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Effect of Flaxseed on Blood Lipid Level in Hyperlipidemic Patients

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Abstract:

Introduction: Hyperlipidemia is one of the most important risk factors of ischemic heart disease. Previous studies showed that flaxseed has the potential to improve lipid profiles. In this study we investigated the effects of flaxseed powder intake on lipid profiles of patients with hyperlipidemia.

Materials and Methods: This study was a randomized controlled clinical trial. Seventy patients with hyperlipidemia participated in the research. After detailed diet and lifestyle education, blood samples were collected from the participants. Patients with hyperlipidemia were randomly divided in to two intervention and control groups. The intervention group received 30 g of raw flaxseed powder every day for 40 days. Serum lipids were measured again in two groups after that time. Activity and food intakes of two groups were recorded.

Results: In the intervention group, weight and body mass index were considerably reduced. Total cholesterol was reduced in the intervention group and increased in the control group, both of which were significant. Low density lipoprotein significantly increased in the control group and reduced in intervention group; also, triglyceride was increased in the control group and reduced in the intervention group, which were significant Table **1**.

Conclusion: Based on the findings obtained in this research, flaxseed powder intake desirably reduced serum lipids. The differences between two groups on the basis of analysis of covariance test were significant. In all cases except for the HDL-c, this is an effective intervention. Therefore, flaxseed may be regarded as a useful therapeutic food for reducing hyperlipidemia.

Keywords: Blood lipids, Cardiovascular diseases, Cholesterol, Flaxseed, Hyperlipidemia, Lipid profile.

INTRODUCTION

About 20 million people 65 years old and older die every year due to cardiovascular diseases (CVD); otherwise, they will be debilitated or sustain heavy therapeutic costs and socioeconomic outcomes [1]. Hyperlipidemia is one of the main factors of cardiovascular diseases and prevalent problems in the society [2]. Prevalence of high blood lipid is increasing; for example, approximately 69% of people with metabolic syndrome are hypercholesterolemic and 65% are hypertriglyceridimic [3]; also, 40% of renal patients are hyperlipidemic [4]. Based on the statistics obtained from NCD (non-communicable diseases) studies conducted in Iran, hyperlipidemia prevalence is approximately 23% [5]. Hyperlipidemia causes the formation and progress of atherosclerosis plaques and finally coronary heart diseases (CHD) [6,7]. Prevention of cardiac diseases with nutritional interventions is an important strategy and lowering blood lipids plays a very important role in reducing cardiovascular diseases and increasing life span, so that 10% reduction of total serum cholesterol reduces CVD incidence by about 30% [8]. Studies have shown that CVD can be prevented by changing lifestyle, including nutritional changes, not smoking and increasing physical activity [9]. Nutritional changes play an important role in prevention of hyperlipidemia. For example, reduction of saturated fatty acids (SFA) is one of the most important nutritional recommendations for reducing the incidence of CVD, because it is effective on blood cholesterol [10]. Meta-analysis of clinical trials has shown that cardiovascular diseases will be prevented considerably by replacing polyunsaturated fatty acid (PUFA) with saturated fatty acids (SFAs) [10]. In many clinical trials and epidemiological studies, it has shown that nutritional factors such as grains, fish, plant sterols, soy protein, and isoflavones have improved blood lipids profile [11]. Another therapeutic method is using herbs which have been considered as a treatment for reducing the risk of cardiovascular diseases [12]. One of the herbs, which are reported to have useful potential effects on reducing blood lipids, is flaxseed with scientific name of Linum Usitatissimum from Linaceae family [13]. Flaxseed contains 41% fat, 20% protein, and 28% fiber [14]. Protein of flaxseed is similar to soy protein. Another useful compound of flaxseed is lignan [14]. The major part of its fat is α-Linolenic acid (ALA). Results of several clinical trials have shown that foods with ALA reduce apoplexy and mortality in men and have a reverse relationship with the incidence of cardiac diseases by reducing serum cholesterol and triglyceride levels [12, 15]. It is also have

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Table 1. Main Results of the flaxseed on blood lipids.

