Coenzyme Q10 in Combination With Triple Therapy Regimens Ameliorates Oxidative Stress and Lipid Peroxidation in Chronic Gastritis Associated With H. pylori Infection

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Abstract
Chronic gastritis associated with H. pylori infection causes oxidative stress in the stomach. This study aimed to evaluate the therapeutic effects of coenzyme Q10 among gastric patients infected by H. pylori. By a clinical trial, chronic gastric patients infected by H. pylori were randomly divided into 2 groups: intervention and placebo. The placebo group received a standard triple therapy regimen, and the intervention group received the triple regimen + coenzyme Q10 (CoQ10). Mean inflammation score; serum levels of 3 serum markers were then compared. A total of 100 participants of whom 67% were female were evaluated. The mean age of participants was 59.4 ± 11.4 years. The mean inflammation score was considerably decreased at the end of the study, in the intervention group. The mean levels of total antioxidant capacity (TAC) and glutathione peroxidase (GPx) at the end of the study were reduced among the triple therapy group (P < .05, P = .03 respectively). The mean levels of TAC and GPx were significantly higher among the intervention group at the end of the study compared with those at the start of the study. The combination of triple therapy with CoQ10 demonstrated an effective outcome on the mucosal inflammation, and stress oxidative in patients with chronic gastritis.

Keywords
chronic gastritis, H. pylori, coenzyme Q10 (CoQ10), total antioxidant capacity (TAC), glutathione peroxidase (GPx), malondialdehyde (MDA), inflammation

Gastritis is an inflammatory response of gastric mucosa to injury and is characterized by infiltration of inflammatory cells including lymphocytes and plasma cells. This inflammation involves primarily superficial mucosa and gastric glands that may cause severe destruction of glands, atrophy, and metaplasia. Various etiologic factors can result in gastritis including chemical, immunologic and genetic factors as well as infectious diseases.¹,² According to some reports, oxidative stress and antioxidant activities of the enzymes are affected by H. pylori infection and gastric cancers during gastritis.³,⁴ Oxidation is the phenomenon of transferring an electron from one atom to another that is a vital process for aerobic cells. The electron is captured by oxygen, and the energy needed for this transference is applied by adenosine triphosphate.⁵,⁶ Any disturbance of the oxidation process causes deleterious effects such as oxidation of enzymes, proteins, carbohydrates, DNA, and lipids of cells’ mucosa.⁷,⁸ Some studies have reported that inefficient intake of antioxidants and vitamins has been accompanied by increasing risks of cancer. For example, the reduction of vitamin A or carotenoids was associated with increased risk of mortality because of pulmonary cancers.⁹–¹¹ Also, the serum level of ascorbic acid was reduced among patients suffering from cancers of the colon, breast, stomach, and respiratory system.¹²,¹³ The main role of antioxidants during cancer diseases is to act as a scavenger for free radicals that can launch lipid peroxidation.¹⁴ Coenzyme Q10 (CoQ10), primarily detected in mitochondria in 1957, is synthesized naturally in the human body and has an essential effect on the production of energy via aerobic

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Submitted for publication 22 January 2015; Revised 28 March 2015; accepted 31 March 2015.

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metabolism and cellular respiration.15 This molecule has a key role in cellular metabolism, antioxidant protection, and organ activities.16 In addition, CoQ10 plays a main role in some important cellular activities including the electron transport chain in mitochondria and homeostasis regulation.17 The antioxidant effects of CoQ10 among patients with cardiovascular diseases, different organ cancers such as colon, prostate, breast, and lungs, and its anticancer effects in laboratory media have been reported by many studies.18–20 Recent experimental studies have revealed the antioxidant effects of CoQ10 in experimental models in the prevention of oxidative injuries as well as lipid peroxidation production during gastritis.21 There have been no studies performed on the antioxidant characteristics or other gastrointestinal effects of CoQ10 among chronic gastritis patients, and this study aimed to evaluate the antioxidant effects of CoQ10 on oxidative stress and lipid peroxidation among gastric patients affected by H. pylori infection.

