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ORIGINAL ARTICLE

Alterations in paraoxonase-1 levels and oxidative status with the eradication of *Helicobacter pylori* infection

Helicobacter pylori enfeksiyonunun eradike edilmesi ile paraoksonaz-1 düzeylerinde ve oksidatif durumdaki değişiklikler

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ABSTRACT • **Background and Aims:** To compare the plasma paraoxonase-1 levels and oxidative stress markers in patients with different states of *Helicobacter pylori* infection. **Materials and Methods:** Patients with dyspeptic symptoms and referred for upper gastrointestinal system endoscopy were consequently included and grouped according to the presence of *Helicobacter pylori* infection. *Helicobacter pylori* was eradicated in patients with positive rapid urase test. Total antioxidant status, total oxidant status and oxidative stress index were calculated. Paraoxonase-1 levels and oxidative stress markers were compared between 3 groups and in treated patients before and after eradication. **Results:** One hundred eighty nine patients were included the study. In eighty two patients *Helicobacter pylori* were positive without the presence of duodenal ulcer, in 49 patients *Helicobacter pylori* were positive with the presence of duodenal ulcer and *Helicobacter pylori* were negative in 58 patients. In evaluation of paraoxonase-1 levels in women, there were not any statistically significant difference between groups but *Helicobacter pylori* negative patients had statistically significantly higher values than other 2 groups among men. Total antioxidant status levels were statistically significantly higher in both genders in *Helicobacter pylori* negative patients than other 2 groups. There were a statistically significant increase in total antioxidant status and paraoxonase-1 levels with the successful eradication of *Helicobacter pylori* infection. **Conclusion:** Plasma paraoxonase-1 and total antioxidant status were decreased while total oxidant status and oxidative stress index were increased in the patients with *Helicobacter pylori* infection. The differences were more prominent in males who are more prone to atherosclerotic diseases. Moreover, with the eradication of *Helicobacter pylori* infection, both paraoxonase-1 levels and total antioxidant status were increased significantly.

Key words: *Helicobacter pylori*, oxidative status, paraoxonase-1

ÖZET • **Giriş ve Amaç:** *Helicobacter pylori* enfeksiyonunun farklı kliniklerine sahip hastalarda plazma paraoksonaz-1 seviyelerini ve oksidatif stres belirteçlerini karşılaştırmak. **Gereç ve Yöntem:** Dispeptik semptomları olan ve üst gastrointestinal sistem endoskopisi için yönlendirilen hastalar çalışmaya dahil edildi ve *Helicobacter pylori* enfeksiyonu varlığına göre gruplandırıldı. Hızlı üreaz testi pozitif olan hastalarda *Helicobacter pylori* eredike edildi. Paraoksonaz-1 düzeyleri ve oksidatif stres belirteçleri, *Helicobacter pylori* pozitif olup duodenal ülseri olan ve olmayan grup ve *Helicobacter pylori* negatif olan gruplar arasında ve tedavi edilen hastalarda eradikasyon öncesi ve sonrasında karşılaştırıldı. **Bulgular:** Çalışmaya 189 hasta dahil edildi. 82 hastada duodenum ülseri olmadan *Helicobacter pylori* pozitif, 49 hastada duodenum ülseri varken *Helicobacter pylori* pozitif, 58 hastada *Helicobacter pylori* negatifti. Kadınlarda paraoksonaz-1 düzeyleri değerlendirildiğinde gruplar arasında istatistiksel olarak anlamlı bir fark bulunmazken, *Helicobacter pylori* negatif hastaların değerleri erkeklerde diğer 2 gruba göre istatistiksel olarak anlamlı derecede yüksekti. *Helicobacter pylori* negatif hastalarda total antioksidan kapasitesi düzeyleri her iki cinsiyette de diğer 2 gruba göre istatistiksel olarak anlamlı derecede yüksekti. *Helicobacter pylori* enfeksiyonunun başarılı bir şekilde ortadan kaldırılmasıyla total antioksidan kapasitesi ve paraoksonaz-1 düzeylerinde istatistiksel olarak anlamlı bir artış oldu. **Sonuç:** *Helicobacter pylori* enfeksiyonu olan hastalarda plazma paraoksonaz-1 ve total antioksidan kapasitesi azalırken total oksidatif durum ve oksidatif stres indeksi arttı. Aterosklerotik hastalıklara daha yatkın olan erkeklerde farklılıklar daha belirgindi. Ayrıca *Helicobacter pylori* enfeksiyonunun ortadan kaldırılmasıyla hem paraoksonaz-1 düzeyleri hem de total antioksidan kapasitesi önemli ölçüde arttı.

