Clinical Biochemistry 47 (2014) 369–377

Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

The limited effect of omega-3 polyunsaturated fatty acids on cardiovascular risk in patients with impaired glucose metabolism: A meta-analysis

Tengfei Zheng [a,1], Jing Zhao [a,1], Yushu Wang [a], Wennan Liu [b], Zhihao Wang [c], Yuanyuan Shang [a], Wei Zhang [a], Yun Zhang [a], Ming Zhong [a,*]

[a] Key Laboratory of Cardiovascular Remodeling and Function Research, Chinese Ministry of Education and Chinese Ministry of Public Health, Department of Cardiology, Qilu Hospital of Shandong University, Jinan 250012, PR China
[b] Department of Cardiology, Tianjin Medical University General Hospital, Tianjin 300052, PR China
[c] Key Laboratory of Cardiovascular Proteomics of Shandong Province, Department of Geriatrics, Qilu Hospital of Shandong University, Jinan 250012, PR China

ARTICLE INFO

Article history:
Received 10 October 2013
Received in revised form 27 November 2013
Accepted 28 November 2013
Available online 14 December 2013

Keywords:
Cardiovascular risk markers
Docosahexaenoic acid
Eicosapentaenoic acid
Omega-3 polyunsaturated fatty acids
Impaired glucose metabolism

ABSTRACT

Objectives: The impacts of marine-derived n−3 polyunsaturated fatty acids (n−3 PUFAs) on cardiovascular risk are not well known. We conducted this meta-analysis to determine the effects of n−3 PUFAs on cardiovascular outcomes and cardiovascular risk markers in patients with impaired glucose metabolism (IGM).

Design and methods: We searched PUBMED, EMBASE, The Cochrane Library and reference lists of relevant papers for high quality randomized controlled trials comparing dietary intake of n−3 PUFAs with placebo in IGM patients. Data was extracted and quality assessed independently by two reviewers. Authors were contacted for missing information. Overall estimates were calculated using a random-effects model or a fixed-effects model, and the possibility of publication bias was examined using a funnel plot. Subgroup analyses were conducted to explore the association between the risk markers and study characteristics.

Results: Our meta-analysis included 19 studies, 24,788 patients. Compared with placebo, n−3 PUFAs had no statistically significant reduce effect on cardiovascular mortality, major cardiovascular events, all-cause mortality or composite endpoint of all-cause mortality or hospitalization for cardiovascular cause, however it can significantly reduce the level of triglycerides (weighted mean difference [WMD] −0.25 mmol/L; 95% CI −0.37 to −0.13: $p < 0.001$; 12 trials, 13,921 patients).

Conclusion: Marine-derived n−3 polyunsaturated fatty acids have no protective effect on cardiovascular mortality, major cardiovascular events, all-cause mortality and composite endpoint of all-cause mortality or hospitalization for cardiovascular cause in IGM patients, but can reduce triglyceride level.

Introduction

The marine-derived n−3 polyunsaturated fatty acids (n−3 PUFAs) eicosapentaenoic acid and docosahexaenoic acid are important dietary supplements. They are considered to have the effect of protecting against cardiovascular disease, improving neurodevelopment and stabilizing membrane structure. There are three forms of n−3 PUFA supplements: triglyceride, ethyl ester and free fatty acids. The free fatty acid form of n−3 PUFAs is the most easily absorbed, as it does not require pancreatic lipase hydrolysis and has the best bioavailability, particularly when consumed in conjunction with a low-fat diet. Much research has been focus on the cardiovascular effects of n−3 PUFA consumption. Early GISSI-Prevenzione trial [1] and JELIS trial [2] reported n−3 PUFAs reduced all-cause mortality and major coronary events in post-myocardial infarction patients and the general population significantly. In 2010, Alpha Omega trial [3] and other two large long-term randomized controlled double-blind trials [4,5] indicated that n−3 PUFAs had no preventive effect on major adverse cardiovascular events, and two recent systematic reviews [6,7] pointed out that n−3 PUFA supplementation was not associated with a lower risk of cardiovascular endpoints. These subsequent evidences made people begin to doubt the role of n−3 PUFAs in the primary and the secondary prevention of cardiovascular disease. The trials that studied the impact of n−3 PUFAs on cardiovascular disease also included impaired glucose metabolism (IGM) patients. Subgroup analyses of GISSI-Prevenzione trial [8], JELIS trial [9] and GISSI-HF trial [10] showed that all-cause mortality and major coronary events reduced significantly after n−3 PUFA supplementation in diabetic and IGM patients, but not in non-diabetic or non-IGM patients. Can n−3 PUFAs play better cardiovascular protective effect in IGM patients? In addition to the above-mentioned results of the subgroup analyses, two prospective

* Corresponding author at: #107 West Wenhua Road, Department of Cardiology, Qilu Hospital, Shandong University, Jinan 250012, PR China. Fax: +86 53186169356.
E-mail address: sduzhongming@gmail.com (M. Zhong).
[1] Co-first author and they contributed equally to this work.

0009-9120/$ – see front matter
http://dx.doi.org/10.1016/j.clinbiochem.2013.11.025

cohort analyses [11,12] found that n−3 PUFA rich diet can significantly reduce the risk of cardiovascular morbidity and all-cause mortality in diabetic women. However, recently published ORIGIN trial performed in 12,536 patients found that n−3 PUFAs did not prevent death or any cardiovascular outcomes in patients with dysglycemia [13]. This meta-analysis will focus on the role of n−3 PUFAs on cardiovascular risk in IGM patients, including primary endpoints and cardiovascular risk markers.

