Review paper

Diet and *Helicobacter pylori* infection

Łukasz Hołubiuk, Jacek Imiela

Department of Social Nursing, Medical University of Warsaw, Warsaw, Poland

Gastroenterology Rev 2016; 11 (3): 150–154
DOI: 10.5114/pg.2016.61487

Key words: *Helicobacter pylori*, diet, phytopharmaceuticals.

Address for correspondence: Łukasz Hołubiuk MD, Department of Social Nursing, Medical University of Warsaw, 27 Ciolka E. St, 01-445 Warsaw, Poland, phone: +48 694 057 724, e-mail: lholubiuk@wp.pl

Abstract

Helicobacter pylori infection has accompanied man for thousands of years. In some infected patients, a complex and dynamic pathogen-host reaction triggers pathogenic pathways resulting in development, *inter alia*, of atrophic gastritis, peptic ulcer disease (both gastric and duodenal), gastric adenocarcinoma, and MALT lymphoma. Large-scale eradication therapy is associated with a rapid increase in antibiotic resistance, gut flora composition disturbances, and increased risk of development, *inter alia*, of paediatric infectious diarrhoeas, atopic diseases, and oesophageal adenocarcinoma. Our diet contains many substances with potent antibacterial activity against *H. pylori*. Dietary interventions enable a decrease in *H. pylori* colonisation and result in a decrease in gastritis prevalence, thus potentially lowering the risk of gastric adenocarcinoma development.

Introduction

Despite the fact that research on *Helicobacter pylori* and its role in pathogenesis of gastric and duodenal diseases was initially conducted in the second half of the 19th century, scientific breakthroughs were not observed until the 1980s. At that time, Robin Warren and Barry Marshall from the University of Perth published in Lancet the results of their studies on so-called *Campylobacter*-like organisms (CLOs) and their association with gastritis. The actual amount of publications makes *Helicobacter pylori* the second, after *Escherichia coli*, most commonly studied and described pathogen [1].

Helicobacter pylori (*Campylobacterales* order) is a helical, Gram-negative bacillus that colonises the human's oral cavity and stomach. In developing countries, the rate of colonised subjects amounts to 70–80%, whereas in developed countries this rate is approximately 13% to 50% of the population [2].

Diseases associated with *Helicobacter pylori* infection

In the majority of patients, *H. pylori* infection is asymptomatic, in the form of mild gastritis without hydrochloric acid secretion disorders. The ulcerative phenotype of *H. pylori* infection, observed in 15–20% of infected persons, is associated with an increased inflammation of pre-pyloric stomach, hypergastrinaemia, increased hydrochloric acid secretion, and peptic ulcers (both gastric and duodenal). The gastric cancer phenotype of *H. pylori* infection, observed in approximately 1% of infected persons, is characterised by an increased inflammation within the gastric corpus, mucous membrane atrophy in pre-pyloric stomach, decreased hydrochloric acid secretion, and significantly increased risk of gastric cancer development [3]. Indications for eradication therapy, apart from gastric cancer and peptic ulcer disease, are as follows: MALT lymphoma, atrophic gastritis, dyspepsia, immune thrombocytopenia, iron deficiency anaemia of unknown origin, B_{12} vitamin deficiency and previous treatment of gastric cancer or MALT lymphoma, as well as family history of those malignancies. Moreover, eradication therapy can be realised on the patient's request [4].

In recent years, a potential role of *H. pylori* infection in the development of, *inter alia*, non-alcoholic steatohepatitis, insulin resistance, type 2 diabetes mellitus, colon adenomas and adenocarcinoma, bile ducts cancer, dementia, psoriasis, and chronic utricaria has also been recognised [5, 6].

