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ORIGINAL ARTICLE

Linseed oil increases HDL_3 cholesterol and decreases blood pressure in patients diagnosed with mild hypercholesterolaemia

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Abstract

Background: Linseed oil has cardio-protective effects. However, its antihypertensive action has not yet been well characterised.

Aim: The primary purpose of the study was to evaluate the effect of short-term dietary supplementation with linseed oil on blood pressure (BP) and lipid metabolism in patients with mild hypercholesterolaemia. The secondary aim was to assess the effect of linseed oil on nitric oxide pathway and selected serum trace metals.

Methods: 150 volunteers: 43 men (49.9 ± 11.5 years) and 107 women (53.2 ± 10.3 years), diagnosed with mild hypercholesterolaemia, were assessed prospectively for BP and lipid levels, before and after lipid-lowering diet plus linseed oil supplementation at a dose of 15 mL daily for four weeks (study groups) or four-weekly lipid-lowering diet (control group). Multivariate logistic regression analysis was used to determine the effect of linseed oil on BP after adjustment for age, sex, height, body weight, body mass index, smoking status, and alcohol consumption.

Results: Supplementation with linseed oil significantly decreased low-density lipoprotein (LDL)- and non-high-density lipoprotein (HDL) cholesterol, and increased HDL- and HDL_3- cholesterol levels. Additionally, linseed oil decreased diastolic BP in men (95% confidence interval [CI]: –6.0 to –1.1, $p < 0.006$), whereas in women linseed oil reduced ($p < 0.001$) systolic BP (–3.6 mmHg; 95% CI: –5.8 to –1.5) as well as diastolic BP (–4 mmHg; 95% CI: –5.8 to –2.1). Women with higher BP displayed an increase in serum L-arginine level ($p < 0.01$). In the logistic regression model oil consumption was associated with a decrease in mean BP (adjusted odds ratio 3.85; 95% CI 1.32–11.33).

Conclusions: Our findings confirm the benefit of short-term linseed oil use in mild hypercholesterolaemia, particularly in patients with increased blood pressure.

Key words: linseed oil, lipids, blood pressure, nitric oxide

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INTRODUCTION

Essential polyunsaturated fatty acids (PUFAs) are involved in the processes of intracellular signalling, and thus may modify cardiovascular risk factors. However, data regarding the effects of nutraceutical supplementation on the incidence of cardiovascular outcomes are lacking [1]. Omega-3 (n-3) fatty acids: docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and α-linolenic acid (ALA), can modify the residual cardiovascular risk. All these acids improve lipid pattern [2, 3] and insulin sensitivity [4], attenuate oxidative stress [5], and decrease prothrombotic [6] as well as proinflammatory [7] potentials.

The impact of PUFAs on blood pressure (BP) in hypertonic or normotonic patients is less clear, although most clinical studies show the hypotensive effect of n-3 fatty acids [8, 9]. The hypotensive effect of PUFAs is usually observed in patients aged > 45 years, taking higher doses of PUFAs (above 3–4 g per day) for a duration of > 12 weeks. Likewise, in children, high n-3 PUFA levels were associated with lower BP [10]. Hypotensive effect has also been documented with regard to DHA and EPA. Intake of n-3 PUFAs at a dose of over 3 g per day resulted in systolic BP (SBP) decrease of 5.5 mmHg on average and diastolic BP (DBP) drop of 3.5 mmHg on av-

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erage, and the hypotensive effect of DHA was stronger than one achieved with EPA [11].

The antihypertensive effect of n-3 fatty acids would not be unexpected because one of the concepts possibly explaining pathogenesis of hypertension is the membrane hypothesis. According to this hypothesis, changes in the structure and function of cell membranes are connected to numerous effects leading to increased BP. Meanwhile, fatty acids are a fundamental component of cell membrane structure and have a significant effect on its properties such as fluidity, permeability, ion transport, calcium binding, and prostaglandin synthesis [12]. However, some studies do not support the major role of n-6 or n-3 PUFA intake in BP change over time [13].

The role of linseed oil — rich in ALA — in BP regulation also remains unclear. When used in relatively small doses in normotonic and hypertonic patients, it either decreased arterial BP [8, 9, 14] or had no vascular effect [15–17]. Also, the mechanisms underlying the vascular action of ALA are ambiguous. In some experiments performed in vitro, decreased prostacyclin production in perfused aorta [18] or increased aortic ring reactivity to phenylephrine [19] were observed in vessels obtained from rats fed with linseed oil. A diet rich in linseed oil restored endothelial function in spontaneously hypertensive rats [20] and alleviated hypertension induced by n-3 PUFA deficiency [21].