Materials and Methods

This study was approved by the research ethics committee of Ilam University of Medical Sciences, Ilam, Iran, and was received institutional review board approval of EC/92/H/213 (clinical trial registration code: IRCT2014070118310N1). All patients completed informed consent forms before starting the study.

Study Protocol

By a double-blind clinical trial, all dyspeptic patients attending the gastrointestinal clinics for endoscopic evaluation in Ilam city during 2012–2013 were enrolled in this study. Patients who were confirmed to have H. pylori infection by both endoscopy and histopathology evaluations were randomly divided into 2 groups: treatment and placebo.

Exclusion criteria were pregnancy, lactation, recent antibiotic application (6 recent weeks), recent attempt at H. pylori treatment, recent stomach surgery, positive history of alcohol consumption or addiction, having infections or malignancies in other organs, cardiovascular diseases, diabetes, inflammatory bowel disease, autoimmune diseases, and respiratory diseases. Inclusion criteria were patients who had suffered from confirmed dyspepsia and H. pylori infection. Patients were informed about the study’s aim, and all the participants completed consent forms. All the demographic data were collected by a standard questionnaire and via interview, and the clinical results were entered into prepared forms. Before endoscopy, a 10-mL vein blood sample was taken from each patient and kept in lithium-heparin tubes. A biopsy sample was taken from the antrum part of the stomach for H. pylori cultivation and urease testing, and 2 other samples were taken from the antrum and corpus for histopathologic evaluations. If at least 1 of the 3 tests of urease, H. pylori cultivation and histopathology evaluation was negative, patients were considered to be negative for H. pylori infection and were entered in the control group; otherwise, they were considered infected with H. pylori and were entered in the treatment group.

Patient Groups

Patients were divided into 2 groups: triple therapy regimen and triple therapy + CoQ10. The triple therapy regimen used in this study included bismuth subcitrate (120 mg/kg once a day), tetracycline (500 mg once a day), and metronidazole (400 mg/kg 3 times a day). The Q10 coenzyme, (Nature Med Company, USA), was applied at a dosage of 2 mg/kg/day. The whole treatment period was 6 weeks, and patients were not given any other drugs during this period. All the participants were prohibited from smoking during the study period. The types and dosages of drugs were not changed during treatment period. At the end of study, a 10-mL vein blood sample was taken from each patient to be compared with the samples taken at the start of this study.

Urease Test

An antral biopsy specimen was placed in a CLO test (Trimed Specialities, Osborne Park, Western Australia), which detected the presence of H. pylori urease (Marshall). The CLO test was read 1 and 24 hours after sampling.

Helicobacter pylori Cultivation

Antral biopsy specimens were placed into a transport medium (Portagerm pylori, bioMérieux, Marc l’Etoile, France) and sent by courier in a cool transport container (Sarstedt, Orsay, France) to the same bacteriology laboratory. All the specimens were cultured on the same day and were processed according to a previously described protocol.22

Measurement of Lipid Peroxidation and Stress Oxidative

Total antioxidant status (TAC) was measured using a kit supplied by Randox Laboratories Ltd. (Cat. No. NX2332). The plasma sample volume was 5 µL in a total assay volume of 305 µL. Color production was measured at 600 nm with a read time of 5 minutes.

Glutathione peroxidase (GPx) was measured using a kit supplied by Randox Laboratories Ltd. (Cat. No. RS505), using the appropriate whole-blood control (SC692). The whole blood (50 µL) was diluted with 1 mL of RANSEL diluting agent and incubated for 5 minutes. One milliliter of double-strength Drabkin’s solution was added, and assays were performed within 20 minutes. GPx activity was measured at 340 nm, using a sample volume of 5 µL in a total reaction volume of 285 µL.
Malondialdehyde (MDA) was assayed as a marker of lipid peroxidation using a colorimetric reaction that uses 1-methyl-2-phenylindole as chromogen. Condensation of 1 molecule of MDA with 2 molecules of 1-methyl-2-phenylindole under acidic conditions results in the formation of a chromophore with a maximum absorbance at 586 nm. A 7.6 mM solution of 1-methyl-2-phenylindole (MPI) was prepared immediately prior to use, in 33% methanol in acetonitrile. A 650-µL aliquot of MPI was placed in each test tube, to which 200 µL of plasma was added. The tubes were mixed well, and 150 µL of 10M HCl was added. After mixing once more, the tubes were sealed, and incubated for 60 minutes at 45°C. After incubation, the tubes were chilled in an ice bath and spun at 10 000g for 5 minutes. The absorbance at 586 nm was measured and subtracted from the blank value, obtained by replacing plasma with water. A calibration graph was prepared using 4, 8, 16, and 20 µmol/L of 1,1,3,3-tetramethoxypropane in 20 mM Tris-HCl, buffer (pH 7.4).

