Changes of serum adipocytokines and body weight following Zingiber officinale supplementation in obese women: a RCT

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Abstract
Purpose The present randomized, double-blind, placebo-controlled study aimed to evaluate the effect of Zingiber officinale (ginger) consumption on some metabolic and clinical features of obesity.
Methods Eighty eligible obese women (aged 18–45 years) were randomly assigned to either ginger or placebo groups (receiving 2 g/day of ginger powder or corn starch as two 1 g tablets) for 12 weeks. Body mass index (BMI) and body composition were assessed every 4 weeks, and serum levels of leptin, adiponectin, resistin, insulin and glucose were determined before and after intervention. The homeostasis model assessment of insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI) were also calculated.
Results Ginger consumption significantly decreased BMI, serum insulin and HOMA-IR index, along with increasing QUICKIs as compared to the placebo. Moreover, significant reductions in serum leptin, resistin and glucose were observed in both groups, especially in ginger group with nonsignificant differences between groups. The body composition and serum levels of adiponectin were not significantly changed in study groups.
Conclusion In conclusion, our findings demonstrate a minor beneficial effect of 2 g ginger powder supplementation for 12 weeks on weight loss and some metabolic features of obesity. However, given the lack of data in this area, ongoing clinical trials are needed to further explore ginger’s effectiveness.

Keywords Zingiber officinale Roscoe · Obesity · Adipocytokines

Introduction
Obesity, the excessive accumulation of body fat, is a major risk factor for the global prevalence of chronic diseases [1]. In fact, the adipose tissue contributes to these comorbidities through the secretion of signaling molecules, termed adipokines [1–3]. Adiponectin as the most abundant adipokine exerts both insulin-sensitizing and anti-atherogenic effects, and its concentration increases with weight loss [4]. In contrast, leptin and resistin have been implicated in the pathogenesis of insulin resistance and atherosclerosis along with their pro-inflammatory properties. Leptin has also a primary role in the body weight regulation through controlling food intake and energy expenditure. Despite the elevated levels of leptin in obese patients, its efficiency is low, most likely due to the increased leptin resistance. Moreover, the circulating levels of these hormones decrease as body weight declines [1, 5, 6].

To date, several strategies have been investigated to manage this public health issue, particularly the use of medicinal plants as a possible effective way for weight loss and also correction of metabolic imbalance of adipokines [7].

Ginger (Zingiber officinale Roscoe, family Zingiberaceae) is one of the most widely used spices and medicinal plants around the world. There are some scientific evidences regarding its various pharmacological activities including anti-inflammatory and antioxidant [8, 9], glucose
and lipid lowering [10, 11], antiemetic [12] and anticancer effects [13].

The anti-obesity and weight-lowering effect of ginger and its components has also been recently considered, and there are some promising results from in vitro and rodent in vivo studies [14–19]. In addition, evidences from experimental studies indicate that ginger maybe affect the circulating level of cytokines [19–23]. However, scientific research in humans is very limited [24, 25]. To the best of our knowledge, the effect of ginger consumption on adipocytokines levels has been investigated just in one pilot study [24]. Accordingly, the aim of the present randomized, double-blind, placebo-controlled study was to investigate the effect of ginger supplementation on weight loss and some serum adipocytokines in obese women.

Methods and materials

Subjects

Eighty eligible healthy obese women, aged 18–45 years and BMI of 30–40 kg/m², were voluntarily participated in our study, through a general call schedule across the city of Tabriz, Iran.

Subjects were excluded in the case of clinically diagnosed diabetes mellitus, cardiovascular disease, gallstone, hypo- or hyperthyroidism, deep depression, pregnancy, breast feeding or menopause, being on a weight-lowering diet, taking medications that could influence weight, smoking, subjects with high physical activity, taking nutritional supplements and being hypersensitive to ginger.

The study was approved by the Ethics Committee of Tabriz University of Medical Science (reference number 92154), and the study was registered on the Iranian Registry of Clinical Trials (http://www.irtct.ir) with the identification No. 201311172017N18. All subjects were made aware of the content of the study and signed a written consent form, at the beginning of study.

