ORIGINAL ARTICLE

Peripheral lymphocyte DNA damage and oxidative status after eradication therapy in patients infected with *Helicobacter pylori*

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KEY WORDS

Helicobacter pylori, oxidative stress index, peripheral lymphocyte DNA damage, total antioxidant status, total oxidant status

ABSTRACT

INTRODUCTION *Helicobacter pylori* infection has been shown to cause inflammation, increased production of reactive oxygen species, and oxidative DNA damage in the gastric mucosa. However, the effect of eradication treatment on DNA damage in patients infected with *H. pylori* is unclear.

OBJECTIVES The objective of this study was to investigate the effect of eradication treatment on peripheral DNA damage and oxidative status in patients wth *H. pylori* infection.

PATIENTS AND METHODS The study involved 42 patients positive for *H. pylori* (Hp+) and 25 patients negative for *H. pylori* (Hp–). Peripheral lymphocyte DNA damage was assessed using the alkaline comet assay and plasma oxidative status was determined. Measurements were conducted at baseline and 2 weeks after eradication treatment.

RESULTS The total antioxidant status (TAS) was lower in Hp+ patients than in Hp– patients ($P < 0.05$), while the total oxidant status (TOS), oxidative stress index (OSI), and peripheral lymphocyte DNA damage were higher ($P < 0.001$ for all parameters). TOS, OSI, and peripheral lymphocyte DNA damage were significantly lower after eradication treatment ($P < 0.001$ for all parameters), while TAS was significantly higher ($P < 0.05$). There was no correlation between TOS, OSI, peripheral lymphocyte DNA damage, and TAS and the histopathological degree of antral gastric inflammation in the Hp+ group ($P > 0.05$).

CONCLUSIONS Our results suggest that *H. pylori* eradication significantly decreases peripheral lymphocyte DNA damage and oxidative stress. Eradication treatment might help prevent the development of gastric cancer in patients with *H. pylori* infection.

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INTRODUCTION *Helicobacter pylori* is a noninvasive, microaerophile, nonspore-forming, and spiral-shaped microorganism.[1] *H. pylori* interaction with genetic and environmental factors and diet jointly affects the risk of developing human disorders. *H. pylori* causes chronic atrophic gastritis, intestinal metaplasia, dysplasia, and carcinoma in humans.[2] Also, *H. pylori* infection induces gastric epithelial cell apoptosis.[3] Moreover, several reports have suggested that *H. pylori* might be a major determinant in the development of gastric cancer.[4,5] This is considered to be due to pathogen-inherent virulence factors and the type and intensity of the oxidative stress induced by inflammation.[6] Furthermore, eradication of *H. pylori* infection in combination with antibiotic therapy cures most cases of gastric lymphoma and slows the progression to gastric adenocarcinoma.[7]

Bacterial products and reactive oxygen species (ROS) released at the site of inflammation can

damage DNA, which occurs at the early stage of gastric carcinogenesis. Genomic damage has also been reported to be associated with many pathological conditions and processes (e.g., various cancers, neurodegenerative diseases, inflammation/infection, aging).[8,9] Moreover, *H. pylori* causes inflammation in the gastric mucosa, which eventually produces large amounts of ROS and causes DNA damage.[10,11]

The comet assay (single-cell gel electrophoresis) is a well-established genotoxicity test. It is quick, easy, and allows to make observations at the level of single cells.[12] This simple and sensitive technique has been used for example to assess the extent of endogenous DNA damage. Furthermore, the comet assay is potentially useful in estimating DNA damage at the single-cell level, and it allows to identify DNA damage in individual cells.[13,14]

Plasma total antioxidant status (TAS) is an accurate index of oxidative stress and provides a measure of total plasma defenses against oxidative stress.[15] An inverse relationship between TAS and peripheral lymphocyte DNA damage was determined previously.[16,17] Several studies have reported that peripheral lymphocyte DNA damage is caused by multiple factors including oxidative stress[18,19] and inflammation.[20]

There are conflicting data about the effect of *H. pylori* eradication on the level of DNA damage.[21-25] Thus, the objective of this study was to investigate the effect of eradication treatment on peripheral lymphocyte DNA damage measured using the comet assay along with oxidative status parameters in patients with *H. pylori* infection.

