ORIGINAL ARTICLE





Higher dietary total antioxidant capacity is inversely associated with *Helicobacter pylori* infection among adults: A case–control study

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Received: 26 October 2020 / Accepted: 18 January 2022 / Published online: 5 August 2022 \odot Indian Society of Gastroenterology 2022

Abstract

Introduction Antioxidants appear to hinder the actions of *Helicobacter pylori* (*H. pylori*). The aim of this research was to evaluate the association between dietary total antioxidant capacity (DTAC) and *H. pylori* infection.

Methods A case–control study was carried out among 200 patients with *H. pylori* infection and 402 healthy subjects (18–55 years). Dietary data were collected using a validated 168-item quantitative food frequency questionnaire. DTAC was calculated based on the oxygen radical absorbance capacity of each food (except for coffee) reported by the US Department of Agriculture. **Results** Compared with participants in the lowest tertile of DTAC, those in the highest tertile had a significantly lower odds ratio (OR) in the crude model (OR, 0.29; 95% CI, 0.14–0.61; *p* for trend = 0.001), model 1 (adjustment for age and sex) (OR, 0.37; 95% CI, 0.24–0.58; *p* for trend < 0.001), and model 2 (adjustment for model 1 plus body mass index, waist circumference, physical activity, smoking, dietary intake of energy and fat) (OR, 0.20; 95% CI, 0.10–0.40; *p* for trend ≤ 0.001).

Conclusions A high DTAC is associated with a reduced risk of *H. pylori* infection in adults. Further studies are mandatory to elucidate the mechanisms and a dose–effect relationship.

Keywords Chronic diseases · Dietary total antioxidant capacity · Helicobacter pylori · Obesity

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Bullet points of study highlights

What is already known?

• Dietary total antioxidant capacity (DTAC) has been regarded as a useful tool to assess the relationship between cumulative antioxidant food capacity and several chronic disorders.

What is new in this study?

• Our findings showed that a high DTAC is associated with a reduced risk of *H. pylori* infection in adults.

What are the future clinical and research implications of the study findings?

• Futher observational studies and clinical trials are needed to investigate the exact relationship between DTAC and the risk of *H. pylori* infection.

Introduction

Approximately 4.4 billion individuals suffer from *Helicobacter pylori* (*H. pylori*) infection worldwide [1], a recognized Gram-negative microaerophilic pathogen replicated on the surface of the gastric epithelium that can cause gastritis and gastric cancer [2]. Moreover, many studies report that *H. pylori* infection is associated with an increased risk of pancreatic disease [3], lymphoma [4], and atherosclerosis [5].

H. pylori infection is influenced by genetic and environmental factors [6], as well as eating habits of the hosts [7]. Regarding the latter, studies suggest that dietary antioxidants (e.g. vitamins and minerals) play an important role in reducing active oxygen species and gastric inflammation caused by *H. pylori* [8]. So much so that vitamin C and E levels are lower in patients positive for *H. pylori* infection than in those without [8]. Thus, impaired antioxidant and anti-inflammatory defenses could cause or exacerbate a chronic condition associated with *H. pylori* infection.

The evaluation of an antioxidant compound alone cannot reflect the total antioxidant potency of the diet; hence, the dietary total antioxidant capacity (DTAC) has been used as a suitable indicator of overall antioxidants across the diet, whereby the synergistic and potential effects of the dietary antioxidant are assessed [9, 10]. More importantly, DTAC is strongly correlated with serum total antioxidant capacity [11], with recent research showing its efficacy in reducing the risk of chronic diseases [12]. For instance, there is a link between higher DTAC values with lower concentrations of metabolic and oxidative stress biomarkers [13] as well as reduced risk of diabetes [14], ulcerative colitis [15], hypertension [16], and heart diseases [17], which are common risk factors or diseases alongside *H. pylori* infection [18–21].

A number of in vivo and animal studies have shown the ability of antioxidant-rich foods to decrease *H. pylori* infection and associated oxidative stress, in which garlic, ginger, quercetin, green tea, and cranberry are some candidates [22–25]. To the best of our knowledge, however, the association between DTAC and the risk of *H. pylori* infection has not yet been investigated [26]. Therefore, we aimed to investigate the association between DTAC and the risk of *H. pylori* infection in adults.

