Original Article

Postprandial long-chain n-3 polyunsaturated fatty acid response to krill oil and fish oil consumption in healthy women: a randomised controlled, single-dose, crossover study

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Background and Objectives: Krill oil (KO) and fish oil (FO) are good sources of health-benefiting long chain n-3 polyunsaturated fatty acids (LC n-3 PUFA), EPA and DHA. There are conflicting outcomes on the bioavailability of LC n-3 PUFA from KO compared with FO. This study investigated the postprandial incorporation of LC n-3 PUFA into plasma lipids following consumption of 5 capsules of KO or FO in comparison with olive oil (OO) control in healthy women. **Methods and Study Design:** 10 women (aged 18-45 years) consumed a high-fat (15 g) breakfast, supplemented with 5 g of KO, FO, or OO in a random order with a minimum seven-day washout period between the supplementations. The LC n-3 PUFA content in KO was 907 mg compared with 1441 mg in FO. Blood samples were collected in the fasting state and for the next 5 hours after test meal consumption on an hourly basis. **Results:** Significant increases in plasma EPA concentrations were observed starting at 2 h after KO and FO consumption ($p<0.05$). There were no significant changes in either DHA or DPA between the three groups. The increases in plasma EPA concentrations were similar between the KO and FO groups ($p>0.05$). **Conclusions:** The lower dose (31%) of EPA from KO led to a similar plasma EPA concentration as in the FO group, suggesting that EPA from KO may be more efficiently incorporated into plasma. This may be related to the high content of phospholipids and free fatty acids in KO.

Key Words: krill oil, fish oil, LC n-3 PUFA, EPA, postprandial response

INTRODUCTION

The long-chain omega-3 polyunsaturated fatty acids (LC n-3 PUFA) eicosapentaenoic acid (EPA, C20:5n-3) and docosahexaenoic acid (DHA, C22:6n-3) have been recommended for cardiovascular disease prevention.[1,2] LC n-3 PUFA reduce plasma triglycerides,[3] inflammatory cytokines and C-reactive protein levels.[4,5] EPA and DHA have different biological functions.[6,7] EPA directly competes with arachidonic acid (AA, 20:4n-6) in relation to the production of anti- and pro-inflammatory lipid mediators including eicosanoids, resolvins, and maresins.[8] Moreover, EPA-derived eicosanoids are associated with anti-platelet aggregation and vasodilation.[9] DHA plays an essential role in the development of the central nervous system and visual function.[10] Another LC n-3 PUFA is DPA, although to date there are limited health benefits, it has shown positive effects on platelet function in vivo.[11] Although these LC fatty acids can be synthesised via enzymatic desaturation and elongation from alpha-linolenic acid, (ALA, 18:3n-3), the conversion rate from ALA in humans is very low (approx. 5% for EPA and <0.5% for DHA).[12-14] Therefore, humans largely rely on dietary sources, especially seafood such as oily fish (mackerel, tuna, salmon, herring) and shellfish for these important fatty acids.[15,16] It has been well reported that the level of EPA and/or DHA in the plasma and erythrocytes can be increased following the consumption of seafood or supplementation with marine oils.[17-20]

Human consumption of fish-derived food products has increased steadily, and the global capture of fish will become unsustainable in the future. Krill, a shrimp-like marine zooplankton, has been identified as an alternative source due to its wide and abundant distribution.[15] The main commercially available krill oil is extracted from Antarctic krill (*Euphausia superba*), living in the Southern Ocean, and it has become an important source of LC n-3 PUFA in the last decade.[15] In krill oil, EPA and DHA

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are found in the phospholipid fraction (predominantly phosphatidylcholine), free fatty acids, and in the triglycerides (TAG) whereas in fish oil they are mainly in TAG.[15,21,22] Previous studies have suggested that LC n-3 PUFA from phospholipids (PL) may lead to a more efficient incorporation of these fatty acids into plasma and erythrocytes compared with those esterified to TAG.[17,23]

There are three postprandial studies, which have investigated the short-term incorporation of LC n-3 PUFA into the plasma from krill oil compared with fish oil.[17,24,25] Schuchardt et al[17] and Yurko-Mauro et al[24] compared krill oil with re-esterified fish oil TAG or ethyl-esters fish oil while Kohler et al[25] compared krill oil with krill meal and fish oil over 72 hours. The results from these studies are not consistent. Kohler et al[25] found a significantly higher incorporation of EPA and DHA into the plasma phospholipids from krill oil compared with fish oil. In contrast, neither Schuchardt et al[17] nor Yurko-Mauro et al[24] observed a significantly higher incorporation of EPA and DHA into plasma phospholipids from krill oil. These latter two studies reported substantial variability between participants, which limited their capacity to detect significant differences between the study oils. There are also three longer-term studies, which have compared the bioavailability of LC n-3 PUFA from krill oil with fish oil.[18,24,26] The only study which reported a significantly higher incorporation of EPA from krill oil versus fish oil was that of Ramprasath et al.[26] Therefore, the information available from the literature is not consistent with regards to the bioavailability of EPA (and DHA) from krill oil in comparison with fish oil. The term "bioavailability" is often used in these studies, however true bioavailability measures the rate and extent to which a drug/compound reaches the systemic circulation.[27] In a nutrition context, the term bioavailability is similar to digestibility which refers to how much of a given nutrient is retained in the body; this implies that faecal losses have been estimated which is rarely or never the case in n-3 PUFA studies.[28]

It has also been reported that there are gender-specific differences in the contribution of LC n-3 PUFA in different tissues. Compared with men, women tend to have a higher omega-3 index,[29] and also a significantly higher level of both AA and DHA in the total plasma and plasma phospholipids.[30] Women have also been found to respond to n-3 supplementation differently to men.[31] Furthermore, the influence of age on the gender differences in the fatty acid composition has been observed.[30] Available studies, which have compared the efficacy of krill oil and fish oil, have either focused only on male participants or mixed gender cohorts, and typically with a wide age range. The data from those studies have been conflicting with large inter-participant variabilities.[17,24,25] The aim of this study was to compare the postprandial bioavailability (incorporation) of equal amounts of krill oil with fish oil in healthy young women. This is the first postprandial study to compare krill oil with fish oil supplementation in young women, which also included a control (olive oil) treatment. All participants were recruited from a narrow age group (18-45 years) to minimise variations between participants. We investigated the effect of a single same dose of krill oil in comparison with fish oil on postprandial plasma fatty acid composition, and plasma and chylomicron lipid levels. This study will provide useful information on how young women respond acutely to krill oil supplementation.