PATIENTS AND METHODS

Subjects

A total of 67 patients who underwent upper gastrointestinal endoscopy for evaluation of dyspeptic symptoms were included in this prospective study. Patients were classified into 2 groups according to the presence of *H. pylori* infection. Forty-two patients were positive for *H. pylori* (Hp+) and 25 patients were negative (Hp–).

We excluded patients treated with antibiotics or receiving drugs interfering with free radical production, such as nonsteroidal anti-inflammatory drugs or antioxidant supplements (e.g., vitamins C, A, and E, and selenium), patients with systemic infection or with a history of gastrointestinal surgery. The other exclusion criteria were as follows: reported or clinically suspected alcohol abuse (defined as chronic consumption of ethanol exceeding 80 g/d in men and 40 g/d in women), use of proton pump inhibitors and/or anti-H_2 receptor antagonists and aspirin. All patients were nonsmokers.

After overnight fasting, topical pharyngeal anesthesia was applied and upper endoscopy was performed by an experienced endoscopist using a videoendoscope (Olympus GIF XQ 30, Tokyo, Japan).

After the initial endoscopy, a total of 42 Hp+ subjects received the same eradication therapy: amoxicillin 1 g b.i.d. clarithromycin 500 mg b.i.d. and lanzoprazole 30 mg b.i.d. for 1 week.

H. pylori clearance was consistently shown in 37 patient by the 13C-urea breath test, which was performed 2 weeks after the first procedure. The value of the test over 3% was considered as indicative of *H. pylori*.

The study protocol was carried out in accordance with the Helsinki Declaration as revised in 2000. All subjects were informed about the study protocol and provided their written consent.

Diagnosis of *H. pylori* infection

During upper gastrointestinal endoscopy, 2 antral biopsy samples were obtained for the rapid urease test (CLO test) and histopathologic examination. *H. pylori* was considered to be present when the rapid urease test and histological examination were positive. Biopsy material was stained with hematoxylin and eosin for histopathological examination and evaluated according to the updated System of Sydney.[26] If the urease test and histology were positive, the diagnosis of *H. pylori* infection was confirmed. If both tests were negative, the patient was considered *H. pylori*-negative.

Measurement of the total antioxidant status

Plasma TAS was measured using an automated method developed by Erel.[27] The results are expressed as mmol Trolox equiv./l.

Measurement of the total oxidant status

Serum total oxidant status (TOS) was measured using a novel automated method developed by Erel.[28] The results are expressed as μmol H_2O_2 equiv./l.

Determination of the oxidative stress index

The percent ratio of TOS to TAS level was accepted as the oxidative stress index (OSI).[29] OSI (arbitrary unit) = TOS (μmol H_2O_2 equiv./l)/TAS (mmol Trolox equiv./l).

DNA damage determination by alkaline comet assay

After an overnight fasting, 6 ml of peripheral blood sample was withdrawn into a heparinized tube from each subject, kept on ice, and lymphocyte isolation for the comet assay was performed within 2 hours as described elsewhere.[30]

The endogenous DNA damage in lymphocytes was analyzed by the alkaline comet assay according to Singh et al.[12] with a minor modification. After electrophoresis, the slides were stained with ethidium bromide (2 μ/ml in distilled H_2O; 70 μl/slide), covered with a coverslip and analyzed using a fluorescence microscope (Nikon). Images of 50 randomly selected cells (25 cells from each of the 2 replicate slides) were analyzed visually from each subject, as described elsewhere.[30,31] Each image was classified according to the intensity of the fluorescence in the comet tail and was given a value of either 0–3 or 4 (from undamaged class 0 to maximally damaged class 4) (FIGURE), so