Methods

Data sources and searches

We did a computerized search of PUBMED, EMBASE, and The Cochrane Library through June, 2013 by using the following search terms: "omega 3 fatty acid or fish oil or eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA)" and "non-insulin dependent diabetes mellitus (NIDDM/type 2 diabetes mellitus) or impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) or dysglycemia" and "randomized controlled trial". We searched eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), as most n−3 PUFA supplements contain only EPA and DHA. We also reviewed reference lists of relevant reviews.

Study selection

Included studies met the following criteria. First, we included clinical randomized controlled trials of adult IGM patients, which include impaired fasting glucose patients, impaired glucose tolerance patients and type 2 diabetic patients. Second, the trials must be placebo or vegetable oil controlled (no restrictions were placed on the range of compounds). Third, the trials must be single or double blind design. Fourth, the quality score must be higher than 3 points. No restrictions were placed on the type of dietary PUFA supplementations, duration of the trial and language of publication. If the effect of dietary PUFA supplementations can't be separated from the effect of simultaneously applied interventions, then this trial was excluded. Although no restrictions were placed on language when searching, only full English text was included in the meta-analysis.

Data extraction and quality assessment

The study characteristic information that we extracted was as shown in Table 1. We extracted following primary outcomes and cardiovascular risk markers: cardiovascular mortality, major cardiovascular events, all-cause mortality, and composite endpoint of all-cause mortality or hospitalization for cardiovascular cause, triglyceride (TG), total cholesterol (TC), LDL-cholesterol, HDL-cholesterol, HbA1c, fasting plasma glucose (FPG), blood pressure (BP), heart rate (HR), and flow-mediated dilation (FMD). Continuous variables were expressed in the form of the mean and standard deviation (SD). If SD was not provided, we derived it where possible from the 95% confidence interval (CI) or standard error (SE). Some outcome data whose means and SDs were unavailable were not pooled in meta-analysis. We tended to pool the means and SDs of changes from baseline. However, if these data were not available, we pooled the means and SDs of final values. For crossover design studies, data were used only from the first intervention period; if it was unavailable, and the study had a washout period which was equal to intervention period or longer, the final values of the data were used. For factorial design studies, data of the results of n−3 PUFAs versus matched control were used, including all participants regardless of whether they had other interventions. Where serial measurement of an outcome was given during the intervention phase, data were obtained from the final measurement since that measurement was considered the conclusion of the study. Where the study used two sets of doses, included comparisons of EPA and DHA or more than one control group, a sensitivity analysis was carried out to determine which comparison gave the smallest effect size, which was then reported as the main result [14].

A score developed from the criteria of Jadad was utilized to assess study quality, which had a possible range from zero to five [15]. It was considered as high quality if a study scored range from three points to five points.

The literature search, data extraction and quality assessment were undertaken independently and blindly by two authors using a standardized approach. Any disagreements were resolved by a third reviewer.

Data synthesis and analysis

The analysis was carried out by using STATA statistical software (version 11.0, 2010, Stata Corporation). Heterogeneity was assessed using the chi-squared test with the significance set at a p value of <0.1 and the extent of the observed heterogeneity was assessed by the I^2 (ranging from 0% to 100%). All analyses were initially done using a fixed-effects model, and if heterogeneity across studies was observed, the analyses were done with a random-effects model. Pooled RRs or WMDs were reported with 95% CIs, and a two-tailed $p < 0.05$ was considered statistically significant for all analyses.

The presence of publication bias was investigated and quantified using Egger test and Begg funnel plots of WMD versus its standard error for cardiovascular risk markers [16,17].

Results

Literature search

As shown in Fig. 1, a total of 583 potentially eligible studies were identified through computerized searching, of which 535 were excluded after reviewing the study abstracts, leaving 48 studies for a more detailed evaluation. Two additional eligible studies were identified by reviewing reference lists of relevant reviews. Of these 50 studies, 31 were excluded for the following reasons: Duplicate reports or subanalyses (n = 4), English article is unavailable (n = 2), no data on cardiovascular risk factor (n = 5), only abstract available (n = 2), quality score less than three (n = 15), and cross designed studies without washout and the first phase data (n = 2). In total, 19 studies were therefore included in this meta-analysis [10,13,18–34].

Study characteristics and quality

The baseline characteristics of the 19 included studies are shown in Table 1. These studies were published from 1990 to 2013. Thirteen used a parallel design [10,18,19,21,23–26,28,30,32–34], three used a crossover design [20,22,29] and the remaining three used a factorial design [13,27,31]. All included studies were published in English. A total of 24,788 patients were studied, with study sample sizes ranging from ten to 12,536, dose of EPA + DHA ranging from 0.36 g/d to 10 g/d, and intervention duration ranging from six weeks to six years. We used means and SDs of the changes from baseline of four studies [13,23,27,30] and means and SDs of final values of the rest.

Primary outcomes

Four trials followed up exceeded one year and reported primary outcomes. Subgroup analysis of GISSI-HF study contained 1974 subjects with diabetes, the median follow-up was 3.9 years, the dose of n−3 PUFAs was 1 g/d [10]; subgroup analysis of Alpha Omega trial contained 1014 diabetic patients, the median follow-up was 40.7 months, the dose of EPA and DHA was 360 mg/d [31]; the ORIGIN trial included 12,536 participants with dysglycemia, the median follow-up was 6.2 years, the dose of n−3 fatty acids was 1 g/d [13]; subgroup analysis