⁰.

The relationship between *H.pylori* and obesity is complex. Obesity and metabolic syndrome are based on mostly genetic and lifestyle habits in individuals with *H.pylori* negative². Some studies are suggested that the risk of *H.pylori* doesn't increase in obese individuals. Also, the presence of CagA antibodies and *H.pylori* bacteria have been shown not to be associated with BMI or serum leptin levels^{61,62}. However, increase of appetite and BMI are associated with elevating plasma ghrelin levels after *H.pylori* eradication⁴⁷.

In the etiology of ischemic heart disease, the *H.pylori* is one of the frequently investigated issue. It can cause ischemic heart diseases by inducing the platelet activation and aggregation⁶³. Also, the presence of folate deficiency is reported to be an another reason for the risk of ischemic stroke and myocardial cases seen in patients with *H.pylori* infection⁶⁴.

Neurological diseases are also thought to be associated with *H.pylori*. Neurological damage in Parkinson's patients is suggested to be associated with *H.pylori*¹⁵. Mitochondrial damage and autoimmunity caused by *H.pylori* is supposed to play a triggering factor for the mechanisms of Parkinson's disease⁶⁵. There is a relationship between Alzheimer and *H.pylori* infection⁶⁶ and an improvement in cognitive and functional status in Alzheimer's disease patients in the case of *H.pylori* eradication was successful⁶⁷.

H.pylori infection plays a role in the pathogenesis of several skin diseases. In particular, the prevalence of *H.pylori* infection was reported to be high in patients with urticaria and it is associated with an increased risk of chronic urticaria⁶⁸. Acne rosacea, which is associated with *H.pylori* and gastritis, is another skin disease. *H.pylori* is associated with the aetiology of rosacea, as a triggering factor and *H.pylori* eradication treatment provides symptomatic relief in patient with acne rosacea^{64,69}.

H.pylori infection is related with reduced growth rate in older children and exposure to *H.pylori* infection in early childhood causes malnutrition and growth retardation in particular in the presence of insufficient food intake⁷⁰. *H.pylori* infection can lead to a series physiological changes that influence morbidity and mortality in

childhood. Hypochlorhydria is associated with *H.pylori* infection in adults and children. Hypochlorhydria leads to malabsorption of several nutrients and increases susceptibility to enteric infections such as giardiasis, cholera, typhoid and nontyphoidal salmonellosis. These infections lead to diarrhea which may lead to malnutrition and growth retardation in children².

Conclusion

H.pylori infection affects 50% of the world's population with the prevalence being the highest in developing countries¹. *H.pylori* is associated with several diseases especially gastrointestinal system disease. In the presence of bacteria, results in malabsorption and malnutrition causing changes in appetite via affecting gastrointestinal hormone levels^{12,15,19}. As a consequences of malabsorption, bioavailability of some micronutrients decreases. In particular iron, vitamin B₁₂ and folic acid deficiency seen in patients with *H.pylori* infection^{2,43}. Certain foods and nutrients are effective for the prevention and the eradication therapy of *H.pylori*. In order to achieve the best results in preventing the disease, promoting healthy diets and lifestyle strategies must fully recognize the essential role of healthy nutrition throughout the entire life course.

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