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Omega-3 Induced Change in Clinical Parameters of Rheumatoid Arthritis

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The aim of this study was showing the suppressive effect of fish oil supplementation on clinical symptom in rheumatoid arthritis. Forty two patients with Rheumatoid Arthritis (RA) entered a trial to determine the clinical and biochemical effects of dietary supplementation with fractionated fish oil fatty acids. A randomized study design with 4 and 8 week treatment periods were used. Treatment with non-steroidal anti-inflammatory drugs and with disease modifying drugs was continued throughout the study. There were significant improvement of RF ($p = 0.009$), ESR ($p = 0.003$) and serum CRP ($p = 0.002$) after 8 weeks fish oil supplement, but after 4 weeks the RF ($p = 0.004$) only showed significant improvement. This study shows that dietary fish oil supplementation is effective in suppressing clinical symptoms of rheumatoid arthritis.

Key words: Omega-3, rheumatoid arthritis, erythrocyte sedimentation rate, rheumatoid factor, C-reactive protein

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INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic inflammatory disease characterized by joint swelling, synovial inflammation and cartilage destruction (Hirayama *et al*., 2002). Management of patients with RA involves patient education, physical and occupational therapy and administration of disease modifying antirheumatic drugs (Quinn *et al*., 2001; Lipsky *et al*., 2000). Methotrexate (MTX) is presently the preferred disease modifying antirheumatic drug for patients with active RA because of its long-term effectiveness in clinical practice (Newsome, 2002). Notwithstanding, many patients do not experience disease remission and continue to have signs and symptoms of active disease while taking a maximally tolerated dose (Maetzel *et al*., 2000). Supplementation of fish oil rich in eicosapentaenoic acid (EPA) (20:5 ω-3) and docosahexaenoic acid (DHA) (22:6 ω-3) might have successful results in the treatment of rheumatoid arthritis (Barbosa *et al*., 2003). Although improvement in some clinical parameters has been shown, especially in the number of tender joints (Kremer *et al*., 1990), duration of morning stiffness and less frequently, handgrip strength, Ritchie's articular index (Magaro *et al*., 1988), medical global assessment (Sköldstam *et al*., 1992), intensity of pain (Goldberg and Katz, 2007) and the overall clinical response of fish oil supplement is considered modest (Kremer, 2000). Thus, the purpose of the present study was to verify whether modification of diet with fish oil could improve clinical and laboratory parameters of disease activity in patients who had RA.

MATERIALS AND METHODS

This study was conducted from 12th June 2006 to 10th October, 2007.

Patients: After clinical evaluation at the Rheumatology Outpatient Service, 42 patients with RA, according to the American College of Rheumatology criteria (Hochberg *et al*., 1992), were included in this study. The mean age of patients who finished the study (33 female and 9 male) was 43±19 year (range 25-65 year). All patients gave informed consent and the study protocol was fully approved by the local ethical committee of the Ahwaz Joundishapour University of Medical Sciences (AJUMS, Ahwaz, Iran). In this randomized, patients were assigned to one of three groups:

- **Group 1:** Before consumption of the fish oil
- **Group 2:** 4 weeks after consumption of the fish oil
- **Group 3:** 8 weeks after consumption of the fish oil

Clinical assessment and evolution was done according to the following criteria:

- Duration of morning stiffness (in minutes)
- Joint pain intensity, on a five-point scale (0 = absent; 1 = mild; 2 = moderate; 3 = severe; 4 = very severe)
- Onset of fatigue (in minutes) after walking
- Ritchie's articular index for pain joints (Ritchie *et al*., 1968)
- Right and left grip strength (in mmHg) measured with a sphygmomanometer cuff inflated to 20 mmHg, with an average of three determinations for each hand
- Patient's global assessment of disease activity (0-10 cm visual analog scale: 0 = symptom free; 10 = very severe)
- Classification of functional status in RA according to revised criteria of the American College of Rheumatology (Hochberg *et al*., 1992) (class 1: completely able to perform usual activities of daily living, e.g., self-care, work and leisure; class 2: able to perform usual self-care and work activities but limited in leisure activities; class 3: able to perform usual self-care activities but limited in work and leisure activities and class 4: limited in ability to perform usual self-care, work and leisure activities)
- Patient's satisfaction in activities of daily living based on a modified Stanford Health Assessment Questionnaire (Pincus *et al*., 1983), in which the patient answers eight questions concerning his/her ability to perform some activities and a four-point scale is applied (0 = always; 1 = mostly; 2 = sometimes; 3 = never)

Laboratory evaluation was done by laboratory blood parameters: C-reactive protein and rheumatoid factor (nephelometry), Rheumatoid Factor (RF), erythrocyte sedimentation rate (Wester green's method) and hemoglobin. All patient have taken 2 g MaxEPA (contains 41.1% unsaturated fat, 17.8% ecsapentanoic acid (EPA) and 11.6% docosahexanoic acid (DHA); R.P. Scherer Canada, Windsor, Ontario, Canada) daily during first 4 weeks followed by 3 g day^{-1} for second 4 weeks. These supplements are consumed while patients continue to take their background medications, such as non-steroidal anti-inflammatory drugs like codeine, methotrexate and prednisolone.