Eradication therapy

Pharmacological therapy of *Helicobacter pylori* infection is based on at least two antibiotics combined with a double dose of proton-pump inhibitor (PPI). The esti-

mated efficacy of this therapy is 82% (triple regimen) to 92% (sequential therapy). New therapeutic regimens, containing fluoroquinolones (levofloxacin and moxifloxacin), exhibit high efficacy (85% and 90%, respectively) and good safety profile, but their use is limited by high costs [7]. The problem of eradication therapy is the abruptly increasing resistance of *H. pylori* to the most commonly used antibiotics. Moreover, eradication therapy requires multiple-day complex drug administration and is associated with side effects, mainly gastrointestinal (e.g. diarrhoea, nausea, and taste disturbances), which can lead to treatment discontinuation. In addition to antibiotic resistance, it is believed that lack of observance to doctor's prescriptions is the main cause of eradication failure.

Long-term antibiotic treatment results in qualitative and quantitative modification of gut flora, selection of resistant strains of *H. pylori* and other intestinal bacteria, enhances colonisation of GI tract by *Candida* fungi, and can lead to severe *Clostridium difficile* infection [8].

Helicobacter pylori has accompanied man for at least 58,000 years [9]. More and more data indicates that bacterial colonisation, as well as long-term negative consequences, may also provide some benefits to the host. It is known that *H. pylori* infection can mitigate the course of infection with other more virulent intestinal pathogens, e.g. *Vibrio cholerae* [10] and may protect against diarrhoeagenic gastrointestinal infections in children [11]. Reports on atopic asthma and other atopic diseases prevalence reduction in the *H. pylori*-infected population as well as on the reduction of coeliac disease, irritable bowel syndrome (IBS), gastro-oesophageal reflux disease (GORD), and oesophageal adenocarcinoma frequency were also published [12].

An eradication therapy has been known for last few decades. Long-term disruptions of long-lasting association between pathogen and host as well as 'profit and loss account' for normal population are difficult to predict.

Alternative methods of *Helicobacter pylori* infection treatment

In light of the above considerations, questions concerning the potential association between complete eradication and *H. pylori* infection-associated disease reduction as well as the link between reduction of colonisation with methods other than antibiotics and potential achievement of predefined goals, especially gastric cancer development reduction, seem to be of key importance. The main studies on alternative therapies include substances of plant origin, probiotics, peptides, and polysaccharides [13]. Although alternative therapies do not allow for permanent *H. pylori* eradication, they reduce bacterial colonisation, the degree of stomach inflammation, and mucosal atrophy [14, 15]. Some methods enhance the efficacy of traditional antibiotic treatment and simultaneously prevent antibiotic side effects [16–18].

In this paper, I have focused on readily available food products with proven bacteriostatic or bactericidal properties against *H. pylori*, highlighting those in which its anti-*H. pylori* effectiveness *in vivo* was confirmed in humans. Relatively low cost, overall availability, and lack of side effects are the main advantages of such methods.

Lactoferrin

Lactoferrin is a glycoprotein of the transferrin family, exhibiting antibacterial properties. It chelates iron ions, and thus limits the availability of this element to bacteria. Lactoferrin is present in mothers' and cow's milk, neutrophils' granules, saliva, and tears. It is an element of non-specific immunity.

In their study, Wang *et al.* demonstrated in a mouse model that lactoferrin decreased bacterial colonisation and *H. pylori*-induced gastritis [14]. In a meta-analysis of prospective randomised trials assessing the impact of lactoferrin addition to triple or quadruple eradication regimens, lactoferrin significantly increased the rate of effective eradications and decreased side effect severity [16]. Beside a reduction in the availability of iron ions, lactoferrin may exhibit synergistic effects with antibiotics due to facilitation of their penetration through the cell membrane.

Isothiocyanates

In traditional medicine, sauerkraut juice has been considered as an efficacious remedy for peptic ulcer disease for centuries. Brassica vegetables (among others cauliflower, swede, headed cabbage, rape, radish) contain substances called isothiocyanates. The above-mentioned substances exhibit anti-cancer activity, such as: apoptosis induction, inhibition of cellular proliferation, and modulation of liver cytochromes involved in carcinogen metabolism. In a prospective trial involving approximately 18,000 Chinese patients, an association between the risk of malignancy occurrence, *inter alia*, gastric cancer, and urine isothiocyanate metabolite concentration was assessed. During the 16-year observation concerning a group of patients with high levels of urine isothiocyanates metabolites, the risk of gastric cancer occurrence was lower. This effect was independent of the body mass index (BMI) value; however, it was not observed in smokers and patients with regular alcohol intake. The authors believe that the protective effect of isothiocyanates should be attributable, *inter alia*, to their bactericidal activity against *H. pylori* [19].

