

Comparison of bioavailability of krill oil versus fish oil and health effect

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Background: The aim of this review is to summarize the effects of krill oil (KO) or fish oil (FO) on eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) incorporation in plasma phospholipids or membrane of red blood cells (RBCs) as shown in human and animal studies. Furthermore, we discuss the findings in relation to the possible different health effects, focusing on lipids, inflammatory markers, cardiovascular disease risk, and biological functions of these two sources of long-chain n-3 polyunsaturated fatty acids (PUFAs).

Methods: A literature search was conducted in PubMed in January 2015. In total, 113 articles were identified, but based on selection criteria, 14 original papers were included in the review.

Results: Studies on bioavailability of EPA and DHA from KO and FO in humans and animals are limited and the interpretation is difficult, as different amounts of EPA and DHA have been used, duration of intervention differs, and different study groups have been included. Two human studies – one postprandial study and one intervention study – used the same amount of EPA and DHA from KO or FO, and they both showed that the bioavailability of EPA and DHA from KO seems to be higher than that from FO. Limited effects of KO and FO on lipids and inflammatory markers in human and animal studies were reported. Gene expression data from animal studies showed that FO upregulated the cholesterol synthesis pathway, which was the opposite of the effect mediated by KO. KO also regulated far more metabolic pathways than FO, which may indicate different biological effects of KO and FO.

Conclusion: There seems to be a difference in bioavailability of EPA and DHA after intake of KO and FO, but more studies are needed before a firm conclusion can be made. It is also necessary to document the beneficial health effects of KO with more human studies and to elucidate if these effects differ from those after regular fish and FO intake.

Keywords: human studies, animal studies, gene expression, cardiovascular disease, long-chain polyunsaturated fatty acids, inflammation, lipid metabolism

Introduction

Fish consumption reduces the risk of developing cardiovascular disease (CVD) and CVD mortality.^{1,2} Intervention trials with fish and fish oil (FO) have shown reduced total mortality and CVD risk.³⁻⁶ Fatty fish and FO are rich in long-chain n-3 polyunsaturated fatty acids (PUFAs), namely, eicosapentaenoic acid (EPA, 20:5 n-3) and docosahexaenoic acid (DHA, 22:6 n-3). One of the beneficial health effects of long-chain n-3 PUFAs may be mediated by reduction in plasma triglycerides (TGs).⁷ The effect of long-chain n-3 PUFAs on inflammation is uncertain.^{8,9}

The American Heart Association dietary guidelines for long-chain n-3 PUFAs and fish intake for primary prevention of coronary diseases are two servings of fatty fish

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per week.⁹ This recommendation will provide an amount of 250–500 mg EPA + DHA per day.¹⁰ A food-based approach for achieving adequate intake of long-chain n-3 PUFAs is recommended.¹¹ However, for individuals who do not like fish or for other reasons choose not to include fish in their diet, nutritional supplements may be a good alternative for supply of long-chain n-3 PUFAs.

Because fish is a restricted resource, there is a growing interest in exploiting alternative sources of long-chain n-3 PUFAs. Krill oil (KO) is extracted from Antarctic krill (*Euphausia superba*), which is a rich source of long-chain n-3 PUFAs. Krill is by far the most dominant member of the Antarctic zooplankton community in terms of biomass and, thus, attractive for commercial harvest. Persistent organic pollutants (POPs) accumulate in marine ecosystems and in the lipid reserve of organisms, and these are efficiently removed from FO through processing and purification.¹² Limited data exist if the content of POPs in FO and KO are comparable. In a recent study,¹³ a comparison between the toxicological profiles of KO and FO products showed that the two KO products included in the study were ranked as containing intermediate levels of POP contaminants when compared overall to the FO products analyzed in the study.

Both FO and KO contain a high proportion of EPA and DHA, but in contrast to FO, KO contains a major part of these fatty acids in the form of phospholipids (PLs) (mainly phosphatidylcholine).¹⁴ In fish, the fatty acids are mainly stored as TGs, whereas in krills, 30%–65% of the fatty acids are incorporated into PLs.¹⁴ Whether fatty acid esterification in TGs or PLs has impact on the efficiency of absorption of the fatty acids into the blood and on serum lipid levels are issues for discussion. Because PLs comprise the structure of cell membranes, long-chain n-3 PUFAs in the form of PLs might facilitate the passage of fatty acids through the intestinal wall and increase the bioavailability of these fatty acids in KO, compared to when they are consumed from FO. The overall fatty acid composition in KO resembles that of FO, but the EPA content is higher.¹⁴ This makes the ratio between EPA and DHA different between KO and FO. FO often has a ratio of approximately 1:1, while KO has a ratio of 2:1.¹⁵ The functional similarity of EPA and DHA lies in their ability to alter cell membrane PL fatty acid composition, disrupt lipid rafts and signal transduction, and regulate gene expression, either directly by activating transcription factors such as peroxisome proliferator-activated receptors or by activating membrane-bound receptors such as the G protein-coupled receptor GPR120.¹⁶ The functional difference between EPA and DHA is in the synthesis of eicosanoids (prostaglandins,

thromboxanes, and leukotrienes), whereby they compete with arachidonic acid (AA, 20:4, n-6) as a substrate for cyclooxygenase and lipoxygenase, which gives rise to different biological responses.¹⁷ Additionally, EPA gives rise to E-series resolvins and DHA gives rise to D-series resolvins and protectins, which are anti-inflammatory mediators, which may also explain the different biological responses of EPA and DHA.¹⁷

In addition to long-chain n-3 PUFAs, KO also contains the antioxidant astaxanthin, which may have a possible health effect.¹⁸ Whether these differences in EPA and DHA levels and astaxanthin can mediate the different biological functions of FO and KO remains unclear.

