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The effect of ginger on blood sugar and urine protein in patients with type 2 diabetes mellitus; a clinical trial

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ABSTRACT

Introduction: The prevalence of diabetes mellitus has been increasing exponentially and its complications are a major cause of morbidity and mortality. Ginger is one of the herbal remedies which has preventive effects on nephropathy in animal models in some studies.
Objectives: We aimed to investigate the effect of ginger on urine protein analysis and blood glucose levels in diabetic patients.
Patients and Methods: In a clinical trial, 98 patients with type 2 diabetes were randomly divided into two groups; the intervention group received 500 mg of *Zingiber* as capsule, daily in addition to routine therapies, since control group received only conventional treatments for diabetes. Before and after intervention, blood glucose, urine microalbumin and hemoglobin A1c (HbA1c) were measured.
Results: The findings showed that *Zingiber* decreased HbA1c levels in diabetic patients (P=0.006), however, it did not have a significant effect on fasting blood glucose (P=0.179), 2 hours post-prandial glucose levels (P= 0.272), and the microalbuminuria quantity in urine (P=0.109).
Conclusion: In our study, the hypoglycemic short-term effects of ginger observed as a reduction of HbA1c, however its effect on reducing blood glucose levels [FBS and 2 hours postprandial glucose (2hpp)] was not significant, therefore ginger can be considered as a supplementary agent in the treatment of diabetes. However it is recommended to conduct more studies to obtain results with more reliability.
Trial registration: The trial protocol was approved by the Iranian Registry of Clinical Trial (identifier: IRCT2017103025732N27; https://www.irct.ir/trial/21503, ethical code; IR.SEMUMS.REC.1395.207).

Implication for health policy/practice/research/medical education:
Diabetes is a leading cause of morbidity and mortality. Diabetes in its early stages is curable by using herbal medicine. Since antiquity, diabetes has been treated with plant medicines. Recent scientific investigation has confirmed the efficacy of many of the herbs, some of which are remarkably effective. Zingiber has long term effect on diabetes and can be useful in prevention of diabetes complications.
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Introduction

Diabetes mellitus is a chronic disease characterized by hyperglycemia and glycosuria (1,2). The prevalence of diabetes mellitus has been increasing dramatically over the past two decades. Statistically, those with diabetes mellitus were about 30 million in 1985 that reached 382 million people in 2013, making it a growing and a costly global problem (3). According to the World Health Organization (WHO) forecast by 2035, more than 592 million people worldwide will suffer from diabetes and given the increased prevalence of type-2 diabetes mellitus compared to type 1, most people will be with type-2 diabetes. The prevalence of diabetes is similar in most women and men and among most age groups. However, the highest number of people with diabetes in various regions is as 40-59 age groups in the world (4).

The causes of hyperglycemia in the patient with diabetes mellitus are decrease in insulin secretion from pancreatic

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beta cells (β-cells), decrease in glucose absorption from blood by the cells, and excessive increase in the level of glucose production in the body. Type 1 diabetes is caused by a severe decrease or lack of entire insulin hormone. The causes of type 2 diabetes include a heterogeneous group of disorders associated with varying degrees of resistance to insulin, disorder in insulin and its reduction, and an excessive increase in glucose production in the body (2). Diabetes leads to metabolic disorders that cause pathophysiologic changes in body organs. The incidence of diabetic complications for example in America, is regarded as the main cause of end-stage renal disease (ESRD), non-traumatic lower limb amputation, and adult blindness (4). Complications associated with diabetes are divided into vascular and non-vascular groups which are similar in both diabetes 1 and 2, mostly due to the lack of control over the progression of the disease (5). Vascular complications of diabetes are divided into micro-vascular complications (retinopathy, nephropathy and neuropathy) and macro-vascular complications (coronary artery disease, peripheral arterial disease and cerebrovascular disease), with micro-vascular complications being specific to type 2 diabetes (4). Various reports show the role of oxidative stress and free radicals in developing and intensifying complications of diabetes, such as nephropathy (6). Nephropathy is a complication of diabetes mellitus, showing itself as proteinuria and changes in the level of glomerular filtration rate (GFR) (5). Controlling blood sugar and blood pressure, controlling RAS (renin–angiotensin system) and using antioxidants can be beneficial in delaying diabetic nephropathy (5,7). Accordingly, proper and consistent control of hyperglycemia in patients with diabetes has a critical role in reducing the incidence and severity of micro and macro-vascular complications (8).