Sulforaphane, the highest concentrations of which (in the form of a precursor called glucoraphanin) are observed in broccolis and their sprouts, is one of the isothiocyanates inhibiting growth of *H. pylori*. Sulforaphane also exhibits in vitro bactericidal activity against *H. pylori* (MIC – 2 µg/ml), including clarithromycin-resistant strains [20]. In the study by Yanaka *et al.* involving asymptomatic patients with confirmed *H. pylori* infection, a broccoli sprout intake of 70 g/day (containing 420 µmol of glucoraphanin) resulted in significant decrease of colonisation intensity, which was assessed in urea breath test and *H. pylori* antigen stool test. This therapy was well tolerated, and no adverse effects associated with broccoli sprouts intake were reported [21].

Phenolic derivatives

Many fruits exhibit *in vitro* bacteriostatic activity against *H. pylori*. It is believed that the antibacterial activity of fruit extracts results from their content of phenolic derivatives [22]. Highbush blueberry extract exhibits *in vitro* activity reducing *H. pylori* adhesion to mucous, erythrocytes, and gastric epithelial cell culture. In their study, Chatterjee *et al*. proved that raspberry, strawberry, blackberry, and bilberry extracts demonstrate potent bacteriostatic activity against clarithromycin-resistant *H. pylori* strains [23].

Zhang *et al*. conducted a prospective randomised double-blinded trial involving 189 adults with *H. pylori* infection, who were drinking 250 ml of blueberry juice during a 90-day period. In 14.46% of patients, urea breath test was negative on the 35th day. The above-mentioned effect was also maintained on the 90th day [24].

Honeys

Antibacterial activity of honeys is attributable, *inter alia*, to their high osmolarity, and low pH and hydrogen peroxide content. Some types of honeys, such as oak tree and manuka honeys, exhibit potent *in vitro* bacteriostatic activity against *H. pylori* and inhibit urease activity. In the study assessing nutrition habits of 150 patients with dyspepsia, honey intake at least once a week was associated with significantly lower prevalence of *H. pylori* infection [25].

Oils and fatty acids

In 1994, Thompson *et al*. demonstrated that polyunsaturated fatty acids, omega-3 and -6, inhibit *in vitro* growth of *H. pylori* [26]. Moreover, oils of plant origin contain many polyphenols exhibiting bacteriostatic activity against *H. pylori*. In laboratory conditions, the following food products exhibit bacteriostatic activity against *H. pylori*: blackcurrant seed oil, fish oil, carrot seed, or grapefruit seed oils [27].

In their prospective trial, Castro *et al*. demonstrated the bacteriostatic activity of olive oil [28], whereas Ito *et al*. in their Japanese study indicated that polyunsaturated fatty acids intake decreases the prevalence of atrophic gastritis [15].

Probiotics

Certain probiotic strains exhibit antibacterial activity resulting from, *inter alia*, their capability to modify immunologic response of the host, secreting antibacterial substances such as lactic acid and disturbing bacterial adherence mechanisms [29].

A systematic review of five randomised controlled trials demonstrated that the addition of *Sacharomyces boulardii* to the triple *H. pylori* eradication therapy was associated with increased eradication rate and diminished incidence of gastrointestinal side effects [17]. In the study by Armuzzi *et al*., supplementation of Lactobacillus GG along with triple therapy did not affect the eradication rate but was associated with reduction of treatment-related side effects [18].

A number of diet components have been shown to have potential anti-*H. pylori* activity in *in vitro* and animal models.

Thus far, the outcomes in human trials have been mixed. Garlic, vitamin C and E, green tea, red wine, and liquorice have been most commonly investigated as potential therapeutic agents [13]. Further well-designed clinical trials are required to determine their effectiveness in affected populations, as a treatment option and preventive measure.