The aim of this review is to summarize the effects of long-chain n-3 PUFAs after intake of KO or FO on EPA and DHA incorporation in plasma PLs or membrane of red blood cells (RBCs) in humans and animals. Furthermore, we aim to discuss the findings in relation to the possible different health effects, focusing on lipids, inflammatory markers, CVD risk, and biological function of these two sources of long-chain n-3 PUFAs.

Methods for selection of studies from the literature

A literature search was conducted in PubMed in January 2015 using the following terms: “[krill oil and absorption], [krill oil and bioavailability], [krill oil and health effects], [krill oil and omega-3], and [krill oil and n-3].” In total, 113 articles were identified, but after removing duplicates and studies not including KO in human or animal experiments, 45 papers were screened by reading abstracts. In total, 31 studies were excluded based on the following criteria: not an original paper (n=13), not using FO and KO in the same study (n=14), and health effects other than lipid levels, inflammation, and endocannabinoid levels (n=4). In total, 14 original papers were included in the review. Among these, seven were clinical trials and seven were animal studies. The search was limited to English literature and the search was conducted to obtain any literature published before January 2015. One of the researchers performed the literature search and both of the researchers independently extracted the data.

Results

Human studies

Seven human randomized trials – five double-blind^{19–23} and two open-label^{15,24} ones – investigating the effects of KO compared with FO were identified (Table 1). Three of the studies^{19,21,24} included healthy subjects (between 20 years

and 50 years), two studies^{20,22} included healthy overweight or obese subjects (35–64 years), and two studies^{15,23} included healthy subjects with normal or slightly elevated lipid levels and patients with hyperlipidemia (mean age: 40–50 years). All but one study (only male in the study by Schuchardt et al²¹) included both male and female subjects.

Two of the studies provided similar amounts of FO and KO, but different amounts of EPA and DHA.^{22,23} Three of the studies compared similar amounts of EPA and DHA in FO and KO,^{19–21} and two studies gave both different amounts of oil and EPA and DHA.^{15,24} In two of the studies, the effect of different forms (triglyceride, ethyl ester and phospholipid forms) of EPA and DHA was compared.^{21,24} One study²¹ was a postprandial study lasting up to 72 hours after intake, whereas the intervention period in the remaining studies ranged from 4 weeks to 12 weeks.

Bioavailability

Five of the seven studies reported effects of these oils on bioavailability and/or plasma fatty acid composition of EPA and DHA.^{15,19,21,22,24} Ramprasath et al¹⁹ administered similar amounts of EPA and DHA (600 mg EPA and DHA) as KO or FO to 24 healthy subjects in a 4-week crossover trial. They showed that consumption of both KO and FO increased plasma EPA and DHA levels, plasma levels of total n-3 fatty acids, level of RBC EPA, and the sum of EPA and DHA concentrations in RBCs (omega-3 index) compared with control. Intake of KO significantly increased plasma EPA levels, the level of total n-3 PUFAs, the level of RBC EPA, and the omega-3 index to a greater degree compared with FO. The change in omega-3 index after consumption of KO was two-fold higher than that with FO. Maki et al²² administered the same amount of KO and FO, but different amounts of EPA and DHA, in a 4-week randomized controlled trial with 76 overweight and obese men and women. The subjects were given 2 g/d of KO (216 mg/d EPA and 90 mg/d DHA), menhaden oil (MO) (212 mg/d EPA and 178 mg/d DHA), or olive oil (OO). The increase in plasma EPA and DHA concentrations were similar for the KO and MO groups and both were significantly different compared to the control group given OO. Ulven et al¹⁵ administered different doses of KO and FO and different amounts of EPA and DHA in a 7-week randomized trial with 113 subjects with normal or slightly elevated total blood cholesterol and/or TG levels. The subjects were given 3 g/d of KO (EPA + DHA = 543 mg) or 1.8 g/d of FO (EPA + DHA = 864 mg). A third group did not receive any supplementation. They found a significant increase in plasma EPA, DHA, and DPA (docosapentaenoic acid) levels in the

subjects supplemented with both KO and FO compared with the controls, but there were no significant differences in the changes in any of the n-3 PUFAs between the FO and the KO groups despite the difference in n-3 dose. All these results support the hypothesis that EPA and DHA from KO have a better bioavailability compared to those from FO.

In contrast, Laidlaw et al²⁴ administered different amounts of oil, as well as EPA and DHA from four different n-3 supplements, in a 28-day crossover trial with 35 healthy subjects. The four supplements and doses were reesterified TG (rTG) FO (EPA, 650 mg; DHA, 450 mg), ethyl ester (EE) FO (EPA, 756 mg; DHA, 228 mg), PL KO (EPA, 150 mg; DHA, 90 mg), and TG salmon oil (SO) (EPA, 180 mg; DHA, 220 mg). The increase in whole-blood n-3 fatty acids after rTG supplementation was statistically significantly greater than for the other products; moreover, the whole-blood DHA increase, EPA + DHA increase, and EPA increase was greater than the increase of the PL and TG products. When comparing the PL KO and the TG SO groups, which had similar daily intake of EPA (150 mg and 180 mg, respectively), the mean whole-blood EPA percentage increase was almost identical in the two groups, suggesting that the structural form of EPA does not seem to play a role on the bioavailability.

Schuchardt et al²¹ compared the bioavailability of identical doses of EPA + DHA (1,680 mg) from KO to that of other chemical forms of EPA and DHA in a double-blinded crossover postprandial study lasting up to 72 hours after intake. They gave 12 healthy male subjects a single dose of FO capsules consisting either of rTG or of EE or KO capsules consisting of EPA + DHA mainly as PLs. They found that the EPA, DHA, EPA + DHA, and total n-3 fatty acid levels in plasma PLs were higher after the KO treatment compared to the levels after rTG and EE treatment; however, this was not statistically significant, even though a trend was observed for difference in EPA bioavailability between rTG and KO. This may suggest that the bioavailability of EPA and DHA in plasma PLs is higher from KO compared to that from FO.

