Fish oil fatty acids improve postprandial vascular reactivity in healthy men

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ABSTRACT
Chronic fish oil intervention had been shown to have a positive impact on endothelial function. Although high-fat meals have often been associated with a loss of postprandial vascular reactivity, studies examining the effects of fish oil fatty acids on vascular function in the postprandial phase are limited. The aim of the present study was to examine the impact of the addition of fish oil fatty acids to a standard test meal on postprandial vascular reactivity. A total of 25 men received in a random order either a placebo oil meal (40 g of mixed fat; fatty acid profile representative of the U.K. diet) or a fish oil meal (31 g of mixed fat and 9 g of fish oil) on two occasions. Vascular reactivity was measured at baseline (0 h) and 4 h after the meal by laser Doppler i ontophoresis, and blood samples were taken for the measurement of plasma lipids, total nitrite, glucose and insulin. eNOS (endothelial NO synthase) and NADPH oxidase gene expression were determined in endothelial cells after incubation with TRLs (triacylglycerol-rich lipoproteins) isolated from the plasma samples taken at 4 h. Compared with baseline, sodium nitroprusside (an endothelium-independent vasodilator)-induced reactivity \( (P = 0.024) \) and plasma nitrite levels \( (P = 0.001) \) were increased after the fish oil meal. In endothelial cells, postprandial TRLs isolated after the fish oil meal increased eNOS and decreased NADPH oxidase gene expression compared with TRLs isolated following the placebo oil meal \( (P \leq 0.03) \). In conclusion, meal fatty acids appear to be an important determinant of vascular reactivity, with fish oils significantly improving postprandial endothelium-independent vasodilation.

INTRODUCTION
Endothelial dysfunction, characterized by a decrease in vascular reactivity, is highly prognostic of future cardiovascular events [1,2]. Evidence is now emerging in the literature that mechanisms involved in the control of vascular tone are influenced by dietary factors, with total dietary fat intake and fatty acid composition being a potentially important modulator. In particular, there is a limited, but convincing, body of evidence to indicate positive benefits of diets rich in the long-chain \( n-3 \) PUFAs (polyunsaturated fatty acids) EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) on endothelial function and vascular reactivity, when assessed after an overnight fast [3–6]. However, individuals spend a large proportion of the day in the postprandial state and the acute impact of dietary factors on postprandial vascular reactivity is poorly understood.

Over the last decade, a number of studies have examined the impact of meal fat quantity on vascular reactivity measured 2–8 h after a meal, but inconsistent findings have been reported. Although some studies

Key words: docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), human umbilical vein endothelial cell (HUVEC), triacylglycerol-rich lipoprotein (TRL), vascular reactivity.

Abbreviations: ACh, acetylcholine; apoB, apolipoprotein B; DHA, docosahexaenoic acid; eNOS, endothelial NO synthase; EPA, eicosapentaenoic acid; FBS, fetal bovine serum; HUVEC, human umbilical vein endothelial cell; LDH, lactate dehydrogenase; NEFA, non-esterified fatty acid; PPAR-\( \gamma \), peroxisome-proliferator-activated receptor-\( \gamma \); PUFA, polyunsaturated fatty acid; RT, reverse transcription; Sf, Svedberg flotation rate; SNP, sodium nitroprusside; TAG, triacylglycerol; TRL, TAG-rich lipoprotein.

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have observed no relationship, a greater number have indicated that increasing the total fat content of a test meal reduces both cardiac and peripheral vascular reactivity [7]. In general, high-fat meals (50–105 g of fat) have been shown to impair endothelium-dependent vasodilation compared with low-fat meals (less than 10 g of fat). A number of studies have suggested that the greater postprandial TAG (triacylglycerol) response after a high-fat meal may be responsible for this effect [8–10].

Only two studies have examined the impact of EPA and DHA on postprandial vascular reactivity [9,10]. In the study by Vogel et al. [9], the consumption of a meal containing canned red salmon was shown to have little impact on flow-mediated dilation. In subjects with Type 2 diabetes, an improvement in vascular reactivity was observed with the addition of both marine and plant sources of n−3 PUFAs to a MUFA (mono-unsaturated fatty acid)-rich meal, but this association was only observed when the results for the study group was analysed according to fasting TAG concentration [10]. Lower postprandial TAG concentrations measured after the EPA- and DHA-containing meal were inversely correlated with the increase in flow-mediated dilation only in the subjects with Type 2 diabetes with fasting TAG ≥ 1.69 mmol/l.

