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A RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL OF OMEGA 3 SUPPLEMENTATION IN JUVENILE IDIOPATHIC ARTHRITIS: IMPROVEMENT IN DISEASE ACTIVITY AND FUNCTIONAL STATUS

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ABSTRACT

Background: A variety of drugs either alone or in combination are used in treatment of juvenile idiopathic arthritis (JIA) with varying success to suppress symptoms or modify disease activity. Omega 3 has been recommended in treatment and prevention of inflammatory, autoimmune diseases such as rheumatoid arthritis. Researches on JIA are limited. **Aim:** to evaluate the effect of omega 3 supplementation on disease activity and functional status in JIA. **Subjects and methods**: This study was a randomized double-blind placebo-controlled 12-week trial. Sixty six patients with JIA were randomized (1:1) to receive omega 3 supplements (2 gm/ day) orally or placebo. Medications remained stable throughout the study. Disease activity was assessed using Juvenile Disease Activity Score in 27 joints (JDAS-27). Functional status was assessed using the Childhood Health Assessment Questionnaire (CHAQ). Laboratory investigations were performed for all patients including determination of hemoglobin concentration (Hb in g/dL), ESR in mm/h, and C-reactive protein (CRP in mg/L). Levels of IL-1 and TNF-α level were measured using radioimmunoassay. **Results:** At baseline, groups were similar in demographic, biochemical, disease activity criteria and drug dose treatment. After 12 weeks omega 3 supplements significantly improved the JDAS-27, CHAQ-DI score, ESR, C reactive protein, TNF-α, and IL-1 levels ($p< 0.05$). **Conclusion:** These results confirm the anti-inflammatory effects of omega 3 supplementation in a dose of

2 gm/day for 12 weeks and its effective role in decreasing disease activity and improving functional status in JIA patients.

KEYWORDS: Omega 3 supplementation**;** rheumatoid arthritis; JDAS.

INTRODUCTION

JIA is generally considered a clinical syndrome involving several disease subsets, with a number of inflammatory flows, leading to persistent synovial inflammation and associated damage to articular cartilage and underlying bone.[1] One main inflammatory process in the pathophysiology of the JIA consists of over production of tumour necrosis factor that leads to overproduction of many cytokines such as interleukin 1β, and 6 which cause persistent inflammation and joint destruction.[2,3,4] The disease arises in a genetically susceptible individual due to environmental factors ; antigen-driven autoimmune process or uncontrolled activation of the innate immune system.[5,6,7]

The possible role of nutritional manipulation in the treatment of inflammatory disease has increased along with proper understanding of immunity, eicosanoid metabolism, and cellular biology.[8] Nutrient supplementation as add-on therapy in JIA has witnessed a marked scientific interest due to preclinical and clinical studies on supplementation with omega 3.[9]

Several clinical studies in rheumatoid arthritis (RA) patients have demonstrated modest but reproducible beneficial effects on the joint tenderness of supplements with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) at doses of 2.3–7.1 g per day.[10] Recent studies indicate that polyunsaturated fatty acids (PUFAs), including EPA and DHA, and anti-inflammatory agents can potentially decrease inflammation through several mechanisms, including inhibition of tissue inflammation induced by arachidonic acid (AA) pathway,[11,12] prevention of AA release by lipoprotein lipase,[13] reduction in AA contents of cell membranes[14] and inhibitory effects on activation of cyclooxygenase-2 pathway, an enzyme that converts AA to prostaglandin E2 and thromboxane A2.[15,16]

Immunologic studies have shown the inhibitory effects of omega-3 fatty acids on the production of different cytokines by immune cells.[17] Little investigations have been carried out to confirm the effect of omega-3 fatty acids on inflammatory biomarkers among JIA patients, but the findings have not been consistent.[18,19,20] The purpose of the current study

was to evaluate the effect of omega 3 supplementation on diseases activity and functional status in JIA.

SUBJECTS AND METHODS

Patients: Sixty six patients diagnosed as active JIA recruited from the Pediatrics Allergy and Immunology Clinic, Ain Shams University. Patients were eligible if they met the Edmonton Inter-national League of Associations for Rheumatology criteria (second revision) for diagnosis of JIA.[21]

Study design: The present study is a double blind randomized controlled clinical trial. Patients were randomly allocated to receive each day either 4 capsules Omega-3 fatty acid (500 mg per capsule) or 4 placebo capsules (containing olive oil 500 mg per capsule) for 12 weeks.

