Garlic Extract Therapy in Children With Hypercholesterolemia

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Objective: To determine whether garlic extract therapy is efficacious and safe in children with hypercholesterolemia.

Design: Randomized, double-blind, placebo-controlled clinical trial.

Setting: Specialized pediatric lipid disorders ambulatory clinic.

Participants: Thirty pediatric patients, aged 8 to 18 years, who had familial hyperlipidemia and a minimum fasting total cholesterol level greater than 4.8 mmol/L (185 mg/dL).

Intervention: An 8-week course of a commercially available garlic extract (Kwai [Lichtwer Pharma, Berlin, Germany], 300 mg, 3 times a day) or an identical placebo.

Main Outcome Measures: Absolute and relative changes in fasting lipid profile parameters.

Results: The groups were equivalent at baseline and compliance was similar in the 2 groups (P = .45). There was no significant relative attributable effect of garlic extract on fasting total cholesterol (+0.6% [95% confidence interval, −5.8% to +6.9%]) or low-density lipoprotein cholesterol (−0.5% [95% confidence interval, −8.7% to +7.6%]). The lower limits of the confidence intervals did not include −10%, the minimum relative attributable effect believed to be clinically important. Likewise, no significant effect was seen on the levels of high-density lipoprotein, triglycerides, apolipoprotein B-100, lipoprotein (a), fibrinogen, homocysteine, or blood pressure. There was a small effect on apolipoprotein A-I (+10.0% [95% confidence interval, +1.2% to +16.5%] P = .03). There were no differences in adverse effects between groups.

Conclusion: Garlic extract therapy has no significant effect on cardiovascular risk factors in pediatric patients with familial hyperlipidemia.


Editor’s Note: I’m going to be disowned by my family for publishing anything negative about garlic. On the other hand, this is exactly the kind of study needed to determine the effects of complementary medicine.

Catherine D. DeAngelis, MD

Detection and management of hypercholesterolemia in children remains controversial.1-3 Dietary management with reduced fat and cholesterol intake is the cornerstone of therapy in children, together with attention to other cardiovascular risk factors.4 However, a small proportion of children with hypercholesterolemia will meet the criteria for treatment with lipid-lowering medication.4 The standard for drug therapy in children is treatment with bile acid–binding resins, which are associated with poor acceptability, tolerance, and compliance, and achieve only modest reductions in lipid profile levels.5 Recently, there has been some interest in alternative therapies. Garlic (Allium sativum) and garlic extracts have been reported to be variably effective in managing hypertension and hypercholesterolemia,6-8 although this remains to be proven conclusively.9,10 Given concerns about the safety of long-term pharmacologic therapy in children, there is considerable interest in assessing potential “natural” treatments. To our knowledge no data regarding use of garlic extract preparations in treating hypercholesterolemia in children have been reported. This study determined tolerance, compliance, safety, and efficacy of therapy.
PARTICIPANTS AND METHODS
SAMPLE SELECTION

Participants were recruited from the pediatric lipid disorders clinic of St Joseph’s Hospital, Hamilton, Ontario, which provides assessment and management of children with primary lipid abnormalities. Some patients who had participated in previous clinical trials in the clinic were recruited by telephone and all other patients were recruited at the time of routinely scheduled clinic visits, until the sample size (N=30) was reached. All patients recruited met the inclusion criteria. Records of the number of patients approached and the proportion giving consent were not kept. Inclusion criteria were patient age (8-18 years old), a positive family history of hypercholesterolemia or premature atherosclerotic cardiovascular disease in first-degree relatives, a minimum fasting total cholesterol level at enrollment higher than 4.8 mmol/L (>185 mg/dL), participation in a dietary counseling program, and compliance with a National Cholesterol Education Program Step II diet for at least 6 months. Exclusion criteria included the presence of secondary causes of hyperlipidemia or a history of major surgery or serious illness 3 months or less prior to enrollment. This population was chosen because most of the patients unambiguously met criteria for pharmacologic therapy.1

ETHICS

Ethics approval was obtained from the Research Ethics Board of the St Joseph’s Hospital, and all parents and/or patients gave informed consent.