Supplements preparation

Dried rhizomes of ginger (Zingiber officinale Roscoe, Chinese yellow ginger) were purchased from a local market in Tabriz. They were authenticated by morphologic comparison with different standard texts by Nutrition Research Center, Tabriz University of Medical Science (Tabriz, Iran). The ginger rhizomes were finely ground and then prepared as tablets containing 1 g ginger powder in each (Pharmaceutics Laboratory, Faculty of Pharmacy, Tabriz University of Medical Science). Besides, the placebo tablet consisted of corn starch and other excipients in order to match the weight of ginger tablet. The tablets were placed in the identical containers and were labeled with two codes by a third person not directly involved in our study. In addition, for blinding of subjects, a slight amount of ginger powder was added to the placebo tablets’ container to give ginger odor during opening the door.

Study design

This study utilized a randomized, double-blind, placebo-controlled design. The sample size was calculated based on a 90 % power and a 5 % significance level, considering the leptin variables from the study of Mansour et al. [24], which necessitated at least 28 cases in each group. But assuming a 40 % dropout, 40 cases were assigned in each group. Participants (n = 80) were randomly assigned to the ginger or placebo group (n = 40) using a random number table and were instructed to take two tablets per day (30 min before meal) for 12 weeks. Tablets were given to the participants every 4 weeks. The subjects were also instructed to maintain their usual dietary and exercise pattern throughout the study. Besides, the subjects were instructed to precisely record their food intake for three consecutive days at baseline, weeks 6 and 12. Dietary data (energy values and macronutrient content) were analyzed using Nutritionist 4 software (First Databank; Hearst, San Bruno, CA, USA).

Clinical parameters

Blood samples were obtained from all subjects at the beginning and end of intervention after a 12-h overnight fasting (water permitted). Serum samples were separated by centrifugation and stored at −80 °C until analysis.

Serum levels of leptin, resistin and total adiponectin were measured using the human ELISA kits (leptin and resistin: BioVendor-Laboratorni Medicina, Brno, Czech Republic and adiponectin: Orgenium Laboratories, Vantaa, Finland), according to the manufacturers’ instructions.

Fasting serum glucose enzymatically analyzed with a commercial kit (Pars Azmun Co., Tehran, Iran). Serum insulin concentration was also determined using the human ELISA kit (Monobind Inc., Lake Forest, CA, USA). Insulin resistance index was estimated by the homeostasis model assessment of insulin resistance (HOMA-IR) using the following formula: [fasting serum insulin (µU/ml) × fasting serum glucose (mg/dl)/405] [17]. Moreover, insulin sensitivity was determined using quantitative insulin sensitivity check index (QUICKI) by the following formula: [1/log insulin (µU/ml) + log glucose (mg/dl)] [26].

Furthermore, BMI (weight (kg)/height (m²)) was calculated from the height and weight, using the calibrated
equipment, every 4 weeks. Body composition [total body fat mass (FM), total body fat-free mass (FFM) and total body water (TBW)] was also assessed by an 8-electrode bioelectrical impedance analyzer with a 0.1 kg precision (Tanita BC-418 MA; Tanita Co., Tokyo, Japan), every 4 weeks.

**Statistical analyses**

Data were analyzed using SPSS software, version 21.0 (IBM Corp., Armonk, NY, USA). The normal distribution of variables was tested by the Kolmogorov–Smirnov test, and also considering the mean and SD. Possible differences at baseline among treatment groups were assessed by independent sample \( t \) test for normally distributed parameters and the Mann–Whitney test for nonparametric data. At the end of intervention, differences between groups were analyzed using the analysis of covariance (ANCOVA) for normally distributed parameters (the baseline values and BMI differences employed as covariates) and Mann–Whitney test for nonparametric variables. Moreover, to assess within-group differences of biochemical parameters, paired-sample \( t \) test and the nonparametric Wilcoxon signed-rank test were employed. The repeated-measures analysis of variance was also performed to assess within-group differences of BMI and fat mass in time trend. Results are reported as mean \( \pm \) SD, if not otherwise stated. The percent changes were also calculated as follows: \( \frac{\text{after}-\text{before}}{\text{before}} \times 100 \). The significance level was set at \( p < 0.05 \).

