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The Effect of Ginger on Blood Lipid and Lipoproteins in Patients with Type 2 Diabetes: A Double-Blind Randomized Clinical Controlled Trial

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ABSTRACT

Background: Preliminary clinical trials showed that ginger improved lipid profile in type 2 diabetes patients (T2D). This trial was carried out to determine the effect of ginger on blood lipid and lipoproteins in T2D. **Methods**: this is a randomized, double-blind, placebo-controlled trial on 88 T2D conducted in. The patients were randomly divided into two groups of ginger (GG) and placebo (PG), the GG consumed daily 3 one-gram capsules containing ginger powder whereas the other group received capsules of the same color and number as GG but containing cellulose microcrystalline, both after taking meals and for eight weeks. Serum total cholesterol (TC), triglycerides (TG), HDL-c, LDL-c, Apo B_{100} and Apo A_1 were measured at the baseline and the end of trial. **Results**: Out of 88 patients who participated in the trial, 81 of them accomplished it. No significant changes were observed in mean of TC, TG, HDL-c, and Apo B_{100} within and between the groups. Serum LDL-c and LDL-c/HDL-c ratio were decreased significantly in the GG (P = 0.03, P = 0.028) at the end of trail but they were not significantly different between the two groups. Serum Apo A_1 was increased significantly in the GG ($P < 0.05$) and PG ($P < 0.05$) at the end of trial but it was not significantly different between the two groups. **Conclusions:** This study indicated that daily consumption of 3 g of ginger powder in capsules for 8 weeks by T2D leads to lowering of LDL-c, LDL-c/HDL-c ratio, and Apo A_1. Therefore, consumption of this supplementation is appropriate for this patients.

Keywords: *Ginger; Diabetes Mellitus; Blood Lipids; Lipoproteins*

Introduction

Diabetes mellitus is characterized by chronic hyperglycemia resulting from impaired insulin action/ secretion. Type 2 diabetes (T2D) accounts for more than 90% of diabetes and is associated with lipid and carbohydrate metabolic disorders (American Diabetes Association). The number of patients with diabetes are estimated to be more than 366 million in 2030 which is more than twice of the rate in 2000 (Wild et al., 2004). Most of the new cases will be from the developing countries and seemingly Middle East will suffer most from diabetic prevalence till 2020 (Seidell, 2000, Wild et al., 2004). The prevalence of T2D is

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high in the Middle East; the rate of 7.7% has been reported for Iran (Esteghamati *et al.*, 2008).

Impaired insulin-stimulated glucose metabolism is a common feature in obese and diabetic participants. It is entrenched that insulin resistance in peripheral tissues is tightly associated with elevated circulating lipids and tissue lipid accumulation (McGarry, 2002). The mechanism studies showed that excessive free fatty acid and fatty acid oxidation inhibit glucose transport into peripheral tissues, i.e., the first rate-limiting step in glucose metabolism(Fink et al., 1992, Randle et al., 1963, Roden et al., 1996).

Virtually, about 3/4 of the world's population have trust in traditional treatments, especially herbal treatments; until the mid-19th century at least 80% of the medicines were herbal derivatives (Gilani and Rahman, 2005). Ginger (Zingiberofficinale, Roscoe Zingiberaceae) is one of the most widely consumed spices worldwide. From its origin in the southeast Asia towards Europe, it has a long history of use as a herbal medicine in treating a variety of ailments including vomiting, pain, indigestion, and cold induced syndromes (Wang and Wang, 2005, White, 2007). More recently, it was reported that ginger also possesses anti-cancer, anticlotting, anti-inflammatory, and analgesic activities (Ali et al., 2008, Chrubasik et al., 2005).

Ginger is an herb, the herbal properties of which are similar to those of non-steroid anti–inflammatory drugs (NSAIDs), therefore, it can regulate biochemical pathways activated with chronic inflammation such as diabetes (Grzanna et al., 2005). Laboratory studies have indicated that ginger bears anti-inflammatory effect which can prevent arachidonic acid metabolism with inhibition of cyclooxygenase and lipooxygenase pathways (Srivastava, 1984, Srivastava and Mustafa, 1992). As a result, there is the possibility for ginger to have this effect due to inhibition of prostaglandins and leukotrienes production (Surh et al., 1998). Gingerols are one of the ginger active components which inhibit production of inflammation-causing prostaglandins. Ginger effects on hepatic cholesterol biosynthesis is reduced and possibly it converts cholesterol to bile acids, which stimulates and enhances its excretion (Verma et al., 2004).

