

The Effect of Flaxseed Oil Supplementation on Body Composition and Inflammation Indices in Overweight Adults With Pre-Diabetes

Nutrition and Metabolic Insights
Volume 15: 1–7
© The Author(s) 2022
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/11786388221090083



Elham Shareghfarid¹, Azadeh Nadjarzadeh^{2,3}, Neda Heidarzadeh-Esfahani⁴, Yasaman Azamian⁴ and Salimeh Hajiahmadi^{2,3}

¹Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Islamic Republic of Iran. ²Nutrition and Food Security Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Islamic Republic of Iran. ³Department of Nutrition, School of Public Health, Shahid Sadoughi University of Medical Sciences, Yazd, Islamic Republic of Iran. ⁴Department of Nutritional Science, School of Nutritional Science and Food Technology, Kermanshah University of Medical Sciences, Kermanshah, Islamic Republic of Iran.

ABSTRACT

BACKGROUND: Flaxseed has rich content of alpha linolenic acid for preventing pro inflammatory process. The aim of present study is exploring the effect of flaxseed oil supplementation on inflammatory biomarkers and body composition in overweight adults with pre-diabetes.

MATERIAL AND METHODS: this double-blind randomized clinical trial conducted with 80 overweight pre-diabetic patients in 2 clusters (flaxseed oil group (2000-mg daily) and control group) across a 14-week period. Anthropometric indices, body composition and inflammatory indices were measured between 2 groups before and after the treatment.

RESULT: this study found a significant decrease in visceral fat level in the intervention group ($P = .009$) and control group ($P = .004$) at the end of the survey. However, the mean change of it ($P = .06$) was not significant. Also, this study showed that percentage of body fat ($P = .31$) and its mean change ($P = .6$) did not have significantly different between the 2 groups at the 14th week. The skeletal muscle% had a significant rise in the intervention group ($P = .005$) and control group ($P = .003$) by the end of 14th week. However, the mean change of it ($P = .19$) was not significant between the 2 groups. In addition, there was no significant change in the fasting blood glucose ($P = .7$), C reactive protein ($P = .12$) and TNF- α ($P = .22$) between the 2 groups at the end of study.

CONCLUSION: It showed that flaxseed oil supplementation cannot improve body composition and inflammation.

KEYWORDS: Diabetes mellitus, inflammation, glucose, body weight, linseed oil, adipose tissue, muscle, skeletal

RECEIVED: December 2, 2021. **ACCEPTED:** March 1, 2022.

TYPE: Original Research

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CORRESPONDING AUTHOR: Salimeh Hajiahmadi, Department of Nutrition, School of public health, Shahid Sadoughi University of Medical Sciences, Central Administration, Bahonar Sq., Yazd, 8916978477, Islamic Republic of Iran. Email: salimeh.hajiahmadi@gmail.com

Introduction

Overweight and obesity are the most important risk factor for non-communicable diseases (NCDs) particularly diabetes.¹ Although in recent decades, there have been a partly downwards trend regarding their prevalence especially in developing countries, modeled estimates have predicted a significant increase in this epidemic by 2030.²

Genuinely, there is a direct correlation between overweight and increasing in inflammatory factors, adipokines in particular which plays a crucial role in causing metabolic disorders such as diabetes.^{3,4}

Recent outcomes emphasis that modest changes in life style and dietary intake can lead to delay the outset these complications specifically for people with prediabetes.⁵

Consumption of products containing high omega-3 fatty acids is considered as an effective way in this regard due to their anti-inflammatory properties. Proposed mechanisms include

regulating adipokine, such as adiponectin and leptin; alleviating adipose tissue inflammation and promoting adipogenesis.⁶ Flaxseed oil as a rich source of omega-3 provides high content of the α -linolenic acid (ALA) which might contribute to a significant extent to reduce inflammation.⁷ This source of ALA has potential health benefits, such as anti-chemotactic, anti-inflammatory, anti-atherosclerotic, and antioxidant.⁸

The systematic review and meta-analysis represented the effectiveness of flaxseed and its products on the improvement of inflammatory markers in various groups, however, results emphasized on the lack of sufficient evidence in prediabetes individuals.⁹

The systematic review to evaluate the anti-inflammatory effects of flaxseed did not find sufficient proof in terms of effectiveness of flaxseed on diminishing C-reactive protein. All the same, it seems that this supplement can ameliorate this index in obese populations.¹⁰



