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Effect of garlic on serum adiponectin and interleukin levels in women with metabolic syndrome

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ABSTRACT

Background: Metabolic syndrome is considered to be an inflammatory situation with highly production of adipokines. Garlic and its products are known to induce anti-inflammatory effects. However, no data are available on the anti- inflammatory effects of garlic in subjects with metabolic syndrome.
Objectives: This study was designed to investigate the effects of a chemically wellcharacterized garlic preparation on biomarkers for inflammation, and lipid metabolism in subjects with metabolic syndrome.
Patients and Methods: This study was a double-blind, randomized, placebo-controlled trial in 40 adult women, aged > 18 year, who were diagnosed to have metabolic syndrome based on ATPIII criteria and 10 normal women. The cases were randomly assigned to 2 parallel treatment groups: garlic tablets (1.8 g/d), or placebo. Serum adiponectin, interleukin 6, TNF α and lipid profiles were measured at baseline and after 6 weeks of treatment and anthropometric measurements were recorded.
Results: Compared to the placebo group, garlic treatment resulted in significantly lower weight and waist circumference in women with metabolic syndrome. No effect on weight was detected in normal subjects with garlic. None of the inflammatory biomarkers and plasma lipid levels showed significant differences between the garlic-treated and the placebo groups.
Conclusions: This study confirms that garlic has no effect on major plasma lipoproteins and furthermore has no impact on inflammatory biomarkers in women with metabolic syndrome.

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Background

Diet is a key factor in the development of some human diseases, including cardiovascular disease. The health-benefits of fruit and vegetable consumption, because of the anti-inflammatory properties of their phytochemical components, have been suggested (1). One such source is garlic (Allium sativum). The majority of garlic (65%) is water, and the bulk of the dry weight is composed of fructose-containing carbohydrates, followed by sulfur compounds, protein, fiber, and free amino acids (2). It also contains high levels of saponins, phosphorus, potassium, sulfur, zinc, moderate levels of selenium and Vitamins A and C, and low levels of calcium, magnesium, sodium, iron, manganese, and B-complex vitamins; garlic also has a high phenolic content (3). Recently interest in garlic as a preventive factor in cardiovascular diseases has increased. Some studies showed an effect for garlic in lowering plasma lipid concentrations and preventing progressive atherosclerotic changes and consequently reducing the incidence of cardiovascular events (4-6). Other studies however do not support these observations and reported no significant effects on these variables (7-9). Clustering of some cardiovascular risk factors such as abdominal obesity, dyslipidemias, hypertension

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and glucose intolerance has been recognized as metabolic syndrome (10), of which central obesity was suggested to be the basic component. Obesity is associated with chronic inflammation due to overproduction of proinflammatory cytokines, including tumor necrosis factor (TNF)-α. In vitro studies show that high concentrations of garlic decrease cytokine production in endothelial cells, suggesting anti-inflammatory properties (11, 12). To our knowledge, no studies have reported the effects of garlic on inflammatory biomarkers in the metabolic syndrome in humans.

Objectives

This study was designed to investigate the effects of garlic on markers of inflammation associated with CVD. In addition, the effects of garlic on plasma lipid concentrations, fasting plasma glucose and body weight were investigated.

Patients and Methods

Subjects

This is a double-blind, randomized, placebo-controlled study with 3 parallel groups. A total of 50 women, aged more than 18 years, including 40 cases with metabolic syndrome (MS) and 10 normal female controls were completed the study. All the subjects with MS were outpatients at the Endocrine Clinic of Valieasr general Hospital of Zanjan University of Medical Sciences, and were diagnosed with metabolic syndrome based on the ATPIII criteria (13). All the subjects with acute or chronic infection or inflammatory disorders were excluded. They were also excluded if they were smokers, pregnant or used any medication (i.e. aspirin, metformin, steroid or nonsteroidal anti-inflammatory drugs) that interferes with the measures of the study or affects insulin sensitivity. All the subjects with known diabetes mellitus and those with triglyceride levels over 400 mg/dL were also excluded. Normal subjects without any cardiovascular risk factors were volunteers who drawn from the same socioeconomic population. Approval for the study was obtained from the ethics committee of Zanjan University of Medical Sciences. All participants were notified about the goals of the study, and informed consent was obtained.The study was registerd in IRCT, code number: 138706121179N1.

