Sharifi et al., Med Chem 2017, 7:11
DOI: 10.4172/2161-0444.1000476

Medicinal chemistry

Research Article Open Access

The Effect of Oral Administration PUFAs on Oxidative Stress in Patients Infected by *Helicobacter pylori* with Dyspeptic Symptom

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Abstract

Objective: *Helicobacter pylori* is a main etiological parameter in chronic active gastritis, gastric duodenal ulcers and gastric malignancy. Particular polyunsaturated fatty acids (PUFA) play roles in inhibitory effect on bacterial propagation. Therefore, this study investigated the protective effects of PUFAs against oxidative stress in patient infected with *H. pylori* with dyspeptic symptom.

Methods: This study is a double blind clinical trial whose target population was 34 patients infected with *H. pylori* with dyspeptic symptom. Patients were divided into two groups. The first group was treated with standard therapy without supplement (control), and the second group was treated with Standard Therapy and PUFAs supplement, ω-3, ω-6 and ω-9 (case group) for 2 weeks. Two biopsies from Antrum and body of stomach of all patients were collected before and after the treatment. The biopsy samples were used for quick urease test and measurement of Superoxide Dismutase, Glutathione Peroxidase, and total antioxidant capacity.

Results: In gastric mucosa mean levels of total capacity antioxidant were significantly increased in case group comparing with control group. Also, the mean of superoxide dismutase enzyme activity and glutathione peroxidase activity increased significantly in case group compared with control group (p value <0.001).

Conclusion: The findings revealed that administration of PUFAs supplement can increase total antioxidant capacity and activity of antioxidant enzymes in patients infected with *H. pylori*.

Keywords: *H. pylori*; Oxidative stress; Dyspepsia; PUFAs

Introduction

Helicobacter pylori is a gram-negative bacterium, single cell, multi-flagella which affects approximately 75% of the people in the world, and it is considered as a main etiological parameter in chronic active gastritis, gastric duodenal ulcers and gastric malignancy. *H. pylori* infection is the most important causes in peptic ulcers and other gastrointestinal disorders [1,2]. Previous investigations have revealed that *H. pylori* infection could often lead to increased pre-inflammation cytokines secretor such as interleukins and C-reactive proteins in the gastric epithelial cells [3-9]. In addition, this pathogen could be elevating Reactive Oxygen species (ROS) levels in gastric mucosa, and treatment infection leads to decrease of oxidative stress [10]. According to the previous investigations which were performed in mouse gastric tissue, increasing of superoxide radicals secreted from of *H. pylori* increases oxidative stress levels. This increasing may be due to production of oxygen species such as superoxide produced by neutrophil cells recruited to the gastric epithelial cells. This radical can react with the presence of NO in gastric juice and lead to the produce nitrite peroxide which is highly toxic and harmful for gastric tissues [11,12]. Although proper treatment regimen with clarithromycin is accepted as the standard triplet therapy, drug resistance is reported the most common issue in eradication of *H. pylori* infections [13-15]. Currently, findings have suggested that particular polyunsaturated fatty acids (PUFAs) play roles in inhibitory effect on bacterial propagation. The mechanisms have been described for PUFAs bacteria inhibitory effects in gastric including disrupt cell membrane and modulation the synthesis of mucosal anti-inflammatory prostaglandins, for example Prostaglandin E2 (PGE2) [16]. In fact, the improvement in duodenal ulcer treatment has led to the increasing in nutritional consumption of PUFAs [17]. Previous studies have revealed that the superoxide dismutase enzyme plays crucial roles in elimination of ROS including superoxide radicals to protect against the oxidative lesions and maintain homeostasis effects [18,19]. Therefore, evaluation of superoxide dismutase enzyme activity (SOD) is considered as an important parameter for analysis of oxidative lesions created by *H. pylori* infection [20]. In addition, according to the findings, determination of glutathione peroxides enzyme (GPX) activity is considered useful for assessment of *H. pylori* infection due to depletion glutathione storages which may lead to producing free radicals [21,22]. Due to high prevalence of *H. pylori* infection and increasing of oxidative stress markers in patients infected with this bacteria and probable beneficiary effect of PUFAs, this study aimed at assessing total antioxidant capacity (TAC), SOD and GPX enzymes activity in stomach tissue in the *H. pylori* infected patients.