METHODS

Study participants

Ten healthy women aged between 18–45 years within BMI 20–30 (kg/m^2), who had not experienced menopause, were recruited by emails to all Victoria University staff and students, and flyer advertisements via the Victoria University Nutritional Therapy Teaching Clinic, the general public, community centres, and local medical practices. Participants were screened for their suitability for the postprandial study using a medical questionnaire and anthropometric measurements prior to enrolling into the study. Participants were excluded if they were cigarette smokers; pregnant or lactating; or had heart, liver, kidney or inflammatory bowel disease; diabetes; or medications interfering with lipid metabolism or lowering blood lipids; allergy to fish or seafood; or had consumed oily fish more than twice a week or supplements including omega-3 fatty acids in the past four weeks prior to the study.

Study design

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and the protocol was approved by the Ethics Committee of Victoria University Human Research (HRE 14-040). The written informed consent was obtained from all participants prior to the study. This trial was registered with the Australian and New Zealand Clinical Trial Registry (ACTRN 12615000620527). The study was a randomised crossover design with three test meals supplemented with different oils consumed in a randomised order with seven days wash-out period between the test meals (Figure 1). During the study period, all participants were instructed to maintain their habitual diet and not to consume fish/seafood or omega-3 fortified foods more than twice a week.

Prior to the study day, the participants were required to consume a low-fat dinner such as pasta, and avoid drinking alcohol and strenuous physical activity, and fast for approximately 10 h overnight. On the study day, standardised procedures were performed where the participants arrived at the clinic between 7 a.m. and 9 a.m. and a fasting blood sample (0 h, 10 mL) was collected via intravenous cannulation by a qualified practitioner. The participants then consumed a single test meal (breakfast), which consisted of 150 g of fresh mashed potato mixed with 15 g of olive oil, together with 5 × 1 g capsules of krill oil or 5 × 1 g capsules of fish oil with 250 mL of water. Krill oil and fish oil are very different in colour, smell, and taste so for this trial both oils were provided as capsules rather than as oils in order to provide a degree of blinding to the trial. For the control treatment, the participants consumed 5 g of olive oil added into the mashed potato in place of the five capsules (1 g each) of the krill oil or fish oil. It was recognized that the 5 g of krill oil and fish oil do not contain identical amounts of LC n-3 PUFA, but it was deemed that was preferable to maintain the test oils as blinded a fashion as possible, and minimise the participants withdrawing from the trial owing to smell and taste

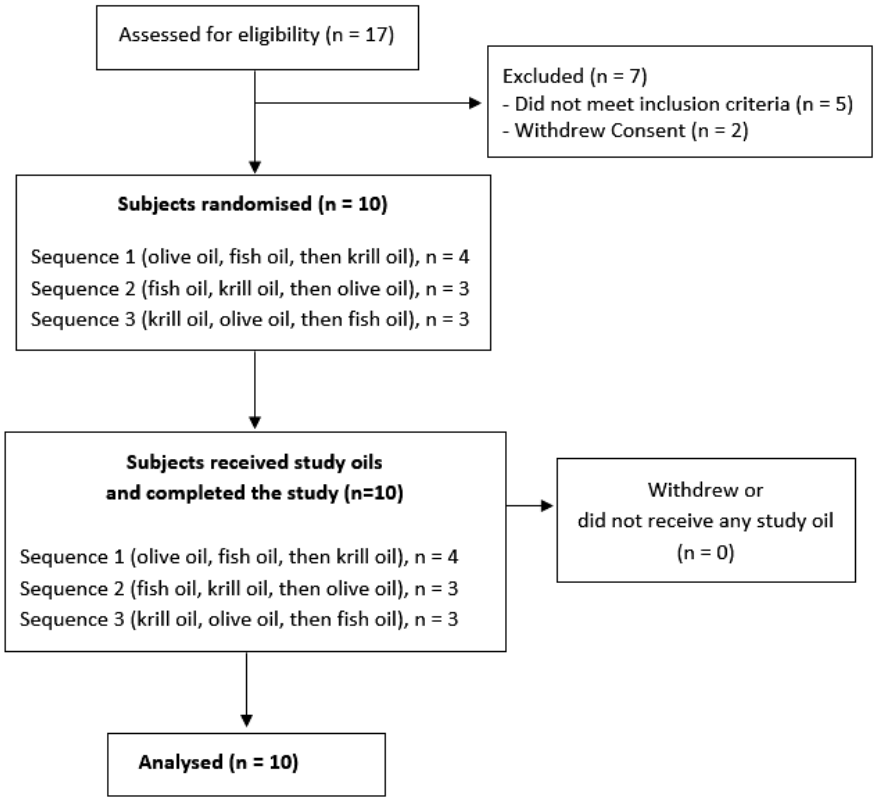

Figure 1. Flow chart of study design. Each participant, in a random order, received each of the three treatments (olive oil, krill oil, or fish oil). There was a seven-day washout between each test meal.

considerations. All participants finished the test meal, including the capsules, within 15 min and they were only allowed to drink water during the intervention period of 5 h. After the test meal consumption, postprandial blood samples (10 mL) were collected at every hour for 5 h, thus making a total of six blood samples per participant per test meal.

