Advanced Pharmaceutical Bulletin, **2013**, 3(2), 273-276
doi: http://dx.doi.org/10.5681/apb.2013.044
http://apb.tbzmed.ac.ir/

Anti-Inflammatory Effects of *Zingiber Officinale* in Type 2 Diabetic Patients

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ARTICLEINFO

Article Type:
Research Article

Article History:
Received: 29 November 2012
Revised: 17 January 2013
Accepted: 17 January 2013
ePublished: 20 August 2013

Keywords:
Ginger
Inflammation
TNF-α
Diabetes

ABSTRACT

Purpose: Low-grade inflammation, a common feature in type 2 diabetes (DM2), causes some chronic complications in these patients. The present study was aimed to evaluate the effects of ginger (*Zingiber officinale*) on pro-inflammatory cytokines (IL-6 and TNF-α) and the acute phase protein hs-CRP in DM2 patients as a randomized double-blind placebo controlled trial. ***Methods:*** A total of 64 DM2 patients randomly were assigned to ginger or placebo groups and received 2 tablets/day of each for 2 months. The concentrations of IL-6, TNF-α and hs-CRP in blood samples were analyzed before and after the intervention. ***Results:*** Ginger supplementation significantly reduced the levels of TNF-α (P = 0.006), IL-6 (P = 0.02) and hs-CRP (P = 0.012) in ginger group in comparison to baseline. Moreover, the analysis of covariance showed that the group received ginger supplementation significantly lowered TNF- α (15.3 ± 4.6 vs. 19.6 ± 5.2; P = 0.005) and hs-CRP (2.42 ± 1.7 vs. 2.56 ± 2.18; P = .016) concentrations in comparison to control group. While there were no significant changes in IL-6 (7.9 ± 2.1 vs. 7.8 ± 2.9; P > .05). ***Conclusion:*** In conclusion, ginger supplementation in oral administration reduced inflammation in type 2 diabetic patients. So it may be a good remedy to diminish the risk of some chronic complications of diabetes.

Introduction

Ginger (*Zingiber officina*le) has been cultivated for thousands of years as a flavoring agent and cooking spice. In addition, it has been used in traditional systems of medicine for a wide range of ailments including pain, muscholar aches, fever, sore throats, indigestion and vomiting.[1] On the other hand, recent studies showed some benefits of ginger to treat musculoskeletal disorder,[2] nausea and vomiting,[3] inflammation or inflammatory states[4] such as osteoarthritis,[4,5] migraine,[6] cancer[7], hyperlipidemia and hyperglycemia.[1,8]

According to the results of some in vitro studies, rhizome of ginger and its main components, gingerols and shogaols, can inhibit synthesis of several pro-inflammatory cytokines including IL-1, TNF-α and IL-8 along with inhibiting prostaglandin (PG) and leukotriene (LT) synthesis enzymes.[9]

More recently, investigations showed that ginger has an effect on several genes encoding cytokines, chemokines and the inducible enzyme cyclo-oxygenase-2 (COX-2).[10] Besides, it has been shown that the components of ginger are more effective than conventional non-steroidal anti-inflammatory drugs (NSAIDs) with fewer side effects.[11]

Therefore, there is a hypothesis that ginger may have useful effects on diabetes with a chronic low-grade inflammation. Chronic hyperglycemia increases circulating levels of inflammatory biomarkers such as IL-6 (IL6), tumor necrosis factor-α (TNF-α) and C-reactive protein (CRP). TNF-α and IL-6, as the major cytokines, initiate inflammatory responses and cause the production of CRP as an acute-phase reactant.[12] Moreover, lots of evidences showed that low-grade inflammation, a common feature in type 2 diabetes mellitus (DM2), play a major role in pathogenesis of its secondary complications such as atherothrombosis.[13]

Although, ginger has hypoglycemic and anti-inflammatory effects, just a few studies have reported its anti-inflammatory activity during diabetes.[14] An animal study on the anti-inflammatory effects of ginger extract on diabetic rats reported the reduced level of TNF-α consequent to ginger extract treatment.[15] Therefore, the present study was planned to evaluate the effect of ginger powder supplementation on pro-inflammatory cytokines (IL-6, TNF-α) and hs-CRP in DM2 patients.

