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Effects of ginger on serum glucose, advanced glycation end products, and inflammation in peritoneal dialysis patients

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ABSTRACT

Objective: The aim of this study was to investigate the effects of ginger supplementation on serum glucose, advanced glycation end products, oxidative stress, and systemic and vascular inflammatory markers in patients on peritoneal dialysis (PD).

Methods: In this randomized, double-blind, placebo-controlled trial, 36 patients on PD were randomly assigned to either the ginger or the placebo group. The patients in the ginger group received 1000 mg/d ginger for 10 wk, whereas the placebo group received corresponding placebos. At baseline and the end of week 10, serum concentrations of glucose, carboxymethyl lysine, pentosidine, malondialdehyde (MDA), high-sensitivity C-reactive protein (hs-CRP), soluble intercellular adhesion molecule type 1 (sICAM-1), soluble vascular cell adhesion molecule type 1 (sVCAM-1), and sE-selectin were measured after a 12- to 14-h fast.

Results: Serum fasting glucose decreased significantly up to 20% in the ginger group at the end of week 10 compared with baseline ($P < 0.05$), and the reduction was significant in comparison with the placebo group ($P < 0.05$). There were no significant differences between the two groups in mean changes of serum carboxymethyl lysine, pentosidine, MDA, hs-CRP, sICAM-1, sVCAM-1, and sE-selectin.

Conclusion: This study indicated that daily administration of 1000 mg ginger reduces serum fasting glucose, which is a risk factor for hyperinsulinemia, dyslipidemia, peritoneal membrane fibrosis, and cardiovascular disease, in patients on PD.

Introduction

Cardiovascular disease (CVD) is the most common cause of mortality in patients with chronic renal failure, including those on peritoneal dialysis (PD). The frequency of CVD in dialysis patients has been reported as 3 to 45 times greater than that observed in the general population, and nearly 50% of mortality in these patients is attributable to CVD [1,2]. The cause of increased CVD in PD patients is multifactorial. High serum concentrations of glucose [3], advanced glycation end products (AGEs) [4,5], oxidative stress [6–8], and systemic and vascular inflammation markers [9–13] are some of the most important risk factors for CVD in these patients. Additionally, these risk factors could result in peritoneal membrane fibrosis and ultrafiltration failure [14–18].

Ginger (*Zingiber officinale*) is a nontoxic spice with negligible side effects and is generally recognized as safe by the FDA [19,20]. In recent years, it has been proven that ginger consumption can

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reduce fasting serum glucose [21,22] and systemic inflammation markers, such as C-reactive protein, in patients with diabetes type 2 [21,23]. Additionally, some in vitro and animal studies indicated that ginger could result in the reduction of AGEs [24,25], vascular inflammation markers [26,27], and oxidative stress [28–32]. According to the available literature, no study in these fields has been performed yet in PD patients. Therefore, the present study was designed to investigate the effects of ginger supplementation on serum glucose, AGEs, oxidative stress, and systemic and vascular inflammation markers in this patient population.

Material and methods

This was a randomized, double-blind, placebo-controlled trial.

Participants and ethical aspects

Thirty-six patients (21 men and 15 women) undergoing continuous ambulatory peritoneal dialysis (CAPD) in the age range of 29 to 79 y were recruited from the Peritoneal Dialysis Unit of Shafa Clinic in Tehran, Iran. Patients enrolled in this study were free from inflammatory diseases, infectious diseases especially peritonitis, and gastrointestinal diseases. None of the patients were taking steroidal and/or nonsteroidal anti-inflammatory drugs, or warfarin. Additionally, patients who had regularly used ginger less than 1 mo before the start of the study were excluded. The study protocol was approved by the Ethics Committee of the National Nutrition and Food Technology Research Institute of Iran. The study was in adherence with the Declaration of Helsinki. Written, informed consent was obtained from all patients before initiating the study. This clinical trial was registered at Iranian Registry of Clinical Trials (IRCT) with number IRCT201312062716 N2.

Protocol

The patients, after stratification based on diabetes, were allocated to either a ginger or placebo group by blocked randomization. Patients in the ginger group received 1000 mg of ginger as four capsules daily for 10 wk; the placebo group received four corresponding placebo capsules containing starch. Ginger capsules and corresponding placebos were produced by the Gol Daru Pharmaceutical Company, Esfahan, Iran. Participants were advised not to change their dietary habits, physical activities, and drug regimens. At baseline and at the end of the 10^{th} week, 7 mL of blood was obtained from each patient after a 12- to 14-h fast. Blood samples were kept at room temperature (20°C–25°C) for 20 min. After clotting, the samples were centrifuged at 2000*g* for 10 min. The samples of serum were separated into small aliquots and were frozen at −70°C, until use.

