Garlic Powder and Plasma Lipids and Lipoproteins

A Multicenter, Randomized, Placebo-Controlled Trial

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Background: Garlic powder tablets have been reported to lower serum cholesterol levels. There is widespread belief among the general public that garlic powder tablets aid in controlling cholesterol levels. However, much of the prior data demonstrating the cholesterol-lowering effect of garlic tablets involved studies that were inadequately controlled.

Objective: To determine the lipid-lowering effect of garlic powder tablets in patients with hypercholesterolemia.

Methods: This was a randomized, double-blind, placebo-controlled, 12-week, parallel treatment study carried out in 2 outpatient lipid clinics. Entry into the study after 8 weeks of diet stabilization required a mean low-density lipoprotein cholesterol level on 2 visits of 4.1 mmol/L (160 mg/dL) or lower and a triglyceride level of 4.0 mmol/L (350 mg/dL) or lower. The active treatment arm received tablets containing 300 mg of garlic powder (Kwai) 3 times per day, given with meals (total, 900 mg/d). This is equivalent to approximately 2.7 g or approximately 1 clove of fresh garlic per day. The placebo arm received an identical-looking tablet, also given 3 times per day with meals. The main outcome measures included levels of total cholesterol, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol after 12 weeks of treatment.

Results: Twenty-eight patients (43% male; mean ± SD age, 58 ± 14 years) received garlic powder treatment and 22 (68% male; mean ± SD age, 57 ± 13 years) received placebo treatment. There were no significant lipid or lipoprotein changes in either the placebo- or garlic-treated groups and no significant difference between changes in the placebo-treated group compared with changes in the garlic-treated patients.

Conclusion: Garlic powder (900 mg/d) treatment for 12 weeks was ineffective in lowering cholesterol levels in patients with hypercholesterolemia.

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ARTICLES IN the lay press continue to advocate the use of garlic as an effective method to lower serum cholesterol levels. A recent meta-analysis of carefully selected trials reported that the use of garlic tablets, equivalent to approximately half to 1 clove per day, decreased total serum cholesterol levels by approximately 9%. Many of the studies cited in the meta-analysis were carried out without standardized laboratory measurements and did not control for any dietary effect. Most of the studies in the meta-analysis did not describe the method of cholesterol analysis.

Garlic has also been reported to reduce elevated blood pressure levels. However, many of these studies were unblinded, of short duration, and included small numbers of patients.

In an effort to clarify the potential effect of garlic tablets on plasma lipids, a carefully conducted double-blind, randomized, placebo-controlled study was carried out on diet-treated and stable patients with hypercholesterolemia at the Yale University Cardiovascular Disease Prevention Center, New Haven, Conn, and The Christ Hospital Cardiovascular Research Center, Cincinnati, Ohio.

The primary objective of the study was to evaluate the effects of garlic powder tablets (Kwai) on levels of total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol (LDL-C) in patients with mild to moderate hypercholesterolemia. Secondary objectives included the effect of garlic powder tablets on apolipoprotein B, apolipoprotein A1, and lipoprotein(a) levels. The tolerability of the garlic powder tablets was also evaluated.

RESULTS

A total of 88 patients entered the diet lead-in phase and 50 patients who met the
SUBJECTS AND METHODS

The protocol was approved by the institutional review boards of both institutions.

STUDY DESIGN

Patients were recruited from the lipid clinics of both institutions. The protocol required 4 weeks of a National Cholesterol Education Program step I or a more restricted fat diet without the use of lipid-lowering medications prior to the first eligibility visit. Four additional weeks of diet compliance were documented before randomization. Thereafter patients were randomized to 12 weeks of treatment with either garlic powder or matching placebo therapy. Dietary counseling by a trained and registered dietitian and dietary assessment were continued throughout the study using a 3-day diet diary and Food Rating Record (FRR) score.3 Plasma lipid and lipoprotein levels were assessed after the initial diet lead-in period. Entry into the study was based on a mean plasma LDL-C level, determined at 2 visits (4 and 2 weeks before randomization), of 4.1 mmol/L (160 mg/dL) or higher (with no single value <4.0 mmol/L [155 mg/dL]), and a mean plasma triglyceride level lower than 4.0 mmol/L (350 mg/dL).