Study design

From a list of 102 adult subjects with known metabolic syndrome who were outpatients of endocrine clinic,50 people were selected with simple random sampling and recalled. They were randomly assigned to 1 of the 2 treatment arms by a nurse. The subjects received either the garlic preparation (daily dose of 1.8 g; two 300 mg garlic tablets three times per day) or placebo (2 garlicmatching placebo tablets morning, noon and evening). An additional 12 normal volunteer women were serially assigned to the third arm of the study and received garlic tablets with the same doses of the cases. The total treatment period was 6 wk with follow-up visits scheduled after 2, 4, and 6 wk. On these visits the study medication was counted, their medical history was taken and adverse

Table 1. Characteristics of the study population (Data are shown as Mean ± SE)

Parameter	Metabolic syndrome placebo group (No. = 20)		Metabolic syndrome garlic group (No. = 20)		Normal women on garlic (No. = 20)	
	Before	After	Before	After	Before	After
Age	47.9 ± 3	-	50.5 ± 2.9	-	49.2 ± 3.4	-
BMI [a]	29.1 ± 0.9	29 ± 0.8	29.6 ± 0.8	29 ± 0.9	26.6 ± 1.4	26.1 ± 1
Waist circumference (cm)	103.3 ± 2.7	103 ± 2.7	103.9 ± 2	102 ± 2	87 ± 4.3	88.1 ± 4
Systolic blood pressure (mm Hg)	122 ± 3.1	119 ± 2.5	123 ± 3	122.5 ± 2.9 [j]	109 ± 3.1	104 ± 4.2
Diastolic blood pressure (mm Hg)	77 ± 2.1	77.5 ± 1.6	81.5 ± 2.7	81 ± 2.6	75.5 ± 3	72 ± 2.9
FPG [b] (mmol/l)	6.26 ± 0.58	6.2 ± 0.4	5.7 ± 0.27	5.4 ± 0.2	4.6 ± 0.19	4.46 ± 0.14
Chol [c] (mmol/l)	5.7 ± 0.3	6.37 ± 0.3 [i]	5.5 ± 0.3	5.4 ± 0.3	4.5 ± 0.4	4.7 ± 0.4
TG [d] (mmol/l)	2.5 ± 0.24	2.8 ± 0.25	2.7 ± 0.2	2.75 ± 0.35	1.39 ± 0.25	1.14 ± 0.14
HDL [e]**-c** (mmol/l)	1.01 ± 0.03	1.09 ± 0.2 [i]	1.08 ± 0.05	1.07 ± 0.08	1.28 ± 0.09	1.48 ± 0.1
Insulin (pmol/l)	45.8 ± 12.3	38.1 ± 8.3	48.3 ± 11	51.8 ± 15.9	27 ± 7.2	29.8 ± 11.8
HOMA index [f]	1.8 ± 0.48	1.4 ± 0.32	1.7 ± 0.38	1.9 ± 0.7	0.88 ± 0.27	0.85 ± 0.28
Adiponectin (ng/ml)	87.7 ± 15	72.5 ± 14.2	91.9 ± 13.3	70.8 ± 8.8	56.5 ± 9.6	36.2 ± 6 [k]
IL6 [g] (pg/ml)	0.85 ± 0.4	0.61 ± 0.19	1.3 ± 0.49	1.13 ± 0.55	0.7 ± 0.2	1.3 ± 0.2
TNF α [h] (pg/ml)	1.66 ± 0.28	2.17 ± 0.4	2.35 ± 0.39	2.18 ± 0.5	1.89 ± 0.3	5.5 ± 0.8 [k]

