Omega-3 Fatty Acids Therapy in Children with Nonalcoholic Fatty Liver Disease: A Randomized Controlled Trial

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Objective To evaluate the efficacy and safety of omega-3 fatty acid supplementation in children with nonalcoholic fatty liver disease (NAFLD).

Study design Overweight/obese children with NAFLD (n = 76; median age, 13 years; IQR, 11.1-15.2 years) were eligible to participate in the study. The diagnosis of NAFLD was based on elevated alanine aminotransferase (ALT) to ≥30% of the upper limit of normal (ULN) and liver hyperechogenicity on ultrasound. Patients were randomized to receive omega-3 fatty acids (docosahexaenoic acid and eicosapentaenoic acid, 450-1300 mg/day) or placebo (omega-6 sunflower oil). The primary outcome was the number of patients who demonstrated decreased ALT activity by ≥0.3 times the ULN. Secondary outcomes included alterations in liver function tests, liver hyperechogenicity, insulin resistance, and other metabolic markers after 6 months of intervention.

Results Out of 76 enrolled patients, 64 completed the trial and were analyzed. After 6 months, we found no significant differences between the omega-3 and placebo groups in the number of patients with decreased ALT by ≥0.3 times the ULN (24 vs 23) or in median (IQR) ALT activity (48.5 [31-62] U/L vs 39 [27-55] U/L), liver hyperechogenicity, insulin resistance, or serum lipid levels. However, patients in the omega-3 group had lower levels of aspartate aminotransferase (28 [25-36] U/L vs 39 [27-55] U/L; *P* = .04) and gamma-glutamyl transpeptidase (26 [17.5-36.5] U/L vs 35 [22-52] U/L; *P* = .04), and significantly higher levels of adiponectin.

Conclusion Omega-3 fatty acid supplementation did not increase the number of patients with decreased ALT levels and it did not affect liver steatosis on ultrasound, but it improved aspartate aminotransferase and gamma-glutamyl transpeptidase levels in children with NAFLD compared with placebo. *(J Pediatr 2015;166:1358-63).*

Trial registration Registered with ClinicalTrials.gov: NCT01547910.

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The diagnosis of nonalcoholic fatty liver disease (NAFLD), a common liver abnormality in children aged 2-19 years,[1] is based on histological criteria of liver biopsy specimens.[2] Liver disease may progress to cirrhosis. The principle of treatment is amelioration of risk factors, such as obesity/overweight and insulin resistance. Previous systematic reviews have addressed the effectiveness of pharmacotherapy (including dietary supplements) in treating NAFLD.[3] An analysis of 15 randomized controlled trials identified metformin, YHK, and carnitine in high doses (3 g/day) as promising agents, demonstrating a significant effect on normalizing alanine aminotransferase (ALT) levels. In a meta-analysis of randomized controlled trials for the treatment of NAFLD, Musso et al[4] found that thiazolidinediones, such as pioglitazone or rosiglitazone, could improve insulin sensitivity, steatosis, and inflammation of the liver. However, the use of thiazolidinediones may be associated with excessive weight gain and hepatotoxicity, and the duration of therapeutic effect is poor.

Dietary supplements, such as polyunsaturated fatty acids (PUFAs), appear promising. In a randomized controlled trial, Nobili et al[5] investigated the effect of supplementation with docosahexanoic acid (DHA) on liver fat content and liver tests in children with NAFLD. Two groups received either DHA (250 or 500 mg) or placebo daily for 6 months. DHA in both doses was found to reduce liver fat (as assessed by abdominal ultrasound) and insulin resistance; however, no effect was seen on ALT or body weight.

ALT	Alanine aminotransferase	GGTP	Gamma-glutamyl transpeptidase
AST	Aspartate aminotransferase	LC	Long chain
BMI	Body mass index	NAFLD	Nonalcoholic fatty liver disease
DHA	Docosahexanoic acid	PUFA	Polyunsaturated fatty acid
eCRF	Electronic case report form	ULN	Upper limit of normal
EPA	Eicosapentaenoic acid	WC	Waist circumference

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In the present randomized controlled trial, we evaluated the efficacy and safety of omega-3 fatty acid supplementation in children with NAFLD.