Plasma lipids

Among the seven studies, four studies reported the effect on plasma TGs and lipoproteins.^{15,19,22,23} In the study by Ramprasath et al,¹⁹ the total cholesterol and low-density lipoprotein (LDL) cholesterol concentrations in the plasma were increased after intake of both KO and FO compared with control, whereas serum TG and high-density lipoprotein (HDL) cholesterol concentrations did not change with any of the treatments. The response on lipoproteins did not differ between the groups in the studies by Maki et al²² and Ulven

Table 1 Human studies with krill oil and fish oil

Study	Study design	Intervention	Amount of n-3 PUFA	Duration	Individuals
Laidlaw et al (2014) ²⁴	Open-label, randomized, crossover study	Four groups: 1) concentrated rTG FO, 2) EE FO, 3) PL KO, and 4) TG SO.	Group 1: EPA, 650 mg; DHA, 450 mg. Group 2: EPA, 756 mg; DHA, 228 mg. Group 3: EPA, 150 mg; DHA, 90 mg. Group 4: EPA, 180 mg; DHA, 220 mg	28-day period, followed by a 4-week washout period	35 healthy subjects (male and female)
Ramprasath et al (2013) ¹⁹	Double-blinded, randomized, placebo-controlled crossover trial	Three treatment groups: 1) KO, 2) FO, and 3) placebo control, CO.	Three treatment groups including KO or FO providing 600 mg of n-3 PUFAs	4 weeks' treatment, with an 8-week washout period	24 healthy volunteers with BMI of 23.8±3 kg/m ²
Ulven et al (2011) ¹⁵	Open single-center, randomized, parallel-group designed study	KO: 3.0 g/d (n=41), FO: 1.8 g/d (n=40) vs no dietary intervention (n=41).	KO: 543 mg EPA + DHA; FO: 864 mg EPA + DHA vs no dietary intervention	7 weeks	113 subjects with normal or slightly elevated total blood cholesterol and/or TG levels
Banni et al (2011) ²⁰	Randomized, double-blind, controlled, parallel clinical trial	2 g/d dose of KO (n=21), MO (n=23), or OO (n=19).	KO: 309 mg/d of EPA/DHA 2:1; MO: 390 mg/d of EPA/DHA 1:1	4 weeks	63 subjects: healthy overweight or obese men and women, with waist circumference of ≥102 cm (men) or ≥88 cm (women)
Schuchardt et al (2011) ²¹	Randomized, double-blind crossover trial	Three EPA + DHA formulations: 1) FO rTGs, 2) FO EEs, and 3) KO (mainly PLs).	Total EPA + DHA intake: 1,680 mg for all three groups. Groups 1 and 2: EPA intake 1,080 mg and DHA intake 672 mg. Group 3: EPA intake 1,050 mg and DHA intake 630 mg	Postprandial study: measurements recorded 2 h, 4 h, 6 h, 8 h, 24 h, 48 h, and 72 h after capsule ingestion	12 healthy young men between 20 years and 50 years and with BMI between 20 kg/m ² and 28 kg/m ²
Maki et al (2009) ²²	Randomized, double-blind parallel-arm trial	Three groups: 1) 2 g/d of KO, 2) 2 g/d MO, and 3) 2 g/d control OO. Four 500 mg capsules per day.	KO: 216 mg/d EPA and 90 mg/d DHA; MO: 212 mg/d EPA and 178 mg/d DHA	4 weeks	76 healthy overweight and obese men and women, 35–64 years of age, with waist circumference of ≥102 cm (men) or ≥88 cm (women)

Age	Fatty acid composition	Lipids	Inflammation and oxidative stress	Other health effects
35±14 years	Higher increase in omega-3 fatty acids after rTG supplementation compared with the PL and TG products. The PL group intake of EPA was similar to that of the TG group, and the whole-blood EPA increase was almost identical.			Intake of rTG was most beneficial in reducing Omega-3 Serum Equivalence Score and the Omega-3 Red Blood Cell Equivalence Score as surrogate markers for cardiovascular risk.
28.2±5.4 years	Both KO and FO increased plasma EPA and DHA levels, plasma levels of total n-3 PUFAs, and RBC EPA level compared with CO. KO increased plasma EPA levels, the level of total n-3 PUFA, RBC EPA level and omega-3 index more compared to FO.	Total and LDL-C concentrations were increased following KO and FO supplementation compared with control. No change in serum TG and HDL-C concentrations with any of the treatments.		
KO: 38.7±11.1 years; FO: 40.3±14.8 years; control: 40.5±12.1 years	A significant increase in plasma EPA, DHA, and DPA in KO and FO groups compared with the controls. No differences between FO and KO groups.	No differences in serum lipids between the study groups.	No differences in markers of oxidative stress and inflammation between the study groups	
35–64 years of age			Intake of KO significantly decreased 2-AG in obese, but not in overweight, subjects. No effect of MO or OO treatments on 2-AG. There was no effect of KO, MO, or OO on arachidonoyl ethanolamine (AEA)	
31±5 years	The EPA, DHA, EPA + DHA, and total n-3 PUFA levels in plasma PLs were higher after KO treatment, compared to rTG and EE. The DHA, EPA + DHA, and total n-3 PUFA uptake from the rTG FO formulation was higher compared to the same from EE FO, and the EPA uptake was higher after EE FO treatment than after rTG FO treatment.			
KO: 49.4±1.7 years; MO: 49.6±1.4 years; and placebo: 47.4±1.6 years	The increase in plasma EPA and DHA was similar for the KO and MO groups, and both were significantly different compared to the control group.	No differences in lipoprotein lipids between groups.	No differences in hsCRP and F2-isoprostanes between groups	No difference in glucose homeostasis markers between groups. Systolic blood pressure declined significantly more in the MO group than in the control group.

