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Original Article

Co-supplementation of Flaxseed and Hesperidin Improves Atherogenic Dyslipidemia in People with Excess Weight: A Randomized Controlled Clinical Trial

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ABSTRACT

Background and Objectives: The increase in the risk of cardiovascular diseases, one of the leading causes of death in the world, due to obesity is significant. This study was carried out suggesting palliative effects of the combination of brown flaxseed and hesperidin on atherogenic dyslipidemia in obese people.

Materials and Methods: In this randomized controlled study, 44 obese adults were randomly assigned to lifestyle modification (control group) or receiving combined brown flaxseed (30 g) and hesperidin (2 × 500 mg capsules) (intervention group) for 12 w. Atherogenic indices, anthropometric parameters and dietary intakes were recorded. The trial was registered in clinicaltrial.gov. with reg. no. NCT03737422.

Results: After 12 w of intervention, body mass index decreased significantly in groups; however, decrease of body mass index in intervention group was significantly higher than that in control group (p = 0.034). Comparing changes of atherogenic indices between the two groups indicated a significant difference in triglyceride glucose index, atherogenic index of plasma and cholesterol index between the two groups. After adjusting results for condetecteders, including baseline value of the outcome and mean changes in body mass index, waist circumference and energy intake, differences became significant for Castelli risk index-II and lipoprotein combine index.

Conclusions: The current results have shown that intake of a combination of flaxseed and hesperidin with lifestyle modification effectively improves atherogenic dyslipidemia.

Keywords: Atherogenic dyslipidemia, Flaxseed, Hesperidin, Lifestyle modification, Obesity

Highlights

- Twelve weeks of supplementation with 30 g of flaxseed and 1 g of hesperidin could significantly improve the atherogenic lipid profile.
- The combination of flaxseed and hesperidin caused significant weight loss in obese people.
- The combination of flaxseed and hesperidin significantly improves atherogenic indicators.
- Flaxseed and hesperidin co-supplementation with lifestyle modification can improve atherogenic dyslipidemia.

Introduction

The obesity epidemic has been increased rapidly, with nearly one-third of the global population are classified as overweight or obese (1). Compared to 1980s, the current rates of obesity have been tripled (2). It is increasingly recognized as a major public health problem. Obesity is strongly associated with several metabolic disorders, including atherogenic dyslipidemia. This condition is addressed by an abnormal lipid profile, usually marked by

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high levels of triglycerides (TG) and low-density lipoprotein cholesterol (LDL-C) with decreased levels of high-density lipoprotein cholesterol (HDL-C). This type of lipid profile increases the risk of cardiovascular diseases (CVD), which are within the leading causes of illness and mortality (3, 4). Atherogenic indices are quantitative indicators used to assess atherogenic status and cardiovascular risks. These indices are good predictive values for atherogenic dyslipidemia abnormalities (5, 6).

Furthermore, Obesity plays an important role in insulin resistance, which subsequently affects lipid metabolism and results in dyslipidaemia. Additionally, occurrence of dyslipidaemia is significantly higher in obese individuals, as shown in multiple demographic studies. For example, studies involving civil servants in Nigeria detected that a significant proportion of obese individuals showed dyslipidaemia, emphasizing that excess body weight is a major factor in development of atherogenic lipid profiles (7, 8). Understanding links between obesity and atherogenic dyslipidaemia is essential for finding effective prevention and intervention strategies to lower cardiovascular risk in affected populations. With the global increases in obesity rates, it is becoming increasingly vital for public health initiatives to focus on these links. As stated previously, excess body weight increases likelihood of developing metabolic disorders such as coronary artery disease and dyslipidaemia (9-13). Dyslipidaemia associated with obesity is typically marked by increased levels of triglyceride-rich lipoproteins and decreased levels of HDL-C. In individuals with obesity, not only HDL levels are affected, but also changes occur in HDL distribution patterns and abnormal HDL metabolism, which frequently results in dysfunction of HDL particles (14-16). Therefore, dyslipidemia and obesity are prevalent disorders that need addressing to decrease cardiovascular risk and likelihood of complications associated with obesity. Lifestyle habits can include pro-detected effects on atherosclerotic cardiovascular disease (ASCVD) risks (17). Nutrition is one of these habits that can trigger genetic predisposition and then lead to dyslipidemia. An adequate supply of nutrients is the most effective method to prevent metabolic disorders (18).