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

The systematic review in 2019 declared that flaxseed products can decrease circulating concentration of HS – C– reactive protein and tumor necrosis factor alpha (TNF α), but it is not able to alter C-reactive protein and Interleukin 6 (IL6).¹¹ Regarding to lack of data in prediabetes individuals, its results could not be generalized to all prediabetes. Nevertheless, investigations on obese men and women with prediabetes show that daily ground flaxseed consumption had no significant effect on sensitivity C-reactive protein, adiponectin, and high-sensitivity interleukin-6.⁵

Systematic analyses of RCTs showed that flaxseed is a good option for improving body composition and weight management especially in overweight and obese groups, however, it emphasizes that more research is needed to prove these results.¹² The systematic review and meta- analysis aimed to evaluate the effectiveness of herbal medicine in obesity and metabolic syndrome managements demonstrates that flaxseed can reduce appetite, but its anti- obesity effects is still controversial.¹³

Although these researches have strongly supported the efficiency of flaxseed consumption in enhancing inflammation and body composition, there is nothing in the way of accurate findings regarding this influence in overweight prediabetes patients. So the aim of present study is evaluating the effect of flaxseed oil on body composition and inflammatory indices in overweight adults with pre-diabetes.

Methods

Trial design

This study was a randomized double-blind placebo-controlled clinical trial registered in the Iranian registry of clinical trials (www.irct.ir: IRCT20120913010826N27). In the current study, overweight individuals with impaired fasting glucose (IFG)¹⁴ (fasting blood glucose 100–125 mg/dl) and BMI 25–29.9 were included. Exclusion criteria were as follows: receiving hypoglycemic oral medications or insulin, acute and chronic disease apart from glucose tolerance disorder, any sensitivity to flaxseed oil, history of smoking, extreme activity or special diet (more than 150 minutes of aerobic activity with a moderate intensity per week or 75 minutes of aerobic activity with heavy intensity per week, eliminating one or more than 1 group of foods from their routine diet, amenorrhea, taking anti-inflammatory medications (steroidal and non-steroidal anti-inflammatory drugs); consuming flaxseed, flax oil, or fish oil supplement (once or several times a week constantly), consuming fish by over 340 g per week, and using soybean once or several times a week routinely.¹⁵

The procedures followed in this study were according to the Helsinki Declaration. Among 323 overweight patients without history of diabetes aged 30–48 years old (referred to Isfahan cardiovascular research center, Isfahan, Iran, between January and May 2016), only 80 people were included. All participants were informed about protocol of the study. Written informed consent was obtained from all subjects prior to the intervention.

Study design

Participants were allocated to the two treatment arms to receive flaxseed oil supplement (2000-mg, Barij Essence Co., Kashan, batch number 226016) or placebo containing oral paraffin (2000-mg paraffin) twice a day for 14 weeks. Flaxseed oil supplements and placebos capsules were similar in shape and size and manufactured by Barij Essence (Kashan, Iran).

Randomization assignment was performed using randomly computer-generated numbers by a third party in the research group. All participants (patients, healthcare providers, data collectors, and outcome assessors) were blinded by unawareness of the groups.

To assess compliance, the remaining supplements were counted and subtracted from the amount of supplements provided to the subjects. To increase compliance, the drug quota of the individuals was delivered as 2 weeks to the participants, and after this period, they were contacted and invited to receive the next quota. The individuals who did not follow the study protocol were excluded.

Assessment of anthropometric measures

Weight and body composition was measured in the fasting state with bare feet and minimal clothing by scale and Omron body composition monitor. Calculating body composition in Omron's algorithm is based on the Bioelectrical Impedance Method as well as height, weight, age, and gender.

The height was measured with bare feet on the nearest 0.5 centimeter (cm) using a height Seca wall stadiometer while 4 parts of the body being attached against the wall. The method of calculating BMI was dividing weight by height squared in meters.

Lifestyle assessment

The three-day food records and International Physical Activity Questionnaire¹⁶ were completed to detect the energy, macro- and micronutrient intake and level of physical activity at the beginning of the study along with the 7th and 14th weeks. Furthermore, participants were requested not to change their ordinary physical activity, diet, drug regimens, and lifestyle and not to take any nutritional supplements during the treatment.

Biochemical assessment

At baseline and end of the intervention, after 10 to 12 hours of fasting 5 ml of blood sample was taken from all participants. Serum samples were disjoined from the whole blood by centrifugation at 2606.8 \times g for 10 minutes and were stored at -80°C before analysis. The fasting venous blood samples were assembled in ethylenediaminetetraacetic acid-treated vacutainers to evaluate fasting blood glucose and inflammatory indices.