Number of Patients	Intervention/Duration	Diet	Blood Sampling	Results
35 patients (intervention group)	30 gr raw flaxseed powder/for 40 days	Recommendations for low fat diet	2 times: before intervention And at the end	Weight: significant reduction BMI: significant reduction TC: significant reduction LDL-c: significant reduction HDL-c: Non significant increase TG: significant reduction
35 patients (control group)	-	Recommendations for low fat diet	2 times: before intervention And at the end	Weight: Non significant reduction BMI: Non significant reduction TC: significant increase LDL-c:significant increase HDL-c: Non significant reduction TG: significant increase

BMI: Body Mass Index, TC: Total Cholesterol, LDL-c: Low Density Lipoprotein, HDL-c: High Density Lipoprotein, TG: Triglyceride

antiarrhythmic functions by affecting ion channels and nuclear receptors. In addition, α-Linolenic acid has useful effects on lipid profiles and inflammation [16]. In some animal studies, effect of flaxseed oil on the reduction of cholesterol serum level, triglyceride, and phospholipids has been reported and attributed to its α-Linolenic acid content [12, 17]. It seems that hypocholesterolemic effect of flaxseed results from interaction of its compounds, *i.e.* high amounts of α - Linolenic acid, lignin complex, and fiber [2, 6]. Previous human [2, 15, 18, 19 and 20] and animal [21-23] studies have reported the beneficial effect of intake of flaxseed on lipid profiles and reduction of blood cholesterol, such an effect has not been found in some other studies [24, 25]. One study has shown that women who ate 30 gr/d of flaxseed for three months have reduced total cholesterol (TC) by 7% and low density lipoprotein (LDL-c) by 10%; but, it has no effect on triglyceride (TG) and high density lipoprotein (HDL-c) [9]. In another study, effect of flaxseed fiber on the fat secreted from feces was studied and LDL-c reduction was found [26].

MATERIALS AND METHODS

This study was a randomized parallel controlled clinical trial. Statistical population included all people referring to Laboratory of Noor and Hazrat Ali Asghar Hospital in 2013 for checkup.

The sample included 80 patients with hyperlipidemia and inclusion criteria were affliction with hyperlipidemia, age of 25 to 50 years old, no intake of supplement and medicines, no pregnancy and lactation, and disobedience from a special diet. Ten people were excluded from the project due to lack of cooperation and 70 people were left, who gave an informed consent and were randomly divided into two groups containing 35 people. The intervention group received 30 g flaxseed for 40 days. Dietary recommendations relating to blood lipid were explained orally to both groups. The food intakes and three-day activities were recorded at the beginning, in the middle, and at the end of the study. Serum LDL-c, TC, TG, and HDL-c levels of patients were measured and recorded before starting. Weight, height, and BMI of both groups were measured before starting and blood samples were taken from all people after completing the project. Lipid profiles were measured and recorded. In the blood sample collection, the subjects were asked to fast for 12 hrs. Weights were measured at the end of study.

Biochemical Tests

Serum levels of TC, HDL-c, and TG were determined by using spectrophotometric method and special kits for quantitative diagnosis of TC, HDL-c, and TG from Pars Azmoon Company. LDL-c was calculated using computational methods and Frieldwald formula. This formula obtains an integer for LDL-c when TG is between 150 and 350 mg/dl; in case TG is below 150 or above 350, another formula obtained by Seyed Ali Ahmadi *et al.* In a study entitled "The Impact of Low Serum Triglyceride on LDL-Cholesterol Estimation" was used [27].

Food Intake Evaluation

Three days Food records forms were recorded from each person. The mentioned values for each food were converted into grams according to a guide for household measures and then each food and beverage was included in N_4 program for the evaluation of energy and nutrients. For statistical analysis, the amounts of food items were entered into SPSS18 program.