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Materials and Methods

Study Design

This study was a randomized, double blind, placebo controlled trial performed on type 2 diabetic patients with at least 2 years experience. Subjects were recruited from diabetes association in Tabriz, Iran. The study was approved by Medical Ethical Committee of the Tabriz University of medical science under the number of 5/4/3832. Exclusion criteria were insulin therapy at baseline or during the study, smoking, presence of pregnancy and breastfeeding, consumption of ginger or other botanical supplements, any acute illnesses and presence of some chronic diseases including kidney, liver, cardiovascular, and gastrointestinal diseases. 64 eligible patients with the age group of 38-65 yrs of either sex fulfilled consent paper prior to inclusion in the study.

Sample size was determined based on data from previous study[16] by considering $\alpha = 0.05$ with power of 80%. The sample size was computed as 25 per group. Regarding a possible loss to follow-up, a safety margin of 30% was determined, and therefore 32 patients were allocated in each group.

Treatment

All patients were randomly assigned to two groups of 32 subjects in each to receive either ginger or placebo one tablet twice a day immediately after lunch and dinner for 8 weeks. The patients were instructed to maintain their diet and physical activity during the intervention. All subjects were permitted to consume their usual medications according to their physicians' recommendation. The three-day food record was taken from all patients at the beginning and end of intervention to be confidant of constant dietary intake.

Tablets Preparation

Fresh rhizomes of zingiber officinale were purchased from local market and were ground as a fine particle after drying. The powder was delivered to a pharmaceutical lab (Tabriz university of medical science, Iran) to prepare tablets containing 1 gram ginger in each. Starch was also used to make placebo. The tablets were placed in the identical bottles by a third person not directly involved in this study. This person labeled the bottles with 2 cods which retained unknown for researchers until the end of intervention. To evaluate the compliance of patients, bottles containing ginger (or placebo) tablets were given monthly.

Anthropometric and Biochemical Assessments

Anthropometric parameters including height and weight were measured at the beginning and end of the intervention to calculate body mass index (BMI) as the formula (Wt/Ht2). Body weight was measured without shoes and light clothing by using a Seca scale (Seca, Hamburg, Germany). Heights were also measured using a statiometer (Seca) without shoes.

Blood samples (5ml) were taken in a 12-14 hrs fasting state (water permitted) at the beginning and after two months of intervention. The serum was obtained by high speed centrifugation and was frozen immediately at −70 °C until assay. The concentration of hs-CRP was measured by spectrophotometer method using parsazmun kit. IL-6 and TNF-α were also assayed using ELISA kits according to the manufacturer's instruction.

Statistical Analysis

The data were analyzed by SPSS software (version 17; SPSS Inc., Chicago, IL) and the results were expressed as mean ± standard error. The normality of the distribution of variables was determined by the Kolmogorov-Smirnov test. The background characteristics and baseline experimental data in the 2 groups were compared using independent sample *t*-tests and chi-squared test. Analysis of covariance (ANCOVA) was used to identify any differences between 2 groups after intervention, adjusting for baseline measurements and covariates including age and hypoglycemic drugs. The changes of anthropometric measurements and the concentration of IL-6, TNF-α and hs-CRP were assessed by paired sample *t*-tests in each group. Differences with $P < 0.05$ were considered to be statistically significant.[17]

Results

Of 64 patients initially recruited, 6 persons were excluded during the study. In ginger group 2 persons did not consume tablets according to plan, one person traveled and one person needed to change his medication during the intervention. In placebo group also one people did not consume tablets according to plan and one person traveled.

Participants represented good compliance with the ginger consumption and no serious adverse side effects or symptoms were reported except for two patients with slight heart burn in the beginning of intervention. Despite the differences in consumed hypoglycemic drugs, it remained constant for all participants during the study.

Table 1 shows baseline anthropometric parameters and the levels of IL-6, TNF-α and hs-CRP in two groups. There were no statistically significant differences between the ginger and placebo groups ($P > 0.05$).