(Continued)

Table 1 (Continued)

Study	Study design	Intervention	Amount of n-3 PUFA	Duration	Individuals
Bunea et al (2004) ²³	Double-blind, randomized trial	Four groups: Group A: KO (2–3 g daily); Group B: KO (1–1.5 g daily); Group C: FO (3 g daily); Group D: placebo (3 g/d, microcrystalline cellulose).	Group A: KO 2 g/d (BMI <30 kg/m ²), 3 g/d (BMI >30 kg/m ²). Group B: KO 1 g/d (BMI <30 kg/m ²), 1.5 g/d (BMI >30 kg/m ²). Group C: FO 3 g/d (180 mg EPA +120 mg DHA/g of oil). Group D: placebo 3 g/d (microcrystalline cellulose).	12 weeks	120 patients with hyperlipidemia and with blood cholesterol levels between 194 mg/dL and 348 mg/dL (18–85 years)

Abbreviations: 2-AG, 2-arachidonoylglycerol; BMI, body mass index; d, days; DHA, docosahexaenoic acid; EE, ethyl ester; EPA, eicosapentaenoic acid; F2-isoprostanes, 8-iso-prostaglandin F2a (8-iso-PGF2a); FO, fish oil; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; h, hours; KO, krill oil; LDL-C, low-density lipoprotein cholesterol; MO, menhaden oil; OO, olive oil; PL, phospholipid; PUFA, polyunsaturated fatty acid; RBC, red blood cell; rTG, reesterified triglyceride; SO, salmon oil; TG, triglyceride; CO, corn oil; DPA, docosapentaenoic acid.

et al.¹⁵ However, a significant increase in LDL cholesterol was observed within the FO group, and a significant increase in the HDL cholesterol/TG ratio was observed within the KO group in the study by Ulven et al.¹⁵

Bunea et al²³ investigated the effect of intake of KO and FO for 3 months on blood lipids in a randomized controlled study of 120 patients with hyperlipidemia. There were four groups; two KO groups (2–3 g/d, and 1–1.5 g/d; dependent on body mass index), an FO group (3 g FO [180 mg EPA and 120 mg DHA/g oil]), and a control group given placebo. Both total and LDL cholesterol were reduced in all groups receiving KO and FO (within-group differences); however, the KO groups had a greater decrease than patients receiving FO. In contrast, subjects in the placebo group showed increased mean total cholesterol and LDL cholesterol levels. HDL cholesterol increased in all patients receiving KO or FO, whereas the level of HDL cholesterol was unchanged in the placebo group. KO taken in doses of 2 g/d and 3 g/d reduced the blood TGs level significantly, whereas a daily dose of 1.0 g and 1.5 g KO, FO, and placebo resulted in a nonsignificant reduction of blood TGs level (all within-group changes). Both FO and KO performed significantly better than placebo in the regulation of TG, total cholesterol, and HDL cholesterol levels.

Other cardiovascular risk markers

Five out of seven studies investigated the effect on other cardiovascular risk markers.^{15,20,22–24} Laidlaw et al²⁴ also investigated the effect of the supplements on the OmegaScore, Omega-3 Serum Equivalence Score, and the Omega-3 RBC

Equivalence Score as surrogate markers for cardiovascular risk. They found that the rTG FO supplement was the most successful in reducing risk according to these parameters, with the EE FO supplement being quite similar, and the PL KO and TG SO supplements being less successful. However, this is not surprising as the difference in scores is calculated by the difference in plasma EPA and DHA levels.

Maki et al²² investigated the effect of KO and FO responses on glucose homeostasis, high-sensitivity C-reactive protein, F2-isoprostanes, weight, and diastolic blood pressure and demonstrated that these parameters did not differ among the groups. The systolic blood pressure declined modestly in both the KO and MO groups, while increasing in the control group; however, only the difference between the MO and the control group was significant. Ulven et al¹⁵ observed no statistically significant differences in the serum markers of oxidative stress and inflammation between the study groups. Bunea et al²³ showed that both KO and FO reduced blood glucose levels, whereas placebo treatment resulted in a nonsignificant increase (all within-group changes). The between-group comparison showed that intake of 1 g and 1.5 g KO was significantly more effective than 3 g FO in reducing glucose levels, whereas 2 g and 3 g KO led to significantly greater reduction of glucose compared to 3 g FO. Both FO and KO performed significantly better than placebo in the regulation of glucose levels.

Plasma endocannabinoids have been suggested to be involved in the regulation of the homeostasis of body com-

Table 1 (Continued)

Age	Fatty acid composition	Lipids	Inflammation and oxidative stress	Other health effects
51±9.46 years		KO and FO reduced total cholesterol. Placebo increased total cholesterol. Similar effects were observed for LDL-C. KO and FO significantly increased HDL-C, whereas the level of HDL-C was unchanged in the placebo group. KO taken as 1 g/d, 2 g/d, and 3 g/d reduced TG. A nonsignificant reduction of TG after a daily dose of 1.5 g/d KO, FO, and placebo.		Blood glucose levels were reduced by KO and FO, whereas placebo treatment resulted in a nonsignificant increase of blood glucose

position by regulating food intake and energy expenditure. In a randomized controlled trial, Banni et al²⁰ investigated whether an intake of 2 g/d of KO (309 mg/d of EPA/DHA), MO (390 mg/d of EPA/DHA), or OO for 4 weeks could modify plasma endocannabinoids in overweight and obese subjects. Intake of KO, but not MO or OO, significantly decreased 2-arachidonoylglycerol in obese subjects, but not in overweight subjects. There was no effect of KO, MO, or OO on arachidonylethanolamine in either obese or overweight subjects; thus, KO seemed more efficient than FO in reducing plasma endocannabinoid levels.