Statistical Analysis
Data are presented as mean ± standard deviation (SD). Statistical analysis was performed using SPSS version 19.0. Demographic characteristics of the 2 groups were compared using the Student t test and Fisher’s exact test. Endoscopic and histological grading were compared at the start and end of the therapy using Wilcoxon signed rank test. For TAC, GPx, and MDA results, the paired Wilcoxon signed rank test was used to compare the alterations. The Mann-Whitney U test was used when comparing the scores between the 2 groups. The significance level employed was P < .05.

Results
Demographic characteristics of participants are shown in Table 1. In total, 100 participants (50 patients for each group) were evaluated, of whom 58% were female and 42% were male. The mean ± SD of age for all the participants was 59.4 ± 11.4 years. The difference in mean age of participants between the 2 groups was not significant (P = .2). The mean body mass index among participants in the triple therapy + CoQ10 group was 26.2 ± 5.1 kg/m² and in the triple therapy group was 27.4 ± 3.5 kg/m² (P = .22). The frequencies of use of nonsteroidal anti-inflammatory drugs among the triple therapy + CoQ10 and triple therapy groups were 35% and 39%, respectively, showing no significant difference between the 2 groups (P = .7). Also, alcohol consumption did not show any significant difference between participants in the triple therapy + CoQ10 and the triple therapy groups (25% vs 23%). The frequency of smoking showed a nonsignificant difference among participants (P = .09): triple therapy + CoQ10, 28%; and triple therapy, 32% (Table 1).

TAC Variations
The TAC for the triple therapy and the triple therapy + CoQ10 groups at the start of the study was 2.3 ± 0.3 and 2.4 ± 0.4 mmol/L, respectively. After the 6 weeks of treatment, the end level of TAC in the triple therapy group was 2.2 ± 0.4 mmol/L and in the triple therapy + CoQ10 was 3.2 ± 0.4 mmol/L. In the triple therapy group, no significant difference was found between TAC level at the end of the study compared with that initially in the study (P > .05). But in the triple therapy + CoQ10 group, TAC level showed a significant difference at the end of study compared with that at the start of the study (Figure 1).

The mean levels of GPx for triple therapy and triple therapy + CoQ10 groups at the start of the study were 39.8 ± 6.7 and 46.5 ± 9.3, respectively. After the study period, GPx level at the end of study in the triple therapy group was 35.48 ± 7.26 and in the triple therapy + CoQ10 group was 52.3 ± 8.4, respectively. GPx level at the end of the study compared with the start of the study showed a

Table 1. Demographic and Histopathology Characteristics of the Patient Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Triple Therapy Group (n = 50)</th>
<th>Triple Therapy + CoQ10 Group (n = 50)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (m/f)</td>
<td>23/27</td>
<td>17/33</td>
<td>0.08</td>
</tr>
<tr>
<td>Age (y)</td>
<td>61.0 ± 12</td>
<td>57.9 ± 10.9</td>
<td>0.2</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.4 ± 3.5</td>
<td>26.2 ± 5.1</td>
<td>0.2</td>
</tr>
<tr>
<td>NSAID (%)</td>
<td>39</td>
<td>35</td>
<td>0.7</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>32</td>
<td>28</td>
<td>0.09</td>
</tr>
<tr>
<td>Alcohol (%)</td>
<td>23</td>
<td>25</td>
<td>0.76</td>
</tr>
</tbody>
</table>

CoQ10, coenzyme Q10; BMI, body mass index, NSAID, nonsteroidal anti-inflammatory drug.

