EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 6
Issue: 4
46-50
Year: 2019

"THE POSSIBLE PROTECTIVE EFFECT OF OMEGA-3 AGAINST METOCLOPRAMIDE INDUCED HYPERLIPIDEMIA IN RATS"

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Article Received on 09/02/2019 **Article Revised on 01/03/2019** **Article Accepted on 23/03/2019**

ABSTRACT
Metoclopramide (MCA) is one of prokinetic drugs. It is used for the treatment upper gastrointestinal motility disorders such as diabetic gastroparesis, nausea, vomiting and gastroesophageal reflux. It increases serum prolactin level that elevates lipid profile especially triglyceride level. Omega−3 fatty acids are polyunsaturated fatty acids that important for normal physiology and metabolism. It is effective treatment for patients with hypertriglyceridemia at recommended doses. The present study aimed to evaluate the possible protective effect of omega-3 in treatment of MCA-induced hypertriglyceridemia in rats. Hyperlipidemia and hyperprolactinemia was evaluated using biochemical examinations. In this study, MCA treated group showed highly significant elevation in serum prolactin and triglyceride (TG) levels. The levels of total cholesterol (TC) and low density lipoproteins (LDL) were significantly increased compared to both control and co-treated groups with omega-3. However, the high density lipoprotein was decreased significantly in MCA treated rats. Conclusion, these results suggest that omega-3 has a marked protective and therapeutic effect against MCA hyperlipidemia.

KEYWORDS: Dyslipidemias, metoclopramide, omega-3 fatty acids, total cholesterol, triglycerides, low density lipoproteins, high density lipoproteins.

INTRODUCTION
Dyslipidemia is an abnormal elevation of lipids and lipoproteins in the blood.[1] It is the most common cause of many diseases such as atherosclerosis, cardiovascular disease, and acute pancreatitis. It also involved in sudden death syndrome. Dyslipidemia may be primary or secondary. It is characterized by abnormal elevation of TC, LDL, TG or decrease in HDL level. It is mainly due to genetic causes, other causes such as diabetes or metabolic syndrome.[2]

Metoclopramide is a prokinetic agent and commonly used for treatment of stomach and esophageal problems, nausea and vomiting, help to emptying of the stomach in patients with gastroparesis, gastroenteritis and gastroesophageal reflux.[3] It is also used in treatment of migraine.[4] It has common side effects such as tardive dyskinesia, feeling tired, diarrhea, extrapyramidal effects and feeling restless.[5] It is a dopamine antagonist and also it increases serum prolactin that elevates cholesterol and TG level.[6] This is a dangerous side effect during treatment of diabetic or hyperlipidemic patients with MCA. Therefore, it is important to treat hypetriglyceridemia for patients receive MCA to avoid and decrease the risk of pancreatitis and cardiovascular disease.

Omega−3 fatty acids are polyunsaturated fatty acids that important for normal metabolism and human physiology.[7] They are α-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). They possess antiinflammatory, antiarrhythmic, and antithrombotic properties. It has been approved that fibrates, niacin, and omega-3 reduces TG, cholesterol and VLDL levels.[8] In our study, we will focus on the potential protective and therapeutic effect of omega-3 on MCA hyperlipidemia. So, we assess the possible protective effect of omega-3 on lipid profile during chronic MCA treatment.

MATERIALS AND METHODS
Chemicals and drugs
Metoclopramide hydrochloride was purchased from Sigma Chemical Company, (MO763, USA). Omega-3 was obtained from South Egypt Drug industries company, Egypt. The omega 3FAs supplement used in the current study is composed of highly refined fish oil consisted of 13% of Eicosapentaenoic acid minimum (EPA), 9% Docosahexaenoic acid minimum (DHA), and 52-59% Linoleic acid. Saline (0.9%) was obtained from El-nasr Chemical Company, Egypt.