The purpose of the study was to evaluate the effect of short-term dietary supplementation with linseed oil on BP and lipid metabolism in patients with moderate hypercholesterolaemia. We also sought to assess the effect of linseed oil on nitric oxide (NO) pathway and selected trace metals in the blood.

METHODS

Subjects

The present open-labelled study was performed on a group of 150 volunteers: 43 men aged 49.9 ± 11.5 years and 107 women aged 53.2 ± 10.3 years. On the basis of cholesterol level, clinical examination, and family history, all patients were diagnosed with mild hypercholesterolaemia. Patients were asked to complete the dietary frequency questionnaire and supply data on their lifestyle, illnesses, family diseases, and medications. In all subjects, anthropometric data were collected using calibrated equipment and standardised methodology. Body mass index (BMI) was estimated as the body mass divided by the square of the body height (kg/m^2). A medical examination was carried out. Arterial BP was measured by the auscultatory method using daily calibrated aneroid manometer SB27332M with stethoscope SB10783G (ABC Euroscience, NASCO Authorised Distributor). Arterial pressure was measured on both upper limbs after a 10-min rest in the sitting position. For analyses, the higher values of the pressure were selected, and mean arterial pressure (MAP) was calculated. Cardiovascular risk was stratified individually according to the Pol-SCORE 2015 scale [22].

The experimental protocol was compliant with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and conducted with the approval of the Local Ethics Committee (No. KB-516/2012). Patients gave written, informed consent to participate in the study.

Studied groups

The main criterion for inclusion in the study was the diagnosis of hypercholesterolaemia [22] that previously had not been treated pharmacologically or non-pharmacologically. In low or moderate cardiovascular risk patients, increased concentrations of low-density lipoprotein cholesterol (LDL-C) have been accepted as values ≥ 115 mg/dL, in high-risk patients as levels ≥ 100 mg/dL, and in very high-risk patients as levels ≥ 70 mg/dL [22]. Criteria for exclusion were: hypothyroidism, chronic kidney disease with proteinuria, chronic dialysis, poorly controlled diabetes, cholestasis, hormone disorders or chronic steroid treatment, as well as treatment with non-selective β-blockers, tocilizumab, or protease inhibitors used in the treatment of patients with HIV. Participants were assigned to the groups of patients on a low-fat diet supplemented with linseed oil (study groups) or to the control group following only a low-fat diet. Linseed oil was given at the volume of 30 mL daily for four weeks. The low-fat dietary interventions ranged from very low-fat diet (≤ 10% of caloric intake) to more moderate goals of ≤ 30% of caloric intake. The intensity of the interventions varied from pamphlets or instructions given at baseline, in accordance with the recommendations of the European Society of Atherosclerosis. The control of linseed oil intake was performed on the basis of oral declaration of volunteers in face-to-face interviews with the participants.

Depending on baseline BP in comparison to the control group, patients from the study groups were divided into group I with higher values of BP and group II with lower BP, similar to controls. The criterion for group I was the so-called high normal pressure (SBP 130–139 mmHg and/or DBP 85–89 mmHg), and for group II and control — lower values of pressure. The control group (group III) included normotonic subjects. However, in two men and nine women hypertension had been diagnosed prior to the study. Four of them (one man and three women) were chronically treated with an angiotensin converting enzyme inhibitor or a sartan at a low dose. Also, in groups I and II, there were altogether 11 subjects diagnosed with hypertension, previously qualified for non-pharmacological treatment. In groups I and II no hypotensive drugs were used.

Biochemical measurements

Venous blood was taken from subjects after 12 h of fasting and centrifuged at 3500 g for 15 min at 4°C. Serum samples were stored at a temperature of –80°C. Serum total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) were measured using the SPINREACT (SantEsteve De Bas, Girona, Spain) enzymatic assay. LDL-C was estimated among patients with a TG concentration lower

than 4.52 mmol/L (400 mg/dL) by means of the Friedewald formula. The QUANTOLIP® HDL (Technoclone GmbH, Vienna, Austria) precipitation test was used to measure HDL_2-C and HDL_3-C levels. The non-HDL-C was calculated as the difference between TC and HDL-C concentrations. Non-esterified fatty acids (NEFAs) were measured colourimetrically using enzymatic RANDOX tests.

The serum concentrations of copper and zinc were determined by atomic absorption spectrometry using Solaar M6, ThermoElemental Co spectrometer. Copper concentrations were determined by flame absorption spectrometry (FAAS) in an air-acetylene flame at a wavelength of 324.8 nm (and 213.9 nm for zinc) with deuterium background correction. Calibration curves were determined using CPI International's Single-Element Cooper (Zinc) standard at 1000 μg/mL. Seronorm™ Trace Elements Serum-certified serum metal standards were used to control the content of copper and zinc.