DESIGN

The study was a randomized, double-blind, placebo-controlled clinical trial. Patients were instructed to stop taking any lipid-lowering medications for at least 8 weeks before the study. The medication used in the study was formulated by an independent pharmacist. The medication consisted of 1 whole 300-mg tablet of garlic extract (Kwai, Lichtwer Pharma, Berlin, Germany) containing 0.6 mg of allicin placed in a gelatin capsule with inert filler. One bulb of Chinese-grown garlic provides the same amount of allicin as that provided by 6 tablets of garlic extract. The placebo consisted of an identical gelatin capsule filled with the same inert filler only. Participants were instructed to take 1 capsule 3 times a day for an 8-week period (the manufacturer’s recommended dosage for adults is 1 to 2 tablets 3 times a day). There was no information to guide dosing in pediatric patients, and the lower limit of the recommended adult dosage was chosen arbitrarily.

RANDOMIZATION PROCEDURE

Randomization was carried out independently by one of us (B.W.M.) not involved in application of the study. Using blocks of 6, a random number generator was used to create an assignment list, which was supplied to the independent pharmacist who then assigned patients consecutively when they were enrolled and their medication dispensed. The randomization list also specified the amount of medication to dispense, which covered the 8-week treatment period and a random number of additional capsules, so that all patients would have unused medication to return at the end of the study.

BLINDING

The patient nurse coordinator (E.H.) and supervising physician (W.T.C.) responsible for recruitment, application of the study, and assessment were blinded as to the group assignment and total amount of medication dispensed. The independent pharmacist was not directly involved in the care of the study subjects.

COMPLIANCE

No direct biologic measure of compliance was taken. Unused medication at the end of the study period was returned and counted by the nurse coordinator. The amount of medication taken by each patient was assumed to be the amount dispensed minus the amount returned. Compliance was expressed as the percentage of medication assumed taken vs the percentage expected to be taken if given the original patient’s allotted medication. All enrolled patients completed all components of the study protocol, and there was no incident of unmasking of patient assignment.

BASELINE CHARACTERISTICS

There were 16 male and 14 female patients in the study, and mean age at enrollment was 14.0±2.3 years. All patients had a positive family history of first-degree relatives with hypercholesterolemia and premature atherosclerotic heart disease. Mean fasting lipid values at baseline were total cholesterol, 6.86±1.52 mmol/L (265±59 mg/dL); LDL, 5.33±1.45 mmol/L (206±56 mg/dL); HDL, 0.95±0.22 mmol/L (37±8 mg/dL); and triglycerides, 1.26±0.52 mmol/L (112±46 mg/dL). The mean apolipoprotein B-100 level was 1.46±0.36 g/L (146±36 mg/dL); and apolipoprotein A-I, 1.12±0.14 g/L (112±8 mg/dL).

RESULTS

ENROLLMENT

Thirty patients were initially enrolled in the trial and were randomly assigned to one of two groups of 15. One patient was unable to swallow the capsules and withdrew from the study; another patient was recruited and was with a commercially available garlic extract preparation in lowering cholesterol levels in participants with hypercholesterolemia. We hypothesized that compliance would be greater than 75% during the course of an 8-week study period, that less than 5% of the patients treated with the garlic extract preparation would experience unpleasant body odor, and that a mean relative attributable reduction in low-density lipoprotein (LDL) levels of 10% would be noted.
compliance was complete throughout the study period. Compliance was also assessed from a daily logbook completed by the patient for the first week of the study, and from questionnaires completed at 4 and 8 weeks after medication was started.

MAIN OUTCOME MEASURES

Blood samples from patients who had fasted were assessed at baseline and at study endpoint on the following factors: total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol (with LDL cholesterol calculated), lipoprotein(a), apolipoproteins B-100 and A-I, homocysteine, and fibrinogen. These assays were performed in a single standardized lipid research laboratory with acceptable coefficients of variation. In addition, blood pressure was assessed at both time points.

SAFETY MONITORING

A complete physical examination that included an assessment of height and weight was performed at baseline and at study endpoint by one of us (W.T.C.). We collected data regarding symptoms and signs with the first-week daily logbook and midpoint and endpoint questionnaires. Participants were instructed to contact study personnel immediately if important adverse effects were noted or if the patient developed serious illness, required surgery, or required other pharmacologic treatment during the study period. Serum chemistry studies and complete blood cell counts were assessed and compared at baseline and endpoint.