Ginger is effective in lowering blood triglyceride levels, it may increase both the rate and activity of arterial lipoprotein lipase that causes breakdown of triglycerides in blood vessels and also led to a decrease in plasma triglycerides. In some other studies, the levels of triglycerides and very low density lipoprotein (VLDL) were lower in patients receiving ginger (Bhandari et al., 2005, Shirdel et al., 2009). No side effects have been reported in humans in taking ginger (Srivastava and Mustafa, 1992). Doses greater than 4 g of ginger daily in patients receiving concomitant blood-thinning drug such as warfarin or aspirin should be taken with caution. Ginger, in people who suffer from gallstones interferes and increases the production of bile (Bordia et al., 1997).

Preliminary clinical trials showed that ginger improved lipid profile in diabetic patients (Andallu et al., 2003). When ginger was used in combination with other herbs, significant physiological changes, including reduction of body weight, skin thickness, waist/hip circumference, as well as reduction of serum triglyceride (TG) and total cholesterol (TC) in diabetic and hyper lipidemic patients were observed (Kamal and Aleem, 2009, Paranjpe et al., 1990).

In study accomplished by ElRokh et al., in Egypt, anti lipidemic effects of ginger on diabetic mice were investigated, the results represented a significant decrease of serum TC, TG, and LDL-c by ginger in the diabetic mice (ElRokh *et al.*, 2010). Also, it significantly increased HDL-c (Tripathi et al., 2007). In another study conducted by Shirdel et al., in Iran, the anti-diabetic and anti-lipedemic effects of ginger on diabetic mice affected by alloxan monohydrate was investigated, then it was compared with Glibenclamide. The results represented a significant decrease of serum glucose, TG, VLDL, and LDL-c by ginger in the diabetic mice (Shirdel et al., 2009). Also, the TC and TG lowering effects in T2D were investigated (Alizadeh-Navaei et al., 2008).

Despite different scientific evidences, there is no agreement regarding various effects of ginger.

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Moreover, only few studies have been conducted on ginger and its relation with blood lipid in patients with diabetes. This study was, therefore, carried out to determine the effect of ginger on blood lipid and lipoproteins in patients with T2D.

Materials and Methods

Participants and design of study: This is a randomized, double-blind, placebo-controlled trial on 88 patients with T2D conducted in Yazd Diabetes Research Center. Inclusion criteria were: having T2D for at least 10 years, fasting blood glucose (FBG) < 180 mg/dl and 2h-blood-glocose < 250 mg/dl, no pregnancy or lactation, no autoimmune disorder, no cardiac ischemic or renal diseases, no thyroid and chronic inflammatory diseases, peptic ulcer and infection, no regular consumption of ginger or other herbal drugs, no sensitivity to ginger, body mass index (BMI) < 40 kg/m^2, no consumption of triglyceride or cholesterol-, estrogen-, progesterone-lowering drugs, and no consumption of any supplements such as vitamin C, E, and omega-3 during 2 months before starting the research.

Exclusion criteria were: No observation of research protocol (no consumption of more than 20% of the capsules), any sensitivity due to ginger consumption reported by the patient or noticed after starting the study, consumption of vitamin, mineral or other nutritional supplements, consumption of alcohol or narcotic drugs, and any variation in patients' routine treatment according to physicians' resolution (i.e., variation in type and dose of the drugs to be consumed, and treatment with insulin).

Dose, type of supplement, and intervention duration: The patients were categorized into two groups of ginger (GG) and placebo (PG) through table of random numbers, the GG consumed daily 3 one-gram capsules containing ginger powder whereas the other group received capsules of the same color and number as GG but containing cellulose microcrystalline, both after taking meals and for eight weeks.