Plant seeds, especially flaxseed (*Linum usitatissimum*), have received significant interests for their potentials in preventing lipid disorders (19). Flaxseed is the most abundant plant source of omega-3 fatty acids (specifically α-linolenic acid or ALA) and phytohormones known as lignans. The plant provides high-quality proteins and dietary fibers. Furthermore, flaxseed may serve as a source of phenolic compounds. Due to the positive physiological effects of its constituents, this seed is addressed as a functional food (20). Based on the results of a meta-analysis, flaxseed supplementation may be beneficial to modulate cardiometabolic and lipid profile (21). Furthermore, hesperidin (Hsd), a flavonoid from citrus species, includes various biological characteristics, particularly for the prevention of CVDs (22). Cardioprotective effects of Hsd have clearly been established in numerous clinical studies. A recent meta-analysis revealed that Hsd significantly decreased LDL, total cholesterol (TC) and TG. the findings of this meta-analysis suggested that Hsd administration could benefit patients with CVDs by decreasing LDL, TC and TG (23).

It seems that a multidisciplinary approach is needed to promote the successful implementation and maintenance of dietary changes. Regarding that the effects of flaxseed supplementation on lipid profile are still controversial and the requirement to further high-quality studies to definitively verify the clinical effectiveness of Hsd in treating cardiovascular complications, the present study was designed to assess effects of flaxseed and Hsd on atherogenic indices of dyslipidemia in people with excess weight.

Materials and Methods

A randomized, parallel controlled, open-label clinical trial was carried out on 44 adults, who referred to three medical centers in Tehran, Iran. The study protocol was approved by the Ethics Committee of National Nutrition and Food Technology Research Institute, Tehran, Iran. The clinical trial protocol was registered at ClinicalTrials.gov as NCT03734510. First, written consents were signed by the participants. Eligible participants, who met inclusion criteria, were assigned into two groups randomly. Inclusion criteria included patients aged 18–70 years old with BMI of 25–40 kg/m^2. Exclusion criteria included patients with NAFLD, hepatitis, gastrointestinal, cardiac, renal, pulmonary, autoimmune and thyroid diseases as well as severe metabolic abnormalities, professional athletes, pregnant or lactating women, patients prescribed with drugs for hyperglycemic, dyslipidemia and inflammation and those with history of weight-loss surgery or programs.

Using random numbers table, participants were allocated into two groups of intervention group received daily two capsules containing 500 mg of Hsd and 30 g of brown milled flaxseed for 4 w, while the control group did not receive any supplements. All participants (intervention and control groups) were instructed to dietary modification and monitored for a similar time. Compliance with the study protocol was assessed based on the supplements (Hsd and flaxseed) that were not used and returned to the researchers. Phone calls were made to remind use of the supplements and to inform about possible side effects of the intervention, every 2 w.

Anthropometric assessment

Anthropometric measurements were carried out at the beginning and at the end of the study. Height was assessed

to the nearest 1 cm without shoes and weight were assessed to the nearest 0.1 kg in light clothing without shoes. The BMI was calculated by dividing body weight (kg) by the square of height (m²). Waist and hip circumferences were assessed following standardized procedures by a trained investigator.