SAMPLE SIZE

Sample size estimation was based on the assumption that a 10% relative attributable reduction in the LDL cholesterol level was the minimum treatment deemed to be clinically important to justify use of medication. This assumption was based on a report that the drug caused a 12% reduction in cholesterol levels in adults. Also, the only pharmacologic therapy approved for use in children who have hyperlipidemia is treatment with the bile acid-binding resins, which results in a reduction in the LDL of 10% to 15%. Hypothesized LDL level lowering was −10%±5% (mean±SD) in the garlic extract and 0%±5% in the placebo groups, for a standardized treatment effect of 2.0. With a β level of .80 and an α level of .05, the estimated sample size was 11 patients per group, increased to 15 patients to compensate for potential dropouts.

PROCEDURES

After obtaining informed consent, eligible study participants were instructed to stop taking all lipid-lowering medication for at least 8 weeks. At their initial clinic visit, patients were assessed for the following: fasting baseline blood studies, cardiovascular risk assessment including dietary assessment by food frequency questionnaire, family history questionnaire, and results from physical examination. Patients were given instructions regarding completion of the logbook and were asked to complete midpoint and endpoint questionnaires. They were then directed to the independent pharmacist who dispensed the study medication. Patients were reminded by telephone to complete the questionnaires. At the end of the 8-week study period, patients returned to the clinic with all remaining medications and the completed questionnaires and were assessed for the following: fasting blood studies, history including dietary assessment by food frequency questionnaire, and results from physical examination.

DATA ANALYSIS

Data are reported as frequencies, medians with ranges, and means with SDs as appropriate. Characteristics at baseline were compared between groups using the Fisher exact test, χ² test, Kruskal-Wallis analysis of variance, and t test. Patient changes in height, weight, blood pressure, and blood test results were assessed with paired t tests for each group. Mean differences in the changes between the 2 groups were compared with a Student t test. Difference in mean percent compliance between the 2 groups was assessed with a Student t test. Differences between groups in changes in lipid profile parameters adjusted for compliance were assessed with a general linear regression model. Statistical significance was set at P<.05.

(112±14 mg/dL). Median lipoprotein(a) level was 155 g/L (15.5 mg/dL) and ranged from 24 to 2262 g/L (2.4-226.2 mg/dL), with 9 patients (30%) having significantly elevated levels. The mean fibrinogen level was 2.48±0.51 μmol/L and the homocysteine level was 7.37±2.02 μmol/L, with all patients within the normal range. No patient had hypertension and 5 patients (17%) occasionally used tobacco products (<5 cigarettes per day). Bile acid–binding resins had been previously used in 13 patients (43%); the remaining patients had been managed with dietary therapy only. All patients were judged to be sufficiently compliant with dietary goals.

TEST OF RANDOMIZATION

Patient characteristics at baseline were not significantly different between the 2 groups, with the exception of higher homocysteine levels in the placebo group and a greater proportion of men in the garlic extract group (Table 1).

COMPLIANCE

There were no significant differences between groups regarding compliance throughout the study period. From the logbooks completed during the first week, patients in the placebo group took a mean of 93%±12% of expected doses vs 86%±27% in the garlic extract group (P=.34). On the midpoint questionnaire, patients in the placebo group responded that they had taken all of their medication a median of 6.25 days of the last 7 days (range, 3.5-7 days) vs a median of 7 days (range, 0-7 days) in the garlic extract group (P=.34). At endpoint questionnaire, patients in the placebo group responded that they had taken all of their medication a median of 7 days of the last 7 days (range, 0-7 days) vs a median of 6 days (range, 0-7 days) in the
garlic extract group (P=.34). From returned medication counts at the end of the study, compliance during the study period was a mean of 78%±22% of expected in the placebo group vs 72%±21% in the garlic extract group (P=.45). Based on compliance and body weight at baseline, mean dose taken during the study period was 0.029±0.013 mg/kg per day in the placebo group vs 0.023±0.008 mg/kg per day in the garlic extract group (P=.13). Compliance during the study period was not significantly related to patient age or sex, previous experience with lipid-lowering medication, or fasting lipid profile parameters at baseline.