Patients were excluded from participation if they had any secondary cause of hypercholesterolemia including hypothyroidism, nephrotic syndrome (treatment with hormones known to affect lipids, uncontrolled diabetes), unstable angina, or myocardial infarction occurring within 2 months of entry into the study, active liver disease, chronic renal disease (creatinine level >265 µmol/L [>3 mg/dL]), or severe metabolic or endocrine disorders. All lipid-lowering drug regimens were discontinued 6 weeks before entry into the study.

Eligible patients were randomized to receive either active garlic powder therapy (Kwai) or matching placebo therapy. The random assignment to placebo or garlic powder treatment was determined by the sponsor (Lichtwer Pharma, Berlin, Germany). Randomized patient treatment sets were sent by the sponsor, which were stratified by center with the investigators blinded to the treatment allocation. A dosage of 300 mg of garlic powder was given 3 times daily with meals (total, 900 mg/d). Each tablet is equivalent to approximately 0.9 g of fresh garlic, and those randomized to active treatment received the equivalent of about 1 clove of fresh garlic per day. The study drugs (garlic powder and placebo tablets) were identical in terms of smell and appearance.

An FRR score based on a 3-day diet diary was determined after 4 weeks and 8 weeks of diet stabilization and after 12 weeks of double-blind treatment. A blood sample was drawn to determine lipids, lipoproteins, apolipoproteins, and safety studies at each visit. The apolipoprotein analysis included apolipoprotein B, apolipoprotein A1, and lipoprotein (a) levels. Safety laboratory studies included a chemistry profile and complete blood cell count. Measurement of heart rate and seated blood pressure was performed at each visit. Complete physical examinations were carried out prior to and following 12 weeks of active treatment.

The patients were seen after 6 and 12 weeks of therapy. At these visits, they were asked about any adverse effects. After 6 weeks of double-blind therapy, dietary recommendations were reinforced.

PREPARATION OF THE GARLIC POWDER TABLETS

The garlic powder tablets were coated tablets containing dried garlic powder that was prepared by freeze-drying fresh garlic. During the specific drying process, destruction of the structure of the garlic plant is avoided, thus preserving the separation of allin and the enzyme, allinase. Allin is an S-allylcysteine sulfoxide that is odorless. When allin is acted on by allinase, allicin is formed. Allicin, which has the characteristic garlic odor, is thought to be the active ingredient in the garlic plant. The tablet containing the separated allin and allinase is odorless. After digestion of the surface coating of the tablet in the gastrointestinal tract and water penetration, allin is converted into allicin. This

DIET STABILITY

Diet compliance and stability as measured by FRR scores are shown in Table 2. There were no significant differences between the 2 treatment groups after 4 and 8 weeks of diet stabilization and after 12 weeks of active therapy (P = .34, P = .27, and P = .62, respectively.) Although dietary compliance in both groups decreased during the study as judged by FRR scores, these within-group changes were not significant (placebo-treated group, P = .21; garlic-treated group, P = .34). The FRR scores of 12.0 (6.5) in the placebo-treated group and 11.0 (6.6) in the garlic-treated patients after 12 weeks of treatment indicate that a relatively low-fat diet was followed. An FRR score of 12 is considered compliant with the National Cholesterol Education Program step I diet.

COMPLIANCE TO MEDICATION

Mean compliance for both placebo-treated and garlic-treated groups through the 12-week treatment phase was approximately 90%. There were no significant differences in the compliance rate between the placebo-treated and garlic-treated groups (mean compliance:}

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weeks 0-6 of treatment, 90.6% vs 88.7%, respectively, \( P = .07 \); weeks 6-12 of treatment, 90.9% vs 90.2%, respectively, \( P = .09 \).

### STATISTICAL ANALYSIS

Baseline and posttreatment lipid parameters and vital signs were compared using a paired \( t \) test for within-group changes, and a 2-way analysis of variance for change between the garlic-treated and placebo-treated groups. A 2-way analysis of covariance was used for those lipid parameters for which there were significant baseline differences. Age and body mass index (a measure of weight in kilograms divided by the square of the height in meters) in the garlic-treated and placebo-treated patients was compared using the Student \( t \) test. Other demographic information including sex, race, history of coronary heart disease, smoking, hypertension, and diabetes was compared using a Fisher exact test. Baseline evaluations of the lipid and lipoprotein parameters were the means of measurements obtained at 3 visits: 4 and 2 weeks before randomization and at the visit that randomization occurred. Baseline apolipoprotein measurements were obtained at the visit at which randomization occurred. After 12 weeks of therapy, the same parameters were compared with the baseline parameters. Results are reported for baseline parameters and percentage change from baseline.