The researchers gained access to these supplements by Bou-Ali Sina Herbal Drug Researchers Corporation in Qom, Iran. Follow-up of the patients so as to control them for consumption of capsules, response to the relevant questions, and prevention of sample loss, was performed weekly by telephone and every other week via monitoring the patients referring to Yazd Diabetes Research Center to receive capsules for the couple of weeks to come.

It is noteworthy that not all the supplements were totally delivered to the participants. To be assured of the consumption of supplement and placebo by the participants and calculation of rate of capsules consumption compliance, the participants were asked to first deliver the empty boxes of capsules and then receive the new ones needed for the next two weeks. The participants were also advised not to change their usual diet, to stop self-reliant changes of their supplements doses, and to stop physical activities during the intervention.

Measurements: General information including age, weight, height, gender, marital status, occupation, education, duration of being affected by the disease, type and dose of the drugs required for diabetes control, were recorded through interview with the patients. Height was recorded by a standard clinical stadiometer with an accuracy of 0.1 cm. Weight was measured with light clothes and without shoes, through a balance with 100g accuracy, both at the beginning and the 8th week of the intervention. BMI was calculated as weight in kilograms divided by height in meters squared. To study the patients' diet in terms of daily intake of energy, carbohydrate, protein, fiber, and total fat, a 24-hours dietary recall questionnaire was used both at the beginning and the end of intervention. Nutritionist IV software (Nutritionist IV Diet Analysis, First Data Bank Division, Hearst Corp., San Bruno, CA) was applied to analyze 24-hours dietary recall data.

After 12 hours of fasting, a 10 ml sample of venous blood was taken from each patient by the laboratory technician at the beginning and the end of intervention. The centrifuge of the samples was performed at room temperature and at 3000 rpm for 10 minutes to separate serum. Then, the sera were collected into sterile micro tubes. After

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labeling, the samples were stored at – 80 °C in the central laboratory of Yazd Diabetes Research Center until the second sampling procedure.

Serum TC, TG, and HDL-c were measured enzymatically using commercial kits (Pars Azemoon, Tehran, Iran) (Auto analyzer; Echo Plus Corporation, Roma, Italy). LDL-c was calculated by the Friedewald equation (Fukuyama et al., 2008). However, samples with TG more than 400 mg/dl were analyzed with standard enzymatic methods. Serum concentrations of Apo B_{100} and Apo A_1 were determined by immunoturbidimetric methods using commercial kits (Pars Azemoon, Tehran, Iran) through alpha-classic auto analyzer (made in Iranazma Corporation, Mashhad, Iran).

Ethical considerations: The aims and methods of study were explained to the patients and the informed written consent was received from them. Also, the research was approved by Ethics Commission of Deputy for Research in Shahid Sadoughi University of Medical Sciences. This study has also been registered at the Iranian registry of clinical trials (www.irct.ir) with IRCT 201104246278N1 code.

Data analysis: The data were analyzed by SPSS version 11 (SPSS Inc., Chicago, IL, USA). Kolmogorov–Smirnov test was used to determine quantitative data distribution, paired *t*-test to compare mean of normal distribution variables in the two groups before and after the intervention, and Student *t*-test to compare the mean of variables between the two groups. The results of the quantitative data with normal distribution were reported as mean ± SD. The significance level was set at *P*-value equal or less than 0.05.

Results

Out of 88 patients who participated in the study, the following cases were excluded from the intervention: 4 patients who had no tendency to continue, 1 for her husband's death and 2 for travel, the remaining 81 patients accomplished the study and thus investigated (**Figure 1**).

All the patients received oral hypoglycemic agents, 50 (61.7%) were female and 31 (38.3%) male. The mean age of the patients in the GG and PG were 49.83 ± 7.23 and 51.05 ± 7.70 years, respectively. The baseline characteristics of patients did not differ significantly between the two groups (**Table 1**). In addition, BMI did not significantly change within each group during the study. There were no significant differences in daily dietary intake of total energy and some nutrients between the two groups at baseline and the end of the intervention (**Table 2**).The TC, TG, LDL-c, HDL-c, LDL-c /HDL-c ratio, Apo A_1, Apo $B_{100,}$ and BMI are shown in **Table 3**. No significant changes were observed in serum concentrations of TC, TG, HDL-c, and Apo B_{100} within and between the groups before and after the intervention.

