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Thiol/disulphide homeostasis in *H. pylori* infected patients

Ahmed Ramiz Baykan[1], Cemile Biçer[2], Emre Gerçeker[3], Özcan Erel[2], Serkan Cerrah[4], Bülent Albayrak[1], Mustafa Utlu[5], Ayşe Kargılı[6]

[1]*Department of Gastroenterology, Erzurum Regional Training and Research Hospital, Erzurum, Turkey*
[2]*Department of Biochemistry, Yıldırım Beyazit University, Ankara, Turkey*
[3]*Department of Gastroenterology, İzmir Gazi Hospital, İzmir, Turkey*
[4]*Department of Gastroenterology, Elazığ Medikalpark Hospital, Elazığ, Turkey*
[5]*Department of Internal Medicine, Erzurum Regional Training and Research Hospital, Erzurum, Turkey*
[6]*Department of Endocrinology, Erzurum Regional Training and Research Hospital, Erzurum, Turkey*

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ABSTRACT

Objectives: The aim of the study was to evaluate the oxidative stress level in patients, diagnosed with *H. pylori* infection, using a novel marker (thiol/disulphide homeostasis) and to compare the level in infected individuals with that in healthy volunteers.

Methods: A total of 60 patients diagnosed with gastritis, erosive gastritis or ulcer by endoscopy were included and biopsied. The 30 patients diagnosed with *H. pylori* and 30 healthy individuals were enrolled. Medical histories, physical examination results, body mass index (BMI), hemogram, free triiodothyronine (FT3), free thyroxine (FT4), thyroid stimulating hormone (TSH), urea, creatinin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, total cholesterol, triglycerides, high density lipoprotein (HDL), low density lipoprotein) LDL and thiol/disulphide levels obtained in the study groups were compared.

Results: There was no significant difference between the total thiol, native thiol, disulphide/native thiol and dissulphide/total thiol ratios of the patient and control group. When the *H. pylori* patients were stratified by endoscopic evaluation as having mild (superficial gastritis or normal appearance) or severe (ulcer or erosive areas) symptoms, there were significant differences in disulphide, disulphide/native thiol, disulphide/total thiol and native thiol/total thiol levels. We also observed BMI and the total, native thiol levels of *H. pylori* patients were inversely related.(r: 0.562, $p = 0.001$; r: 0.0552, $p = 0.002$).

Conclusions: Thiol/disulphide homeostasis is likely to differ with both duration and severity of *H. pylori* infection. Further investigations are needed to investigate the effect of *H. pylori* on oxidative stress.

Keywords: *H. pylori*, thiol, oxidative stress

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Helicobacter pylori is a Gram-negative bacillus about 0. 6×3.5 micron in size, infecting more than 50% of the world's population and regarded as the most common infection worldwide [1].The disease is typically acquired in childhood and continues throughout life [2]. As in many chronic diseases, most patients are asymptomatic, but chronic inflammation may result in gastric ulcers and gastric cancer [3, 4]. Chronic inflammation due to *H. pylori*, also may play a role in the pathogenesis of extragastric diseases such

Address for correspondence: *Ahmed Ramiz Baykan, MD, Erzurum Regional Training and Research Hospital, Department of Gastroenterology, Erzurum, Turkey*
E-mail: ahmedbaykan@hotmail.com

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as atherosclerosis, acute coronary syndrome, chronic immune thrombocytopenic purpura and insulin resistance [5-8].

Reactive oxygen species (ROS) are produced in the human body as a result of normal aerobic metabolism and a balance between production and inactivation is required. Excess production of ROS can lead to a situation of oxidative stress, which is responsible for many pathological processes [9].

Oxidative stress in the gastric mucosa as a result of *H. pylori* infection is a crucial contributing factor to gastric carcinogenesis. Reportedly, infection was shown to correlate with increased damage due to oxidative stress of the gastric mucosa [10]. Although reversible upon bacterial eradication [11], the consequences of oxidative stress are evident through observed changes in global lipid and protein expression [12] and an increase in damaged biomolecules, such as DNA (modification of bases, telomere shortening) [13]. Additionally, anti-oxidant capacity is also reduced due to decreased levels of antioxidant molecules, such as glutathione (GSH) [14] in the gastric mucosa of *H. pylori* infected patients. Chronic inflammation and bacterial virulence factors associated with microbial pathogens causes cellular damage through rupturing lysosome, damaging mitochondria, producing endoplasmic stress and dysregulation of cellular ions balance. These cellular dysfunctioning leads to oxidative stres cathepsin B production, nuclear and mitochondrial DNA damage and genetic instability [15].