Measurements

Serum concentration of high-sensitivity C-reactive protein (hs-CRP) was determined by enzyme-linked immunosorbent assay (ELISA) kits (Diagnostics Biochem Canada, Ontario, Canada) with an intra-assay coefficient of variation (CV) of 6.8%. Serum concentrations of soluble intercellular adhesion molecule type 1 (sICAM-1), soluble vascular cell adhesion molecule type 1 (sVCAM-1), sE-selectin, carboxymethyl lysine, and pentosidine were determined by ELISA kits (Cusabio Biotech, Wuhan, China). Intra-assay CVs for serum sICAM-1, sVCAM-1, sE-selectin, carboxymethyl lysine, and pentosidine were 5.8%, 5.8%, 6.8%, 6.7%, and 6.3%, respectively. Serum malondialdehyde (MDA) concentration was assessed using colorimetry method by commercial kits (Cayman Chemical, Ann Arbor, MI, USA), with an intra-assay CV of 5.8%. Serum concentrations of glucose, creatinine, and urea were assessed using various colorimetry methods by commercial kits (Pars Azemoon, Tehran, Iran) with the aid of a Selectra 2 Autoanalyzer (Vital Scientific, Spankeren, The Netherlands). Intra-assay CVs for serum glucose, creatinine, and urea were 1.4%, 5.6%, and 3.7%, respectively.

Patients were weighed at baseline and the end of weeks 5 and 10. Additionally, the dietary intakes of participants were assessed using a 3-d dietary recall (2 d during the week and 1 d on the weekend) at baseline and the end of weeks 5 and 10. Patients' diets were analyzed by Nutritionist IV software (N Squared Computing, San Bruno, CA, USA).

Dialysis adequacy (as total Kt/V per week) was determined for each patient based on blood urea concentration, 24-h urine volume, urine urea concentration, 24-h dialysate drain volume, dialysate urea concentration, weight, height, and age, using a Kt/V calculator [33]. The peritoneal equilibration test (PET) for glucose was performed for each patient based on a 2-L 4.25% dextrose dwell with dialysate samples at 0 and 4 h and the calculation of the ratio of dialysate glucose concentration at time 4 to dialysate glucose level at time zero (D4/D0). The percent of glucose absorbed from the dialysate was determined based on the 1-D4/D0 formula [34,35].

Compliance

For the ascertainment of patient compliance, each patient was provided with a fixed number of capsules and instructions to return the unused capsules at the end of the study. The degree of compliance for each patient was determined according to the number of returned capsules. The compliance of all patients was >90% and no adverse events were reported.

Statistical analysis

Statistical analysis of data was performed using the Statistical Package for the Social Sciences (SPSS, Inc., Chicago, IL, USA) for Windows version 21.0. A χ^2 test was used to compare qualitative variables between the two groups. Because all quantitative parameters according to the Kolmogorov-Smirnov test had normal distributions, the *t* test and paired *t* test were used to compare parameters between and within groups, respectively. Because dietary and anthropometric parameters were measured 3 times during the study, analysis of variance for repeated measurements was used to compare data among these time points. Additionally, as there was a significant reduction in dietary energy intake at the end of week 10 in comparison with week 5, we removed the effect of this confounding factor on serum concentrations of biochemical parameters, including serum glucose, by analysis of variance for repeated measurements, and then compared serum concentrations of biochemical parameters between baseline and the end of week 10.

The results are expressed as mean ± SE, and differences were considered statistically significant at $P \leq 0.05$.

Results

Of the 38 CAPD patients initially enrolled, one in each group was eliminated because of lack of cooperation.

The baseline characteristics of the patients did not differ significantly between the two groups (Table 1). There were no significant differences in dialysis adequacy and the percent of glucose absorbed from the dialysate between the two groups at baseline and the end of week 10 (Table 1).

There were no significant differences in mean dietary intake of energy, protein, carbohydrate, fiber, total fat, saturated fatty

Table 1
Baseline characteristics of patients in the two group

Characteristics	Ginger (n = 18)	Placebo (n = 18)
Age (y)*	56 ± 2.5	58 ± 3
Serum urea (mg/dL)*	77 ± 4	76 ± 6
Serum creatinine (mg/dL)*	4 ± 0.3	3.8 ± 0.2
Duration of peritoneal dialysis (y)*	3.9 ± 0.5	3.4 ± 0.4
Sex		
Men (%)	11 (61)	10 (56)
Women (%)	7 (39)	8 (44)
Smokers (%)	2 (11)	3 (17)
Diabetes (treatment with insulin) (%)	6 (33)	8 (44)
Type of dialysis solutions		
1.5% glucose (%)	9 (50)	7 (39)
2.5% glucose (%)	2 (11)	1 (5.5)
4.25% glucose (%)	0 (0)	1 (5.5)
1.5% + 2.5% (%)	5 (28)	8 (44.5)
2.5% + 4.25% (%)	2 (11)	1 (5.5)
Intake of supplement		
Vitamin B_6 (%)	3 (17)	3 (17)
Vitamin E and/or C (%)	11 (61)	12 (67)
Intake of cholesterol lowering drugs (statins) (%)	10 (56)	10 (56)
Dialysis adequacy (weekly total Kt/V)*		
Baseline	1.9 ± 0.09	1.7 ± 0.08
Week 10	1.8 ± 0.09	1.8 ± 0.12
Glucose absorbed from the dialysate (%)*		
Baseline	66% ± 0.02%	65% ± 0.02%
Week 10	66.5% ± 0.02%	65.5% ± 0.02%

* Presented as mean ± SE.