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Review

Influence of omega-3 polyunsaturated fatty acid-supplementation on platelet aggregation in humans: A meta-analysis of randomized controlled trials

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ABSTRACT

Objective: Increased platelet activity predicts adverse cardiovascular events. The objective was to assess the effects of long-chain omega-3 polyunsaturated fatty acid (*n*-3 PUFA)-supplementation on platelet aggregation.

Methods and results: We conducted a meta-analysis of randomized controlled trials identified using PubMed, Embase and the Cochrane Library. Fifteen studies were included. In comparison to placebo using the random-effect model, *n*-3 PUFA-supplementation significantly reduced adenosine diphosphate-induced platelet aggregation (standard mean difference [SMD] = −1.23 with 95% confidence interval [CI] −2.24 to −0.23, $p = 0.02$) and platelet aggregation units, determined using the VerifyNow® rapid platelet-function assay system (SMD = −6.78 with 95% CI −12.58 to −0.98, $p = 0.02$). There was a trend toward decreased collagen-induced (SMD = −0.70 with 95% CI −0.72 to 0.33, $p = 0.18$) and arachidonic acid-induced platelet aggregation (SMD = −0.43 with 95% CI −2.26 to 1.40, $p = 0.64$) compared with controls; however, statistical significance was not reached.

Conclusions: Our meta-analysis demonstrates that *n*-3 PUFA-supplementation is associated with a significant reduction in platelet aggregation when the participants were at poor health status, but not in healthy persons. High-risk patients with cardiovascular disease and even diabetics may potentially benefit from *n*-3 PUFAs therapy. However, *n*-3 PUFAs may not be effective in primary prevention. Larger trials need to be carried out to confirm the present findings.

Contents

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1. Introduction

Platelets play a primary role in clot development and wound healing, but are also involved in the pathological process of thrombus formation and blood vessel occlusion. Platelet aggregation, a critical physiological response to vessel injury, has long been recognized as critical for hemostatic plug formation and thrombosis [1]. Platelet aggregation testing is routinely requested at many institutions. Agents that physiologically activate platelets *in vivo* include adenosine diphosphate (ADP), collagen, arachidonic acid (AA), thromboxane A2, epinephrine, thrombin and serotonin [1]. Inhibition of platelet aggregation has been a drug development target in the prevention and treatment of many atherothrombotic disorders for almost two decades [2].

Dietary supplementation with long-chain omega-3 polyunsaturated fatty acids (*n*-3 PUFAs, eicosapentaenoic acid [EPA], docosahexaenoic acid [DHA]) can have beneficial effects on a number of risk factors for cardiovascular disease [3]. Some studies have focused on the effects of *n*-3 PUFAs on platelet aggregation; however, studies in the published literature have yielded equivocal results. We therefore performed this meta-analysis using published data from randomized controlled trials (RCTs) to analytically explore the effects of *n*-3 PUFA-supplementation on platelet aggregation.

2. Methods

2.1. Strategy to search randomized trials

The Database of Abstracts of Reviews of Effectiveness and the Cochrane Database of Systematic Reviews were searched for related reviews. We searched the databases PubMed (http://www.ncbi.nlm.nih.gov/pubmed, 1966 – July 2011), the Cochrane Library (http://www.cochrane.org) and EMBASE (http://www.embase.com, 1982 – July 2011) for randomized clinical trials that presented the effects of *n*-3 PUFAs on platelet aggregation. In addition we examined the reference lists and related links of retrieved articles in PubMed to detect studies potentially eligible for inclusion. No language restrictions were used.

The following terms were used in the search: “omega-3 fatty acid”, “*n*-3 fatty acid”, “polyunsaturated fatty acid”, “fish oil”, “fatty acid”, “eicosapentaenoic acid”, “docosahexaenoic acid” and “α-linolenic acid”. Each of the terms was paired with the following: “platelet function” and “platelet aggregation”. The search was limited to studies in human adults.

2.2. Study selection

2.2.1. Inclusion criteria

(1) Study design had to meet the following criteria: randomized, placebo-controlled parallel or crossover trial; duration of treatment of at least 1 week; (2) population enrolled were adults aged 18 years or above; (3) the intervention group received *n*-3 PUFAs; the comparison group received placebo; and (4) the data included measurement of the mean initial and final platelet aggregation.

2.2.2. Exclusion criteria

Studies were excluded if we were unable to obtain adequate details of study methodology, results or investigators.

2.3. Data collection and analysis

2.3.1. Selection of studies

Two investigators (Gao LG and Cao J) independently assessed and abstracted relevant trials that met the standardized, predefined criteria. The initial screen for potential relevance excluded articles whose titles and/or abstracts were clearly irrelevant. The following data were extracted: study characteristics (author, publication year, study design, sample size, and type of intervention), treatment regimen (dose of *n*-3 PUFAs and intervention duration), population characteristics (age, sex and health status), and mean changes in platelet aggregation. The second or third intervention arms of 5 studies [4–8] were also included in the meta-analysis and one study, conducted by Mackay et al. [9], was divided into two interventions compared with controls. A third reviewer resolved discrepancies. Changes in platelet aggregation after *n*-3 PUFA-supplementation compared with placebo were calculated using previously described methods [10].

2.3.2. Quality assessment

Study quality was independently assessed (by Gao LG and Mao QX), by focusing on randomization, blinding, reporting of withdrawals, generation of random numbers, and concealment of allocation [11]. A combined quality score was obtained by adding the scores for each criterion. Thus, quality score could range from 0 to 5 points. High-quality RCTs scored $\geq$3 points, whereas low-quality RCTs scored $<$3 points.

2.4. Statistical analysis

Our meta-analysis and statistical analyses were performed with Stata software (version 10.0; Stata Corporation, College Station, TX) and REVMAN software (version 5.0; Cochrane Collaboration, Oxford, United Kingdom). The heterogeneity of the included studies was examined using the Cochran chi-squared test. The Mantel–Haenszel fixed-effect model or the random-effects (DerSimonian and Laird) model was chosen for meta-analysis of the comparison of platelet aggregation change due to *n*-3 PUFA-supplementation as compared with placebo. Publication bias was assessed with funnel plots and the Egger regression test.

To identify the possible source of heterogeneity within these studies, previously defined subgroup analyses were performed (*n*-3 PUFA dose, study duration, health status and antiplatelet treatment).