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RESEARCH ARTICLE

Blood pressure-lowering effects of long chain n-3 fatty acids from meals enriched with liquid fish oil and from microencapsulated powder

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ABSTRACT

Background: Diet plays an important role in the etiology of hypertension. Blood pressure (BP)-lowering properties of long chain n-3 polyunsaturated fatty acids (LC n-3 PUFA) are promising. The aim was to investigate whether different formulations of fish oil differently affect blood pressure in community-dwelling adults. The hypothesis was that fish oil formulations would improve BP in comparison with a placebo.

Methods: In this 4-week randomized, placebo-controlled, doubly-blinded dietary intervention study, participants ($N = 99, >50$ years) from the capital area of Iceland were randomized into three groups. Group 1 ($n = 38$) received 6 meals/week fortified with a liquid fish oil and placebo powder. Group 2 ($n = 30$) received conventional (unfortified) meals and microencapsulated powder. Group 3 ($n = 31$) was the control group which received conventional meals and placebo powder. Calculated on a weekly basis, the amount of EPA + DHA provided was 1.5 g/d. Systolic (SBP) and diastolic BP (DBP) were measured before and after the intervention period.

Results: Seventy-seven subjects finished the study (77.8%). Drop-out rates were not different between groups. According to multivariate statistics, endpoint SBP was lower in Group 1 (−7.0 mmHg, $p = 0.037$) and in Group 2 (−7.2 mmHg, $p = 0.037$) as compared with Group 3. There was no significant difference in DBP between the groups.

Conclusion: Our study shows that LC n-3 PUFA from microencapsulated powder are equally effective to meaningfully reduce SBP as LC n-3 PUFA from meals enriched with liquid fish oil in comparison with a control group.

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Cardiovascular disease; diet; bioavailability

Introduction

Hypertension is a risk factor of cardiovascular diseases (He & MacGregor 2007). Diet plays an important role in the etiology of hypertension, as obesity and nutrient intake, e.g., sodium, potassium, or dietary patterns, e.g., Mediterranean diet, are known to affect blood pressure (BP) (Gay et al. 2016). The BP-lowering properties of long chain n-3 polyunsaturated fatty acids (LC n-3 PUFA) from liquid supplements have been thoroughly investigated and confirmed (Morris et al. 1993; Appel et al. 1993; Geleijnse et al. 2002; Mori 2006), with commonly used doses of 4–5 g LC n-3 PUFA per day leading to clinically significant reductions in BP. The largest effects are usually achieved in elderly and hypertensives patients, a smaller blood pressure reduction is seen in normotensive participants (Appel et al. 1993; Mori 2006). Several biological mechanisms have been suggested to explain the benefits of LC n-3 PUFA on BP, e.g., changes in phospholipids composition, platelet aggregation, and vasodilatation (Rogers et al. 1987; Hashimoto et al. 1999; Lund et al. 1999; Johansen et al. 1999; Véricel et al. 1999; Engler & Engler 2000).

Oily seafood is the main dietary source of LC n-3 PUFA. The Nordic Nutrition Recommendations recommend that LC n-3 PUFA should at least contribute to 1% of total energy intake (E%) (Nordic Councils of Ministers 2012). Despite recommendations and awareness of the benefits from seafood consumption, food habits have changed over the years and current LC n-3 PUFA intake is usually low (Steingrimsdottir et al. 2002; Nordic Councils of Ministers 2004; Thorgeirsdottir et al. 2011). Although the use of seafood supplements is a tradition in many Nordic countries, relatively recent data show that the majority of the population does not use them regularly (Thorgeirsdottir et al. 2011; Mai et al. 2013).

Thus, attempts have been made to fortify food accordingly. However, it can be problematic to fortify foods with LC n-3 PUFA from marine sources, because

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they have a strong odor and taste that can be hard to hide. As an alternative, flavor neutral microencapsulated oil rich in marine LC n-3 PUFA in powder form has been suggested for fortification of foods. Microencapsulation of a liquid is a process in which small droplets are coated to give small units with useful properties. Available studies on LC n-3 PUFA have mainly focused on technical aspects and bioavailability. Bioavailability of such formulations has been reported to be comparable with liquid fish oil or fish oil encapsulated in gelatin caps (Higgins et al. 1999; Wallace et al. 2000; Hinriksdottir et al. 2015). However, studies, which use microencapsulated LC n-3 PUFA to investigate clinical outcomes, e.g. BP, are currently not available according to our best knowledge.

