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Meta-analyses

Omega-3 fatty acids as a treatment for non-alcoholic fatty liver disease in children: A systematic review and meta-analysis of randomized controlled trials

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SUMMARY

Background: The most typical chronic liver disease in children and adolescents is non-alcoholic fatty liver disease (NAFLD). The dietary addition of ω-3 polyunsaturated fatty acids (PUFAs) provides a promising therapy for children with NAFLD due to its convenience and safety; however, several studies suggested contradictory results for PUFA supplementation in children. Hence, we performed a systematic review and meta-analysis to evaluate the effectiveness of PUFA supplementation in children with NAFLD.

Methods: Published randomized controlled trials (RCTs) that evaluated the effectiveness of the dietary addition of PUFA in children with NAFLD were considered. The primary result was the alteration in hepatic steatosis grade on ultrasound after treatment. The secondary outcomes included alanine aminotransferase (ALT), aspartate aminotransferase (AST), C-reactive protein (CRP) and components of metabolic syndrome. Predefined sensitivity analysis was also performed to explore possible explanations for heterogeneity in the evaluations.

Results: In total, 4 studies with 263 subjects were identified. PUFA supplementation was associated with significantly improved hepatic steatosis grade on ultrasound (risk difference: 25%, 95% *CI*: 12–38%), without heterogeneity ($P = 0.27$, $I^2 = 24\%$). Sensitivity analysis confirmed the robustness of our findings. PUFA supplementation could decrease AST levels after 6 months, but could only reduce ALT levels after 12 months. PUFA did not have a significant effect on most components of metabolic syndrome and the CRP level.

Conclusion: ω-3 PUFA supplementation can improve liver steatosis and liver functions, and it is a potential food supplementation to treat NAFLD in children.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most frequently diagnosed chronic liver disease in pediatric population. In a recent study from the Yangtze River Delta region, a prevalence of 5.0% was found in students 7–18 years of age, increasing remarkably with obesity [1]. Children with NAFLD are more likely to have psychosocial comorbidities, higher cardiovascular risk profile and metabolic complications [2]. Moreover, children with NAFLD may develop cirrhosis and end-stage liver disease with the resulting requirement for liver transplantation [3]. Because of the frequency of pediatric NAFLD in childhood and the extensive complications, early intervention is necessary.

Currently, the primary method in treating NAFLD in children is lifestyle modification targeting gradual weight loss by increasing physical exercise and improving diet habits [4]. Although lifestyle modification has been showed to be effective in treating NAFLD in children, compliance to the intervention is poor. Hence, great effort was put into the development of a pharmacological treatment. To date, 3 types of drugs have been tested in children with NAFLD, including insulin sensitizer, an antioxidant, and cytoprotective agents [5,6]. However, none of these treatments was established to be efficient and safe.

Recently, the role of fish oil in treating NAFLD has been increasingly recognized. In adults, a recent systematic review

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indicated that ω-3 polyunsaturated fatty acids (PUFAs) could decrease liver fat content [7]. However, no study in children was included in their study because there was no related trial published at that time. A recent study in children showed ω-3 PUFA supplementation did not affect serum alanine aminotransferase (ALT) levels and liver steatosis on ultrasound [8]. On the contrary, another trial suggested that docosahexanoic acid (DHA) supplementation could decrease liver fat contents [9]. In consideration of the diversity, we performed the current systematic review and meta-analysis to determine the effectiveness of fish oil supplementation in children with NAFLD.

2. Methods

The current systematic review and meta-analysis were disclosed following the recommendations proposed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) groups and Cochrane Collaboration [10,11]. We have not reported a review protocol for the current study.

2.1. Search strategy

The databases PubMed, Cochrane Central Register of Controlled Trials, CINAHL, Embase, Web of Science, Scopus, and Chinese Biomedical Literature Database were systematically searched. The search strategy included the title, abstract words, and subject headings pertaining to fish oil ("fish oil," "EPA," "eicosapentaenoic acid," "eicosapentanoic acid," "DHA," "docosahexaenoic acid," "docosahexanoic acid," "omega-3," and "n-3"), NAFLD ("NAFLD," "fatty liver," "hepatic steatosis," "steatohepatitis," "NASH," "aminotransferase," "ALT," "AST," and "transaminases") and children ("child*," "adolescen*," "pediatr*," and "paediatr*"). The last search was conducted on February 11, 2016. The search strategy was limited to humans but there were no study design or language restrictions. Additionally, the reference list of pertinent articles was also examined to determine possible relevant studies.

