Effects of Low-Dose Acetylsalicylic Acid (Aspirin) + Fish Oil in Patients with Diabetes Mellitus

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Abstract

Aspirin, also known as acetylsalicylic acid (ASA), is a medication used to reduce pain, fever or inflammation. Many diabetics are insensitive to aspirin's platelet anti-aggregation effects. The possible modulating effects of coadministration of aspirin and fish oil in subjects with diabetes are poorly characterized. Aspirin alone and in combination with fish oil reduced platelet aggregation in most participants. Five of 7 participants classified as aspirin insensitive 1 week after daily aspirin ingestion were sensitive after the combination. Although some platelet aggregation measures correlated positively after aspirin and fish oil ingestion alone and (in combination) in all individuals, correlation was only observed in those who were aspirin insensitive after ingestion of the combination. However, the benefits of combining EPA (eicosapentaenoic acid) + DHA (docosahexaenoic acid) with aspirin on platelet function or other inflammatory parameters have not received much attention. We hypothesized that the combination of low-dose aspirin and ω3 fatty acids of fish oil would be more effective than aspirin alone in reducing platelet aggregation and related mechanisms that potentiate the atherosclerotic process in subjects with type II diabetes.

Keywords: Omega-3 fatty acids (Fish oil) • Acetylsalicylic acid (Aspirin) • Eicosapentaenoic acid • Docosahexaenoic acid • Platelet function • Cyclooxygenase-1 • Antiplatelet.

Introduction

Aspirin has long been a stalwart and inexpensive therapy for the prevention of cardiovascular disease (CVD) as well as in the acute treatment of acute myocardial ischemia. It is well established that low-dose aspirin (81-162 mg/day) has the potential to reduce the rate of recurrent vascular events with a 44% reduction in risk of myocardial infarction, and is associated with a much lower risk of gastrointestinal bleeding than higher doses [1,2]. In the primary prevention setting, however, evidence supporting a benefit is much less clear for all individuals and those with diabetes mellitus. Its benefits in preventing CVD have been most widely ascribed to its antiplatelet effects as aspirin reduces the production of the very potent platelet aggregation against thromboxane A2 through the acetylation of cyclooxygenase-1 (COX-1). However, excess thromboxane release has been shown to occur in type 2 diabetic patients with CVD [3].

Current evidence suggests that patients with aspirin insensitivity do not benefit from other antiplatelet drugs. In addition, the combination of aspirin with other antiplatelet drugs, such as clopidogrel, is associated with a significantly higher risk of major bleeding than with aspirin alone. In contrast, emerging evidence from clinical trials and observational studies suggests that combining the omega-3 (ω 3) fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) together with aspirin may be more beneficial than using aspirin alone [4,5]. EPA and DHA have known anti-inflammatory, anti-platelet aggregation, and CVD preventive effects. EPA and DHA may be especially beneficial for individuals with insulin resistance due to the underlying abnormal fatty acid and lipoprotein milieu, characterized by elevated circulating free fatty acids, low blood and tissue levels of ω3 fatty acids, and increased concentrations of highly atherogenic oxidized low density lipoprotein (LDL) [6].

However, the benefits of combining EPA+DHA with aspirin on platelet function or other inflammatory parameters have not received much attention. We hypothesized that the combination of low-dose aspirin and ω3 fatty acids of fish oil would be more effective than aspirin alone in reducing platelet aggregation and related mechanisms that potentiate the atherosclerotic process in subjects with type II diabetes.

Methods and Participants

We enrolled 30 adults aged 40 to 80 years with type 2 diabetes mellitus based on the criteria from the Executive Committee of the American Diabetes Association Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. These criteria include having symptoms of diabetes plus casual plasma glucose concentration ≥200 mg/dl (11.1 mmol/l), a plasma glucose ≥126 mg/dl (7.0 mmol/l) after an 8 hr fast, or a 2-hour plasma glucose ≥200 mg/dl during an oral glucose tolerance test. Glucose measurements were performed as described by the World Health Organization [7-10]. Participants could not take vitamins, nutritional supplements, or herbal preparations for the study duration. Exclusion Criteria were: a diagnosis of CVD including coronary heart disease, congestive heart failure, peripheral vascular disease, stroke, or atrial fibrillation; history of malignancy, except subjects who have been disease-free for greater than 10 years, or whose only malignancy has been basal or squamous cell skin carcinoma; history of peptic ulcer or gastrointestinal bleeding in the past 5 years, diagnosed bleeding disorder, use of antiplatelet or antithrombotic therapy, defined as clopidogrel, ticlopidine, cilostazol, dipyridamole, trapidil, warfarin, and argatroban, oral contraceptive use, and daily use of NSAIDs. Other exclusion criteria were a calculated creatinine clearance <60 mg/dL, signs of obstructive hepatic disease, or any other obvious metabolic disease that would influence lipid metabolism, based upon a screening complete blood count and comprehensive metabolic profile, pregnancy, surgery within 30 days of screening, history of drug or alcohol abuse, or current weekly alcohol consumption >14 units/week (1 unit = 1 beer, 1 glass of wine, 1 mixed cocktail containing 1 ounce of alcohol), allergy to aspirin or fish/fish oil, and tobacco use. The use of any diabetes medications was permitted, including insulin.

