Effect of Flaxseed Consumption on Central Obesity, Serum Lipids, and Adiponectin Levels in Overweight or Obese Women: A Randomized Controlled Clinical Trial

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Abstract

Background: Flaxseed may be beneficial for the management of obesity due to its high content of alpha-linolenic acid, fiber, and lignans. Objective: We aimed to evaluate the effects of Flaxseed consumption on serum lipids, adiponectin, leptin, and weight loss in overweight or obese women. Methods: This randomized controlled clinical trial involved 60 overweight or obese women. Participants were randomly allocated to two groups; a) a balanced diet plus 30 g/day milled Flaxseed and b) a balanced diet plus 30g/day milled rice (as control group), for 12 weeks. Anthropometric indices, serum lipids, leptin, and adiponectin levels were measured at baseline and at the end of intervention. Results: After 12 weeks of intervention, there were significantly higher reductions in waist circumference (WC) and waist to hip ratio (WHR) (both P<0.05) in the flaxseed group compared to the controls. Moreover, adiponectin level was significantly increased in the flaxseed group (17.15±6.1) compared to the controls (16.83±10.5), (P=0.001). However, there were no significant differences in serum lipid levels between the study groups before and after the intervention (all p>0.05). Conclusion: Flaxseed consumption may improve adiposity markers, as well as adiponectin levels Thus, flaxseed consumption could be an adjunctive therapy to attenuate central obesity. Serum lipid profile has not changed significantly after flaxseed consumption. Keywords: obesity, flaxseed, adiponectin, Leptin, blood lipids

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Results : After 12 weeks of intervention, there were significantly higher reductions in waist circumference (WC) and waist to hip ratio (WHR) (both P <0.05) in the flaxseed group compared to the controls. Moreover, adiponectin level was significantly increased in the flaxseed group (17.15±6.1) compared to the controls (16.83±10.5), (P=0.001). However, there were no significant differences in serum lipid levels between the study groups before and after the intervention (all p>0.05).

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What's already known about this topic?

the findings from previous clinical trials are still controversial. Therefore, we aimed to supplement whole flaxseed to understand its effects on serum adipokines (adiponectin and leptin),Anthropometric indices and lipid profile among overweight or obese women.

What does this article add?

our findings showed that flaxseeds could potentially reduce visceral obesity and decrease the risk of obesity through increasing adiponectin concentration.

Keywords : obesity, flaxseed, adiponectin, Leptin, blood lipids

Introduction

Obesity is one of the most important inflammatory diseases and its prevalence is increasing across the world (1). Obesity and overweight are associated with increased risk of several chronic disorders, and certain types of cancers (2).

It has been found that expression and secretion of adiponectin within the adipose tissue decreases in obese individuals (7). Adiponectin is the most prevalent adipokine which has beneficial effects on metabolism, fatty acids catabolism, low density lipoprotein cholesterol (LDL-C) oxidation, insulin sensitivity and suppression of inflammation (5, 6). Moreover, leptin has a energy balance regulation role, various hormonal functions as well as highly correlated to body fat mass(8).

Flaxseed or linseed (*Linum usitatissimum* L. seed) known as a functional food contains healthy components such as alpha linolenic acid (ALA), lignans, dietary fibers and a variety of antioxidants and phytoestrogens (12, 13).

Flaxseed lignans has numerous health benefits. For instance, it can regulate expression and secretion of adipokines such as adiponectin and leptin (14-17). It has been shown that ALA has anti-inflammatory, antithrombotic and anti-arrhythmic effects (16, 18, 19). ALA can deposit in adipose tissue where it may affect adipose tissue function and adipokine secretion (7). Besides ALA, flaxseed is a rich source of phytoestrogens (lignan) with potential benefits including cardio-protective and endocrine regulation effects (20, 21). These components are proposed to modify blood lipids levels mainly through regulating the gene expression of enzymes involved in the fatty acids metabolism (22-24). Previous studies in experimental models found an attenuating effect of flaxseed supplementation on serum lipids abnormalities and adiponectin and leptin secretion (25-28). However, the findings from clinical trials are conflicting(29, 30).