Experimental animals

Adult Wister male rats weighing 200-250 gm were purchased from Animal House Assiut University, were used in this study. Rats were housed in cages under suitable temperature 22-25°C and humidity. Animals were allowed free access to standard chow diet and water. All the experiments were approved by the Ethics Committee of Faculty of Medicine, Assiut University.

Experimental design

Thirty rats were divided into three groups each group contain 10 animals. First group was the control group received 1ml saline 9% orally/daily/3 weeks. 2nd group received MCA hydrochloride 20 mg/kg orally/daily/3 weeks.[9] 3rd group received MCA combined with omega-3 200 mg/kg orally/daily/3 weeks.[10] Drugs were administered by gastric gavage tube for three weeks. On the last day of our experiment, rats were sacrificed by decapitation. Blood samples were collected in sterile tubes, frozen and stored at – 20°C until assayed.

Experimental procedures

A) Determination of serum prolactin concentration

Serum samples were examined for prolactin level on day 21 using ELISA kit (Life Diagnostics, Inc) and expressed as ng/ml.

B) Determination of serum lipid profile

Serum samples were examined for TC, TG, and High density lipoprotein colorimetrically by spectrophotometer using TC kit, Serum TG kit, and HDL-C kit (Spectrum, Germany) and expressed as (mg/dl). Serum LDL was estimated according to Friedewald formula, 1972.[11]

Statistical analysis

Data are expressed as the mean ± standard error (SE). Statistical analysis was done using a one-way analysis of variance (ANOVA), followed by Dunnett test for multiple comparisons, using GraphPad Prism 5.03 (GraphPad Software, Inc.). For all statistical comparisons, a **P** value < 0.05 was statistically significant and **P** value < 0.01 was statistically highly significant.

RESULTS

Determination of serum prolactin level

In MCA treated group, prolactin level was highly significantly elevated in comparison to control group after 21 day. Also, Concurrent administration of MCA with omega-3 showed highly significant increase in prolactin level (fig 1).

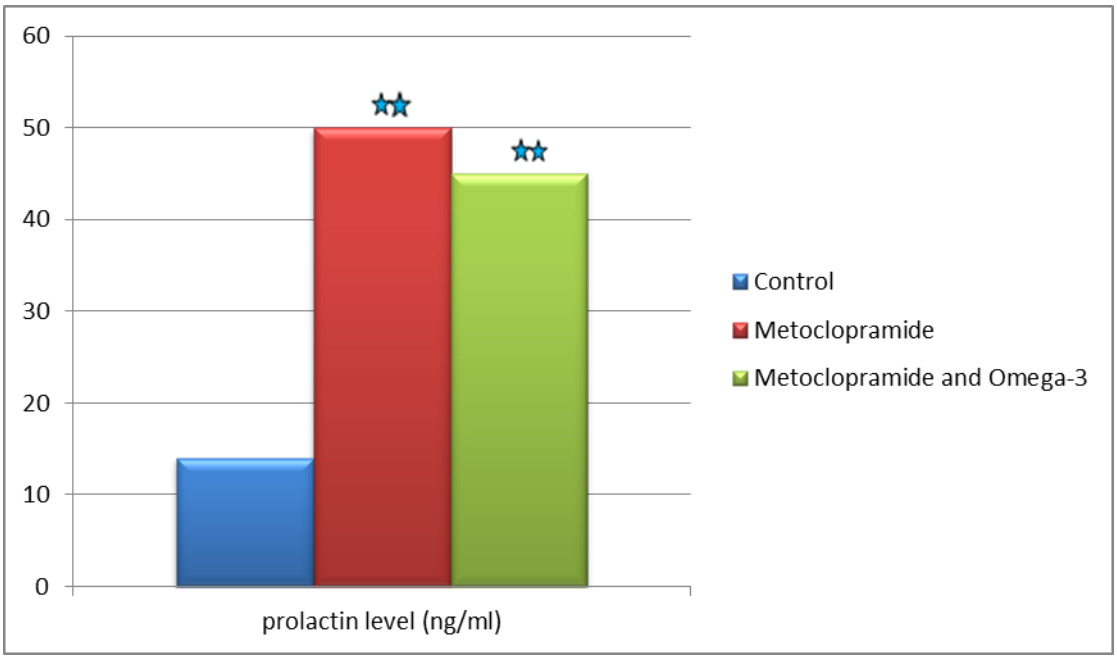

Fig. 1: Effect of oral administration of MCA alone, coadminstration of MCA with omega-3 on serum prolactin level.