Protocols

This was an 8-week sequential-therapy clinical trial. All study visits were conducted at the University of Rochester's Clinical Research Center (CRC). Our study was designed to examine the acute (4 hour) and chronic (7 day) effects of aspirin in the absence or presence of fish oil supplementation. Over-the-counter standard (not enteric) 81 mg aspirin tablets were used [11].

The fish oil capsules were over-the-counter with each containing 1000 mg of fish oil (OmegaRx brand; Zone Labs, Marblehead, MA) and a dose consisted of 4 capsules (4000mg). Subjects were required to eat a standardized low-fat meal designed by the CRC dieticians the night before each study visit and to not eat or drink except water for 8 hours prior to each visit. During each study visit where subjects had phlebotomy performed 4 hours after the ingestion of a study agent, a standardized low-fat breakfast designed by the dieticians

was provided <30 min post the initial phlebotomy. Less than 30 minutes after the participant finished their breakfast the study agent was ingested. Subjects were permitted to ambulate but not to eat within the CRC [12]. They were asked not to consume any flax seed or fish oil other than the fish oil study agent and to limit fish consumption to no more than twice each week during the entire study. Following a pre-trial 10-day aspirin-free period, a baseline blood sample was obtained (blood draw 1, or BD1) and each participant then ingested a single dose (81 mg) of aspirin. Four hours later, after remaining within the CRC and fasting, a second phlebotomy was performed (BD2) and each participant then took aspirin 81 mg/day for 7 days. After the 7-day treatment, participants returned for a third phlebotomy (BD3) and they then began a 35-day regimen of fish oil (4g/day containing 1600 mg EPA and 800 mg DHA) treatment and discontinued aspirin unless it was prescribed by their doctor [13]. Some participants (n=8) were taking aspirin as prescribed by their doctor but they were required to have an aspirin-free period for 10 days prior to their next study visit. Participants then returned for a fourth blood sample (BD4) after 28 days of fish oil before which they were required to be aspirin-free for at least 10 days. They then ingested a single dose (81 mg) of aspirin, remained in the CRC and fasted, and a fifth phlebotomy (BD5) was obtained 4 hours later. They remained on the fish oil supplement together with 81 mg/day of aspirin for the final 7 days of the study. The sixth and final blood sample (BD6) was obtained on that final day. Thus BD1-3 were obtained in the absence of fish oil supplementation, whereas BD4-6 were obtained following at least 28 days of fish oil ingestion. BD2 and BD5 reflect the acute effects (4 hrs) of aspirin, whereas BD3 and BD6 reflect the chronic effects (7 days) of aspirin ingestion. Tests performed at all study visits included physical examination, platelet function measurements, serum concentrations of EPA, DHA, leptin and adiponectin, and plasma Thromboxane B2 (TXB2) concentrations [14]. We also measured NF - kappaB activation in peripheral blood mononuclear cells (Figures 1-4).

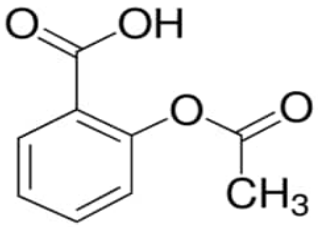

Figure 1: acetylsalicylic acid (Aspirin).

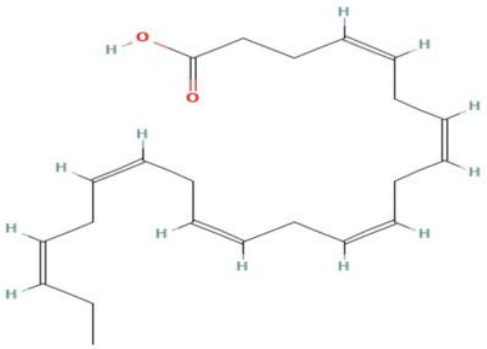

Figure 2: Docosahexaenoic acid (DHA).