Study oils

The study oils including krill oil and fish oil capsules (both products from Swisse Wellness Pty Ltd., Melbourne, VIC, Australia) were purchased from the local pharmacy. The fatty acid profile of these oils was analysed using the gas chromatography (GC) prior to the commencement of intervention. The participants consumed study oils 5 × 1 g krill oil capsules or 5 × 1 g fish oil capsules, which equated to a total EPA, DPA, and DHA intakes of 907 mg for the krill oil and 1441 mg for fish oil, as shown in Table 1. The equal number of oil capsules was provided with the intention of having participants blinded. The single capsule fill weight was 1054 mg for krill oil and 1063 mg for fish oil, and these values were used to calculate the EPA, DPA, and DHA contents. As expected, the olive oil was rich in oleic acid (79%) and devoid of LC n-3 PUFA. The krill oil and fish oil were typical of such oils, as reported in the literature, and contained 18% and 29% of total LC n-3 PUFA, respectively.

Dietary assessment

Dietary records using a 24 h recall form were analysed to identify the LC n-3 PUFA intake using FoodWorks version 8 (Xyris software, Brisbane, QLD, Australia) with NUTTAB 2010 and AUSNUT 2013 based on Australian Food Composition Database. LC n-3 PUFA intake of each participant was monitored throughout the study period using a 24 h dietary recall each time when the partic-

Table 1. LC n-3 PUFA in study oils

	Krill oil		Fish oil	
	Per capsule	5 capsules	Per capsule	5 capsules
LA (18:2n-6), mg	13.3 (0.2)	67	11.9 (0.2)	60
ALA (18:3n-3), mg	7.2 (0.2)	36	6.6 (0.1)	33
AA (20:4n-6), mg	6.6 (0.5)	33	14.7 (0.8)	74
EPA (20:5n-3), mg	108.4 (1.4)	542	157.3 (2.6)	786
DPA (22:5n-3), mg	13.4 (1.0)	67	36.3 (5.0)	182
DHA (22:6 n-3), mg	59.5 (0.8)	298	94.6 (2.7)	473
Total LC n-3 PUFA, mg	181.3	907	288.2	1441

AA: arachidonic acid; ALA: alpha linoleic acid; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; DPA: docosapentaenoic acid; LA: linoleic acid.

Values are expressed as mean (±SE) of five randomly chosen oil capsules mixed together and analysed six times using GC. The total LC n-3 PUFA represents the sum of EPA, DHA, and DPA.

ipant visited the clinic.

Identification of lipids in dietary oils

The lipid classes of test oils were analysed using thin-layer chromatography (TLC) on silica gel 60 plates (Merck, Darmstadt, Germany) together with a standard (Nu-Chek Prep Inc., C18-5A) using the solvent mixture petroleum ether: diethyl ether: acetic acid (85:15:2, v/v/v). The solvent was allowed to equilibrate for at least 20 min prior to use. The samples were spotted on silica gel 60 TLC plates and allowed to develop to within 2 cm of the top of TLC plate. The plates were removed and air-dried, then sprayed with a solution of dichlorofluorescein in methanol (0.05%) and viewed under a UV light.[32] The only major lipid classes observed in olive oil and fish oil were TAG, with a minor band in the sterol region in the case of fish oil; in contrast, the krill oil had an obvious band in TAG region, a weak band in the free fatty acid (FFA) region, and a distinct band at the origin which is where phospholipids remain in this solvent system (data not shown).

Plasma fatty acid analysis

Modified transesterification method of Lepage and Roy[33] was used in this study. Briefly, 200 μL blood samples were mixed with an internal standard, heneicosanoic acid, C21:0 (Nu-Chek Prep, Inc., Elysian, MN, USA) in methanol: toluene (4:1 (v/v)) and then reacted with 200 μL of acetyl chloride for 1 h at 100 °C to form fatty acid methyl ester (FAME). Then 5 mL of 6% potassium carbonate (K_2CO_3) in distilled water was added and the blend was thoroughly vortexed prior to centrifugation at 3000 × g for 10 min to separate the layers. The toluene-rich layer was removed and evaporated to dryness under nitrogen gas, and the FAME was then dissolved in petroleum spirit.

The resulting FAME was separated by GC (Varian Star 3400Cx, Agilent Technologies, CA, USA) equipped with an SGE BPX 70 capillary column (60 m × 0.25 mm internal diameter, 0.25 μm film thickness) (SGE Analytical Science, Melbourne, Australia), and a flame ionization detector (FID). 2 μL of samples were injected in splitting mode (1:10) with helium as the carrier gas. The FAME was identified by comparison with a standard FAME mixture, GLC reference standard 403 (Nu-Chek Prep, Inc., Elysian, MN, USA).

Lipid fractions of plasma

Total lipids were extracted from plasma as described by Ghasemifard et al[34] and then TAG and phospholipid were isolated by thin layer chromatography (TLC). In brief, 700 μL of plasma was mixed with 3.5 mL of dichloromethane: methanol (2:1, v/v) containing 0.01 mg butylated hydroxytoluene and reference internal lipid standards, triheptadecanoin, C17:0 (NuChek Prep, Inc., Elysian, MN, USA) and 1, 2-diheptadecanoyl-sn-glycero-3-phosphocholine, C17:0 (Avanti Polar Lipids, Alabaster, AL, USA). Isolated TAG and PL fractions from the TLC plates were transmethylated with 5% H2SO4 in methanol prior to fatty acid methyl ester (FAME) analysis by GC as described above. Due to time constraint, samples from four of the 10 participants were randomly chosen for analysis of lipid fractions to assess the impact of krill oil, fish oil, and olive oil.

