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Effect of Omega-3 as Adjuvant Therapy to Methotrexate on Lipid Profile in Iraqi Patients with Active Rheumatoid Arthritis

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Abstract

Rheumatoid arthritis (RA) is a common inflammatory disease associated with many extra-articular features. The aim of the current study is to assess the influence of omega-3 fatty acids (EPA,DHA) on serum lipids in patients with active RA. Fifty patients with active RA using MTX were participated in this study. Patients were allocated to take either omega-3 (1000 mg) capsule three times daily or capsules prefilled with glucose as placebo and were evaluatedat zero time (baseline) and after 12 weeks for lipid profile parameters. The RA disease activity was measured using DAS28-ESR and CDAI. After 12 weeks of starting adjuvant treatment with either omega-3 or placebo, it's found that only TG decreased significantly by omega-3 ($p<0.01$) while other parameters (TC, HDL-c, LDL-c) showed no significant difference between the effect of omega- 3 and placebo. In Conclusion, omega-3 significantly decreased TG levelin patient with active rheumatoid arthritis.

Index terms— rheumatoid arthritis, omega-3, lipid profile.

1 Introduction

heumatoid arthritis (RA) is a systemic chronic inflammatory disease of unknown etiology that primarily targets synovial tissues (1,2) and affecting both articular tissues and extra-articular organs (3).Rheumatoid arthritis is associated with increased mortality, which is predominantly due to accelerated coronary artery atherosclerosis (4). Cardiovascular (CV) morbidity and mortality are increased twofold in RA patients compared to those of the general population (5,6).The association between lipids and CV risk in RA appears to be more complex than in the general population, with systemic inflammation being a notable contributor to the lipid profile changes (7). Inflammation leads to pro-atherogenic changes of the lipoprotein metabolism and an increased disease activity is associated with lower total cholesterol (TC) levels and even more depressed high density lipoproteincholesterol (HDLc) levels and lowered Apolipoprotein-A1 (apo-A1) levels (8). Besides that, active inflammation increases oxidized fatty acids in circulating lipoproteins, promoting low density lipoprotein (LDL) oxidation and HDL dysfunction, thereby increasing atherosclerotic risk (9). The atherogenic lipid profile and subclinical atherosclerosis are features of early RA, which improved after therapy. Early intervention and control of the disease activity may reduce the risk of atherosclerosis and CV events in patients with RA (10).

Omega-3 FA, found primarily in fatty fish with high oil content, consists of both eicosapentaenoic acid (EPA) anddocosahexaenoic acid (DHA) (11). Omega-3 fatty acids (EPA, DHA) have several actions in number of body system. EPA and DHA lower elevated triglyceride levels by inhibition of acyl coenzyme A (CoA): 1,2-diacylglycerol-O-acyltransferase,the enzymes responsible for triglyceride synthesis; so, the esterification and release of other fatty acids are inhibited. Alsoomega-3 fatty acids appear to induce peroxisomal ß-oxidation in the liver. Hepatic nuclear receptors, such as peroxisome proliferator-activated receptors (PPARs), are thought to mediate the hypolipidemic effect of polyunsaturated fatty acids. Because of a high affinity for PPAR-? and PPAR subclasses, omega-3 fatty acids may also up regulate the metabolism of fatty acids in the liver (12).Also its observed an inhibitory effect of fish oil supplementation on TXA 2 synthesis, may thus explain its inhibitory

effect on TNF? and IL-1? synthesis (13). In a previous study, the omega-3 (fish oil) used in combination with borage seed oil in 156 rheumatoid arthritis patients with active joint inflammation and found that both oils might be useful treatment for rheumatoid arthritis patients who are at increased risk for cardiovascular disease compared with general population (14).The aim of the current study is to assess the influence of omega-3 fatty acids (EPA, DHA) on serum lipids in Iraqi patients with active RA.

2 II.

3 Patients and Methods

4 a) Patients

Seventy two patients with active RA using MTX were participated in this study; only fifty patients completed the follow up. Patients were allocated to take either omega-3, 1000 mg capsule(300 mg EPA,200 mg DHA) three times daily or a capsule prefilled with glucose as placebo. In addition to twenty five apparently healthy subjects participated in this study.Omega-3 was brought from AdrienGagnon, Canada. Whereas glucose was bought from SDI, Samarra, Iraq. Patients were

5 b) Inclusion criteria c) Exclusion criteria

Patients with juvenile RA, patients with coexistence other connective tissue diseases, patients already on omega-3, presence of contraindication to omega-3 (patients with chronic anticoagulant treatment and hemorrhagic disorder),known allergy to or intolerance of omega-3,severe liver disease, pregnancy, breast feeding, patients using high dose of steroid (? 7.5 mg of steroid).diabetic patients, patients with inactive RA.

6 d) Patients groups

Active RA patients who participated in this study were diagnosed by a specialized physician depending on: patient medical history, physical examination and laboratory data. Patients consent inform and ethical approval were performed for each patient.

7 e) Clinical and laboratory evaluation

For all patients enrolled in this study, direct interview was performed to evaluate disease manifestations, symptoms, medical history, and laboratory findings. Clinical evaluation of patients for tender and swelling joints was done by specialized rheumatologist at zero time(baseline) and after 12 weeks. The RA disease activity was measured using DAS28-ESR (16) and CDAI (17). DAS28 and CDAI can be calculated according to the following formula: DAS28 = 0.56 (TJC) 0.5 +0.28(SJC) 0.5 +0.70ln (ESR) +0.014(VAS) CDAI=TJC+SJC+PrGA + PtGA Blood specimen collection and laboratory analysis (at baseline and after 12 weeks) of lipid profile (TC, TG, HDL-C) was done by specialized laboratory researchers who did not participate in this study. LDL-C level was estimated according to the Friedewald formula (18).