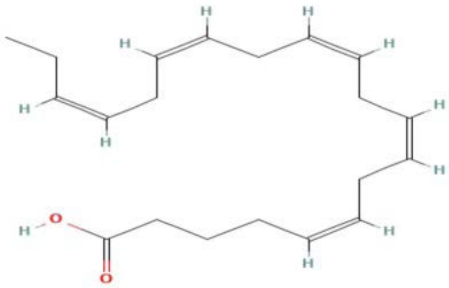

Figure 3: Eicosapentaenoic acid (EPA).

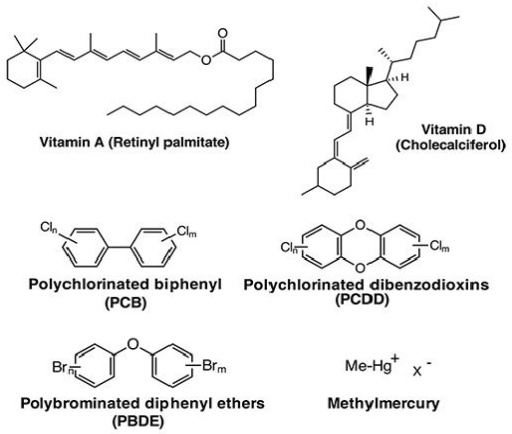

Figure 4: Constituents of Fish oil.

Results and Discussion

In this study, we systematically investigated the effects of low-dose aspirin alone or together with fish oil supplementation on platelet aggregation and relevant mediators in adult subjects with type 2 diabetes mellitus. For the study population as a whole, aspirin alone had generally similar effects as aspirin plus fish oil supplementation on platelet aggregation measures after both 4 hours and 7 days of aspirin ingestion. However, the combination of aspirin plus fish oil appeared to be more effective than aspirin alone in attenuating stimulus-induced platelet aggregation in the subset of subjects who were least sensitive to aspirin alone. In this group of aspirin insensitive individuals more correlation of platelet aggregation reduction effects were observed after the ingestion of both aspirin and fish oil. This suggests that the combined effects on platelet function may be through different mechanisms and more synchronous than with aspirin alone. In addition, we observed novel effects of aspirin on serum leptin levels and circulating leukocytes that we discuss further below.We found that the effect of aspirin on platelet function in adults with type 2 diabetes mellitus was heterogeneous, and influenced by duration of ingestion and the stimulus used to induce platelet aggregation in vitro. Using arachidonic acid and collagen as agonists, inducible platelet aggregation declined progressively between 4 hours and 7 days of ingestion. In contrast, ADP induced aggregation was more variable, and the effects of aspirin tended to decrease between 4 hours and 7 days of ingestion. Platelet aggregation by ADP has been shown to be greater in those with diabetes mellitus than non-diabetic individuals and our results regarding the acute aspirin effect on this aggregation mechanism suggest that is may be time-dependent. Although in general the effects of aspirin alone (BD1-3) were similar to aspirin plus fish oil (BD4-6), close inspection of the research revealed that combination therapy influenced stimulus-induced platelet aggregation under some conditions. For example, the combination of low-dose aspirin and fish oil (BD5-BD4) trended toward attenuated collagen-induced aggregation more than aspirin alone (BD2-BD1) when measured 4 hours following ingestion. The variability in effects and a relatively small sample size limited our ability to be certain as to whether effects between these treatments differed significantly. However,we used a mixed model statistical approach, which allowed us to adjust for the effects of major potential confounders. In a recent study, we reported that combination therapy of aspirin plus fish oil reduced platelet aggregation and thrombogenesis (measured using the PFA-100 closure time metric) whereas each alone did not in a cohort of healthy adults.We suspect that alterations in lipid metabolism influenced the results of combination therapy in the present study of type 2 diabetics, which will need to be followed up in future studies. One consideration is the generation of an oxylipin metabolite of EPA (resolvin E1) generated via the interaction with aspirin, which has been shown to reduce platelet function by down-regulating both thromboxane A2- and ADP-induced aggregation , effects that parallel what we observed. In addition, the doses of EPA, DHA, and aspirin we used are similar to those used in humans in whom resolvin E1 generation has been enhanced. Another consideration is the evidence that 81 mg of aspirin per day, but not higher doses,leads to the generation of another oxylipin (15-epi-lipoxin A4) and its increase in human blood correlates negatively with thromboxane B2 concentrations [15].

