Brief Report

Effect of a Garlic Oil Preparation on Serum Lipoproteins and Cholesterol Metabolism

A Randomized Controlled Trial

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Context.—Garlic-containing drugs have been used in the treatment of hypercholesterolemia even though their efficacy is not generally established. Little is known about the mechanisms of action of the possible effects on cholesterol in humans.

Objective.—To estimate the hypocholesterolemic effect of garlic oil and to investigate the possible mechanism of action.

Design.—Double-blind, randomized, placebo-controlled trial.

Setting.—Outpatient lipid clinic.

Patients.—We investigated 25 patients (mean age, 58 years) with moderate hypercholesterolemia.

Intervention.—Steam-distilled garlic oil preparation (5 mg twice a day) vs placebo each for 12 weeks with wash-out periods of 4 weeks.

Main Outcome Measures.—Serum lipoprotein concentrations, cholesterol absorption, and cholesterol synthesis.

Results.—Baseline lipoprotein profiles were (mean [SD]): total cholesterol, 7.53 (0.75) mmol/L (291 [29] mg/dL); low-density lipoprotein cholesterol (LDL-C), 5.35 (0.78) mmol/L (207 [30] mg/dL); high-density lipoprotein cholesterol (HDL-C), 1.50 (0.41) mmol/L (58 [16] mg/dL); and triglycerides, 1.45 (0.73) mmol/L (127 [64] mg/dL). Lipoprotein levels were virtually unchanged at the end of both treatment periods (mean difference [95% confidence interval]): total cholesterol, 0.085 (−0.201 to 0.372) mmol/L (3.3 [−7.8 to 14.4] mg/dL), $P = .54$; LDL-C, 0.001 (−0.242 to 0.245) mmol/L (0.04 [−9.4 to 9.5] mg/dL), $P = .99$; HDL-C, 0.050 (−0.028 to 0.128) mmol/L (1.9 [−1.1 to 4.9] mg/dL), $P = .20$; triclycerides, 0.047 (−0.229 to 0.135) mmol/L (4.2 [−20.3 to 12.0]) mg/dL, $P = .60$. Cholesterol absorption (37.5% [10.5%] vs 38.3% [10.7%], $P = .58$), cholesterol synthesis (12.7 [6.5] vs 13.4 [6.6] mg/kg of body weight per day, $P = .64$), mevalonic acid excretion (192 [66] vs 187 [66] µg/d, $P = .78$), and changes in the ratio of lathosterol to cholesterol in serum (4.4% [24.3%] vs 10.6% [21.1%], $P = .62$) were not different in garlic and placebo treatment.

Conclusions.—The commercial garlic oil preparation investigated had no influence on serum lipoproteins, cholesterol absorption, or cholesterol synthesis. Garlic therapy for treatment of hypercholesterolemia cannot be recommended on the basis of this study.

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GARLIC (*Allium sativum*) has been advocated as a remedy for the treatment and prevention of a number of diseases. As a pharmaceutical product, its putative cardioprotective properties, such as lipid-lowering and blood pressure–lowering, antioxidant, antiplatelet, and fibrinolytic effects,[1,2] seem interesting. Studies investigating garlic's lipid-lowering effect are sometimes flawed in design because they lack adequate description of the methods and patients studied or are overtly subjected to conflicts of interest. Meta-analyses found overall effects of between 9% and 12% reduction of total cholesterol.[3,4] However, the confidence in these data is limited by the poor quality of the underlying studies and the possibility of a publication bias in that there are fewer than expected studies reporting negative results.[5] Likewise, meta-analyses based on published reports rather than on individual patient data may be misleading,[6] implying that meta-analyses provide false-positive test results.[7] The value of meta-analyses as accurate predictors of treatment outcome as compared to prospective randomized controlled trials has been questioned.[8] Well-designed recent studies[7,9] found no lipid-lowering effects, while 3 other studies reported some efficacy.[10-12]

We hypothesized that the modest lipid-lowering effect found in meta-analyses may be further understood if more were known about the possible mechanisms of the action of garlic-containing drugs on cholesterol metabolism. We designed a double-blind, randomized, placebo-controlled, cross-over trial to investigate possible influences of a garlic preparation on serum lipoproteins and cholesterol metabolism. We used a steam-distilled garlic-oil preparation.

Methods

Patients.—Patients with moderate hypercholesterolemia (total cholesterol, 6.2-9.0 mmol/L [240-348 mg/dL]; triglycerides, <3.0 mmol/L [<265 mg/dL) were recruited through the local newspaper. None of the 26 unpaid patients randomized for the study (1 later dropped out because of a scheduling conflict) had taken any lipid-lowering drugs or drugs that would interfere with lipid metabolism for 8 weeks, though some were taking antihypertensive medication, hormone replacement drugs, or thyroid hormones. After ensuring that patients who had given consent to participate were free of active liver or renal diseases, diabetes, thyroid dysfunction, a history of coronary heart disease, any pathological laboratory values in the clinical chemistry or hematological routine parameters, and alcohol or other drug abuse, they entered the study whose protocol had been approved by the ethics committee of the faculty of medicine at Bonn University and performed in

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accordance with Declaration of Helsinki guidelines.