Summary

The understanding of the mechanisms and factors determining asymptomatic and symptomatic course of *H. pylori* infection and its long-term effects is the key to selection of patients with potential benefit from eradication therapy. Treatment of all *H. pylori* colonised populations seems to be less probable and could be potentially associated with negative effects within asymptomatic carriers. Currently, the agents used in eradication regimens are associated with many negative effects, including rapidly increasing antibiotic resistance.

The possibility of *H. pylori* infection treatment with food products seems to be a very attractive option due to relatively low cost, availability, and lack of adverse effects. At present, most of the data confirms the antibacterial activity of broccoli sprouts, highbush blueberry juice, and some types of plant oils. Keenan *et al.*

[30] obtained promising results from their studies assessing *in vitro* effect of the combined use of different substances of plant origin with established anti-*H. pylori* activity. A synergistic effect, *inter alia*, of broccoli sprout extract and blackcurrant seed oil was demonstrated. Despite the fact that many studies confirm the antibacterial activity of substances contained in food products, the low number of prospective randomised trials assessing their use in clinical practice is striking. Lack of patentability and failure in achievement of permanent eradication, seen in previous studies, are the potential reasons for the above described situation. However, from the population's health perspective, reduction of *H. pylori* colonisation intensity without the use of antibiotic treatment seems to be a promising alternative.

Conflict of interest

The authors declare no conflict of interest.