Genetic instability resulting from *H. pylori* infection is not clear [16, 17]. Cells are exposed to reactive oxygen species during oxidative processes, and antioxidants like thiol groups, often referred as mercaptans, function to counteract the process that are induced [18]. Thiols are organic compounds that including a sulfhydryl (-SH) group bonded to a carbon atom. A very large proportion of the plasma thiol pool consists of albumin and other proteins, with smaller proportion of low molecular weight thiols such as cysteine, cysteinyl glycine, glutathione, homocysteine and γ-glutamylcystein [19]. The thiol proteins, thiol groups of low molecular weight compounds, cysteine residues and other control groups are reversible converted to disulphide bonds by oxidant molecules. Reduction of disulphide bonds regenerates thiol groups to maintain thiol/disulphide homeostasis [20, 21] (Figure 1). In this study, we compared the thiol/disulphide ratios and plasma thiol levels in *H. pylori* infected patients and healthy controls.

METHODS

This study was performed in accordance with the Helsinki Declaration and it was ethically approved by the institutional committee (ethics committee approval number: 37732058-53/671). The study was conducted between july 2016 and october 2016 at Erzurum Training and Research Hospital. Sixty patients admitted to gastroenterology clinic at various times were included, 30 with *H. pylori* infection and 30 uninfected controls.

Helicobacter infection was detected according to endoscopic biopsy. Patients without *H. pylori* infection as a result of endoscopic biopsy; evaluated as control group. Patients with *H. pylori* infection and control group were stratified by mild (superficial gastritis or normal endoscopic appearance) or severe (ulcer or

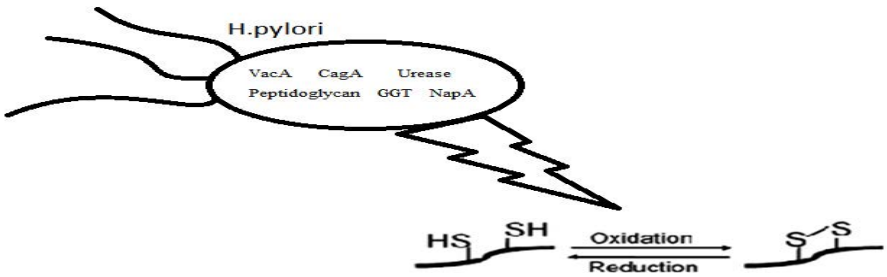

Figure 1. Oxidative stress leads to the formation of unwanted disulphide bonds in the cytoplasm, a process termed disulphide stress. Upon return to non-oxidative conditions, cellular reductases like thioredoxin reduce the cysteine modifications and restore the original protein activity.

erosive areas) symptoms. Patients with other infections, cardiovascular disease, diabetes mellitus, thyroid disease and histories of hypertension history or smoking were excluded. Patient medical histories were obtained, After the measurement of weight and height according to the standard protocol, body mass index (BMI) was calculated using the following formula: BMI (kg/m^2) = weight (kg) / height^2 (m^2).

Endoscopic biopsy specimens were evaluated in department of pathology at Erzurum Training and Research Hospital. Specimens were stained with hematoxylin eosin (H & E) and giemsa for detecting *H. pylori* infection. Results reported by the pathologist.

All blood samples were obtained after a fasting period of 12 hours. A complete blood count, free triiodothyronine (FT3), free thyroxine (FT4), thyroid stimulating hormone (TSH), urea, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, total cholesterol, triglycerides, high density lipoprotein (HDL), low density lipoprotein) LDL were measured. Biochemical analyses were studied by architectc16000 clinical chemistry analyzer (Abbot), complete blood count was studied by sysmex, and thyroid function tests were studied by immulite 2000×pi (Siemens).