Changes in FRR scores in the garlic-treated and placebo-treated groups were compared using a paired \( t \) test. The FRR scores in the garlic-treated patients were compared with scores of the placebo-treated patients at baseline and after 12 weeks of treatment using 2-way analysis of variance.

Mean percentage of compliance to study medication was calculated as the percentage of prescribed tablets consumed based on counts of returned study medication. Mean percentage of compliance in the 2 groups was compared using 2-way analysis of variance.

With the number of patients eligible for evaluation and an SD of 10%, comparing the changes in LDL-C levels in the garlic-treated and placebo-treated groups, the study had 80% power to detect a difference of 8.7%.

Unblinding of the patient’s treatment assignment occurred after all the data were reviewed and coded, all queries resolved, and quality assurance audit completed.

### VITAL SIGNS

There was a small but statistically significant increase in diastolic blood pressure from baseline in the placebo-treated group, but no significant changes in blood pressure, heart rate, or body mass index were demonstrated.
in the garlic-treated group (Table 3). There were no significant differences in any of the vital sign measurements when changes in the garlic-treated patients were compared with changes in the placebo-treated patients.

**LIPID, LIPOPROTEIN, AND APOLIPOPROTEIN PARAMETERS**

There were significant differences in the baseline levels of total cholesterol, LDL-C, and apolipoprotein B between those randomized to garlic treatment and those randomized to placebo (Table 4). There were no other significant baseline differences in the lipid, lipoprotein, or apolipoprotein parameters.

There were no significant within-group changes during therapy, and no significant differences when the percentage of change in the placebo-treated patients was compared with the percentage of change in the garlic-treated patients. There were no trends in any particular direction.

Because of the baseline differences in the mean levels of total cholesterol, LDL-C, and apolipoprotein B in the 2 treatment groups, an analysis of covariance was performed, in addition to the analysis of variance for these parameters. When using the 2-way analysis of covariance model, with the baseline values as covariants, the groups still did not differ significantly. In fact, the adjusted mean percentages of change using the 2-way analysis of covariance model for total cholesterol, LDL cholesterol, and apolipoprotein B levels in the 2 groups were closer together than what they were in the unadjusted form. For total cholesterol level, the adjusted mean (SE) percentage change in the placebo-treated group was −0.07 (2.0) and in the garlic-treated group 1.17 (1.8) compared with the unadjusted mean (SD) percentage change of 0.07 (2.0) and 1.64 (1.8) in the 2 treatment groups. For LDL cholesterol, the adjusted mean (SE) percentage change for the placebo-treated group was −0.33 (2.3) and in the garlic-treated group 1.2 (2.0) compared with the unadjusted mean (SE) percentage change of −0.35 (2.3) and 1.82 (7.5) for the 2 treatment groups. For apolipoprotein B, the adjusted mean (SE) percentage change for the placebo-treated group was 4.30 (2.7) and in the garlic-treated group 4.36 (2.5) compared with the unadjusted mean (SE) percentage change of 4.93 (11.6) and 4.29 (11.2) for the 2 treatment groups.

### Table 3. Mean Change of Vital Signs*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment Group</th>
<th>Baseline</th>
<th>Change</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP, mm Hg</td>
<td>Placebo</td>
<td>123.3 (12.7)</td>
<td>−0.1 (6.5)</td>
<td>.46</td>
</tr>
<tr>
<td></td>
<td>Garlic</td>
<td>119.3 (15.2)</td>
<td>2.2 (12.4)</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>Placebo</td>
<td>71.7 (9.2)</td>
<td>4.2† (6.5)</td>
<td>.16</td>
</tr>
<tr>
<td></td>
<td>Garlic</td>
<td>73.2 (9.6)</td>
<td>1.1 (7.0)</td>
<td></td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>Placebo</td>
<td>68.5 (11.2)</td>
<td>−1.1 (7.6)</td>
<td>.87</td>
</tr>
<tr>
<td></td>
<td>Garlic</td>
<td>71.8 (8.1)</td>
<td>−0.7 (9.0)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>Placebo</td>
<td>27 (5)</td>
<td>0.08 (0.6)</td>
<td>.75</td>
</tr>
<tr>
<td></td>
<td>Garlic</td>
<td>26 (3)</td>
<td>0.03 (0.6)</td>
<td></td>
</tr>
</tbody>
</table>

*All values are mean (SD). BP indicates blood pressure; BMI, body mass index, which is a measure of weight in kilograms divided by the square of the height in meters.