Anahtar kelimeler: *Helicobacter pylori*, oksidatif durum, paraoksonaz-1

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INTRODUCTION

Helicobacter pylori (H. pylori) is a Gram negative, spiral-shaped bacteria that is the dominant microorganism within the stomach (1). Interestingly it may persist in the gastric niche for years leading to a chronic infection (2). *H. pylori* locally affects the gastric epithelial cells and besides may alter the innate and adaptive immune system of host by causing production of pro-inflammatory cytokines as well as the anti-inflammatory cytokines to enable itself to escape from immune system (3,4). These 2 mechanisms play a central role in the development of chronic inflammation. Chronic infections, including *H. pylori* infection, may trigger a chronic inflammatory state that results in endothelial dysfunction and atherosclerosis (5).

The data about the association of *H. pylori* infection with the oxidative status is furthermore accumulating (6). *H. pylori* infection has been associated with gathering of reactive oxygen species (ROS) and consequently increased oxidative stress that results in DNA damage in gastric mucosa (7). In a study of Mashimo et al., ROS production was reported to be significantly increased in individuals with *H. pylori* infection and also to decline significantly after *H. pylori* eradication (8).

Nowadays, atherosclerosis is clearly defined as an inflammatory process that begins with the oxidation of low density lipoprotein (LDL) on the arterial wall (9). Nevertheless, high-density lipoprotein (HDL) plays an essential role in the prevention of atherosclerosis by inhibiting the oxidation of LDL. The paraoxonase (PON)-1 is an anti-inflammatory and antioxidant enzyme located on HDL that prevents LDL oxidation by hydrolyzing lipid peroxides (10).

In this study we aimed to compare the plasma PON-1 levels and oxidative stress markers [including total oxidant status (TOS), total antioxidant status (TAS), and oxidative stress index (OSI)] and to define the results of *H. pylori* infection eradication on these markers in patients with different states of *H. pylori* infection. By this way we aimed to determine the effects of *H. pylori* eradication on oxidative stress status and serum PON-1 levels of patients, which may be the indirect determinants of atherosclerotic process.

MATERIALS and METHODS

Patients admitted with dyspeptic symptoms and referred for upper gastrointestinal system endoscopy to Gastroenterology Department of Yıldırım Beyazıt University, Ankara, between January 2011 and January 2012 were consequently included in this study. The study was approved by the Ankara Yıldırım Beyazıt University Ethics Committee, numbered 2011-232 and written informed consent was obtained from each patient prior to enrolling in the study.

Patients with the history of rheumatologic or cardiovascular diseases, with systemic or local active infection, pregnant or lactating women and those who had received *H. pylori* eradication treatment previously were excluded from the study. Moreover, patients treated with proton-pump inhibitors, antibiotics, bismuth salts or H_2 receptor blockers in the previous 4 weeks were also not included in the study.

Upper gastrointestinal system endoscopy was performed with Olympus Evis Exera 160 videoendoscopes (Olympus America, Inc., Center Valley, PA, USA) to all patients. Biopsies were obtained from antrum for rapid urease test to determine the presence of *H. pylori* infection in all patients.

Patients were grouped according to the presence of *H. pylori* infection and duodenal ulcer as *H. pylori* positive patients with duodenal ulcer, *H. pylori* positive patients without duodenal ulcer and *H. pylori* negative patients. *H. pylori* was eradicated in patients with positive rapid urease test in the pres-

ence of duodenal ulcer with the eradication protocol of lansoprazole 30 mg twice daily, amoxicillin 1 g twice daily, clarithromycin 500 mg twice daily and bismuth salt 240 mg twice daily given for 14 days. Results of eradication treatment were evaluated with C^{14} urea breath test after an overnight fasting at the end of 2nd week. From all patients at the time of diagnosis and from the treated patients 6 weeks after eradication, for the second time, serum samples were obtained and stored at -80 °C.

Age, gender, and body mass index (BMI) of patients were recorded. Body mass index was calculated as body weight (kg) divided by squared height in meters (m2). In laboratory tests, platelet count, hemoglobin, white blood cell (WBC), fasting blood glucose, creatinine, aspartate amino transferase, alanine aminotransferase, total cholesterol, LDL-cholesterol, HDL-cholesterol and triglyceride levels were recorded.