Serum concentrations of L-arginine, and asymmetric and symmetric dimethylarginine (ADMA and SDMA, respectively) were determined by high-performance liquid chromatography using a spectrofluorescence detector.

Serum concentrations of the 8-epi prostaglandin F_{2alpha} (8-epi-$PGF_{2\alpha}$) were determined using ELISA assays by EIAab® WUHAN EIAAB Science Co., Ltd. (Wuhan, China).

Characteristics of the supplement

In this study cold pressed linseed oil (Plant Oils Vis Natura, Kamieniec Wroclawski, Poland) was used. The content of fatty acids in the oil was determined with gas chromatography, and the proportion of n-3 to n-6 fatty acids was 2.2:1 [23].

Statistical analysis

The χ^2 and Shapiro-Wilk tests were used to test the normal distribution of variables. In case the hypotheses of normality of variable distributions were rejected, nonparametric tests were used for the analysis (Mann-Whitney U test for independent group comparisons, Kruskal-Wallis test with post hoc test, and Wilcoxon pair order for comparison of group variables). Multivariate tables and McNamara tests were used for qualitative variables. For normal distributions ANOVA parametric tests with post hoc tests (Tukey test, NIR test for unequal numbers) and t-paired tests for dependent variables were used. Linear correlations were evaluated on the basis of the Spearman rank order analysis.

Multivariate logistic regression analysis was used to determine the effect of linseed oil on blood pressure, after adjustment for age, sex, height, body weight, BMI, smoking status, and alcohol consumption. The qualitative prediction was the use of linseed oil, and the dependent variable was the decrease in SBP, DBP, or MAP. P-values < 0.05 were assumed to be statistically significant. Statistical analysis was performed using Statistica 12.5 statistical package (StatSoft, Krakow, Poland).

RESULTS

The mean anthropometric data were similar in all groups, and the median BMI values were typical of the overweight/obesity category. About 17% of women and 33% of men were tobacco smokers, and about 58% of women and 77% of men reported moderate alcohol consumption (defined as consumption of one alcohol unit per day for women and 1–4 units per day for men). In women in group I, SBP, DBP, and MAP were higher in comparison to controls ($p < 0.01$, $p < 0.001$, and $p < 0.001$, respectively), whereas in men in group I, MAP values were significantly higher than in controls, exceeding the upper range of the norm, i.e. 100 mmHg (Table 1).

Because the main inclusion criterion for all patients was mild hypercholesterolaemia without other lipid disturbances, the levels of lipid parameters such as TC, LDL-C, HDL-C, and TG did not differ significantly between groups (Table 2).

In the medical examination, none of the subjects were found to have clinical symptoms of hyperlipidaemia, such as xanthomas or arcus senilis in the outer edge of cornea. Cardiovascular risk estimated as a 10-year absolute risk for cardiovascular death was low (≤ 1%) in 73 subjects, moderate (> 1% and < 5%) in 48 persons, and high (≥ 5% and < 10%) in 29 patients. Based on cholesterol levels (Table 2) and family history, polygenic hypercholesterolaemia was suspected in all subjects.

The supplementation with linseed oil, given at the volume of 30 mL daily for four weeks, significantly influenced the lipid pattern in all subjects with mild hypercholesterolaemia. In group I (patients with higher BP) and in group II (patients with lower BP), linseed oil decreased LDL-C and non-HDL-C but increased HDL-C and HDL_3-C levels. Decreases in serum TG and changes in NEFAs were statistically significant in group II (Table 3).

In all patients, a positive linear correlation between TG and NEFAs ($r = 0.274$, $p = 0.01$) and between BMI and NEFAs ($r = 0.260$, $p = 0.01$) was shown, as well as a negative linear dependence between TG and HDL_3-C ($r = –0.4397$, $p < 0.001$).

It cannot be ruled out that women took linseed oil more reliably than men, although the differences in the effect of the oil on lipids in both sexes were not statistically significant (Table 4).

In both groups of subjects treated with linseed oil, aside from the hypolipemic effect, a decrease in SBP, DBP, and MAP was observed (Table 3). In all men consuming linseed oil, the hypotensive effect (–4 mmHg) concerned DBP (95% confidence interval [CI]: –6.0 to –1.1, $p < 0.006$) but not SBP (95% CI: –0.9 to 10.9, $p = 0.09$). In women, linseed oil reduced both SBP (–3.6 mmHg; 95% CI: –5.8 to –1.5, $p < 0.001$) and DBP (–4 mmHg; 95% CI: –5.8 to –2.1, $p < 0.001$). In the control group, after four weeks of using a low-cholesterol diet, SBP and DBP values did not change significantly in men (95% CI: –5.6 to 6.7, $p = 0.858$ for SBP and 95% CI: –9.0 to 1,0, $p = 0.103$ for DBP) or in women (95% CI: –3.3 to 3.8, $p = 0.868$ for SBP and 95% CI: –2.3 to 4.3, $p = 0.532$ for DBP).

