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Original Article

The impact of *Helicobacter pylori* eradication on the oxidative stress index

Mehmet Polat, Yaşar Nazlıgül

Department of Internal Medicine, Keçiören Training and Research Hospital, Ankara, Turkey

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Corresponding Author: Mehmet Polat, drmehmetpolat@gmail.com

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ABSTRACT

Aims: The oxidative stress index is the ratio between total antioxidant status (TAS) and total oxidant status (TOS). In this study, we aim to assess the pre and post-eradication oxidative stress status of patients with *Helicobacter pylori* infection.

Methods: A total of 100 patients with *H. pylori*-positive were included in the study. Pre and post-eradication TAS, TOS, and oxidative stress index (OSI) of patients were compared. P<0.05 was assumed statistically significant.

Results: TAS, TOS, and OSI levels did not change significantly following *H. pylori* eradication (p>0.05). 57 of 100 patients infected with *H. pylori* achieved eradication.

Conclusion: This study demonstrates TAS, TOS, and OSI levels may not change following *H. pylori* eradication.

Keywords: *Helicobacter pylori*, oxidative stress, eradication treatment

INTRODUCTION

Helicobacter pylori (*H. pylori*) is an active, urease positive, and (-) gram bacterium curved or thin spiral-shaped, with 4-6 flagella at one end.[1] Approximately half of the World's population is infected with this bacterium. In general, *H. pylori* infection is often seen in socio-economically undeveloped societies. The prevalence of *H. pylori* infection in Turkey has been reported up to 70-80% in adults and 64% in children. *H. pylori* is found in 70% of patients with a stomach ulcer, 90-95 % of patients with a duodenal ulcer, and 90 % of patients with stomach cancer.[2,3]

H. pylorus produces free oxygen radicals in the organism by targeting the mitochondria in the cell and causes oxidative stress.[4] It is thought that *H. pylori* infection has a key role in gastric cancer development as it creates stress by increasing the production of free oxygen radicals, which in turn causes DNA damage.[5,6] It is thought that oxidative stress has also a role in the pathogenesis of various diseases.[7]

Oxidative stress index (OSI) is defined as the ratio of the TOS to TAS level. The organism tries to deal with the reactive oxygen metabolites due to metabolic and physiological processes with enzymatic and/or non-enzymatic reactions. Therefore, it is aimed that the organism does not get harmed by these reactive oxygen metabolites. An increase in the oxidant and/or decrease in the antioxidant status leave the organism vulnerable to reactive oxygen radicals and cause cell damage.[8] Antioxidant molecules inhibit these harmful reactions and protect the organism from oxidative stress.[9,10]

In this study, we aim to investigate whether *H. pylori* eradication leads to a change in TAS, TOS, and OSI in patients infected with *H. pylori*.

METHODS

The study was approved by the Keçiören Training and Research Hospital Clinical Researches Ethics Committee (Date:07.04.2009, Decision No: 2009/04/31). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This is a single-center, prospective, and self-controlled study. A total of 100 patients who applied to internal medicine and gastroenterology polyclinics with dyspeptic complaints between April and November 2009 were enrolled in the study.

The diagnosis of *H. pylori* infection depended on the finding of a biopsy taken from the gastric antrum and/or corpus.

Patients were informed about the study and written consent was obtained from those who accepted to participate in the study. Criteria to include in the study were:

1. To be between 30-60 years old
2. Absent of hypertension, heart failure, diabetes, chronic obstructive pulmonary disease, hyperlipidemia, malignancy, liver and kidney failure, cerebrovascular disease,
3. No addiction such as drugs, smoking, and alcohol,
4. Absence of anemia (Hb should be above 12 g/dl), absence of abnormalities in kidney and liver tests, and total bilirubin value below 2 mg/dl
5. Not to be pregnant
6. Not to be on therapy of a proton pump inhibitor, H_2 receptor blocker, antibiotic, or nonsteroidal anti-inflammatory drug in the last 1 month

Patients received 2×30 mg lansoprazole, 2×500 mg clarithromycin, and 2×1000 mg amoxicillin for *H. pylori* treatment for 14 days. 6- 8 weeks following this therapy, a 14C urea-breath test (Heliprobe, Kibion AB Uppsala, Sweden) was applied as eradication control. Urea-breath test was used in a way by collecting breath samples using a dry cartridge system 10 minutes after the capsule form containing 14C urea/citric acid mixture was given with 250 ml of water after 1 night of fasting and following that by evaluating with Geiger-Müller counter.