Isolation of plasma and chylomicrons

EDTA blood samples were centrifuged at 3000× g at 4 °C for 10 min to obtain plasma. 2.7 mL of the EDTA plasma was overlaid with 2.4 mL saline solution (density =1.006 kg/L) to obtain chylomicron. Fractions were spun using ultracentrifugation at 36,000× g at 22 °C for 30 min (Sigma 3-30K).[35,36] The top layer (approx. 1.5 mL) was aspirated to remove the chylomicron fraction. All plasma and chylomicron samples were aliquoted into cryotubes and kept at −80 °C until further analysis.

Plasma lipid profiles and blood glucose

The concentration of total cholesterol, TAG, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) in plasma, and the concentration of total cholesterol and TAG in the isolated chylomicron were measured using a Thermo Fisher Indiko™ auto-biochemistry analyser by enzymatic colorimetric methods using commercially available kits (CHOL, Triglycerides, Glucose HK, HDL A B) as per the manufacturer's instructions (Thermo Fisher Scientific Inc., Melbourne, VIC, Australia).

Statistical analysis

The power calculation to determine the minimum number of participants to detect a difference in plasma LC n-3 PUFA, plasma TAG based on a previous postprandial study[19] was 6, using a two tailed *t*-test at the 5% significance level for a power of 90%. Data were expressed as means ± standard error of the mean (SE) except for participant characteristics (mean±standard deviation). All data were analysed using SPSS version 22 and GraphPad Prism version 6.04. Distributions of data were also analysed for normality prior to data analysis. Postprandial plasma fatty acids were analysed to determine the significant effects of oil consumption on changes from baseline by time, test meal, and interaction between the time and test meal using two-way analysis of variance (ANOVA) for repeated measures, and post-hoc analysis was undertaken using the Tukey test. The net incremental area under the curve from baseline (net iAUC) over the postprandial period was calculated using the trapezoid rule and comparison between the net iAUC of test meals was performed using one-way ANOVA for repeated measures and the Tukey test for post-hoc comparison. $p<0.05$ was considered significant.

RESULTS

Participant characteristics and intake of dietary LC n-3 PUFA at baseline

The 10 healthy women who completed the crossover study with three test meals had a mean age of 28.5±9.3 years, systolic blood pressure (113±10.9 mmHg) and diastolic blood pressure (70.8±9.9 mmHg) with a BMI of 25.8±3.6 (kg/m^2). All participants completed a 24 h dietary recall on each study day, which was analysed using FoodWorks version 8. The daily intake of LC n-3 PUFA from the 24 h recall was 106±91.0 mg. There was no significant difference in LC n-3 PUFA intakes from food for each participant between the study days.

Plasma fatty acid composition

The participant's baseline concentrations of EPA, DHA or DPA in plasma were not significantly different among the three test meals. EPA concentrations significantly rose after krill oil and fish oil consumption compared with olive oil consumption and reached steady state by 2 h as shown in Figure 2. There was a significant difference in EPA concentrations between krill oil and fish oil consumption at 4 h. As expected, no significant changes in the proportion of EPA were observed following olive oil consumption.

There were no consistent increases in DHA following krill oil and fish oil consumption (Figure 2). There was a significant difference between krill oil and olive oil at 5 h (p=0.010), and between fish oil and olive at 1 h (p<0.01) and 5 h (p=0.027). There was a significant difference in DHA between krill oil and fish oil at 2 h (p=0.040). The proportions of DPA after krill oil and fish oil consumption were not significantly different from each other or from olive oil, apart from at 5 h of krill oil consumption which was significantly greater in comparison with olive oil (p=0.026).

There were no significant effects of diet intervention on the concentration of plasma AA between three test meals. The concentrations of plasma AA showed significant differences between krill oil and fish oil consumption at 3 h (p=0.043). The concentrations of linoleic acid (LA) and oleic acid (OA) after krill oil and fish oil consumption were not significantly different from each other or from olive oil. There was one exception at 2 h with fish oil consumption resulting in significantly greater concentrations in comparison with olive oil (p=0.039).

The postprandial net iAUC values of EPA in both krill oil and fish oil groups were significantly different from the olive oil group (p=0.010 and p=0.017, respectively), however, there was no significant difference between krill oil and fish oil groups (p=0.850) (Figure 2). While the net iAUC for the fish oil group was not significantly different from the krill oil, the fish oil group had a 12% higher value than the krill oil group (p>0.05). The net iAUC values for the total n-3 PUFA (EPA, DPA, and DHA) were significantly greater after krill oil and fish oil consumption compared with olive oil consumption (p<0.001), however there was no significant difference between krill oil and fish oil groups (p=0.980) (Figure 2).

