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Effects of Omega-3 Fatty Acids Supplementation on Oxidative Stress and MMP2/9 in Patients with Gastric Cancer During Chemotherapy

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Abstract: A double blind clinical trial study was conducted on 30 adult patients with different kinds of gastric malignancies during chemotherapy in Ardebil, Iran in 2010. After measurement of anthropometric and biochemical factors, about 3 g ω-3 fatty acid and placebo were given daily to omega and placebo groups for 6 weeks, respectively. Blood samples were taken to measure lipid profiles, MMP2, MMP9 and MDA, total antioxidants, PON1 and arylesterase enzymes at the beginning and at the end of 4th and 6th weeks. After interventions; weight, HDL, PON1 and arylesterase enzymes in omega group were significantly higher than placebo group at the end of 6th week ($p<0.05$). The serum levels of MMP2, MMP9 and MDA in omega group were less than placebo group ($p<0.05$). While weight, BMI, HDL, total antioxidants, arylesterase serum and PON1 were significantly increased, MMP2 and MMP9 were decreased after consumption of ω-3 fatty acid ($p<0.05$). In placebo group, the mean of weight and BMI were decreased but MDA, MMP2 and MMP9 were increased significantly during study ($p<0.05$). This study showed that the ω-3 fatty acid may be useful as a good complementary therapy for gastric cancer patients during chemotherapy.

Key words: Oxidative stress, MMP2, MMP9, gastric cancer, Ardabil, Iran

INTRODUCTION

Gastric cancer is a major public health burden. Globally, it is the second leading cause of cancer-related death with 738,000 deaths annually all over the world (Ferlay *et al*., 2010). In Iran while the Northern and Northwestern regions are high risk areas for gastric cancer, there are several intermediate and low risk populations in other geographical areas (Malekzadeh *et al*., 2009). Ardabil, a Northwestern province has the highest incidence of gastric cancer in Iran (Sadjadi *et al*., 2003). Gastric cancer is a multi-factorial disease and many factors such as genetic factors (Munoz *et al*., 2001; Nomura *et al*., 2003), *Helicobacter pylori* (Uemura *et al*., 2001), reactive oxygen species (Hansson *et al*., 1994), environmental factors including smoking, high salt intake and a diet with an insufficient level of antioxidants are involved in the pathogenesis of gastric cancer (Malekzadeh *et al*., 2009; Mojtahedi *et al*., 2007; Rahimi *et al*., 2011). There are a few researches indicating that ω-3 fatty acids may be beneficial for human cancer therapy (Barber *et al*., 2001; Bougnoux *et al*., 1999). It has been shown that fish oil significantly increases the activity of antioxidant enzymes and decreases lipid peroxidation in gastric mucosa of rats (Bhattacharya *et al*., 2006). Omega-3 fatty acids may be useful in preventing of oxidative stress-induced apoptosis by inhibiting the apoptotic genes expression and DNA fragmentations of gastric epithelial cells (Yu *et al*., 2009). Supplementing the diet with ω-3 fatty acids may have role in cancer treatment and enhancement of the efficacy of various chemotherapy drugs against cancer (Hardman, 2004). Tumor tissues in gastric cancer over expresses the Matrix Metalloproteinases (MMPs) in comparison to normal mucosa (Grigioni *et al*., 1994; Honda *et al*., 1996) also it is well known that high MMP-2 and MMP-9 levels related to poor overall survival (Sier *et al*., 1996). MMPs are a family of zinc dependent enzymes that not only play important roles in physiologic breakdown and remodeling of the extracellular matrix (Nagase and Woessner, 1999) but are also involved in pathologic conditions including tumor progression invasion and metastasis (Ala-Aho and Kahari, 2005; Stamenkovic, 2000). Inhibition of MMPs may therefore, represent a successful strategy for the

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treatment of gastric cancer disease. Only a limited number of studies have been performed in relation to the effects exerted by ω-3 fatty acids on MMPs production. Other studies demonstrated that ω-3 fatty acid inhibits the activity and expression of the MMP-2 and MMP-9 in tumor cells (McCabe *et al*., 1999; Suzuki *et al*., 1997). The aims of the present study were to examine the effect of ω-3 fatty acids supplementation on oxidative stress and MMP2/9 in gastric cancer patients during chemotherapy.