Patients and researchers were blinded to treatment assignment during the entire study. The patients were instructed to continue their regular drug treatment schedule. Patients' dietary fat intake was kept constant throughout the study. Each patient kept a daily food diary.

All patients had full history taken and were subjected to clinical examination.
Written informed consent was obtained from parents after explanation of the aim of the study. The protocol was approved by Ethical and Research Committee of the National Research Centre.

Evaluating disease activity: Disease activity was measured using a validated score, the JADAS-27(Juvenile Arthritis Disease Activity Score-27).[22] This score includes four measures: physician global assessment of disease activity using visual analog scale (VAS), parent global assessment of child's well-being determined by VAS, count of joints with active disease (evaluating 27 joints), and erythrocyte sedimentation rate (ESR).

The JADAS-27 includes the following joints: cervical spine, elbows, wrists, metacarpophalangeal joints (from the first to third), proximal interphalangeal joints, hips, knees, and ankles. ESR is normalized to a score ranging from 0 to 10, by the formula (ESR-20)/10. JADAS-27 is calculated as the simple linear sum of the scores of its four components, which yields a total score of 0-57, with higher scores associated with worse disease activity. JADAS-27 was assessed at baseline and after 12 weeks.

Evaluating health status: Health status was assessed by the Childhood Health Assessment Questionnaire (CHAQ) that measures the functional status distributed among a total of 30 items scored from 0 to 3 (without difficulty, with some difficulty, with much difficulty, and unable). [23] The scores were assessed at baseline and after 12 weeks (at the end of the study).

Laboratory evaluation: Laboratory investigations were performed for all patients at baseline and after 12 weeks of the study, including determination of hemoglobin concentration (Hb in g/dL), ESR in mm/h by Westergren method, and C-reactive protein (CRP in mg/L) detection by the latex agglutination slide test.

Serum concentrations of tumour necrosis factor-alpha (TNF-α), interleukin-1β (IL-1) were measured by multiplex enzyme-linked immunosorbent assay (ELISA) (Millipore®, Merck KgaA, Darmstadt, Germany).

Statistical Analysis: the data were entered into the SPSS statistical software (v. 16) and analysed using descriptive statistics, paired and independent t-test. Additionally, $P<0.05$ was considered as statistically significant.

RESULTS

Of the sixty six JIA patients, sixty patients continued the study for 12 weeks (30 males and 30 females). 6 subjects dropped out during the 12 weeks treatment period: four due to loss of follow up and two due to refusal to continue taking the supplement.

Baseline characteristics of completers in both groups are shown in Table 1. in all, 60 patients enrolled in the trial: 30 in the placebo group and 30 receiving the omega 3 supplement. The two groups did not differ with respect to clinical and demographic variables (age, sex, body mass index, disease duration, severity assessed by JDAS-27, treatment doses); and thus, any change at the end of the study would be attributed to the supplementation.

Table 1. Baseline characteristics of JIA patients who completed the study

Variable	Mean ± SD		P value
	Placebo (n=30)	Omega 3 (n=30)	
Age (years)	12.3± 3.6	13.6 ± 4.3	> 0.05
Females, n (%)	15 (50)	15 (50)	-
Body mass index (kg/m^2)	23.5 ± 3.1	22.1± 2.4	> 0.05
Disease duration (years)	6.95± 2.7	7.08 ± 3.7	> 0.05
Concurrent MTX use, n (%)	30 (100)	30 (100)	-
Dose (mg/m2/week)	15.57± 4.81	15.14± 5.07	> 0.05
Concurrent glucocorticoid use, n (%)	15(50)	14(46)	> 0.05
Dose (mg/kg/day)	0.15 ± 0.03	0.14± 0.05	> 0.05
JDAS-27	41.97 ± 7.13	40.34 ± 8.24	> 0.05

MTX, *methotrexate ;* ***JDAS-27****, Juvenile Arthritis Disease Activity Score-27.*

Changes in clinical parameters are listed in Table 2. After 12 weeks omega 3 supplements significantly improved the JDAS-27, CHAQ-DI score, ESR, C reactive protein, TNF-α, and IL-1 levels ($p< 0.05$). No significant changes in Hgb levels in both groups after 12 weeks.

