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SHORT COMMUNICATION

# Effects of flaxseed supplementation on erythrocyte fatty acids and multiple cardiometabolic biomarkers among Chinese with risk factors of metabolic syndrome

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**Abstract**
*Purpose* We investigated effects of ground whole flaxseed supplementation on erythrocyte polyunsaturated fatty acids (PUFAs) and serum biomarkers of inflammation, endothelial dysfunction, oxidative stress, and thrombosis in Chinese with risk factors of metabolic syndrome (MetS).
*Methods* This study was a secondary analysis of a 12-week, randomized, parallel-group trial in participants screened for MetS. The analysis included only those with 2 or more components of MetS before receiving either lifestyle counseling (LC, $n = 90$) or LC + 30 g/day flaxseed supplementation (LCF, $n = 83$).
*Results* Compared to the LC group, those in the LCF group experienced significant increases in total erythrocyte n-3 PUFAs, α-linolenic acid, eicosapentenoic acid, and docosapentenoic acid (all $P < 0.001$), while total n-6 PUFAs ($P < 0.05$) and n-6/n-3 ratio decreased ($P < 0.001$). Arachidonic acid increased significantly in the LC group ($P < 0.001$), and serum high-sensitivity C-reactive protein, interleukin-18, soluble intracellular adhesion molecular-1, E-selectin, and plasminogen activator inhibitor-1 declined significantly in both groups (all $P < 0.05$), but no between-group differences were observed. There was no significant change in serum interleukin-6, tumor necrosis factor-α, soluble vascular adhesion molecular-1, monocyte chemoattractant protein-1, and oxidized low-density lipoprotein in either group.
*Conclusions* These data suggest that flaxseed supplementation increases erythrocyte n-3 PUFAs, decreases n-6 PUFAs and n-6/n-3 ratio in participants with risk factors of MetS, but has no additional benefits beyond the lifestyle consulting for the multiple biomarkers tested in the current study.

**Keywords** Flaxseed · PUFA · Cytokines · Metabolic syndrome

**Abbreviations**

| | |
|---|---|
| ALA | α-Linolenic acid |
| PUFA | Polyunsaturated fatty acid |
| MetS | Metabolic syndrome |
| LC | Lifestyle counseling |
| LCF | LC + 30 g/day flaxseed |
| FAME | Fatty acid methyl ester |
| hsCRP | High-sensitivity C-reactive protein |
| IL-6 | Interluekin-6 |
| TNF-α | Tumor necrosis factor-α |
| MCP-1 | Monocyte chemotactic protein-1 |
| sICAM-1 | Soluble intercellular adhesion molecule-1 |
| sVCAM-1 | Soluble vascular adhesion molecule-1 |
| PAI-1 | Plasminogen activator inhibitor-1 |
| ox-LDL | Oxidized low-density lipoprotein |
| IL-18 | Interleukin-18 |
| EPA | Eicosapentenoic acid |
| DHA | Docosahexenoic acid |
| DPA | Docosapentenoic acid |

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LA Linoleic acid
AA Arachidonic acid

## Introduction

Flaxseed is a rich source of α-linolenic acid (ALA), plant lignans, and dietary fiber [1]. Beyond its own benefit to metabolic disorders, ALA could be converted to long-chain n-3 polyunsaturated fatty acids (PUFAs) and induce decrease in n-6/n-3 PUFA ratio to have further favorable effect [2, 3]. However, few studies have been carried out in people with or at high risk for metabolic syndrome (MetS), a condition closely associated with cardiovascular diseases and diabetes [4]. Besides, most studies in this regard were conducted in western populations, and it remains unknown how n-3 PUFAs would be changed by flaxseed supplementation in Asian people who have different diet.

MetS is often accompanied by inflammation, endothelial dysfunction, oxidative stress, and thrombosis which are linked with the pathogeneses of cardiometabolic diseases [5]. Previous studies indicate that flaxseed and its derivatives have moderate protective effects on some of these biomarkers [6–10]. But little is known regarding the effect of whole flaxseed in individuals who exhibit MetS risk factors. In the present study, we investigated effects of ground whole flaxseed supplementation on erythrocyte PUFAs, and biomarkers of inflammation, endothelial dysfunction, thrombosis, and oxidative stress in Chinese screened for MetS.