Methods

Participants

This case–control study was conducted on *H. pylori*–infected patients and healthy individuals who had been referred to the Hazrat Rasoul Hospital, Tehran, Iran, during 2019–2020. Patients had an age range of 18–60 years. Median length from diagnosis of *H. pylori* infection was 6 months. Regarding the laboratory and clinical methods, blood anti-*H. pylori* serum Ig G antibody against *H. pylori* was tested by the commercial enzyme-linked immunosorbent assay (ELISA) kit (Pishtaz Teb Co, Tehran, Iran), heliprobe 14C-urea breath test (UBT) respiratory test (Hazrat Rasoul Hospital, Tehran, Iran), fecal *H. pylori* antigen, endoscopy, gastric biopsy, rapid urease test, and microscopic and pathological examination were performed.

The control group (case and control matched in terms of age and sex) was twice in number than the case group. They did not have *H. pylori* infection with the usual diagnostic methods, confirmed by a gastroenterologist, and had no history of gastrointestinal diseases (e.g. irritable bowel syndrome, inflammatory bowel disease, gastric or duodenal ulcer, celiac disease, malignant or benign gastric tumor).

Individuals under specific diets for the management of any disease or weight loss, individuals with a history of gastrointestinal malignant diseases, and pregnant and lactating women were not included in the study. All study participants, after entering the study, completed the informed written consent form. Because of reported energy intakes outside of the range of \pm 3 standard deviation (SD) from the mean energy intakes of the population, 6 subjects were excluded from the analysis. Finally, 200 cases and 402 controls remained in the final analysis (Supplementary Fig. 1).

A registered dietician was the interviewer in order to obtain answer to the survey questions by the participants and also to reduce bias. Also, a validated General Exercise Physical Activity Questionnaire (GPPAQ) was used to assess the level of physical activity of the participants [27]. This study was approved by the research council and ethics committee of the Iran University of Medical Sciences, Tehran, Iran.

Anthropometric assessment

Data on anthropometric measures were collected by a trained dietician. Body weight was assessed using a digital scale, while participants were wearing light clothes and no shoes, and recorded to the nearest 100 g. Height was measured with a tape measure to the nearest 0.5 cm while in a relaxed standing position, without shoes. We calculated the body mass index (BMI) as weight (kg) divided by height in meters squared (m²).

Dietary assessment and DTAC calculation

Dietary intake of study participants was assessed using semiquantitative food frequency questionnaires (FFQ) with 168 food items. The validity and reliability of the questionnaire were confirmed in previous studies [28]. For each food item, a standard unit or portion size was specified and participants were asked how often, on an average, they had consumed that amount over the past year. The frequency of consumption for each food item was reported per day, week, month, or year by the study participants, and individual foods items were converted to the average daily consumption of each food item. Nutrient and energy levels of foods were adapted for Iranian food using Nutritionist 4 software (First DatabankInc., Hearst Corp., San Bruno, CA., USA).

The DTAC was calculated based on the oxygen radical absorbance capacity of each food (except for coffee) reported by the (United States Department of Agriculture) USDA Oxygen Radical Absorbance Capacity (ORAC) database and expressed as millimoles of trolox equivalent/100 g of food (mmol/100 g) [29]. According to studies, the ORAC index has a higher correlation with serum antioxidant levels than the ferric reducing ability (FRAP) and trolox equivalent antioxidant capacity (TEAC) indices [11, 30]. Also, this index includes more food items and nutrients than other available

indices due to more accurate evaluation [31]. Conversely, other indicators include spices and even cooked and frozen foods [30, 31].

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software (version 19.0; SPSS Inc., Chicago, IL., USA). The normality of variables was evaluated by Kolmogorov–Smirnov and histogram tests. For the variables that do not have a normal distribution, logarithmic equivalent (Ln transformation) was used. Also, independent-sample *t* test was used for comparing the mean of DTAC as well as the general characteristics and hematological parameters among case and control groups. For assessing the relation between the DTAC index and *H. pylori* infection in adjusted models, multiple logistic regressions were used. The data were presented as mean \pm SD and odds ratio (OR) with 95% confidence interval (CI), and in all results, the significance level was determined as *p* < 0.05.

Results

The mean \pm SD for the age and BMI of the study population (41.7% women) were 41.2 \pm 8.9 years and 26.3 \pm 4.8 kg/m², respectively. There was no difference regarding sex, age, marital status, and use of medication and supplements, as well as alcohol intake among the case and control groups. On the other hand, those patients positive with *H. pylori* infection significantly had higher BMI (28.0 [6.5] vs. 24.7 [3.2] kg/m², p < 0.001) and smoking (7.3% vs. 2.7% were current smokers, p = 0.019) compared to control groups (Table 1).

