

**ORIGINAL RESEARCH**

Medicine Science 2020;9(1):39-44

**Evaluation of helicobacter pylori eradication therapy with serum myeloperoxidase levels****Meside Gunduzoz<sup>1</sup>, Servet Birgin Iritas<sup>2</sup>, Servet Guresci<sup>3</sup>, Murat Buyuksekerici<sup>4</sup>, Osman Gokhan Ozakinci<sup>5</sup>, Yasar Nazligul<sup>6</sup>**<sup>1</sup>Ankara Occupational Diseases Hospital, Department of Family Medicine, Ankara, Turkey<sup>2</sup>The Council of Forensic Medicine, Department of Ankara Branch Directorate, Ankara, Turkey<sup>3</sup>Numune Education and Research Hospital University of Health Sciences, Department of Pathology, Ankara, Turkey<sup>4</sup>Occupational and Environmental Diseases Hospital, Department of Pharmacology, Ankara, Turkey<sup>5</sup>Occupational and Environmental Diseases Hospital, Department of Public Health, Ankara, Turkey<sup>6</sup>Kecioren Teaching and Research Hospital, Department of Gastroenterology, Ankara, Turkey

Received 24 October 2019; Accepted 19 November 2019

Available online 24.02.2020 with doi:10.5455/medscience.2019.08.9131

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**Abstract**

Helicobacter pylori (H. pylori) is associated with chronic gastritis, peptic ulcers, and gastric adenocarcinomas. H. pylori-infected patients produce reactive oxygen species (ROS) in gastric mucosa. Production of ROS induces the myeloperoxidase (MPO) activity. This study aims the determination of the relationship between MPO level and H. pylori infection and eradication therapy. One hundred seven (107) patients were enrolled in the study. H. pylori were detected by histopathological examination of the specimens. The patients were divided into two groups: Group 1 (H. pylori-negative), Group 2 (H. pylori-positive). The tissue MPO activity and serum MPO levels of these two groups were compared. Patients with H. pylori infection received eradication therapy. Post-treatment serum MPO levels were also compared. Histopathological examination revealed that 28(26.2%) patients were H. pylori-negative (Group 1), whereas 79(73.8%) patients were H. pylori-positive (Group 2). Tissue MPO activity of the groups was compared, and a significant difference was found between two groups, 0.5(1) and 2(1), respectively ( $p<0.001$ ). There was no significant difference between the groups in terms of serum MPO levels 2.19(1.91) ng/mL and 2.69(2.45) ng/mL, respectively ( $P=0.266$ ). There was a significant difference between pre-treatment and post-treatment serum MPO levels after eradication therapy 2.69(2.45) and 1.26(2.36), respectively ( $p=0.002$ ). Consequently, MPO levels may be determinant in monitoring the effectiveness of H. pylori eradication therapy.

**Keywords:** Helicobacter pylori (H.pylori), myeloperoxidase (MPO), H.pylori eradication therapy, reactive oxygen species (ROS)**Introduction**

Nearly half of the world's population is infected with Helicobacter pylori (H.pylori) [1]. H.pylori, associated with gastric cancer, has become a challenging pathogen since its discovery in 1983 and confirming its oncogenicity in 1994 [2-4]. However, the role of H.pylori in carcinogenesis has not been identified. H.pylori is also be held responsible for non-gastric diseases like coronary heart disease (CAD), atherosclerosis, insulin resistance and diabetes mellitus [5]. In a small number of patients, the infection spontaneously disappears within a few weeks to a few months and the mucosa returns to normal. However, in most cases, the host's immune response is insufficient to eliminate the infection; chronic gastritis characterized by intense lymphoplasmacytic infiltration,

increased polymorphic neutrophils [6,7]. The relationship between H.pylori and gastric cancer is obvious. Persistent inflammation of the gastric mucosa with H. pylori results in atrophic gastritis, a risk for gastric cancer. Atrophic gastritis has an intense neutrophil infiltration. Myeloperoxidase (MPO) is released from neutrophils, which creates gastric mucosal damage [8-10].