The treatment of diabetes is based on the three pillars; continuous aerobic exercise, a low-carbohydrate diet and medications. Therapeutic goals include eliminating symptoms of hyperglycemia, lowering and eliminating the long-term complications of micro-vascular and macro-vascular diabetes, and providing a better and more natural life for the patients throughout their lives (4,6). Nowadays, traditional medicine and medicinal herbs have become important in treating various diseases like diabetes. One of the antioxidant drugs used in the treatment of diabetes is ginger, which is a good auxiliary treatment given its low side effects in long term administration (1). Ginger is obtained from a yellow plant with purple veins with the scientific name *Zingiber officinale*. Although ginger is commonly referred to as the root of the plant, the part used is essentially the swollen underground stem of the plant. Ginger is a genus of grassy perennial Zingiberaceae family with about 70 species native to southeastern Asia with narrow, straw-like stems and shiny green arrowhead leaves that grow from tuberous rhizome (9,10). Their flowers are yellowish-green with a purple edge and creamy spots and small conical inflorescence with dense ears with stems growing out of ground in the summer (11). Among the ginger properties, one can state strengthening the immune system, anti-inflammatory properties, protective effects against colorectal cancer, anti-nausea and anti-thyroid effects in pregnant women, strong antioxidant effect, liver detoxifier, anti-hyperglycemia, anti-constipation and anti-palpitation (9-14).

Ginger has a protective effect and helps improve the kidney damage of diabetic patients (10). For instance, ginger antioxidants are gingerol, shogaols, and some phenolic derivatives of ketones, resulting in the loss of free radicals in the organs of the body, including the kidneys (13,15).

Ginger extract can help improve long-term diabetes control, resulting in increased insulin secretion and insulin release, as well as increased glucose clearance is in the peripheral tissues responding to insulin (9). Ginger kidney protective effect can be similar to metformin and prevent phosphorylation due to AMP-activated protein kinase activity (16,17).

A substance in ginger called gingerol is effective in increasing the use of glucose by cells without the need for insulin. Moreover, it is seen that insulin sensitivity increases drastically and therefore serum insulin decreases while using it. Moreover, the levels of low-density lipoprotein cholesterol and triglyceride in their blood have decreased (9). Ginger reacts with serotonin receptors since the effect of these receptors reverses insulin secretion. Accordingly, treatment with ginger reduces the level of glucose by 35% and increases insulin in the plasma by 10%. Ginger inhibits the synthesis of inflammatory factors in the body, as well as having a reverse effect to that of hyperglycemia in the body (18,19).

However, the high consumption of ginger may cause heartburn, interactions with cardiac and diabetic drugs and stimulate central nervous system disorders. Moreover, pregnant women, those with kidney and bile stones, and those using blood diluents should be careful the excessive use.

Objectives

Given its antioxidant and anti-inflammatory properties, we examine the effect of ginger on changes of blood glucose and microalbuminuria in diabetic patients.

Patients and Methods

Study design

In this clinical trial study, 116 individuals over 18 years of age admitted to endocrinology clinic of Kowsar hospital in Semnan, Iran with type 2 diabetes mellitus, were divided into two groups using blocked randomization with randomly selected block sizes. The inclusion criteria were patients more than 18 years old who treated with insulin

or glucose lowering drugs with non-nephrotic proteinuria and a GFR more than 50 mL/min/1.73 m². The exclusion criteria were being pregnant or lactating women, patients with liver illness, or symptomatic biliary or kidneys stones, active malignancies, alcohol users, active infections and warfarin users. The patients were randomly assigned to receiving ginger (case), control groups using random allocation sampling method, and underwent intervention in three months. Five patients from the intervention group were excluded from the study (one patient due to acute cholecystitis and four patients due to loss to follow up). Forty-eight patients in the intervention group received 500 mg of ginger as 250 mg capsules (Goldaru Pharmaceutical Company) besides receiving blood glucose drugs before lunch and before dinner for 12 weeks. Three patients in the control group excluded due to loss to follow up and 50 patients in the control group received no medicines and only received the same drugs that they had already used. Prior to the intervention and after that, the fasting blood glucose (FBS) and postprandial blood glucose 2 hours after meals 2 hours postprandial glucose (2hpp), hemoglobin A1c (HbA1c) and the value of urine microalbumin was measured. A checklist containing demographic and laboratory data for before and after intervention was applied.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. This paper was extracted from the thesis of Haniyeh Movahed, at the department of internal medicine, Semnan University of Medical Sciences. Moreover, the study protocol was registered in the Iranian Registry of Clinical Trials (identifier: IRCT2017103025732N27; https://www.en.irct.ir/trial/21503). The study was approved by the ethics committee of the Semnan University of Medical Sciences (#IR.SEMUMS.REC.1395.207). Additionally, informed consent was obtained from all of the patients.