Animal studies

Seven papers investigating the effect of KO compared with FO in animal models were identified (Table 2). The main purpose of these studies was to study the effects of KO and FO on inflammation and/or lipid metabolism^{25–29} and on arthritis.³⁰ One study³¹ investigated the effect of different sources of n-3 fatty acids on digestibility, tissue deposition, eicosanoid metabolism, and oxidative stability.

Bioavailability

Among the seven papers, four studies reported data on bioavailability and digestibility of EPA and DHA from KO and FO.^{26,27,29,31} In one of the studies, the same amounts of FO or KO, but different amounts and structural forms of EPA and DHA (TG versus PL), were used in the experiments,²⁹ while in two studies, different amounts of FO and KO, but similar doses of EPA and DHA were used in the experiments.^{26,27}

Tou et al³¹ examined the effects of different sources of n-3 PUFAs.

Tillander et al²⁹ used a high-fat diet model and fed the mice with similar doses of KO and FO for 6 weeks. The content of EPA and DHA was lower in KO compared to that in FO, but both groups showed significantly increased plasma and liver PLs of EPA and DHA compared to controls. No difference in increase of EPA and DHA was seen between the FO and the KO groups, which indicates that KO may have a higher bioavailability compared to FO.

Vigerust et al²⁶ used a high-fat-diet transgenic mouse model expressing human tumor necrosis factor (TNF) and fed the mice with similar doses of EPA and DHA from KO and FO for 6 weeks. In the plasma, EPA and DHA significantly increased in both groups compared to controls. The increase in plasma EPA and DHA between the two groups did not differ, suggesting that the bioavailability is not dependent on the structural form of EPA and DHA. Batetta et al²⁷ fed Zucker rats with similar doses of EPA and DHA for 4 weeks, and they reported that plasma EPA and DHA were higher in the FO and KO groups compared to the levels in the corn oil, (CO) group. In the study by Tou et al,³¹ Sprague Dawley rats were fed a high-fat diet consisting of different marine oils, all containing different amounts of EPA and DHA, for 8 weeks. They measured the digestibility using the formula [(fatty acid intake – fecal fatty acids)/(fatty acid intake)] × 100 and showed no significant difference in EPA digestibility among rats fed the different marine oils. The DHA digestibility was higher in SO- than KO-fed rats. There were no significant

Table 2 Animal studies with krill oil and fish oil

Study	Animal model	Amount of n-3 PUFA	Duration	Experimental diet	Plasma lipids and plasma fatty acid composition (EPA and DHA)
Tillander et al (2014) ²⁹	Male C57BL/6j mice	Control: EPA 0.03 E%, DHA 0.05 E%; FO group: EPA 8.97 E%, DHA 6.40 E%; KO: EPA 5.23 E%, DHA 2.28 E%	6 weeks	Mice were fed ad libitum either a high-fat diet (HF) containing 24% (w/w) fat (21.3% lard and 2.3% soy oil) (n=9), HF diet supplemented with FO (15.7% lard, 2.3% soy oil, and 5.8% FO) (n=6), or HF diet supplemented with KO (15.7% lard, 2.3% soy oil, and 5.7% KO) (n=6).	FO significantly reduced total C, CEs, free C, TGs, and PLs compared to control. KO significantly reduced NEFA compared to control. No significant differences between FO and KO. FO and KO significantly increased EPA and DHA compared to control. No significant differences between KO and FO.
Vigerust et al (2013) ²⁶	Male transgenic mice expressing human TNF α	Control: EPA 0.03 wt%, DHA 0.05 wt%. FO: EPA 5.23 wt% and DHA 2.82 wt%. KO: EPA 5.39 wt% and DHA 2.36 wt%	6 weeks	Mice were fed ad libitum either a high-fat diet (HF) containing 23.6% (w/w) fat (21.3% lard and 2.3% soy oil) (n=10), HF diet supplemented with FO (18.5% lard, 2.3% soy oil, and 2.9% FO) (n=8), or HF diet supplemented with KO (15.6% lard, 2.3% soy oil, and 5.8% KO) (n=8).	KO significantly reduced TGs compared to control. KO and FO significantly reduced total C, CE, free C, HDL-C, and non-HDL-C compared to control. FO significantly reduced LDL-C compared to control. No significant difference between FO and KO. KO and FO significantly increased plasma EPA and DHA compared to control. No significant differences between FO and KO.
Ferramosca et al (2012) ²⁵	Male Wistar rats	Control: 0 g EPA and 0 g DHA/100 g diet. FO: 0.20 g EPA and 0.29 g DHA/100 g diet. KO: 0.30 g EPA and 0.17 g DHA/100 g diet	1–6 weeks	Rats were fed ad libitum a standard diet, supplemented with 2.5% olive oil (control), 2.5% FO, or 2.5% KO.	KO and FO significantly decreased TG and C compared to control. KO had a more pronounced effect.
Tou et al (2011) ³¹	Female Sprague Dawley rats	CO and FxO: EPA and DHA not detected. KO: 13.2 mg EPA/g diet and 4.6 mg DHA/g diet. MO: 5.5 mg EPA/g diet and 2.0 mg DHA/g diet. SO: 10.0 mg EPA/g diet and 1.9 mg DHA/g diet. TO: 2.6 mg EPA/g diet and 2.9 mg DHA/g diet	8 weeks	Rats were fed AIN-93G diet, which consisted of replacing 7% lipids with 12% lipid by weight. The dietary oils consisted of one of the following: 1) CO (n=10), 2) FxO (n=10), 3) KO (n=10), 4) MO (n=10), 5) SO (n=10), 6) TO (n=10).	
Burri et al (2011) ²⁸	Male CBA/j mice	Control: EPA and DHA 0 g/100 g diet. KO: 0.19 g EPA/100 g diet and 0.11 g DHA/100 g diet. FO: 0.17 g EPA/100 g diet and 0.11 g DHA/100 g diet	12 weeks	Mice were fed AIN-93M diet containing 4% lipid from soybean oil, or soybean oil substituted with 1.1% FO or 1.5% KO. Total n-3 PUFA amount: 0.31% (FO) and 0.29% (KO).	No significant changes in plasma TG, total C, free fatty acids, PL, glucose, and insulin within or between any of the groups.