MATERIALS AND METHODS

Study design: A double blind clinical trial study was conducted in Nutrition Research Center of Tabriz University of Medical Sciences in Iran in 2010. The study was approved by Medical Ethical Committee of the Tabriz University of Medical Sciences and recorded with identification code of IRCT201011095144N1 in Iranian Registry of Clinical Trials. Thirty adult patients with different stages of malignancies of gastric cancer undergoing chemotherapy in Imam and Fatemi Hospitals of Ardabil city were randomly selected. They were divided in two groups; omega and placebo. The aims and study protocol were explained to the subjects and a written consent was taken prior to fill in a questionnaire. Only patients >30 years old were selected to participate in the study. Subjects having diseases inducing cachexia such as heart, lung and renal disease, AIDS, acute leukemia, diabetes, multiple myeloma and individuals undergoing surgery were excluded. Staging procedure based on imaging results of cancer was used for patients with gastric cancer and only Stages II and III were included in the study.

Anthropometric indices and biochemical parameters were collected in the beginning, middle and the end of chemotherapy period as well as changes of weight, BMI and biochemical parameters were calculated for both groups in the same time. Omega group were taken 10 capsules per day, each containing 180 mg Eicosapentaenoic Acid (EPA) and 120 mg Docosahexaenoic Acid (DHA) in 1 g fish while the placebo group were given placebo. The drug and placebo administrated three times a day for 6 weeks. Blood samples in three times at beginning, 30 and 45 days after interval were collected by venipuncture and then sera separated. All samples were kept frozen at -80°C until analyzed.

Treatment schedule: The chemotherapy regimen consisted of: once every 3 weeks docetaxel (Taxotere; Sanofi-aventis, Bridgewater, NJ) 75 mg m^{-2} (day 1) plus cisplatin 75 mg m^{-2} (day 1) and fluorouracil 750 mg/m^2/day continuous infusion (days 1-5; DCF) according to Ajani's protocol (Ajani *et al*., 2007).

Anthropometric measurements: Anthropometric parameters (weight, height and body mass index) were measured for all patients at the beginning, middle and end of the study. Height and weight were obtained using a portable digital scale and portable digital Stadiometer. Height and weight were measured without shoes by trained research assistants. Weight was measured to the nearest 0.1 kg using portable digital scales with a range of 0-200 kg. BMI was calculated using the data recorded for height and weight.

Biochemical measurements: Fasting venous blood samples were taken for measurement of lipid profiles [(triglycerides, total cholesterol, High Density Lipoprotein (HDL) and Low Density Lipoprotein (LDL) cholesterol)], Matrix Metalloproteinase (MMP) (MMP2, MMP9), Malondialdehyde (MDA), total antioxidants, Paroxonase1 (PON1) and arylesterase enzymes at the beginning and the end of 4th and 6th weeks. MMP-9 and MMP-2 Enzyme Linked Immunosorbent Assay (ELISA) kits were purchased from Bender Med Systems (Vienna, Austria) and Boster (Boster, Wuhan, China), respectively. Serum samples were diluted 1:10 and 1:100 according to the manufacturer's specifications for MMP-9 and MMP-2 assay, respectively.

For the accuracy of assessment, duplicate assay were performed. Quantification of immunoreactive MMP2 and MMP-9 was carried out on 96 well microtiter ELISA plates using standard protocols. The color formation was measured at 450 and 630 nm (Anhos, 2000 microplate reader) and the sample concentration of MMP-9 and MMP-2 was estimated using Multicalc program (Wallac, Turku, Finland). Serum PON1 activity (high salt, no salt) toward paraoxon was determined as described before (Furlong *et al*., 1988) with little modification in the absence (basal activity) and presence of 2.63 M NaCl.