MAIN OUTCOME MEASURES

There were no significant differences in the relative treatment effect of garlic extract therapy regarding any of the primary outcome variables (Table 2). The mean baseline and study endpoint values for fasting lipid profile parameters for each group are shown in the Figure. The significant relative increase in apolipoprotein A-I is associated with a P value of .03, which must be viewed in light of the effect of multiple comparisons. The lower limits of the 95% confidence intervals around the relative changes in total cholesterol (−5.8%) and LDL cholesterol (−8.7%) do not meet the empirically defined minimum treatment effect of −10% to achieve clinical importance. In general linear regression modeling, there were no significant differences between groups in changes in primary outcome variables after controlling for compliance. In the garlic extract group, the absolute and relative changes in primary outcome variables were not significantly correlated with compliance or dose taken during the study period.

### Table 1. Comparison of Baseline Characteristics*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo Group (n = 15)</th>
<th>Garlic Extract–Treated Group (n = 15)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male/female</td>
<td>5/10</td>
<td>11/4</td>
<td>.07</td>
</tr>
<tr>
<td>Age, y</td>
<td>14.1 ± 2.5</td>
<td>13.9 ± 2.2</td>
<td>.83</td>
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<tr>
<td>Weight, kg</td>
<td>54 ± 17</td>
<td>59 ± 18</td>
<td>.45</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>21.1 ± 4.2</td>
<td>22.6 ± 5.3</td>
<td>.40</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>102 ± 9</td>
<td>102 ± 9</td>
<td>.85</td>
</tr>
<tr>
<td>Diastolic</td>
<td>60 ± 8</td>
<td>63 ± 10</td>
<td>.38</td>
</tr>
<tr>
<td>Occasional tobacco use, No. (% of patients)</td>
<td>3 (20)</td>
<td>2 (13)</td>
<td>1.00</td>
</tr>
<tr>
<td>Fasting lipid profile, mmol/L (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>6.66 ± 1.46 (257 ± 56)</td>
<td>7.06 ± 1.61 (276 ± 62)</td>
<td>.49</td>
</tr>
<tr>
<td>LDL–C†</td>
<td>5.07 ± 1.38 (196 ± 53)</td>
<td>5.59 ± 1.52 (216 ± 59)</td>
<td>.34</td>
</tr>
<tr>
<td>HDL–C†</td>
<td>0.96 ± 0.18 (37 ± 7)</td>
<td>0.95 ± 0.25 (37 ± 10)</td>
<td>.87</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.38 ± 0.61 (122 ± 54)</td>
<td>1.14 ± 0.38 (101 ± 34)</td>
<td>.22</td>
</tr>
<tr>
<td>Apolipoproteins, g/L (mg/dL)</td>
<td>1.16 ± 0.13 (116 ± 13)</td>
<td>1.07 ± 0.13 (107 ± 13)</td>
<td>.08</td>
</tr>
<tr>
<td>Apolipoprotein A-I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apolipoprotein B-100</td>
<td>1.43 ± 0.35 [143 ± 35]</td>
<td>1.49 ± 0.38 [149 ± 38]</td>
<td>.63</td>
</tr>
<tr>
<td>Median [range] lipoprotein(a), mg/L (mg/dL)</td>
<td>113 [24, 955] (11.3 [2.4, 95.5])</td>
<td>207 [32, 2262] (20.7 [3.2, 226.2])</td>
<td>.17</td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>2.54 ± 0.47</td>
<td>2.43 ± 0.56</td>
<td>.56</td>
</tr>
<tr>
<td>Homocysteine, µmol/L</td>
<td>8.25 ± 2.32</td>
<td>6.49 ± 1.17</td>
<td>.02</td>
</tr>
</tbody>
</table>

*Unless otherwise stated values are expressed as mean ± SD.
†LDL-C indicates low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol. Numbers in parentheses are 95% confidence intervals. Numbers in brackets are conventional units.