2.2. Study selection

Two independent reviewers (CLH and XQH) screened studies using the criteria: (1) articles were randomized controlled trials (RCTs); (2) subjects were younger than 18 years; (3) fish oil was administered orally for at least 4 weeks; and (4) liver steatosis was the outcome of interest. Reviews, observational studies, cross-sectional studies, studies in adults, and studies without outcomes of interest were not included. Discrepancies within the selection method were independently resolved by a third reviewer (WYF).

2.3. Data extraction and quality assessment

Two reviewers (CLH and XQH) independently extracted information and evaluated the risk of bias, and the discrepancies were solved by a third reviewer (WYF). The following information was extracted: the year of publication, the first author's name, study locations, study design characteristics, sample size, participants' gender, age at examination, duration of intervention, doses and types of fish oil, inclusion criteria, and the primary and secondary results. The primary result was the change in hepatic steatosis grade on ultrasound after treatment. The secondary outcomes included ALT, aspartate aminotransferase (AST), insulin resistance (IR), C-reactive protein (CRP), body mass index (BMI) z-score, triglycerides (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-c), systolic blood pressure (SBP) and diastolic blood pressure (DBP). We personally contacted the authors whose studies did not provide relevant data.

We implemented the Cochrane Collaboration's tool for determining risk of bias to qualitatively examine the selected studies. The tool was consistent in 7 particular domains, specifically sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and 'other bias' (referring to the sample size calculation in the current study). Quality assessment was performed at the study level. Studies were considered to have a low risk of bias if every one of the previously mentioned domains were evaluated as "low risk of bias." Studies were regarded as having a high risk of bias if 1 or more of the above domains were determined to be "uncertain risk of bias" or "high risk of bias."

2.4. Statistical analyses

The statistical analyses were done using RevMan software (version 5.3, Cochrane, Oxford, UK). Dichotomous data was analyzed using risk differences (RDs) with 95% confidence intervals (*CI*s). Heterogeneity among the studies was evaluated using *Q* and I^2 statistics. $P < 0.1$ was regarded as statistically significant for *Q*. Heterogeneity was considered low, moderate and high with I^2 values of 25%, 50%, and 75%, respectively. Combined analyses were computed with fixed-effect models if no substantial heterogeneity was determined, while random-effect models were used in instances of substantial heterogeneity across the included studies. Sensitivity analysis was performed by omitting each study in turn while pooling results from the remainder. *P* values were two-tailed and statistical significance was set at 0.05.

3. Results

3.1. Search results

The study selection process is summarized in the PRISMA flow diagram (see Fig. 1). In summary, an aggregate of 852 potentially relevant evaluations were pinpointed by literature search. After reading the title and abstract, 11 articles remained for the detailed full-text assessment. Of the 11 studies, 7 were excluded: 3 were from the same study samples, 1 was not an RCT, 1 was a study protocol, 1 was conducted in adults, and 1 did not have an outcome of interest. Finally, 4 studies met the inclusion criteria.

3.2. Study characteristics

The attributes of the studies are recounted in Table 1. Of the 4, 1 was published in 2011, and the other 3 were published in 2015. A total of 263 participants (132 for placebo and 131 for fish oil supplementation) were counted in our systematic review. The mean (median) age of the participants was from 10.8 to 13.8 years. Two of the included studies were accomplished in developed nations, and the other 2 were conducted in developing countries. The duration of intervention varied between 6 and 12 months. All of the trials used parallel study designs. The types of ω-3 fatty acids in 2 studies were DHA and PUFA (comprised of DHA and EPA) in the other 2 studies. The dose of ω-3 fatty acids ranged from 250 mg/d to 1300 mg/d. The study by Nobili et al. was carried out in 2 doses (250 mg/d and 500 mg/d), and we selected the 500 mg/d group to be the "treatment" group for the meta-analysis. Of the four studies, 1 was limited to obese children, 2 studies were limited to overweight or obese children, and 1 did not specify the BMI criteria. The percentage of participants who dropped out after