Statistical analysis: All analysis was done with the SPSS 13.0 software. Distribution of age, sex, disease duration and number of medications was analyzed with Fisher's exact test. Percentage of change from baseline of clinical and laboratory parameters was calculated with analysis of

variance. Statistical significance was set at $p<0.05$. Result values are presented as Mean±SD.

RESULTS AND DISCUSSION

In this study the biochemical parameters of RA patients were compared before and after 4 and 8 weeks fish oil supplements consumption. There were significant improvement of RF ($p = 0.009$), ESR ($p = 0.003$) and serum CRP ($p = 0.002$) after 8 weeks fish oil supplement, but after 4 weeks the RF ($p = 0.004$) only showed significant improvement (Table 1) (Fig. 1a-c). We have evaluated joints of the study patients clinically after 4 and 8 weeks consumption of fish oil (Table 2). In this sequence 64.2% of the patients in the end of 4 weeks and 80.9% of the patients after the 8 weeks consumption of fish oil supplement show the statistically significant ($p<0.05$) reduction in inflammated joints number. In 95.2% of the patients 4 weeks and 100% of them after the 8 weeks after consumption of fish oil supplement the involved joints has shown statistically significant ($p<0.05$) reduction. In 66.6% of the patients after 4 weeks and 83.3% after the 8 weeks of consumption of fish oil supplement the decrease in their cynovium fluid was more and shows statistically significant ($p<0.05$) improvement. Also in 80.9% of the patients after the 4 weeks consumption of fish oil the global assessment physician according to the results has shown statistically significant enhancement. The mean and standard deviation of weight and BMI of the study patient before and after 4 and 8 weeks consumption of fish oil supplement has shown in Table 3. There were no statistically significant difference in weight and BMI before and after the consumption of fish oil supplement (Table 3).

The beneficial effects of fish oil ω-3 fatty acids were more commonly observed, in agreement with the studies of Kremer *et al.* (1990). The 1.0 -3.0 g dose of fish oil ω-3 fatty acids used in the present study is the minimum daily dose recommended in patients who have RA (Kremer, 2000). The RA disease is a chronic inflammation cynovial disease with the indefinite reason. In this disease the cure is done with the help of drug for the control of pain and inflammation of the patient. So, the patient will gain the necessary abilities for the suitable movement along with the relieving of the pain and inflammation. In the usual cure of this disease, the drug therapy is started according

Table 1: Effects of different types of fish oil supplement consumption on RF, ESR and CRP in individuals

	Group			p- value* (weeks)	
Test	1	2	3	4	8
CRP	15.34±4.04	11.67±3.62	8.25±3.17	NS	0.002
RF	15.97±3.42	13.22±3.34	12.08±3.60	0.004	0.009
ESR	40.45±3.93	23.07±4.31	24.77±3.89	NS	0.003

Data are expressed as Mean±SD. n = 42, Group 1: Before consumption of the fish oil; Group 2: 4 weeks after consumption of the fish oil; Group 3: 8 weeks after consumption of the fish oil; ESR: Erythrocyte Sedimentation Rate; RF: Rheumatoid Factor; CRP: C-reactive protein. *Comparing patients' biochemical parameters between baseline and after 4 and 8 weeks with respect of fish oil consumption; NS: Not significant