Plasma fatty acid composition in TAG and PL

The plasma LC PUFA in TAG and PL fractions from four

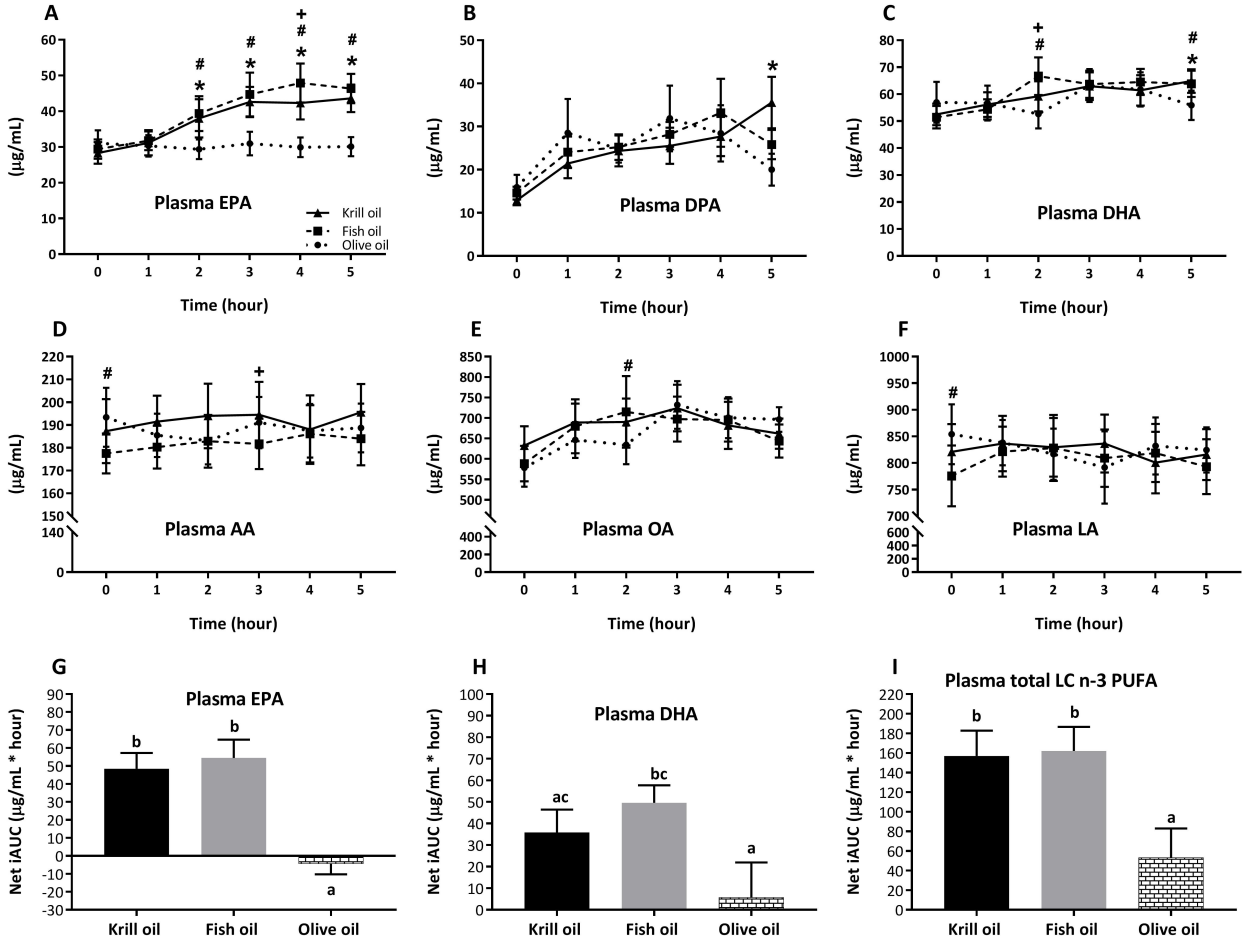

Figure 2. Postprandial changes in plasma oleic acid and polyunsaturated fatty acid concentrations after consuming test meals containing krill oil, fish oil or olive oil (control). (A) plasma EPA; (B) plasma DPA; (C) plasma DHA; (D) plasma AA; (E) plasma OA; (F) plasma LA; (G) net incremental area under the curve (net iAUC) of plasma EPA; (H) net iAUC of plasma DHA; (I) net iAUC of total LC n-3 PUFA including EPA, DHA, and DPA. Values are expressed as mean ± SEM for 10 participants. # and * in graphs (A) and (C), indicate significant differences between fish oil (#) or krill oil (*) and olive oil (p<0.05) consumptions. Different superscripts in graphs G-I represent significant difference among the test meal consumptions. AA, arachidonic acid; EPA, eicosapentaenoic acid; DPA, docosapentaenoic acid; DHA, docosahexaenoic acid; LA, linoleic acid; OA, oleic acid.

randomly selected participants, were analysed and the data are shown in Figure 3. In the fish oil group for plasma TAG, there was a trend (non-significant) for the EPA and DHA to increase with time (data not shown). This was reflected in the net iAUC (panels A and B Figure 3). In the krill oil group for plasma PL fraction, there was a trend for both EPA and DHA to increase with time (data not shown). This was reflected in the net iAUC (panels C and D Figure 3).

Postprandial plasma and chylomicron lipids

The baseline total cholesterol, TAG, HDL, LDL, and glucose in plasma and chylomicron were not significantly different between test meals (Tables 2 and 3). There were no significant effects of the test meals on plasma lipids and glucose, although there were significant time effects on all parameters (cholesterol, TAG, LDL, HDL, and glucose) in plasma, and cholesterol and TAG in chylomicron (Table 2 and Table 3). Plasma TAG increased after 1 to 3 h consumption for all three test meals, however these changes were not statistically significant (Table 2). There were also no significant effects of the test meals on chylomicron lipids and glucose (only cholesterol and TAG presented in Table 3) except for fish oil consumption, which resulted in significantly higher TAG at 1 and 2 h ($p<0.05$). By 4 h, the TAG in chylomicron had returned to the baseline. The net iAUC values of changes in lipids and glucose in plasma and chylomicron were also not significantly different between the test meals (data not shown).

DISCUSSION

This crossover study investigated the postprandial LC n-3 PUFA responses to krill oil and fish oil consumption in healthy women, in a randomised crossover design. In order to maintain the participants being blinded to which treatment they were taking, the study design provided either 5 capsules (5 g) of krill oil or 5 capsules (5 g) of fish oil to participants. This design resulted in a 31% lower dose of EPA and 37% lower dose of total LC n-3 PUFA dose from krill oil than fish oil in the breakfast meal (542 mg EPA and 907 mg LC n-3 PUFA from krill oil versus 786 mg EPA and 1441 mg LC n-3 PUFA from fish oil).