## Method

### Study design and participants

The current study was a secondary analysis of a randomized, placebo-controlled parallel-group trial which determined the additive effects of flaxseed supplementation on individuals screened for MetS following low-intensive lifestyle counseling (LC) [11]. Details of intervention have been described elsewhere [11]. Briefly, a total of 189 participants aged 35–65 years were randomly assigned to the LC ($n = 94$) or LC + 30 g/day of flaxseed (LCF, $n = 95$) groups. Potential candidates were screened for MetS using the updated National Cholesterol Education Program Adult Treatment Panel III criteria for Asian Americans [4]. However, due to discrepancies in screening between physicians and study staff, not all study participants met the full criteria of MetS. Therefore, the current analysis was restricted in 173 (92 %) participants with at least 2 MetS components ($n = 90$ from the LC group and $n = 83$ from the LCF group), to represent those at high risk for more severe conditions.

### Intervention

All participants were offered lifestyle counseling by a registered dietitian based on the American Heart Association guidelines [11]. In addition, each participant received two 100 g isocaloric breads accounting for about 1,800 kJ/day. The breads for LCF group contained 30 g ground whole flaxseed providing 7 g ALA per day. Participants were instructed to partially substitute the bread for staple foods in their diets while maintaining their usual levels of energy intake, physical activity, and medications. Adherence was evaluated by recording leftover bread on a daily basis; compliance was estimated to be 98.7 % [11]. Because the control and the flaxseed breads had different appearances and taste, the study was considered single-blinded. The study protocol was approved by the Institutional Review Board of the Institute for Nutritional Sciences, and all participants provided written informed consent.

### Measurements

At the beginning and completion of the intervention, fasting blood samples were collected, separated, aliquoted, and stored at −80 °C until analysis [11]. Erythrocyte fatty acids were extracted by hexane and isopropanol, and incubated with a mixture of methanol and sulfuric acid for fatty acid methyl esters (FAMEs). FAMEs were identified by gas chromatography coupled with positive chemical ionization using methane as the reagent gas (Agilent 6890 GC-5975B). Relative amounts of each fatty acid were calculated as the percentages of each fatty acid in comparison with the total. Serum high-sensitivity C-reactive protein (hsCRP) was assessed using a high-sensitivity immunoturbidimetric assay on a Hitachi 7080 automatic analyzer with commercial kits (Roche Diagnostics, Mannheim, Germany). Other biomarkers were measured by commercial ELISA kits, including interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), monocyte chemotactic protein-1 (MCP-1), soluble intercellular adhesion molecule-1 (sICAM-1), soluble vascular adhesion molecule-1 (sVCAM-1), plasminogen activator inhibitor-1 (PAI-1), E-selectin (R&D Systems, Inc., Minneapolis, USA), oxidized LDL (ox-LDL [Mercodia AB, Uppsala, Sweden]), and interleukin-18 (IL-18 [MBL International, Woburn, USA]).

### Statistical analyses

An intention-to-treat principle was applied. Pre-post differences were compared using paired Student's $t$ tests. Between-group differences were assessed using general linear models after controlling for baseline values of respective biomarkers. Data were analyzed using Stata