Evaluating Physical Activity

Physical activity rate of each patient was converted into a continuous quantitative variable by using the physical activity questionnaire. This questionnaire has been prepared in previous studies in Europe and its validity has been confirmed by a physical activity daily questionnaire and CSA (accelerometer ambulatory monitor model 7164) [28]. Validity and reliability of this questionnaire were confirmed in Iran by Kilishadi *et al.* in a study on adolescents [29]. In addition to being simple, this questionnaire was prepared in 9 rows based on intensity of physical activity (metabolic equivalent: MET), which showed immobility (MET=0.9) to intensive activities (MET>6) from top to bottom. Multiplication of this number by its performance time shows intensity

Table 2. Comparing basic variables and food intakes and physical activity in two studied groups.

Variables	Case	Control	Pvalue
Age (y)	43.35±1.14	40.48±1.4	0.12
Sex Male Female	 12(34.3%) 23(65.7%)	 13(37.1%) 22(62.9%)	0.8
Activity (MET-h/day) First day Second day Third day	 34.18±0.97 34.69±0.87 33.59±0.77	 33.72±1.01 33.66±0.95 34.17±1	0.805
Calorie (kcal)	1938.6±109.03	1925.66±62.09	0.93
Protein (gr)	60.57±4.34	61.18±3.39	0.91
Carbohydrate (gr)	236.48±17.99	234.09±12.44	0.913
Fat (gr)	83.41±5.41	82.73±4.13	0.909
Cholesterol (mg)	137.37±14.97	135.75±11.31	0.931
SFA (gr)	35.40±19.33	34.92±19.38	0.986
MUFA (gr)	19.32±1.74	19.15±1.33	0.94
PUFA (gr)	28.71±2.28	28.66±2.39	0.98
oleic acid (gr)	18.38±3.07	17.87±2.92	0.904
Linoleic acid (gr)	24.61±2.23	24.26±2.21	0.912
Linolenic acid (gr)	0.49±0.077	0.48±0.069	0.990
EPA (gr)	0.009±0.0057	0.004±0.0008	0.36
DHA (gr)	0.023±0.01	0.013±0.003	0.372
Vit E (mg)	12.68±2.6	11.82±2.2	0.803
Vit D (μg)	0.49±0.13	0.55±0.14	0.756
Total fiber (gr)	17.9±2.92	18.07±2.88	0.968

of activity in time unit (MET). This questionnaire has been validated for adolescents and the physical activities spent in different jobs have not been questioned, so it was adjusted and corrected in the present study. This was done by adding options about physical activity spent for different jobs by the physical activity questionnaire validated by Norman *et al.* in Sweden this was classified based on intensity of different jobs [30]. Finally, the hours spent for each of the physical activities was multiplied by MET value of the activity and the obtained numbers of MET-h were summed and value of MET-h/day was calculated.

Statistical Analysis

In this study, SPSS 18 statistical software was used for including information and statistical analysis of data. The quantitative variables were reported as mean and standard error and descriptive variables as number and percent. Normality of data distribution was evaluated by K-S test of normal probability plot (P-P plot). Non-normal variables with right skewed distribution were also normalized by logarithmic conversion. Within-group comparisons were made by paired Hotelling's T^2 test and between-group comparisons were performed by multivariate analysis of covariance (MANCOVA). P value<0.05 was considered significant.

RESULTS

Comparison of basic variables and food intake and physical activity level in intervention and control groups is given in Table **2**. In this study, 35 people with hyperlipidemia were included in the intervention group and 35 were in the control group. Changes in activity were not significant in both groups. Within-group changes were used for comparison of activity between two groups, the results of which were not significant. Therefore, activity level did not have any effect as a confounding factor. Food intake was evaluated and compared in terms of calorie, protein, fat, cholesterol, saturated fatty acid, mono unsaturated fatty acids (MUFA), poly unsaturated fatty acids (PUFA), oleic acid, Linolenic acid, linoleic acid, Eicosapentaenoic acid (EPA), Docosahexaenoic acid (DHA), vitamin E, vitamin D and fiber. They

Table 3. Effect of flaxseed on lipid parameters and anthropometric indices.