Paraoxonase activities was measured using paraoxon substrate. The rate of paraoxon hydrolysis (diethyl-p-nitrophenylphosphate) was measured by monitoring the increase of absorbance at 412 nm at 37 °C. The amount of generated p-nitrophenol was calculated from the molar absorptivity coefficient at pH 8, which was 17,000 M^{-1} cm^{-1}. Paraoxonase activity was expressed as U/L serum. Paraoxonase phenotype distribution was determined by a double substrate method that measures the ratio of paraoxonase activity (with 1M NaCl in the assay) (11).

Total antioxidant status (TAS) and total oxidant status (TOS) were measured by the colorimetric method developed by Erel and oxidative stress index (OSI) was calculated as the ratio of TOS (µmol H2O2 Eq/l) to TAS (mmol Trolox Eq/l) (12,13).

Statistical Analysis

Data were analyzed using SPSS version 18 for Windows (Chicago, IL, USA). Parametric continuous variables were expressed as mean ± standard deviation, and categorical variables were presented as numbers and percentages. Categorical variables were analyzed with the χ^2 test. Paired group comparisons were performed with independent sample t test for variables with normal distribution and oneway Anova was used to determine the significance between 3 groups. Differences between the same patients before and after treatment were analysed by paired sample t test. A p-value < 0.05 was considered to be statistically significant.

RESULTS

Totally 189 patients (92 female and 97 male) were included in the study. Among those patients, in 82 patients *H. pylori* were positive without the presence of duodenal ulcer, in 49 patients *H. pylori* were positive with the presence of duodenal ulcer, and in 58 patients *H. pylori* were negative. PON-1 levels and oxidative status were determined in all patients at the time of endoscopy.

General characteristics and laboratory data of study participants are summarized in Table 1. Concerning general biochemical data, there was not any statistically significant difference between groups in regards of platelet count, hemoglobin, fasting blood glucose, creatinine, aspartate amino transferase, alanine aminotransferase, total cholesterol, LDL-cholesterol, HDL-cholesterol and triglyceride levels. However, in terms of WBC, WBC was statistically significantly higher in *H. pylori* positive patients with duodenal ulcer than other groups.

Since there was a statistically significant difference in gender between groups and gender difference may affect the PON-1 levels or oxidative stress status; the patients were divided into 2 according to their genders and then PON-1 levels and oxidative stress status were evaluated. In evaluation of PON-1 levels in women, there was not any

Table 1 General characteristics and laboratory data of study participants.

	***H. pylori* (+) (n: 82)**	***H. pylori* (+) Ulcer (+) (n: 49)**	***H. pylori* (-) (n: 58)**	**p**
Age (years)	41.0 ± 12.97	38.77 ± 12.65	45.35 ± 13.26	0.11
Gender (F/M)	**42/40**	**15/34**	**35/23**	**0.013**
BMI (kg/m^2)	26.34 ± 5.32	25.39 ± 4.14	27.66 ± 4.66	0.09
Smoking	28 (34.1)	24 (48.9)	8 (13.8)	**0.004**
Hgb (mg/dl)	13.70 ± 1.84	13.97 ± 1.72	13.25 ± 2.09	0.20
WBC (x10^3/L)	6.87 ± 1.57	7.85 ± 1.82	7.07 ± 1.57	**0.008**
PLT (x10^3/L)	230.14 ± 53.73	293.70 ± 31.39	253.01 ± 71.44	0.25
Glucose (mg/dl)	97.26 ± 19.11	97.31 ± 39.29	92.07 ± 13.00	0.50
Creatinine (mg/dl)	1.05 ± 0.60	0.98 ± 0.17	1.09 ± 0.72	0.52
AST (U/L)	22.80 ± 7.94	21.39 ± 8.12	21.20 ± 10.78	0.65
ALT (U/L)	23.91 ± 10.32	26.17 ± 15.40	20.87 ± 9.42	0.19
T. Chol (mg / dL)	189.28 ± 46.10	170.02 ± 38.43	188.70 ± 41.60	0.14
LDL (mg / dL)	116.23 ± 24.16	104.63 ± 30.05	116.52 ± 31.78	0.28
HDL (mg / dL)	44.06 ± 11.99	39.85 ± 8.09	47.83 ± 26.28	0.16
Triglyceride (mg / dL)	148.52 ± 91.56	131.51 ± 81.71	137.07 ± 75.50	0.45

H. pylori: Helicobacter pylori; BMI: Body mass index; Hgb: Haemoglobin; WBC: White blood cell; PLT: Platelet count; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; T. chol: Total cholesterol; LDL: Low density lipoprotein; HDL: High density lipoprotein.

Table 2 PON-1 levels and oxidative stress status in females.