The thiol/disulphide homeostasis assay has been previously described. Briefly, disulphide bonds were reduced to form free functional thiol groups. Unused sodium borohydride reductant was consumed and removed with formaldehyde, and both reduced and native thiol groups were determined after reaction with 5,5'-dithiobis-(2-nitrobenzoic) acid. Half the difference between total thiols and native thiols was recorded as the dynamic disulphide homeostasis value. After determination of native thiols (-SH), disulphide (-SS) and total thiols (-SH + -SS), disulphide/total thiol percent ratio (-SS/-SH+-SS), disulphide/native thiol percent ratio (-SS/-SH) and native thiol/total thiol percent ratio (-SH/-SH+-SS) were calculated. Blood samples drawn for determining the thiol/ disulphide level were centrifuges and the plasma was stored at −80 degrees until used. Assays were performed by an automated clinical chemistry analyser (Cobas 501, Roche), and the results were reported as µmol/L.

Statistical Analysis

Data were expressed as mean ± standard deviation (SD). Qualitative variables were assessed by Chisquare test. Correlation analyses were performed using Pearson's correlation test or Spearman's correlation test. The differences between the different groups of controls and patients were analyzed by unpaired test or Mann-Whitney U test. A p value < 0.05 was considered significant. Data were analyzed with the SPSS® for Windows computing program (Version 17.0).

RESULTS

A total of 60 patients, 18 men and 42 women were included in the study; the demographic characteristics and laboratory results are shown in Table 1. The patients in the *H. pylori* group were significantly older (45 years of age) than participants in the control group (39 years of age, $p = 0.004$). There were no significant differences in BMI, biochemical test results, including lipid profiles and thyroid function tests in the two groups. There were no significant between-group differences in complete blood count results except haematocrit. The haemoglobin values were lower in the controls than in the *H. pylori* group, but the difference did not reach significance ($p > 0.05$).

Both total thiol (medians of 447 µmol/L and 442 µmol/L, p = 0.59) and native thiol (medians of 431 µmol/L and 410 µmol/L, $p = 0.55$) were lower in the *H. pylori* than in the control group, but the differences were not significant. Median disulphide levels were 14 µmol/L in the control group and 15 µmol/L in the *H. pylori* group, and no significant differences in disulphide/native thiol, disulphide/total thiol, native thiol/total thiol were found (3.6%-3.4%, 3.3%-3.2% and 9.32%-9.34%, respectively; p = 0.95).

When the *H. pylori* patients were stratified by mild (superficial gastritis or normal endoscopic appearance) or severe (ulcer or erosive areas) symptoms, significant differences were observed in mean disulphide, disulphide/native thiol, disulphide/total thiol and native thiol/total thiol levels (13.4 µmol/L and 17.4 µmol/L, $p = 0.008$; 3.27% and 4.21%, $p = 0.022$; 3.06% and 3.86%, $p = 0.022$ and 93.8 and 92.2%, $p = 0.022$, respectively)

In addition, native thiol level was found to decrease with both age ($p = 0.19$ and BMI ($p = 0.031$). Pearson correlation analysis confirmed significant

Table 1. Demographic characteristics and laboratory results of the study participants