†P<.01, using a point t test for within-group changes from baseline.

### Table 4. Mean Percentage of Change for Lipid Parameters*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment Group</th>
<th>Mean (SD) Baseline</th>
<th>Mean (SD) Change, %</th>
<th>Mean (SE) Adjusted Change, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>Placebo</td>
<td>6.4† (0.5) [250 (20)]</td>
<td>0.07 (10.2)</td>
<td>−0.07 (2.0)</td>
</tr>
<tr>
<td></td>
<td>Garlic</td>
<td>7.1 (0.9) [274 (34)]</td>
<td>1.64 (6.8)</td>
<td>1.17 (1.8)</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>Placebo</td>
<td>4.4† (0.4) [172 (14)]</td>
<td>−0.35 (12.1)</td>
<td>−0.33 (2.3)</td>
</tr>
<tr>
<td></td>
<td>Garlic</td>
<td>4.9 (0.8) [188 (31)]</td>
<td>1.82 (7.5)</td>
<td>1.2 (2.0)</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>Placebo</td>
<td>1.2 (0.2) [47 (8)]</td>
<td>−1.73 (12.0)</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Garlic</td>
<td>1.3 (0.3) [52 (11)]</td>
<td>2.90 (10.8)</td>
<td>...</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>Placebo</td>
<td>1.8 (0.6) [160 (51)]</td>
<td>7.66 (21.5)</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Garlic</td>
<td>1.9 (0.8) [171 (75)]</td>
<td>0.38 (26.3)</td>
<td>...</td>
</tr>
<tr>
<td>Apolipoprotein B, g/L</td>
<td>Placebo</td>
<td>1.5† (0.1)</td>
<td>4.93 (11.6)</td>
<td>4.39 (2.7)</td>
</tr>
<tr>
<td></td>
<td>Garlic</td>
<td>1.6 (0.2)</td>
<td>4.29 (11.2)</td>
<td>4.36 (2.5)</td>
</tr>
<tr>
<td>Apolipoprotein Aₙ, g/L</td>
<td>Placebo</td>
<td>1.4 (0.2)</td>
<td>−1.74 (10.8)</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Garlic</td>
<td>1.5 (0.3)</td>
<td>2.60 (13.0)</td>
<td>...</td>
</tr>
<tr>
<td>Lipoprotein (a), g/L</td>
<td>Placebo</td>
<td>0.3 (0.3)</td>
<td>2.08 (28.4)</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Garlic</td>
<td>0.4 (0.3)</td>
<td>−2.56 (21.9)</td>
<td>...</td>
</tr>
</tbody>
</table>

* LDL indicates low-density lipoprotein; HDL, high-density lipoprotein; and ellipses, not applicable. Comparing the percentage of change in the garlic-treated group with the percentage of change in the placebo-treated group did not reach statistical significance using a significance level of .05. This did not change when using the adjusted percentage of change for total cholesterol, LDL cholesterol, and apolipoprotein B levels.

†At baseline, total cholesterol, LDL cholesterol, and apolipoprotein B levels were statistically significant in the garlic-treated group compared with the placebo-treated group (P<.01, P<.05, and P<.05, respectively). An adjusted percentage of change was calculated for these parameters using an analysis of covariance with baseline values as covariants.
Testing for differences between the 2 clinical sites showed no statistically significant differences ($P>.20$ for all parameters).

**ADVERSE EFFECTS**

In the garlic-treated group, 3 patients (11%) complained of a garlic breath that was perceived by them or was perceived by others, and 2 patients (7%) described a change in body odor. No similar symptoms were elicited from placebo-treated patients. One of the patients with garlic breath dropped out of the study as a result of these symptoms. In addition to this patient, there were 6 other adverse events that resulted in discontinuation of study drug. Of these, 3 patients were in the garlic-treated group (1 patient with intestinal obstruction and 2 with abdominal discomfort) and 3 patients were in the placebo-treated group (1 each with epigastric burning, myocardial infarction, and chest pain). The myocardial infarction, chest pain, and intestinal obstruction were considered unrelated to study drug by the investigators. One patient in the placebo-treated group withdrew from the study unrelated to any adverse event.

Other adverse effects, which did not result in discontinuation of study drug, did not differ significantly between the 2 treatment groups.