The main finding from this study was that the plasma EPA rose to the similar extent after krill oil and fish oil consumption (Figure 2). Neither DHA nor DPA showed significant elevations over the course of the study. Other postprandial studies comparing the effects of krill oil and fish oil have shown that in the first 72 hours, the EPA incorporation into plasma lipids occurred more efficiently compared with DHA.[24] While there is no clear explanation for this result, apart from differences in the turnover rates of EPA and DHA in plasma lipid fractions, the increase in EPA over the 5-hour postprandial period at the present study is consistent with those studies. It is unlikely that the EPA arose from endogenous ALA metabolism. Firstly, the EPA content of the capsules was 15 to 21 times greater than the ALA content. Secondly, the ratio of LA to ALA in the breakfast meal was greater than 16:1, making it unlikely that ALA was significantly metabo-

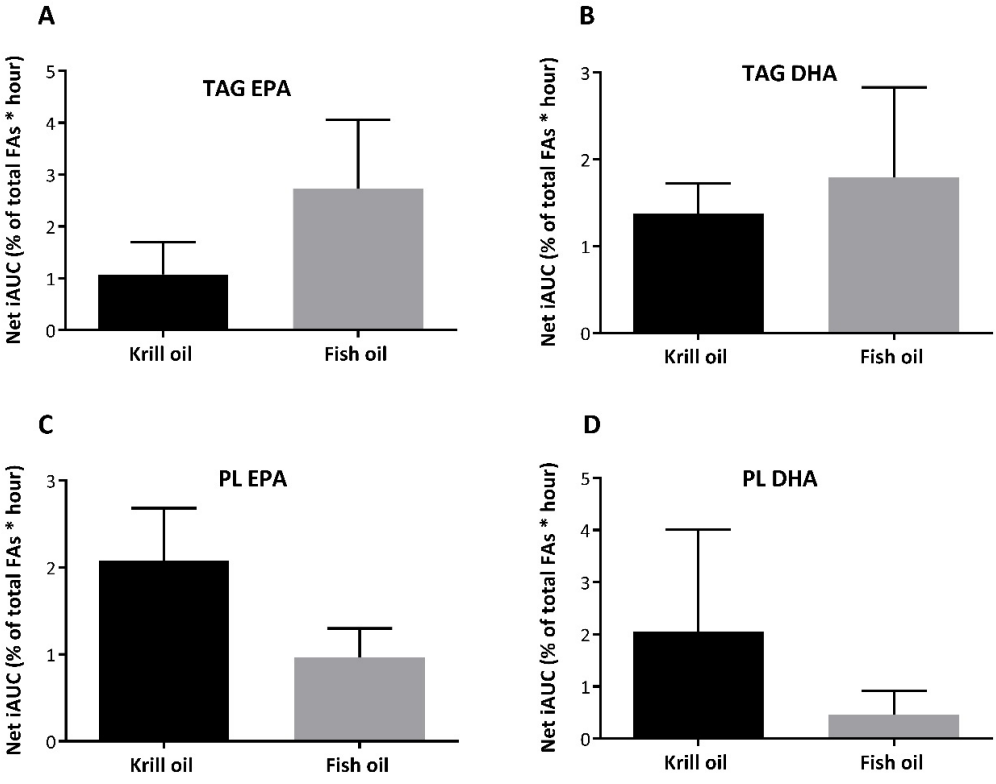

Figure 3. Postprandial changes in EPA and DHA composition in plasma TAG and PL after consuming test meals containing krill oil, fish oil or olive oil (control) (pilot data). (A) Net incremental area under the curve (Net iAUC) of EPA in TAG; (B) Net iAUC of DHA in TAG; (C) Net iAUC of EPA in PL; (D) Net iAUC of DHA in PL. Values of net iAUC from baseline are expressed as % of TAG or PL fatty acids * hour (mean ± SEM) for 4 participants. There were no significant differences observed between krill oil and fish oil consumption over the 5-hour postprandial period. TAG, triglyceride; PL, phospholipids

Table 2. Postprandial changes in plasma lipids and glucose

mmol/L	Test meal	Time 0	Time 1	Time 2	Time 3	Time 4	Time 5	*p* value	
Cholesterol	Olive oil	5.1 (0.2)	4.9 (0.2)	4.8 (0.2)*	4.8 (0.2)*	4.8 (0.2)*	4.8 (0.2)	Time	0.042
	Fish oil	4.8 (0.2)	4.7 (0.2)	4.7 (0.2)	4.7 (0.2)	4.8 (0.2)	4.8 (0.2)	Meal	0.428
	Krill oil	4.9 (0.2)	4.9 (0.2)	4.7 (0.2)	4.9 (0.2)	4.9 (0.2)	4.9 (0.2)	Interaction	0.213
TAG	Olive oil	0.9 (0.1)	1.0 (0.2)	1.0 (0.2)	1.0 (0.2)	1.0 (0.2)	0.9 (0.2)	Time	0.005
	Fish oil	1.0 (0.1)	1.2 (0.2)	1.2 (0.2)	1.1 (0.2)	1.0 (0.1)	0.9 (0.1)	Meal	0.477
	Krill oil	1.0 (0.1)	1.2 (0.2)	1.1 (0.2)	1.1 (0.2)	1.0 (0.1)	0.9 (0.1)	Interaction	0.628
LDL	Olive oil	3.3 (0.2)	3.1 (0.1)*	3.0 (0.1)*	3.1 (0.1)*	3.1 (0.1)*	3.1 (0.2)	Time	0.000
	Fish oil	3.0 (0.1)	2.8 (0.1)	2.8 (0.1)	2.9 (0.1)	3.0 (0.2)	3.0 (0.2)	Meal	0.096
	Krill oil	3.0 (0.1)	3.0 (0.1)	2.9 (0.1)	3.0 (0.2)	3.1 (0.1)	3.1 (0.1)	Interaction	0.069
HDL	Olive oil	1.4 (0.1)	1.3 (0.1)	1.3 (0.1)*	1.3 (0.1)*	1.3 (0.1)*	1.3 (0.1)*	Time	0.000
	Fish oil	1.4 (0.1)	1.4 (0.1)*	1.3 (0.1)*	1.3 (0.1)*	1.4 (0.1)*	1.4 (0.1)	Meal	0.227
	Krill oil	1.4 (0.1)	1.4 (0.1)	1.3 (0.1)	1.4 (0.1)	1.3 (0.1)	1.4 (0.1)	Interaction	0.801
Glucose	Olive oil	5.4 (0.1)	6.0 (0.4)	5.2 (0.2)	4.9 (0.1)	5.0 (0.1)	5.0 (0.1)	Time	0.000
	Fish oil	5.4 (0.2)	5.8 (0.2)	5.2 (0.2)	5.2 (0.2)	5.2 (0.1)	5.1 (0.1)	Meal	0.674
	Krill oil	5.4 (0.1)	6.1 (0.4)*	5.4 (0.1)	5.1 (0.1)	5.1 (0.1)	5.0 (0.1)	Interaction	0.540