Table 2. Change from baseline in clinical and laboratory parameters of JIA patients during the double blind phase

Parameter	Mean ± SD		P value
	Placebo (n=30)	Omega 3 (n=30)	
JDAS-27 Baseline Δ Mean 12 weeks ± SD	41.97 ± 7.13 -1.4± 0.7	40.34 ± 8.24 - 10.8± 1.2	> 0.05 < 0.05
CHAQ-DI score Baseline Δ Mean 12 weeks ± SD	1.7± 0.3 -0.2 ± 0.2	1.7± 0.4 -0.7 ±0.3	> 0.05 < 0.05
Hgb (g/dL) Baseline Δ Mean 12 weeks ± SD	10.9± 1.42 1.45 ± 0.01	11.79 ± 1.47 0.14 ± 0.3	> 0.05 > 0.05
ESR (mm/h) Baseline Δ Mean 12 weeks ± SD	54.3 ± 23.9 -6.7 ± 4.1	50.5 ± 26.46 -25.8 ± 16.3	> 0.05 < 0.05
C-reactive protein positive(mg/L) Baseline Δ Mean 12 weeks ± SD	9.67 ± 3.11 -1.31 ± 0.93	10.44± 3.21 -6.24 ± 1.09	> 0.05 < 0.05
TNF- α (pg/mL) Baseline Δ Mean 12 weeks ± SD	9.34 ± 1.44 -0.69 ± 0.50	9.08 ± 1.80 -4.43 ± 0.88	> 0.05 < 0.05
IL-1β (pg/mL) Baseline Δ Mean 12 weeks ± SD	14.3 ± 4.1 -0.50 ± 0.4	14.1± 3.9 -7.14± 0.6	> 0.05 < 0.05

JDAS-27*, Juvenile Arthritis Disease Activity Score-27;* ***CHAQ-DI,*** *Childhood Health Assessment Questionnaire- Disability Index.*

DISCUSSION

The course of JIA is highly variable, ranging from a mild, self-limiting form to a very aggressive form. The management of patients with JIA is difficult. A variety of drugs either alone or in combination are used with varying success to suppress symptoms or modify disease activity in addition to possibility of number of side effects that may disturb treatment.[24] It has been found that some foods or food related products can provoke or alleviate rheumatic symptoms.[25] It is also known that alteration of the dietary fatty acid composition modulate the production of eicosanoids.[26]

This present study sought to elucidate the effect of omega 3 supplementation on disease activity and functional status in patients with JIA. Researches dealing with effect of omega 3 in adult rheumatoid arthritis are numerous.[10,11,12] On the contrary, There is limited research studies performed on children and adolescents.

This study confirms that supplementation of 2 g/ day of omega 3 for 12 weeks had anti-inflammatory effect with decreased disease activity and improved functional status in JIA patients. Omega 3 supplementation for 12 weeks significantly improved the JDAS-27 with increment of - 10.8± 1.2, ESR with increment of -25.8 ± 16.3 , CRP with increment of -6.24 ± 1.09 , CHAQ-DI score with increment of -0.7 ±0.3 , TNF- α and IL-1 β levels with increment of -4.43 ± 0.88 and -7.14± 0.6 .

Dietary omega 3 poly unsaturated fatty acids (n-3 PUFA) are modulators of the lipid content of membrane phospholipids, where they are able to affect cell function, and precursors for eicosanoid production which mediate inflammation, cytokine synthesis and cell communication. Metabolism of n-3 PUFA produces docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) which form the respective eicosanoids of the three and five series.[27]

Omega 3 fatty acids capsule used in this study contained 300 mg EPA and 200 DHA.

Both fatty acids have close homology with arachidonic acid (20:4 n-6; AA), with EPA and AA differing only in the presence or absence of the omega-3 (n-3) double bond respectively. Both EPA and DHA are competitor substrates that inhibit oxidation of AA by the cyclooxygenase (COX) and lipoxygenase enzymes that are essential in the production of eicosanoids.[28]

It was found that DHA and EPA are able to decrease the production of AA-derived eicosanoids and decrease the production of pro-inflammatory cytokines TNF-a, IL-1b and IL-6, decrease lymphocyte proliferation and reactive oxygen species.[29,30]

Several investigators have studied the effects of dietary fish-oil supplements in adult patients with rheumatoid arthritis. The most often observed benefit with fish-oil supplementation is an improvement in the number of tender joints on physical examination[31], although some authors reported improvement in the Ritchie Articular Index and in morning stiffness.[32] Studies on JIA are quite rare especially those with placebo double blind trials. So, we suggest that this study can add to the confirmation of the value of omega 3 supplementation for JIA patients.

CONCLUSION

Results of this study confirm the anti-inflammatory effects of omega 3 supplementation in a dose of 2 gm/day for 12 weeks and its effective role in decreasing disease activity and improving functional status in JIA patients

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