The baseline characteristics of the study participants explained. All 30 subjects completed the study. A total of 37 were recruited and 7 did not complete the study due primarily to conflicts between their schedules and study visit

requirements. All participants tolerated the aspirin and fish oil study agents. The mean concentrations of DHA and EPA in the study capsules were 406 ± 42 mg/ml and 330 ± 46 mg/ml, respectively. Baseline plasma concentrations averaged 106 ± 48 µg/ml for DHA and 13 ± 7 µg/ml for EPA, which increased to 190 ± 65 µg/ml ($p<0.0001$) for DHA and 61 ± 26 µg/ml for EPA ($p<0.0001$) 28 days after fish oil ingestion (BD4-BD1). Concentrations also increased ($p<0.0001$) for BD6-BD1 and BD4-BD3, respectively (data not shown).

Figure 5 show the effects of ingesting aspirin alone (BD1-BD3) or aspirin + fish oil (BD4-BD6) on platelet aggregation induced by the three different agonists, namely arachidonic acid, ADP and collagen (Figure 5). Results in the research are expressed as the change in platelet aggregation (measured in ohms using aggregometry) 4 hours following a one-time ingestion of aspirin (BD2-BD1 vs. BD5-BD4), as well as after 7 days of daily aspirin intake (BD3-BD1 vs. BD6-BD4). In addition, by comparing platelet aggregation at BD3-BD2 vs. BD6-BD5, we also determined whether the effects of aspirin vs. aspirin + fish oil changed over time. Platelet aggregation induced by the agonist arachidonic acid, with a baseline level of 15.9 ohms (95% CI: 14.1-17.6), was reduced by aspirin alone and aspirin + fish oil at all-time points except after 4 hours when combined with fish oil. Platelet aggregation induced by a low dose of ADP (2.5µM) was modestly reduced, from 11.9 ohms (95% CI: 5.7-18.1) at baseline, by acute aspirin ingestion and aspirin + fish oil after 4 hours. Aggregation induced by higher concentrations of ADP (5 and 10 µM) was not affected by either aspirin or aspirin + fish oil at any time point (data not shown). Collagen-induced aggregation at low dose (1 µg) was reduced, from a baseline level of 16.2 ohms (95% CI: 14.0-18.4), by aspirin + fish oil after 4 hours ($p<0.05$) and aspirin as well as aspirin + fish oil after 7 days. Finally, aggregation with high dose collagen (2 µg) was reduced by aspirin after 7 days (data not shown) but this was not significantly different than aspirin + fish oil ($p>0.05$). Aspirin alone tended to be more effective than aspirin + fish oil ($p>0.05$) between 4 hours and 7 days but these effects were also not significantly different ($p>0.05$).

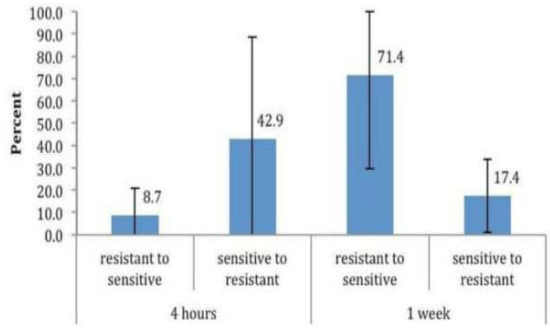

Figure 5: Combination therapy appears to decrease the numbers of subjects who are aspirin resistant Frequency distribution of subjects defined as aspirin sensitive or resistant (see text) expressed as percent change from aspirin resistant with aspirin alone to aspirin sensitive with aspirin + fish oil, and vice versa, both 4 hours and 1 week after ingestion. Bars represent percent change and 95% CI.

The research demonstrate the effects of aspirin and fish oil ingestion on plasma and serum mediators known to influence platelet aggregation. These data are organized similar to those in research to highlight differences between conditions. Thromboxane B2 concentrations, with an average baseline level of 5.8 pg/mL (95% CI: 4.8 - 6.8), were significantly reduced by aspirin and aspirin + fish oil at each time point after ingestion. Aspirin + fish oil tended to reduce TXB2 more than aspirin alone 4 hours after ingestion, whereas aspirin alone trended toward reduced concentrations more than aspirin + fish oil between 4 hours and 7 days after ingestion. Adiponectin concentrations, averaging 7.4 ng/mL (95% CI: 2.2 - 12.6) at baseline, were not significantly changed by either treatment at any time (data not shown). Leptin concentrations, with an average baseline level of 2.4 ng/mL (95% CI: 1.9 - 2.8), were significantly reduced following acute aspirin ingestion whether or not subjects were taking concomitant fish oil. Interestingly, leptin levels returned to baseline following longer term 7-day aspirin therapy.

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