Effects of a convenience drink fortified with n-3 fatty acids on the n-3 index

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There is strong evidence that the intake of EPA and DHA reduces the risk of adverse cardiac events. Fish and fish oil capsules are not necessarily an ideal source of EPA and DHA for every individual. The aim of the present study was to evaluate the effect of a convenience drink enriched with 500 mg EPA and DHA on the n-3 index, a biomarker of EPA and DHA status in an individual. Of the 190 subjects with atherosclerotic disease screened between February and June 2009, 50 were recruited based on an n-3 index <5%. Participants were randomly assigned to receive a convenience drink supplemented either with n-3 fatty acids (n 40, 200 mg EPA and 300 mg DHA) or placebo (n 10, 1.1 g linoleic acid, C18:2n-6, from maize oil) daily for 8 weeks. The primary end point was a change in the n-3 index. Intention-to-treat analysis was done. After 8 weeks of daily intake of 200 mg EPA + 300 mg DHA, the mean n-3 index increased from 4.37 (SD 0.51) to 6.80 (SD 1.45)% (P<0.001). Interindividual variability in response was high (CV of the Δ, c = 0.21). The control group showed no change in the n-3 index. The results showed that daily intake of a convenience drink supplemented with n-3 fatty acids leads to a significant increase of the n-3 index with high interindividual variability in response. Dose and preparation used were safe, well tolerated and highly palatable.

Atherosclerosis: n-3 Fatty acids: EPA: DHA

Substantial evidence from large intervention studies indicates that 1 g/d of the two marine n-3 fatty acids EPA and DHA reduces major adverse cardiac events such as sudden cardiac death (SCD), and fatal and non-fatal myocardial infarction(1–4). Recent meta-analyses estimated these reductions to be between 13 and 17 relative % (5). However, when assessing blood levels of EPA and DHA, e.g. by the n-3 index, larger differences in the incidence of SCD are seen: incidence of SCD with an n-3 index >8% was 10% of the incidence of SCD with an n-3 index <4% (6–8). Moreover, the n-3 index represents tissue levels of EPA and DHA, e.g. levels of those in the cardiac tissue(9,10). For these and other reasons, the n-3 index was suggested as a biomarker of EPA and DHA status in an individual (11).

Sources of EPA and DHA, such as fish, especially long-living predatory fish, can be contaminated with methylmercury and other substances (12,13), whereas fish oils or encapsulated concentrated derivatives of fish oils may not be palatable to every individual, a problem shared by fish. Therefore, fortifying food otherwise devoid of EPA and DHA is currently evaluated as an alternative. Concerns exist, however, whether the matrix, i.e. the carrier food, plays a role in bioavailability of the fortifier. Also, there is a debate whether the different chemical forms of EPA and DHA (e.g. TAG, phospholipids and ethyl esters) impact on bioavailability (14).

Therefore, we addressed the question whether a convenience drink enriched with 940 mg n-3 fatty acids (200 mg EPA, 300 mg DHA and 100 mg docosapentaenoic acid) impacts on the n-3 index of human subjects with atherosclerosis, a condition in which an increased intake of EPA and DHA is recommended. Palatability and safety were also assessed.

Subjects and methods

Study subjects

From February until June 2009, patients with known atherosclerotic disease such as previous myocardial infarction or coronary revascularisation, and those with positive angiography or ultrasound were asked to participate in the present study. Inclusion criteria were (1) evidence for atherosclerotic disease; (2) a low n-3 index <5% to recruit participants reasonably homogeneous in their n-3 index. Exclusion criteria were (1) age less than 30 years or more than 75 years, (2) BMI higher than 30 kg/m², (3) intake of n-3 fatty acid supplements or consumption of more than two portions of oily fish (e.g. salmon, sardines, albacore tuna and mackerel) per week, (4) serious bleeding disorder or the concurrent use of platelet inhibitors and anticoagulants, (5) any acute and life-threatening condition such as collapse and shock, acute myocardial infarction, stroke or embolism in the last 3 months, (6) significant medical co-morbidity, (7) seriously limited life expectancy, (8) insulin-treated diabetes mellitus, (9) allergy, intolerance or history of...
hypotheses to components of study intervention; (10) pregnancy, breast-feeding and childbearing potential without any medically accepted method of contraception. Patients were asked not to participate if they were participating in another study, had no adequate fluency in German or English to complete baseline and follow-up interviews, or had a history of non-compliance or known drug or alcohol abuse/dependence in the past 2 years.