Table 1. Characteristics of the studied groups

	Group I (with higher BP) 15 men, 25 women	Group II (with lower BP) 16 men, 43 women	Control group (with lower BP) 12 men, 39 women
Age [years]:			
Men	49.0 ± 15.1	53.1 ±10.2	46.9 ± 7.1
Women	52.7 ± 9.7	51.4 ± 10.7	55.9± 9.7
Height [cm]:			
Men	1.8 ± 0.1	1.8 ± 0.1	1.8 ± 0.1
Women	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.1
Body mass [kg]:			
Men	95.4 ± 13.9	88.3 ± 10.5	89.6 ± 14.3
Women	70.8 ± 11.7	74.5 ± 15.6	69.3 ± 13.5
BMI [kg/m^2]:			
Men	30.8 (26.2; 32.4)	27.5 (24.8; 29.1)	28.4 (27.6; 32.1)
Women	25.4 (23.2; 29.4)	27.3 (23.6; 31.1)	26.8 (22.5; 28.6)
SPB [mmHg]:			
Men	136.0 ± 20.0	127.0 ± 21.0	127.0 ± 8.4
Women	131.0 ± 16.0*	123.0 ± 14.0	120.0 ±15.0
DPB [mmHg]:			
Men	84.0 ± 9.3	81.0 ± 10.3	81.0 ± 7.0
Women	82.0 ± 9.8**	77.0 ± 8.7	73.0 ± 10.3
MAP [mmHg]:			
Men	101.6 ± 12.4**	96.1 ± 13.4	96.4 ± 6.8
Women	98.7 ± 11.6**	92.2 ± 10.2	89.0 ± 11.3
Diabetes mellitus:			
Men	0 (0)	0 (0)	1 (10)
Women	3 (12)	4 (8)	0 (0)
Hypertension:			
Men	3 (20)	1 (6)	2 (16)
Women	5 (20)	2 (4)	9 (23)
Smokers:			
Men	5 (33)	7 (43)	2 (17)
Women	1 (4)	7 (14)	10 (25)
Pack-years:			
Men	12.6 ± 14.0	23.4 ± 15.8	10.5 ± 6.3
Women	40.0 ± 0.0	8.2 ± 6.5	15.1 ± 15.3

Data are show as mean ± standard deviation, median and interquartile range, or number (percentage). BMI — body mass index; BP — blood pressure; SBP — systolic blood pressure; DSP — diastolic blood pressure; MAP — mean arterial pressure; *p < 0.01, **p < 0.001 — statistically significant differences with respect to the control group

In the logistic regression model, which was constructed using backward stepwise regression, the association between linseed oil consumption and changes in BP was estimated.

Table 2. Lipids before dietary supplementation with linseed oil (groups I–II) and in the control group

	Group I (with higher BP) 15 men; 25 women	Group II (with lower BP) 16 men; 43 women	Control group (with lower BP) 12 men; 39 women
TC [mg/dL]:			
Men	224.0 ± 42.0	238 ± 40	234 ± 37
Women	237.0 ± 35.0	241 ± 46	228 ± 46
LDL-C [mg/dL]:			
Men	142.0 ± 32.0	160.0 ± 35.0	162.0 ± 51.0
Women	155.0 ± 34.0	150.0 ± 44.0	144.0 ± 42.0
HDL-C [mg/dL]:			
Men	51.6 ± 11.0	54.1 ± 12.9	42.5 ± 11.7
Women	59.9 ± 15.8	63.0 ± 19.5	63.7± 15.2
HDL_2-C [mg/dL]:			
Men	12.2 ± 3.8	13.1 ± 5.0	9.5 ± 4.2
Women	15.9 ± 7.8	18.0 ± 9.5	18.7 ± 7.8
HDL_3-C [mg/dL]:			
Men	39.3 ± 8.3	41.0 ± 9.3	33.0 ± 8.6
Women	44.0 ± 9.4	44.9 ± 11.4	44.9 ± 10.5
Non-HDL-C [mg/dL]:			
Men	172.0 ± 48.6	184.0 ± 36.2	191.0 ± 39.6
Women	177.0 ± 35.1	179.0 ± 48.3	165.0 ± 47.5
TG* [mg/dL]:			
Men	192.0 ± 346.0	124.0 ± 53.6	177.0 ± 123.0
Women	111.0 ± 71.6	144.0 ± 86.3	103.0 ± 56.7
NEFA* [mmol/L]:			
Men	0.485 ± 0.26	0.439 ± 0.28	0.586 ± 0.36
Women	0.588 ± 0.26	0.540 ± 0.19	0.540 ± 0.25