Following the urea-breath test, blood was taken from the patients and centrifuged at 4000 rpm for 10 minutes in the biochemistry laboratory; plasma was taken in the Eppendorf tube and kept at -86°C. Plasma kept was taken out when the work was completed and made dissolved. Total oxidant status (TOS) and total antioxidant status (TAS) were studied using the Total Oxidant Status Assay Kit and Total Antioxidant Status Assay Kit (Rel Assay Diagnostics®, Gaziantep, Turkey) on the SIEMENS ADVIA 2400 spectrophotometric autoanalyzer device. The following formula was used to calculate the oxidative stress index.

$$OSİ = \frac{\text{TOS, µmol } H_2C_2 \text{ equivalent/L}}{\text{TAS,µmol Trolcx equivalent/L}} \text{ X } 100$$

Statistical Analysis

Data were analyzed by using Statistical Package for Social Sciences (SPSS) 15.0 package program (SPSS Inc. USA). The normal distribution of the data was analyzed with the Kolmogorov-Smirnov test. In the analysis of normally distributed numerical data independent sample t-test; in the analysis of data that were not normally distributed Mann-Whitney U test was used. The chi-square test was used in order to analyze whether there was a difference in terms of gender distribution among the groups. p value less than 0.05 ($p<0.05$) was considered statistically significant in statistical comparisons.

RESULTS

A total of 100 patients with *H. pylori*-positive and who were given eradication treatment were included in the study; a total of 46 men 29 of whom with *H. pylori* eradication and 17 without; a total of 54 women 28 of whom with eradication and 26 without. Demographic and laboratory data of the patient groups are given altogether in the **Table 1**. No significant difference was found in oxidative stress levels between eradicated and non-eradicated groups. Because all the patients included in the study were *H. pylori* positive, no comparison could be made with those with *H. pylori* negative.

Table 1. Demographic and laboratory data of the study groups

	H. pylori eradication (fail), n=43	*H. pylori* eradication (succes), n= 57	P value
Gender, female/male	26/17	28/29	>0.05
Age, years	42.7±7.9	46.0±8.5	>0.05
TAS	2.5±0.4	2.5±0.3	>0.05
TOS	14.6±5.5	15.5±7.9	>0.05
OSI	0.6±0.20	0.6±0.25	>0.05

DISCUSSION

This study investigated the impact of *H. pylori* eradication on the oxidative stress status of patients with *H. pylori* infection. Since the previous studies demonstrated the increased oxidative stress in patients with *H. pylori* infection, whether *H. pylori* eradication is related to recovery in oxidative stress status is not clear. However, this study failed to reveal the impact of *H. pylori* eradication on oxidative status in those patients.

Oxidative stress, named as the imbalance between the production of free oxygen radicals and other oxidants and anti-oxidant defense, is the damage that is caused by reactive oxygen products on biological structures such as proteins, lipids, carbohydrates, and DNA.