Methods

This multicenter, randomized, double-blind, placebo-controlled clinical trial was conducted in 4 Polish pediatric departments. The main aim of this study was to assess the efficacy of omega-3 long chain (LC)-PUFAs in children with NAFLD. Full details of the trial protocol, study design, and rationale have been described previously.[6]

The inclusion criteria were: (1) age >5 and <19 years; (2) overweight or obesity (according to International Obesity Task Force body mass index (BMI) charts[7]); (3) ALT activity ≥1.3 times the upper limit of normal (ULN); (4) presence of hyperechogenic liver on ultrasound or liver histology consistent with NAFLD/nonalcoholic steatohepatitis; and (5) written consent obtained from the patient and/or a legal representative. The exclusion criteria were: (1) age <5 or >19 years; (2) history of significant alcohol consumption; (3) any known pathological conditions affecting the liver eg, hepatitis B or C virus infection, chronic or acute liver failure, cholestasis, metabolic diseases, such as α1-antitripsin deficiency, Wilson disease, diabetes mellitus, and hypothyroidism; (4) treatment with vitamin E, statins, antihypertensives, ursodeoxycholic acid, probiotics, or metformin within 3 months before randomization; (5) history of parenteral nutrition; and (6) unlikely to cooperate with the study regime. The patients recruited for the study received dietary counsling in their previous therapy, which proved ineffective.

Treatment Groups

The eligible patients were randomized into blocks of 4 individuals, stratified by center, to either fish oil containing omega-3 LC-PUFA (DHA and eicosapentaenoic acid [EPA] in a 3:2 proportion [450-1300 mg/day]) or placebo (sunflower oil, containing omega-6 LC-PUFA) for 24 weeks.

The study drug and placebo were administered orally twice a day in the same dose and formulation of brown, oval-shaped capsules. The dose of omega-3 was dependent on patient weight (Table I).

The omega-3 fatty acids, obtained from marine algae, and placebo were supplied and blinded by Hasco-Lek (Wroclaw, Poland) from the composition of Incromega DHA 500 TG SR (Croda Poland, Krakow, Poland) and Incromega EPA 500 TG SR (Croda Poland).

Table I. Dosage of omega-3 LC-PUFAs

Body weight, kg	Approximate total omega-3, mg/d	DHA, mg/d	EPA, mg/d
<40	450	267	177.5
40-60	900	534	355
>60	1300	800	532.5

In addition, all patients were regularly instructed by an experienced dietician in each center to comply with an individually prescribed diet, which, in combination with increased physical activity, was aimed at producing a slow reduction in body weight (approximately 0.5 kg/week). Extensive dietary data were collected using a validated food frequency questionnaire. The level of physical activity and sedentary lifestyle were assessed using the modified International Physical Activity Questionnaire.

The study protocol was approved by the Children's Memorial Health Institute's Bioethical Committee. Written informed consent was obtained from all participants. The Consolidated Standards of Reporting Trials flowchart is presented in the Figure (available at www.jpeds.com).

Randomization

The list of random treatment assignments was generated using StatsDirect version 2.7.9 (StatsDirect, Altrincham, United Kingdom). Randomization was fixed and balanced in blocks of 4 individuals, and stratified according to center, to 2 arms: omega-3 and placebo. The treatment allocation was done using a central randomization. Investigators sent their randomization requests by fax to the central randomization center responsible for the randomization process. In return, they received a random number that was subsequently allocated to the choice of one of the products (designated 100 or 101). Patient data were entered and organized in an electronic case report form (eCRF). Both the eCRF and the randomization process were monitored by the external clinical research organization.

Follow-Up Visits

Study visits were scheduled at 12 weeks and 24 weeks after randomization. At the baseline visit (week 0) and final visit (week 24), patients underwent physical examination, including anthropometric measurements (height, weight, and waist circumference [WC]); heart rate and blood pressure; laboratory tests, including hematology, ALT, aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGTP), bilirubin, international normalized ratio, fasting glucose and insulin; fasting lipid profile; adipokines and cytokines; abdominal ultrasound; dietary assessment (using the food frequency questionnaire); and physical activity assessment (using the International Physical Activity Questionnaire).

The visit at week 12 included a routine physical examination with vital signs, simple laboratory tests (ALT, AST, GGTP, bilirubin, international normalized ratio, fasting glucose and insulin) and anthropometry, as well as dietary and physical activity assessments.[6]

Liver biopsy evaluation was not mandatory in this study; however, it was proposed for clinical reasons to selected patients who presented with elevated ALT persisting for longer than 6 months during weight reduction therapy. Any potential adverse events were reported at each visit throughout the study. Data for all investigations were entered into the eCRF and stored there anonymously.