Data are show as mean ± standard deviation. Conversion factors (CFs) to SI units are as follows: CF for cholesterol — 38.67; CF for TG — 88.57. BP — blood pressure; HDL-C — high-density lipoprotein cholesterol; LDL-C — low-density lipoprotein cholesterol; NEFA — non-esterified fatty acids; TC — total cholesterol; TG — triglycerides
*The p-value was checked by the Kruskal-Wallis test. For other parameters it was denoted by the ANOVA test

After adjustment for confounding factors, such as age, height, body mass, BMI, cholesterol, smoking status, and excessive alcohol consumption, the effect of dietary supplementation with linseed oil on MAP was significant. Oil consumption was associated with a decrease ($p < 0.01$) in MAP (aOR [adjusted odds ratio] 3.85, 95% CI 1.32–11.33).

In group I, due to higher BP in comparison to control, L-arginine, ADMA, SDMA, 8-epi-$PGF_{2\alpha}$, as well as blood concentrations of metals such as copper and zinc were determined. Linseed oil used for four weeks led to an increase in L-arginine ($p < 0.01$) and ADMA ($p < 0.05$), but only in women. Simultaneously, zinc levels in women decreased ($p < 0.05$). The

Table 3. Changes in lipids and blood pressure induced by linseed oil (groups I–II) in comparison to controls

Before (I) and after (II) supplementation and/or hypolipemic diet	Group I (n = 40)			Group II (n = 59)			Control group (n = 51)		
	Mean ± SD	p	CI (–95%; +95%)	Mean ± SD	p	CI (–95%; +95%)	Mean ± SD	p	CI (–95%; +95%)
Total-C I [mg/dL]	238 ± 34		–23;	238 ± 34.6		–20;	232 ± 42		–9;
Total-C II [mg/dL]	224 ± 27	**0.003**	–5	227 ± 33.4	**0.017**	–2	232 ± 34	0.995	9
LDL-C I [mg/dL]	155 ± 30		–23;	151 ± 42.5		–29;	148 ± 42		–8;
LDL-C II [mg/dL]	140 ± 24	**< 0.001**	–8	138 ± 31.6	**0.048**	2	149 ± 31	0.791	10
Non-HDL-C I [mg/dL]	181 ± 37		–23;	176 ± 31.9		–20	172 ± 46		–9;
Non-HDL-C II [mg/dL]	167 ± 28	**0.003**	–5	165 ± 31.3	**0.017**	–2	172 ± 38	0.995	9
HDL-C I [mg/dL]	57 ± 5		1;	62 ± 20		0;	60 ± 17		–3;
HDL-C II [mg/dL]	61 ±20	**0.022**	8	65 ± 20	**0.041**	5	60 ± 17	0.878	3
HDL_2-C I [mg/dL]	15 ± 7		0;	17 ± 9.0		–3;	17 ± 8		–3;
HDL_2-C II [mg/dL]	19 ±11	**0.030**	7	17 ± 10	0.751	2	15 ± 8	0.086	0
HDL_3-C I [mg/dL]	42 ± 10		0;	45 ± 12		1;	44 ± 12		–2;
HDL_3-C II [mg/dL]	45 ± 14	**0.026**	5	47 ± 14	**0.007**	4	44 ± 11	0.661	3
TG I [mg/dL]	150 ± 23		–92;	142 ± 78		–50;	115 ± 70		–30;
TG II [mg/dL]	114 ± 84	0.198	19	111 ± 60	**0.003**	–10	106 ± 64	0.344	10
NEFA I [mmol/L]	0.5 ± 0.3		0;	0.5 ± 0.2		0;	0.5 ± 0.3		0;
NEFA II [mmol/L]	0.5 ± 0.2	0.167	0	0.6 ± 0.2	**0.035**	0	0.5 ± 0.3	0.541	0
SBP I [mmHg]	133 ± 18		–89	124 ± 17		–6;	122 ± 14		–3;
SBP II [mmHg]	127 ± 13	**0.001**	–2	121 ± 12	**0.036**	0	122 ± 13	0.819	3
DBP I [mmHg]	83 ± 10		–6;	78 ± 9		–6;	75 ± 10		–3;
DBP II [mmHg]	78 ± 10	**0.001**	–2	74 ± 10	**0.001**	–1	75 ± 10	0.082	3
MAP I [mmHg]	99 ± 12		3;	93 ± 11		1;	91 ± 11		–3;
MAP II [mmHg]	94 ± 10	**< 0.001**	7	90 ± 10	**0.003**	5	91 ± 10	0.985	2

Group I — patients with higher BP; group II and control group — patients with lower BP; p-level of statistical significance in t-paired test for dependent samples; SD — standard deviation; CI — confidence interval; other abbreviations — see Tables 1 and 2

consumption of linseed oil had no significant effect on the serum concentrations of SDMA or isoprostane levels (Table 5).