Figure 1. Effect of triple therapy or triple therapy + CoQ10 treatment on serum level of TAC (mmol/L) in chronic gastritis patients. *P < .05 end level compared with the initial level in the triple therapy + CoQ10 group. **P < .05 end level in triple therapy + CoQ10 group compared with the end level in the triple therapy group. CoQ10, coenzyme Q10; TAC, total antioxidant status; SD, standard deviation.
**Figure 2.** Effect of triple therapy or triple therapy + CoQ10 treatment on the serum level of GPx (µg HGB) in chronic gastritis patients. *P < 0.05 at the end of the study compared with the start of the study in the triple therapy group. **P < 0.05 end compared with the start of the study in triple therapy + CoQ10 group. ***P < 0.05 at the end of the study in triple therapy + CoQ10 group compared with the end of the study in the triple therapy group. CoQ10, coenzyme Q10; GPx, glutathione peroxidase; SD, standard deviation.

**Figure 3.** Effect of triple therapy or triple therapy + CoQ10 treatment on chronic inflammation score on serum level of MDA (µmol/L) in chronic gastritis patients. *P < 0.05 in the end of study compared with start of the study in triple therapy group. **P < 0.05 end level compared with initial level in triple therapy + CoQ10 group. ***P < 0.05 end level in triple therapy + CoQ10 group compared with end of the study in the triple therapy group. CoQ10, coenzyme Q10; MDA, malondialdehyde; SD, standard deviation.

significant difference in the triple therapy group (P < 0.05). In the triple therapy + CoQ10 group, GPx level at the end of the study was significantly higher than that at the start of the study. Similar to TAC, the variation rates for GPx levels among placebo and treatment groups showed a decreasing trend in placebo and an increasing trend in the treatment group (Figure 2). The mean levels of MDA for placebo and treatment groups at the start of the study were 2.7 ± 0.7 and 2.4 ± 0.7 µmol/L, respectively. At the end of the study, MDA levels showed an increasing trend in the placebo and a decreasing trend in the treatment group. In the triple therapy group, the mean MDA levels at the beginning and the end of the study were 2.7 ± 0.3 and 2.9 ± 0.4, respectively. In the triple therapy + CoQ10 group, the serum levels of MDA at the beginning and the end of the study were 2.4 ± 0.5 and 1.8 ± 0.5, respectively. In the triple therapy group, a significant difference was found between the MDA level at the start of the study and that at the end of study (P < 0.05). In the triple therapy + CoQ10 group as well as the triple therapy group, the GPx level at the end of the study showed a significant difference compared with that at the start of the study (P < 0.05; Figure 3).

**Discussion**

*Helicobacter pylori* infections are among the most common infectious diseases and *H. pylori* is a human pathogen that involves about half the human population. These infections are more prevalent in developing countries than in developed countries. The major cause of gastric diseases such as gastritis, peptic ulcer, gastric mucosal atrophy, and gastric cancer is known as *Helicobacter pylori* and free radicals. Reactive activated oxygen species (ROS) leave extensive damage from the attack of nucleic acids, proteins, and lipids in the cell. In normal conditions, a trace amount of ROS level is produced and is omitted by the natural defense system of the body. In some conditions, an overwhelming amount of ROS are produced that cannot be omitted by the natural defense system of the body. These conditions result in severe cellular damages.