Biochemical parameter assessment

To assess lipid profile, blood samples were collected at the beginning and at the end of the study. The TC, HDL-C and TG were assessed using commercial kits after 12–14 h of overnight fasting. The LDL-C level was assessed using Friedewald equation (24). Atherogenic indices were assessed using the following formulas (25-30):

Triglyceride glucose (TyG)

$$= \text{Index } Ln\left(\frac{fasting\ triglycerides\ \left(\frac{mg}{dL}\right) \times\ fasting\ glucose\ \left(\frac{mg}{dL}\right)}{2}\right)$$

$$\text{Castelli Risk Index} - \text{I (CRI} - \text{I)} = \frac{total\ cholestrol\ \left(\frac{mmol}{L}\right)}{HDL - C\ \left(\frac{mmol}{L}\right)}$$

$$\text{Castelli Risk Index} - \text{II (CRI} - \text{II)} = \frac{LDL - C\ \left(\frac{mmol}{L}\right)}{HDL - C\ \left(\frac{mmol}{L}\right)}$$

$$\text{Triglyceride to HDL} - \text{C ratio} = \frac{TG\ \left(\frac{mmol}{L}\right)}{HDL - C\ \left(\frac{mmol}{L}\right)}$$

Atherogenic Coefficient (AC)

$$= \frac{total\ cholestrol\ \left(\frac{mmol}{L}\right) - HDL - C\ \left(\frac{mmol}{L}\right)}{HDL - C\ \left(\frac{mmol}{L}\right)}$$

$$\text{Atherogenic Index of Plasma (AIP)} = Log_{10}\left(\frac{triglycerides\ \left(\frac{mmol}{L}\right)}{HDL - C\ \left(\frac{mmol}{L}\right)}\right)$$

Lipoprotein Combine Index (LCI)

$$= \frac{total\ cholestrol\ \left(\frac{mmol}{L}\right) \times\ triglycerides\ \left(\frac{mmol}{L}\right) \times LDL - C\ \left(\frac{mmol}{L}\right)}{HDL - C\ \left(\frac{mmol}{L}\right)}$$

Dietary intake assessment

To assess dietary intake, participants completed three 24-h dietary recall questionnaires at the beginning and end of the study. These recalls included at least one weekday and one weekend day. A professional nutritionist analyzed these data by Nutritionist IV software (First Databank, San Bruno, CA, USA). Database was modified with reference to the existing national Iranian food composition table, developed by the Iranian National Institute of Nutrition and Food Technology.

Statistical analysis

Kolmogorov-Smirnov test was used to assess the normality distribution of variables. Parametric and nonparametric descriptive tests were used for data analysis, depend on their normal or abnormal distribution. Chi-squared or Fisher exact test for categorical variables were used to assess differences in groups at baseline. Independent and Paired-t tests were used for between and within-group comparisons of the variables, respectively. The $p < 0.05$ was recorded as significant level. Moreover, SPSS v.20.0 software (SPSS, Chicago, IL, USA) was used for statistical analysis.

Results

Sixty-one subjects were recruited to the study; of which, 44 met all the inclusion criteria and successfully completed the study (Figure 1). Baseline characteristics of all 44 participants are present in Table 1. The mean BMI of the participants was 33.74 ±5.18 (BMI range, 27.78–46.65) and 48% (n = 21) of them were male. No statistical difference was detected in demographic characteristics of the participants between the two groups. Mean ±SD (standard deviation) of atherogenic indices is stated in Table 2, based on the study group. At the beginning of the study, two groups were similar for atherogenic statuses.

Table 1. Baseline characteristics of the participants

	Control n= 22	Flaxseed/Hesperidin n= 22	*P* Value
Age	47.86 ± 11.31	43.45 ± 10.55	0.189
Sex (M/F)	10/12	11/11	0.887
Weight	90.57 ± 14.72	94.05 ± 15.54	0.450
Hight	165.09 ± 11.48	167.41 ± 9.71	0.474
BMI	33.49 ± 5.38	33.98 ± 5.08	0.758
Waist Circumference	104.95 ± 8.26	105.41 ± 6.43	0.840
Smoking	1	4	0.345
Energy intake	2406.58 ± 441.41	2520.64 ± 518.43	0.436

Values are means ± SDs for continuous variables and percentages for categorical variables.
Independent t-test for quantitative variables and χ^2 test for qualitative variables.