Colorimetric enzymatic kit (Pars Azmoon Co.) was used for measuring fasting blood glucose concentration. TNF- α was also measured using ELISA method by Orgenium kit. In addition, hs-CRP concentration was determined by means of ELISA (via Hitachi911 chemistry and immunoassay(Sentinel) analysis).

Statistical analysis

Data with normal distribution were reported by means (\pm SD) and data with abnormal distribution were reported by medians (\pm IR). To investigate normal distribution of the variables, Shapiro-Wilk and Kolmogorov-Smirnov tests were applied. Independent sample t-test and Mann-Whitney were used to examine the dietary intake and participant characteristic variation between 2 groups. Differences in the beginning and end of the study in each group were evaluated by paired t-test or Wilcoxon.

Repeated measures analysis of variance (ANOVA) was done for evaluating statistical significance and time and type of intervention as the factors.

For assessing the correlation between dietary intake and time and intervention multivariate analysis was performed. $P \leq .05$ was considered as statistically significant. Statistical analysis was performed by SPSS 22 (IBM Company, Armonk, NY, USA). Furthermore, Nutrition 4 software was employed to analyze the data of the three-day registration of food.

Through continuous data sample size determinations, a sample size of 35 participants was necessary to provide a power of 80% to detect a minimum 1 mg/l decrease in CRP with a standard deviation of 1.5 at 95% confidence.^{5,17} Hence, a preliminary number of 40 number per group was enrolled to supply sufficient numbers to identify differences by repeated measurement analysis of variance and allow for a 13% dropout rate in each group over the course of the study.

Result

Forty participants in control group and 40 participants in intervention group were enrolled. During the follow up, 4 participants in control group and 8 participants in intervention group were failed (Figure 1). In both groups the overall compliance was about 90%. So, statistical analysis was conducted with 32 participants as treatment group and 36 participants as control. Sixty-eight individuals completed the study (32 in intervention group & 36 in control group).

There were no statistically significant differences in BMI ($28.07 \pm 1.55 \text{ kg/m}^2$) and age (44.92 ± 10.97 years) of participants before treatment between intervention and control group. No significant differences were found in other variables at baseline (Tables 1 and 2).

Comparison of the mean value of body composition and inflammatory indices has been shown in Table 3.

At the end of this survey, Weight ($P = .97$) and body mass index ($P = .73$) were not significantly changed between groups. Furthermore, their mean changes were not also significant at the end of study ($P = .97$ for weight and $P = .78$ for BMI).

In addition, analysis showed that mean changes of C reactive protein ($P = .12$) and fasting blood glucose ($P = .55$) were not significant at the end of the treatment. At the end of 14th week, averages of the very factors ($P = .7$ for FBG and $P = .12$ CRP) were also insignificant. When it comes to TNF- α , although this index was significantly unchanged in control group ($P = .02$) at the 14th week, the mean change of it ($P = .14$) was not significant at the end of study. Moreover, results show that the percentage of body fat was not significantly altered between 2 groups ($P = .31$) at the end of 14th week. The mean change of body fat% ($P = .6$) was not also significant between the 2 groups.

The skeletal muscle% had a significant rise in the intervention group ($P = .005$) and control group ($P = .003$) by the end of 14th week. However, there was nothing in the way of significant different between 2 groups ($P = 0.12$) at the end of study. In addition, the mean change of it ($P = .19$) was not significant between the 2 groups.

The data indicated a significant decrease in Visceral fat level in the intervention group ($P = .009$) and control group ($P = .004$) by the end of the 14th week. However, the mean changes of this index ($P = .06$) was not significant between the 2 group.

Discussion

To the best of our knowledge, no study has reported the effect of flaxseed oil supplement on inflammatory biomarkers and body composition in pre-diabetic overweight people. So, we examined the effect of flaxseed oil on these indices during fourteen weeks. Flaxseed oil has significant amount of ω -3/ ω -6 fatty acids. Investigations have declared that consuming the minimum of 2 gr flaxseed oil for at least 12 weeks is sufficient to obtain the greatest increase in RBC n-3 FA content and other tissue which can lead to effective conversion alpha linolenic acid.^{18,19} Hence, effectiveness of this dose have been evaluated over this study. Our study declared that flaxseed oil consumption over 14-week period cannot improve inflammation and body composition in overweight prediabetes people.