Myeloperoxidase, the lysosomal enzyme, localized in polymorphonuclear neutrophils and monocytes and released in oxidative stress. MPO catalyzes the reaction producing hypochlorous acid (HOCl) which causes DNA damage in the host cell [11]. In a study, the MPO level of neutrophils was found to be higher in gastric cancer patients than the healthy control group [12]. With H.pylori inflammation, ROS production, MPO activity, tissue factor, and plasminogen activator inhibitor release are stimulated [13].

Myeloperoxidase plays an active role in the antibacterial mechanism associated with  $H_2O_2$  and has a bactericidal effect on microorganisms such as Escherichia coli, Lactobacillus acidophilus, Staphylococcus aureus and Actinobacillus

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actinomycetemcomitans [14]. In response to infectious agents and other stimuli, the phagocytic cells of the immune system (neutrophils, eosinophils, and monocytes/macrophages) show a rapid consumption of O<sub>2</sub>, called respiratory burst. Respiratory burst is the main source of superoxide, hydrogen peroxide, hydroxyl radical, HOCl and reactive nitrogen compounds (RNOS). Recent research has shown that high MPO levels are associated with atherosclerotic diseases, coronary artery disease (CAD) formation, and myocardial infarction (MI) [15].

Increased MPO activity combined with decreased catalase (CAT) activity creates an environment of increased reactive oxygen species (ROS) that are implicated in various cancers and chronic respiratory inflammation [16].

Eradication treatment is indicated for *H. pylori* infection. With eradication treatment, *H. pylori*-associated gastric cancer formation can be prevented [17]. After the eradication of *H. pylori*, the patients who have unexplained iron deficiency anemia and immune thrombocytopenic purpura (ITP) in addition to *H. pylori* gastritis, showed improvement in other conditions also [18].

In this study, we investigated gastric mucosa and serum MPO enzyme levels in *H. pylori* infected patients and the effect of eradication therapy on serum MPO level.

## Material and Methods

Patients admitted to Gastroenterology Clinic and underwent esophago-gastroduodenal endoscopy between 2010 and 2012 were assessed for enrollment. The medical ethics committee of Ankara University (12.09.2011 / 35-766) approved the study protocol and all patients gave informed consent. All patients were informed about the study protocol and written consent was obtained from each. Patients between 18 and 65 years of age were included in the study. Patients with previous gastric surgery, cholecystectomy, liver failure, renal failure, cardiac failure, malignancy, chronic obstructive pulmonary disease, diabetes mellitus, cerebrovascular disease, collagen tissue disease were excluded. Patients' medical history, liver function tests, kidney function tests, blood glucose tests and physical examination results were used to identify the presence of exclusion criteria. Patients who received antibiotics, histamine two receptor antagonists or proton pump inhibitors within the past two weeks and patients with alcohol and tobacco consumption were also not included.

Venous blood samples were drawn from all patients at the time of admission. Aspartate Transaminase (AST), Alanine Transaminase (ALT), Gamma-Glutamyl Transferase (GGT), Alkaline Phosphatase (ALP), total protein, albumin, total bilirubin, direct bilirubin, total cholesterol, high-density lipoprotein, low-density lipoprotein (LDL), triglycerides, sedimentation, white blood cell count, hemoglobin and platelet count were analyzed within 30 minutes. Blood samples were centrifuged and stored at -80°C until the analysis of serum MPO activity.

Endoscopic examinations were performed using Fujinon, EG-450WR5. During endoscopy, biopsy samples from antrum and corpus were taken for histopathological examination and *H. pylori* diagnosis. For histopathological assessment, the Sydney Classification was used, and the samples were stained with

hematoxylin and eosin. *H. pylori* was identified by Giemsa staining.

Measurement for the human MPO activity, the human MPO Instant ELISA kit of eBioscience Company, was used. The serum MPO level was measured following the instructions of the manufacturer. The serum MPO level was given in pg/mL. MPO kit was purchased from Immundiagnostik AG. Data were analyzed using GraphPad Prism version 4.0 c (GraphPad Inc., San Diego, California, USA).