Therefore, in order to find the beneficial effects of whole flaxseed supplementation as an adjunct therapy to balanced diet on serum adipokines, body weight, Waist Circumference (WC) and lipid levels, we conducted the present trial on overweight or obese women.

Methods

Study participants

The present study was a randomized, double-blind, placebo-controlled clinical trial in which 60 overweight or obese women aged 25 to 50 years, with a body mass index (BMI) 25-35 kg/m^2 and regular menstrual cycles participated. Participants were excluded if they met one or more of the following criteria: 1) any chronic disease such as cardiovascular, renal, liver and infectious diseases as well as cancer, diabetes mellitus, and thyroid disorders, 2) with history of allergy to flaxseed, 3) being pregnant or lactating, 4) taking any medications that could affect lipid metabolism (Steroids, anti-hyperglycemic agents, statins), 5) taking supplements including multivitamins and minerals and also, herbal preparations, and 6) history of smoking or alcohol and drug abuse. The minimum sample size estimated for each group was 25 at a power (1–β)

of 80% and α=0.05 for a two-arm parallel study with two-tailed testing to detect a difference of 4 ng/mL in serum adiponectin concentration with a standard deviation of 5 ng/mL, obtained from a previous study (31). Assuming a 10% drop out, a total number of 60 participants was considered for this study. The study protocol, risks, and benefits were clarified

to the participants, and they signed a written informed consent at the time of enrollment. This study was approved by the Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran (registration No. IR.SUMS.REC.1395.22) and was registered at Iranian Registry of Clinical Trials website (IRCT2016050327733N1).

Study design

The participants were randomly assigned to consume a balanced diet containing 30 g/day brown milled flaxseed (flaxseed group: n=30) or 30 g/day raw milled rice (control group: n=30) for 12 weeks. Random allocation was performed using blocked randomization method. The study participants, investigators, and outcome assessors were blinded to the type of interventions into which the individuals were allocated. The shape, color, and texture of milled rice were similar to the flaxseed product. For this purpose, we added edible colors to milled rice at the laboratory of pharmacy in Shiraz University of Medical Sciences. Calorie requirement of each subject was estimated using the estimated energy requirement (EER) equation (32). All diets consisted of 55% carbohydrates, 18% proteins, and 27% fats. Also, we provided a portion-size descriptive booklet of common foods for each participant. All the brown flaxseed products were purchased from registered herb provider Maleki Commercial Co. (Iran) and stored in a cool, dark, and dry place. They were milled within a week before delivery to the patients. Participants were asked to mix the powder with their dessert or daily meals (e.g., yogurt, salads, and soup) preferably for lunch. Moreover, participants were advised to maintain their usual physical activity during the intervention.

To assess the participants' adherence to the intervention, we asked them to bring back any unused flaxseed/placebo at each follow-up visit, so the investigators can estimate their adherence to supplementation during the study period. Participants were excluded if they consumed less than 90% of flaxseed/placebo. Follow-up assessments were done every 4 weeks (on 4th, 8th, and 12th weeks) in which participants were provided with enough supplement for the next four weeks. All measurements including anthropometric indices, blood levels of lipid profiles, leptin, adiponectin as well as dietary intakes and physical activities were performed at the baseline and at the end of the study (week 12).

Assessment of anthropometric indices and blood lipid profile

Anthropometric indices (height, weight, waist and hip circumferences) were measured for each participant at the baseline (week 0) and at the end of the study (week 12). Height was measured to the nearest 0.1 cm using a stadiometer (Seca 214 portable stadiometer) without shoes. Weight was recorded to the nearest 0.1 kg in light clothes, using a digital scale (Seca 881, Germany). BMI was calculated as body weight (kg)/height squared (m^2). WC was measured to the nearest 0.1 cm by a non-stretch measuring tape in standing position, between the lower rib and iliac crest (33).