**Results**

From eighty volunteer women who were recruited the study, ten participants did not complete the study as shown in Fig. 1. One person from the ginger group withdrew because of pregnancy, and nine participants from the placebo group dropped out because of traveling \( (n = 2) \), pregnancy \( (n = 3) \), using antidepressant agents \( (n = 2) \), diagnosed hypothyroidism \( (n = 1) \), pregnancy \( (n = 3) \) and rheumatoid arthritis \( (n = 1) \). None of the subjects discontinued the study because of the adverse effects of ginger or placebo.
Table 1 Baseline characteristics of the participants in both groups

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Ginger group (n = 39)</th>
<th>Placebo group (n = 31)</th>
<th>p value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>35.25 ± 7.30</td>
<td>34.54 ± 7.91</td>
<td>0.699</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>34.34 ± 3.61</td>
<td>35.46 ± 3.41</td>
<td>0.192</td>
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<tr>
<td>Body fat mass (kg)</td>
<td>36.63 ± 6.14</td>
<td>37.50 ± 7.80</td>
<td>0.605</td>
</tr>
<tr>
<td>Body fat-free mass (kg)</td>
<td>50.58 ± 3.65</td>
<td>50.84 ± 4.22</td>
<td>0.781</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>94.20 ± 13.50</td>
<td>94.48 ± 15.31</td>
<td>0.936</td>
</tr>
<tr>
<td>Insulin (µU/ml)</td>
<td>5.20 (2.30, 8.50)</td>
<td>3.40 (1.40, 5.50)</td>
<td>0.066</td>
</tr>
<tr>
<td>Leptin (ng/ml)</td>
<td>33.05 ± 14.75</td>
<td>35.61 ± 13.89</td>
<td>0.461</td>
</tr>
<tr>
<td>Adiponectin (µg/ml)</td>
<td>2.00 (1.00, 3.00)</td>
<td>3.00 (1.00, 5.00)</td>
<td>0.014</td>
</tr>
<tr>
<td>Resistin (ng/ml)</td>
<td>6.97 ± 1.63</td>
<td>6.05 ± 1.48</td>
<td>0.017</td>
</tr>
</tbody>
</table>

Values are mean ± SD

** p values are based on the independent sample t test for normally distributed parameters and Mann–Whitney test for nonparametric variables

*Values are presented as median (25th, 75th percentiles) for the nonparametric variables

**Baseline data are shown just for study subjects who completed the study

The baseline characteristics of the participants are shown in Table 1. At the beginning of study, there was no significant difference between groups in aforesaid parameters, except for adiponectin (p = 0.014) and resistin concentration (p = 0.017).

Consumption of ginger for 12 weeks significantly reduced BMI (p = 0.019) (see Fig. 2), serum insulin (p = 0.021) and HOMA-IR index (p = 0.014), while increasing QUICKI (p = 0.045) as compared to the placebo (see Table 2), whereas there was no significant difference in changes of body composition (Fig. 2), fasting blood glucose and circulating levels of adipokines between groups (p > 0.05, see Table 2).

Furthermore, within-group analyses showed that BMI, serum glucose, insulin, leptin and resistin levels significantly decreased in ginger group (p < 0.0001), along with significant reduction in the HOMA-IR and increase in QUICKI (p < 0.0001), whereas in the placebo group, there was only a significant reduction in serum glucose (p = 0.008), leptin (p = 0.001) and resistin (p < 0.0001) levels (Table 2). However, these decreases were more pronounced in the ginger group than those in the placebo group (percent changes of glucose: −7.51 vs. −6.16 %, leptin: −20.25 vs. −11.42 % and resistin level: −38.64 vs. −36.11 %).

The circulating level of total adiponectin was also slightly decreased in both groups, particularly in placebo group (p > 0.05). Our results revealed a slight and nonsignificant increase in fat mass in both groups (Fig. 2) which was mainly due to the total body water (TBW) changes during measurements. Hence, TBW was utilized as a covariate during ANCOVA test (Fig. 2).