Materials and Methods

Sample collection

In this study, thirty-four patients were divided into two groups, the case and control, who were referred to the clinical endoscopy of medical

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Received October 25, 2017; **Accepted** October 28, 2017; **Published** November 04, 2017

Citation: Sharifi R, Nouri M, Dolatkhah H, Estakhri R, Shirmohammadi M, et al. (2017) The Effect of Oral Administration PUFAs on Oxidative Stress in Patients Infected by *Helicobacter pylori* with Dyspeptic Symptom. Med Chem 7: 324-328. doi: 10.4172/2161-0444.1000476

university of Tabriz, from September 2014 to August 2015. Individuals were assessed in control and cases groups including, 9 males and 8 females with mean age 51.52 ± 10.47, 57.29 ± 10.69, respectively. The control group was treated with common antibiotics (standard therapy including omeprazole, amoxicillin, and clarithromycin) without supplement administration, and the case group was treated with the same antibiotics and PUFAs supplement for two weeks. Three capsules per day including PUFAs supplement, Natural Factors North America (SKU 2269) 1200 mg, contains Fish Oil Blend 400 mg. Flaxseed Oil 400 mg, Borage Oil 400 mg, were consumed by patients. In this study, patients with gastric cancer, diabetic's patient, patient with renal disease, patient who have used omega supplement three month before the study were excluded from the further study due to failure in consumption of supplement and interference in the results. The patients' gastric biopsies were collected in a fasting condition by GI specialist. The biopsies were kept in -70 ℃. For all patients we provided written informed consent and the treatment was performed under the supervision of GI specialist. After treatment, endoscopy was taken again from these patients, and by obtaining gastric biopsy in a fasting condition, the eradication of *H. pylori* and elimination of active chronic gastritis were followed. Once again, the samples collected from patients were transferred to the related department for further examinations. In addition, Ethics, and Human Rights Committee in medical university of Tabriz approved the present study.

Measurement of Total Antioxidant Capacity (TAC)

FRA (Ferric Reducing Ability) method is used for determination of TAC in stomach juice which is based on the reducing of Fe^{+3} to Fe^{+2} in presence of TPTZ (Tripyridyl-S-Triazine). The Fe^{+2}-TPTZ complex is a violet and has a maximum absorbance in 593 nm. The reducing ability of stomach juice is correlated with increasing of Fe^{+2}-TPTZ concentration, and therefore increasing of absorbance in 593 nm [23].

Measurement of glutathione peroxides and superoxide dismutase enzymes activities in gastric juice

In order to investigate usefulness of PUFAs as a supplementary therapeutic agent, the glutathione peroxides and superoxide dismutase enzymes activities were assessed in gastric juice. All of the samples were collected and kept at -20°C for further analysis. Then, the glutathione peroxidase activity was assessed by Randox kit as a calorimetric method [24], and superoxide dismutase enzymes activities were determined using ultraviolet colorimetric assay by Randox kit according to the manufacturer's protocol [25].

Statistical analysis

The mean of TAS, MDA, amounts and mean of GPX and SOD activity of gastric biopsy of samples was calculated, and due to the independently of studied groups, the mean of results was calculated in each group using SPSS statistical software (21 version), and normal distribution of results were examined by Shapiro Wilkes test. The results which had normal distribution were compared in two groups with Independent sample t-Test. When these tests were considered significant that p value was less than 0/05 (p<0/05).

Results

Several clinical parameters such as fast blood sugar (FBS), cholesterol and triglyceride were assessed in case and control subjects (Table 1). According to the findings, there were no significant differences between the factors assessed in case and control groups (*p* value>0.005). In the present study, when the sexuality types and age parameters were compared in patients and normal individuals, there were not found any significant differences in both groups (*p* value>0.05).

The glutathione peroxidase and superoxide dismutase enzyme activity levels were assessed in case and control groups using ultraviolet colorimetric assay. The findings revealed that the SOD activity was significantly different in case group (*p* value<0.001), and it was increased in the subjects that obtained combinations of PUFAs therapeutic supplementary agent and standard triplet-antibiotics regime (19.77 ± 3.02 IU/mg protein) compared with the individuals who were treated only with standard triplet-antibiotics 10.14 ± 3.51 IU/mg protein (Figure 1).

As it can be seen in Figure 2 the mean activity of glutathione peroxidase was compared in two groups. The results showed that the mean of GPX activity in case group who were treated with combination of PUFAs and standard triplet-antibiotics (11.03 ± 2.50 IU/mg protein) was increased significantly (p value<0.001) in comparison with GPX activity of control group who were treated solely with standard therapy (4.58 ± 2.30 IU/mg protein).

Finally, we determined a TAC in the gastric mucosal in both patients of two groups. The results revealed that PUFAs therapeutic regime can increase (*p* value<0.0001) TAC in the case group subjects (1.08 ± 0.17 mmol/L) compared with the control group subjects (0.68 ± 0.26 mmol/L) (Figure 3).