The present study was approved by the ethics committee of the Faculty of Medicine of the Ludwig-Maximilians-University of Munich, registered at clinicaltrials.gov (NCT00886704) and conducted according to the guidelines laid down in the Declaration of Helsinki and Good Clinical Practice. Written informed consent was obtained from all the subjects before participating, allowing analysis of all the clinical and laboratory data mentioned in the present paper. The study was initiated, designed, conducted and evaluated by the investigators, and the sponsor had no role in study design, data acquisition or evaluation, or in preparation of the manuscript.

Study design

The present study was a randomised, placebo-controlled, single-centred study, in which comparison of two matching convenience drinks was done. The primary end point was a single-centred study, in which comparison of two matching convenience drinks was done. The primary end point was a change in the n-3 index. Predefined secondary end points were palatability and safety of 500 mg/d EPA (200 mg) and DHA (300 mg), both of which were assessed by a questionnaire including a visual analogue scale (1 stands for very poor and 10 for very good) and changes in blood lipids, heart rate and blood pressure.

After screening, and a 1 d run-in (to assess acceptability of the convenience drink), an 8-week intervention period followed with daily intake of an n-3-supplemented convenience drink (verum) or n-6-supplemented convenience drink (placebo). At the screening visit (t0), run-in (t1) and at the end-of-study visit at week 8 (t8), blood samples and clinical parameters were obtained. Furthermore, the patients were asked about their food habits, especially about their fish intake or intake of n-3 fatty acids. Venous blood was collected by venepuncture from the subjects at t0 in non-fasting state to measure the n-3 index, and at t1 and t8 after an overnight fast to measure additional blood parameters (blood glucose, HbA1c, cholesterol, HDL and LDL cholesterol, TAG, creatinine, aspartate aminotransferase, alanine aminotransferase and γ-glutamyl transferase). At week 4 (t4), a telephone follow-up was conducted regarding palatability, adverse events and compliance. Study participants were requested to ingest one drink per day completely within minutes during the day at a time of their convenience, to discard the container and not to alter their current diet.

The convenience drink used (Smartfish®) was manufactured by NEN AS in Oslo, Norway upon instructions from Smartfish AS using patented compositions and processing steps. Verum and the placebo containers looked identical and contained 200 ml of the drink. The verum drink contained 1·8 % salmon oil (3·6 g salmon oil/drink). Thus, each verum drink contained approximately 940 mg n-3 fatty acids, of which 300 mg were DHA, 200 mg EPA and 100 mg docosapentaenoic acid. The placebo drink contained 1 % maize oil (57 % linoleic acid). Thus, each placebo drink contained approximately 1·1 g n-6 fatty acids. Apart from the placebo drink containing slightly more water (0·8 %), the other ingredients/compositions were identical in both the drinks: energy content of 486 kJ (116 kcal); 0·6 g protein, of which 720 mg were milk proteins; 22 g carbohydrates, of which 160 mg were lactose; 4 g total fat, of which 0·6 g were SFA; 1·8 g monounsaturates; 1·4 g polyunsaturates and 0·85 μg vitamin D.

Laboratory methods

Erythrocyte fatty acid composition was analysed according to the HS-Omega-3 Index® methodology as described previously[56]. Fatty acid methyl esters were generated from erythrocytes by acid transesterification and analysed by GC using a GC2010 Gas Chromatograph (Shimadzu, Duisburg, Germany) equipped with a SP2560, 100 m column (Supelco, Bellefonte, PA, USA) using hydrogen as the carrier gas. Fatty acids were identified by comparison with a standard mixture of fatty acids characteristic of erythrocytes. The results are given as EPA + DHA expressed as a percentage of total identified fatty acids after response factor correction. The CV for EPA + DHA was 5 %. Analyses were quality controlled according to Deutsches Institut für Normung International Organisation for Standardisation 15 189.