Several studies have suggested that the mechanism through which high-fat meals inhibit vascular reactivity is via the induction of a temporary state of fat-induced oxidative stress [11,12]. An excess generation of reactive oxygen species, such as the superoxide anion, in the subendothelial space has been shown to lead to a decrease in the bioavailability of NO, an important endothelium-derived vasodilator [13]. The major source of the superoxide anion in the vasculature is the NADPH oxidase family of enzymes [14]. Studies in animals have suggested that chronic fish oil supplementation may lead to beneficial effects on endothelial function via decreases in tissue oxidative stress and induction of antioxidant enzyme activity [15]; however, very little is known about the effects of fish oil fatty acids on cellular redox status during the postprandial state.

The aim of the present study was to determine whether the addition of fish oil fatty acids (equivalent to two portions of oily fish) to a standard test meal could improve postprandial vascular reactivity at the level of the microcirculation. Underlying molecular mechanisms were investigated by determining the concentration of potential mediators of reactivity in the circulation and by using ex vivo cell culture studies.

**MATERIALS AND METHODS**

A total of 25 healthy males [age, 46 (4) years; and BMI (body mass index), 25.5 (0.8) kg/m²; values are means (S.E.M.)] were studied on two occasions. Subjects were excluded if they had any metabolic disorders (e.g. diabetes or any other endocrine or liver diseases), were taking dietary supplements [e.g. high-dose fish oil supplements (>1 g of EPA and DHA per day) or high doses of antioxidant vitamins (>800 µg of vitamin A, 60 mg of vitamin C, 10 mg of vitamin E or 400 µg of β-carotene)], were heavy drinkers (>30 units of alcohol per week) or were taking medication that could affect lipoprotein metabolism or blood pressure. The subjects were asked to abstain from alcohol and organized exercise regimens for 24 h before each postprandial investigation. A low-fat evening meal (<10 g of fat) was consumed on the evening before each study day.

The design of the study was a single blind crossover in which subjects attended the clinical unit at the University of Reading on two occasions separated by at least 1 week. Two test meals of different fatty acid composition were given to the volunteers in the form of a warm chocolate drink, containing the test oils, and toast white bread with strawberry jam. This meal contained 42.8 g of fat, with 40 g provided by the test oil source and the remainder by additional meal items. The placebo oil meal consisted of a 4:1 mixture of palm olein and soybean oil (placebo oil; Aarhus United), providing a fatty acid profile representative of a typical U.K. diet. The fish oil meal contained 31 g of the placebo oil and 9 g of anchovy fish oil (Ocean Nutrition), providing 5.4 g of DHA plus EPA (ratio 3:2), which is equivalent to the levels found in two portions of oily fish. The nutrient and fatty acid composition of the test meals are shown in Tables 1 and 2 respectively.

Following a 12 h overnight fast, the subjects attended the investigation unit and forearm microvascular function was performed using laser Doppler imaging with iontophoresis. A baseline (0 h) blood sample was then taken before the test meal was given and consumed within 15 min. A second blood sample was taken and microvascular function was assessed 4 h after the meal. No food was allowed during the 4 h test period, but decaffeinated sugar-free drinks were provided ad libitum.

Ethical consent for the study was provided by the University of Reading Research and Ethics Committee.

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**Table 1 Composition of the test meals**
The composition was determined from manufacturers’ data and from food tables [27]. Nesquik is a chocolate-flavoured milkshake mix manufactured by Nestlé.