Variables	Control group	*H. pylori* positive group	*p* value
Sex			
Male	9	9	0.78
Female	21	21	0.78
Age (years)	39	45	**0.004**
Native thiol (-SH) (µmol/L)	431 ± 47.31	410.8 ± 34.07	0.55
Total thiol (-SH + -SS) (µmol/L)	457 ± 42.34	442.2 ± 34.15	0.59
Disulphides (-SS) (µmol/L)	14.9 ± 5.49	15.02 ± 4.87	0.98
-SS/-SH (%)	3.602 ± 1.970	3.490 ± 1.272	0.95
-SS/Total -SH (%)	3.35 ± 1.67	3.26 ± 1.54	0.95
-SH/Total -SH (%)	93.2 ± 2.25	93.4 ± 1.19	0.95
BMI (kg/m²)	25.9	24.7	0.39
WBC (10^3/µL)	8.03 ± 2.49	8.16 ± 3.34	0.86
Hemoglobin (g/dL)	13.90 ± 1.72	14.65 ± 1.17	**0.05**
Hemotocrit (%)	42.70 ± 5.16	45.27 ± 3.39	**0.02**
Platelet (10^3/µL)	282.90 ± 69.24	277.10 ± 71.58	0.75
MCV (fL)	84.40 ± 6.80	87.03 ± 3.19	0.06
FT3 (ng/dL)	3.18 ± 0.57	3.40 ± 1.71	0.63
FT4 (ng/dL)	1.07 ± 0.13	1.79 ± 2.66	0.27
TSH (µIU/mL)	1.38 ± 1.10	1.07 ± 0.85	0.24
Glucose (mg/dL)	98.23 ± 16.28	98.13 ± 16.71	0.98
Creatinin (mg/dL)	0.71 ± 0.13	0.71 ± 0.26	0.91
Total cholesterol (mg/dL)	182.62 ± 60.81	183.73 ± 52.35	0.95
Triglyceride (mg/dL)	132.81 ± 66.67	131.83 ± 81.66	0.97
HDL (mg/dL)	47.68 ± 8.50	44.92 ± 9.34	0.41
LDL (mg/dL)	116.31 ± 50.05	123.92 ± 54.97	0.69
Total protein (g/dL)	7.35 ± 0.83	7.48 ± 0.58	0.60
Albumin (g/dL)	4.42 ± 0.30	4.44 ± 0.32	0.81
AST (U/L)	22.26 ± 8.23	23.30 ± 8.73	0.63
ALT (U/L)	21.60 ± 11.93	22.83 ± 12.35	0.69
GGT (U/L)	26.17 ± 26.36	24.23 ± 14.09	0.72
ALP (U/L)	138.13 ± 77.51	99.57 ± 50.51	0.31

BMI = Body mass index, WBC = White blood cell, MCV = Mean corpuscular volume, FT3 = Free triiodothyronine, FT4 = Free thyroxine, TSH = Throid stimulating hormone, HDL = High density lipoprotein, LDL = Low density lipoprotein, AST = Aspartate aminotransaminase, ALT = Alanine aminotransaminase, GGT = Gamma glutamyl transferase, ALP = Alkaline phosphatase

negative correlations of native thiol and total thiol levels with BMI (r = –0.278, $p = 0.031$ and $p = 0.0032$, respectively), blood urea nitrogen (r = −0.277, $p = 0.037$) and HDL level (r = –0.462 and r = –0.469, $p = 0.012$ and $p = 0.010$, respectively) (Table 2).

We found a significant correlation between BMI and total thiol and native thiol. No significant correlation was found in the control group. There was a significant negative correlation between the patient group and BMI. (Table 3).

Table 2. Pearson correlation analysis confirmed significant negative correlations of native thiol and total thiol levels with BMI, blood urea nitrogen and HDL level

		Native thiol	Total thiol
BMI	Pearson Correlation	-0.278	-0.278
	Sig. (2-tailed)	**0.031**	**0.032**
Glucose	Pearson Correlation	-0.065	-0.069
	Sig. (2-tailed)	0.625	0.602
Creatinine	Pearson Correlation	0.049	0.036
	Sig. (2-tailed)	0.711	0.788
Urea	Pearson Correlation	-0.277	-0.277
	Sig. (2-tailed)	**0.037**	**0.037**
GGT	Pearson Correlation	0.088	0.108
	Sig. (2-tailed)	0.506	0.416
Albumin	Pearson Correlation	0.143	0.107
	Sig. (2-tailed)	0.290	0.428
Total cholesterol	Pearson Correlation	0.217	-0.252
	Sig. (2-tailed)	0.240	0.172
Triglyceride	Pearson Correlation	-0.011	-0.020
	Sig. (2-tailed)	0.950	0.909
HDL	Pearson Correlation	-0.462	-0.469
	Sig. (2-tailed)	**0.012**	**0.010**
LDL	Pearson Correlation	-0.197	-0.239
	Sig. (2-tailed)	0.296	0.204
Hemoglobin	Pearson Correlation	0.159	0.186
	Sig. (2-tailed)	0.230	0.159
Platelet	Pearson Correlation	-0.022	-0.037
	Sig. (2-tailed)	0.871	0.779
FT3	Pearson Correlation	0.310	-0.307
	Sig. (2-tailed)	0.084	0.087
FT4	Pearson Correlation	-0.028	-0.003
	Sig. (2-tailed)	0.877	0.988
TSH	Pearson Correlation	-0.141	-0.192
	Sig. (2-tailed)	0.305	0.161