Variable	Before	After	P.value1*	P.value2**
Weight (kg)				
Case	75.6±1.93	74.6±1.87	<0.001	<0.001
Control	75.6±1.5	75.4±1.5	0.29	
BMI (kg/m^2)				
Case	27.28±0.61	26.78±0.59	<0.001	<0.001
Control	27.68±0.43	27.63±0.42	0.23	
TC (mg/dl)				
Case	226±6.2	214.5±5.2	0.026	<0.001
Control	214.8±5.7	231.2±4.5	<0.001	
LDL-c (mg/dl)				
Case	133.8±7.76	130.7±5.6	0.537	0.046
Control	126.7±6.74	136.3±6	0.013	
HDL-c (mg/dl)				
Case	49.18±1.5	49.45±1.5	0.85	0.543
Control	49.34±1.2	49.28±0.96	0.886	
TG (mg/dl)				
Case	226.05±18.7	176.6±11.1	<0.001	<0.001
Control	213±15.6	230.68±14.4	0.003	

*: Comparing before and after of each variable in each group
**: resulted from MANCOVA for comparing the studied outcomes between two groups (adjustments were made for baseline values and calorie)

did not have significant difference in any case. Therefore, effect of diet of two groups was also excluded as the confounding factor (Table **2**).

Percent of changes in each of the variables was calculated for each group and compared between two groups using MANOVA. Results showed that BMI was reduced by 2.12% in the intervention group and 0.18% in the control group. Weight was reduced by 1.32% and 0.26% in the intervention and control groups, respectively. These changes were significant. Multivariate p value was equal to 0; *i.e.* two groups were different in terms of change in BMI and weight.

Effect of calorie was adjusted in the comparison of two groups in terms of BMI and weight. Difference of two groups was significant in lipid profiles in terms of changes due to difference in total cholesterol and triglyceride and LDL-c.

Mean weight was 75.6 (SE: 1.93) in the intervention group and reached 74.6 (SE: 1.87) after 40 days of intervention; this reduction was significant. Mean weight was 75.6 (SE: 1.50) in the control group at the beginning of the project and reached 75.4 (SE: 1.50) after completion of the project, which was not significant.

Mean BMI in the intervention group was reduced from 27.28 (SE: 0.60) to 26.78 (SE: 0.59), which was significant. In the control group, BMI was reduced from 27.68 (SE: 0.43) to 27.63 (SE: 0.42) that was not significant.

Mean total cholesterol in the intervention group was 226.05 and reached 214.53 after the intervention; this reduction was statistically significant. In the control group, total cholesterol increased from 214.85 to 231.22; this increase was significant.

Mean LDL-c in the intervention group was reduced from 133.8 to 130.74, which was statistically significant. Mean LDL-c in the control group was increased from 126.77 to 136.28 which was significant.

Mean HDL-c in the intervention group was increased from 49.18 to 49.45, which was not significant. Mean HDL-c in the control group was reduced from 49.34 to 49.28 that was not been significant.

Mean TG in the intervention group was 226.05 and was reduced to 176.6 after the intervention that was significant and it was 213 in the control group and increased to 230.68 after completion of the project that was significant (Table **3**).

The differences between two groups on the basis of analysis of covariance test were significant. In all cases except for the HDL-c, it is an effective intervention (Table **3**).

DISCUSSION

The results obtained in this study and comparison of lipid profiles before and after intake of flaxseed showed that intake of flaxseed powder significantly reduced TC, LDL-c and TG and increased HDL-c, which were not significant (Table **1**). Generally, diet enriched with flaxseed can cause reduction in LDL-c by 0 to 18% and in TC by 0 to 11%. In most studies, no change has been found in HDL-c level and