Other blood parameters were determined by the Department of Clinical Chemistry – Klinikum Innenstadt (Ludwig-Maximilians-University, 80 336 Munich, Germany) using routine clinical chemistry methods.

Statistical analyses

The power calculation is based on that of Harris & von Schacky[56], where 0·5 g of EPA and DHA was given for 20 weeks, and the n-3 index rose from 4·7 (SD 0·9) to 7·9 (SD 1·7) %. Due to the 120 d lifespan of the erythrocytes, half as big a change within 8 weeks was anticipated, i.e. a change of +1·65 (SD 1·2) %. The usual assumptions were made (α = 5 % and power = 80 %). A weighted randomisation with a ratio of 4:1 (verum:placebo, to maximise information on safety and palatability of verum) was computer generated by the monitor in blocks of five. According to a web-based case estimate, the necessary sample size was fifty participants for the present parallel-design study (http://hedwig.mgh.harvard.edu/sample_size/size.html). Analysis was by intention-to-treat.

The results are presented as the means and standard deviations. Statistical differences were calculated using unpaired t test for the comparison of intervention v. control, and paired t test for the comparison of baseline with the end of the trial. Differences with P values <0·05 were considered statistically significant. Data were examined with PASW Statistics for Windows (release 17.0.2; Chicago, IL, USA).

Results

Screening group

Of the 190 subjects who were screened and gave informed consent, only 50 were enrolled. The main exclusion criterion (about 95 %) was an n-3 index >5·0 % (Fig. 1). Additional subjects were excluded because of the lack of any evidence.
for atherosclerotic disease, hospitalisation or lactose intolerance. Most of the individuals screened were recruited from special training groups for patients with coronary artery disease. Characteristics of these individuals were 114 male and 76 female subjects, mean age 65·0 (SD 6·8) years, mean BMI 25·83 (SD 3·09) kg/m² and mean n-3 index 5·94 (SD 1·41) %. The distribution of the n-3 index among the individuals screened is shown in Fig. 1.

Study group

Fifty subjects fulfilled the inclusion criteria and were randomly assigned (Fig. 2). Forty subjects (eleven female and twenty-nine male subjects; mean age 65·1 (SD 6·10) years) were assigned to receive the convenience drink supplemented with n-3 fatty acids, and ten subjects (five female and five male subjects; mean age 64·5 (SD 5·95) years) were assigned to the placebo group (supplemented with n-6 fatty acids). Erythrocyte fatty acid composition, including the median value of the n-3 index in the verum group (4·37 (SD 0·51)), did not differ significantly from that of the placebo group (4·63 (SD 0·34) %). There were also no significant differences in blood and clinical parameters among the two groups at baseline (Table 1). All the ten subjects who received n-6 fatty acids and thirty-eight subjects who received n-3 fatty acids finished the trial.

Primary end point

After 8 weeks of daily intake of a convenience drink fortified with n-3 fatty acids, the n-3 index increased significantly (P<0·001) from mean 4·37 (SD 0·51) to 6·80 (SD 1·45) % in the verum group (Fig. 3) in comparison to the placebo group. There was a high variability in response. The mean increase was 2·43 (SD 1·48) % (CV of the Δ, cv = 0·21) with a minimum of −0·03 % and a maximum of 7·16 %. The increase was independent of BMI (Pearson’s correlation coefficient r = −0·104; P = 0·524) and age (r = 0·006; P = 0·973), and there was no significant difference (P = 0·988) in response between male and female participants.

In the placebo group, no significant change in the n-3 index was measured after 8 weeks (mean 4·71 (SD 0·73) %) compared with the baseline (mean 4·63 (SD 0·34) %) (Fig. 4).

The fatty acid composition in erythrocytes in the verum group showed significant changes compared with the placebo group as shown in Table 2. In the placebo group, only eicosenoic acid and docosapentaenoic acid differed significantly from the baseline values, indicating that the control intervention indeed served as a placebo.