Multiple regression analysis revealed linear correlations between serum essential metals and some lipids in serum: a negative relationship between zinc and HDL-C levels ($r = –0.38$, $p < 0.05$), as well as between zinc and HDL_3-C ($r = –0.37$, $p < 0.01$).

There was also a negative correlation between zinc and L-arginine ($r = –0.32$, $p < 0.05$), as well as a positive correlation between copper and L-arginine ($r = 0.3392$, $p < 0.05$). Moreover, a positive relationship between serum copper and asymmetric dimethylarginine was shown ($r = 0.5570$, $p < 0.001$). The secondary result of linseed oil hypolipaemic and hypotensive actions was a significant cardiovascular risk factors reduction in almost 30% of subjects. No adverse effects of a four-week linseed oil supplementation were observed; this nutraceutical was completely safe.

DISCUSSION

All patients included in this study were diagnosed with mild hypercholesterolaemia. In all cases, the suspected type of hypercholesterolaemia was polygenic hypercholesterolaemia, based on medical and family history, as well as clinical and laboratory findings. This type is particularly dependent on environmental factors, including the diet. The quality of dietary habits of the majority of the adult Polish population

Table 4. Comparative summary of linseed oil-induced changes in lipids in men and women

Changes in lipids:	Group I (with higher BP)	Group II (with lower BP)	Control group (with lower BP)
Total-C [mg/dL]:			
Men	–6.6 ± 30.4	–13.2 ± 32.0	–4.4 ± 38.9
Women	–18.2 ± 24.0	–10.5 ± 33.5	1.2 ± 26.3
LDL-C [mg/dL]:			
Men	–5.6 ± 19.4	–11.5 ± 25.1	–2.1 ± 38.4
Women	–19.9 ± 21.8	–14.0 ± 64.5	2.0 ± 28.7
Non-HDL-C [mg/dL]:			
Men	–6.3 ± 30.0	–13.0 ± 32.1	–4.5 ± 38.9
Women	–18.2 ± 24.0	–10.4 ± 33.5	1.2 ± 26.4
HDL-C [mg/dL]:			
Men	3.7 ± 7.8	0.4 ± 9.5	–2.2 ± 5.6
Women	4.9 ± 12.5	3.4 ± 9.8	0.3 ± 11.4
HDL_2-C [mg/dL]:			
Men	2.5 ± 4.9	–0.1 ± 5.7	–1.6 ± 3.2
Women	4.4 ± 11.7	–0.4 ± 9.4	–1.3 ± 5.4
HDL_3-C [mg/dL]:			
Men	1.3 ± 5.1	–0.9 ± 6.1	–0.9 ± 6.4
Women	3.7 ± 8.3	3.4 ± 6.1	0.8 ± 6.5
TG [mg/dL]:			
Men	–1.2 ± 61.8	–5.0 ± 58.1	–25.5 ± 121
Women	–15.5 ± 51.3	–37.4 ± 74.6	–5.8 ± 49.7
NEFA [mmol/L]:			
Men	–0.0 ± 0.3	0.1 ± 0.2	0.0 ± 0.3
Women	–0.1 ± 0.3	0.1 ± 0.2	–0.1 ± 0.3

Data are presented as mean ± standard deviation. Abbreviations — see Table 2

Table 5. Metabolic changes in patients with higher blood pressure (n = 40) supplemented with linseed oil

	Before supplementation	After supplementation
8-epi-$PGF_{2\alpha}$ [pg/mL]:		
Men	3.1 ± 2.4	3.1 ± 2.9
Women	3.5 ± 2.1	3.1 ± 2.6
L-arginine [μmol/L]:		
Men	24.1 ± 7.1	27.4 ± 5.7
Women	26.6 ± 6.6	29.2 ± 7.3**
ADMA [μmol/L]:		
Men	0.416 ± 0.041	0.417 ± 0.034
Women	0.403 ± 0.049	0.421 ± 0.046*
ARG/ADMA:		
Men	58.4 ± 17.5	66.6 ± 18.2
Women	66.4 ± 16.8	69.9 ± 18.7
SDMA [μmol/L]:	0.259 ± 0.038	0.258 ± 0.037
Men	0.250 ± 0.060	0.254 ± 0.057
Women		
Copper [μg/dL]:		
Men	93.3 ± 10.7	94.2 ± 12.8
Women	111.0 ± 15.9	112.0 ± 13.0
Zinc [μg/dL]:		
Men	87.6 ± 11.4	85.2 ± 9.0
Women	86.3 ± 10.1	82.7 ± 9.8*