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity</th>
<th>Carbohydrate (g)</th>
<th>Fat (g)</th>
<th>Protein (g)</th>
<th>Energy (kJ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test oil</td>
<td>40</td>
<td>0</td>
<td>40</td>
<td>0</td>
<td>1478</td>
</tr>
<tr>
<td>Skimmed milk</td>
<td>150</td>
<td>7.5</td>
<td>0.2</td>
<td>5.1</td>
<td>213</td>
</tr>
<tr>
<td>Nesquik powder</td>
<td>25</td>
<td>20.0</td>
<td>0.8</td>
<td>0.8</td>
<td>380</td>
</tr>
<tr>
<td>Skimmed milk</td>
<td>15</td>
<td>7.8</td>
<td>0.2</td>
<td>5.3</td>
<td>228</td>
</tr>
<tr>
<td>White bread</td>
<td>73</td>
<td>51.3</td>
<td>1.6</td>
<td>8.5</td>
<td>1014</td>
</tr>
<tr>
<td>Jam</td>
<td>30</td>
<td>27.5</td>
<td>0</td>
<td>0</td>
<td>47</td>
</tr>
<tr>
<td>Total</td>
<td>114.1</td>
<td>42.8</td>
<td>19.7</td>
<td>19.7</td>
<td>3360</td>
</tr>
</tbody>
</table>
Table 2  Fatty acid composition of the test meals

<table>
<thead>
<tr>
<th>Fatty acid</th>
<th>Placebo oil meal (%)</th>
<th>Fish oil meal (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myristic acid (C14:0)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Palmitic acid (C16:0)</td>
<td>32.0</td>
<td>26.1</td>
</tr>
<tr>
<td>Stearic acid (C18:0)</td>
<td>4.0</td>
<td>3.9</td>
</tr>
<tr>
<td>Oleic acid (C18:1)</td>
<td>42.0</td>
<td>34.4</td>
</tr>
<tr>
<td>Linoleic acid (C18:2)</td>
<td>20.0</td>
<td>16.0</td>
</tr>
<tr>
<td>Linolenic acid (C18:3)</td>
<td>1.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Arachidonic acid (C20:4)</td>
<td>—</td>
<td>1.6</td>
</tr>
<tr>
<td>Docosapentaenoic acid (C22:5)</td>
<td>—</td>
<td>7.9</td>
</tr>
<tr>
<td>DHA (C22:6)</td>
<td>—</td>
<td>1.6</td>
</tr>
</tbody>
</table>

The fatty acid composition was determined from manufacturers’ data.

and written informed consent was obtained from the subjects before the study began.

Assessment of vascular reactivity

Peripheral microvascular function was assessed using a validated technique which quantifies the vasodilator responses to 1% ACh (acetylcholine; endothelium-dependent vasodilation) and 1% SNP (sodium nitroprusside; endothelium-independent vasodilation), delivered transdermally using iontophoresis. This non-invasive in vivo method provides a robust surrogate marker of vascular function in other parts of the body and is described in detail elsewhere [16,17]. Briefly, prior to the assessment of vascular reactivity, subjects were taken to a temperature-controlled room (22–24 °C) to rest for 30 min to ensure stable baseline conditions. For the vascular reactivity measurement, participants lay in a semi-recumbent position with their right arm supported on an armrest. A temperature probe and iontophoresis chambers were attached to the volar aspect of the forearm, with ACh and SNP introduced into the anodal and cathodal chambers respectively. Following a basal measurement of skin perfusion, an incremental constant current was delivered progressively in 5 µA steps (5, 10, 15 and 20 µA) to yield a total charge (current × time) of 8000 coulombs during the measurement. A series of 15 scans was performed as the current increased from 0 to 20 µA (with a further five scans performed after the current had been switched off), and skin perfusion was measured using a laser Doppler imager (Moor Instruments). For each scan, median flux values were determined within each of the iontophoresis chambers and plotted against the cumulative charge (0–8000 coulombs). The within-day and between-day coefficients of variation for this method are both < 10% [16].

Analytical procedures

Blood samples were collected into EDTA tubes, and the plasma was separated by centrifugation at 1700 g for 10 min in a bench-top centrifuge at 4 °C. Plasma for lipoprotein isolation and analysis of lipids, glucose, insulin and nitrate were stored at −80 °C. TAG and glucose were measured with an ILAB 600 clinical chemistry analyser (Instrumentation Laboratory) using enzyme-based colormetric tests supplied by the manufacturer. NEFAs (non-esterified fatty acids) were analysed as above using a kit supplied by Alpha Laboratories. All samples for each subject were analysed within a single batch, and the inter-assay coefficient of variation was < 4% for all analytes.