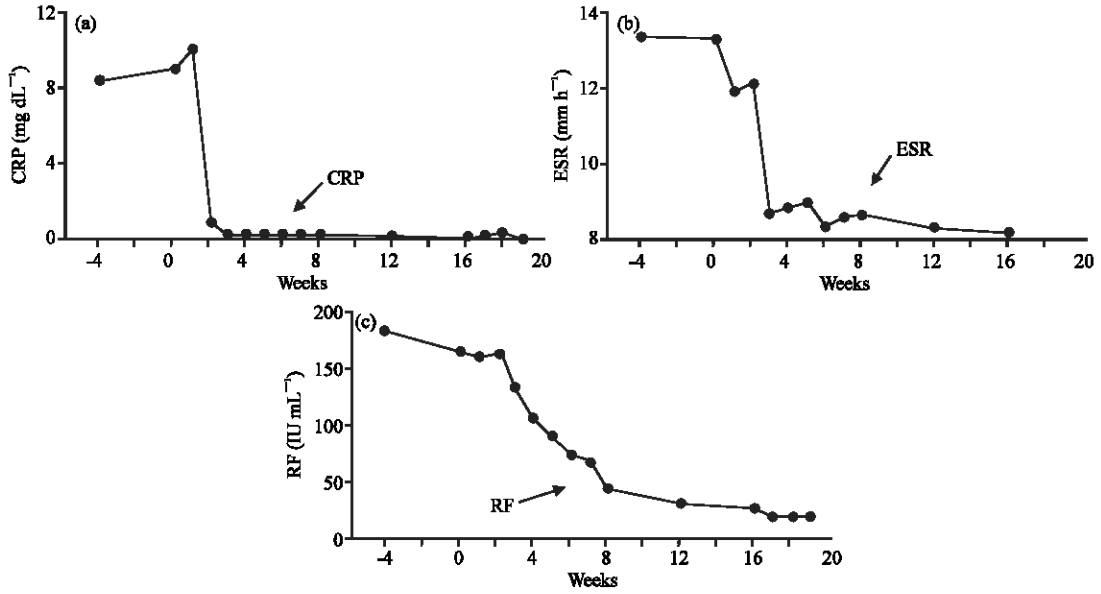

Fig. 1: The (a) CRP (C-Reactive Protein), (b) ESR (Erythrocyte Sedimentation Rate) and (c) RF (Rheumatoid Factor); Values after consumption of fish oil supplements

Table 2: Clinical results of the joints in the study patients before and after 4 and 8 weeks consumption of the fish oil supplement

	Groups									
	1		2			3			Result	
Symptoms	No.	Percentage	No.	Percentage	p-value	No.	Percentage	p-value	A	B
Inflammated joints	42	100	27	64 .2	0.005	34	80.9	0.0043	8	9.1
Decrease in the cynovium fluid quantity	42	100	28	66.6	0.0072	35	83.3	0.0041	7	16.7
Global-assent patient	42	100	34	80.9	0.0025	40	95.2	0.0058	2	4.8
Involved joints	42	100	40	95.2	0.002	42	100.0	0.0038	0	0.0

Group 1: Before consumption of the fish oil; Group 2: 4 weeks after consumption of the fish oil; Group 3: 8 weeks after consumption of the fish oil; A: No. of patients who has not recovered; B: The percentage of the patients who have not recovered

Table 3: The calculated mean and standard deviation of the weight and BMI among study patients, before and after consumption of the fish oil supplements

	Fish oil supplement consumption			p-value*		
	Groups			Groups		
Variables	1	2	3	1	2	3
Weight (kg)	70.93±12.12	12.41±71.34	12.54±71.70	NS	NS	NS
BMI (kg m^{-2})	6.24±4.540	4.61±26.40	4.72±26.53	NS	NS	NS

*With respect of fish oil consumption. NS: Not significant; BMI: Body mass index

to the patient condition, seven group of drugs have been used for the treatment of RA which are as salisilates, non-steroidal anti inflammation drugs (NSAIDS), the anti inflammation factors, non-steroidal anti-inflammatory drugs like codeine, methotrexate and prednisolone.

PGE_2 and LTA_4 and also EPA have the effect of the releasing on the formation of TNFα and IL-IB (inflammable substance). In an uncontrolled study, 24 patients with RA were maintained on this diet for 4 weeks. While pain, joint swelling and joint tenderness scores improved, there was no improvement in duration of morning stiffness, ESR, or CRP (McDougall *et al*., 2002). Surprisingly, another research studies have shown that the consumption of fish oil supplement causes the decrease in the number of inflammated joints and decrease in the morning stiffness (Skoldstam *et al*., 1992). The results of the present study show that in the 80.9% of patient, the number of inflammated joints and 100% of patient the involved joints after the consumption of the fish oil supplement for 8 weeks has been decreased significantly.

The results of the present study show that RF, ESR and CRP after the consumption of the fish oil has been decreased with statistically significant values, which shows the decrease in the inflammation, therefore, the consumption of the fish oil leads to the recovery of the condition of the patients which are suffering from rheumatoid arthritis.

Fish oil, primrose oil has anti-inflammatory activity and can be used with successful results in rheumatoid arthritis patients. Liver and kidney functions were improved during natural oil treatments. On recommendation, fish oil is recommended to be given in rheumatoid arthritis patients. These natural oils might be given alone or during treatment with synthetic drugs to permit reduction of dose level of the later, so as to minimize their side effects. We recommend prospective studies on the use of these natural oils either alone or in conjunction of different anti-inflammatory synthetic drugs (which may have synergistic effects with each other) for longer periods of time in rheumatoid arthritis patients.

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