Fig. 2 Effect of ginger compared to the placebo supplementation on BMI (a) and fat mass (b). *p < 0.05 based on the repeated-measures analysis of variance. †p < 0.05, the comparison between groups by analysis of covariance (ANCOVA) with the baseline values and energy intake differences, employed as covariates for BMI and the baseline values, energy intake differences and total body water differences, as covariates for body composition data.
Table 2  Effect of ginger compared to the placebo supplementation on some biochemical parameters in obese women

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Ginger group</th>
<th>Placebo group</th>
<th>p value</th>
<th>Effect size</th>
<th>Observed power</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Before intervention</td>
<td>After intervention</td>
<td>Changes (%)</td>
<td>p value**</td>
<td>Before intervention</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>94.20 ± 13.50</td>
<td>86.17 ± 8.25</td>
<td>−7.51 ± 9.67</td>
<td>&lt;0.0001</td>
<td>94.48 ± 15.31</td>
</tr>
<tr>
<td>Leptin (ng/ml)</td>
<td>33.05 ± 14.75</td>
<td>26.00 ± 12.44</td>
<td>−20.25 ± 23.75</td>
<td>&lt;0.0001</td>
<td>35.61 ± 13.89</td>
</tr>
<tr>
<td>Resistin (ng/ml)</td>
<td>6.97 ± 1.63</td>
<td>4.32 ± 1.33</td>
<td>−20.85 ± 9.96</td>
<td>&lt;0.0001</td>
<td>6.05 ± 1.48</td>
</tr>
<tr>
<td>Adiponectin b (µg/ml)</td>
<td>2.00 (1.00, 3.00)</td>
<td>1.5 (1.00, 3.00)</td>
<td>− 0.711 3.00 (1.00, 5.00)</td>
<td>0.0007</td>
<td>3.00 (1.00, 5.00)</td>
</tr>
<tr>
<td>Insulin b (µU/ml)</td>
<td>5.20 (2.30, 8.50)</td>
<td>2.40 (1.80, 4.00)</td>
<td>− &lt;0.0001</td>
<td>3.40 (1.40, 5.50)</td>
<td>2.30 (1.80, 3.70)</td>
</tr>
<tr>
<td>HOMA-IR b</td>
<td>1.20 (0.55, 1.82)</td>
<td>0.53 (0.38, 0.84)</td>
<td>− &lt;0.0001</td>
<td>0.83 (0.28, 1.26)</td>
<td>0.49 (0.39, 0.86)</td>
</tr>
<tr>
<td>QUICKI b</td>
<td>0.37 (0.34, 0.42)</td>
<td>0.42 (0.39, 0.45)</td>
<td>− &lt;0.0001</td>
<td>0.39 (0.36, 0.48)</td>
<td>0.43 (0.39, 0.45)</td>
</tr>
</tbody>
</table>

Ginger group: n = 39; Placebo group: n = 31

** p values are based on the paired-sample t test for normally distributed parameters and Wilcoxon signed-rank test for nonparametric data
† p values indicate the comparison between groups by analysis of covariance (ANCOVA) with the baseline values and BMI differences, employed as covariates
†† p values indicate the comparison between groups by Mann–Whitney test

Percent changes, effect size and observed power are presented just for normally distributed parameters

Values are presented as median (25th, 75th percentiles) for the nonparametric variables
Discussion

The present randomized, double-blind, placebo-controlled study was designed to determine whether 12-week ginger supplementation could influence some of the obesity-related features and serum adipokines levels. Our results revealed that ginger consumption resulted in a slight, but statistically significant decrease in BMI along with nonsignificant reductions in serum leptin and resistin as compared to the placebo group. However, body fat mass and serum total adiponectin level had no significant change in any groups.