The basal assay mixture included 760 μL of assay [0.132 M Tris -HCl (pH 8.5), 1.32 mM $CaCl_2$], 40 μL serum and 200 μL of 6 mM freshly prepared paraoxon (Sigma Chemical Co.). The rate of hydrolysis at 37°C was determined at 40 nm for 5 min. PON1 activity was calculated using molar extinction coefficient of 18.05×103 M cm^{-1} and was expressed as IU L^{-1} where IU is the number of μmol of paraoxon hydrolyzed per min. For NaCl-stimulate assay 2.63 M NaCl was added into above described mixture.

Phenylacetate was used as a substrate to measure the arylesterase activity. About 10 μL of a 1:40 dilution of serum was mixed with 200 μL of substrate [3.26 mM phenylacetate in 9 mM Tris-HCl (pH 8) 0.9 mM $CaCl_2$]. The rates of hydrolysis at 25°C were determined at 270 nm for 4 min. The molar extinction coefficient of 1310 M cm^{-1} was used for calculation of activity and units were expressed as micromoles of phenylacetate hydrolyzed per minutes.

Serum Total Antioxidant Capacity (TAC) was determined by colorimetric method using RANDOX kit (Randox Labolatories) by Cecil 8000 spectrophotometer. Serum MDA levels were measured thriobarbituric acid reactivity. Samples were heated with thriobarbituric acid under acidic condition and after cooling, the colored product was extracted into n-butanol. The pink color absorbance was measured at 530 nm. MDA standards were prepared with 1, 1, 3, 3-tetraethoxypropane. Other laboratory tests were assayed with routine automated procedures.

Statistical analysis: Data were analyzed by descriptive and analytical statistical methods using SPSS 14 Software.

Paired independent sample t-test and repeated measures were used for data analysis. Statistically significant level for all tests was considered as $p<0.05$.

RESULTS AND DISCUSSION

The results obtained of anthropometric factors during study were shown in Table 1. There were no significant differences regarding to anthropometric and biochemical factors between the omega and placebo groups in beginning study (Table 1 and 2). The average age in omega and placebo groups was 62.2±13.9 and 66.1±11.7 years, respectively. About 67% of the participants were male and 33% were female. Table 2

Table 1: The comparison of anthropometric factors in two groups

Factors	Duration	Omega group	Placebo group	p-value
Weight (kg)	Before	56.7±10.2	56.2±6.9	0.86
	After 4 weeks	58.3±9.40^{+}	54.3±6.6^{+}	0.18
	End of week 6	59.2±8.90^{+*}	52.6±5.6^{+*}	0.02**
BMI (kg m^{-2})	Before	20.4±2.70	20.6±2.6	0.85
	After 4 weeks	20.9±2.50^{+}	19.9±2.4^{+}	0.26
	End of week 6	21.1±2.40^{+*}	19.5±2.4^{+*}	0.08

Values are mean±SD, $^{+}p<0.05$ vs. baseline, *$p<0.05$ vs. 4 weeks; **$p<0.05$ in independent sample t-test between two groups