**Table 1** Baseline characteristics of LC and LCF groups

| Variables | LC ($n = 90$) | LCF ($n = 83$) | $P$ value |
|---|---|---|---|
| Age (year) | 48.7 ± 7.9 | 48.9 ± 8.1 | 0.84 |
| Male | 50 (55.6) | 47 (56.6) | 0.89 |
| Weight (kg) | 71.1 ± 10.8 | 70.2 ± 9.8 | 0.57 |
| BMI (kg/m$^2$) | 25.5 ± 2.4 | 25.1 ± 2.3 | 0.30 |
| Waist circumference (cm) | 90.1 ± 7.6 | 89.2 ± 6.2 | 0.41 |
| SBP (mmHg) | 134.5 ± 14.5 | 134.4 ± 17.0 | 0.98 |
| DBP (mmHg) | 85.9 ± 8.8 | 86.3 ± 11.3 | 0.80 |
| Glucose (mmol/l) | 6.34 ± 1.39 | 6.48 ± 1.89 | 0.58 |
| Triglycerides (mmol/l) | 2.38 ± 1.48 | 2.17 ± 0.97 | 0.26 |
| Total cholesterol (mmol/l) | 6.16 ± 1.67 | 6.07 ± 1.53 | 0.72 |
| HDL cholesterol (mmol/l) | 1.39 ± 0.47 | 1.41 ± 0.39 | 0.67 |
| Metabolic syndrome | 64 (71.1) | 57 (68.7) | 0.73 |
| Self-reported drinking, yes | 49 (54.4) | 55 (66.3) | 0.11 |
| Self-reported smoking, yes | 20 (22.2) | 23 (27.7) | 0.40 |

Data are mean (SD) for continuous variables and $n$ (%) for categorical variables, and compared between groups by ANOVA or $\chi^2$ test, respectively

*LC* lifestyle counseling, *LCF* lifestyle counseling plus 30 g/day flaxseed, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

(version 9.2; College Station, TX), and a two-sided <0.05 was considered statistically significant.

## Results

As shown in Table 1, the two groups were well balanced after randomization. Table 2 shows erythrocyte PUFAs and cardiometabolic biomarkers at 0 and 12 weeks in LC and LCF groups. Of note, flaxseed supplementation significantly increased total n-3 PUFAs, while decreased total n-6 PUFAs and n-6/n-3 ratio. Specifically, there were significant increases in erythrocyte ALA, eicosapentenoic acid (EPA), and docosapentenoic acid (DPA), but not docosahexenoic acid (DHA) in the LCF group compared to the LC group (all $P < 0.001$). In addition, linoleic acid (LA) decreased in both groups, while arachidonic acid (AA) increased significantly in the LC group but not in the LCF group, with no differences noted between arms. Overall, no significant treatment effects were found for biomarkers of inflammation, endothelial dysfunction, thrombosis, and oxidative stress at the end of intervention, although serum hsCRP, IL-18, E-selectin, sICAM-1, and PAI-1 decreased in both groups.

## Discussion

In our study, flaxseed supplementation in Chinese with risk factors of metabolic syndrome significantly increased total n-3 PUFAs, and ALA, EPA and DPA, but not DHA, in consistent with most of previous studies conducted in western people [8]. In fact, few studies reported changes of DHA status in humans [2, 3, 8, 9, 12]. This might be explained by the fact that ALA prevents downstream desaturation by monopolizing delta-6-desaturase, the enzyme desaturates not only ALA to C18: 4n-3, but also C24: 5n-3 to DHA in the pathway of n-3 PUFA biosynthesis [13]. Previous studies suggested humans to be poor DHA synthesizers because our ancient diet, unlike modern ones, was rich in DHA [3]; hence, it is possible that the body has not developed additional means to convert sufficient DHA from ALA. On the other hand, the observed changes in LA and total n-6 PUFAs in both groups may attribute to the lifestyle counseling offered in our study in which reduction in fat intake was encouraged [11]. Beyond that, increased ALA may competitively suppress conversion of LA and accumulation of long-chain n-6 PUFAs, which in our study could be reflected by unchanged AA in the LCF group in comparison with increased erythrocyte AA in the LC group. Consequently, we found flaxseed supplementation lead to a preferable change in n-6/n-3 ratio which has been suggested to be associated with lower risks of many chronic diseases including cardiovascular diseases and diabetes [14].