For the detection of myeloperoxidase activity in tissues, immunohistochemical staining with anti-myeloperoxidase antibody (rabbit polyclonal, 1:100; Thermo, USA) was applied for 30 minutes, using an indirect peroxidase method on the autostainer (Bond; Leica Biosystems, Newcastle, UK). Normal tonsil tissue was used as a positive control. Cytoplasmic staining in granulocytic cells in gastric biopsies was accepted as a positive result. The extent of staining was scored as follows: negative (no staining in inflammatory cells), mild (staining of less than 10% of inflammatory cells), moderate (staining of 10% to 50% of inflammatory cells), severe (staining of more than 50% of cells). In the evaluation of Tissue MPO activity, categories were compared numerically also. For this purpose, the categories for tissue MPO activity scored as; Negative (no staining in inflammatory cells), mild (less than 10% staining of inflammatory cells), moderate (10% to 50% staining of inflammatory cells), severe (over 50% staining of cells) activities.

Patients who were diagnosed with *H. pylori* received quadruple therapy including rabeprazole 20 mg b.i.d., colloidal bismuth subcitrate 600 mg b.i.d., tetracycline 500 mg q.i.d. and metronidazole 500 mg t.i.d. for 14 days. Eight weeks after eradication therapy, patients were assessed with the C14 urea breath test (Heliprobe, Kibion AB Uppsala, Sweden). Patients with negative urea breath test were drawn blood samples again for MPO measurement. Blood samples were centrifuged and stored at -80°C until assay.

SPSS version 15 was used for statistical analysis. Continuous variables were expressed as mean or median according to their homogeneity, and categorical variables were expressed as a ratio. The normal distribution of the variables was assessed using the Kolmogorov Smirnov test. Comparison of variables was made with Student's t-test, Mann Whitney U test or Chi-square test, where applicable. Wilcoxon test was performed for comparison of pre and post-treatment serum MPO levels. P-value <0.05 was considered as statistically significant.

## Results

In total, 107 patients were included in the study. *H. pylori*-negative group (Group 1) was 28 patients and *H. pylori*-positive group (Group 2) was 79 patients. Serum and tissue MPO activity were examined in 107 patients, serum MPO levels of 43 patients were determined following eradication therapy. The demographic and clinical characteristics of the patients in Group 1 and 2 are shown in Table 1. There was no significant difference between the groups in terms of gender and age.

Tissue MPO levels were significantly higher in Group 2 than in Group 1 (p <0.001). Serum MPO levels were not significantly different between Group 1 and Group 2 patients (P = 0.266) (Table 2).

**Table 1.** Laboratory and demographic parameters of groups

| Parameters               | H. Pylori negative group (n=28) * | H. Pylori positive group (n=79) * | P value |
|--------------------------|-----------------------------------|-----------------------------------|---------|
| Mean age, years          | 35.2 (± 11.5)                     | 36.0(± 10.4)                      | 0.731   |
| Female/male (n %)        | 17/11 (%60.7/39.3)                | 44/35 (%55.7/44.3)                | 0.645   |
| WBC (kμ/L)               | 6.9(±2.4)                         | 7.1(±1.8)                         | 0.774   |
| Albumin (mg/dL)          | 4.3(0.44)                         | 4.3(0.28)                         | 0.911   |
| HDL (mg/dL)              | 43.2(± 12.3)                      | 44.6(± 11.4)                      | 0.589   |
| Glucose (mg/dL)          | 89(13.25)                         | 89(16)                            | 0.559   |
| HGB (g/dL)               | 13.9(2.58)                        | 14.6(2.4)                         | 0.129   |
| Thrombocyte (103/μL)     | 228(±65.6)                        | 224(±55.4)                        | 0.738   |
| Sedimentation (mm/hour)  | 8(16.25)                          | 7(13)                             | 0.249   |
| AST (U/L)                | 20(7.5)                           | 21(8)                             | 0.865   |
| ALT (U/L)                | 16(13)                            | 19(17.25)                         | 0.177   |
| GGT (U/L)                | 16(10.5)                          | 17(10.5)                          | 0.744   |
| ALP (U/L)                | 71.5(75.5)                        | 72(61.25)                         | 0.821   |
| Total protein (mg/dL)    | 7.4(± 0.4)                        | 7.4(±0.4)                         | 0.886   |
| Total Bilirubin (mg/dL)  | 0.83(0.67)                        | 0.74(0.46)                        | 0.411   |
| Direct Bilirubin (mg/dL) | 0.18(0.17)                        | 0.18(0.11)                        | 0.425   |
| BUN (mg/dL)              | 25.5(8.63)                        | 23.7(12.2)                        | 0.994   |
| Creatinine (mg/dL)       | 0.79(0.24)                        | 0.8(0.2)                          | 0.755   |
| LDL (mg/dL)              | 92.2(47.75)                       | 97.4(44.6)                        | 0.356   |
| Triglyceride (mg/dL)     | 75(76.5)                          | 85(82.5)                          | 0.392   |