BMI = Body mass index, GGT = Gamma glutamyl transferase, HDL = High density lipoprotein, LDL = Low density lipoprotein, FT3 = Free triiodothyronine, FT4 = Free thyroxine, TSH = Throid stimulating hormone

Tablo 3. Pearson correlation analysis of BMI between patient and control group

	Total thiol		Native thiol	
Patient group	Pearson Correlation	-0.562	Pearson Correlation	-0.552
	Sig. (2-tailed)	**0.001**	Sig. (2-tailed)	**0.002**
Control group	Pearson Correlation	-0.072	Pearson Correlation	-0.061
	Sig. (2-tailed)	0.704	Sig. (2-tailed)	0.747

BMI = Body mass index

DISCUSSION

In this study; total thiol, native thiol and disulphide levels, which playing key roles in responding to oxidative stress in patients with *H. pylori* infection, were evaluated. No significant differences between the infected patients and control participants were observed even though total thiol and native thiol levels were lower in the *H. pylori* patients. Total and native thiol levels were correlated with BMI, HDL, BUN levels.

Thiols are organic compounds that include a sulfhydryl group with a critical role in reacting to oxidative stress in cells, and many previous studies investigated low molecular weight protein thiols. In this study, the method preciously described by Erel and Neselioglu [22] was used to determine plasma dynamic thiol disulphide level. In Naja *et al*.'s study [23], evaluated total thiol as oxidative stress level, has found no significant difference in the plasma thiol level in *H. pylori* infected patients compared with controls.

H. pylori has several virulence factors (CagA,VacA, urease, GGT, etc). These factors are strongly associated with carcinogenesis, severity of inflammation, duodenal ulcer, and probably different levels of oxidative stres [24]. There are some studies, emphasizing the importance of these virulence factors (vag A +, GGT +, NapA +) in relation to the severity of oxidative stress [25-27]. In our study when the endoscopic results were stratified as mild (normal or only superficial gastritis) and severe (ulcer or erosion formation), statistically significant differences in disulphide, disulphide/native thiol, disulphide/ total thiol and native thiol/ total thiol values obtained (Figure 2).

Thioredoxins are highly conserved throughout a wide range of organisms, and they are essential for the isurvival of oxygen-sensitive cells. The gastric pathogen *H. pylori* uses the thioredoxin system to maintain its thiol/disulfide balance. The glutathione-glutaredoxin (GSH) reduction system is often used in

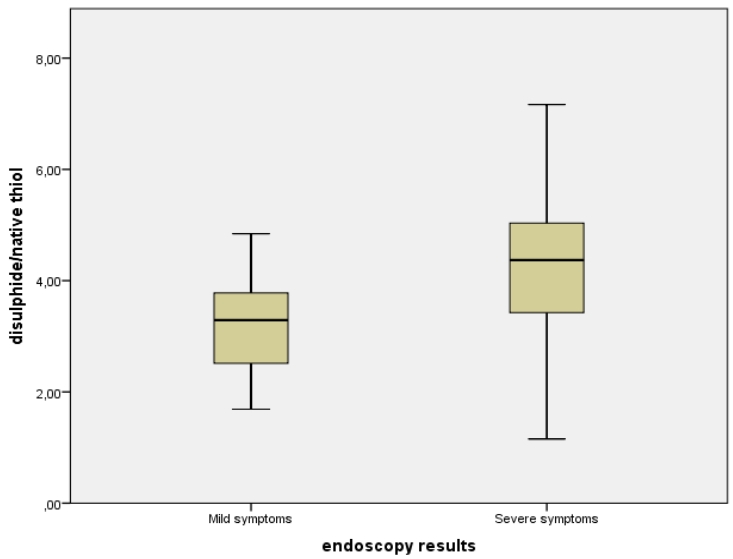

Figure 2. Disulphite/native thiol distribution in groups. Significant differences were observed in mean disulphite/native thiol levels when the *H. pylori* patients were stratified by mild or severe symptoms ($p = 0.02$)