Secondary end points

Palatability, assessed by a visual analogue scale, of the convenience drink in the placebo group was 8·30 (SD 1·64) at t₄ and 8·50 (SD 1·84) at t₈; in the verum group, it was 8·15 (SD 1·60) at t₄ and 8·39 (SD 1·71) at t₈. Tolerability, also assessed by visual analogue scale, in the placebo group was 9·10 (SD 1·60) at t₄ and 8·60 (SD 2·50) at t₈; in the verum group, it was 9·08 (SD 1·20) at t₄ and 9·15 (SD 1·58) at t₈. Taste as well as tolerability was not significantly different in any comparison. As shown in Table 1, all measured parameters did not differ significantly between the placebo and verum groups.
Two verum recipients withdrew from the study. One patient withdrew from the study because of a hypertensive crisis (day 14), and the other because of skin itching (day 7). On the telephone follow-up at week 4 ($t_4$), only the verum recipients reported about changes (one lower international normalised ratio was detected during checkup by a general practitioner, two slightly lower blood pressures were detected by home blood pressure measurement, three looser stool, one flatulence and one polyuria) and observations (one malodorous stool, one loose stool, one weight gain, one flatulence, one increased libido, one diarrhoea for the first 3 d after the start of the treatment and one episode of obstipation for about 10 d) since the start of the study. At the end-of-study visit ($t_8$), three placebo recipients reported about observations (one weight gain, one loose stool and one harder stool), and seven verum recipients reported about changes (three loose stool, one increased blood pressure and one slightly lower blood pressure were detected by home blood pressure measurement, one hard stool and one less hunger) and eleven reported about observations (four weight gain, one slight nausea, one flatulence, three loose stool, one itching and one hard stool).

### Discussion

The present study demonstrated an increase in the mean n-3 index after daily intake of EPA (200 mg) and DHA (300 mg)
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for 8 weeks from mean 4.37 (SD 0.51)% to mean 6.80 (SD 1.45)% (P < 0.001). Although the study population was recruited based on an n-3 index < 5% and was rather homogeneous in this respect, individual responses differed strikingly in the intervention group, whereas the n-3 index was stable in the control group. No major problems were noted in terms of safety and palatability.

**Interindividual differences in n-3 index**

The n-3 index of the screening group in the present study (190 subjects with atherosclerotic disease) ranged from 2.94 to 9.91% and had a Gaussian distribution (Fig. 1), which is in line with former studies (15–17). A number of factors, such as dietary intake, age, sex, BMI, presence or absence of diabetes, genetic influences and disposition of energy, impact on the

**Table 2. Fatty acid (FA) composition in erythrocytes at baseline and at the end of the study**

(Mean values and standard deviations)

<table>
<thead>
<tr>
<th>Total FA (%)</th>
<th>t0</th>
<th>t8</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n 10)</td>
<td>n-3 FA (n 40)</td>
</tr>
<tr>
<td>C14 : 0</td>
<td>0.52 (0.16)</td>
<td>0.51 (0.23)</td>
</tr>
<tr>
<td>C16 : 0</td>
<td>21.24 (1.19)</td>
<td>21.66 (1.04)</td>
</tr>
<tr>
<td>C16 : 1</td>
<td>0.20 (0.25)</td>
<td>0.19 (0.31)</td>
</tr>
<tr>
<td>C18 : 0</td>
<td>0.59 (0.31)</td>
<td>0.63 (0.27)</td>
</tr>
<tr>
<td>C18 : 1</td>
<td>0.59 (0.25)</td>
<td>0.53 (0.32)</td>
</tr>
<tr>
<td>C18 : 2 n-6</td>
<td>16.16 (1.34)</td>
<td>17.35 (2.65)</td>
</tr>
<tr>
<td>C18 : 2 n-6t</td>
<td>0.13 (0.06)</td>
<td>0.13 (0.11)</td>
</tr>
<tr>
<td>C18 : 2 n-6c</td>
<td>0.02 (0.01)</td>
<td>0.03 (0.04)</td>
</tr>
<tr>
<td>C20 : 1 n-9</td>
<td>0.29 (0.15)</td>
<td>0.27 (0.22)</td>
</tr>
<tr>
<td>C20 : 3 n-6</td>
<td>0.30 (0.12)</td>
<td>0.26 (0.10)</td>
</tr>
<tr>
<td>C20 : 3 n-6t</td>
<td>1.83 (0.35)</td>
<td>1.88 (0.71)</td>
</tr>
<tr>
<td>C22 : 4 n-6</td>
<td>16.46 (1.78)</td>
<td>16.06 (2.33)</td>
</tr>
<tr>
<td>C24 : 0</td>
<td>0.73 (0.35)</td>
<td>0.82 (0.34)</td>
</tr>
<tr>
<td>C20 : 5 n-3</td>
<td>0.67 (0.21)</td>
<td>0.64 (0.14)</td>
</tr>
<tr>
<td>C22 : 5 n-6</td>
<td>0.60 (0.14)</td>
<td>0.55 (0.16)</td>
</tr>
<tr>
<td>C22 : 6 n-3</td>
<td>3.96 (0.28)</td>
<td>3.73 (0.49)</td>
</tr>
</tbody>
</table>