its concentration has been reduced by 16% only in one study. In some studies flaxseed increase TG and in some studies it has decreased TG. No effect has been found in some studies. Change in lipid profiles may be depends on intake form of flaxseed, sex of the subjects, lipid values of them and age of subjects [31]. In previous studies age of subjects has been effective as a confounding factor; younger people have reduced concentration of TG due to intake of flaxseed, while no effect has been found in older people. In most studies which have found beneficial effect of flaxseed on lipid profiles, about 30-50gr/d flaxseed has been consumed [28]. So in this study, 30gr flaxseed was used. Since all compounds in flaxseed are effective in lipid profiles, intake of whole flaxseed may have a higher effect. In the meta-analysis showed that intake of 38gr/d whole flaxseed significantly reduced TC and LDL-c, while this change was not found with flaxseed oil [11]. Flaxseed contains a high amount of fiber. Approximately 28% of the seed`s weight and 25% of total fibers are soluble. It has been shown that water soluble form has decreasing effects on cholesterol and reduces TC and LDL-c (-0.45 and -0.057 mmol/L/gram respectively). Soluble fibers in flaxseed contain gums, mucilage, and its main insoluble fiber including cellulose [21]. In a study by Mette Kristensen *et al.* on effect of flaxseed fiber on the reduction of cholesterol and increase of the secreted fat through feces, results showed that intake of 5 gr flaxseed fiber per day increased the fat in feces and significant reduction was found in TC and LDL-c [26]. In another study which was conducted to support these findings, taking 5 gr gum derived from flaxseed per day for 3 months reduced TC by 10% and LDL-c by 16%. In that study, fiber in the flaxseed was regarded as the effective factor for reducing blood lipid. Physiological mechanism of the effect of fiber on fat is due to the secretion of biliary acids and then intake of cholesterol in the liver for compensating for bile reproduction and lower delivering of cholesterol to lipoproteins [26]. Flaxseed is an oilseed in which oil comprises between 38 and 45% of the seed content depending on environmental culture situation [14]. Flaxseed oil is generally alpha-linolenic acid (ALA) which is regarded an Omega 3 fatty acid [15]. Epidemiological studies have shown that replace ALA instead of saturated fatty acids reduces blood lipids. Intake of flaxseed oil significantly increases ω_3 content in the plasma or membrane of erythrocytes and reduces ω_6 to ω_3 ratio. This is a useful change for prevention of the CVD incidence. In many studies, great attention has been paid to flaxseed oil owing to high content of alpha-linolenic acid which is a precursor for EPA and DHA. Also, significantly useful effects on cardiovascular diseases have been proved in different epidemiological studies and RCTs [15]. Flaxseed contains phytic acid which is comparable to what is available in soybeans and peanuts. It has three types of phenolic compounds: Lignans, Flavonoids, and Phenolic acids. 1 to 26mg/g of Lignans is found in flaxseed. Lignans available in flaxseed is 75 to 100 times more than other plant sources [32]. The most important Lignan in flaxseed is Secoisolariciresinol diglucoside (SDG) which is metabolized in the intestine and converted into phytoestrogens; it has antioxidant effects and is similar to phytoestrogen in soybean [32, 33]. Zhang *et al.* found a significant reduction in TC (22%) and LDL-c (24%) among hypercholesterolemic patients after 8 weeks of consuming 600 mg/d lignan derived from flaxseed (SDG) [34]. The study on the effect of SDG extracted from flaxseed on cholesterol level in rabbits concluded that SDG reduced atherosclerosis resulting from hypercholesterolemia which was due to reduction of serum cholesterol, LDL-c, and lipid peroxidization and increase in HDL-c and antioxidant reserve [7]. Purified lignan alone has shown to reduce TC and LDL-c. Indeed, this effect has been found in animal studies; there are still limited studies on human samples and only 5 studies have used lignan supplement. In the study which was conducted by An Pan *et al.* on the effect of lignan derived from flaxseed on glycemic control, lipid profiles, and condition of inflammatory factors in the patients with type 2 diabetes, intake of 360 mg/d lignan taken from 27-60 g whole flaxseed for 12 weeks had no effect on lipid profiles. The lignan available in flaxseed had a positive effect in preventing and postponing diabetes progress in animal models due to its strong antioxidant activity [31]. Lignan also inhibits (PEPCK) gene expression which makes a inhibitor enzyme for gluconeogenesis in the liver [35]. Considering the previous meta-analysis on the effect of flaxseed on lipid profiles, it was mentioned that initial value of blood lipids had a strong effect on changes in concentration of lipids. Useful effect of flaxseed and its derivatives on blood lipids was found when initial blood lipids were relatively high [11]. In this study, a similar case occurred and changes in the subjects who had a high level of TC and TG were much more significant than those whose TC and TG were slightly higher than normal limit. In other studies, reducing effect of cholesterol in flaxseed and its derivatives for women was more considerable than men. This difference was more intensive in menopausal women who were susceptible to increased LDL-c concentration due to shortage of estrogen. The reason for differences between women and men is unknown and may be due to type of intervention, basic value of lipid profiles, or biological differences [11]. Sex distribution in two intervention and control groups was equal in this study. In the most of previous studies, significant effects of flaxseed and its derivatives on HDL-c and TG have not been found [11], while in this study significant effects have been observed on reduction of TG in the intervention group. Results of different RCTs showed that reducing effect of flaxseed on lipid profiles was more evident when intervention by whole flaxseed was performed [11]. The study which was conducted by Hongyu Wo *et al.* on the effect of lifestyle and intake of flaxseed or walnut supplement on metabolic syndrome did not find the positive effect of flaxseed on lipid profiles [36]. One of the considerable points in that study was that food matrix had an effect on physiological responses of the body and solving flaxseed fiber in water was more effective than the cooked fiber along with bread. In another study about the cardiovascular effects of flaxseed and its omega-3 fatty acid, alpha-linolenic acid, it was mentioned that grinding or milling flaxseed increased bioavailability of nutrient of the plant to the body [9]. Therefore, in the present study, the samples were asked to consume raw flaxseed powder along with water which was not heated, because food matrix is effective for its impacts in the body based on the previous studies. Lipoic acid is a natural compound of antioxidant which has a protective effect against risk factors of CVD, because production of free radicals oxidizes LDL-c and finally leads to destruction of cellular compounds and start of athrogenesis process. In the study on effect of flaxseed oil and lipoic acid compound on reduc-