Lipids and composition of fatty acids in liver (EPA and DHA)	Other lipid effects	Inflammation and oxidative stress	Other effects
<p>FO and KO significantly increased total C compared to control. FO significantly increased PLs compared to control. No significant difference between KO and FO. FO and KO significantly increased EPA and DHA in PLs compared to control. No significant differences between FO and KO.</p> <p>KO and FO significantly increased EPA and DHA compared to control. Significant lower DHA increase mediated by KO compared to that by FO.</p>	<p>FO significantly reduced VLDL-C, HDL-C, and VLDL-TG compared to control. VLDL-C reduction by FO was significantly different from that by KO.</p> <p>KO significantly increased the production of acylcarnitine classes compared to control. The increase was significantly different from that caused by FO.</p>	<p>FO significantly increased the hepatic content of the proinflammatory cytokine IL17 compared to control. No differences of other cytokines between groups.</p>	<p>FO mainly increased the expression of genes involved in fatty acid metabolism. KO specifically decreased the expression of genes involved in isoprenoid/cholesterol metabolism and lipid synthesis.</p> <p>KO increased peroxisomal and mitochondrial oxidation of fatty acids. KO significantly increased ACOX1 activity. KO and FO increased CPTII activity and downregulated expression of genes involved in fatty acid synthesis, and cholesterol import and synthesis. KO significantly decreased the expression of <i>Ldlr</i> more than FO.</p>
<p>KO and FO significantly reduced TG and C compared to control. KO had a more pronounced effect.</p>			<p>The activity, the protein level, and the expression of the transport protein for citrate across the mitochondrial inner membrane were reduced by KO and FO, which was more pronounced in KO group. ACC and FAS activity was reduced by KO and FO, being the highest in KO group.</p>
<p>EPA significantly highest after intake of SO. KO, MO, and SO significantly increased EPA-TG compared to FxO. KO and FxO significantly increased EPA-PL compared to MO, SO, and TO. SO and TO significantly increased DHA compared to CO. KO, MO, SO, and TO significantly increased DHA-TG and DHA-PL compared to CO. MO, SO, and TO significantly increased DHA-TG compared to KO.</p>	<p>In gonadal adipose tissue, EPA significantly highest after intake of KO. DHA significantly highest after intake of KO, MO, and TO compared to FxO intake. DHA significantly highest after intake of MO and TO compared to SO intake. In retroperitoneal adipose tissue, EPA significantly highest after intake of KO. DHA significantly highest after intake of KO and MO compared to SO intake.</p>	<p>No significant differences in urinary 13,14-dihydro-15-keto PGE2 or 11-dehydro TXB2 among groups. No differences in RBC TBARS among groups. Serum TBARS and liver TAC significantly highest after intake of MO compared to KO, SO, and TO intake. No significant differences in gene expression of Zn/Cu SOD, Mn SOD, CAT, or GSH-Px among groups.</p>	<p>No significant differences in EPA digestibility among rats fed marine oils. DHA digestibility was significantly higher after intake of SO compared to KO-fed rats. No differences in DHA digestibility in rats fed MO or TO compared to SO- or KO-fed rats.</p> <p>KO downregulated the expression of genes involved in glucose, fatty acid, and cholesterol synthesis. FO modulated fewer pathways than KO. FO did not modulate key metabolic pathways regulated by KO. FO upregulated the cholesterol synthesis pathway.</p>

(Continued)

Table 2 (Continued)

Study	Animal model	Amount of n-3 PUFA	Duration	Experimental diet	Plasma lipids and plasma fatty acid composition (EPA and DHA)
Ierna et al (2010) ³⁰	Male DBA/1 mice, induced with arthritis following 25 days of feeding	CO: EPA and DHA 0 g/100 g diet. KO: 0.30 g EPA/100 g diet and 0.14 g DHA/100 g diet. FO: 0.29 g EPA/100 g diet and 0.18 g DHA/100 g diet.	68 days	Mice were fed AIN-93G diet with substitution of soybean oil with a blend of oils. The three diets (control and diet supplemented with FO or KO) were similar for total fatty acids, and FO and KO were balanced for EPA and DHA.	
Batetta et al (2009) ²⁷	Male Zucker rats	CO: EPA and DHA 0 g/100 g diet. KO: 0.30 g EPA/100 g diet and 0.14 g DHA/100 g diet. FO: 0.29 g EPA/100 g diet and 0.18 g DHA/100 g diet.	4 weeks	Rats were fed AIN-93G diet with substitution of soybean oil with a blend of oils. The three diets (control, and diet supplemented with FO or KO) were similar for total fatty acids, and FO and KO were balanced for EPA and DHA.	KO and FO significantly reduced LDL-C compared to control. FO and KO significantly increased TG compared to control. No difference in HDL-C. FO and KO significantly increased EPA and DHA compared to CO.