*10, Timepoint for the screening visit; 8, timepoint for the end-of-study visit.*
n-3 index\(^{17,18}\). Furthermore, each person is metabolically unique, with idiosyncrasies in digestion, absorption, tissue distribution and cellular metabolism\(^6\). The enzymes \(\Delta 5\) desaturase and \(\Delta 6\) desaturase, encoded by fatty acid desaturase 1 and fatty acid desaturase 2, are the rate-limiting enzymes in the desaturation of \(\alpha\)-linolenic acid to EPA, and vary inter-individually in their expression\(^{19,20}\). Apart from that, only a third of human subjects seem to be able to convert \(\alpha\)-linolenic acid to EPA\(^{21}\). Together, the mentioned factors may explain the normal distribution of the n-3 index in our screening group.

**Selection bias in screening group?**

The mean n-3 index in the screening group was 5.94 (SD 1.41)\%, which was much higher than expected\(^22\). Most of the screened individuals were from special training groups for patients with coronary artery disease. Participants in these groups are probably ‘healthy compliers’, since they spend time and money, and display a high level of motivation, self-initiative and health consciousness. Healthy compliers tend to belong to an above-average socio-economic group\(^{23,24}\). Cohen et al.\(^{25}\) showed that EPA and DHA levels are positively associated with socio-economic status (household income, education and occupation).

**Increase of the n-3 index by the convenience drink**

In the present study, daily intake of 200 mg EPA and 300 mg DHA in a convenience drink for 8 weeks increased the n-3 index from mean 4.37 (SD 0.51) to 6.80 (SD 1.45)\%, or by 2.43\% (P<0.001). This increase was higher than expected in our case estimate based on a previous dose–response study\(^6\). In the previous study, intake of fish oil capsules containing 500 mg EPA and DHA for 20 weeks increased the n-3 index significantly from 4.7 (SD 0.9) to 7.9 (SD 1.7)\%, or by 3.2\% (n 22; P<0.001)\(^6\). In another study, Harris et al.\(^{26}\) showed that an intake of 485 mg EPA and DHA, provided as fish or capsules, for 16 weeks increases the n-3 index in a similar way (fish group: 4.0 (SD 0.6) to 6.2 (SD 1.4)\%, n 11; P<0.0001; capsule group: 4.3 (SD 1.0)% to 6.2 (SD 1.4)\%, n 12; P<0.0001). Although supplementation periods are not directly comparable, we conclude that the convenience drink used in the present study might be an effective alternative to fish oil capsules.

**Impact on clinical events**

The 500 mg/d dose of n-3 fatty acids investigated was a dose suggested by the International Society for the Study of Fatty Acids and Lipids and other scientific bodies\(^{27}\) because this dose seems to decrease the risk for death from CHD in healthy adults and might be ideal for primary prevention\(^{28}\). Based on circumstantial evidence, the mean increase of the n-3 index of 2.43 (SD 1.48)% from 4.37 (SD 0.51) to 6.80 (SD 1.45)% observed in the present study is associated with an estimated 70% decrease in the risk for SCD\(^{29}\), and a less pronounced decrease in the risk for other cardiovascular events, such as the acute coronary syndrome\(^3\). The estimates in risk reduction mentioned, however, need to be substantiated by further research.