### Table 2. Absolute and Relative Attributable Treatment Effects of Garlic Extract Therapy*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Absolute Effect, % (95% Confidence Interval)</th>
<th>Relative Effect, % (95% Confidence Interval)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting lipid profile, mmol/L (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>+0.10 (−0.29, +0.49) [+4 (−11, +19)]</td>
<td>+0.6 (−5.8, +6.9)</td>
<td>.86</td>
</tr>
<tr>
<td>LDL–C†</td>
<td>+0.04 (−0.35, +0.43) [+2 (−14, +17)]</td>
<td>−0.5 (−8.7, +7.6)</td>
<td>.90</td>
</tr>
<tr>
<td>HDL–C†</td>
<td>+0.03 (−0.11, +0.17) [+1 (−4, +7)]</td>
<td>+0.3 (−2.6, +2.8)</td>
<td>.29</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>−0.18 (−0.66, +0.30) [−16 (−58, +27)]</td>
<td>−7.2 (−44.6, +30.2)</td>
<td>.70</td>
</tr>
<tr>
<td>Apolipoprotein A-I</td>
<td>+0.09 (−0.01, +0.17) [+9 (−1, +17)]</td>
<td>+10.0 (−15.0, +25.0)</td>
<td>.03</td>
</tr>
<tr>
<td>Apolipoprotein B-100</td>
<td>+0.02 (−0.08, +0.12) [+2 (−8, +12)]</td>
<td>+0.8 (−7.3, +8.8)</td>
<td>.85</td>
</tr>
<tr>
<td>Lipoprotein(a), mg/L (mg/dL)</td>
<td>−71 (−138, −5) [−7.1 (−13.8, −0.5)]</td>
<td>−9.0 (−30.2, +12.2)</td>
<td>.40</td>
</tr>
<tr>
<td>Fibrinogen, g/L (mg/dL)</td>
<td>−0.19 (−0.64, +0.26) [+19 (−64, +26)]</td>
<td>−7.8 (−26.3, +10.6)</td>
<td>.40</td>
</tr>
<tr>
<td>Homocysteine, µmol/L</td>
<td>+0.67 (−0.45, +1.79) [+8 (−10, +28)]</td>
<td>+10.5 (−5.3, +26.4)</td>
<td>.19</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>+2.1 (−7.1, +11.3)</td>
<td>+2.3 (−6.8, +11.4)</td>
<td>.61</td>
</tr>
<tr>
<td>Diastolic</td>
<td>0 (−6.5, +6.5)</td>
<td>−0.4 (−11.9, +11.1)</td>
<td>.94</td>
</tr>
</tbody>
</table>

*LDL-C indicates low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol. Numbers in parentheses are 95% confidence intervals. Numbers in brackets are conventional units.
While pharmacologic lipid-lowering therapy has been shown to be effective in reducing cardiovascular morbidity and cardiovascular mortality rates and total mortality rates in adults, management of hyperlipidemia in children remains controversial. Our study showed no significant reduction attributable to garlic extract therapy in recognized cardiovascular risk factors in children with familial hyperlipidemia, with the exception of a small increase in apolipoprotein A-I levels.

Patients are increasingly seeking alternative therapies for their illnesses, despite the fact that scientific evidence supporting the effectiveness and safety of these therapies is often lacking or conflicting. Garlic has been used for centuries to treat a wide range of ailments. Recently, perhaps driven by hypotheses from dietary epidemiologic studies, there has been renewed interest in garlic and garlic preparations and their potential cardiovascular benefits. Several studies have shown improvements in lipid profile parameters, hypertension, platelet aggregation, and plasma viscosity and fibrinolytic activity. The mechanisms by which garlic or its active components might cause these effects have not been determined. Methodologic flaws of these studies and direct drug company sponsorship also weaken the strength of evidence of these studies. A more recent meta-analysis was more guarded in its support of an important treatment effect related to garlic-extract therapy. A recent clinical trial showed no significant lowering of cholesterol levels and no effect on LDL oxidizability, cholesterol synthesis, or LDL receptor expression. In addition, to our knowledge, no study has shown any relationship between garlic extract therapy and reductions in cardiovascular morbidity and cardiovascular mortality rates or total mortality rates. Our study further supports this skepticism. Clearly, large-scale, well-designed studies are needed in this area.

Many patients may elect to adopt or persist with using garlic extract therapy despite a lack of scientific evidence supporting its effectiveness. To date, reports of adverse effects related to garlic extract therapy with commercially available preparations have been limited to unpleasant body odor and mild allergic reactions. No significant adverse effects that could be attributed to garlic extract therapy were noted in this study. Adverse effects on growth and development have not been studied, nor have adverse effects related to long-term use.

In summary, in a randomized, double-blind, placebo-controlled clinical trial of garlic extract therapy in hypercholesterolemic children, we found that this treatment course had no significant effect on cardiovascular risk factors.

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REFERENCES