TAG: triglycerides; LDL: low-density lipoprotein cholesterol; HDL: high-density lipoprotein cholesterol.
Values are expressed as mean (±SE) for 10 women.
*Significant difference ($p<0.05$) compared with the baseline for each test meal.

Table 3. Postprandial changes in chylomicron lipids

mmol/L	Test meal	Time 0	Time 1	Time 2	Time 3	Time 4	Time 5	*p* value	
Cholesterol	Olive oil	2.2 (0.2)	2.1 (0.2)	2.2 (0.1)	2.3 (0.2)	2.1 (0.2)	2.4 (0.1)	Time	0.555
	Fish oil	2.1 (0.2)	2.3 (0.1)	2.3 (0.2)	2.1 (0.1)	2.0)0.5)	2.2 (0.1)	Meal	0.107
	Krill oil	2.4 (0.1)	2.4 (0.1)	2.4 (0.2)	2.3 (0.2)	2.3 (0.2)	2.4 (0.1)	Interaction	0.870
TAG	Olive oil	0.4 (0.1)	0.7 (0.1)	0.6 (0.1)	0.7 (0.1)	0.5 (0.1)	0.6 (0.1)	Time	0.001
	Fish oil	0.6 (0.2)	0.9 (0.2)*	0.8 (0.2)*	0.7 (0.1)	0.6 (0.1)	0.5 (0.1)	Meal	0.541
	Krill oil	0.6 (0.1)	0.8 (0.1)	0.7 (0.1)	0.7 (0.1)	0.6 (0.1)	0.5 (0.1)	Interaction	0.254

TAG: triglycerides.
Values are expressed as mean (±SE) for 10 women.
*Significant difference ($p<0.05$) compared with the baseline for each test meal.

lised to EPA in this study.

There are a number of possible explanations why a 31% lower dose of EPA from krill oil compared with fish oil could result in a similar concentration of plasma EPA. Firstly, while there was a 12% higher net iAUC for EPA in the fish oil group, this was not significantly different to the krill oil group. It is possible that with a higher number of participants a significant difference might have been found in the study. Secondly, in krill oil, it has been reported that EPA is mainly found in the free fatty acids and phospholipids (phosphatidycholine and phosphatidylethanolamine) compared with fish oils where the EPA is in the TAG.[22] The digestion and absorption of fatty acids from PL and TAG do not follow identical pathways, as reported in previous studies.[37-39] These authors proposed that dietary phospholipids might be transported into the bloodstream, following digestion and absorption, in chylomicrons, HDL or as lyso-phospholipids bound to albumin. In contrast, dietary TAG fatty acids are mostly transported via chylomicrons, followed by uptake in the liver and redistribution of the TAG fatty acids into different lipids of exported lipoproteins (very low-density lipoproteins, etc.).[37-39] There have been no available studies looking at these different digestion and absorption possibilities for LC n-3 PUFA from krill oil, however we suggest that over the time of 5 h postprandial period, the EPA from the krill oil lipids may be more efficiently digested and absorbed than EPA from fish oil TAG, resulting in a similar short-term EPA concentration (bioavailability) in plasma lipids.

Krill oil also contains a higher level of free fatty acids (FFA) compared with fish oil.[22] FFA have been shown to result in an increased apparent bioavailability compared with esterified forms of LC n-3 PUFA.[28] While no mechanisms have been established, it has been suggested the reason is that pancreatic lipase has a significantly reduced efficiency towards hydrolysis of EPA and DHA from fish oils.[40] Thus, both the free fatty acids and phospholipids from krill oil might contribute to the increased short-term uptake of EPA into plasma lipids compared with fish oil, which might help to explain the present results.

In the current study, we examined EPA, DPA, and DHA levels in plasma TAG and PL in four of the participants and these preliminary data revealed that EPA from krill oil was mainly taken up in the PL fraction while EPA from fish oil was found mainly in the TAG fraction, highlighting that in the postprandial period EPA from oils rich in TAG (fish oil) or rich in PL and FFA (krill oil) are not incorporated into plasma lipids in the same manner. It is possible that such differences might contribute to an explanation of why a 31% lower EPA dose from krill oil might lead to the similar total plasma concentration of EPA over the 5 h postprandial period in this study. Further studies are required to understand the fate and rate

of incorporation of LC n-3 PUFA from dietary PL.