Table 2: The comparison of biochemical factors in two groups

Factors	Duration	Omega group	Placebo group	p-value
MMP2 (ng mL^{-1})	Before	99.7±81.6	99.2±60.6	0.990
	After 4 weeks	65.0±34.2^{+}	128.5±65.9	0.003**
	End of week 6	61.2±35.2^{+*}	137.8±62.2^{+}	0.001**
MMP9 (ng mL^{-1})	Before	134.5±16.3	124.7±9.9	0.560
	After 4 weeks	127.5±22.4^{+}	133.5±10.6^{+}	0.360
	End of week 6	121.4±26.5^{+*}	147.7±7.8^{+*}	0.003**
Triglycerides (mg dL^{-1})	Before	146.1±52.6	112.4±35.9	0.051
	After 4 weeks	122.4±31.8^{+}	136±85.7	0.570
	End of week 6	107.5±37.4^{+*}	126.7±31.3	0.140
Total cholesterol (mg dL^{-1})	Before	149.3±45.7	141.9±34	0.620
	After 4 weeks	176.7±29.9	159.1±50.9	0.200
	End of week 6	191.2±79.1^{+}	144.7±44.6	0.030
HDL cholesterol (mg dL^{-1})	Before	39.3±5.80	39.9±4.2	0.720
	After 4 weeks	42.2±3.90	40±5.7	0.230
	End of week 6	44.3±3.60^{+}	39.7±5.5	0.010**
LDL cholesterol (mg dL^{-1})	Before	86.1±34.9	80.9±28.2	0.660
	After 4 weeks	100.5±36.1	91.7±36.3	0.500
	End of week 6	111.6±28.7^{+}	81.3±36.2	0.020**
MDA (mmol mL^{-1})	Before	0.25±0.08	0.27±0.14	0.650
	After 4 weeks	0.27±0.12	0.50±0.22	0.010**
	End of week 6	0.29±0.12	0.61±0.26^{+}	0.000**
Total antioxidants (mmol L^{-1})	Before	0.27±0.08	0.35±0.14	0.057
	After 4 weeks	0.30±0.12^{+}	0.36±0.17	0.270
	End of week 6	0.41±0.16^{+}	0.44±0.19	0.570
PON1 (IU L^{-1}) (no salt)	Before	2550.9±835.3	2576.3±1074.6	0.940
	After 4 weeks	3321.1±1082.5^{+}	2189.9±1195.2	0.010**
	End of week 6	4500.3±1243.9^{+*}	1901±1128.9	0.001**
PON1 (IU L^{-1}) (high salt)	Before	9469.9±3325.7	9097±4598.7	0.800
	After 4 weeks	9433.9±4803.6	9855.1±7055.3	0.850
	End of week 6	13380.9±7008.4^{+}	8050.1± 4328.1	0.020**
Arylesterase (mmol/L/min)	Before	405.7±180.8	514.8±169.8	0.090
	After 4 weeks	537.4±231.2	507.8± 200.9	0.710
	End of week 6	962.7±623.6^{+*}	511.9±342.5	0.020**

Values are mean±SD, $^{+}p<0.05$ vs. baseline, *$p<0.05$ vs. 4 weeks; **$p<0.05$ in independent sample t-test between two groups

shows average values for biochemical factors in 2 groups. Weight, HDL, PON1 and arylesterase enzymes of omega group were significantly higher than placebo group at the end of week 6 ($p<0.05$). Although, serum MDA was increased in both groups during intervention however, its increasing rate was significantly higher in placebo group comparing to omega group ($p<0.05$). Although, serum total antioxidants was increased in both groups during the study but there was no significant differences between two groups. Concentrations of triglycerides and total cholesterol show no significant difference between two groups (Table 2). Weight, BMI, HDL, LDL, total antioxidants, arylesterase and PON1 serum activity were increased while the serum levels of MMP2 and MMP9 decreases significantly in omega group ($p<0.05$). The recent results are in contrast to placebo group where the mean values of weight and BMI were decreased; MMP2, MMP9 and MDA levels of serum were significantly increased during the study ($p<0.05$). About 67% of patients were in Stage II and remaining are in Stage III. Weight at the time of gastric cancer diagnosis for Stage II was significantly higher than Stage III patients (73±11 kg vs. 65±9 kg) ($p<0.05$). However, comparing other anthropometric and biochemical factors between Stage II and III patients displayed no significant differences during the study.