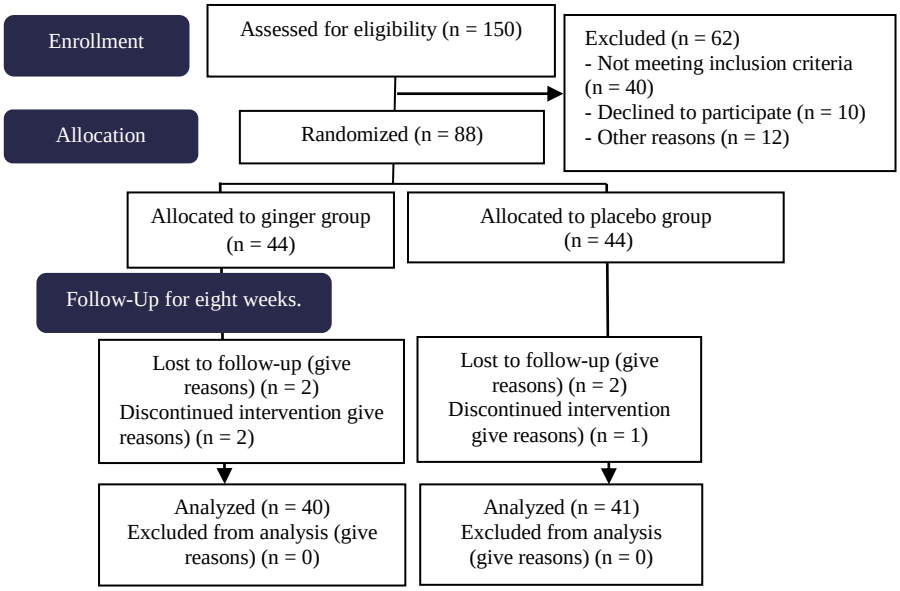

Figure 1. Diagram of the study

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Table 1. Comparison of qualitative and quantitative variables before the intervention.

Groups/ Variables	Placebo (n = 41) Mean ± SD	Ginger (n = 40) Mean ± SD	P-value[a]
Age (year)	51.05 ± 7.70	49.83 ± 7.23	0.46
Height (cm)	162.21 ± 9.24	159.00 ± 10.08	0.15
Weight (kg)	74.63 ± 11.48	71.20 ± 16.08	0.27
Body mass index (kg/m^2)	28.51 ± 4.95	28.09 ± 5.29	0.71
Gender	n (%)	n (%)	
Male	18 (43.9)	13 (32.5)	0.2[b]
Female	23 (56.1)	27 (67.5)	

[a]: Student *t*-test; [b]: Chi square test

Table 2. Comparison of daily dietary intake of energy and some nutrients before and after the intervention in ginger and placebo groups

Variables	Baseline	End	P-value[b]
Energy (kcal)			
Ginger Group	1331.74 ± 32 9.70	1321.22 ± 452.99	0.36
Placebo Group	1363.35 ± 457.28	1389.14 ± 549.28	0.60
P-value[a]	0.89	0.79	
Carbohydrate (g)			
Ginger Group	151.04 ± 60.93	145.85 ± 76.99	0.18
Placebo Group	170.07 ± 72.77	158.07 ± 70.05	0.06
P-value	0.15	0.28	
Protein (g)			
Ginger Group	54.22 ± 21.44	52.03 ± 16.63	0.58
Placebo Group	50.91 ± 24.24	54.37 ± 24.94	0.47
P-value	0.51	0.62	
Fat (g)			
Ginger Group	58.52 ± 14.22	61.04±19.56	0.66
Placebo Group	55.34 ± 15.65	61.76±26.83	0.06
P-value	0.28	0.66	
Cholesterol (mg)			
Ginger Group	250.18 ± 362.66	177.58 ± 232.84	0.17
Placebo Group	170.54 ± 252.64	168.76 ± 179.60	0.15
P-value	0.07	0.78	
Fiber (g)			
Ginger Group	8.65 ± 4.26	8.31 ± 6.64	0.25
Placebo Group	9.29 ± 4.01	7.99 ± 4.97	0.07
P-value	0.41	0.84	
Salt (g)			
Ginger Group	3.47 ± 0.54	3.51 ± 0.65	0.99
Placebo Group	3.39 ± 0.47	3.63 ± 0.97	0.31
P-value	0.50	0.85	