One study showed that daily consumption of 40 grams of ground flaxseed in people with insulin resistance during 12 weeks does not show changes in CRP, interleukin 6 and TNF α levels.²⁰ Study in pre-diabetic obese or overweight people also showed that intaking ground flaxseed in various amounts (13 g and 26 g) did not affect on inflammatory markers such as CRP, interleukin-6 and adiponectin.⁵ In regard to our study, Consumption of 2 g/day of flaxseed oil for 12 weeks in healthy individuals also had no effect on CRP and TNF α levels.²¹ Results from a study by Coblij et al²² on 62 healthy individuals who consumed 3.6g of flaxseed oil per day for 12 weeks also

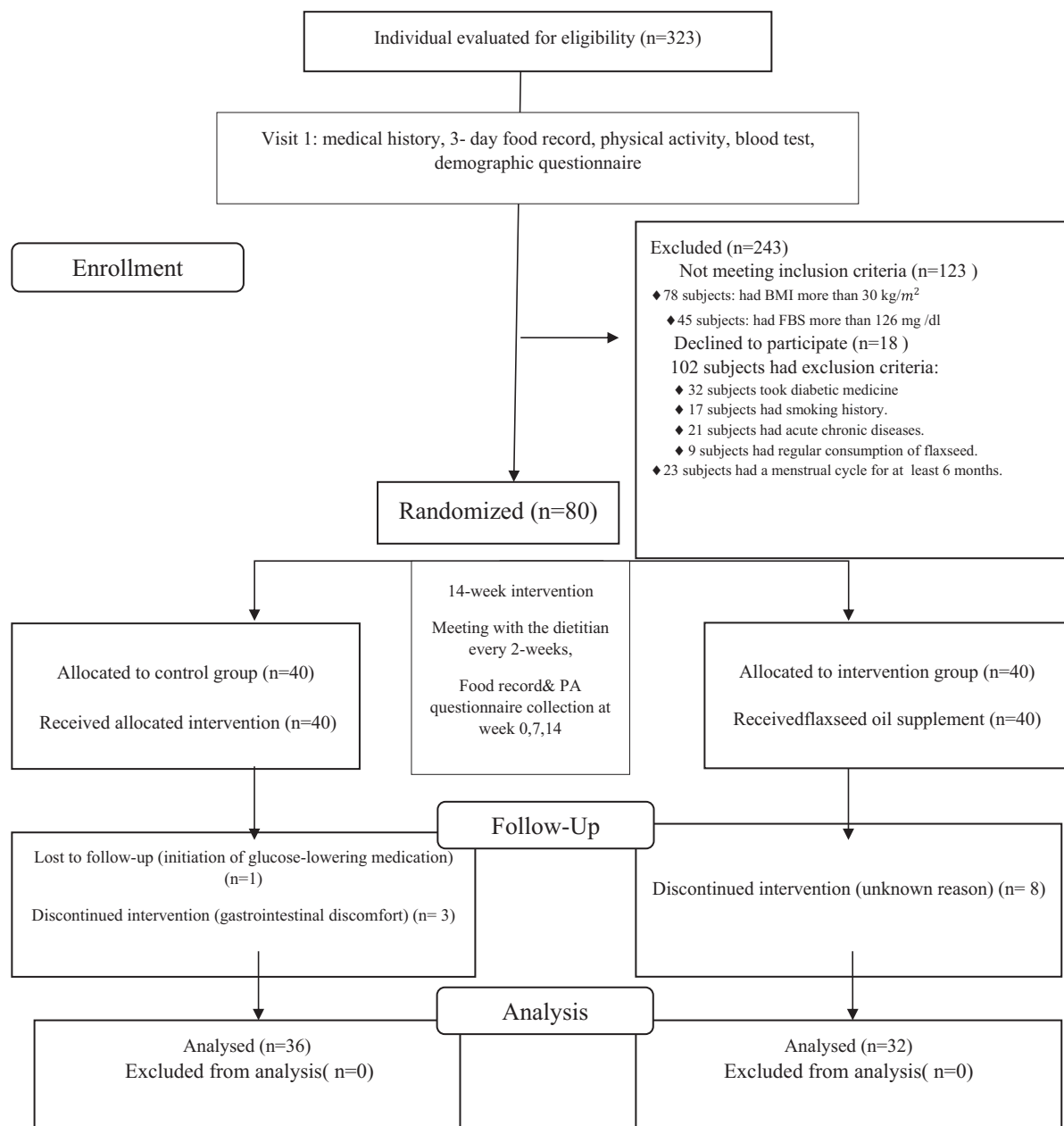


Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

showed that taking this supplement did not change the levels of CRP and TNF α in these people. Similarly, results of the present study illustrated that there were no significant changes in inflammatory indices between the 2 groups by the end of the 14th week. Surprisingly, the level of TNF α in control group was significantly unchanged at the end of study. As long as the mean change of this index between 2 groups was not significant at 14th week, this stability may be due to differences in initial levels of RBC n-3 FA content between 2 groups.