This study demonstrated ω-3 fatty acids to be an efficient oral supplementation in patients with gastric cancer. In spite of MMP9 and MMP2 researchers found that weight and arylesterase enzyme increases after intervention at the end of week 6 in omega group comparing to placebo group which is similar to previous studies (Giacosa and Rondanelli, 2008; Moses *et al*., 2004). Oral ω-3 fatty acids supplementation increases the weight gain in patients and protects against weight loss during chemotherapy. The weight increase can be caused by the fact that dietary supplementation of ω-3 fatty acids attenuates the adverse effects secondary to chemotherapy such as anorexia (Baracos *et al*., 2004; Conklin, 2002; Kapoor, 2009).

In this study, researchers demonstrated a effective decrease in MMP-2/-9 concentration upon administration of DHA and EPA. MMPs involve in extracellular matrix degradation and play a critical role in pathologic conditions including tumor progression invasion and metastasis (Ala-Aho and Kahari, 2005; Egeblad and Werb, 2002; Stamenkovic, 2000). Although, showed production of MMP2 and MMP9 mRNAs are reduced by ω-3 fatty acid (Tsuzuki *et al*., 2007) but the exact mechanisms are still unknown. Studies on evaluation of the effect of MMP inhibitors on patients with various types of cancer have reported different level of success (Bramhall *et al*., 2002; Zucker *et al*., 2000). While some *in vitro*, animal models and clinical studies clearly showed the involving of MMPs in tumor growth and invasion others claimed that synthetic MMP inhibitors as anticancer agents, failed to improve patient's outcome in clinical trials (Zucker *et al*., 2000). It seems that ω-3 can improve the disease outcome by inhibition of MMP9/2. A significant survival benefit from therapy with MMPs inhibitor has been described in gastric cancer (Bramhall *et al*., 2002). Albeit the evaluation of survival rate was out of the scopes in current investigation but decrease in MMP2/9 by ω-3 may have role in improving of patient's survival.

It is generally accepted that oxidative stress plays an important role in the apoptosis of gastric epithelial cells (Tsuzuki *et al*., 2007). Antioxidant enzymes are the primary mechanisms for scavenging reactive oxygen species. The activities of these antioxidant enzymes are normally decreased in many tumor cells (Oberley *et al*., 1989; Tisdale and Mahmoud, 1983). The result in consistent with previous studies showed that plasma level of MDA is higher in gastric cancer patients (Bakan *et al*., 2002). showed the antioxidant enzymes activities are related to malignancy in gastrointestinal cancers (Kekec *et al*., 2009). Researchers found that total antioxidant and MDA increases in both groups during intervals but increment rate of antioxidant in omega group is higher than placebo. Antioxidant rise in omega group may have inhibition on MDA.

The ω-3 fatty acids show antioxidant action in various cells and tissues through inhibition of apoptotic gene expression and DNA fragmentation of gastric epithelial cells (Yu *et al*., 2009). Omega rich diets impair the release of arachidonic acid from membranes by replacing arachidonic acid with oleic acid, EPA and DHA in phospholipids' membranes so they can modify the release of free radicals (Mitjavila *et al*., 1996). Tumor cells have lower polyunsaturated fatty acid content than nonmalignant tissues (Cheeseman *et al*., 1984), possibly as a compensation that protects against their sensitivity to free radicals. The results show that Increasing in the MDA level was controlled through total antioxidants, arylesterase serum and PON1 augment due to ω-3 fatty acids consumption.

CONCLUSION

Reserchers conclude that ω-3 fatty acid may be beneficial in gastric cancer during chemotherapy through controlling MDA increment as well as the decreasing serum levels of MMP2/9. Besides, ω-3 fatty acid intake did demonstrate additive effects on increasing serum

antioxidant enzyme levels in the patients which may be used as a good complementary therapy for gastric cancer. These results suggest an important role for dietary supplements, rich in ω-3 polyunsaturated fatty acids in weight-stabilizing of gastric cancer patients.

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