Given these considerations, the aim was to investigate whether different formulations of fish oil differently affect blood pressure. We conducted a randomized, doubly blinded, dietary intervention trial that investigated the effects of LC n-3 PUFA on systolic (SBP) and diastolic BP (DBP) in community-dwelling adults. The LC n-3 PUFA were either consumed as microencapsulated fish oil powder or in meals enriched with liquid fish oil over a 4 weeks period. The hypothesis was that both fish oil supplementation would improve BP in comparison with a placebo.

Materials and methods

Subjects

All participants ($N = 99$) from the capital area of Iceland were recruited through advertisements on the Internet, through e-mail lists at the University of Iceland, and through advertisements published in regional health care facilities. The study was conducted from May until October 2013. Inclusion criteria were age 50 years or over and regular consumption of fish or fish meals (defined as at least once a week according to information given by the participants). The only exclusion criterion was a previous record of digestive disease, e.g., cholestasis, Cohn's disease, which could interfere with the digestion or absorption of dietary fat. The participants were apparently healthy. The study was approved by the National Bioethics Committee (VSNb201302008/03.07) and was notified by the Data Protection Authority (S6241/2013). All persons gave their written informed consent prior to their inclusion in the study.

Study design

This was a 4-week randomized, placebo-controlled, doubly-blinded dietary intervention study (Figure 1). The subjects were randomized into three groups. Group 1 ($n = 38$) received 6 meals/week fortified with a liquid oil blend (see below) providing 1.75 g EPA and DHA daily and 6 sachets of placebo powder. Group 2 ($n = 30$) received 6 conventional (unfortified) meals/week and 6 sachets of microencapsulated powder (22.7 g) providing 1.75 g EPA and DHA daily (see below) and group 3 ($n = 31$) was the control group, which received conventional meals and placebo powder. Calculated on a weekly basis, the amount of EPA + DHA provided was 1.5 g/d ($1.75 \times 6/7$).

In the current study, we used fortified meals instead of liquid fish oil. The reason, therefore, was twofold: this made blinding easier and we hoped for better tolerance. The meals were fortified with fish oil and olive oil blend provided by BioActive Foods AS, Trondheim, Norway (www.1life63.com). The microencapsulated LC n-3 powder (particle size 30–50 µm) was also from

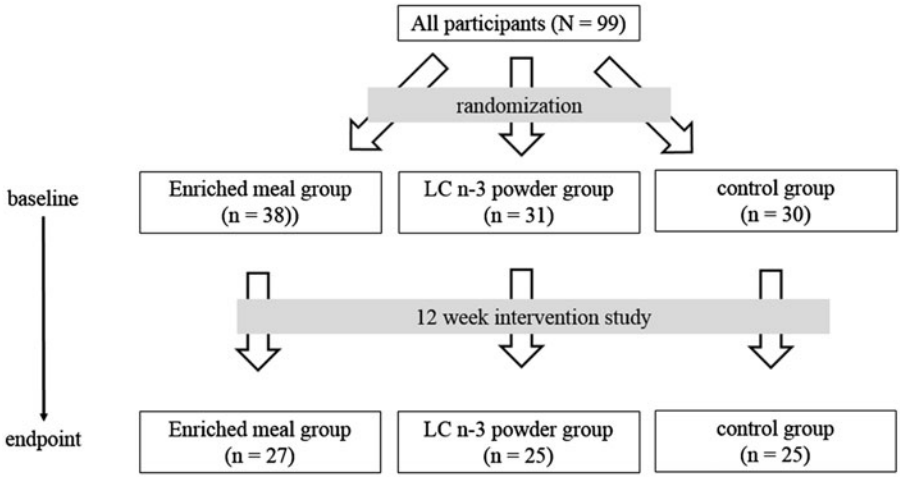


Figure 1. Flowchart. Systolic blood pressure = dark grey. Diastolic blood pressure = light grey.

BioActive Foods in Norway and is based on the same oil blend (Table 1). The participants received 6 powder sachets each week and were given written instructions on how to use the powder. The meals were produced by Grimur Kokkur ehf, Vestmanneyjar, Iceland (www.grimurkokkur.is/en). All the dishes were kept frozen until cooking or heating. The nutrient profile of each meal is given in Table 2. The fat content of the meals was between 5.3 and 11.1% of total weight (including water). Enriched meals always contained more fat than conventional meals with a mean difference of 3.3% of total weight. LC n-3 PUFAs partly replaced other fat normally used in the recipes and/or were added. The conventional meals did not provide any noteworthy amount of LC n-3 PUFA (0.12 g per day).