In contrast, the investigation on a diabetic rat model declared that flaxseed oil consumption assisted to improve inflammatory indices especially TNF α and IL-6.²³ Furthermore, outcomes demonstrate that flaxseed plays a crucial role in reducing oxidative stress in individuals with T2D,²⁴ hemodialysis groups with

lipid abnormalities²⁵ and people with ulcerative colitis.²⁶ Actually, it seems that flaxseed shows better anti-inflammatory effects in people with high levels of inflammation. It is important to conduct more researches to accept this point.

The study on overweight women, who consumed ground flaxseed, emphasized that this supplement cannot improve body composition and insulin-related indices.²⁷ Additionally, the investigation on hypercholesteremic subjects with overweight also showed that flaxseed oil cannot significantly modulate energy expenditure and body composition.²⁸

Other studies on overweight adolescences,²⁸ old adults with overweight²⁹ did not also support the effectiveness of flaxseed on improving body composition. In fact, these outcomes are consistent with the current survey. However, the

Table 1. Baseline characteristics of individuals in the two groups.

VARIABLE	INTERVENTION GROUP (N=32)		CONTROL GROUP (N=36)	
	MEAN ± SD	PERCENTAGE	MEAN ± SD	PERCENTAGE
Sex (% , n)	Female	21.9(n=7)		83.3(n=30)
	Male	78.1(n=25)		16.7(n=6)
Physical activity (%)	Light	25(n=8)		13.9(n=5)
	Average	68.8(n=22)		83.3(n=30)
	Intensive	6.3(n=2)		2.8(n=1)
Age (years)	45.37 ± 12.47		44.37 ± 9.71	
Height (m)	1.67 ± 0.08		1.67 ± 0.07	
Weight (Kg)	78.80 ± 8.91		78.63 ± 7.79	
BMI (kg/m ²)	28.32 ± 3.45*		28.23 ± 2.53*	
FBS (mg/dl)	100 ± 3.5*		100 ± 7*	
Hs-crp (mg/l)	1.03 ± 1.92*		1.20 ± 1.17*	
TNFα (pg/ml)	1.55 ± 2.26		2.06 ± 1.57	
body fat (%)	34.1 ± 9.23		34.1 ± 9.51	
Skeletal muscle (%)	28.89 ± 5.97		29.4 ± 6.72	
Visceral fat level	14.26 ± 4.95		12 ± 4.39	

Values are the means ± SD.

*Median ± Interquartile range.

P values were obtained using chi-square for categorical variables (independent sample t test for normal values and Mann-Whitney for non-normal values).

P values ≤ .05 are shown in bold.

systematic review in relation to evaluating the effect of flaxseed supplement on body composition delineates that flaxseed has positive effects on body composition in individuals with BMI of ≥ 30 .¹² Besides, consuming flaxseed oil in obese individuals with non-alcoholic fatty liver disease led to reduction in body fat.³⁰ It assumed that higher BMI has a potent moderating impact on effectiveness of this supplement regarding body composition. Surprisingly, in this study we observed a significant decrease in visceral fat level as well as skeletal muscle in each group at 14th week. As far as the mean changes for these variations were no significant at the end of study, these improvements may be due to the optimal level of demographic indicators in the study population that followed a healthy lifestyle.

Machado AM and colleagues compared the effects of brown and golden flaxseeds on body weight and BMI in overweight adolescents. This study found that brown and golden flaxseed did not significantly affect these indices.³¹ Moreover, Salehghadimi and colleagues showed that supplementation with flaxseed oil did not have a statistically significant effect on anthropometric indices include weight, body mass index, hip circumference and waist circumference.³² Additionally, other

study on overweight hypercholesterolemia individuals ruled out the effectiveness of flaxseed oil on reducing body weight and BMI.²⁸ These results support our conclusions.

The investigation on overweight and obese adults disclosed that whole flaxseed can considerably decrease body weight.³³ A meta-analysis of 45 RCTs suggested a significant reduction in body weight, BMI and waist circumference after treatment with whole flaxseed. Subgroup analyses showed that using whole flaxseed in doses ≥ 30 g d⁻¹ and ≥ 12 weeks' duration of intervention, especially in participants with higher BMI (≥ 27 kg m⁻²) had positive effects on body composition. So, whole flaxseed is a good choice for weight management especially in overweight and obese participants.¹² Indeed, further investigations are essential to evaluate the effect of various source of flaxseed on groups with different BMI ranges.