Abbreviations: 2-AG, 2-arachidonoylglycerol; ACC, acetyl Co-A carboxylase; ACOX1, peroxisomal acyl-CoA oxidase; AEA, N-arachidonylethanolamine; C, cholesterol; CAT, catalase; CE, cholesterol ester; CoA, coenzyme A; CO, corn oil; CPTII, carnitine palmitoyltransferase II; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FAS, fatty acid synthetase; FxO, flaxseed oil; FO, fish oil; HDL, high-density lipoprotein; GSH-Px, glutathione peroxidase; IL, interleukin; ;IL-1 α , interleukin-1 α , KO, krill oil; LDL-C, low-density lipoprotein cholesterol; LDLR, LDL receptor; LPS, lipopolysaccharide; MAGL, monoacylglycerol lipase; MO, menhaden oil; NEFA, nonesterified fatty acid; OO, olive oil; PGE2, prostaglandin E2; PL, phospholipid; PUFA, polyunsaturated fatty acid; RBC, red blood cell; SO, salmon oil; SOD, superoxide dismutase; TAC, total antioxidant capacity; TBARS, thiobarbituric acid-reactive substances; TG, triglyceride; TNF α , tumor necrosis factor alpha; TO, tuna oil; TXB2, thromboxane B2; VAT, visceral adipose tissue; VLDL, very-low-density lipoprotein; AIN, American Institute of Nutrition rodent diet, SAT, subcutaneous adipose tissue.

differences in DHA digestibility in rats fed MO or tuna oil (TO) compared to SO- or KO-fed rats.

Plasma lipids

Among the seven studies, five studies reported the effects on plasma lipids.^{25–29}

In two of the studies,^{25,29} the authors used the same amount of FO or KO, containing different amounts and EPA and DHA, in the experiments. Tillander et al²⁹ found no differences in plasma lipids between the FO and the KO groups after 6 weeks. However, within the FO group, total plasma cholesterol, cholesterol ester, free cholesterol, TGs, and PLs were significantly reduced compared to the same in controls. In contrast, Wistar rats fed the same amount of FO and KO for 1–6 weeks showed significantly decreased plasma TG and total cholesterol compared to controls, but these effects seemed to be more pronounced after KO intake compared

to FO intake.²⁵ The reason for this discrepancy may be that Tillander et al²⁹ used mice on a high-fat diet and not lean rats, and moreover, the amount of oil differed between the two studies.

In three of the studies, similar amounts of EPA and DHA from KO and FO were used in the experiments, and the dose of EPA and DHA was similar between the experiments.^{26–28} Vigerust et al²⁶ did not observe any significant difference between the effects of KO and FO on plasma lipids, but KO significantly reduced plasma TG compared to controls, suggesting that KO is more effective than FO in lowering plasma TG. However, LDL cholesterol was significantly reduced in the FO group compared to controls, thus suggesting that FO is more effective than KO in lowering plasma LDL cholesterol. Total plasma cholesterol, free cholesterol, and HDL cholesterol were however significantly reduced in both groups compared to controls, but no differences between KO

Lipids and composition of fatty acids in liver (EPA and DHA)	Other lipid effects	Inflammation and oxidative stress	Other effects
<p>FO and KO significantly reduced TG compared to control. KO significantly reduced TG to a greater extent compared to FO. FO and KO significantly increased EPA and DHA compared to control. EPA was significantly higher in PL after FO and KO intake compared to control. DHA PL was significantly increased by KO compared to control.</p>	<p>Heart TG was significantly reduced by KO compared to control. FO and KO significantly increased EPA and DHA in VAT and SAT TG and PL compared to control. In heart, KO and FO significantly increased EPA and DHA in TG and PL compared to control.</p>	<p>KO increased clinical arthritis more slowly compared to control. Hind paw thickness and histopathology associated with arthritis were significantly reduced by KO compared to control. FO significantly increased serum IL1α and IL13 compared to control.</p> <p>No differences in proinflammatory and anti-inflammatory cytokines in any groups. In macrophages incubated with LPSs, TNFα secretion was significantly lower after intake of FO and KO compared to control. No difference between FO and KO. In VAT, lower level of AEA induced by KO and FO compared to control. 2-AG level lowered by KO. In liver and heart, AEA lowered by KO and FO, more pronounced effect by KO. 2-AG increased by KO.</p>	<p>A significantly higher weight gain by KO compared to control.</p> <p>In VAT, MAGL activity was decreased by FO and KO compared to control. In heart, MAGL activity significantly decreased by KO compared to control.</p>

and FO were observed. These data are in line with the results of Batetta et al,²⁷ who showed that KO and FO significantly reduced LDL cholesterol compared to control. In contrast, Burri et al,²⁸ who fed mice for 12 weeks with similar amounts of EPA and DHA, did not see any changes in plasma lipids in any of the groups. These conflicting results may be due to the longer period of supplementation and probably because the mice were lean and not fed a high fat diet, as was done by Batetta et al²⁷ and Vigerust et al,²⁶ respectively.

Inflammation

Vigerust et al²⁶ did not observe any substantial difference in levels of proinflammatory cytokines between treatment groups. Batetta et al²⁷ compared the effects of KO and FO on ectopic fat and inflammation in obese rats. Lipopolysaccharides significantly increased the release of TNF α from all three groups; however, the increase was higher

in the control compared to FO- and KO-treated groups, with no difference between these two groups. In these obese rats, KO also seemed to have a more pronounced inhibitory effect on the endocannabinoid system compared to FO, which is in accordance with the results of the human study by Banni et al.²⁰

Ierna et al³⁰ used an arthritis-induced mouse model to show that clinical arthritis score and hind paw swelling were significantly reduced in the KO group compared to controls. Mice fed the KO also had lower infiltration of inflammatory cells into the joint and synovial layer hyperplasia when compared to control. Thus, in this mouse model, KO seems to be more efficient compared to FO, in the treatment of arthritis. KO did not modulate the levels of serum cytokines, whereas consumption of FO increased the level of interleukin (IL)-1 α and IL-13.³⁰ Tou et al³¹ observed no significant effects on the Series-2 prostaglandins, thromboxane B metabolites,

and markers of oxidative stress when rats were fed different marine oils.

Biological effects

In four studies, the aim was to understand biological effects of KO and FO by studying gene expression levels and protein activity in the liver.^{25,26,28,29} Ferramosca et al²⁵ fed the same amount of FO and KO to rats and both oils significantly reduced the hepatic activity and expression of the mitochondrial tricarboxylate carrier. They also observed that FO and KO significantly reduced the activity of enzymes catalyzing de novo lipogenesis compared to the activity in controls. Tillander et al²⁹ used quantitative polymerase chain reaction (PCR) to study changes in hepatic gene expression after KO and FO supplementation. FO mainly increased the expression of genes involved in fatty acid metabolism, while KO specifically decreased the expression of genes involved in isoprenoid/cholesterol and lipid synthesis.