*Statistically significant difference (p<0.05) in comparison to control group.

**Statistically highly significant difference (p<0.01) in comparison to control group.

Determination of lipid parameters

Metoclopramide administration for 3 weeks resulted in highly significant elevation in the level of TG in comparison to control and combined treatment of MCA and omega-3 as shown in figure 2. Both TC and LDL showed significant elevation in MCA treated group compared to rats that received either vehicle or co-treatment of MCA and omega-3. Treated group with MCA showed significant reduction in HDL-C level compared to both control and group that received co-administration of MCA and omega-3 (figure 2).

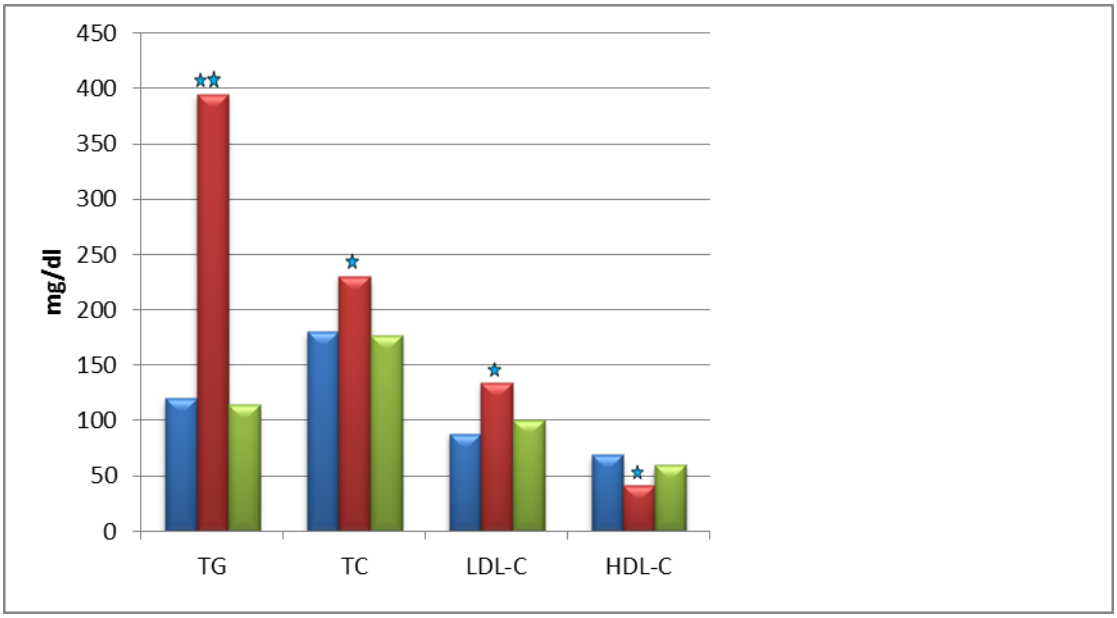

Fig. 2: Effect of MCA orally, cotreatment of MCA with omega-3 in comparison to control group on lipid parameters level in serum.

*Statistically significant difference ($p<0.05$) in comparison to control group.