[a] BMI: Body Mass Index, [b] FPG: Fasting Plasma Glucose, [c] Chol: Cholesterol, [d] TG: Triglycerides, [e] HDL: High Density Lipoprotein, [f] HOMA Index: Homeostasis Model Assessment Index, [g] IL6: Interleukin 6, [h] TNF α: Tumor Necrosis Factor α, [i] $P < 0.05$ for difference between baseline and after intervention in metabolic syndrome group, [j] $P<0.05$ for difference between baseline and after intervention in metabolic syndrome garlic group, [k] $P < 0.05$ for difference between baseline and after intervention in normal women garlic group

events were recorded. The participants were asked not to change their diet or physical activity during the study and to report any changes. The 300 mg tablets of garlic were manufactured (Amin pharmaceutical co., Isfahan, Iran) and matching placebo tablets were produced under standard manufacturing practice standards (Tehran University of Medical Sciences, Tehran, Iran). All study medication was labeled, and dispensed by the Valieasr Hospital endocrine clinic.

Measurements

Body weight was measured to the nearest 0.1 kg with a balanced beam scale, while wearing light clothing, and height was measured with a stadiometer to the nearest 0.5 cm. BMI was calculated based on the weight/height^2 formula. Waist circumference between the lowest rib and the iliac crest, at the level of umbilicus, was measured in duplicate to the nearest millimeter using flexible tape. Blood pressure was measured with the subject seated using a random zero sphygmo-manometer. Systolic (Korotkoff phase I) and diastolic (Korotkoff phase V) blood pressure was measured twice on the left upper arm and the average of the two measurements was used for analysis.In all the women, blood samples were collected between 8.00-9.00 AM, after at least 12 hours of fasting. The basal levels of adiponectin, insulin, interleukin 6 (IL6), tumor necrotizing factor α (TNF α) and plasma glucose were measured, and a lipid profile was also obtained. The Homeostasis Model Assessment Index (HOMA Index) was used to determine the level of insulin resistance and was calculated according to the following equation:

[Insulin (μU/mL)] [FPG (mmol/L)] /22.5. Insulin resistance was diagnosed in cases with a HOMA index of more than 2.1, (14).

Insulin levels were measured via an electrochemiluminescence immunoassay (ECLIA) using commercially available kits (Roche, German), and adiponectin was measured using human adiponectin ELISA kits (Biovendor, Germany) with a limit of detection 7 ng/ml. Intra and inter-assay CV for the assay were 7 and 8 % in the lower limit and 6.4% and 7.3% for upper limit concentrations respectively. TNF-α was measured with the use of ELISA kits (Bender medsystem), with a sensitivity of 5pg/ml and inter and intra-assay CVs of 8.1 and 7.7% respectively. IL 6 was measured by ELISA kits (Bender medsystem). The sensitivity of the kit was 0.92 pg/mL. Inter and intra-assay CV for the kits were 5.2% and 3.4% respectively.

Statistical methods

Data are presented as Mean ± SE. Between group comparisons of changes in lipid and adipokines parameters were done using one-way ANOVA. Mann-Whitney test was used for those variables without normal distribution. Within group assessments of changes in the parameters were analyzed by paired the t-test and Kruskal-Wallis Test. Significance of differences was evaluated using the SPSS version 11.5 and defined at a 0.05 level of confidence.

Results

At the end of the study, of 50 subjects with MS, five in the garlic group and six in the placebo arm did not complete the study and were excluded. Of 12 normal subjects, who entered in the study, 10 completed it. All the excluded subjects were followed by telephone. No complication with the medication was reported by the excluded subjects. One additional subject with MS entered later to the placebo arm of the study and finally the study population consisted of 50 subjects, 20 subjects with metabolic syndrome in the garlic group, 20 subjects with metabolic syndrome in the placebo group, and 10 normal subjects in the garlic group. No significant differences were observed in the baseline characteristics among the 3 groups. The adverse events reported in this study were mild and data showed a good compliance for the medications. Clinical parameters and markers of inflammation at the 6 week assessment of women with metabolic syndrome before and after intervention are shown in *Table1.*