8 LDL -C (mg/dl) =TC -(TG/5) -HDL -C f) Statistical Analysis

Statistical software (SPSS version 19, Chicago, IL, USA) was used for data input and analysis. The results were expressed as mean ± standard deviation (SD).One-way analysis of variance (ANOVA) was used to examine the degree of difference among studied groups. Chi-square test was used to test the significance of association between variables. Paired T test was used to test the significance of difference in means of pre and post treatment. Unpaired T test was used to test the significance of difference in the mean of two independent samples. Value less than 0.05 were considered significant, P values less than 0.01 were considered highly significant and P values less than 0.001 were considered very highly significant.

9 Result

Of a total of 92 patients who were randomized in this study, 50 completed the 12 weeks of treatment (25 from the omega-3 group and 25 from the placebo). In addition to twenty five apparently healthy subjects participated in this study as a control group. The three groups did not differ significantly in baseline characteristics ($p>0.05$, table1). Baseline lipid profile parameters showed that Total cholesterol level in RA patients of both omega-3 and placebo group was highly significantly higher than that in the control group($p<0.01$), Triglyceridelevel in RA patients of both omega-3 and placebo group was very highly significantly higher than that in the control group ($p<0.001$). Whilethere is a non significant difference in HDLc and LDLc level between RA patients of both omega-3 and placebo group and subjects in the control group($p>0.05$, table 2).After 12 weeks of starting adjuvant treatment with either omega-3 or placebo, we found that only TG decreased significantly by omega-3 ($p<0.01$)while other parameters showed no significant difference between the effect of omega-3 and placebo ($p>0.05$, table **??**).

10 Discussion

The effect of treatment with omega-3 (fish oil) as adjuvant to MTX on lipid profile was investigated in this study. The result of this study showed there was a highly significant difference in serum TC, TG level between RA patient and control subject. While there was a non significant difference in HDL-C, LDL-C level. Several studies have examined serum levels of lipid in RA patients compared to control; one of them done by Georgiadis et.al which demonstrate elevation in TC, LDL-C and TG level in RA patients but decrease in HDLc level, and this atherogenic lipid profile can be improved by initiation of therapy (19).while another study done by Lazarevicet.al Demonstrate that RA patients had significantly decreased concentration of total serum lipids, TC, LDL-C, and HDL-C, compared to control (20). The result of our study showed that there was a non significant difference between the effect of omega-3 and placebo on TC, LDL-C, and HDL-C level, despite there was a significant increase in HDL-C (2.98%) for patient taken omega-3; similar finding was report in study done by Willers et.al (21).Whereas in another study using Patients with RA as defined by the ACR 1987 revised criteria (15) and proved to have active RA by calculating either DAS28 or CDAI; all selected patients were on methotrexate treatment.

11 III.

12 IV.

omega-3 fatty acid supplements in dose 3.5gm for 18 month was sufficient to significantly decrease TC, LDL-C, and increase HDL-C level (14); this can be attributed to the short duration of our study in comparison to the above study that continued for 18 months. In the present study, the result showed that omega-3 produce a highly significant reduction in TG compared to placebo; our result agree with finding reported in many other studies comparing different doses of omega-3 to placebo in patient with RA (21,14).Omega-3 reduced TG by more than 3%. Such result can be explained according to the fact that omega -3 has beneficial effect on blood lipid parameters (22),an inhibition of hepatic fatty acid synthesis by EPA and DHA and impaired triglyceride synthesis are among some of the mechanism proposed for the plasma TG -lowering effect of omega-3(23).

13 Conclusion

Omega-3 is significantly reducingtriglyceride level in patient with active rheumatoid arthritis.

Figure 1:

Rheumatoid Arthritis
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Figure 2: B

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parameter	Omega-3 n=25	Placebo n=25	Control n=25	p-value
Age(yr)	50.36±12.32	50.08±9.18	49.20±5.58	p>0.05
Gender	female 22(88%)	female 23(92%)	female 21(84%)	p>0.05
	male 3(12%)	male 2(8%)	male 4(16%)	p>0.05
Smoking [n (%)]	0 (0%)	3(12%)	5(20%)	p>0.05
Disease duration (yr)	4.92±6.08	7.16±7.09	-	p>0.05
Dose of MTX	8.10±1.30	7.90±1.18	-	p>0.05
Family Hx of RA n	6(24%)	10(40%)	-	p>0.05
Positive RF n (%)	18(72%)	20(80%)	-	p>0.05
Sc nodule n (%)	5(20%)	20 (%) 5	-	p>0.05

Continuous variables presented as Mean ± Standard deviation
Discrete variables presented as numbers and frequencies.
MTX = Methotrexate n = Number Sc = Subcutaneous
RA = Rheumatoid arthritis RF = rheumatoid factor Hx = History

Figure 3: Table 1 :

2

Parameter	Omega-3	Placebo	Control	P-value
	N=25	N=25	N=25	
TC(mg /dl)	189.28±35.5	184.12±24.3	162.16±23.28	0.003*
TG(mg /dl)	136.12±35.8	122.40±29.2	98.92±18.84	0.000**
HDL-C(mg/dl)	41.56±5.9	40.48±3.17	42.08±3.52	0.425
LDL-C(mg/dl)	120.48±32.5	118.62±24.94	100.08±23.04	0.822

Continuous variables presented as Mean ± Standard deviation

TC=total cholesterol TG=triglyceride HDL-C=high density lipoprotein cholesterol LDL-C=low density lipoprotein cholesterol

Figure 4: Table 2 :

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