** Statistically highly significant difference ($p<0.01$) in comparison to control group.

DISCUSSION

Hyperlipidemia is an abnormal elevation of blood lipids. It increases the risk of developing cardiovascular disease. This risk is presented with atherogenic hyperlipidemia. It is manifested by elevated TG and lowered in HDL-C levels. This is commonly seen in patients with type-2 diabetes and metabolic syndrome.[12] High TG level is a marker of elevated cardiovascular risk beyond that LDL-C level. Treatment of dyslipidemia is directly related to the reduction in risk of cardiovascular disease.[13]

Metoclopramide is a prokinetic drug. It is commonly used as antiemetic to decrease nausea and vomiting in patients with gastro-oesophageal reflux, during treatment of chemotherapy or patients undergoing radiotherapy, and in migraine treatment.[4] MCA is also commonly used in treatment of diabetic gastroparesis.[14] It has common side effects include feeling restless, diarrhea, depression, and movement disorder. It is a dopamine receptor antagonist and increases plasma level of prolactin.[15] Hyperprolactinemia is an important adverse effect of MCA. Prolactin affects the lipid metabolism. Our study showed that MCA group and in co-treatment of MCA and omega-3 group are significantly elevated prolactin levels in comparison to control one. Moreover, this study observed that MCA administration for 21 day caused highly significant elevation ($P<0.01$) in TG level in comparison to both control and treated group with omega-3. Total cholesterol and LDL levels are significantly increased ($P<0.05$) in MCA group compared to control and co-treated group with omega-3. However, the HDL-C level is significantly decreased in MCA treated rats. Therefore, MCA treated group showed hyperprolactinemia and hyperlipidemia in the present study.

Metoclopramide is the main drug accepted by Food and Drug Administration (FDA) for the treatment of gastroparesis.[14] So, MCA plays a role in elevated lipid profile to high risk diabetic patients during treatment of gastroparesis. In the same context, Cincotta et al., (1998)[16] observed that hyperprolactinemia is associated with fattening, hyperlipidemia and other metabolic disorders. Also, patients with metabolic abnormalities and hyperlipidemia have highly predictable daily prolactin level profiles and these various metabolic disorders significantly improved after prolactin inhibitor treatment. Klibanski and his coworker, (1980)[17] showed that hyperprolactinemia associated with hyperlipidemia through direct and indirect effect on lipid metabolism by suppression in the activity of plasma lipoprotein lipase, increased plasma TG, low plasma HDL-C and change activity of hepatic lipase enzyme.

This study declared the possible protective effect of omega-3 against MCA induced hyperlipidemia. Similarly, Kris-Etherton et al., (2002)[18] observed that omega-3 is playing an important role in treatment cardiovascular out comes, and its additive effects in patients receiving anticoagulant, antihypertensive, and lipid-lowering drugs. Moreover, The American Heart Association recommends 2-4 g daily of omega-3 to lower TG levels for cardiovascular patient's.[19] Furthermore, the Endocrine Society observed that omega-3 fatty acids alone or in combination with most commonly used antihyperlipidemic drugs such as statins should be considered a treatment option for moderate-to-severe hypertriglyceridemic patients.[20]

Omega-3 fatty acids are given as supplements or as prescription to decrease TG levels by 25-34%.[21,18] Also,

several studies showed that administration of omega-3 fatty acids for two weeks or more causes significant differences in TG level.[22,23] The magnitude of lowering TG level is dependent on both omega-3 dose and the TG level.[24] Bays et al., (2008)[25] suggested that omega-3 fatty acids lowered serum TG level by decreasing TG synthesis, reducing the conversion of TG to VLDL, decreasing TG secretion, and increasing TG clearance from VLDL Particles. Le Jossic-Corcos and his coworker, (2005)[26] observed that omega-3 decreased TG level through hepatic lipogenesis by reducing the sterol regulatory element-binding protein-1c. This lowered the expression of fatty acid, cholesterol, and TG synthesizing enzymes. Also, it has been suggested that omega-3 enhanced the β-oxidation of fatty acids, resulting in decrease the substrates number available for TG and VLDL synthesis. Furthermore, they also suggested that omega-3 inhibit the main enzymes responsible for hepatic TG synthesis, as diacylglycerol acyltransferase and phosphatidic acid phosphatase. In conclusion, this study observed that omega-3 fatty acids could be treated MCA induced hyperlipidemia. It represents viable antihyperlipidemic treatment options especially for patients with elevated TG levels.

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