	***H. pylori* (+) (n: 42)**	***H. pylori* (+) Ulcer (+) (n: 15)**	***H. pylori* (-) (n: 35)**	**P**
Paraoxonase-1	215.43 ± 94.66	211.06 ± 125.14	238.43 ± 113.56	0.58
TAS	2.08 ± 0.21	2.03 ± 0.19	2.34 ± 0.29	**0.001**
TOS	1.75 ± 2.87	1.87 ± 0.91	1.61 ± 1.17	0.91
OSI	0.78 ± 0.11	0.89 ± 0.51	0.72 ± 0.53	0.74

H. pylori: Helicobacter pylori; TAS: Total antioxidant status; TOS: Total oxidant status; OSI: Oxidant status index.

statistically significant difference between groups but the highest values were determined in *H. pylori* negative patients (Table 2) and when PON-1 levels were determined in men, *H. pylori* negative patients had statistically significantly higher values than other 2 groups (Table 3). TAS levels were statistically significantly higher in both genders in *H. pylori* negative patients than other 2 groups.

H. pylori eradication treatment was prescribed to the 49 *H. pylori* positive patients with duodenal ulcer and the results of eradication treatment were evaluated with C^{14} urea breath test after an overnight fasting at the 2 weeks after finishing treatment end. C^{14} urea breath test could be performed to 29 patients who came for the follow up and among those 24 (7 female, 17 male; mean age: 39.95 ± 13.27 years) had negative results as a sign of successful eradication. Oxidative status and PON-1 levels were re-evaluated in those 24 patients and compared with pre-eradication values

Table 3 PON-1 levels and oxidative stress status in males.

	***H. pylori* (+) (n: 40)**	***H. pylori* (+) Ulcer (+) (n: 34)**	***H. pylori* (-) (n: 23)**	**P**
Paraoxonase-1	201.86 ± 97.66	190.32 ± 90.54	241.94 ± 46.19	0.019
TAS	2.22 ± 0.19	2.16 ± 0.17	2.47 ± 0.23	**0.001**
TOS	1.63 ± 1.36	1.83 ± 1.61	1.54 ± 0.95	0.47
OSI	0.66 ± 0.51	0.87 ± 0.67	0.61 ± 0.44	0.39

H. pylori: Helicobacter pylori; TAS: Total antioxidant status; TOS: Total oxidant status; OSI: Oxidant status index.

Table 4 Comparison of oxidative status of patients before and after *H. pylori* eradication.

	***H. pylori* (+) (n: 24)**	***H. pylori* (-) (n: 24)**	**P**
Paraoxonase-1	182.06 ± 103.53	250.78 ± 103.54	0.028
TAS	2.15 ± 0.20	2.31 ± 0.18	0.006
TOS	1.68 ± 0.69	1.26 ± 1.55	0.24
OSI	0.80 ± 0.38	0.54 ± 0.63	0.09

H. pylori: Helicobacter pylori; TAS: Total antioxidant status; TOS: Total oxidant status; OSI: Oxidant status index.

(Table 4). There was a statistically significant increase in TAS and PON-1 levels with the successful eradication of *H. pylori* infection. Eradication regime was prescribed to 21 patients with rapid urease test positivity but without duodenal ulcer but only 5 of these patients returned to follow-up. As a result these patients were not included in the final analyses.

DISCUSSION

In this study, we have determined that the presence of *H. pylori* infection was associated with significantly decreased TAS compared with the *H. pylori* negative patients in both genders and successful eradication of *H. pylori* was associated with a significant increase in TAS. On the other hand, PON-1 levels were reported to be the highest in *H. pylori* (-) groups in both genders. In men, the differences in PON-1 levels between groups were statistically significant. Moreover, with the eradication of *H. pylori* infection, PON-1 levels were determined to be statistically significantly increased. Due to low number of patients further analyses were not performed according to genders.

Paraoxonase-1 is a well-known antioxidant and negative acute-phase protein that prevents the generation of lipid peroxides and declines during the inflammation (14,15). In recent literature, there is limited number of studies dealing with the association of PON-1 levels and *H. pylori* infection. Aslan et al. reported significantly lower serum paraoxonase levels in *H. pylori* positive group (n: 56) than *H. pylori* negative group (n: 43) together with the arylesterase activities (16). Akbaş et al. reported significantly decreased PON-1 activities in *H. pylori* positive subjects (n: 30) compared with negative subjects (n: 31) but they did not determine any significant correlation between PON-1 and carotid-intima media thickness which was defined as a marker of atherosclerosis (17). Mete et al. studied on 134 patients (103 *H. pylori* positive, and 31 negative) and reported significantly lower PON-1 concentrations in *H. pylori* (+) group (18). In those limited number of studies, the general idea is the

decreased PON-1 levels with the *H. pylori* positivity. However to the best of our knowledge, this is the first study comparing the PON-1 status of patients with duodenal ulcer with ulcer-free patients. Presence of duodenal ulcer did not make any alterations on oxidative status or PON-1 levels compared with *H. pylori* positive subjects alone, in this study. Nevertheless, eradication of *H. pylori* infection resulted in a statistically significant increase in PON-1 in men. Gender difference in regards of PON-1 levels as response to eradication treatment may be associated with the far along response of women, but this may be the topic of a further investigation.