References

1. Kidd M, Modlin IM. A century of Helicobacter pylori: paradigms lost-paradigms regained. Digestion 1998; 59: 1-15.
2. Palateiro B, Bastos A, Ferro A et al. Prevalence of Helicobacter pylori infection worldwide: a systematic review of studies with national coverage. Dig Dis Sci 2014; 59: 1698-709.
3. Bartnik W. Clinical aspects of Helicobacter pylori infection. Pol Arch Med Wewn 2008; 118: 426-30.
4. Bartnik W, Celińska-Cedro D, Dzieniszewski J, et al. Wytyczne Polskiego Towarzystwa Gastroenterologii dotyczące diagnostyki i leczenia zakażenia Helicobacter pylori. Med Prakt 2014; 5: 46-60.
5. Mogaddam R, Yazdanboz A, Ardabili N, et al. Relationship between Helicobacter pylori and idiopathic chronic urticaria: effectiveness of Helicobacter pylori eradication. Postep Derm Alergol 2015; 32: 15-20.
6. Franceschi F, Tortora A, Gasbarrini G, et al. Helicobacter pylori and extragastric diseases. Helicobacter 2014; 19 Suppl. 1: 52-8.
7. Li BZ, Threapleton DE, Wang JY. Comparative effectiveness and tolerance of treatments for Helicobacter pylori: systematic review and network meta-analysis. BMJ 2015; 351: h4052.
8. Adamsson I, Nord CE, Lundquist P, et al. Comparative effects of omeprazole, amoxycillin plus metronidazole versus omeprazole, clarithromycin plus metronidazole on the oral, gastric and intestinal microflora in Helicobacter pylori-infected patients. J Antimicrob Chemother 1999; 44: 629-40.
9. Linz B, Balloux F, Moodley Y, et al. An African origin for the intimate association between humans and Helicobacter pylori. Nature 2007; 445: 915-8.
10. Mattsson A, Lonroth H, Quiding-Jarbrink M, et al. Induction of B cell responses in the stomach of Helicobacter pylori-infected subjects after oral cholera vaccination. J Clin Invest 1998; 102: 51-6.
11. Rothenbacher D, Blaser MJ, Bode G, et al. Inverse relationship between gastric colonization of Helicobacter pylori and diarrheal illnesses in children: results of a population-based cross-sectional study. J Infect Dis 2000; 182: 1446-9.
12. Lin D, Koskella B. Friend and foe: factors influencing the movement of the bacterium Helicobacter pylori along the parasitism-mutualism continuum. Evol Appl 2015; 8: 9-22.
13. Fahey JW, Stephenson KK, Wallace AJ. Dietary amelioration of Helicobacter infection. Nutr Res 2015; 35: 461-73.
14. Wang X, Hirmo S, Willen R, et al. Inhibition of Helicobacter pylori infection by bovine milk glycoconjugates in a BAlb/cA mouse model. J Med Microbiol 2001; 50: 430-5.
15. Ito Y, Suzuki K, Ichino N. The risk of Helicobacter pylori infection and atrophic gastritis from food and drink intake: a cross-sectional study in Hokkaido, Japan. Asian Pac J Cancer Prev 2000; 1: 147-56.
16. Sachdeva A, Nagpal J. Meta-analysis: efficacy of bovine lactoferrin in Helicobacter pylori eradication. Aliment Pharmacol Ther 2009; 29: 720-30.
17. Szajewska H, Horvath A, Piwowarczyk A. Meta-analysis: the effects of Saccharomyces boulardii supplementation on Helicobacter pylori eradication rates and side effects during treatment. Aliment Pharmacol Ther 2010; 32: 1069-79.
18. Armuzzi A, Cremonini F, Bartolozzi F, et al. The effect of oral administration of Lactobacillus GG on antibiotic-associated gastrointestinal side-effects during Helicobacter pylori eradication therapy. Aliment Pharmacol Ther 2001; 15: 163-9.
19. Moy KA, Yuan JM, Chung FL, et al. Isothiocyanates, glutathione S-transferase M1 and T1 polymorphisms and gastric cancer risk: a prospective study of men in Shanghai, China. Int J Cancer 2009; 125: 2652-9.
20. Fahey JW, Haristoy X, Dolan PM, et al. Sulforaphane inhibits extracellular, intracellular, and antibiotic-resistant strains of Helicobacter pylori and prevents benzo[a]pyrene-induced stomach tumors. Proc Natl Acad Sci U S A 2002; 99: 7610-5.
21. Yanaka A, Fahey JW, Fukumoto A, et al. Dietary sulforaphane-rich broccoli sprouts reduce colonization and attenuate gastritis in Helicobacter pylori-infected mice and humans. Cancer Prev Res (Phila) 2009; 2: 353-60.
22. Nohynek LJ, Alakomi HL, Kähkönen MP, et al. Berry phenolics: antimicrobial properties and mechanisms of action against severe human pathogens. Nutr Cancer 2006; 54: 18-32.
23. Chatterjee A, Yasmin T, Bagchi S, et al. Inhibition of Helicobacter pylori in vitro by various berry extracts, with enhanced susceptibility to clarithromycin. Mol Cell Biochem 2004; 265: 19-26.
24. Zhang L, Ma J, Pan K, et al. Efficacy of cranberry juice on Helicobacter pylori infection: a double-blind, randomized placebo-controlled trial. Helicobacter 2005; 10: 139-45.
25. Boyanova L, Iliewa J, Gergova, et al. Honey and green/black tea consumption may reduce the risk of Helicobacter pylori infection. Diagn Microbiol Infect Dis 2015; 82: 85-6.
26. Thompson L, Cocakyne A, Spiller RC. Inhibitory effect of polyunsaturated fatty acids on the growth of Helicobacter pylori: a possible explanation of the effect of diet on peptic ulceration. Gut 1994; 35: 1557-61.
27. Bergonzelli GE, Donnicola D, Porta N, et al. Essential oils as components of a diet-based approach to management of Helicobacter infection. Antimicrob Agents Chemother 2003; 47: 3240-6.

28. Castro M, Romero C, de Castro A. Assessment of Helicobacter pylori eradication by virgin olive oil. Helicobacter 2012; 17: 305-11.
29. Matjaž H, Orel R. Are probiotics useful in Helicobacter pylori eradication? World J Gastroenterol 2015; 21: 10644-53.
30. Keenan JI, Salm N, Hampton MB, et al. Individual and combined effects of food on Helicobacter pylori growth. Phytother Res 2010; 24: 1229-33.

Received: 6.09.2015
Accepted: 24.12.2015