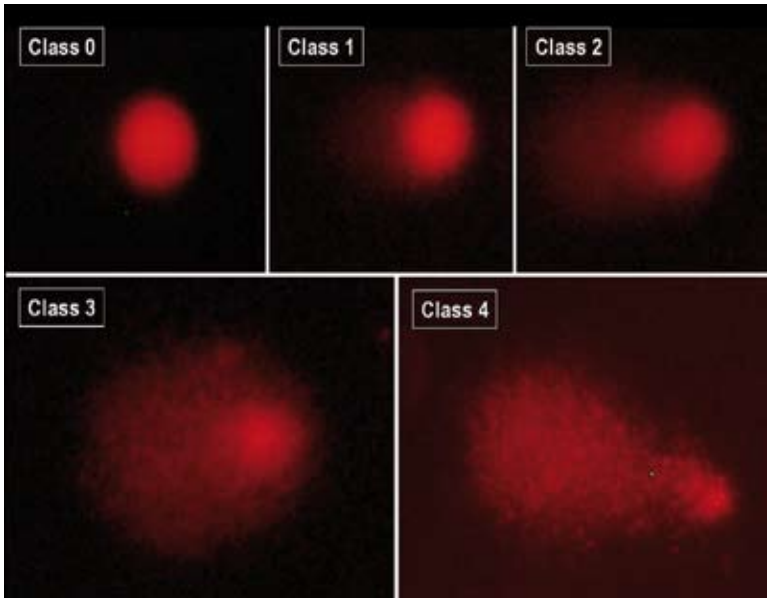

FIGURE Photomicrographs showing the examples of comet classes (class 0 – undamaged; class 4 – maximally damaged)

TABLE 1 Demographic characteristics, peripheral DNA damage, and oxidative status in the study group

Parameters	Hp+ (n = 42)	Hp– (n = 25)	*P*
age, y	38 ±10	36 ±8	NS
women/men	22/20	13/12	NS
BMI, kg/m^2	22.3 ±1.4	21.1 ±1.6	NS
DNA damage, arbitrary unit	84.6 ±28.1	23.1 ±13.2	0.001
TAS, mmol trolox equiv./l	1.61 ±0.29	1.78 ±0.36	0.05
TOS, µmol H_2O_2 equiv./l	6.53 ±1.23	4.92 ±1.54	0.001
OSI, arbitrary unit	4.15 ±1.01	2.92 ±1.38	0.001

Values are presented as mean ± standard deviation.

Abbreviations: BMI – body mass index, NS – nonsignificant, OSI – oxidative stress index, TAS – total antioxidant status, TOS – total oxidant status

that the total scores of slide could be between 0 and 200 arbitrary units.

Blood samples Before the endoscopic preocedure, blood samples were obtained following an overnight fasting. Both at baseline and after eradication treatment in Hp+ patients, peripheral venous blood samples were taken into heparinized tubes in the fasting state. Blood was centrifuged at 3000 rpm for 10 minutes for plasma separation. Plasma samples were stored at –80°C until the analysis of oxidative status parameters.

Statistical analysis The results were expressed as mean ± standard deviation. The comparison of parameters between the Hp+ and Hp– group was performed using the Student's *t* test. The paired sample *t* test was used to compare the levels of DNA damage, TAS, TOS and OSI levels before and after eradication treatment. Correlation analyses were performed using the Pearson's correlation test. The results were considered to be statistically significant when *P* value was less than 0.05.

RESULTS The clinical and demographic data of the study population are shown in TABLE 1. There were no statistically significant differences between the 2 groups with regards to age, sex, and the body mass index ($P > 0.05$) (TABLE 1).

Of 67 patients, 42 had *H. pylori*-associated gastritis confirmed by consistent histology results and a positive urease test. Five patients had bulbar ulcer and signs of duodenal mucosal inflammation. None of the patients were endoscopically diagnosed with gastric ulcer. Twenty-five Hp+ patients were endoscopically diagnosed with antral gastritis. Of 42 patients, 17 had pangastritis.

Patients with *H. pylori* gastritis were assigned to mild (n = 16), moderate (n = 14), and severe (n = 12) gastritis groups, according to the histopathologic degree of inflammation.

After eradication treatment, 5 patients were excluded from the study because the urea breath test was positive. Thus, the results of 37 patients were included in the statistical analysis.

Plasma TAS levels were lower in the Hp+ group than in the Hp– group ($P < 0.05$), while TOS, OSI, and peripheral lymphocyte DNA damage were higher (all $P < 0.001$) (TABLE 1).

Plasma TOS, OSI, and peripheral lymphocyte DNA damage were lower after eradication treatment (all $P < 0.001$), while TAS was higher ($P < 0.05$) (TABLE 2).

After eradication treatment, there were no differences between TOS, OSI, peripheral lymphocyte DNA damage, and TAS in 5 patients ($P > 0.05$). Also, there was no association between TOS, OSI, peripheral lymphocyte DNA damage, and TAS and the histopathological degree of antral gastric inflammation in the Hp+ group ($P > 0.05$). Finally, there was no correlation between TOS, OSI, peripheral lymphocyte DNA damage, and TAS and age in the Hp+ group ($P > 0.05$).