Strengths and limitations

RCT design, acceptable sample size and duration of present study are major strengths of the study. Also, restriction of participants by exclusion criteria for controlling the potential confounders such as hypoglycemic situation and anti-inflammatory drug

Table 2. Dietary intakes of study participants throughout the study.

VARIABLE	INTERVENTION GROUP (N=32)	CONTROL GROUP (N=36)
Energy(kcal)	2409.34 ± 408.79	2360.48 ± 404.89
Carbohydrate (g)	307.20 ± 68.42*	310.80 ± 59.20*
Carbohydrate (%)	49.69 ± 6.26	51.43 ± 4.84
Protein (g)	86.70 ± 34.64*	90.62 ± 27.48*
Protein (%)	15.44 ± 2.61	15.11 ± 1.96
Fat (g)	106.65 ± 19.86*	93.75 ± 36.28*
Fat (%)	36.66 ± 6.65	35.18 ± 5.36
Saturated fat (g)	20.97 ± 10.58*	20.32 ± 5.97*
Linoleic acid (g)	38.41 ± 27.99*	35.10 ± 27.01*
EPA(g)	0 ± 0.01*	0.007 ± 0.01*
DHA(g)	0 ± 0.01*	0.14 ± 0.01*
Linolenic acid (g)	68 ± 0.28*	0.61 ± 0.24*

Data presented as means ± SD. (n=68 for all dietary intake values presented).

*Median ± Interquartile range.

P values were obtained using chi- square for categorical variables (independent sample t test for normal values and Mann-Whitney for non-normal values).

P values ≤ .05 are shown in bold.

usage was another strengths of study. In addition, in present study dietary intake and physical activity was evaluated. Unfortunately, RBC n-3 FA content, blood insulin levels and insulin resistance was not measured in this study.

In the previous study,¹⁵ which was conducted by our group, inflammatory indices underwent a significant increase in the control group at the end of study. Hence, we took it for granted that flaxseed oil might have disclosed effectiveness on the very factors on condition that the number of participants had been increased. As a result, two-fold increase in the sample size should be regarded as the prominent differentiation point in the recent study. Moreover, anthropometric indices were also being investigated along with the very factors.

For future, we recommend researchers to separate lignin from your seed in order to observe the effect of lignin and omega-3 separately on inflammatory markers in pre-diabetic individuals. Also, more studies are needed to look at the possible effects of this supplement on people with high inflammatory index and various BMI range. It is suggested that in the future, studies with larger sample sizes, different doses of flaxseed oil and longer intervention time be performed.

Conclusion

Our study declared that flaxseed oil consumption cannot improve inflammation and body composition in overweight prediabetes people.

Table 3. Mean of body composition and biomarkers of inflammation at the baseline and after 14 weeks of flaxseed oil supplementation in overweight pre-diabetes patients.

VARIABLE		INTERVENTION GROUP (N=32)	CONTROL GROUP (N=36)	
		MEAN ± SD	MEAN ± SD	
Weight(kg)	baseline	78.63 ± 7.79	78.90 ± 8.91	
	Week14	78.90 ± 7.90	78.97 ± 8.91	
BMI(kg/m ²)	Mean changes	0.06 ± 1.68	0.07 ± 1.53	
	baseline	28.23 ± 2.53*	28.32 ± 3.45*	
	Week14	28.17 ± 1.58	28.04 ± 1.71	
Mean changes		0.05 ± 0.58	0.01 ± 0.56	
	FBS(mg/dl)	baseline	100.00 ± 7*	100.00 ± 3.5*
	Week14	103.00 ± 23.25*	107.50 ± 15.75*	
Mean changes		1.50 ± 23.63*	2.50 ± 16.76*	
	TNF-α(pg/ml)	baseline	2.01 ± 1.65*	1.55 ± 2.26*
	Week14	2.01 ± 1.55*	1.55 ± 2.03*	
Mean changes		0.04 ± 0.32*	0.01 ± 0.32*	
	Hs-Crp(mg/l)	baseline	1.20 ± 1.17*	1.03 ± 1.92*
	Week14	1.39 ± 1.98*	0.76 ± 1.53*	
Mean changes		0.19 ± 1.68*	-0.6 ± 1.21*	
	body fat(%)	baseline	34.1 ± 9.51	34.1 ± 9.23
	Week14	32 ± 11.6	28.42 ± 9.55	
Mean changes		-3.62 ± 12.21	-3.27 ± 14.31	
	Skeletal muscle(%)	baseline	29.4 ± 6.72	28.89 ± 5.97
	Week14	30.73 ± 7.21	32.77 ± 5.42	
Mean changes		1.5 ± 4.4*	2 ± 5*	
	Visceral fat level	baseline	12 ± 4.39	14.26 ± 4.95
	Week14	10 ± 7*	10 ± 6*	
Mean changes		0 ± 3*	-2 ± 8*	

Abbreviations: SD, Standard deviation. * Median ± Interquartile range.