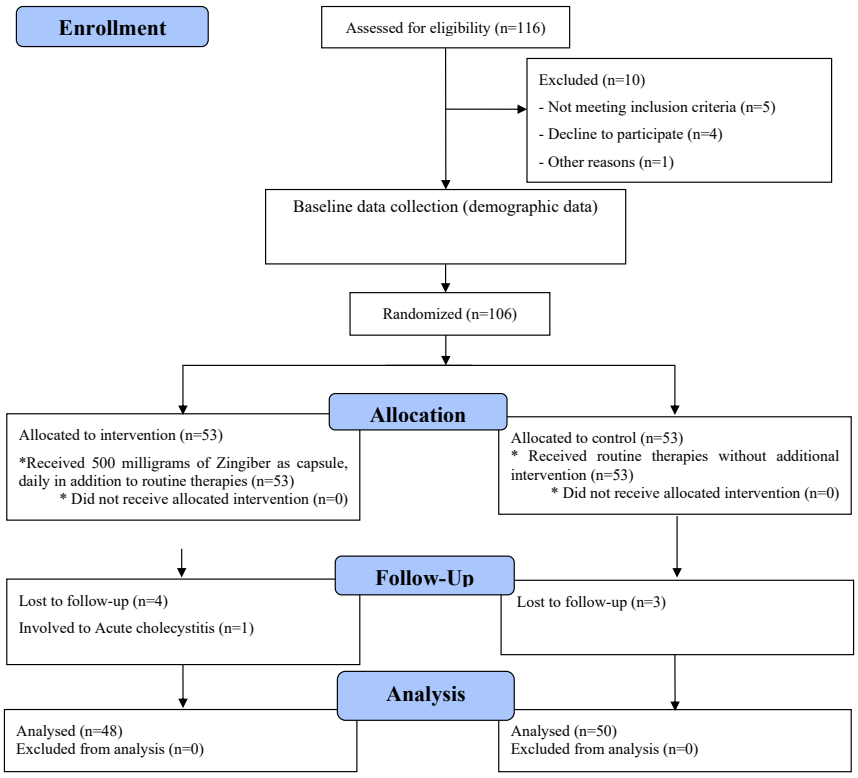
Statistical analysis

Data were analyzed by SPSS 23. The chi-square, Shapiro-Wilk test, *t* test (or Mann-Whitney U test) and Median tests were used to compare two related groups. $P<0.05$ was considered to indicate the significance level.

Results

In this study, 116 patients with type 2 diabetes mellitus were enrolled, 18 patients excluded from study during recruitment and follow-up. Finally 98 patients were entered to statistical analysis, 48 of them were ginger and 50 were as the control group. Therefore, the study was conducted on 48 patients. Figure 1 shows the flow diagram of the study. Around 66.7% of the ginger group and 66% of the control group were female. The two groups were similar for gender ($P=0.944$; Table 1).

Mean (±SD) of age in the ginger group was 61.2 ± 10.7 years and the control group was 59.6 ± 7.9 years ($P=0.414$) (Table 2). The youngest and the oldest patient were 41



Figur 1. Consort flow diagram of the study.

Table 1. Gender distribution between Ginger recipient and control group

Gender	Study group				*P* value
	Ginger Recipient		Control		
	No.	%	No.	%	
Female	32	66.7	33	66	
Male	16	33.3	17	34	0.944
Total	48	100	50	100	

Table 2. Age distribution of the ginger recipient and control group

Age (y)	Study group				*P* value
	Ginger Recipient		Control		
	No.	%	No.	%	
<60	22	45.8	24	48	
60-69	15	31.3	20	40	0.414
>70	11	22.9	6	12	
Total	48	100	50	100	

years and 86 years in the ginger group and 47 years and 78 years in the control group, respectively.

In the ginger group 41.7% and in the control group 36% of patients can be described as overweight or obese (Table 3).

Mean ± standard deviation of FBS before and after intervention in both groups is shown in Table 4. Mean FBS in ginger patients decreased by different 2.38 units, while in the control group increased by 1.46 units; however FBS was not significantly different in the groups ($P=0.197$).

The mean 2-hour postprandial blood sugar in the ginger group decreased by 2.17 units on average while it increased by 7.36 in the control group. Similarly, two-hour hyperglycemic changes were not significantly different between the two groups (Table 5) ($P=0.272$).