Antioxidant products' levels decrease during infection and disrupting this balance causes various pathological changes. When this happens, either the anti-oxidant defense system has weakened or the production of free oxygen radicals has increased or both effects are seen at the same time.[11,12,15] An increase in free oxygen radicals and deficiency in antioxidant systems are accepted to have a role in the etiopathogenesis of gastroduodenal diseases.[16] An important factor for the increase of free oxygen radical levels, which are chemically highly toxic, is also *H. pylori* besides factors such as insufficient antioxidants in the diet and smoking. In the study carried by Davies et al., it is found out that the production of free oxygen radicals has increased in *H. pylori*-positive chronic antral gastritis and there is a correlation between *H. pylori* density in the antral mucosa and free oxygen radicals.[17] One of the characteristic cases of inflammation is the infiltration of the tissue affected by the neutrophils causing the production of ROS in huge amounts in the affected gastric mucosa. It is shown in the studies carried out that the factor causing increased oxidative DNA damage as a result of neutrophil infiltration of the gastric mucosa of *H. pylori* infection is associated with increased ROS production.[18] Moreover, it is known that *H. pylori* infection is associated with increased oxidative stress both in the tissue and the blood.[19,20]

At the same time, it is known that increased oxidative stress plays an important role in gastroduodenal mucosal inflammation observed in the course of *H. pylori* infection, and in the pathogenesis of peptic ulcer and gastric cancer.[21] Gastric epithelium and *H. pylori* also cause the production of IL-8, which contributes to the formation of ROS and at the same time the emergence of IL-1 β, IL-6, IL-8, IL-12, TNF-αand IFN-gamma.[22-26] In general, the production of TNF- α, IL-1 β, IL-6, and IL-8 is correlated with the degree of inflammation, however Bauditz et al., and Tanahashi et al., shown in the studies they carried out that there was no difference between *H. pylori* positive and negative patients. On the other hand, it is shown in several studies that the production of IL-10 and IL-12 is associated with the presence of *H. pylori*.[24-27] Studies have shown that oxidative damage increases in gastric inflammatory diseases (149-151) and that accumulation of oxidative DNA damage in tumor suppressor genes like p53 can have an important role in the formation of gastric cancer.[28-31] DNA damage index has to be determined primarily in most of the methods used to measure oxidative DNA damage. This index can be determined through urinalysis. Although

there are many measurable base damage products in the urine, 8-oxo-dG, which is the most sensitive to oxidation and is easily measured, is preferred.

In studies performed both by direct measurement of 8-hydroxydeoxyguanosine (8-OHdG) residues on DNA and by identifying DNA strand breaks and fpg-sensitive sites, DNA damage was found to be higher in *H. pylori*-infected gastric mucosa than in uninfected normal mucosa.[32-38] Moreover, Laderia et al., in the studies they carried out, found out that oxidative DNA damage was directly associated with the intensity of gastritis in patients with *H. pylori* (+)gastritis and that DNA damage was higher in cases over 50 years of age than in young people.[36] On the other hand, they mentioned in the same study that DNA damage in people infected with *H. pylori* was not only higher in the gastric mucosa but also higher in peripheral leukocytes than in uninfected individuals.[37] Normally, if *H. pylori* infection is increasing oxidative DNA damage, DNA damage is expected to decrease after *H. pylori* eradication treatment.

It has been determined that 8-OHdG level, which has an oxidative DNA stress marker, in the antral mucosa of patients with extensive gastritis is higher than in patients with uninfected gastritis, and that after eradication treatment both 8-OHdG levels in the antral mucosa and gastric juice mutagenicity decrease.[33] Similarly, Hahm et al, reported that 8-OHdG level in biopsy samples taken from gastric mucosa following the eradication treatment in *H. pylori*-positive patients decreased compared to the pre-treatment level.[34] However, in the study Everett et al., carried out to find out DNA damage in epithelial cells obtained from antral biopsy samples in *H. pylori*-positive people, it was reported that DNA damage in normal mucosa is higher than in the area with gastritis and they showed that in biopsy samples taken after 6 weeks of eradication, DNA damage was increased in the gastritis area, but still at a lower level than in the normal mucosa; and they suggested that low DNA damage in gastric epithelial cells infected with *H. pylori* might be due to increased cell transformation in gastritis.[35] Again similarly in the study Farinati et al., carried out they found out that 8- OHdG level increased after *H. pylori* eradication in biopsy samples of antrum in *H. pylori*-infected cases and concluded that eradication treatment would not reduce the damage already occurred.[32] In another study, it was stated that there was no significant difference in urinary 8- OHdGlevels after and before the eradication treatment of children infected with *H. pylori*.[39]