Compared with placebo group, garlic treatment resulted in significantly lower weight (P = 0.04) and waist circumference (P < 0.001) in women with metabolic syndrome. No effect on weight (71.4 ± 3.8 Kg before treatment vs. 71.8 ± 4 Kg after treatment, p = 0.4) and waist circumference (87.8 ± 4.3 cm before treatment vs. 88± 4.4 cm after treatment, p = 0.4) was detected in normal subjects with garlic. None of the inflammatory biomarkers and plasma lipid levels showed significant differences between the garlic-treated and placebo groups with metabolic syndrome *(Table2).*

While significant rise was seen in serum adiponectin concentration in normal subjects with garlic (56.5 ± 9.6 ng/ml after treatment vs. 36.2 ± 9.6 ng/ml before treatment, p = 0.024), no significant changes in other inflammatory biomarkers or lipid concentrations were observed in normal subjects using garlic.

Discussion

This double blind placebo-controlled study demonstrated no effect of a 6-wk treatment with garlic tablets on plasma lipid concentrations of women with metabolic syndrome. Although a significant statistical reduction in weight and waist circumference was seen with garlic, the reduction was not clinically significant. The main finding of this study was that garlic has no detectable effects on TNF-α, interleukin 6 and adiponectin concentrations in women with metabolic syndrome, which makes it unlikely that garlic exerts a beneficial effect on cardiovascular disease prevention by anti-inflammatory or lipid-lowering mechanisms. For a long time a preventive effect on atherogenesis has been considered for garlic because its lipid lowering properties. It has been shown that garlic inhibits enzymes involved in lipid synthesis, decreases platelet aggregation, and prevents lipid per-

Table 2. Average treatment effects of placebo and garlic on clinical parameters and markers of inflammation at the 6-week assessment of women with metabolic syndrome

Parameter (Mean ± SE [a])	**Average treatment effect** (97.5% CI)		**Garlic compared with placebo**	
	Metabolic syndrome Placebo group (No. = 20)	**Metabolic syndrome Garlic group** (No. = 20)	**% Change** (97.5% CI of difference)	**p-value**
Waist circumference (cm)	(-1.2)-(0.6)	(-2.4)-(-0.7)	(-1.2)-(-0.1)	0.036
Systolic blood pressure (mmHg)	(-5.4)-(1.4)	(-3.7)-(2.7)	(1.3) - (1.7)	0.5
Diastolic blood pressure (mmHg)	(-3)-(5.8)	(-5.5)- (5.7)	(-2.5)-(-0.1)	0.7
FPG [b] (mmol/l)	(-3.3)-(11.9)	(-12.3) - (6.6)	(-9)- (-5.3)	0.2
Chol [c] (mmol/l)	(3.6)-(21.6)	(-11.7) - (20.4)	(-15.3)-(-0.8)	0.3
TG [d] (mmol/l)	(-4.8)-(31.6)	(-29)- (41)	(-24.2)-(9.4)	0.6
HDL [e] (mmol/l)	(0.12)-(16.8)	(-14)-(17)	(-14.1)-(0.2)	0.4
Insulin (pmol/l)	(-22)-(208)	(-17.6)-(63)	4.4-(-145)	0.2
Adiponectin (ng/ml)	(-39.4)-(39.2)	(-38)-(44.7)	(1.4)-(5.5)	0.9
IL6 [f] (pg/ml)	(-105.4)-(527)	(-74.8)-(213)	(30.6)-(-314)	0.3
TNF α [g] (pg/ml)	(-49)-(168)	(-55.7)-(100)	(-6.7)-(-68)	0.5

[a] SE: Standard Error of mean, [b] FPG: Fasting Plasma Glucose, [c] Chol: Cholesterol, [d] TG: Triglycerides, [e] HDL: High Density Lipoprotein, [f] IL6: Interleukin 6, [g] TNF α: Tumor Necrosis Factor α