DISCUSSION Oxidative DNA damage is particularly important because it may initiate and promote carcinogenesis.[32,33] Human peripheral mononuclear leukocytes have been widely used to monitor environmentally induced genetic damage by a variety of methods, including micronucleus, chromosome aberration, and sister-chromatid exchange assays.[34] There are various assays for measuring DNA damage, but the comet assay (single-cell gel electrophoresis) is a particularly useful technique.[35] It is simple and sensitive so it quickly gained popularity as a genotoxicity test.[35] Moreover, it has been shown that strand breaks arise from DNA damage generated by oxidative stress.[36] Therefore, we used the commet assay to measure DNA damage in circulating mononuclear leukocytes.

ROS are a crucial factor in the pathogenesis and development of a variety of chronic and degenerative diseases, including cancer and immune dysfunction.[37] ROS have also been shown to cause

TABLE 2 Peripheral DNA damage and oxidative status in patients with *H. pylori*

Parameters	Before eradication treatment	After eradication treatment	*P*
DNA damage, arbitrary unit	86.6 ±28.1	33.3 ±15.7	0.05
TAS, mmol trolox equiv./l	1.61 ±0.29	1.94 ±0.47	0.001
TOS, μmol H_2O_2 equiv./l	6.53 ±1.23	5.03 ±1.94	0.001
OSI, arbitrary unit	4.15 ±1.01	2.70 ±1.21	0.001

Values are presented as mean ± standard deviation.

Abbreviations: see **TABLE 1**

extensive DNA damage, including single-strand breaks, the formation of modified bases, chromosomal damage, and mutations in mammalian cells.[38] Moreover, ROS cause formation of oxidized bases, single-strand breaks, and crosslinking of DNA.[38]

An important type of DNA damage is the base modification 8-hydroxydeoxyguanosine (8-oxodG).[39] Baik et al.[40] demonstrated that *H. pylori* infection may lead to an increase in the 8-oxodG content in the gastric mucosa of patients with *H. pylori* infection. Ladeira et al.[41] reported that in the antrum, the levels of DNA damage are significantly higher in Hp+ patients with gastritis than in noninfected patients with normal mucosa. Also, they found that peripheral blood lymphocytes and the levels of DNA damage are significantly higher in Hp+ patients with moderate and severe gastritis than in noninfected patients.

Siomek et al.[42] reported that *H. pylori*-induced increase in the severity of the lesion is not restricted to the gastric mucosa. They found that in DNA isolated from leukocytes of Hp+ patients, the level of 8-oxodG was significantly higher than in the leukocytes of control subjects. Furthermore, they suggested that premutagenic oxidatively damaged DNA, which is a consequence of infection, may serve as a source of mutations that may lead to cancer development.

In the present study, we measured oxidative status of the study population using TOS and TAS along with the calculation of OSI, an indicator of oxidative stress reflecting the redox balance between oxidation and antioxidation.[27] It is well known that oxidative stres can be defined as an increase in oxidant or a decrease in antioxidant capacity, and various oxidants and antioxidants have additive effects on oxidative status.[43] Although the concentration of plasma oxidants and antioxidants can be measured individually, it may not accurately reflect oxidative status.[44]

In the present study, we observed that Hp+ subjects had higher plasma TOS, OSI, and peripheral lymphocyte DNA damage compared with Hp– subjects. In addition, plasma TAS level was lower in Hp+ subjects compared with Hp– subjects. On the other hand, after eradication treatment of *H. pylori* infection, we found a significant decrease in peripheral DNA damage, TOS and OSI along with a significant increase in the TAS level. A plasma TAS level is an accurate marker of oxidative stress and provides a measure of total plasma defense against ROS. As mentioned above, DNA damage frequently occurs in cells exposed to oxidative stress. Increased oxidative status may initiate lipid peroxidation in cell membranes, damage membrane proteins, or cause DNA fragmentation.[18] In the current study, the presence of an inverse relationship between peripheral lymphocyte DNA damage and TAS suggested that increased DNA damage due to *H. pylori* infection is mainly caused by increased oxidative stress. We observed no relationship between TOS, OSI, peripheral lymphocyte DNA damage, and TAS and the histopathologic degree of antral gastric inflammation in the Hp+ group. Moreover, we could not demonstrate a relationship between TOS, OSI, peripheral lymphocyte DNA damage, and TAS and age in the Hp+ group.