To assess the serum lipids, 5 cc of blood sample was taken form participants after 12 hours of fasting at 7:00 – 8:00 A.M. The whole blood was centrifuged, and the obtained serum was kept at -70°C until the end of study for the further analysis. Serum concentrations of lipid profile including Triglyceride (TG), Total Cholesterol (TC), LDL-C, and High Density Lipoprotein Cholesterol (HDL-C) were measured by the colorimetric method using commercial kits (Pars Azmoon Co., Iran). Serum leptin and adiponectin concentration were measured using ELISA (Enzyme-linked Immunosorbent Assay) by IBL kit (Parsazmun Co., Iran).

Assessment of dietary intake and physical activity

Energy and nutrients intake were estimated using 24-h dietary recalls for three nonconsecutive days (2 weekdays and one weekend day) and then were analyzed using Nutritionist IV (N-Squared Computing, San Bruno, CA, USA). Physical activity was evaluated using international physical activity questionnaire (IPAQ)

for three days (two regular days and one weekend day). It was expressed as MET.h/day by multiplying the time of each physical activity by its relative Metabolic Equivalent Task (MET).

Statistical methods

Normality of each variable was tested by Kolmogorov-Smirnov. Pre- and post-treatment values were compared within groups using paired $t$test. Between-group comparisons were made using independent sample$t$ test. Effects of potential confounding factors were adjusted by the analysis of covariance. All ANCOVA models were adjusted for the baseline values of each variable and mean changes of BMI, WHR, physical activity, and energy intake. $P<0.05$ was considered as statistically significant. SPSS version 22 (SPSS, Inc., Chicago, IL, USA) was used for analysis.

Results

A total of 100 women enrolled and after checking for eligibility, 60 individuals entered the study. During the follow-up, eight participants were excluded (one in the flaxseed group and seven in the control group) due to personal reasons. Finally, 52 subjects (Flaxseed group n= 29 and control group n=23) completed the trial (Fig.1-Flowchart of participants through the study).

Baseline characteristics of participants are shown in (Table1). There were no significant differences in height, weight, BMI, waist and hip circumference of participants between flaxseed and control group at the beginning of the study.

No significant differences were observed between the two groups in mean daily intake of energy, protein, carbohydrate, fat, saturated fatty acids (SFAs), polyunsaturated fatty acids (PUFAs), mono unsaturated fatty acids (MUFAs), omega-6 fatty acids, at the beginning and the end of study. However, the amount of ALA and dietary fiber intake increased significantly in flaxseed group ($P<0.001$ and $P=0.01$ respectively). At the end of the study, ALA intake was significantly different between the two groups ($P<0.001$) (Table 2).

As shown in Table 3, there was significant reductions in serum TG, TC, and LDL-C in the flaxseed group after 12 weeks of the intervention ($P<0.001$ for all), whereas no significant decrease was observed in the control group. In addition, no significant changes were observed in serum HDL-C within each group after 12 weeks. There was no significant difference in serum TC, TG, LDL-C, and HDL-C between the study groups at baseline and at the end of study.

Moreover, weight, BMI, waist and hip circumference ($P<0.001$ for all) and WHR ($P=0.003$) decreased significantly in flaxseed group. Just a significant decrease was observed in hip circumference of the controls ($P=0.004$). Reduction of WC ($P=0.001$) and WHR ($P=0.003$) were significantly more in flaxseed group compared to the controls. After the follow up period, adiponectin concentration increased significantly in flaxseed group ($P<0.001$) which was statistically significant more than the controls ($P=0.002$). In addition, leptin concentration decreased significantly only in the flaxseed group, but this reduction was not statistically significant compared to the controls ($P=0.29$).

Discussion

We examined the effects of flaxseed consumption on anthropometric indices, serum leptin, lipids and adiponectin in overweight or obese women. Our findings indicated that the flaxseed group had significant reduction in weight and anthropometric indices such as waist and hip circumference and WHR. However, flaxseed consumption did not result in statistically significant effect on lipid profile compared to placebo.