Discussion

One of the problems in *H. pylori* infection of stomach tissue is Stress oxidative [26]. Generally speaking, the term Stress oxidative refers to the condition that the cells are exposed to the ROS during life time [27,28]. Inflammation resulted from *H. pylori* infection may be deleterious to the epithelial cells in several mechanisms [29]. For example, reactive oxygen produced by activated neutrophil may lead to the DNA or cells damages. This reaction is performed by host cells

Groups / Clinical and Pathological Factors	Control (n=17)	Case (n=17)	p-value
Age (Years) (Means ± SD)	51.52 ± 10.47	57.29 ± 10.69	0.688
Gender			
Male (n=18)	9	9	0.55
Female (n=16)	8	8	
FBS (mg/dl) (Means ± SD)	88.03 ± 9.36	92.76 ± 10.48	
Cholesterol (mg/dl) (Means ± SD)	136.26 ± 28.46	110.18 ± 20.75	0.153
Triglyceride (mg/dl) (Means ± SD)	93.23 ± 16.85	80.24 ± 10.00	0.187

Table 1: Demographic findings of patients in this study.

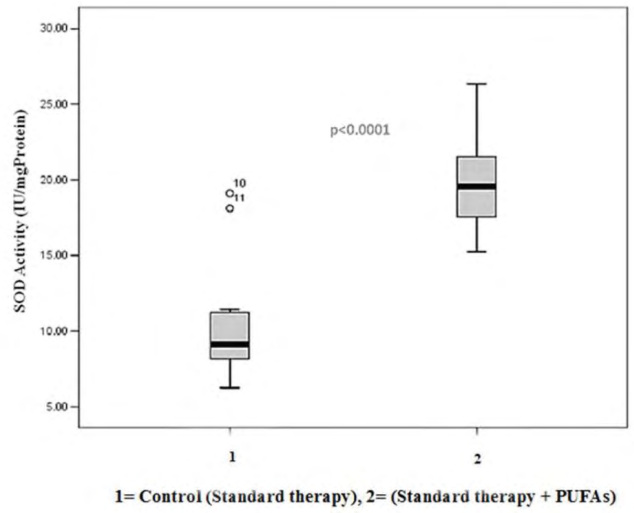

Figure 1: Comparison of mean of SOD activity in gastric mucosa of control and case groups after treatment.

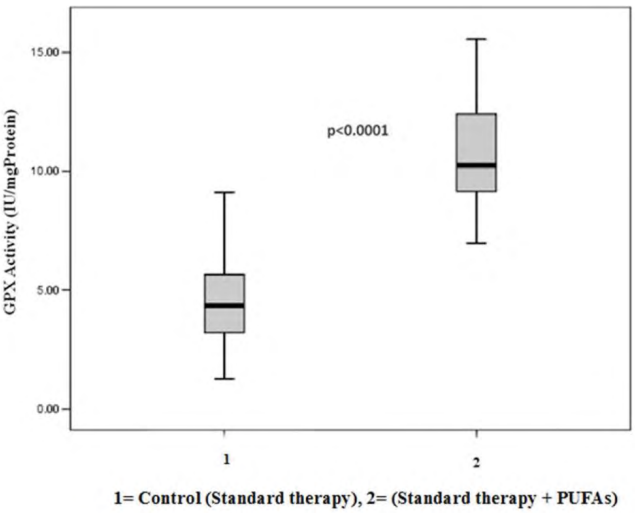

Figure 2: Comparison of mean of GPX activity in gastric mucosa of control and case groups after treatment.

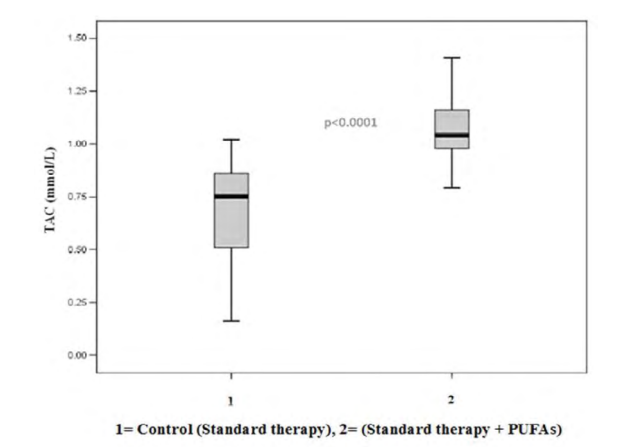

Figure 3: Comparison of TAC level in gastric mucosa of control and case groups after treatment.