These data over the 5-hour postprandial period do not mean that studies conducted over longer periods such as 4+ weeks would yield the same results. For example, it has been reported that short-term (postprandial studies) may reveal different effects compared with longer-term studies (weeks), in terms of incorporation of LC n-3 PUFA into plasma lipid fractions. Studies by Sadou et al[42] and Cook et al[43] reported that uptake of LC n-3 PUFA into plasma lipids in the postprandial period (<12 h) did not mirror the data after more than four weeks of PUFA ingestion. Sadou et al[41] found that at 8 h, the EPA level in plasma PL was only 67% of the plasma TAG EPA levels, while at 30 days the plasma PL EPA levels were 329% of the TAG EPA value. Cook et al[42] showed that significant differences in uptake of LC n-3 PUFA between plasma PL and TAG fractions observed at 12 h postprandially were not evident after two weeks, at which time incorporation of LC n-3 PUFA into plasma phosphatidylcholine was not significantly different between plasma TAG and PL fractions. A possible explanation is that the plasma levels of a fatty acid in short-term (postprandial state) are a function of absorption efficiency and tissue uptake or metabolism. In longer-term, the plasma level of fatty acids is governed by these factors as well as by the incorporation into tissues and turnover of the LC n-3 PUFA. The n-3 index is regarded as the most reliable marker of LC n-3 PUFA in tissue stores, and it has been reported to be inversely associated with the cardiometabolic risks.[43] Further long term studies measuring the n-3 index are highly recommended in order to better understand the potential health benefits of krill oil consumption.

In the present study, the plasma EPA reached a plateau (steady state) at 3 h, however Schuchardt et al[17] showed that EPA concentrations in plasma PL increased steadily from the baseline up to 8 h postprandially for both krill oil and fish oil groups. Kohler et al[25] reported similar findings, in that EPA levels rose after krill oil or fish oil consumption, and that the Tmax for plasma TAG EPA was approximately 10 h and for plasma TAG DHA was approximately 20 h. In contrast, in their study, the Tmax for plasma PL EPA was between 16 h and 25 h, while that for plasma PL DHA was between 48 h and 55 h. This indicates that studies of short duration, such as the present study, do not necessarily give sufficient information to make adequate comparisons between krill oil and fish oil, since the Tmax values for EPA were reported to be between 10 h and 20 h in plasma lipid fractions.[26] In the future, studies of a longer duration should be considered. However, such studies are likely to be less controlled and have significant practical issues such as what foods should be allowed to consume for subsequent meals after the test breakfast (lunch, dinner, etc.).

The data from Kohler et al[25] also indicated differences in the incorporation of LC n-3 PUFA between krill oil and fish oil in the plasma PL and TAG fractions. They found that over the 72 h of the study, there was a significantly greater (1.5 times, $p<0.003$) incremental area under the curve (iAUC) for EPA plus DHA in plasma PL after krill oil consumption compared with fish oil consumption, whereas the iAUC for EPA plus DHA was not different between the two oils in plasma TAG. The present study also showed a trend for increased net iAUC for LC n-3 PUFA in plasma PL for krill oil compared with fish oil, although the results are limited by the small number of participants. A higher incorporation of EPA into plasma PL from krill oil consumption compared with fish oil consumption has been reported by Kohler et al.[17, 25] Consistently, Lemaitre-Delaunay et al[44] have reported differential labelling of plasma lipid fractions over a 6 h period for 13C-DHA administered in phosphatidylcholine form or TAG form. Those data support the idea that PUFA bound to PL or TAG are not digested, absorbed, and subsequently metabolised via identical pathways.

In the present study and those by Kohler et al[25] and Schuchardt et al,[17] it was clear that there was considerable variability between the individual responses of participants to the treatments. It appears from the literature that the inter-participant variability in response to the treatments occurs in both genders and different age groups. The present study included young women, while the study of Schuchardt et al[17] focused on young male participants, and that of Kohler et al[25] looked at the older male and female participants. Ghasemifard et al[28] reviewed in detail the factors which could influence the apparent bioavailability of LC n-3 PUFA. These included matrix of the food, fat content of the test meal, age, gender, dose rate, absorption efficiency (faecal loss), and body weight of the participants. Typically, in studies comparing krill oil and fish oil, these factors are not controlled for and presumably contribute to the inter-participant variability.

The present study has strengths in that it was a randomised crossover postprandial study conducted in a controlled location, which included a control group (olive oil) and was conducted with women participants who were all of a similar age. Nonetheless, that we have not studied men is a limitation. The single gender design was intended to minimise variations between participants. Available studies have either not been gender-specific or of men with large inter-participant variations. The present study, with its focus on young women, was more likely to provide useful information on fatty acid bioavailability from krill compared with fish oil. However, it is acknowledged that the study had several limitations which included being a short time frame (5 h), having a small number of participants (n=10), with participants not totally blinded to test meals (capsule contents have a different colour), and the dose of total LC n-3 PUFA for krill oil being 37% lower than for fish oil. It is possible that the small participant number has obscured the differences between krill oil and fish oil supplementations. Further studies with a larger number of participants are required to determine whether there is a significant difference in the postprandial plasma EPA concentrations between the consumption of two marine oils. It is also important to analyse the lipid fractions in plasma using novel approaches, such as lipidomics, in order to assess the incorporation of the LC n-3 fatty acids into the very large number of molecular species of different lipids which exist in plasma.[45] It is worth noting that, as discussed by Ghasemifard et al,[28] a higher plasma concentration does not necessarily equate to a higher 'bioavailability', since for true bioavailability the faecal losses must be determined. Despite this, most stud-

ies comparing krill oil and fish oil use the term bioavailability.

Conclusions

In this study, we have found that, in young women, 5 g of krill oil supplementation resulted in similarly high plasma EPA concentrations to the same amount of fish oil over a 5-hour postprandial period, despite krill oil containing 31% lower EPA than the fish oil. This is relevant to consumers who are likely choose to consume an equal number of capsules of krill oil or fish oil rather than choose the dose of LC n-3 PUFA. These results suggest that EPA from krill oil may be more efficiently incorporated into plasma due to the high content of phospholipids and free fatty acids in this oil. Further large long-term studies are warranted to determine the impact of krill oil supplementation on long-term tissue stores and the consequential clinical benefits in comparison with fish oil.

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AUTHOR DISCLOSURES

The authors declare no conflict of interest.

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