Table 1. Composition of the microencapsulated LC n-3 PUFA powder and of the liquid oil.

	Content in 100 g powder	Content in 100 g oil
Energy (kcal)	630	
Protein (g)	10	
Carbohydrates (g)	34	
Sugars (g)	15	
Ash (g)	2.5	
Moisture (g)	2.5	
Fat (g)	51	
SFA (g)	15.4	30.2
MUFA (g)	22.9	44.9
OA (g)	18.3	35.9
PUFA (g)	12.1	23.7
n-6 Fatty acids(g)	1.70	3.33
LA (g)	1.34	2.62
GLA (g)	0.07	0.13
AA (g)	0.32	0.63
n-3 Fatty acids (g)	9.40	18.43
ALA (g)	0.34	0.66
ETA(g)	0.21	0.41
EPA (g)	5.30	10.39
DPA (g)	0.56	1.10
DHA (g)	2.40	4.71

OA: oleic acid; LA: linoleic acid; GLA: gamma-linolenic acid; AA: arachidonic acid; ALA: alpha-linolenic acid; ETA: eicosatetraenoic acid; EPA: eicosapentaenoic acid; DPA: docosapentaenoic acid; DHA: docosahexaenoic acid. LC n-3 powder group consumed 22.7 g of powder six times a week corresponding to 1.5 EPA and DHA a day. Enriched meal group consumed 11.5 g of oil 6 times a week corresponding to 1.5 EPA and DHA a day.

There was no difference in salt content between enriched and conventional meals.

Protein powder with light vanilla flavor was used as placebo powder in groups 1 and 3; unfortified meals were used in groups 2 and 3. Subjects were told to exclude all LC n-3 PUFA from their diet at least for 2 weeks before the intervention and also while the intervention lasted. Compliance was assessed by a questionnaire each week when the participants received the meals and powder for the following week. All measurements were conducted at baseline and at endpoint of the study.

Anthropometric measurements

Body weight was measured in light clothing on a calibrated scale (model no. 708, Seca, Hamburg, Germany). Height was measured and body mass index (BMI) was calculated from the recorded height and weight (kg/m^2). For the measurement of waist circumference, a flexible tape was applied horizontally midway between the lowest rib margin and the iliac crest. Body fat percentage was estimated using a hand held bio impedance measurement device (Body Fat Monitor BF 306, Omron Healthcare UK Ltd, Milton Keynes, UK).

Blood parameters

Fasting blood samples from fingertip where collected using a home test kit and sent to the St. Olav's Hospital, Trondheim University Hospital, Norway, where the analyses were conducted. Briefly, the pieces of absorbent paper containing the blood samples were transferred to screw-capped glass vials and treated with 1 ml of 0.5M HCl in MeOH. Samples were then stored at 70 °C in a dry bath for 1 h to achieve transesterification of FAs to FA methyl esters. After cooling, 1 ml of H_2O and 1 ml of saturated KCl were added, before FAs were extracted using 2 ml of hexane. The solvent was

Table 2. Nutrient profile of the test meals.

Sample	Protein (g)	fat (g)	EPA + DHA (% of total fat)	EPA + DHA (g)	CHO (g)[a]	Energy (kcal)[b]
Fish in white sauce (conventional)	13.0	12.4	2.5	0.3	22.4	253.2
Fish in white sauce (enriched)	12.4	20.4	10.4	2.1	18.8	308.4
Gratinated haddock with broccoli (conv.)	12.6	8.6	1.0	0.1	20	207.8
Gratinated haddock with broccoli (enriched)	11.8	10.6	8.5	0.9	22	230.6
Haddock in lobster sauce (conventional)	21.4	10.6	1.9	0.2	14	237.0
Haddock in lobster sauce (enriched)	21.8	18.4	8.9	1.6	11.2	297.6
Haddock in curry sauce (conventional)	23.4	14.6	1.5	0.2	14.2	281.8
Haddock in curry sauce (enriched)	19.8	22.2	9.1	2.0	14	335.0
Fish cakes (conventional)	21.8	9.6	1.3	0.1	30	293.6
Fish cakes (enriched)	19.4	22.0	10.9	2.4	27.2	384.4
Vegetable cakes (conventional)	7.0	17.0	0.0	0.0	48.4	374.6
Vegetable cakes (enriched)	6.6	18.4	7.5	1.4	49.2	388.8

EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid.
[a]Calculated as 100 − water − protein − fat − ash.
[b]Calculated as fat ×9 + protein ×4 + carbohydrates ×4.

then evaporated by N2 and the samples were re-dissolved in 50 ml of hexane. Resultant FA methyl esters were analyzed on a gas chromatography mass spectrometry system. A more detailed description of this method can be found in the publication by Hinriksdottir et al. (2015).

BP measurements

BP measurements were conducted as described in the following paragraph: first, the participant removed outer garments, and the shirtsleeve was rolled up. Then, the subject sat still and at rest, with no change of position for a few minutes before the measurement took place. The subject did not engage in conversation (total rest). The arm of the subject was allowed to rest on a desk to allow the antecubital fossa to be at the same level as the heart. The right arm was used for all subjects on all measurement days. Two readings were taken at intervals of 2 min, and the average of those readings represented the patient's BP. When the Hg difference between the first and second readings was >5 mm, an additional reading was obtained, and then the average of these three readings was used. The same person performed the measurements at baseline and end-point for all subjects. Further instructions according to the user's guide of the equipment used (Medissan, Kent, UK) were followed. Hypertension was defined as either systolic BP (SBP) $\geq$ 130 mmHg at baseline or diastolic BP (DBP) $\geq$ 85 mmHg at baseline (Alberti et al. 2006).

Statistical analyses

The data were analysed using statistical software (SPSS, version 21.0, SPSS, Chicago, IL). Data were checked for normality using the Kolmogorov–Smirnov test. Data are presented as mean ± standard deviation (SD). Baseline differences between groups were assessed using one-way-ANOVA (continuous variables) and Chi-square test (categorical variables).

In order to determine differences between groups in BP, we used a general linear model including group and gender as factor as well as hypertension at baseline, BMI, and age as covariates. Results from the linear models are shown as parameter estimates. The numbers shown in the table are the effect size B, lower confidence limits, higher confidence limits, and p values. The significance level was set at $p \leq 0.05$.

Results

Seventy-seven subjects finished the study (77.8%). Drop-out rates were 28.9%, 16.7%, and 19.4% for group 1, group 2, and group 3, respectively (not significantly different). The most common reason for drop-out was lack of time or lack of interest. Baseline characteristics of the participants are shown in Table 3. Of the participants, 69.7% were women and the gender distribution was equal between groups. There were no baseline differences between the groups besides a higher n6/n3 ratio in the LC n-3 powder group as compared with the other two groups.

Table 3. Baseline characteristics of the participants.

	Enriched meal group ($n = 38$)	LC n-3 powder group ($n = 30$)	Control group ($n = 31$)
Age (years)	57 ± 6	56 ± 6	55 ± 4
Body weight (kg)	82.3 ± 16.3	84.8 ± 16.3	78.6 ± 21.3
BMI (kg/m^2)	28.5 ± 5.2	29.6 ± 6.0	27 ± 5.8
Waist circumf. (cm)	98.1 ± 14.1	103 ± 16.3	94.5 ± 18.2
Body fat (%)	33.7 ± 8.3	34.3 ± 8.6	33.0 ± 7.3
Blood glucose (mmol/L)	6.0 ± 1.7	5.9 ± 1.5	5.7 ± 0.9
EPA[a]	0.93 ± 0.42	0.83 ± 0.26	1.06 ± 0.39
DHA[a]	3.04 ± 1.03	3.16 ± 0.69	3.4 ± 0.78
n6/n3 ratio	8.52 ± 3.81	10.29 ± 3.79	7.64 ± 2.63
Systolic blood pr. (mmHg)	130.0 ± 13.4	130.0 ± 17.1	129.2 ± 18.2
Diastolic blood pr. (mmHg)	77.0 ± 8.3	78.2 ± 9.6	78.8 ± 9.3

LC n-3: long chain n-3 fatty acids; BMI: body mass index; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid.
[a]Whole blood fatty acid measurements from fingertip test (% of total fatty acids).