**Variability in response**

In the present study, the analytical method that was used to determine the n-3 index ensured a high analytical reproducibility, and the use of erythrocytes ensured a low biological variability\(^11\). The biological variability is much lower in erythrocytes than in other blood cells or in plasma\(^31–33\). This is a prerequisite to appreciating the variability in response observed in the present study. We detected a high interindividual variability in response with end points between 4.37 and 11.80\%, although the study population was recruited on an n-3 index <5\% and was rather homogeneous in this respect. Compliance, as assessed by history at visits 4 and r8, was excellent. We did not, however, perform the counts of empty containers. Moreover, the convenience drink was safe, well tolerated and highly palatable. Therefore, we do not think that variability in compliance alone fully explains the variability in response. Study participants were told not to alter their diet during the study. At the screening visit and at the end-of-study visit, patients were asked about their food habits, especially about fish intake or n-3 fatty acid supplementation: no participant reported any changes. The study supplement included 160 mg lactose. Although some study participants, both from verum and control groups, reported symptoms that could be interpreted as lactose intolerance, no participant had a diagnosis of lactose intolerance. Moreover, it does not seem plausible that 160 mg lactose/d could cause gastrointestinal symptoms and a faster intestinal passage with subsequent reduced absorption of nutritional components\(^34\). Interindividual differences in the activity of pancreatic enzymes and gastrointestinal transport mechanisms for fatty acids might contribute to the high interindividual variability in response\(^35,36\), but will have to be examined in further studies. Moreover, some, if not all, factors influencing the n-3 index discussed above might also have an impact on the response of the n-3 index to supplementation\(^37\). Conversely, in longer term studies or studies with higher doses, variability in response might be smaller because tissue accretion responds to time and dose. However, interindividual variability in response to a given dose of EPA and DHA might partially explain variabilities in the results of intervention trials using low doses of EPA and DHA\(^5\). This provides a rationale for clinical studies using target n-3 index levels and flexible doses, as opposed to the current fixed dose approach.

**Safety**

In 1997, the US Food and Drug Administration granted generally recognised as safe status to refined menhaden fish oil\(^38\). In doing so, the agency indicated that the consumption of up to 3 g/d of EPA and DHA from all sources would be considered safe. As already shown in the GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico) trial, daily intake of 1 g n-3 fatty acids is safe. Adverse reactions, also seen in the present study, and mostly gastrointestinal disorders\(^2\), a pattern also seen in the large the Japan EPA Lipid Intervention Study trial using 1.8 g EPA ethylester, are of minor clinical relevance\(^39\). The participants of the present study received 500 mg/d EPA and DHA. Although the present study was too small to detect rare side effects,
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the n-3 preparation and dose used were safe and well tolerated. HbA1c levels of all the study participants increased significantly (P < 0.001) compared with the baseline values from 5.81 (SD 0.46) to 5.93 (SD 0.44) %, but there was no difference in HbA1c levels between the groups at the end of the study. The participants of the present study were told not to alter their current diet, so the increase of the HbA1c might be explained by daily addition of 22 g carbohydrates with the study supplement.

Strengths and limitations

Strengths of the study include (1) a homogeneous participant population, (2) a good palatability and tolerability of the product investigated, making good compliance likely; (3) standardised fatty acid analysis according to Deutsches Institut für Normung International Organisation for Standardisation 15 189 using the HS-Omega-3 Index®. Limitations were that the study (1) was a single-centre study, (2) too small to detect rare side effects; (3) was 8 weeks relatively short in duration.

Conclusion

The present investigation demonstrated that daily intake of a convenience drink enriched with 200 mg EPA and 300 mg DHA for 8 weeks increased the n-3 index significantly. The dose and the preparation used were safe and well tolerated. Therefore, the convenience drink studied appears to be a viable alternative to fish or fish oils. A large variability in response was observed, which requires further studies. The variability in response provides a rationale for future studies targeting a predefined n-3 index with flexible doses of n-3 fatty acids.

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