Previous studies have shown that eradication of *H. pylori* infection affects the level of DNA damage.[21-25] However, the results of these studies are conflicting, probably due to different methods used to measure DNA damage. A number of studies reported that 8-OHdG levels were significantly decreased after eradication treatment in patients with *H. pylori* infection.[22,23] Conversely, Everett et al.[24] found that DNA damage was significantly lower 6 weeks after eradication treatment in this patient group. On the other hand, several investigators reported that no significant differences were found in the levels of 8-OHdG either before or after eradication treatment.[21,25]

Our study has several limitations. First, it is cross-sectional. However, it is only a preliminary study and was designed to obtain information about oxidative stress by measuring plasma peripheral lymphocyte DNA damage and oxidative status in patients with *H. pylori* infection. Second, the number of infected patients in our study was small.

In conclusion, *H. pylori* eradication significantly decreases both peripheral lymphocyte DNA damage and oxidative stress. However, we observed no association between oxidative status, peripheral lymphocyte DNA damage, and the histopathologic degree of antral gastric inflammation in patients with *H. pylori* infection. Eradication treatment may help prevent the development of gastric cancer in patients with *H. pylori* infection. Further studies are needed to clarify the mechanisms underlying this association.

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Uszkodzenie DNA w limfocytach krwi obwodowej i stan oksydacyjny po leczeniu eradykacyjnym u chorych zakażonych *Helicobacter pylori*

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SŁOWA KLUCZOWE

całkowita antyoksydacyjna zdolność osocza, całkowita oksydacyjna zdolność osocza, *Helicobacter pylori*, uszkodzenie DNA w limfocytach krwi obwodowej, wskaźnik stresu oksydacyjnego

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STRESZCZENIE

WPROWADZENIE Wykazano, że zakażenie *Helicobacter pylori* powoduje stan zapalny, zwiększoną produkcję reaktywnych form tlenu i oksydacyjne uszkodzenie DNA błony śluzowej żołądka. Wpływ leczenia eradykacyjnego na stopień uszkodzenia DNA u chorych zakażonych *H. pylori* jest jednak niejednoznaczny.

CELE Celem badania była ocena wpływu leczenia eradykacyjnego na uszkodzenie DNA w limfocytach krwi obwodowej i stan oksydacyjny u chorych zakażonych *H. pylori*.

PACJENCI I METODY Do badania włączono 42 chorych z dodatnimi (Hp+) i 25 z ujemnymi (Hp–) wynikami testów na obecność *H. pylori*. Uszkodzenie DNA w limfocytach krwi obwodowej badano metodą rakietkową i określono stan oksydacyjny osocza. Pomiarów dokonano przed leczeniem eradykacyjnym oraz 2 tygodnie po zastosowaniu tego leczenia.

WYNIKI Całkowita zdolność antyoksydacyjna osocza (*total antioxidant status* – TAS) była mniejsza w grupie Hp+ w porównaniu z grupą Hp– ($p < 0,05$), natomiast całkowita zdolność oksydacyjna osocza (*total oxidant status* – TOS), wskaźnik stresu oksydacyjnego (*oxidative stress index* – OSI) i uszkodzenie DNA w limfocytach krwi obwodowej były zwiększone (dla wszystkich parametrów $p < 0,001$). TOS, OSI i uszkodzenie DNA w limfocytach krwi obwodowej były istotnie zmniejszone po leczeniu eradykacyjnym (dla wszystkich parametrów $p < 0,001$), a TAS był istotnie zwiększony ($p < 0,05$). Nie wykazano związku pomiędzy TOS, OSI, uszkodzeniem DNA w limfocytach krwi obwodowej i TAS a stopniem nasilenia procesu zapalnego w trzonie żołądka określonym histopatologicznie w grupie Hp+ ($p > 0,05$).

WNIOSKI Wyniki naszego badania sugerują, że eradykacja *H. pylori* istotnie zmniejsza uszkodzenie DNA w limfocytach krwi obwodowej i stres oksydacyjny. Leczenie eradykacyjne może pomóc w zapobieganiu rozwojowi raka żołądka u chorych zakażonych *H. pylori*.