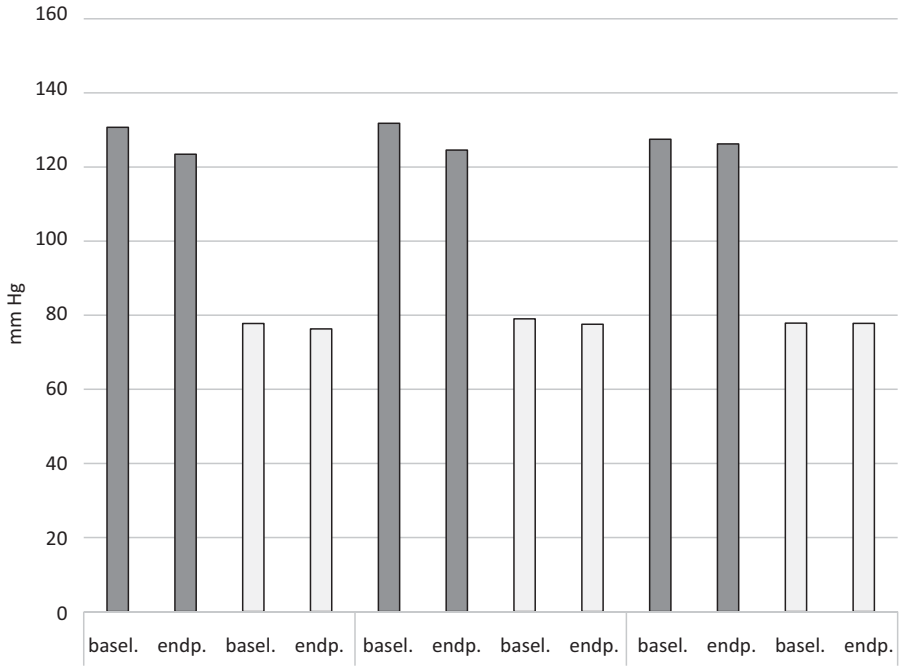
After the intervention, the content of LC n-3 PUFA increased significantly in both LC n-3 PUFA groups but not in the control group. According to the definition by Alberti et al. (2006), 51% of the participants had hypertension at baseline (50.0–53.3% in the groups, not significant difference). Changes in BP did not correlate with baseline levels of fatty acids in blood or with corresponding changes during the intervention. After the intervention SBP decreased by 7.3 ± 11.6 mmHg in group 1 and by 7.2 ± 15.6 mmHg in group 2 and by 1.3 ± 9.0 mmHg. Figure 2 shows SBP and DBP at baseline and at endpoint for the three groups.

According to the linear model (Table 4), there was a significant difference in endpoint SBP between groups (corrected for baseline SBP). There was no significant difference in DBP between the groups (Table 5).

Discussion

The present study investigated the BP lowering effects of LC n-3 PUFA from encapsulated powder and from meals enriched with liquid fish oil in adults. The most important finding is that SBP decreased significantly in both LC n-3 PUFA groups but not in the control group.

In this study, drop-out rate was 22.2%. Participants, who received the encapsulated power, did not show a higher drop-out thus indicating that the powder was



Systolic blood pressure = dark grey
Diastolic blood pressure = light grey

Figure 2. Systolic and diastolic blood pressure at baseline and at endpoint.

Table 4. Linear model for the prediction of endpoint SBP (mmHg).

Parameter estimates				
Dependent variable: reduction in SBP (mmHg)				
Parameter	*B*	95% CI		*p* Value
Intercept	−7.097	−37.392	23.199	0.642
Enriched meal group[a]	−7.020	−13.618	−0.423	0.037
LC n-3 powder group[a]	−7.162	−13.880	−0.445	0.037
Male[b]	6.436	0.653	12.218	0.030
Age (years)	−0.168	−0.668	0.332	0.505
BMI (kg/m^2)	0.622	0.125	1.119	0.015
Hypertension at baseline[c]	−7.620	−13.382	−1.859	0.010

SPB: systolic blood pressure; LC n-3: long chain n-3 fatty acids; BMI: body mass index.
[a]As compared with the control group.
[b]As compared with women.
[c]As compared with normotension.

Table 5. Linear model for the prediction of endpoint DBP (mmHg).