Patients with H. pylori infection had higher intake of energy (2629.1 [779.9] vs. 2282.9 [638.6] kcal/day, *p* = <0.001), protein (94.5 [32.2] vs. 76.4 [24.2] g/day, p = <0.001), carbohydrate (393.2 [122.3] vs. 325.1 [103.2] g/day, p = <0.001), saturated fatty acids (27.5 [10.6] vs. 24.3 [9.2] g/day, p =0.001), fructose (20.5 [8.2] vs. 16.8 [9.8] g/day, p < 0.001), iron (49.3 [29.5] vs. 25.7 [14.0] mg/day, p < 0.001), refined grains (424.2 [236.5] vs. 328.6 [170.3] g/day, p < 0.001), and red and processed meat (0.8 [0.7] vs. 0.4 [0.4] serving/day, p <0.001), with lower intake of total fiber (36.1 [19.0] vs. 60.7 [28.2] g/day, p < 0.001), vitamin E (11.6 [5.7] vs. 12.9 [4.9] mg/day, p = 0.019), vitamin C (127.0 [80.3] vs. 154.0 [70.4] mg/day, p = 0.001), vitamin D (1.5 [1.1] vs. 2.0 [1.7] µg/day, *p* < 0.001), total dairy (317.6 [193.6] vs. 424.9 [246.0] g/day, p < 0.001), whole grains (106.2 [119.4] vs. 163.7 [168.2] g/ day; p < 0.001), and vegetables (232.9 [109.4] vs. 287.0 [170.1] g/day, p < 0.001) (Table 2). The ORs and 95% CIs for H. pylori infection in the tertiles of DTAC are shown in Table 3. Compared with participants in the lowest tertile of DTAC, those in the highest tertile had a significantly lower Table 1 General characteristics

of study participants

	Case ^a $(n = 200)$	Control $(n = 402)$	p-value ^b
Demographic variables			
Age (years)	41.6 (9.1)	40.9 (8.8)	0.769
Female, n (%)	86 (43.1)	179 (44.7)	0.632
BMI (kg/m ²)	28.0 (6.5)	24.7 (3.2)	< 0.001
Physical activity, <i>n</i> (%)			
Low	152 (76.0)	292 (72.8)	0.484
Moderate	38 (19.3)	78 (19.5)	0.465
High	9 (4.7)	30 (7.6)	0.362
Current smokers, n (%)	14 (7.3)	11 (2.7)	0.019
Alcohol drinking, <i>n</i> (%)	15 (7.5)	29 (7.2)	0.175
Married, n (%)	163 (81.5)	302 (75.4)	0.400
Anti-inflammatory drugs use (yes), n (%)	25 (12.6)	45 (11.2)	0.784
Inflammatory disease history, n (%)	16 (0.8)	28 (0.7)	0.406
Vitamin D supplement, n (%)	12 (0.6)	20 (0.5)	0.937
Herbal drug use, n (%)	49 (24.6)	80 (20.1)	0.165

Values are expressed as means \pm standard deviation (SD)

^a Helicobacter pylori group

^b p-values resulted from chi square and Student's t test. BMI body mass index

OR for *H. pylori* infection in the crude model (OR, 0.29; 95% CI, 0.14 – 0.61; *p* for trend = 0.001), model 1 (OR, 0.37; 95% CI, 0.24–0.58; *p* for trend < 0.001), and model 2 (OR, 0.20; 95% CI, 0.10–0.40; *p* for trend \leq 0.001). Thus, the results remained significant after the adjustment for age and sex (model 1) and full adjustment consisting of BMI, waist circumference, physical activity, smoking, and dietary intake of energy and fat, juxtaposed to age and sex (model 2).

Discussion

This study investigated the association between DTAC and *H. pylori* infection through a case–control design. We found that higher DTAC values had an inverse association with *H. pylori* infection. Compared with the lowest DTAC score, those participants with the highest DTAC score had a 71% and 80% lower likelihood of having *H. pylori* infection according to the crude and fully adjusted model, respectively.

To the best of our knowledge, this is the first study that investigated and documented an inverse relationship between DTAC and the odds of *H. pylori* infection, which remains a challenge worldwide [32]. Given that the effects of DTAC have been considered in the management of miscellaneous chronic diseases, such as cardiovascular diseases [17], cancer [33], diabetes [14], and metabolic disorders [13], our findings are of crucial importance to expand the scientific background toward the applicability of DTAC as a feasible tool in *H. pylori* infection per se and associated gastrointestinal diseases and metabolic problems.