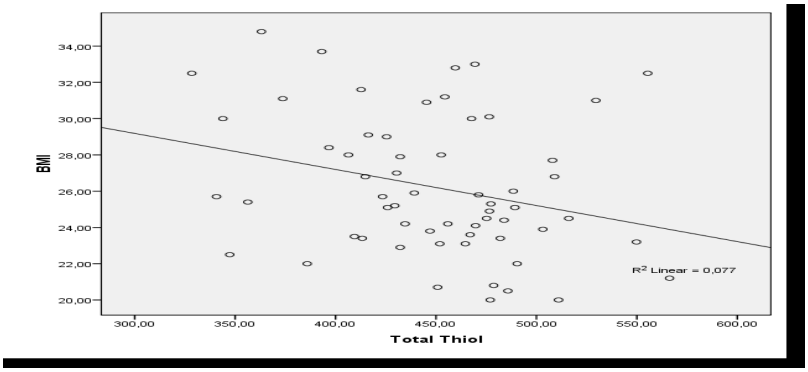

Figure 2. Pearson correlation analysis confirmed negative correlations of total thiol levels with BMI (*H. pylori* positive participants) (r = -0.562, p = 0.001).

addition to the Trx system in bacteria to maintain a reduced state inside the cell [22]. Organisms that lack GSH, such as Lactobacillus casei, Bacillus subtilis, Bacteroides fragilis, Staphylococcus aureus, and *H. pylori*, presumably must rely on the Trx system to maintain thiol/disulfide balance in the cell [21, 23-26]. The mechanisms for the maintenance of this balance in *H. pylori* have not been studied in great detail. Some studies suggest mutation of these genes are important for response to oxidative stress. Also infection with these mutant helicobacter strains may affect the oxidative stress level in host.

In addition to *H. pylori*, there are many other stressors affecting gastrointestinal tract such as nonsteroidal anti-inflammatory drugs, gastric acid, ischemia-reperfusion, and mental stresses. Theses stressors generate free radicals within gastrointestinal tissues. Generally, gastrointestinal tract can withstand such oxidative stresses to some extent by enhancing its antioxidant system [28]. Briefly, the difference results in oxidative stress levels might be due to both host-induced factors, h pylori and its different strains.

Many recent publications have evaluating the correlation between oxidative stress, and obesity [29-32]. Although this condition is thought to be caused by deterioration of oxidant-antioxidant equilibrium as a result of increased inflammation and body distribution along with obesity, there are also studies that have not been found to correlate with BMI and oxidative stress [33, 34]. In our study, We found a significant correlation between BMI, totol thiol and native thiol. However, when the patient and control group were evaluated separately, this negative correlation was evaluated only in the patient group in the pearson correlation analysis. No significant correlation was observed in the control group. We think that this situation is due to increased oxidative stress by addition of obesity in *H. pylori* patients with low total and ative thiol levels. (Figure 3).

Additionally, we also found a significant correlation between HDL, BUN levels and total, native thiol levels. This correlation was also found in other studies with similar method [29, 35, 36].

Limitations

One of the study limitations was that the number of participants in the severity-stratified groups was not large enough to allow for evaluation of subpopulations.

CONCLUSION

In conclusion, no significant correlations of total thiol, native thiol and disulphide levels with the presence of *H. Pylori* were observed, even though total thiol and native thiol levels were lower in the *H. pylori* group. However, total thiol, native thiol and disulphide levels were observed to be significantly decreased in patients with severe symptoms. And we also observed BMI and the total and native thiol levels of *H. pylori* patients were inversely related.

Ethics approval and consent to participate

The study was approved by the Erzurum Training and Research Hospital ethics committee (ethics committee approval number: 37732058-53/671), and was conducted following the ethical guidelines of the Declaration of Helsinki.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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