tion of risk factors of atherosclerosis in rats with high fat diet, it was found that intake of flaxseed oil supplement and lipoic acid significantly reduced plasma fat peroxidization level [16]. Evidence has shown that a high fat diet which is full of saturated fatty acids causes hypercholesterolemia. Flaxseed oil reduces the concentration of TC and LDL-c, also increases expression of hepatic LDL-c receptors; as a result, catabolism of cholesterol increases [16]. Leptin has a reverse relationship with the incidence of atherosclerosis so that those whose leptin level is high have low chance of affliction with atherosclerosis and, when leptin secretion is suppressed with cholesterol available in the flow, athrogenesis is stimulated. Leptin secretion is different in the bodies of different people and depends on energy balance and lipid tissue. High cholesterol suppresses leptin gene expression, while diet full of ω3 and α-Linolenic acid increases leptin. It was shown that intake of flaxseed improved resistance to insulin, hyperlipidemia, atherosclerosis, and hypertension and decreases cardiac arrhythmias. These effects of flaxseed can be partly attributed due to the high content of ALA. Increase of ALA in blood circulation and lipid tissues adjust leptin expression [34]. Review of the articles has shown that all compounds in flaxseed are effective for cholesterol and, perhaps, effect of whole flaxseed is the collection of effects of its compound.

Strengths

There was no significant difference between diet and activity of the subjects; therefore, its confounding effect was excluded.

Limitations

Since whole flaxseed was used in this study, no suitable placebo was found for the control group; as a result, the study could not be double-blind and there was no suitable strategy for studying whether the mentioned amount of flaxseed was really consumed by the intervention group or not.

CONCLUSION

In this study, a significant reducing effect was found in weight, BMI, TC, LDL-c and TG. Due to the presence of this useful effect in flaxseed, it may be regarded as an effective pharmaceutical compound. If other studies confirm these effects of flaxseed, we will be able to recommend to hyperdipidemic and overweight people.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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PATIENT CONSENT

Declared none.

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