To date, there is no cutoff value for DTAC. Herein, we used > 11.76 mmol/100 g for the upper tertile group, which was inversely associated with H. pylori infection compared with < 8.19 mmol/100 g as the lower tertile group. In another case-control study, higher DTAC values were associated with a lower OR of having non-alcoholic fatty liver disease (NAFLD) in adults, whose mean DTAC values were 12,323.6 and 17,563.4 mmol TE/100 g (p < 0.001) for the case and control groups, respectively [34]. Although DTAC was introduced by European authors [35], the majority of the studies were conducted in Iran [10, 34, 36] and, thus, there is a lack of specific DTAC values among the most popular antioxidant-rich diets. Along these lines, further investigation as to DTAC values in the Mediterranean Diet and the DASH Diet is fundamental in an attempt to establish optimal cutoff values, given that these are recognized dietary models that significantly increase the antioxidant status [37, 38]. More interestingly, it must be noted that the DASH Diet has an inverse relationship with *H. pylori* and gastric cancer [39], as well as with chronic diseases associated with H. pylori infection [40].

The putative mechanisms of the effects of nutritional antioxidants on *H. pylori* infection need to be studied. The intake of antioxidants in animals positive for *H. pylori* infection has been shown to reduce both the number of bacteria in the gastric mucosa and the inflammatory process [8, 24]. By virtue of high antioxidant content, functional foods such as garlic, ginger, quercetin, green tea, and cranberry have been shown to reduce *H. pylori* infection alongside increasing plasma total antioxidant capacity (TAC) levels [19–22], in which quercetin and

 Table 2
 Dietary intakes of study

 participants
 Participants

	Case ^a $(n = 200)$	control ($n = 402$)	p-value ^b
Dietary intake			
Energy (kcal/day)	2629.1 (779.9)	2282.9 (638.6)	< 0.001
Carbohydrate (g/day)	393.2 (122.3)	325.1 (103.2)	< 0.001
Protein (g/day)	94.5 (32.2)	76.4 (24.2)	< 0.001
Fat (g/day)	83.8 (30.2)	81.3 (29.2)	0.398
Saturated fatty acids (g/day)	27.5 (10.6)	24.3 (9.2)	0.001
Mono-unsaturated fatty acids	27.2 (9.5)	28.0 (10.6)	0.447
Poly-unsaturated fatty acids	16.8 (7.9)	18.2 (7.5)	0.063
Fiber (g/day)	36.1(19.0)	60.7 (28.2)	< 0.001
Fructose (g/day)	20.5 (8.2)	16.8 (9.8)	< 0.001
Caffeine (mg/day)	145.6 (116.4)	126.2 (107.0)	0.079
Iron (mg/day)	49.3 (29.5)	25.7 (14.0)	< 0.001
Vitamin C (mg/day)	127.0 (80.3)	154.0 (70.4)	0.001
Vitamin E (mg/day)	11.6 (5.7)	12.9 (4.9)	0.019
Vitamin B_{12} (µg/day)	3.8 (3.4)	4.1 (2.4)	0.303
Vitamin D (µg/day)	1.5 (1.1)	2.0 (1.7)	< 0.001
Food groups			
Total dairy (g/day)	317.6 (193.6)	424.9 (246.0)	< 0.001
Whole grain (g/day)	106.2 (119.4)	163.7 (168.2)	< 0.001
Refined grain (g/day)	424.2 (236.5)	328.6 (170.3)	< 0.001
Red and processed meat (serving/day)	0.8 (0.7)	0.4 (0.4)	< 0.001
Fruits (g/day)	343.1 (172.0)	333.9 (257.5)	0.687
Vegetables (g/day)	232.9 (109.4)	287.0 (170.1)	< 0.001

Values are expressed as means ± standard deviation (SD)

^a Helicobacter pylori

^b p-values resulted from Student's t test

epigallocatechin-3-gallate may be considered some examples of food compounds with cytoprotective effects against the *H. pylori*–induced inflammatory response [41]. Seemingly, antioxidant-rich nutrients have a beneficial effect against *H. pylori* infection by controlling toxins that cause bacterial growth due to stimulation of special anionic channels in the plasma membrane linked to the release of bicarbonate and organic anions in gastric cells [42]. These compounds may reduce the action of urease on *H. pylori*, whose enzyme is responsible for the bacterium's survival in the acidic environment [43].