Table 1. Baseline characteristics of study participants[a]

Item	Intervention (ginger)	placebo
Age (yr)	49.27±5.18	53.14±7.9
Sex[b] (M:F)	14:12	16:12
Weight (kg)	79.38±11.87	76.89±14.59
BMI (kg/m2)	29.2±4.07	29.8±5.05
TNF-α (Pg/ml)	16.7±4.4	18.9±5.3
IL-6 (Pg/ml)	8.6±2.7	7.6±3.0
Hs-CRP (Pg/ml)	3.37±2.8	2.23±2.3

[a] Data are presented as means ± standard error
[b] Frequency

Table 2 shows the concentrations of IL-6, TNF-α and hs-CRP before and after intervention in both groups. Ginger supplementation significantly reduced the levels of TNF-α (P=0.006), IL-6 (P=0.02) and hs-CRP (P=0.012) in ginger group in comparison to baseline. These parameters remained unchanged in placebo group during the study.

Table 2. Effects of ginger or placebo consumption on some parameters in diabetic patients[1]

Item	Intervention (ginger)		placebo		P
	Before	after	before	after	
TNF-α (Pg/ml)	16.7±4.4	15.3±4.6*	18.9±5.3	19.6±5.2	0.005
IL-6 (Pg/ml)	8.6±2.7	7.9±2.1*	7.6±3.0	7.8±2.9	0.11
Hs-CRP (Pg/ml)	3.37±2.8	2.42±1.7*	2.23±2.3	2.56±2.18	0.016

1 Data are presented as means ± SD
*P < 0.05 significantly different from baseline according to paired sample t

On the other hand, results of analysis of covariance showed significant differences in TNF-α (P=0.005) and hs-CRP (P=0.016) levels between two groups at the end of study, that were in accordance with the type of consumed hypoglycemic drug, age and baseline values. While no statistically significant differences were observed for IL-6 (P > 0.05) between 2 groups (Table 2).

Discussion

Recent studies have reported that ginger has anti-inflammatory effects[7] which can decline pain associated with rheumatoid and osteoarthritis.[8] On the other hand, the role of inflammation on diabetes has been reported in numerous studies.[18] Cytokines are associated with the pathogenesis of both type 1 and type 2 diabetes through accelerating beta-cell apoptosis and death. Besides, evidence have shows that insulin resistance as a pro-inflammatory status may have existed for years before the occurrence of type 2 diabetes.[19] Moreover, increased CRP, IL-6 and TNF-α are associated with nephropathy, retinopathy and cardiovascular disease in both types of diabetes.[20]

The present study was performed with the aim of assessing the effects of ginger powder on inflammation under diabetic condition. The results showed that ginger supplementation alleviated the inflammation by reduced levels of TNF-α and hs-CRP without any significant effects on IL-6 levels. In consistent with our study Morakinyo et al.[15] indicated that treatment with aqueous and ethanol extracts of ginger in diabetic rats significantly decreased the levels of TNF-α. Besides, Fatehi-Hassanabad et al.[14] reported the anti-inflammatory effects of the aqueous extract of ginger in diabetic mice.

A large body of evidence indicated that the major pharmacological activity of ginger is due to gingerols and shogaols. These compounds reduce prostaglandin synthesis through suppression of cyclooxygenase- 1 and cyclooxygenase-2. It also has been reported that ginger suppresses leukotriene biosynthesis by inhibiting 5-lipoxygenase.[21] In addition, ginger extract was found to inhibit beta-amyloid peptide-induced cytokine and chemokine expression in cell line of human monocytes.[10]

Conclusion

In conclusion, during the present study oral ginger supplementation ameliorated inflammation through reduction in levels of TNF-α and hs-CRP concentrations in blood samples of the patients with type 2 diabetes mellitus. Regarding negligible side effects of ginger, it may be a good remedy for diabetic patients to diminish the risk of some secondary chronic complications.

Acknowledgements

This study was supported by a grant from Research Vice-Chancellor of Tabriz University of Medical Sciences (Tabriz, Iran). The authors thank Tabriz association of diabetes for helping in recruiting patients.

Conflict of Interest

The authors have no conflict of interest.

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