Table 2. Atherogenic indices of the study participants based on the study group at the baseline

	Control group n= 22	Flaxseed/Hesperidin n= 22	*P* Value
TyG	9.04 ± 0.41	8.99 ± 0.55	0.791
CRI-I	6.56 ± 2.72	6.01 ± 1.58	0.435
CRI-II	4.24 ± 2.08	3.89 ± 1.35	0.538
TG/HDL	5.75 ± 3.86	4.86 ± 3.33	0.435
AC	5.57 ± 2.72	5.01 ± 1.58	0.013
AIP	0.33 ± 0.24	0.24 ± 0.27	0.318
LCI	49.67 ± 57.73	41.55 ± 30.27	0.576
CHOLINDEX	2.45 ± 1.04	2.52 ± 0.95	0.841

Mean ± SD (all such values).
TyG: Triglyceride glucose Index; CRI: Castelli Risk Index; AC: Atherogenic Coefficient; AIP: Atherogenic Index of Plasma; LCI: Lipoprotein Combine Index; CHOLINDEX: Cholesterol Index.

Mean changes from baseline in energy intake, anthropometric and atherogenic indicators are present in Table 3. Based on the 3-d dietary recall of the study, energy intake of the two groups significantly decreased after 12 w, although this decrease was not significant. After 12 w of intervention, BMI decreased significantly in the two groups. However, decrease of BMI in the flaxseed/Hsd group was significantly higher than the control group (p = 0.034). Decrease in waist circumference at the end of the study was significant in the flaxseed/Hsd group (p = 0.004) and close to the significant level in the control group (p = 0.051). Decrease in waist circumference was not significant between the two groups (p = 0.183). Intra-group comparison indicated a significant decrease of all atherogenicity indices in the flaxseed/Hsd group. While in the control group, no significant decrease was observed. Comparison of the changes of these indices between the two groups indicated significant differences in TyG, AIP and CHOLINDEX between the two groups. After adjusting results for condetecteders, including baseline value of the outcome and mean changes in BMI, WC and energy, difference became significant for CRI-II and LCI.

Table 3. Mean changes in energy intake and anthropometric and atherogenic indicators from the baseline

	Control group (n = 22)		Flaxseed/Hesperidin group (n = 22)		*P* value [1]	*P* value [2]
	At the end of 12 weeks	Change from baseline	At the end of 12 weeks	Change from baseline		
BMI	33.14 ± 5.91	-0.98 ± 1.22	32.18 ± 5.02	-1.8 ± 1.04	0.034	
P value [3]	0.005		<0.001			
Waist Circumference	103.59 ± 9.21	-3.11 ± 6.1	98.95 ± 8.65	-6.45 ± 9.21	0.183	
P value [3]	0.051		0.004			
Energy intake	2074.82 ± 453.02	-389.51 ± 470.31	2232.34 ± 488.97	-288.3 ± 175.4	0.409	
P value [3]	0.004		<0.001			
TyG	8.96 ± 0.38	-0.07 ± 0.38	8.59 ± 0.46	-0.53 ± 0.23	<0.001	0.002
P value [3]	0.452		<0.001			
CRI-I	5.95 ± 2.11	-0.61 ± 1.56	4.84 ± 1.39	-1.18 ± 1.07	0.215	0.148
P value [3]	0.142		<0.001			
CRI-II	3.79 ± 1.79	-0.44 ± 1.11	2.68 ± 1.23	-1.21 ± 1.27	0.071	0.023
P value [3]	0.133		0.001			
TG/HDL	2.17 ± 0.89	-0.34 ± 1.43	1.39 ± 0.97	-0.77 ± 0.63	0.282	0.069
P value [3]	0.354		<0.001			
AC	4.96 ± 2.11	-0.6 ± 1.56	3.85 ± 1.39	-1.18 ± 1.07	0.227	0.148
P value [3]	0.142		<0.001			
AIP	0.3 ± 0.18	-0.03 ± 0.21	0.07 ± 0.26	-0.19 ± 0.11	0.007	0.011
P value [3]	0.617		<0.001			
LCI	36.34 ± 22.6	-13.33 ± 45.59	18.61 ± 15.9	-27.06	0.288	0.008
P value [3]	0.260		<0.001			
CHOLINDEX	2.24 ± 1.04	-0.21 ± 0.68	2.52 ± 0.95	-1.05 ± 1.04	0.009	0.006
P value [3]	0.239		0.001			