[a]: Student *t*-test; [b]: Paired *t*-test

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Table 3. The comparison of total cholesterol, triglycerides, LDL-c, HDL-c and Apolipoproteins A_1 , as well as $B_{100}$and body mass index before and after the intervention in ginger and placebo groups

Variables	Baseline	End	Changes[c]	P-value[b]
Total cholesterol (mg/dl)				
Ginger Group	190.95 ± 36.40	186.84 ± 33.52	-4.10 ± 35.73	0.47
Placebo Group	185.80 ± 32.05	179.81 ± 32.69	-5.99 ± 31.98	0.23
P-value[b]	0.50	0.34	0.80	
triglycerides (mg/dl)				
Ginger Group	182.80 ± 91.77	174.29 ± 82.08	-8.50 ± 72.37	0.46
Placebo Group	178.48 ± 84.51	172.20 ± 81.81	-6.28 ± 78.59	0.61
P-value	0.82	0.90	0.89	
LDL-c (mg/dl)				
Ginger Group	112.52 ± 22.09	106.10 ± 20.78	-6.41 ± 18.96	0.03
Placebo Group	106.46 ± 18.14	102.94 ± 19.83	-3.51 ± 22.71	0.32
P-value	0.18	0.48	0.53	
HDL-c (mg/dl)				
Ginger Group	42.40 ± 8.16	44.07 ± 10.29	1.67 ± 11.88	0.37
Placebo Group	44.14 ± 9.16	41.95 ± 7.44	-2.19 ± 11.50	0.22
P-value	0.36	0.29	0.14	
LDL-c /HDL-c Ratio				
Ginger Group	2.70 ± 0.54	2.48 ± 0.57	0.005 ± 0.79	0.028
Placebo Group	2.49 ± 0.59	2.49 ± 0.53	0.18 ± 0.92	0.96
P-value	0.1	0.91	0.35	
Apolipoproteins A_1 (mg/dl)				
Ginger Group	120.11 ± 11.49	153.52 ± 11.51	33.41 ± 10.18	< 0.005
Placebo Group	117.78 ± 11.01	151.02 ± 14.43	33.24 ± 10.65	< 0.005
P-value	0.35	0.39	0.94	
Apolipoproteins B_{100} (mg/dl)				
Ginger Group	121.46 ± 21.81	128.16 ± 22.86	6.70 ± 22.49	0.06
Placebo Group	117.70 ± 20.65	122.78 ± 23.85	5.17 ± 17.47	0.06
P-value	0.42	0.31	0.73	
Body mass index (kg/m^2)				
Ginger Group	28.09 ± 5.29	28.05 ± 5.33	0.04 ± 0.32	0.44
Placebo Group	28.51 ± 4.95	28.53 ± .03	-0.02 ± 0.34	0.64
P-value	0.71	0.67	0.38	

[a]: Student *t*-test; [b]: Paired *t*-test; [c]: '-' increase

Serum LDL-c concentration was decreased significantly in the GG (P = 0.03) group at the end of week 8 but serum LDL-c was not significantly different between the two groups before and after the intervention. LDL-c/HDL-c ratio decreased significantly in the GG (P = 0.028) group at the end of week 8, but there was no significant difference between the two groups before and after
the intervention.

Serum Apo A_1 concentration increased significantly in the GG (P < 0.05) and PG (P < 0.05) groups at the end of week 8 compared to the baseline but serum Apo A_1 was not significantly different between the two groups before and after the intervention. Moreover, like BMI mean, no significant difference was observed between the two groups at the beginning and at the end of this study.