Our data suggesting that flaxseed may have additional benefits on central adiposity compared with controls is in line with previous studies (16). Park et al. (34), found that flaxseed lignan (primarily secoisolariciresinol diglucoside) [SDG] might provide beneficial effects on obesity via reducing weight and fat accumulation. Wu et al. (35) showed that flaxseed supplementation (30 g/d) for 12 weeks reduced central obesity, weight and waist circumference when combined with healthy lifestyle counseling. Conversely, Pindea et al. (36), reported no significant change in weight, BMI, and waist circumference following supplementation with 30

g/d flaxseed for 8 weeks. We assume that the duration of the study (less than 12 weeks) might be the reason why no significant anthropometric effects were observed (37).

The exact mechanisms by which flaxseed can ameliorate abdominal obesity remain unclear. Some studies have suggested that a diet rich in PUFAs may result in reduction of abdominal obesity (35), because increasing PUFAs in the diet might act as an important modulator for body fat deposition, Also according to previous studies, the high content of SDG can reduce or prevent obesity through increased fat oxidation (3, 38).

Very few randomized clinical trials have examined the effect of flaxseed supplementation on blood adiponectin and leptin concentration in people who are healthy (31, 39, 40). Some of experimental studies reported remarkable effects of flaxseed on leptin and adiponectin (3,7) and also altered circulating level of these hormone following supplementation with flaxseed (7, 23).

In the present study, the serum concentration of adiponectin increased significantly in the flaxseed group compared to control group. Cassani et al. (41) also showed that weight loss diet with 60 g/d flaxseed supplementation in men with cardiovascular risk factors could improve adiponectin levels. Contrary to present study findings , Hutchins et al. (42), found no significant change in adiponectin levels with flaxseed supplementation in obese men and women with pre-diabetes. This contradictory finding might be due to the association of adiponectin with insulin resistance. According to other studies, response of adiponectin to an intervention might be quite different in an insulin-resistant population than in insulin-sensitive individuals (43-45). Furthermore, Nelson et al. (31) found a decrease in adiponectin levels of healthy overweight adults that were treated by flaxseed oil for 8 weeks which is consistent with our findings. The present study demonstrated that this effect might be attributed to a reduced demand for adiponectin's anti-inflammatory actions in face of high omega-3 fatty acids. In fact, in the case of adiponectin, the dosage of flaxseed given in different studies is critical, because the insulin-sensitizing and anti-inflammatory effects of ALA (the main component of flaxseed products) might deactivate the effects of adiponectin and result in a decreased demand for adiponectin (46). On the other hand, some researchers did not find significant correlation between PUFAs and circulating levels of adiponectin (47). So, they suggested ALA as an activator of peroxysomal proliferator activated receptor gamma (PPARγ) in adipocytes.

The adiponectin inducing effect of flaxseed might be because of its rich content of ALA. It seems that ALA is involved in increasing adiponectin secretion through stimulating transcription factors PPARγ (39). PPARγ is one of the key transcription factors which regulates adipogenesis and it can also control expressions of adiponectin, leptin and glucose transporter type 4 (GLUT4) (48). Moreover, SDG in flaxseeds could act as a PPARγ agonist and regulate adiponectin through an increase in PPARγ DNA binding activity in adipocytes (3). So, Flaxseed could probably be an effective component which can alter the metabolic process in adipose tissues in favor of lower visceral fat accumulation.

It should be noted that different outcome from flaxseed intervention may be related to inter-individual differences involved in the metabolic processes, resulting in altered adiponectin levels in circulation (15).

Previously high concentration of leptin in obese individuals has been reported in several studies (10, 49). We found reduction in serum leptin of both groups. However, this reduction was only significant in the flaxseed group. McCullough et al. (7) have found that leptin expression correlated positively to ALA content of flaxseed, so its effects on obesity related diseases might be due to a change in leptin expression, but in a study by Taylor et al. (37) which investigated the effect of dietary milled flaxseed and flaxseed oil on patients with type2 diabetes, leptin concentration did not change. Zhou et al (50) have suggested that insulin resistance might be correlated to depressed desaturase enzyme activity, so these patients are not able to transform ALA to Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA). This reason could probably why Taylor study could not show beneficial effect of omega-3 PUFAs from flaxseed on leptin levels.