In normal conditions, oxidant and antioxidant production are balanced but when levels of oxidants or antioxidants or both are altered, oxidative stress develops. In many studies, oxidative stress induced by the presence of *H. pylori* infection has been reported. *H. pylori* infection induces production of reactive oxygen species (ROS) directly and indirectly by activating neutrophils (19). Kebabcilar et al. reported the reduced total oxidant status 3 months after successful *H. pylori* eradication (20). Dülger et al. reported decreased TAS levels in *H. pylori* positive patients compared with negative patients while the TOS and OSI levels and peripheral lymphocyte DNA damage were higher (21). An increased level of oxidative stress, determined with increased serum malondialdehyde levels, was reported in *H. pylori*-infected school children by Soundaravally et al. (22). Kumari et al. reported that TOS, and OSI were significantly higher in patients with *H. pylori* positive than *H. pylori* negative non-ulcer dyspepsia and healthy individuals whereas TAS was significantly lower (23). Similarly, we have determined significantly increased TAS in *H. pylori* positive patients compared with the *H. pylori* negative ones. Moreover, TAS increased significantly after the eradication of *H. pylori* infection.

Atherosclerosis is defined as a chronic immune inflammatory disease (24). Although atherosclerosis is clearly linked to chronic inflammation, the data about the association of *H. pylori* infection and atherosclerosis is conflicting. Increased prevalence of *H. pylori* infection in coronary artery disease patients and association between these 2 conditions has been reported before (25,26). However, in some studies conflicting results were also obtained (27,28). However, the data about the cytotoxin associated gene A (Cag-A) positive strains of *H. pylori* infection is stronger. In literature there are many studies reporting an association of atherosclerosis with especially Cag-A positive strains of *H. pylori* infection. Kowalski reported significantly higher *H. pylori* seropositivity in patients with coronary artery disease and moreover Cag-A immunoglobulin G (IgG) detection was also determined to be significantly higher in coronary artery disease than in controls (29). Similarly, Huang et al. investigated the effects of Cag-A positive strains of *H. pylori* infection on 159 patients with coronary heart disease and reported the presence of more serious coronary atherosclerosis in coronary heart disease patients with *H. pylori* Cag-A positive infection (30). In the same way, in a meta-analysis, Cremoni et al. reported an Odds ratio for the association between *H. pylori* seropositivity and stroke as 1.49 and for the association between stroke and anti-Cag-A positivity as 2.23; emphasizing the role of *H. pylori* infection and Cag-A positive strains in atherosclerosis (31).

Fourthly half of the patients with duodenal ulcer had been smoking at the time of diagnosis. This ratio was significantly higher than the other groups. Since smoking has significant impact in total oxidant and antioxidant status of the metabolism this might have affected the results of PON-1 and oxidative markers. But this finding is not surprising since smoking is a well defined factor for the development of peptic ulcers (32).

There are some limitations that should be mentioned in this study. First low number of patients in subgroups restricts us to make a generalization. Secondly, the disease duration, severity or Cag-A positivity of the *H. pylori* infection were not studied that may also alter the inflammatory process of individuals. Thirdly, after treatment, the data was analyzed in 6st week which is a short time for the correction of oxidative stress. Larger studies with longer follow-up may elucidate these points.

In the light of these data we can conclude that plasma PON-1 levels and total antioxidant status were decreased while total oxidant status and oxidative stress index were increased in the patients with *H. pylori* infection as compared to *H. pylori* negative individuals. The differences were more prominent in males who are more prone to atherosclerotic diseases. Moreover, with the eradication of *H. pylori* infection, both paraoxonase-1 levels and total antioxidant status were determined to be increased significantly in as short as 6 weeks of time.

Ethics Committee: *This study protocol was approved by Ethics Committee of Ankara Yıldırım Beyazıt University Faculty of Medicine numbered 2011-232. The study was complied with The World Medical Association Declaration of Helsinki.*

Conflict of Interest: *There is no conflict of interest with any institution or person. No financial support was received.*

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