Yoshida et al created *H. pylori* infection empirically in the study they carried out. They reported that neutrophil infiltration increased clearly in the area where infection occurred and in connection with this, lipid peroxidation and hemorrhagic erosions occurred in the gastric mucosa.[40] Malondialdehyde (MDA) level reflects the damage of free oxygen radicals on lipids and the damage they do on the cell membrane and is accepted as an indicator of oxidative damage.

In the study Drake et al., carried out, MDA concentration in *H. pylori* gastritis was found significantly higher than in those who had normal histology.[41] The 8-OHdG level which is accepted as an indicator of oxidative damage in *H. pylori* gastritis was found to be high by Hahmet. al.[34]

Moreover, in a study by Dinçer et al., carried out in Turkey, the effect of eradication treatment performed on *H. pylori*-infected patients on oxidative DNA damage was searched by comet method and they found that DNA damage decreased following the eradication.[42] According to the findings in our study eradication treatment on *H. pylori*-infected persons does not have an effect on TOS and OSI levels, which are oxidative stress markers.

Antioxidants detoxifying free oxygen radicals in the organism are the substances that prevent or delay oxidative damage in the targeted molecule or even repair the occurred damage, and endogenous or exogenous antioxidants can be effective at different stages of an oxidative case. Enzymes taking place in this system are superoxide dismutase, catalase, and glutathione peroxidase.[43,44] It is thought that in defense against free oxygen radicals, the superoxide dismutase (SOD) enzyme could be the first step among endogenous antioxidant enzymes. In a study SOD and glutathione peroxidase (GPX) activities in the mucosa of patients with gastric ulcers are reported to be decreased compared to normal tissue.[45] In our study, no significant change was detected at TAS levels between *H. pylori* positive and negative patients after eradication treatment was given. It is shown that, C vitamin, which is known as an antioxidant, acts as a free radical scavenger in gastric mucosa and that ascorbyl radical level in *H. pylori* gastritis has increased. Again in the same study, following *H. pylori* eradication with combined treatment, the MDA level was found to be lower compared to before the treatment.[41]

In a study realized in Turkey, a significant decrease in free radical levels was found in the *H. pylori* (+) group with single and combined treatments.[46] In the study, Tanyalçın et al. carried out reduced glutathione levels increased after triple eradication treatment.[47] Again in Turkey, in a study carried out by Bahçecoğlu et al., after eradication treatment of *H. pylori*-infected people, MDA, and glutathione peroxidase activity was found significantly to be lower than in the beginning. Thus, they showed in this study that the eradication of *H. pylori* could eliminate the oxidative stress caused by this microorganism.[48] Oxidative stress is associated with many diseases, including gastric diseases such as chronic gastritis, peptic ulcer, gastric cancer, and MALT lymphoma.[49-51] These gastric diseases are a result of *H. pylori* infection, which is believed to be a major etiologic agent.[50-52]In the presence of *H. pylori* infection; gastric mucosa directly encounters the metabolic products of the bacteria. Rapid regeneration in damaged epithelium cells increases the risk of DNA damage.[53] In our study, after eradication treatment was given in patients infected with *H. pylori*, no significant difference was found between the *H. pylori* positive and negative groups in both antioxidant and oxidative stress levels.

CONCLUSION

Although most of the studies have demonstrated antioxidant and oxidant levels can change following treatment of any infection, studies reporting adverse outcomes similar to our study are quite rare. However, it is thought that oxidative stress would be decreased if antioxidant vitamins are given together with eradication treatment.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Keçiören Training and Research Hospital Clinical Researches Ethics Committee (Date: 07/04/2009, Decision No: 2009/04/31).

Informed Consent: Written consent was obtained from the patient participating in this study.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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