Our findings that flaxseed consumption did not have a significant effect on lipid profile is consistent with that reported by Kaul et al., which showed that among apparently healthy adults, intake of 2 g/day flaxseed oil for 12 weeks had no significant effect on the lipid parameters in blood (51). In contrast, several clinical trials conducted in individuals with elevated levels of blood lipids, reported the beneficial effect of flaxseed

supplementation on decreasing serum lipids (22, 52-55). Torkan et al. showed that consumption of 30 g/d of flaxseed powder in hyperlipidemic patients for 40 days caused a significant decrease in TG, TC, and LDL-C compared to the placebo (54). Moreover, another clinical trial conducted in postmenopausal women with hypercholesterolemia showed a significant reduction in TC and LDL-C compared to the placebo following the flaxseed supplementation at the dosage of 30 g/day for 12 weeks (53). In the present study, the mean serum concentrations of lipids in both study groups were within the normal ranges, which could be the reason for disagreement of our results with previous studies. Not all of the clinical trials that were conducted on patients with hyperlipidemia, resulted in significant effects of flaxseed on blood lipids outcomes. Paschos et al. for example, found that the intake of 15 ml of flaxseed oil for 12 weeks had no significant effect on lipid parameters in patients with dyslipidemia (56). Also, in a study among 62 individuals with baseline values of LDL-C between 130 and 200 mg/dl, intake of 40g/day of flaxseed-containing baked products for 10 weeks did not significantly change LDL-C and even caused a significant decrease in HDL-C in men, but not in women (57). Besides the initial serum lipids, it should be noted that some methodological differences such as small sample size, short duration of follow-up, type of the flaxseed product, the dosage of supplementation, and the degree of adherence to the intervention may be the possible reasons for the discrepancy between the studies.

Several mechanisms have been suggested for the beneficial effect of flaxseed on blood lipids. Flaxseed has a high content of ALA, an omega-3 fatty acid found in plants, as well as its highest amount of lignin among the plant foods (58). It has been shown that these compounds could reduce TC and LDL-C by reducing the gene expression of Sterol Regulatory Element-Binding Protein 1-C (SREBP-1c), which is involved in synthesis of fatty acids, and increasing the mRNA expression of Peroxisome Proliferator-Activated Receptor-α (PPAR-α), which stimulates β-oxidation of fatty acids (22, 24, 59). In addition, flaxseed is a rich source of dietary fibers, both soluble and insoluble. Dietary fiber is proposed to reduce blood cholesterol mainly through increasing bile acid excretion, synthesis of short-chain fatty acids, and insulin sensitivity (60).

This study has some important strengths including the use of an appropriate placebo for flaxseed. In addition, we used whole grain flaxseed instead of flaxseed oil or lignan. Nonetheless, our findings should be considered in light of several limitations. In particular, our sample size was small. Also, the present study cannot distinguish if the effects are due directly to ALA or lignin in flaxseeds. Moreover, whilst some studies found significant effect of flaxseed on lipid profiles, ours found no such effect. The possible reasons for non-significant results following the whole flaxseed products may be due to the differences in the quality of the test product, the amount of bioactive components and their bioavailability in the presence of some compounds such as glycosides and phytic acid (57) in the flaxseed products.

Conclusion

Overall, daily consumption of 30 g milled flaxseed for 12 weeks among overweight or obese women had no significant effect on blood lipid parameters. However, flaxseeds which contains PUFAs and lignan could potentially reduce visceral obesity and is therefore a promising food to help decrease the risk of obesity through increasing adiponectin concentration.

Acknowledgment

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Ethics

All participants signed the written informed consent before initiating the study. The study was approved by the Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran (registration no. IR.SUMS.REC.1395.22) and was registered at Iranian Registry of Clinical Trials website (IRCT2016050327733N1).

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