Despite the changes in erythrocyte PUFA status, we did not observe significant effects of flaxseed supplementation for all measured cardiometabolic biomarkers. The lack of effect for flaxseed on inflammatory markers is in agreement with two earlier intervention studies with whole flaxseed [8, 9]. However, 60 g/day flaxseed in obese persons significantly reduced serum CRP [7]. It has been suggested that at least 10 g/day of ALA is needed to ameliorate inflammation [1], which is higher than the dose used in the present trial. Few studies have investigated effects of whole flaxseed on markers of endothelial dysfunction, thrombosis, and oxidative stress. Previously, ALA, but not lignans from flaxseed, was found to decrease sICAM-1 and E-selectin [1, 6]. In another study, PAI-1 remained unchanged after consumption of 9.5 g/day ALA for 6 months in dyslipidemic participants [10]. Our data also showed that flaxseed treatment did not change ox-LDL levels, which is similar to the findings of Bloedon et al. [9].

The strengths of our study include a relatively large sample that provides sufficient power. Furthermore, the stability of erythrocytes in the circulatory system enables us to investigate longer-term effects of flaxseed supplementation on n-3 status in humans. However, although the duration of our intervention was longer than many previous studies [2], it still may not be sufficient to observe complete changes in erythrocyte PUFAs which might happen if flaxseed supplementation had continued. Second, the n-3 PUFAs in whole flaxseed may have relatively low

**Table 2** Erythrocyte PUFAs, biomarkers for inflammation, endothelial dysfunction, thrombosis, and oxidative stress at baseline and completion in the LC and LCF groups

| Variables | LC ($n = 90$) | | LCF ($n = 83$) | | Treatment effects | $P$ value[b] |
|---|---|---|---|---|---|---|
| | B | E[a] | B | E | | |
| *Erythrocyte PUFAs* | | | | | | |
| Total n-3 (%) | 8.06 ± 1.37 | 8.07 ± 1.31 | 7.96 ± 1.29 | 8.37 ± 1.23*** | 0.39 (0.17 to 0.60) | <0.001 |
| ALA (%) | 0.24 ± 0.10 | 0.22 ± 0.11 | 0.22 ± 0.09 | 0.38 ± 0.15*** | 0.17 (0.13 to 0.21) | <0.001 |
| EPA (%) | 0.58 ± 0.24 | 0.54 ± 0.19** | 0.57 ± 0.24 | 0.65 ± 0.22*** | 0.13 (0.08 to 0.17) | <0.001 |
| DPA (%) | 1.69 ± 0.24 | 1.73 ± 0.26* | 1.64 ± 0.22 | 1.91 ± 0.23*** | 0.21 (0.16 to 0.27) | <0.001 |
| DHA (%) | 5.56 ± 1.12 | 5.59 ± 1.07 | 5.54 ± 1.02 | 5.43 ± 1.00 | −0.14 (−0.31 to 0.03) | 0.10 |
| Total n-6 (%) | 33.94 ± 1.82 | 33.50 ± 1.86** | 34.06 ± 1.59 | 33.16 ± 1.55*** | −0.41 (−0.82 to −0.00) | 0.0495 |
| LA (%) | 15.08 ± 2.04 | 14.10 ± 2.05*** | 15.35 ± 1.88 | 14.21 ± 1.76*** | 0.02 (−0.53 to 0.57) | 0.93 |
| AA (%) | 12.54 ± 0.98 | 12.79 ± 1.12** | 12.62 ± 1.21 | 12.77 ± 1.18 | −0.07 (−0.33 to 0.18) | 0.57 |
| N-6/n-3 ratio | 4.37 ± 0.97 | 4.29 ± 0.90 | 4.41 ± 0.85 | 4.06 ± 0.74*** | −0.26 (−0.41 to −0.11) | <0.001 |
| *Biomarkers for inflammation* | | | | | | |
| hsCRP (mg/l) | 1.12 (0.75−1.97) | 1.11 (0.69–1.85)*** | 1.01 (0.72–2.12) | 1.00 (0.63–1.92)*** | −0.54 (−1.14 to 0.07) | 0.25 |
| IL-18 (pg/ml) | 256.8 (198.6–320.0) | 223.9 (179.7–287.6)*** | 226.9 (192.2–306.8) | 214.5 (177.1–257.4)*** | −7.2 (−20.3 to 5.9) | 0.37 |
| IL-6 (pg/ml) | 0.79 (0.53–1.48) | 0.82 (0.57–1.48) | 0.89 (0.60-1.31) | 0.95 (0.61–1.46) | 0.08 (−0.20 to 0.36) | 0.45 |
| TNF-α (pg/ml) | 1.04 (0.79–1.41) | 1.08 (0.89–1.38) | 1.00 (0.66–1.28) | 1.12 (0.81–1.46) | 0.24 (−0.47 to 0.95) | 0.91 |
| *Biomarkers for endothelial dysfunction* | | | | | | |
| E-selectin (ng/ml) | 40.39 (26.98–49.58) | 33.98 (23.11–42.69)*** | 38.36 (29.31–46.74) | 33.71 (24.83–41.83)*** | 0.92 (−0.94 to 2.77) | 0.45 |
| sVCAM-1 (ng/ml) | 565.0 (493.4–649.9) | 548.7 (455.1–625.9)** | 577.9 (472.4–671.1) | 530.1 (453.9–646.4) | 13.4 (−25.4 to 52.2) | 0.62 |
| sICAM-1 (ng/ml) | 216.5 (178.3–245.7) | 200.0 (165.5–232.6)** | 220.0 (190.8–287.1) | 199.4 (173.6–256.6)* | −4.0 (−13.4 to 5.4) | 0.25 |
| MCP-1 (pg/ml) | 283.7 (244.1–332.0) | 293.4 (254.1–364.9)* | 289.5 (238.4–334.7) | 281.2 (234.5–343.7) | −12.2 (−31.4 to 7.1) | 0.08 |
| *Biomarker for thrombosis* | | | | | | |
| PAI-1 (ng/ml) | 8.80 (7.48–10.58) | 8.13 (6.43–9.55)*** | 8.55 (6.91–11.08) | 7.82 (6.39–9.26)** | −0.03 (−0.70 to 0.64) | 0.86 |
| *Biomarker for oxidative stress* | | | | | | |
| ox-LDL (U/l) | 54.6 (47.2–63.8) | 52.0 (45.7–64.0) | 52.4 (43.6–59.3) | 52.2 (44.2–61.6) | 0.14 (−2.80 to 3.08) | 0.54 |