[1] Based on an independent t-test
[2] Based on an ANCOVA model that regressed changes from baseline on treatment group, baseline value of the outcome and mean changes in BMI, WC and energy.
[3] Based on a paired t-test

Discussion

The current clinical trial on people with obesity revealed that 12 w of supplementation with 30 g of brown flaxseed powder and 1 g of Hsd could significantly improve the atherogenic lipid profile in addition to weight loss. This combination predominantly decreased TyG, CRI-II, AIP, LCI and CHOLINDEX. This included a weak effect on decreasing the ratio of TG to HDL, but failed to affect CRI-I and AC. It is well known that ASCVD is closely linked to the risk of CVDs, the first cause of death worldwide (31). Despite inspiring achievements in prevention, control and treatment of ASCVD, it is still one of the major causes of disability and premature death.

Atherogenic indices express balance of pro-atherosclerotic and anti-atherosclerotic lipoproteins in the blood. Since these address interactions between various lipid components, they can reflect atherogenic dyslipidemia better than that the lipid profile components can separately (32). The current results are similar to those of previous studies on the favorable effects of flaxseed and Hsd on lipid profiles, although the combined effects of these two on atherogenic indices have not been assessed. In a study investigating effects of flaxseed in hypercholesterolemic people, it was reported that consumption of 15 g of flaxseed for 12 w decreased TC and LDL, but included no effects on HDL (33). Furthermore, the high content of omega-3 in flaxseed can be effective in decreasing TG. This effect has been shown in studies, although it included no effects on TC and its components (34).

The ALA in flaxseed can cause favorable effects on lipid profile by modulating lipid homeostasis in the adipocyte-liver axis, improving beta fatty acid oxidation through up and down-regulation of peroxisome proliferator-activated receptor (PPAR)-α and sterol regulatory element-binding protein (SREBP)-1, respectively (35). By decreasing lipogenesis, it decreases TG levels (36). Fibers in flaxseed can improve the lipid profile by decreasing absorption of dietary fats (37).

Naturally, Hsd includes hypolipidemic and antiatherogenic effects. Associated animal studies have indicated inhibitory effects of Hsd on the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and suppression of pancreatic lipase, causing decreases in TG (38, 39). In another study, it was shown that Hsd included favorable effects on decreasing TC and could decrease TG in people with hypertriglyceridemia (39). Authors stated that effects of Hsd on decreasing TG could lead to suppression of small dense LDL, indicating the potential of this flavonoid in preventing progression of atherosclerosis. Conflicting results on effects of Hsd and Hsd on the lipid profile could be partially due to the difference in supplement dose, study population or length of the intervention (40).

Obesity, as a complex multifactorial disease, is the root cause of numerous diseases and directly contributes to the development of CVDs (41). One of the results of this trial was significant weight loss, which seemed majorly due to the use of flaxseed. Findings by Kuang et al. (37) were similar o findings by the current authors; in which, intake of seeds in overweight and obese people led to a significant decrease in weight and TG while daily consumption of 5 g of flaxseed oil in patients with coronary heart disease for 10 w could not lead to significant weight loss (34). Whole flaxseed (42) or lignan (43) and oil (44) can all have weight loss effects. It seems that the major mechanism of dietary fibers in weight loss is suppressing appetite due to increased feeling of satiety, which causes a decrease in energy intake and body weight (45).

Although the current trial included strengths such as use of whole flaxseed, high compliance rate and inclusion of overweight and obese individuals. Limitations of this study should be addressed in interpretation of the findings. Changes at the histological level in the vessels have not been assessed. Although length of the study was relatively appropriate, sustainability of the improvement in atherogenic dyslipidemia in individuals is still unknown. The small sample size was another limitation. In addition, it was not possible to carry out a double-blind study. In conclusion, atherogenic dyslipidemia, especially in overweight and obese individuals, needs lifestyle modification with a special focus on diets to decrease the risk of CVDs. It seems that flaxseed and Hsd co-supplementation with lifestyle modification can improve atherogenic dyslipidemia.

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