Plasma insulin was measured using a specific ELISA incorporating monoclonal antibodies (Dako). Total nitrite levels (a surrogate marker of bioavailable NO) were determined using a commercially available kit following the reduction of nitrate to nitrite (ACTIVE MOTIF; Rixensart). The inter-assay coefficients of variation for these assays were < 6%.

To determine molecular mechanisms underlying the effects of meal fatty acids on postprandial vascular reactivity, TRLs [TAG-rich lipoproteins; Sf (Svedberg flotation rate) > 400, a fraction which contains predominantly chylomicrons] were isolated from the 4 h postprandial plasma samples and incubated with HUVECs (human umbilical vein endothelial cells) to determine the effects on the gene expression of eNOS (endothelial NO synthase; an enzyme involved in the formation of NO from l-arginine in endothelial cells) and NOX-4, the NADPH oxidase subunit expressed in endothelial cells (an enzyme involved in the formation of the superoxide anion).

Cell culture experiments

To ensure sufficient quantities of the Sf > 400 TRL fraction for the cell culture studies, postprandial plasma samples from five different volunteers were pooled before density gradient ultracentrifugation was performed, as described previously [18]. Lipoproteins were passed through PD-10 desalting columns (Amersham Biosciences) and concentrated further using Vivaspin concentrators (Sartorius) before addition to cell cultures. To protect the lipoprotein fraction from oxidation, butylated hydroxytoluene was added at a final concentration of 25 µmol/l. ApoB (apolipoprotein B) was measured in the concentrated lipoprotein fractions in an ILAB 600 clinical chemistry analyser by turbidimetric immunoassay using a kit supplied by Alpha Laboratories.

Pooled HUVECs (Cambrex Bioscience) were maintained in complete medium [endothelial basal medium-2 supplemented with hydrocortisone, FGF-B (fibroblast growth factor-B), VEGF (vascular endothelial growth factor), IGF-1 (insulin-like growth factor-1), EGF (epidermal growth factor), gentamicin sulfate, amphotericin B-1000, heparin, ascorbic acid and 2% (v/v) FBS (fetal bovine serum); Cambrex Bioscience]. For experiments, HUVECs were grown to 60–70% confluence in six-well plates, washed twice with Heps-buffered saline and incubated in lipid-depleted complete medium, where FBS was replaced by 2% (v/v) charcoal-stripped lipoprotein-deficient FBS (Cambrex Bioscience) for 12 h to induce quiescence. Cells were then incubated
with the S1 > 400 fraction (0.5 µg of apoB/ml) for 4 h at 37°C. Only HUVECs passaged less than four times were used in the experiments.

**Real-time RT (reverse transcription)-PCR**

Total RNA was extracted from the cells using RNaseasy Mini Kit and QIA shredder (Qiagen) using protocols recommended by the manufacturer. cDNA was generated from samples (0.8–1.5 µg) of total RNA at 42°C for 50 min (reaction volume, 20 µl) using an oligo(dT)12–18 primer (Invitrogen) and reverse transcriptase (Superscript II; Invitrogen) using protocols recommended by the manufacturer.

Specific primers for NOX-4 (forward primer, 5′-GGTGCTAAGCAGAGCCTCAGC3′; and reverse primer, 5′-GGAAACCTCITCGATCCTCG3′) were designed and real-time RT-PCR was performed as described previously [19]. The primer sequence for eNOS was obtained from Miyomoto et al. [20]. The gene expression of each target gene was normalized to β-actin expression, and the results represent the fold change in mRNA expression relative to the control (no lipoprotein addition), which was arbitrarily defined as 1.

**Cell viability and cytotoxicity**

The LDH (lactate dehydrogenase) concentration in the medium was determined after incubation with the S1 > 400 fraction (0.5 µg of apoB/ml) for 4 h using a commercially available colorimetric cytotoxicity assay (Biogenesis). The cell viability of the monolayers was analysed as described previously [21].

**Statistical analysis**

Results were analysed using SPSS version 12.1 and are presented as means ± S.E.M. The plasma metabolites in the baseline (0 h) and 4 h postprandial samples were analysed using a paired Student’s t test. The microvascular responses to ACh and SNP measured at baseline (0 h) and 4 h after the meals were analysed using two-way repeated measures ANOVA. The fold changes in mRNA gene expression were analysed using an independent Student’s t test. All data were checked for normality and log-transformed, where necessary, before statistical analysis. These data included the microvascular responses to ACh, SNP and NEFAs. Data which could not be normalized (TAG, glucose and insulin) were analysed using the Wilcoxon non-parametric test. Values of $P < 0.05$ were taken as significant.