\*The values are presented as median (interquartile range IQR) or mean (±standard deviation).

Abbreviations: WBC - White Blood Cell; HDL - high-density lipoprotein; HGB – Hemoglobin; AST - aspartate transaminase; ALT – alanine transaminase; GGT - Gamma-Glutamyl Transferase; ALP - Alkaline Phosphatase; BUN - Blood Urea Nitrogen; LDL - low-density lipoprotein.

**Table 2.** Serum and tissue MPO of study groups

|                     | Group 1 (n=28) H. pylori-negative | Group 2 (n=79) H. pylori-positive | P value |
|---------------------|-----------------------------------|-----------------------------------|---------|
| Tissue MPO activity | 0.5(1)                            | 2(1)                              | <0.001  |
| Serum MPO levels    | 2.19(1.91) * ng/mL                | 2.69(2.45) * ng/mL                | 0.266   |

\*The values are presented as median (interquartile range IQR). Abbreviations: H. pylori - Helicobacter pylori; MPO – Myeloperoxidase.

When tissue MPO activity distribution of H.pylori positive and negative groups were examined; 79 patients who were positive for H.pylori, 13 (16.5%) had no tissue MPO activity, 22 (27.8%) were mild, 28 (35.4%) were moderate, and 16 (20.3%) had high levels of tissue MPO activity. Twenty-eight patients with H.pylori negative, 14 (50%) had no tissue MPO activity, 12 (42.9%) were mild, 1 (3.6%) was moderate, and 1 (3.6%) had high levels of tissue MPO activity (Table 3), (Figure 1).

A total of 79 H.pylori positive patients who received eradication therapy; only 46 of them admitted to our clinic a performed urea breath tests, of those 43 were negative, and three were positive. Post-treatment serum MPO levels were found to be significantly lower than pre-treatment serum MPO levels (p = 0.002) (Table 4).