Discussion

The present study indicated that daily consumption of 3 g of ginger powder in capsules by patients with T2D for 8 weeks causes improvement of some indices related to blood lipids control. In our study, ginger powder consumption for 8 weeks had no significant effect on serum TC, TG, HDL-c, or apo B_{100}. One of its definite outcomes is a significant decrease of LDL-c and LDL-c/HDL-c ratio in the GG in comparison with the PG, thus showing the effect of ginger in controlling blood lipids. On the other hand, serum

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concentration of Apo A_1 increased significantly in both the GG and PG groups but no significant difference was observed between the two groups in the level of serum Apo A_1 at baseline or at the end of the study. This finding is in agreement with those of some previous studies but they differ from findings of several other studies.

In a study conducted in Iran, the anti-diabetic and anti-lipedemic effect of ginger on diabetic mice affected by alloxanmonohydrate and its comparison with Glibenclamide were investigated. The result of which represented a significant decrease of serum TG, VLDL, and LDL-c by ginger in the diabetic mice (Shirdel et al., 2009) which is in line with our LDL-c results. In another study accomplished by Singh et al., in India, the blood glucose lowering, lipid lowering, and antioxidant effect of 6-gingerol in T2D db/db mice were investigated. The results showed that treatment of mice with 6-gingerol (100 mg/kg of body weight) for 12 days can significantly ($P < 0.05$) decrease plasma triglycerides, total cholesterol, free fatty acid, and LDL-c (Singh et al., 2009). Results achieved by this study are consistent with the LDL-c results in our study. Al-Amin et al., in Kuwait indicated that an aqueous extract of raw ginger administered daily (500 mg/kg, intraperitoneally) for a period of 7 weeks to streptozotocin-induced diabetic rats produces hypoglycemic, hypocholesterolemic and hypolipidemic properties (Al-Amin et al., 2006). The TC and triglycerides-lowering effect of ginger in this study is inconsistent with what was detected in this study in relation to TC and TG.

In contrast to our research, Bhandari's et al., in India studied, the effect of oral ginger ethanolic extract on diabetic mice, the results of which indicated its significant antihyperglycemic effect and significant TC and TG lowering activity after 20 days (Bhandari et al., 2005). Also Alizadeh et al., in Iran investigated the blood total cholesterol lowering and triglycerides lowering in T2D (Alizadeh-Navaei et al., 2008). These results are in disagreement with our study.

For assessing blood lipids, our study focused on indices such as TC, TG, LDL-c, HDL-c, Apo A_1, and Apo B_{100}, the results of which were not the same. Generally, review of previous studies showed that there have been a few studies on the effect of ginger powder (in capsules) on lipids indices of the diabetic patients. Moreover, the results of researches conducted on human and animals have turned out to be contradictory. This contradiction may be the outcome of disparity in people's responses. Further, this disparity of responses can be the sequel of the patient's baseline data differences, experimental group weight, and other measured indices at the beginning of the study. Moreover, most of the articles published did not mention the type and dose of the drug consumed by the patients; this, however, is not the case in our study. Ginger supplementation for eight weeks was contributed to significant variation in LDL-c, LDL-c/HDL-c ratio, and Apo A_1.

Ginger is an herbal drug, properties of which are similar to those of NSAIDs. Therefore, it can regulate biochemical pathways which are activated with chronic inflammation (such as diabetes) (Grzanna et al., 2005). The high percentage of the patients' compliance in consuming capsules can be regarded as a strong point of the current study. One of the limitations of the present is the rather short period of supplementation i.e., two months; so, for the forthcoming similar investigations, a longer period is suggested. Moreover, the efficacy examination of a longer use of ginger supplementation and its impact on parameters pertinent to inflammation and hormones related to inflammation are suggested as well.

Conclusions

This study indicated that daily consumption of 3 g of ginger powder in capsules for 8 weeks by patients with T2D leads to lowering of LDL-c, LDL-c/HDL-c ratio, and Apo A_1. Therefore, consumption of this supplementation is appropriate for patients; for identifying its other effects, however, some further studies are needed.

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Author contributions

Mozaffari-Khosravi H participated to conception and design of study, managing the project and drafting the manuscript. Bahreini S and Talaei B participated to acquisition of data, data analysis and drafting the manuscript. All authors read the paper and verified it.

Conflicts of Interest

Nothing to declare.

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