**COMMENT**

A great body of folklore has accumulated over several hundred years regarding the benefits of garlic in treating abscesses, coughs, poisonings, parasites, worms, digestive and circulatory problems, and snakebites. In addition, claims have been made that the use of garlic prolongs life and prevents heart attacks. In southern European areas where inhabitants consume large amounts of garlic, the incidence of heart disease is relatively low. There has been some speculation that garlic may play a role in this phenomenon.

The availability of relatively odorless garlic tablets and capsules that contain the ingredient believed to be the active substance in reducing cholesterol levels or providing other health benefits makes a randomized, well-controlled, double-blind study more feasible than it has been in the past. As noted in our study, only 3 (11%) of 28 patients treated with garlic powder experienced garlic breath or garlic body odor. These dried garlic powder preparations contain alliin, a $S$-allylcysteine sulfide. When the alliin is consumed it is altered by enzymes contained in the garlic plant to produce allicin, the substance believed to have medicinal properties. Alliin is odorless, whereas allicin has the characteristic garlic odor. These tablets are considered close in chemical content to those of fresh garlic. Studies in animals have demonstrated that the use of garlic may reverse the increase in serum cholesterol levels after the ingestion of a fatty diet, and some studies also suggest that the use of garlic can prevent the formation of atherosclerotic lesions in animals fed a high-fat diet. The active ingredients of garlic, allicin, and other sulfur compounds may act as 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors reducing the production of cholesterol in the liver. They may also reduce platelet aggregation and clotting.

Several studies have been performed using the same garlic preparation (Kwai) that was used in our study. In a 4-month multicenter, placebo-controlled study in Germany in 30 general practitioners' offices, the ingestion of 800 mg/d of dried garlic powder was associated with a 9% greater reduction in serum cholesterol levels compared with placebo. Those subjects with higher levels of cholesterol experienced a greater decrease in cholesterol levels with treatment. In those with baseline cholesterol levels between 5.2 and 6.5 mmol/L (200-250 mg/dL) a decrease of 4% was observed, whereas in those with baseline levels between 6.5 and 7.8 mmol/L (250-300 mg/dL) an 11% decrease was observed. Reduction in triglyceride levels was 15% higher in the garlic-treated patients compared with those in the placebo-treated group. In that study approximately 12% of the garlic-treated patients experienced a garlic smell. The authors, however, did not attempt to control or evaluate dietary effects, lipid evaluations were carried out in numerous nonstandardized local laboratories, and the lipid results during the trial were not blinded to investigators.

Our placebo-controlled, randomized, double-blind study in which diets were standardized and measured was unable to confirm previous reports of a statistically significant reduction in serum cholesterol and triglyceride levels following the ingestion of garlic. In our study, there were no statistically significant changes in any of the lipid, lipoprotein, or apolipoprotein parameters following the use of garlic powder tablets (900 mg/d). We were also unable to confirm any significant blood pressure lowering effect of garlic.

Although our study was relatively small, our results are consistent with 2 other studies that used a similar study design and found no significant differences in lipid levels between those treated with garlic and placebo. Both studies were diet controlled and used garlic tablets (Kwai).

In all studies in which the expected lipid effect is modest, dietary stabilization becomes a crucial factor in establishing the true lipid-lowering capacity of the treatment under investigation. Our study, like the other 2 studies with negative findings, evaluated the effect of garlic tablet therapy after a modified, low-cholesterol diet had been instituted and with dietary compliance evaluated and quantified throughout the active therapy period.

An additional reason that may explain the difference between our results and the results obtained in the meta-analysis by Warshafsky et al involves the issue of publication bias. Investigators and sponsors are often reluctant to report negative outcomes. Thus it is important to record this negative study to put into perspective the widespread belief that garlic is an effective cholesterol-lowering agent.

While additional well-controlled studies may be necessary to confirm our observations, given the lack of an effect on any of the lipid, lipoprotein, or apolipoprotein parameters in 3 diet-controlled, double-blind, placebo-controlled trials in patients with mild hypercholesterolemia, garlic tablets are unlikely to be useful lipid-lowering agents.
The addition of garlic to food adds to its flavor. It has no known specific toxic effects in most people and is generally well tolerated. However, this study does not support the use of garlic tablets for lowering plasma lipid levels. Additional carefully controlled, longer-term studies are necessary to clarify the exact role of garlic on fibrinolysis and platelet adhesion, both potential targets for preventing coronary heart disease.

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