Data are presented as mean ± standard deviation. 8-epi-$PGF_{2\alpha}$ — 8-epiprostaglandin F_{2alpha}; ADMA — asymmetric dimethylarginine; ARG — arginine; SDMA — symmetric dimethylarginine
*$p < 0.05$, **$p < 0.01$ — statistically significant differences with respect to results obtained before supplementation with linseed oil

does not comply with the recommendations for prophylaxis of cardiovascular diseases [24]. These were the reasons for the choice of non-pharmacological treatment in order to reach the target cholesterol level. The use of linseed oil led to significant lipid changes after four weeks of supplementation. There was a decrease in TC, LDL-C and non-HDL-C, and TG, as well as an increase in HDL-C and HDL_3-C. The positive linear relationship between TG and NEFAs, as well as between BMI and NEFAs, shown in the study are not unexpected because NEFAs are TG-released molecules due to lipase action, whereas NEFA regulation factors include obesity [25]. In the current study, the BMI in most patients was in the overweight/obesity range.

All observed lipid changes induced by linseed oil are known to be associated with cardiovascular risk reduction, including residual risk in metabolic syndrome [2, 26]. In the studied population, only six out of 150 people (4.0%) displayed the criteria for diagnosis of metabolic syndrome, whereas 30% of patients supplemented with linseed oil displayed significant reduction in cardiovascular risk factors. Linseed oil proved to be an effective nutraceutical for reducing the cardiovascular risk factors after four weeks in people with mild hypercholesterolaemia.

On the other hand, this oil was less effective in the context of achieving target cholesterol values. Nowadays, an increasing role in atherogenesis is attributed to non-HDL-C fraction. In this study, the target LDL-C and non-HDL-C levels were estimated individually, and the mean initial LDL-C and non-HDL-C values in all subjects were about 30 to 40 mg/dL higher than target values. As a result of supplementation with linseed oil, despite significant reductions in LDL-C and non-HDL-C achieved in all but 13 patients, no patient achieved target values for these fractions, i.e. 115 mg/dL (3 mmol/L) and 145 mg/dL (3.8 mmol/L), respectively, for LDL-C and non-HDL-C levels.

The effect of linseed oil on plasma cholesterol level in clinical studies has been reported differently [27]. In experimental rabbit and chicken models of hypercholesterolaemia [7, 28], linseed oil did not affect cholesterol concentration, whereas in rat models, it reduced total and non-HDL-C [3] or non-HDL-C and TGs [23]. In this study, we observed that linseed oil increased both HDL_3-C and total HDL concentrations. The reanalysis of the Atherothrombosis Intervention in Metabolic Syndrome with High HDL/High Triglycerides (AIM-HIGH) results, published for the first time in 2011, showed that HDL_3-C, in contrast to other lipoproteins, is a predictor of cardiovascular events [29]. Also, Lee et al. (2010) [30] demonstrated that HDL_3 subfraction was associated with an increased risk of cardiovascular complications in metabolic syndrome. They showed a negative linear correlation between TG and HDL_3-C [30]. We demonstrated the same negative linear correlation ($p < 0.001$) in the population with mild hypercholesterolaemia and without metabolic syndrome.

Increased HDL_3-C was also observed in other studies in patients during fibrate therapy [31]. This increase had been referred to fibrates' agonist action on α-proliferator peroxisome-activated nuclear receptors (PPARα). Natural PPARα agonists include n-3 fatty acids such as docosahexaenoic, eicosapentaenoic, and α-linolenic acids. The latter is contained in large quantities in linseed oil, and in the human organism it may be the source of DHA and EPA. The increase in HDL_3-C due to linseed oil supplementation can be attributed to the effects of natural stimulation of the PPARα receptor signalling pathway and regulation of lipoprotein and endothelial lipase activity [32].