**Table 3.** Comparison of tissue MPO activity distribution between H.pylori positive and negative groups

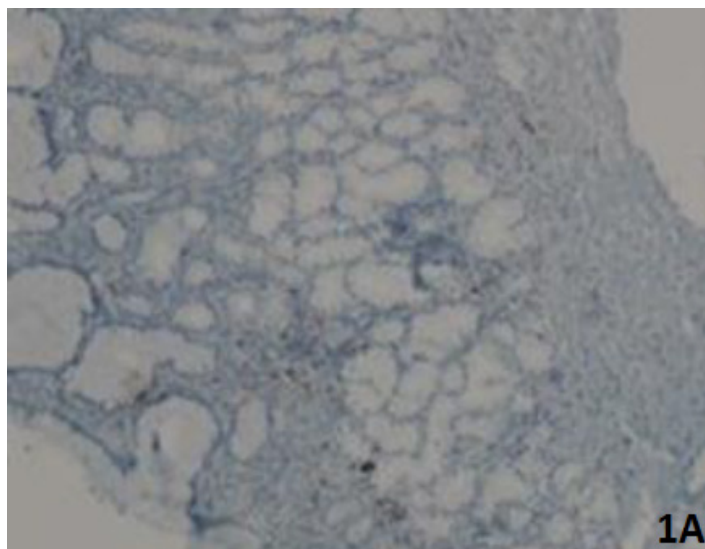
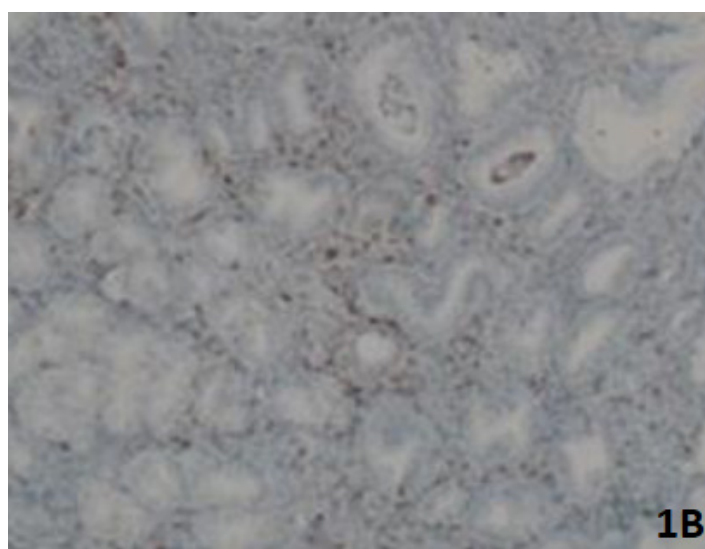
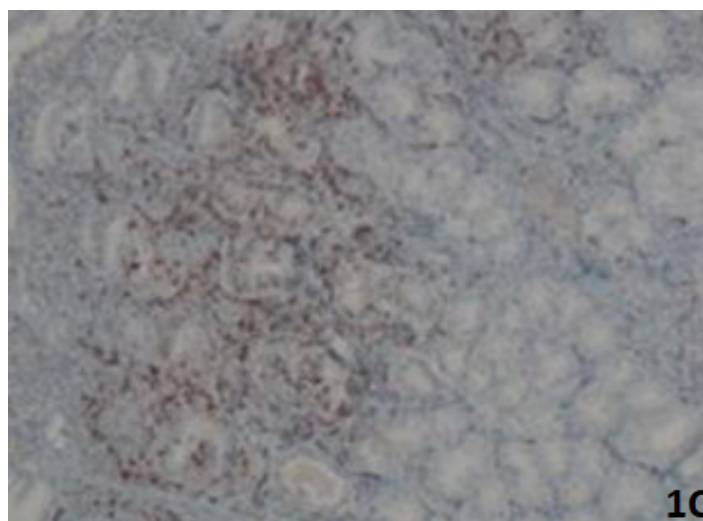
| Tissue MPO activity* | H.pylori positive group | H.pylori negative group |
|----------------------|-------------------------|-------------------------|
| Negative             | 13 (%16.5)              | 14 (%50)                |
| Mild                 | 22 (%27.8)              | 12 (%42.9)              |
| Moderate             | 28 (%35.4)              | 1 (%3.6)                |
| Severe               | 16 (%20.3)              | 1 (%3.6)                |
| Total                | 79 (%100)               | 28 (%100)               |

\*For Tissue MPO activity numeric comparison categories scored as: Negative: No staining in inflammatory cells; Mild: Staining <10% of inflammatory cells; Moderate: Staining 10% -50% of inflammatory cells; Severe: Staining >50% of cells.

**Table 4.** Pre and post-treatment serum MPO activity of study groups

|                    | Pre-treatment<br>H. pylori-positive patients (n=43) | Post-treatment<br>H. pylori-positive patients (n=43) | P value     |
|--------------------|-----------------------------------------------------|------------------------------------------------------|-------------|
| Serum MPO activity | 2.69 (2.45)                                         | 1.26(2.36)                                           | (P=0.002) * |

\*a significant difference was found between the groups. The values are presented as mean (interquartile range IQR).

**1A.** Mild MPO activity in lamina propria (MPO, immunoperoxidaseX100).**1B.** Moderate MPO activity in lamina propria (MPO, immunoperoxidaseX100).**1C.** Severe MPO activity in lamina propria (MPO, immunoperoxidaseX100).**Figure 1.** Scoring the gastric tissue MPO activity either in H. pylori-positive or negative groups patients using immunohistochemical staining with anti-myeloperoxidase antibody (A: Mild; B: Moderate; C: Severe).