*LC* lifestyle counseling, *LCF* lifestyle counseling plus 30 g/day flaxseed, *B* baseline, *E* end of intervention, *PUFA* polyunsaturated fatty acid, *ALA* α-linolenic acid, *EPA* eicosapentenoic acid, *DPA*, docosapentenoic acid, *DHA* docosahexenoic acid, *LA* linoleic acid, *AA* arachidonic acid, *hsCRP* high-sensitivity C-reactive protein, *IL-18* interleukin-18, *IL-6* interleukin-6, *TNF-α* tumor necrosis factor-α, *sVCAM-1* soluble vascular adhesion molecular-1, *sICAM-1* soluble intracellular adhesion molecular-1, *MCP-1* monocyte chemo-attractant protein-1, *PAI-1* plasminogen activator inhibitor-1, *ox-LDL* oxidized low-density lipoprotein

[a] Compared between baseline and end of intervention by paired $t$ test, log-transformation was performed if necessary: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

[b] $P$ values between LCF and LC groups were calculated in general linear models after adjustment of baseline value of respective variables

digestibility due to the high fiber content, though, in a previous study, Austria et al. suggested that ground flaxseed can still induce significant increases in ALA [15].

In conclusion, supplementation with 30 g/day whole flaxseed for 12 weeks increased total erythrocyte n-3 PUFAs, ALA, EPA, and DPA, while decreased total n-6 PUFAs and n-6/n-3 ratio. However, flaxseed did not exert additional benefit on biomarkers of inflammation, endothelial dysfunction, thrombosis, and oxidative stress. Due to the low conversion rate of ALA, flaxseed may not be an alternative to the biologically important DHA and EPA at least on a short-term basis, but may still improve the ratio of n-6 and n-3.

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