against infection agent. However, natural selection makes the necessary potential in bacteria to resist local oxidative pressure [30]. These oxidative defensive mechanisms by host cells not only do not damage bacteria seriously, but also, they are deleterious to host cell itself [31]. These two mechanisms causing free radicals in both bacteria and host cells result in intensive oxidative pressure in *H. pylori* infection. NO molecules have tendency to react with superoxide radicals resulted from *H. pylori* or white cells which is led to peroxynitrite in gastric tissues. This, in turn, strengthens the oxidative stress, and the bacteria become resistant to NO bactericidal effect [31]. According to the therapeutic effects of fatty acids in several illnesses, the present study aimed to assess antibacterial effects and beneficiary effects of fatty acids in reducing oxidative stress in gastric patients infected by *H. pylori*. Previous studies (Toorang and colleagues (2009), Mahdavi and colleagues (2011), Sarbolouki and colleagues (2010) have mentioned various mechanism for the beneficiary effects of omega fatty acids in increasing serum's total antioxidant capacity. Omega-3 fatty acids may increase catalase levels in both of cytoplasm and peroxisome. Therefore, it may improve the defense against free radicals. It has been showed that supplementary consumptions with PUFAs are replaced with PUFAs which are damaged by free radicals. In addition, silencing of gene expression by PUFAs can inhibit oxidative stress resulting in apoptosis. Furthermore, PUFAs can play a role in oxidative stress reduction by alteration prostaglandins synthesis and gene expression as well as regulating antioxidant enzymes [32-34]. It has been shown recently that omega fatty acids may play crucial roles in regulating gene expression of inflammatory factors in various cell lines. This can be effective in reducing oxidative stress. It has been proved that ω-6 linoleic acid can inhibit the growth of *H. pylori in vitro*. This inhibitory effect depends on the unsaturated condition of fatty acid, that is, the number of double bonds in fatty acid molecules [35]. Several studies revealed that consumption of ω-3 PUFAs anti-inflammatory effects while consumption of ω-6 PUFAs produced strong inflammatory factors by locating in cell membrane and metabolization [35]. Correia et al. have proved that inhibitory ability of ω-3 PUFAs in bacteria growth and its colonization solely depends on DHA in mice gastric [36,37]. It has been shown that 100 μM concentration of DHA reduces *H. pylori* growth while concentration greater than 250 μM inhibits the survival of *H. pylori* irreversibly. In addition, it has been demonstrated that DHA may change expression and metabolism of outer membrane proteins and the phenotype of lipopolysaccharides [36,37]. It should be mention that DHA is significantly less effective in the eradication of *H. pylori* from mice gastric mucous comparing with the triplet standard therapy. As a result, if DHA is combined to triplet standard therapy based on clarithromycin, there could be better results in eradication of *H. pylori* comparing with triplet standard therapy alone. None of the mice treated with standard therapy / DHA did not show gastric colonization by bacteria after 2 months of treatment [36]. In this study it has been proved that the combination of family fatty acid omega and standard therapeutic regimes compared with standard therapy with clarithromycin significantly improved oxidative stress. The more the fatty acids are unsaturated, the more effective in reducing oxidative stress. Since the enzymes levels of elongase and desaturase is lower in gastric epithelial, it is not supposed the consumed fatty acids including linoleic acid and alpha-linolenic acid are change to long chains fatty acids such as arachidonic acid and docosahexaenoic acid. Therefore, the reductive effects of fatty acids' oxidative stress are not related to their metabolites. Nevertheless, this effect is related to fatty acids themselves [37]. Not only do these fatty acids influence fluidity and functions of gastric cells by participating in the structure of cell membrane phospholipids, but also, they cause alteration of signaling pathways in these cells [38]. Infection to *H. pylori* in gastric cells results

in IL-8 and therefore it leads to illness intensification. As it has been proven these fatty acids inhibits IL-8 expression in gastric cells *in vitro* [39,40].

Conclusion

The findings revealed that fatty acid omega supplementary consumption can reduce the oxidative stress conditions appeared in patients with *H. pylori* infections. Finally, the analysis of catalase activity and malondialdehyde levels in gastric mucosa as well as comparison of membrane phospholipids profiles in before and after PUFAs treatment regimes is suggested for future investigations.

Acknowledgements

This project consumed huge amount of work, research, and dedication. Still, implementation would not have been possible if we did not have a support of many individuals and organizations. Therefore, we would like to extend our sincere gratitude to all of them.

First of all, we are thankful to Tabriz Liver and Gastrointestinal Disease Research Center and Tehran Islamic Azad University Science and Research Branch for their financial and logistical support and for providing necessary guidance concerning projects implementation.

We are also grateful to Tabriz Endoscopy Department of Imam Reza and Shahid-Madani Hospital for provision of expertise, and technical support in the implementation. Without their superior knowledge and experience, the Project would like in quality of outcomes, and thus their support has been essential.

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