**RESULTS**

The placebo oil and fish oil meals were well-tolerated by the subjects without any unpleasant side effects.

**Plasma metabolites**

Baseline (0 h) and postprandial (4 h) concentrations are shown in Table 3. There were no significant differences in baseline lipid, glucose, insulin or total nitrite concentrations between the study days. Compared with baseline concentrations, there was a significant increase in TAG concentrations following both meals ($P < 0.001$). Total nitrite and NEFA concentrations were also significantly increased 4 h after the fish oil meal ($P < 0.03$; Table 3).

Between-meal comparisons indicated that, at 4 h, the total nitrite and glucose concentrations were significantly greater after the fish oil compared with the placebo oil meal ($P < 0.05$; Table 3). Postprandial TAG, NEFA and insulin concentrations were similar following both meals.

**Microvascular responses to ACh and SNP at baseline and 4 h after the test meals**

Figure 1 shows the baseline (0 h) and postprandial (4 h) skin perfusion responses to ACh and SNP following the placebo oil and fish oil meals. These results are presented as flux units against the cumulative charge (0–8000 coulombs); as the charge increases, there is an increase in drug delivery leading to a greater skin perfusion (flux units). Compared with the baseline (0 h) measurement, there was a significant increase in the vasodilatory response to SNP ($P = 0.024$) and, to a lesser extent, ACh ($P = 0.108$) at 4 h after the fish oil meal (Figure 1). Significant differences

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo oil meal</th>
<th>Postprandial (4 h)</th>
<th>Fish oil meal</th>
<th>Postprandial (4 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (0 h)</td>
<td></td>
<td>Baseline (0 h)</td>
<td></td>
</tr>
<tr>
<td>TAG (mmol/l)</td>
<td>1.44 ± 0.2</td>
<td>2.48 ± 0.4†</td>
<td>1.40 ± 0.2</td>
<td>2.60 ± 0.3†</td>
</tr>
<tr>
<td>NEFAs (µmol/l)</td>
<td>278.0 ± 26.5</td>
<td>308.5 ± 26.4</td>
<td>270.3 ± 21.7</td>
<td>359.4 ± 32.8*</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>5.38 ± 0.1</td>
<td>5.16 ± 0.1‡</td>
<td>5.57 ± 0.1</td>
<td>5.47 ± 0.1</td>
</tr>
<tr>
<td>Insulin (pmol/l)</td>
<td>27.5 ± 2.4</td>
<td>31.7 ± 6.9</td>
<td>28.1 ± 3.7</td>
<td>22.3 ± 3.9</td>
</tr>
<tr>
<td>Total nitrite (µmol/l)</td>
<td>37.8 ± 2.6</td>
<td>34.9 ± 3.3§</td>
<td>33.9 ± 2.0</td>
<td>44.6 ± 3.4†</td>
</tr>
</tbody>
</table>

Table 3 Lipid, glucose, insulin and total nitrite concentrations before and after two high-fat meals in 25 healthy men

Values are means ± S.E.M. *$P = 0.024$ and †$P = 0.001$ compared with baseline concentrations; ‡$P = 0.046$ and §$P = 0.013$ compared with the postprandial fish oil meal concentrations.
Fish oils and postprandial vascular reactivity

Figure 1 Baseline and postprandial microvascular responses to ACh (upper panels) and SNP (lower panels) after the placebo oil and fish oil meals

Values are means ± S.E.M., n = 25. For the fish oil meal, there was a significant increase in the postprandial vasodilatory response to SNP compared with the baseline response (P = 0.024).

were not observed between the baseline and postprandial response to ACh or SNP for the placebo oil meal.

Cell culture experiments

Cell viability and cytotoxicity

Compared with the control (no lipoprotein addition), there was no loss in cell viability or increase in the release of LDH from HUVECs following incubation with the Sf > 400 fraction for a period of 4 h (results not shown).