Our findings are partly supported by the existing experimental studies. Saravanan et al. [19] and Okamoto et al. [22] demonstrated that rodents treated with a high-fat diet (HFD) containing [6] gingerol had significant lower weight gain, fat accumulation, and circulating level of leptin, compared to the HFD control. In another study, ginger aqueous extracts significantly decreased body weight, body fat mass and serum leptin levels in obese diabetic rats compared to the control group [23]. In contrast, Wadikar and Premavalli [27] showed that ginger juice significantly increased weight gain and decreased leptin levels in rats. As there are very limited clinical studies in this regard, it is difficult to compare our results. However, contrary to our findings, Mansour et al. [24] reported that intake of a single-dose hot ginger beverage (with 2 g ginger powder) before a standard breakfast meal had no significant effect on serum leptin, adiponectin and other cytokines levels, as compared to the control group. In another study, ginger consumption (1 g/day) for 10 weeks did not cause any significant change in BMI and body composition of obese men [25].

Overall, it seems that ginger could influence body weight and body composition through some mechanisms such as (1) increasing thermogenesis and energy expenditure by catecholamine-releasing action [18, 24, 28], (2) increasing the lipolysis of white adipose tissue [18, 20, 29] and (3) inhibition of the lipase enzyme and the intestinal absorption of dietary fat [16].

Although the mechanisms of ginger effect on adipokines level have not been clarified, there are evidences from in vitro studies that ginger components can increase the gene expression of some adipokines such as adiponectin [21] and inhibit the gene expression of resistin [20].

The other findings of the present study were significant reduction in serum insulin and HOMA-IR index along with significant increase in QUICKI in ginger compared to the placebo group. Interestingly, these are in accordance with decrease in serum leptin and resistin, as two pro-inflammatory adipokines. Furthermore, serum glucose level was significantly decreased in both groups especially in ginger group, without a significant difference between them.

Our results are in agreement with some earlier reports. More recently, Li et al. [17] demonstrated that ginger extract treatment (100 and 200 mg/kg) significantly decreased serum insulin and HOMA-IR in the high-fat, high-carbohydrate (HFHC) diet-fed rats over 10 weeks, while a marked reduction in blood glucose was observed just in the high-dose ginger extract treatment group (200 mg/kg) compared to HFHC controls. Likewise, Beattie et al. [30] revealed a significant decrease in insulin in mice feeding with a high-fat diet plus 6-gingerol for 8 weeks, but there was not significant difference between groups in serum glucose lowering effect.

Our results are also supported by some previous clinical trials that ginger powder supplementation in type 2 diabetic patients significantly decreased fasting blood glucose, insulin and HOMA-IR and increased the QUICKI versus placebo [11, 31]. However, contrary to our results, ginger consumption (1 g/day) for 10 weeks did not cause any significant change in fasting serum insulin and glucose levels in obese men [25].

Although the mechanisms responsible for these beneficial effects of ginger are not entirely clear, they might result from the increased expression of GLUT-4 and glucose uptake by cells, increased insulin receptors, enhanced pancreatic beta cells’ functions and also modifying the adipokines’ levels as described before [10, 32].

Taken together, this is the first clinical trial aimed to investigate the effect of ginger on some metabolic features of obesity. A potential limitation of this study is that according to our facilities, we used the bioelectrical impedance analyzer for body composition assessment that although is a safe and valuable clinical tool to measure body composition, it is very sensitive to body water changes through some confounders such as drinking water before measurement, drinking tea or coffee 24 h ago [33]. However, we adjusted total body water changes for fat mass and fat-free mass analyses. Moreover, based on experimental studies, it seems that treatment with ginger maybe need higher dose of powder form or using standard extracts to reach more effectiveness, just as a suggestion for future researches, since it is a safe herbal medicine according to existing data and also the FDA’s report on its safety [10].

In conclusion, our findings demonstrate a minor beneficial effect of 2 g ginger powder supplementation for 12 weeks on weight loss and some metabolic features of obesity. However, given the lack of data in this area, it is difficult to explicitly talk about the effectiveness of ginger and further well-designed clinical trials are needed to explore ginger’s potential in management of obesity.

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Compliance with ethical standards

Conflict of interest The authors have declared that there is no conflict of interest.

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27. Wadikar DD, Premavalli KS (2011) Appetizer administration stimulates food consumption, weight gain and leptin levels in male Wistar rats. Appetite 57(1):131–133