## Discussion

This study differs from other studies by the evaluation of both serum and tissue MPO levels in H.pylori infected patients. The effect of eradication therapy was also investigated on serum MPO levels. Tissue MPO activity was found to be significantly increased in H.pylori infection. There was no significant difference in serum MPO levels between H.pylori positive patients and H.pylori negative patients. However, eradication treatment significantly decreased serum MPO levels.

Increased MPO is effective in the antioxidant defense system. MPO is induced by inflammation due to H.Pylori infection.

Induced MPO and HOCl can be effective in local tissue damage, oxidative stress, and cancer pathogenesis. Also, MPO involved in the circulatory system during inflammation may enter the endothelial space and may affect the atherosclerotic process. In a similar study by Sasayama et al. reported that MPO activity in the gastric mucosa was significantly higher in H.pylori-positive patients than in H.pylori-negative patients, but serum MPO activity was not investigated in this study [19].

Similar studies on this subject have shown that patients infected with H.pylori have increased MPO activity in the gastric mucosa, and this increased tissue MPO activity has been associated with atrophic gastritis and gastric cancer due to this gastritis [8,10,11,20].

In another study in which the relationship between gastric cancer and MPO was investigated, the MPO level of neutrophils was found to be high in these patients [12]. Also, H.pylori density and neutrophil infiltration were correlated with MPO levels in gastric mucosa with H.pylori positive gastritis [21-23]. Nevertheless, Akçam et al. investigated the level of MPO activity in gastric mucosa of children infected with H.pylori and not infected with H.pylori. They found no difference in MPO activity between the two groups [24]. However, the number of patients with tissue MPO measured in that study was very low (n = 14).

In the present study, no significant difference was found between H.pylori-positive patients and H.pylori negative patients in serum MPO level. This result may be interpreted as the tissue MPO activity that may be a stronger marker than serum MPO for H.pylori - MPO association. In a similar study by Rautelin et al. H.pylori gastritis and systemic MPO, response relation was investigated and serum MPO levels were reported to increase significantly compared to H.pylori negative patients [25].

In this study, it was shown that there was a significant decrease in serum MPO levels in patients, which became after eradication treatment compared to pre-treatment situation. A similar study on this issue conducted by Nazlıgül et al. has shown that serum MPO levels were significantly reduced after eradication treatment in patients infected with H.pylori. However, in that study, pre-treatment tissue and serum MPO values of H.pylori positive and negative patients were not compared [26]. Also, there are other studies that reported that tissue MPO activity decreased after the eradication of H.pylori [27-30]. Fukuda et al. investigated the neutrophil and MPO activity histologically in H.pylori infected patients after treatment and did not report a significant difference between before and after treatment [31]. However, unlike our study, only H2 receptor antagonists were used for treatment in that study. In another study about this issue, neutrophil infiltration was investigated in the mucosa of patients with a duodenal ulcer and it was observed that neutrophil infiltration containing MPO enzyme decreased as a result of H.pylori eradication treatment [32].

## Conclusion

The ROS produced due to H.pylori infection, results in MPO release from neutrophils. MPO has a strong proinflammatory effect. Decreased MPO activity by H.pylori eradication therapy prevents inflammatory damage to the stomach tissue. Thus, monitoring the effectiveness of H.pylori eradication therapy with MPO levels may reduce the incidence of future gastric neoplasia.

## Limitations

After eradication treatment, H.pylori negativity was evaluated by a noninvasive urea breath test. Therefore, gastric endoscopy did not perform, and post-treatment tissue MPO was not evaluated. Seventy-nine patients with H.pylori were treated with eradication therapy, but 47 efficacy of the treatment of patients was evaluated after eradication in follow up.

## Competing interests

The authors declare that they have no competing interest.

## Financial Disclosure

The authors received no financial support for this study.

## Ethical approval

Medical ethics committee of Ankara University (12.09.2011 / 35-766).

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