oxidation of oxidized erythrocytes and LDL (15, 16). However, most clinical trials have indicated no reduction in total cholesterol with garlic and its effect on blood pressure and oxidative-stress reduction is controversial (17). The different results obtained in clinical trials may be due to usage of different garlic preparations with different dosage, selection of subjects, and duration of trials. Different garlic preparations have different properties. Some toxicity has been reported with raw garlic. Garlic powder must be prepared at a suitable temperature and is associated with some toxicity. No major studies on the efficacy of garlic oils have been reported (18). Aged garlic extracts (AGE) have increased sulfur compounds with the loss of allicin. There is also substantial variability in the contents of garlic preparations, with inadequate definitions of the biologically active and available constituents and their dissolution properties making it difficult to confirm the garlic in these trials. There is some evidence that higher garlic doses are associated with more significant effects. In the present study, we chose a relatively high dose of the garlic tablets (1.8 g/d, approximately equivalent to 9 mg allicin/d) to be able to detect the potentially beneficial effects of garlic. Measurement of garlic components plasma concentrations would have been helpful, but, unfortunately, these were not measured in our study. Our data are in agreement with many of the recent findings that did not observe any effects of garlic on plasma lipids (7, 8). To our knowledge, this is the first report for the effects of garlic on lipid concentrations in subjects with metabolic syndrome. Although a clinically significant rise in HDL-cholesterol was observed in normal women with garlic, this difference was not statistically significant. This result may be due to small sample size of normal women in our study. No significant changes in total cholesterol, triglyceride and low-density lipoprotein cholesterol (LDL-C) were observed in normal women using garlic. Central obesity and consequent insulin resistance are major factors of metabolic syndrome and confer an increased risk of atherosclerosis and cardiovascular disease (CVD). The possible role of inflammatory cytokines originating from adipose tissue in this process is still being elucidated. A growing body of evidence suggests that inflammatory processes play an important role in the pathophysiology of atherosclerosis (19-21). Substances like interleukin (IL)-6 and tumor necrosis factor (TNF)-α, are indicators of oxidative stress and may play a role in promoting adverse vascular outcomes in the metabolic syndrome (9). Low levels of adiponectin and increased leptin also have been reported in this syndrome. Adiponectin is inversely associated with insulin resistance and inhibits inflammation. IL-6 is a cytokine that increases triglyceride formation and insulin resistance. Levels of IL-6 are linked to insulin resistance, adiposity (22), and the metabolic syndrome (23). TNF-α is produced mostly by fatty tissue, but also by macrophages and endothelial cells. Its levels correlate with the amount of adiposity and have been linked to the increase in insulin resistance seen in obesity (24, 25). We chose adiponectin, IL-6 and TNF- α as primary outcomes of this study because of their possible effect on atherogenesis in the metabolic syndrome. Some in vitro studies indicated a reduced cytokine production in endothelial cells with high concentrations of garlic suggesting that it has anti-inflammatory properties (15, 26, 27).

Among limited number of clinical trials performed with garlic and different preparations of garlic, most evaluated the effect of garlic on glucose control, lipid profiles, hypertension and platelet aggregation (1, 7, 28, 29); only two clinical trials have been conducted to evaluate the effect of garlic on inflammatory cytokines, and both have shown that garlic has no effect on these markers (30, 31). Of these, one study was performed in overweight smok-

er subjects, and the other in men with coronary artery disease; our results were in agreement with these two studies and revealed no significant changes in IL-6, TNF-α and adiponectin after a 6-week duration of treatment with garlic tablets, in women with metabolic syndrome. A rise in adiponectin concentration in normal women after garlic administration in this study may suggest a different effects of garlic in different health conditions, suggesting a preventive role for cardiovascular disease with garlic in healthy people. However considering the small sample size of normal subjects and lack of normal people on placebos in this study, any results in the normal group should be interpreted cautiously.

In conclusion, our data demonstrated that a 6-week treatment with a high-dose, garlic tablets had no anti-inflammatory or lipid-lowering effect in women with metabolic syndrome. This suggests that short-time administration of garlic has no significant effect on the inflammatory processes associated with atherosclerosis in a high risk population. Furthermore, increases in adiponectin levels in normal women with garlic showed that garlic tablets may have some anti-inflammatory effects in healthy people, and may prevent cardiovascular events in this group. More investigations with larger sample sizes and longer duration of interventions are recommended.

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Conflict of interest

None declared.

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