Real-time RT-PCR

Figure 2 shows the fold changes of eNOS and NOX-4 mRNA in HUVECs following incubation with postprandial Sf > 400 TRLs isolated after the placebo oil and fish oil meals compared with no lipoprotein addition (control), which is designated as 1. There was a significantly greater up-regulation of eNOS (P = 0.014) and a greater down-regulation of NOX-4 (P = 0.025) mRNA expression following incubation with the fish oil compared with the placebo oil meal TRLs (Figure 2).

DISCUSSION

With the increasing recognition of the pivotal role of vascular dysfunction in the progression of atherosclerosis, the vasculature has emerged as an important target for dietary therapies. Over the past decade, there has been considerable interest in the impact of meal composition...
on postprandial vascular reactivity. Dietary fat, in particular, has emerged as a potential modulator, as a number of studies have shown an impairment in vascular reactivity 2–8 h after high-fat compared with low-fat meals [7]. This is an important observation as individuals spend the majority of the day in the postprandial state and it is likely that these transient changes in vascular reactivity, repeated on a daily basis, could have implications for long-term vascular health and overall cardiovascular risk.

In the present study, we found that a single meal enriched with 5.4 g of DHA and EPA, equivalent to two portions of oily fish, acutely improved postprandial vascular reactivity in our male cohort. Although the improvement in ACh-induced reactivity (endothelium-dependent vasodilation) did not reach significance, a significant increase in the vasodilatory response to SNP (endothelium-independent vasodilation) was observed compared with baseline measurements. In addition, these improvements were associated with a significant increase in postprandial plasma total nitrite levels, a surrogate marker of bioavailable NO. Although chronic long-term vascular reactivity in our male cohort. Although the two portions of oily fish, acutely improved postprandial vascular health and overall cardiovascular risk. It is likely that these transient changes in vascular reactivity, the majority of the day in the postprandial state and it is likely that these transient changes in vascular reactivity, repeated on a daily basis, could have implications for long-term vascular health and overall cardiovascular risk.

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vascular reactivity are unknown, some studies have hypothesized that fish oil supplementation leads to improvements in vascular reactivity by increasing the bioavailability of NO in the vascular wall [26]. This is thought to occur by a number of mechanisms, including (i) an increase in NO production via effects on eNOS gene regulation and post-transcriptional regulation of eNOS phosphorylation, or (ii) a decrease in NO degradation, due to a decrease in reactive oxygen species generation or an increase in antioxidant enzyme activity. Results from the cell culture component of the present study suggest that one or both of these mechanisms may be important. The lipid composition of the postprandial $S_1 > 400$ fraction has been shown to reflect the fatty acid composition of the test meal, and the $S_1 > 400$ fraction isolated after the fish oil meal led to a down-regulation of NOX-4 and an up-regulation in eNOS gene expression compared with TRL particles obtained after the placebo oil meal. In our human study, the improvement in endothelium-dependent vasodilation did not reach significance, but the up-regulation of eNOS expression is consistent with the significant increase in total nitrite concentrations after the fish oil meal. The down-regulation of NADPH oxidase, the major source of superoxide anion in the vasculature, would be predicted to be associated with a decrease in NO degradation. Interestingly, both EPA and DHA have been recognized as ligands for PPAR-γ (peroxisome-proliferator-activated receptor-γ), the transcriptional regulator of both NADPH oxidase and SOD (an antioxidant enzyme). At present, the effects of fish oil fatty acids on PPAR-γ activity and cellular redox status are unknown. As NOX-4 is also expressed in vascular smooth muscle cells, we cannot rule out the possibility that fish oils acutely influenced smooth muscle action directly by modulating the redox status within these cells.

In conclusion, the present study provides novel findings which suggest that the inclusion of EPA and DHA in a meal can improve postprandial vascular reactivity. The mechanism of action appears to be predominately in response to the NO donor SNP. Findings from our cell culture studies indicate that fish oil fatty acids may reduce superoxide formation via the down-regulation of NADPH oxidase. These changes are suggestive of an impact of treatment on the redox status of the vascular wall, with a possible influence on circulating NO levels. However, further studies to determine the underlying mechanisms of how fish oil fatty acids influence postprandial vascular reactivity are merited which focus on both endothelium-dependent and -independent pathways.

ACKNOWLEDGMENTS

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REFERENCES


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