P values were obtained using chi- square for categorical variables (independent sample t test for normal values and Mann-Whitney for non-normal values, for Within group difference (Paired t-test for normal values and Wilcoxon signed-rank test for non-normal values). P values ≤ .05 are shown in bold.

Authors Contribution

Azadeh Nadjarzadeh and Salimeh Hajiahmadi developed and designed the methodology; and creation of models, also they create the main idea of study, conducted the research and investigated the process, specifically data collection, Elham shareghfarid and Neda Heidarzadeh-Esfahani and Salimeh Hajiahmadi writing the initial draft, and participated in revision and pre-publication process.

REFERENCES

- Ahmed SH, Meyer HE, Kjøllesdal MK, et al. The prevalence of selected risk factors for non-communicable diseases in Hargeisa, Somaliland: a cross-sectional study. *BMC Public Health*. 2019;19:878-910.
- Jackson SE, Llewellyn CH, Smith L. The obesity epidemic - nature via nurture: A narrative review of high-income countries. *SAGE Open Med*. 2020;8:2050312120918265.
- Van Gaal LF, Mertens IL, De Block CE. Mechanisms linking obesity with cardiovascular disease. *Nature*. 2006;444:875-880.
- Zulet M, Puchau B, Navarro C, Marti A, Martinez JA. Biomarcadores del estado inflamatorio: nexo de unión con la obesidad y complicaciones asociadas. *Nutrición hospitalaria*. 2007;22:511-527.
- Hutchins AM, Brown BD, Cunnane SC, Domitrovich SG, Adams ER, Bobowicz CE. Daily flaxseed consumption improves glycemic control in obese men and women with pre-diabetes: a randomized study. *Nutr Res*. 2013;33:367-375.
- Albracht-Schulte K, Kalupahana NS, Ramalingam L, et al. Omega-3 fatty acids in obesity and metabolic syndrome: a mechanistic update. *J Nutr Biochem*. 2018;58:1-16.
- Pan A, Yu D, Demark-Wahnefried W, Franco OH, Lin X. Meta-analysis of the effects of flaxseed interventions on blood lipids. *Am J Clin Nutr*. 2009;90:288-297.
- Tamtaji OR, Milajerdi A, Reiner, et al. Effects of flaxseed oil supplementation on biomarkers of inflammation and oxidative stress in patients with metabolic syndrome and related disorders: A systematic review and meta-analysis of randomized controlled trials. *Clin Nutr ESPEN*. 2020;40:27-33.
- Askarpour M, Karimi M, Hadi A, et al. Effect of flaxseed supplementation on markers of inflammation and endothelial function: A systematic review and meta-analysis. *Cytokine*. 2020;126:154922.
- Ren G-Y, Chen C-Y, Chen G-C, et al. Effect of flaxseed intervention on inflammatory marker C-reactive protein: a systematic review and meta-analysis of randomized controlled trials. *Nutrients*. 2016;8:136.
- Rahimlou M, Jahromi NB, Hasanyani N, Ahmadi AR. Effects of flaxseed interventions on circulating inflammatory biomarkers: a systematic review and meta-analysis of randomized controlled trials. *Adv Nutr*. 2019;10:1108-1119.
- Mohammadi-Sartang M, Mazloom Z, Raeisi-Dehkordi H, Barati-Boldaji R, Bellissimo N, Totosy de Zepetnek JO. The effect of flaxseed supplementation on body weight and body composition: a systematic review and meta-analysis of 45 randomized placebo-controlled trials. *Obes Rev*. 2017;18:1096-1107.
- Payab M, Hasani-Ranjbar S, Shahbal N, et al. Effect of the herbal medicines in obesity and metabolic syndrome: A systematic review and meta-analysis of clinical trials. *Phytother Res*. 2020;34:526-545.
- Bansal N. Prediabetes diagnosis and treatment: A review. *World J Diabetes*. 2015;6:296-303.
- Hajiahmadi S, Nadjarzadeh A, Gharipour M, Hosseinzadeh M, Fallahzadeh H, Mohsenpour MA. Effect of flaxseed oil on glycemic control and inflammatory markers in overweight adults with pre-diabetes: A double-blind randomized controlled clinical trial. *J Herb Med*. 2020;24:100387.
- Maddison R, Ni Mhurchu C, Jiang Y, et al. International physical activity questionnaire (IPAQ) and New Zealand physical activity questionnaire (NZPAQ): a doubly labelled water validation. *Int J Behav Nutr Phys Act*. 2007;4:62-69.