Vigerust et al²⁶ showed that KO significantly increased the mitochondrial and peroxisomal fatty acid β -oxidation, as well as the overall carnitine turnover in the liver, which can explain the TG-lowering effect of KO seen in this study. Thus, it seems that KO has a greater potential to promote lipid catabolism. By the use of quantitative PCR, Vigerust et al²⁶ showed that both KO and FO downregulated specific hepatic target genes involved in de novo lipogenesis and genes involved in cholesterol import and synthesis compared to the control-treated groups.

Burri et al²⁸ also fed mice with different amounts of FO and KO to maintain the content of EPA and DHA similar in the two groups to evaluate the efficacy of KO and FO administration on gene expression profiling in liver. Long-chain n-3 PUFAs derived from KO downregulated the activity of pathways involved in hepatic glucose production as well as in lipid and cholesterol synthesis. The data also suggested that KO increases the activity of the mitochondrial respiratory chain. Long-chain n-3 PUFAs derived from FO modulated fewer pathways, even if the content of EPA and DHA was the same as KO, and did not modulate key metabolic pathways regulated by KO. FO also upregulated the cholesterol synthesis pathway, which was the opposite of the effect mediated by KO.

Discussion

Studies on the bioavailability of EPA and DHA from KO and FO in humans and animals are limited and their interpretation is difficult, as different amounts of EPA and DHA have been used, duration of intervention differs among the studies, and different study groups have been included. Two human

studies that are included in this review – one postprandial study and one intervention study – used the same amount of EPA and DHA from KO or FO, and they both show that the bioavailability of EPA and DHA from KO seems to be higher than from that from FO.^{19,21} This strengthens the hypothesis that there is a difference between the bioavailability of PUFAs from KO and FO. In contrast, Laidlaw et al²⁴ showed that similar amounts of EPA from PL KO and TG SO resulted in the same increase in whole-blood EPA, suggesting that there is no difference in bioavailability of DHA from FO and KO. The problem in comparing these studies is that one study analyzed whole-blood fatty acids, while the two other studies used plasma PLs and plasma RBCs. In future studies, the same amount of EPA and DHA from KO and FO should be compared in plasma PLs, RBCs, and whole blood. If possible, adipose tissue biopsies should also be taken to study whether the fatty acids from KO and FO are differently incorporated into adipose tissue, as shown in the animal study by Tou et al.³¹ In animals, one study²⁹ also indicates that KO may have a higher bioavailability compared to FO; however, another study indicates that bioavailability is not dependent on the structural form of EPA and DHA.²⁶

The doses of KO and FO, type of study subjects, and duration of the studies showed very limited effects on lipids and inflammatory markers in human studies. Most of the studies did not see any effects between the groups. In one study,¹⁹ total cholesterol and LDL cholesterol increased following intake of KO and FO compared to controls, while Bunea et al²³ showed reduction in concentration of total cholesterol and LDL cholesterol by KO and FO, as well as reduction in TG by KO. KO (at most doses) was more efficient than FO in reducing glucose and LDL cholesterol, whereas high-dose KO was more efficient in reducing plasma TG than FO.²³

In the future, better-designed clinical studies are warranted to gain insight into the beneficial health effects of KO compared to FO. The animal studies show that there is a very small difference between KO and FO when it comes to health effects. KO seems to be more efficient in reducing the concentration of plasma TG, liver TG, and endocannabinoids, compared to FO, in animal studies. No adverse effects were reported.

Because KO and FO differ in their structural form, this may influence the incorporation of EPA and DHA into cells, resulting in different biological effects. KO also contains the antioxidant astaxanthin that protects the unsaturated bonds in the fatty acid from oxidative damage, which may influ-

ence the biological effects of KO. The possible biological difference between FO and KO was studied in animal models using gene expression analysis.^{25,26,28,29} EPA and DHA possibly regulate the activity of transcription factors by acting as ligands for the peroxisome-proliferator-activated receptor alpha (PPAR α) or influence the activity of sterol regulator element-binding protein 1-c (SREBP1c).^{32,33} Consequently, these fatty acids have the ability to control transcription factor activity, which in turn regulates gene expression. Many of the beneficial health effects of EPA and DHA may be linked to their role of regulating expression of genes encoding proteins involved in transport, uptake, and storage of lipids, as well as enzymes involved in metabolic pathways and processes. The results from the studies included here show that FO upregulated the cholesterol synthesis pathway, which was opposite of the effect mediated by KO. KO also regulated more metabolic pathways than FO because glucose, fatty acid, and lipid metabolism pathways were affected by KO in some studies, and the same biological response was not seen with FO. This difference in biological effect may be caused by the different structure of PLs in KO and TG in FO.

In humans, it is also possible to perform biological studies using peripheral blood mononuclear cells (PBMCs), which are readily available, and FO has previously been shown to be able to modulate gene expression in these cells in human trials.³⁴ PBMC gene expression analysis in human dietary intervention studies with FO and KO can be a powerful tool to understand the underlying molecular mechanisms of the effect mediated by these oils on lipid metabolism and inflammation in humans.

Conclusion

Studies suggest that there may be a difference in the bioavailability of EPA and DHA after intake of KO and FO. However, more human studies designed to compare the effect of KO and FO are needed to conclude if the bioavailability of EPA and DHA differs between KO and FO. Furthermore, it is also necessary to document beneficial health effects of KO with high-quality human studies and to investigate whether these effects differ compared to the effects observed after regular fish and FO intake.

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Disclosure

The authors report no conflicts of interest in this work.

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