Parameter estimates				
Dependent variable: reduction in DBP (mmHg)				
Parameter	*B*	95% CI		*p* Value
Intercept	4.792	−12.964	22.549	0.592
Enriched meal group[a]	−1.245	−5.112	2.622	0.523
LC n-3 powder group[a]	−1.328	−5.266	2.609	0.503
Male[b]	0.866	−2.524	4.255	0.612
Age (years)	−0.142	−0.435	0.151	0.336
BMI (kg/m^2)	0.144	−0.147	0.435	0.328
Hypertension at baseline[c]	−2.665	−6.042	0.712	0.120

DBP: diastolic blood pressure; LC n-3: long chain n-3 fatty acids; BMI: body mass index.
[a]As compared with the control group.
[b]As compared with women.
[c]As compared with normotension.

well tolerated. Adherence to the study protocol was excellent, and according to questionnaires, more than 97% of the provided meals were eaten during the intervention. Additionally, the changes in LC n-3 PUFA in blood were in good accordance with the different LC n-3 PUFA consumption in all the three groups (Hinriksdottir et al. 2015).

In our study, both LC n-3 PUFA interventions reduced SBP by approximately 7 mmHg as compared with control. Several studies have shown that encapsulated powder has bioavailability comparable with liquid fish oil or fish oil in gelatin capsules (Higgins et al. 1999; Wallace et al. 2000; Hinriksdottir et al. 2015). However, it is also important to know whether encapsulated powder exerts the same biological activity, e.g., effects on BP. Currently, no such studies are available in the literature. According to a recent meta-analysis using randomized controlled trials (Campbell et al. 2013), fish oil supplementation results into a statistically significant reduction of BP in hypertensive participants (SBP: 2.6 mmHg; DBP: 1.5 mmHg). In our study, about half of the participants were hypertensive and being hypertensive was a significant predictor of SBP reduction. The reduction in both LC n-3 groups was greater than in the above-mentioned meta-analysis. This is of particular interest, because the dose of 1.5 g/d in our study is lower than doses commonly used to improve BP (Geleijnse et al. 2002). However, it has been also reported that there is no clear dose–response

relationship between BP reduction and LC n-3 PUFA supplementation (Campbell et al. 2013).

We did not find a significant effect of LC n-3 PUFA on DBP. Although the descriptive statistics indicate a reduction by 1.3 mmHg and thus very similar to what others found (Campbell et al. 2013), this difference was not statistically significant. The sample size was small in our study and thus statistical power was limited. Our results are in agreement with several other studies that have shown that LC n-3 PUFA supplementation results in a greater reduction of SBP than of DBP which allowed us to detect significant changes in SBP only (Mori 2006).

Several biological mechanisms have been suggested to explain the effects of LC n-3 PUFA on BP: The antagonistic effects of n-3 PUFA on angiotensin II receptors may be responsible for modulation of hypertension (Juan & Sametz 1986; Juan et al. 1987). Also, increases in cyclooxygenase and lipooxygenase metabolites of EPA such as the vasodilative eicosanoids including the thromboxanes could also act as physiological antagonists, counteracting vasoconstriction caused by angiotensin II (Carey & Siragy 2003). However, in our study, we could not detect an inverse correlation between BP changes and changes in LC n-3 PUFA in blood.

Strengths and limitations

It is a strength of the present study that it was a doubly blinded, randomized dietary intervention trial. Blinding in dietary trials is often difficult, especially when the intervention does not involve supplements but food. It is also a strength that both intervention groups essentially show the same results decreasing the likelihood of a by-chance finding.

It is a limitation that data on dietary intake were not available for our participants. It would have been interesting to associate salt intake with BP outcomes. However, we do not think that lack of dietary intake data weakens the present results. Salt content of food provided in the three intervention groups was identical and it is highly unlikely that sudden changes in salt intake explain the observed reductions in BP. It is a further limitation of the present study the four weeks may not be a sufficient period to see the full effects of LC n-3 PUFA on physiological or disease related outcomes.

Conclusion

Our study shows that LC n-3 PUFA from microencapsulated powder are equally effective to reduce SBP as LC n-3 PUFA from meals enriched with liquid fish oil. Our data also indicate that hypertensive subjects benefit more than normotensive subjects from intake of LC n-3 PUFA.

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The test meals were provided by Grimur Kokkur ehf, Vestmanneyjar, Iceland; the microencapsulated powder was provided by BioActive Foods AS, Trondheim, Norway. None of these three entities participated in data collection, data interpretation or publication.

Disclosure statement

The authors declare no conflict of interests.

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