The mean HbA1c in the ginger group decreased by 0.42 units on average and 0.10 in the control group. HbA1c changes were significantly different between the two groups (Table 6) ($P=0.006$).

The mean urinary microalbumin in patients receiving ginger decreased by 1.15 units on average and in the control group decreased by 1.12 units. However, urinary microalbumin changes were not significantly different between the two groups (Table 7) ($P=0.109$).

Table 3. Distribution of body mass index in ginger and control group

BMI (kg/m²)	Study group				*P* value
	Ginger Recipient		Control		
	No.	%	No.	%	
Normal <25	28	58.3	32	64.0	
Overweight 25-29.9	17	35.4	17	34.0	0.231
Obese >30	3	6.3	1	2.0	
Total	48	100	50	100	

Discussion

One hundred patients with type 2 diabetes randomly were assigned to ginger and control groups (50 patients received ginger and 50 were as the control group). During the first month after receiving ginger, two patients (7.66%) from the ginger recipient group started to grow digestive problems as the most common complication of ginger and were excluded from the study. The group receiving ginger and 66% of the control group were females. The two groups were homogenous regarding gender. The results showed that ginger significantly reduces HbA1c levels in diabetic patients, with no significant effects on the level of FBS and 2hpp glucose and urine micro-albumin levels. Numerous studies conducted on the effects of ginger on diabetes focuced on animal models. Alshathly et al assessed the ginger therapeutic effect against functional and structural alteration in the liver of diabetic rats and concluded that ginger as a natural safe herbal medication has antioxidant, anti-diabetic effect and can be used to support liver functions in diabetic status (20).

In another study by Li et al, ginger has shown prominent protective effects on diabetic nephropathy and other complications in the liver, eye, and neural system (21).

The antioxidant and anti-inflammatory effects of ginger have been examined in human studies. Araujo et al indicated that ginger has hypoglycemic potential and reduces diabetic complications (22). Kulkarni et al reported that ginger is effective as an anti-inflammatory and antioxidant supplement along with anti-TB therapy as it possesses strong free radical scavenging property too (23).

In another study, Tzeng et al examined the effect of ginger on nephropathy in diabetic rats. The results showed an increase in creatinine clearance, a decrease in blood glucose, and a decrease in (10). The result of the review by Li et al showed the protective and preventive effects of ginger in diabetes mellitus, diabetes complications, and other metabolic diseases. The results of this review show that ginger has an anti-hyperglycemic

Table 4. Mean, standard deviation, of fasting blood glucose in ginger diabetic patients and control group

Group	Fasting blood glucose				Difference		*P* value
	Before intervention		After intervention				
	Mean	SD	Mean	SD	Mean	SD	
Ginger	134	29.3	131.7	31.9	2.38	23.3	0.330
Control	140.6	42	142.1	33	-1.46	32.6	0.367
P value	0.704		0.076		0.197		--

Table 5. Mean ± standard deviation of two-hour postprandial blood glucose in ginger diabetic patients and control group

Group	2-hour postprandial blood glucose								Difference		*P* value
	Before intervention				After intervention						
	Mean	SD	Median	IQR	Mean	SD	Median	IQR	Mean	SD	
Ginger	189	51.7	186	69	186.8	54	182	61	2.17	39.6	0.498
Control	201.3	62.9	185.5	69	208.6	50.8	199.5	70	-7.36	45.4	0.194
P value	0.550				0.031				0.197		--

IQR, interquartile range.

Table 6. Mean ± standard deviation, median, and amplitude of hemoglobin A1c quartile before and after treatment and their changes in two groups

Group	Hemoglobin A1c								Difference		*P* value
	Before intervention				After intervention						
	Mean	SD	Median	IQR	Mean	SD	Median	IQR	Mean	SD	
Ginger	7.5	1.1	7.3	1.3	7.1	1	7	1.6	0.42	1.02	0.002
Control	7.6	1.2	7.6	1.3	7.5	1.1	7.4	1.2	0.10	0.99	0.597
P value	0.662				0.053				0.006		-

IQR, interquartile range.