Of note, fiber-rich plant foods elicit health benefits by protecting against oxidative damage, as well as improving glucose metabolism and serum lipids, due to the modulation in the antioxidant status [44–46]. In addition, some previous studies have stated that dietary fibers can alter the variety of specific gut microbes and change the profile of the human gut microbiota [47–50], whose fiber fermentation is microbiota-

 Table 3
 The association between tertiles of dietary total antioxidant capacity and risk of *Helicobacter pylori* infection among the participants of the study

	Tertiles of dietary total antioxidant capacity		<i>p</i> for trend	
	T1	T2	T3	
DTAC (mmol/100 g)	< 8.19	8.19–11.76	> 11.76	
Case/total	94/236	69/197	37/169	
Crude	1.00 (Ref)	0.93 (0.48-1.77)	0.29 (0.14-0.61)	0.001
Model 1*	1.00 (Ref)	0.76 (0.52-1.12)	0.37 (0.24-0.58)	< 0.001
Model 2 [†]	1.00 (Ref)	0.74 (0.42–1.28)	0.20 (0.10-0.40)	< 0.001

* Model 1: adjusted for age and sex

[†] Model 2: adjusted for model 1 and body mass index, waist circumference, physical activity, smoking, dietary intake of energy and fat. *DTAC* dietary total antioxidant capacity, *Ref* reference

dependent [51] and may increase Gram-positive bacteria [52] by decreasing intestinal transit time and pH [53, 54]. Given that *H. pylori* is a Gram-negative bacterium, it may be negatively affected by fiber. Also, diets rich in vegetables, fruits, whole grains, and beans [55] can exert a protective effect against *H. pylori* infection [56, 57], perhaps because of their prebiotic properties [58].

Fresh vegetables are sources of vitamin C, which has been mentioned as a chemopreventive factor against digestive disorders caused by H. pylori infection [56]. Apparently, vitamin C can decrease the stomach cancer risk and exert an effect on the cycle of *H. pylori* infection [59]. Vitamin C is highly concentrated in the stomach mucosa and gastric juice, and has a positive effect on the production and function of immune cells and immunoglobulin [60]. In our study, dietary vitamin C consumption was significantly lower in the case group, thus expanding the clinical wisdom in this regard. Furthermore, in the face of little evidence to support the effects of a particular antioxidant on body composition, dietary antioxidants altogether could indirectly reduce the risk of H. pylori infection and associated problems by favoring the reduction of fat mass and visceral fat, which are well-known risk factors for H. pylori infection [61, 62]. Besides, as a popular antioxidant-rich beverage, coffee had strong in vitro antibacterial activity against H. pylori [63]. Such an action suggests that coffee may be a useful natural inhibitor of gastritis and gastric ulcers through a mechanistic basis; conversely, it must be highlighted that coffee intake is clinically related to gastritis and gastroesophageal reflux disease due to the individuals' sensibility to chlorogenic acid and caffeine [64].

This is perhaps the first study that assessed the relationships between DTAC and H. pylori infection, using considerable sample size and statistical adjustment models in order to mitigate confounding factors. For instance, we used model 1 as a means of adjusting the analysis according to age and sex because these are not only used in traditional medical research but also older age is related to a higher prevalence of H. pylori infection [65], while there is a scientific debate as to the effects of sex on the rate of H. pylori infection [66]. Model 2, in turn, was a way to fully adjust the results for other confounding factors in addition to age and sex. We used BMI, waist circumference, physical activity, and dietary intake of energy and fat in this model in order to avoid problems related to obesity and associated factors, whereas adjusting for smoking because, intriguingly, the risk of *H. pylori* seropositivity may decrease linearly with cigarette consumption whereby increased gastric acidity in the stomach through smoking may be a cause [67]. Finally, it should be noted that, due to the nature of the case-control design, causation cannot be determined by our work and thus further research is warranted to expand the avenues toward the clinical effect of DTAC in H. pylori infection and associated diseases.

We conclude that a high DTAC is associated with a reduced risk of *H. pylori* infection in adults, thereby expanding the importance of increasing consumption of natural dietary antioxidants against the burden of *H. pylori* infection. However, further observational studies and clinical trials are needed to investigate the exact role of DTAC in the prevention and treatment of *H. pylori* infection.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12664-022-01246-3.

Acknowledgements We express our appreciation to the participants of this study.

Author contribution S.F., R.N., and Mh.S. contributed to the conception, design, and statistical analysis. S.F. and H.O.S. contributed to the data collection and manuscript drafting. R.S. and Mh.S. supervised the study. All authors approved the final version of the manuscript

Declarations

Conflict of interest RN, MHS, HOS, MR, SF, NG, and RS declare no competing interests.

Ethics statement The study was performed conforming to the Helsinki declaration of 1975, as revised in 2000 and 2008 concerning human and animal rights, and the authors followed the policy concerning informed consent as shown on Springer.com.

This study was approved by the research council and ethics committee of the Iran University of Medical Sciences, Tehran, Iran.

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