The current study investigated the effects of the Q10 coenzyme on biomarkers of lipid peroxidation and oxidative stress in combination with routine treatments for eradication of *H. pylori* infection among patients infected with these bacteria. The results showed that combination therapy of the triple therapy regimen with CoQ10 increased the level of TAC among patients. The same results were revealed for GPx and MDA levels among patients treated by the combination of the triple therapy regimen and the Q10 coenzyme in comparison with those in the triple therapy group. The results of the current study showed that treatment of chronic gastric patients associated with *H. pylori* infection can improve the antioxidant status and balance the oxidative conditions of these patients. Although the variations of oxidative factors among patients receiving triple drugs were not noticeable, adding the Q10 coenzyme to the triple drug regimen considerably increased the levels of TAC and GPx and decreased the level of MDA and amended the levels of these factors among *H. pylori*-infected patients, similar to those among healthy people. Reduced levels of antioxidants and increased oxidative stress in the body are associated with increased risk of cancer. A decrease in antioxidants such as glutathione has an important antioxidant effect in the body and plays an
important role in protecting cells associated with cellular dysfunction. Anderson showed a decreased level of TAC in patients infected by \textit{H. pylori} compared with healthy individuals and also revealed that treatment of these patients by symbiotic product can increase the serum level of TAC. A study by Bennedsen et al reported that treatment of \textit{H. pylori} among rats with astaxanthin antioxidant reduced gastric inflammation as well as bacterial load and also adjusted the release of cytokines from splenocytes. The anti-inflammatory results reported by Bennedsen et al were relatively in accordance with those in the current study. Sezikli and colleagues showed that the combination of vitamins C and E with the triple drug regimen can increase the eradication of infection caused by \textit{H. pylori}. A study performed by Correa and others showed that antioxidant complements, such as 

Everett reported that patients with \textit{H. pylori} infection have higher levels of different types of activated oxygen as well as higher mucosal MDA levels but a lower level of ascorbic acid in comparison with normal individuals. By using vitamins C and E for patients, they reported an increase in the level of mucosal ascorbic acid. Also \textit{H. pylori} eradication caused a decrease in the levels of ROS and mucosal MDA; however, receiving vitamins alone or in combination with \textit{H. pylori} eradication could not reduce the levels of activated oxygen and mucosal MDA. One of the roles of CoQ10 is an influential endogenous lipophilic antioxidant that protects cellular components from free radicals, same as other antioxidant agents like \textit{α}-tocopherol and ascorbic acid. The CoQ10 antioxidant in this study prevented the oxidative stress and lipid peroxidation in chronic gastritis patients. The gastroprotective action of CoQ10 depends on replenishing the depleted GPx, which was explained in this study (Figure 2). This result revealed improvement with the triple therapy + CoQ10 regimen at the end compared with the initial of the study. The ROS-mediated degradation of cell membrane results in the formation of lipid peroxides and initiates a variety of deleterious squel, including mucosal lesions, increased vascular permeability, and depletion of the mucosal layer. As stated previously, the aim of this study was to investigate the antioxidant properties of CoQ10 among chronic gastritis patients with \textit{Helicobacter pylori} infection. It is possible that CoQ10 prevents oxidative stress and lipid peroxidation by its scavenging properties and by this mechanism could protect gastric mucosa.

The results of our study showed the significant beneficial effects of triple therapy in combination with coenzyme Q10 on oxidative stress and lipid peroxidation. These results also suggest that the use of complementary antioxidants could be a proper strategy to prevent the progress of precancerous injuries. Future studies with larger sample sizes on the effects of coenzyme properties on gastric mucosal and prostaglandin levels in patients with chronic gastritis should be considered to confirm the results of this study. One of the limitations of this study was the short length of the trial and the lack of histopathology evaluations at the end of the intervention.

**Conclusion**

This study revealed an antioxidant effect for CoQ10 among gastric patients with \textit{H. pylori} infection and application of this coenzyme accompanied with the triple drug regimen could improve the conditions of patients with gastritis infected by \textit{H. pylori} bacteria.

**Authors’ Contributions**

A. Rahmani contributed in conducting the study, data acquisition, laboratory analyses, and data interpretation and also wrote the first draft of the article. G. Abangah and A. Moradkhani and M. Hafezi Ahmadi designed and monitored the study and were involved in data analysis and revision of the article. K. Asadollahi involved in conducting the study, data acquisition, and writing up the article. All authors contributed to revisions of the article and reviewed the final version.

**Declaration of Conflicting Interests**

There were no conflicts of interest for this study.

**Funding**

This work was supported by the Faculty of Medicine, Ilam university of Medical Sciences, Ilam, Iran.

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