Table 7. Mean ± standard deviation, median, and amplitude of urinary microalbumin levels before and after treatment and their changes in two groups

Group	Urinary microalbumin level								Difference		*P* value
	Before intervention				After intervention						
	Mean	SD	Median	IQR	Mean	SD	Median	IQR	Mean	SD	
Ginger	31.6	24.3	27	24	30.5	25.2	26.5	30	1.15	17.1	0.339
Control	38.2	51.1	21	20	37.1	46	25.5	25	1.12	24.3	0.202
P value	0.557				0.667				0.109		-

IQR, interquartile range.

effect through stimulation of insulin secretion (9). In a study by AL-Qattan et al, the hypoglycemic effects of garlic and ginger on diabetic rats were assessed. The results of the study showed the hypoglycemic effects of garlic and ginger, reduced progression of diabetic nephropathy in the samples examined (3). The results of our study regarding the level of blood glucose and urine protein were in contrast to empirical studies. It seems that the difference between human and animal studies can be one of the reasons for this inconsistency. In our study, comparing HbA1c in the two groups showed a significant decrease in the ginger recipient group. Our study did not show the decreasing effect of ginger on microalbuminuria. However, our results were based on short-term period study(3 months), regarding positive effects of ginger on reducing HbA1c, which may be seen in the long-term follow-up as in the study by Qattan-Al et al (3). Ramudu et al examined the protective effects of ginger against kidney damage since the results showed that ginger reduces glucose levels and improves the activity of mitochondrial and cytosolic enzymes in diabetic rats (24). One of our points opposite to the study by Ramudu et al, was based on the effect of ginger on renal function. Ramudu et al showed protective effects of ginger against renal damage in diabetic rats. The protective effect of ginger against kidney damage has also been shown in non-diabetic experimental models. Rodrigues et al examined the protective and therapeutic effects of ginger against histopathologic changes of gentamicin-induced tubular toxicity in an animal nephropathy model. Animals from the gentamicin treatment group had a significant decrease in serum creatinine. Gingerol-enriched fraction reduced GM-induced nephrotoxicity, and this effect is due to reductions in oxidative stress and inhibition of inflammatory gene expression (25).

However, comparing microalbuminuria in the two groups in our study did not show a significant difference, which may be due to the short term design of our study and need to be reviewed over a period of more than 12 weeks to reach various outcomes. In some studies, hypoglycemic effects of ginger have been examined in empirical studies. For instance, in the experimental study of Jafri et al, the hypoglycemic effect of ginger in diabetic rats was examined showing that ginger has significant effects on the reduction of blood glucose (1). Our study, conducted on diabetic patients, showed a non-statistically decrease in blood glucose levels (FBS and 2hpp) following the use of ginger. Moreover, our study showed a significant decrease in HbA1c in the ginger receiving group, showing a positive effect on blood glucose reduction and its relative control over the long-term. This is somewhat similar to those in the experimental study by Jafri et al (1). The hypoglycemic effect of ginger has been examined in some human studies as well (26,27).

It was observed that extract of ginger significantly reduced body weights and serum lipid levels in the treated rats. In the same order, serum glucose significantly decreased ($P<0.05$) after 8-day and moreover, elevations in the measured biochemical parameters were significantly ($P<0.05$) attenuated in rats treated with the ginger extract (28).

In the review study by Daily et al, the effects of ginger on type 2 diabetes have been investigated in several randomized clinical trials. The study has stated the significant effects of ginger on reducing FBS and HbA1c resemble our study (27). Reduction in FBS levels and 2 hours after meals were seen in the group receiving ginger, which is similar to the human studies in our study (27).

Although the level of blood glucose (FBS and 2hpp) reduction in our study was not significantly different between the group receiving ginger and the control group, this is inconsistent with the studies mentioned. In our study, ginger consumption had significant reduction in HbA1c, similar to those of other studies (3,28), showing the long-term effects of ginger on reducing and controlling blood glucose levels.

Conclusion

In our study, the hypoglycemic effects of ginger were observed in in short-term follow up. Although its effect on reducing blood glucose levels (FBS and 2hpp) was insignificant. Its effect on the reduction of HbA1c was significant and perhaps ginger can be considered a supplementary agent in the treatment of diabetes. However, getting results with a greater degree of confidence requires more studies.

Limitations of the study

Given some of the limitations of our study, such as the lack of cooperation of some patients in using ginger, it is recommended to conduct studies with more sample size and multiple centers to obtain results with more reliability.

Conflicts of interest

There was no conflict of interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, and double publication) were completely observed by the authors.

Authors' contribution

Conception and design: MF and MY; Literature search and data acquisition: HM; Drafting the manuscript: MF, MY and HM; Analysis and interpretation of data: RG; Critical revision of the manuscript for important intellectual content: MF, MY. All authors read and approved the final paper.

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