- Mohammed SG, Qoronfle MWSEEDS. *Personalized Food Intervention and Therapy for Autism Spectrum Disorder*. Springer; 2020:421-467.
- Khalesi S, Irwin C, Schubert M. Flaxseed consumption may reduce blood pressure: a systematic review and meta-analysis of controlled trials. *J Nutr*. 2015;145:758-765.
- Barceló-Coblijn G, Murphy EJ, Othman R, Moghadasian MH, Kashour T, Friel JK. Flaxseed oil and fish-oil capsule consumption alters human red blood cell n-3 fatty acid composition: a multiple-dosing trial comparing 2 sources of n-3 fatty acid. *Am J Clin Nutr*. 2008;88:801-809.
- Rhee Y, Brunt A. Flaxseed supplementation improved insulin resistance in obese glucose intolerant people: a randomized crossover design. *Nutr J*. 2011;10:44-47.
- Kaul N, Kreml R, Austria JA, et al. A comparison of fish oil, flaxseed oil and hempseed oil supplementation on selected parameters of cardiovascular health in healthy volunteers. *J Am Coll Nutr*. 2008;27:51-58.
- Kochman K, Czauderna M. The necessity of adequate nutrition with diets containing omega-3 and omega-6 fatty acids for proper brain development, function and delayed aging: Review. *J Anim Feed Sci*. 2010;19:511-524.
- Zhu L, Sha L, Li K, et al. Dietary flaxseed oil rich in omega-3 suppresses severity of type 2 diabetes mellitus via anti-inflammation and modulating gut microbiota in rats. *Lipids Health Dis*. 2020;19:1-16.
- Ricklefs-Johnson K, Johnston CS, Sweazea KL. Ground flaxseed increased nitric oxide levels in adults with type 2 diabetes: A randomized comparative effectiveness study of supplemental flaxseed and psyllium fiber. *Obes Med*. 2017;5:16-24.
- Khalatbari Soltani S, Jamaluddin R, Tabibi H, et al. Effects of flaxseed consumption on systemic inflammation and serum lipid profile in hemodialysis patients with lipid abnormalities. *Hemodial Int*. 2013;17:275-281.
- Morshedzadeh N, Shahrokh S, Aghdaei HA, et al. Effects of flaxseed and flaxseed oil supplement on serum levels of inflammatory markers, metabolic parameters and severity of disease in patients with ulcerative colitis. *Complement Ther Med*. 2019;46:36-43.
- Sari-Sarraf V, Amirasan R, Halalkhor F. Effect of concurrent training and flaxseed supplementation on insulin indicators and body composition in overweight women. *Iran J Obstetrics Gynecol Infertility*. 2018;21:9-21.
- Gillingham LG, Robinson KS, Jones PJ. Effect of high-oleic canola and flaxseed oils on energy expenditure and body composition in hypercholesterolemic subjects. *Metabolism*. 2012;61:1598-1605.
- Cornish SM, Chilibeck PD, Paus-Jensen L, et al. A randomized controlled trial of the effects of flaxseed lignan complex on metabolic syndrome composite score and bone mineral in older adults. *Appl Physiol Nutr Metab*. 2009;34:89-98.
- Rezaei S, Sasani MR, Akhlaghi M, Kohanmoo A. Flaxseed oil in the context of a weight loss programme ameliorates fatty liver grade in patients with non-alcoholic fatty liver disease: a randomised double-blind controlled trial. *Br J Nutr*. 2020;123:994-1002.
- Machado AM, de Paula H, Cardoso LD, Costa NMB. Effects of brown and golden flaxseed on the lipid profile, glycemia, inflammatory biomarkers, blood pressure and body composition in overweight adolescents. *Nutrition*. 2015;31:90-96.
- Saleh-Ghadimi S, Kheirouri S, Golmohammadi A, Moludi J, Jafari-Vayghan H, Alizadeh M. Effect of flaxseed oil supplementation on anthropometric and metabolic indices in patients with coronary artery disease: a double-blinded randomized controlled trial. *J Cardiovasc Thorac Res*. 2019;11:152-160.
- Yari Z, Rahimlou M, Poustchi H, Hekmatdoost A. Flaxseed supplementation improves anthropometric measurements, metabolic, and inflammatory biomarkers in overweight and obese adults. *Int J Vitam Nutr Res*. Published online March 7, 2019. doi:10.1024/0300-9831/a000565.