In summary, the role of HDL_3 in the atherogenesis remains unclear. HDL particles are highly heterogeneous with regard to structure, metabolism, and antiatherogenic activity. Some investigations have shown that both acute and chronic inflammation may lead to structural and functional changes of HDL, which render the particles dysfunctional, i.e. proinflammatory [33]. Moreover, it is still disputable which subfractions of HDL are the most beneficial. Smaller HDL_3 molecules, poorer in apoA, have lower than HDL_2-C-binding capacity in the vascular wall, which is responsible for lowering the ability to reverse cholesterol transport to the liver. Also, the protective effect of HDL_3 may be altered in people with hyperlipidaemia. In studies based on various methods, including nuclear magnetic resonance, lipid profile differences in HDL molecules have been shown to be dependent on baseline levels of this lipoprotein fraction [34]. In people with familial hypercholesterolaemia, HDL_3 molecules contain an increased amount of sphingomyelin and saturated fatty acids, resulting in an increase in lipoprotein surface stiffness. The content of surface lipids (phospholipids and free cholesterol) is reduced, while the content of core lipids (esters of cholesterol and triglycerides) is increased [35]. This can change the function of HDL_3 even at its normal blood concentration. In this context, the increase in HDL_3 subfractions after linseed oil supplementation does not necessarily indicate an increase in the antiatherogenic potential. On the other hand, according to several studies, HDL_3 fraction in healthy organisms exhibits strong antioxidant activity. In our study, the impact of linseed oil on the antioxidant capacity, measured by serum 8-epi-$PGF_{2\alpha}$, was not shown.

It is known that PUFAs, as precursors of biologically active metabolites, may impact BP regulation. A meta-analysis of controlled trials suggests that consumption of flaxseed for a duration of 3 to 48 weeks may reduce BP in adults [9]. In this study, we observed a decrease in BP in patients who consumed linseed oil for four weeks. In the multivariate logistic regression analysis model, the effect of linseed oil on BP persisted after adjustment for age, sex, height, body weight, BMI, TC, smoking status, and alcohol consumption. The hypotensive effect of linseed oil was associated with an increase in serum HDL-C and HDL_3-C.

The association between HDL or HDL_3 and BP was previously observed in other studies. Nofer et al. [36] showed that HDL stimulates NO release in human endothelial cells and induces vasodilation in isolated aortae, while in vivo, intraarterial administration of HDL lowered MAP in rats [36]. In hypertensive women, dietary oleic acids decreased BP and simultaneously increased plasma HDL_3-C [37]. In spontaneously hypertensive rats, decrease in BP induced by fish protein was connected with alteration in HDL_3 composition [38]. Hansel et al. [39] described BP-lowering response to amlodipine as a determinant of the antioxidative activity of small, dense HDL_3. One of the hypotensive mechanisms of HDL_3 action may be its antioxidative activity; however, in our study, there was no significant effect of linseed oil on total antioxidant capacity.

Furthermore, in the group of women with higher BP, dietary supplementation with linseed oil resulted in an increase in the concentration of the NO substrate, L-arginine ($p < 0.01$), and asymmetric dimethylarginine ($p < 0.05$), an endogenous inhibitor of NO synthase. In the group of men with higher BP, supplementation with linseed oil resulted in a tendency to an increase in the concentration of the L-arginine. The decrease in BP accompanied by these changes can be attributed to an increase in the level of NO, the strongest endogenous vasodilating agent. The obtained results are consistent with those of experimental studies on mice, where ALA contained in linseed oil increased L-arginine blood levels with minor changes in ADMA [40]. In other studies, conducted in rats, ALA increased NO concentration [23, 41]. It follows that ALA can increase the synthesis of NO from arginine both under experimental conditions and in clinical trials. The increase in ADMA observed in women was probably secondary to an increase in L-arginine. No change in SDMA concentration when consuming linseed oil is a favourable observation because SDMA is a recognised marker of renal dysfunction [42]. The existence of a negative linear

correlation between zinc and L-arginine concentration, as well as a positive dependence between copper and L-arginine (also between copper and ADMA or SDMA), indicates the importance of these essential metals in the NO pathway. The effect of zinc on NO synthase activity was confirmed at the molecular level [43].

In conclusion, linseed oil decreases arterial BP in subjects diagnosed with mild hypercholesterolaemia and moderately elevated or normal BP. At the same time, it increases serum HDL_3-C subfractions and lowers the levels of atherogenic lipids. These metabolic and functional activities of linseed oil may reduce cardiovascular risk. The vascular effect of linseed oil in subjects with increased BP is, at least partially, mediated by NO pathway. The clinical effects of linseed oil supplementation might most benefit patients with moderately increased cardiovascular risk.

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WHAT IS NEW?

Until now, there have been few studies concerning the role of polyunsaturated fatty acids (PUFAs) in blood pressure regulation. The results obtained from different analyses were often conflicting. The mechanisms responsible for blood pressure regulating function of PUFAs have also been unclear.

This is the first study characterising the beneficial effects of short-term linseed oil supplementation both on blood pressure and lipid pattern in patients with mild hypercholesterolaemia, and describing the underlying mechanisms of linseed oil action, including its impact on nitric oxide pathway.

As shown in our study, metabolic and functional activities of linseed oil may reduce cardiovascular risk factors. We hope our findings become useful in clinical practice.