Food Records.—Subjects were advised to adhere to their usual diet during the study, but they were prohibited from taking additional garlic or other food supplements. Food intake was assessed at the end of 2 treatment periods, using 7-day food records that were evaluated by computerized nutrient analysis.

Study Design and Treatment.—The study was a single-center, double-blind, randomized, placebo-controlled, cross-over trial. A marketed enteric coated preparation (Tegra, Hermes Arzneimittel GmbH, Munich, Germany) containing 5 mg of steam-distilled garlic oil bound to a matrix of beta cyclodextrin or matching placebos whose coating tasted like garlic, was used. The daily dosage corresponds to about 4 g to 5 g of fresh garlic cloves or 4000 units of allicin-equivalents per day.[13] The active ingredients are the stable sulfur compounds diallyl disulfide (>30%) and diallyl trisulfide (>25%), which are formed from alliin and allicin.

The patients were randomly assigned to the treatment sequences placebo-garlic or garlic-placebo in blocks of 10 for the first 20 patients and in blocks of 2 for the remaining patients. After randomization, the patients were given placebo for 4 weeks in a single-blind fashion. Thereafter, they received the garlic preparation or placebo for 12 weeks in a double-blind fashion. Then a 4-week, single-blind placebo wash-out was performed followed by the 12-week, double-blind cross-over phase. Lipoprotein concentrations from blood drawn at the beginning and end of each phase were measured enzymatically using standard laboratory procedures. High-density lipoprotein cholesterol (HDL-C) was determined after anionic precipitation of apolipoprotein B–containing lipoproteins. Low-density lipoprotein cholesterol (LDL-C) was calculated according to the method of Friedewald.[14]

Evaluation of Cholesterol Metabolism.—During the last week of each 12-week treatment period, cholesterol absorption and endogenous cholesterol synthesis was measured by the double-isotope continuous feeding method as described by Lütjohann et al.[15] For this purpose the patients took 1 capsule containing [D_6]cholesterol and [D_4]sitostanol 3 times a day for 1 week. The disappearance of deuterated cholesterol and its intestinal bacterial products (coprostanol and coprostanone) relative to deuterated sitostanol were measured in fecal samples by gas chromatography-mass spectrometry. The capsules also contained unlabeled sitostanol as a nonabsorbable fecal flow and recovery marker for the measurement of fecal excretion of neutral and acidic sterols. The patients kept a 7-day dietary protocol to determine their intake of nutrients and cholesterol. Cholesterol synthesis was calculated by subtracting the amount of dietary cholesterol intake from the sum of neutral and acidic sterols excreted in feces.[16] As an additional indicator of short-term changes in endogenous cholesterol synthesis, 24-hour urinary excretion of mevalonic acid was measured by gas chromatography–mass spectrometry as described by Lindenthal et al.[17] The measurement of the cholesterol precursor lathosterol in serum was determined by gas chromatography.[18]

Statistical Analysis and Analytical Precision.—Statistical analysis between lipoprotein concentrations at the end of both treatment periods was performed using *t* statistical tests for cross-over designs (in the case of triglycerides after log transformation of the data), after excluding carryover effects.[19] Correlation between the change in the primary study parameter, low-density lipoproteins (LDL), and the parameters of cholesterol metabolism was analyzed using a simple linear regression model. For all tests a significance level of $P<.05$ was defined. The study was powered at a level of greater than 95% to detect differences between treatment periods of 10% LDL-C lowering (or –0.52 mmol/L [–20 mg/dL]). Statistical analyses were performed using StatView 4.1 for the Macintosh (Abacus Concepts Inc, Berkeley, Calif) and Microsoft Excel 5.0a for the Macintosh (Microsoft Inc, Redmond, Wash). All lipoprotein measurements were performed twice on 2 separate days. The average of the 2 values was used for calculations. Within-individual coefficients of variation of the measures were 4.5% (total cholesterol), 6.2% (LDL-C), 6.8% (HDL-C), and 17.4 (triglycerides), respectively. The laboratory's precision in measurement of lipoproteins (day-to-day coefficient of variation) was 0.99% (total cholesterol), 2.64% (LDL-C), 2.22% (HDL-C), and 1.14% (triglycerides).

Table 1.—Subject Characteristics, Baseline Data, and Differences in Effects (in Millimoles per Liter) Between Placebo and Active Drug Treatments*

Characteristic	Baseline	Differences in Effects Between Placebo and Active Drug	*P*
No. of subjects (F/M)	25 (14/11)	. . .	. . .
Age, y	58.3 (7.5)	. . .	. . .
Body mass index, kg/m^2	25.3 (2.5)	. . .	. . .
Total serum cholesterol, mmol/L [mg/dL]	7.53 (0.75) [291 (29)]	0.085 (−0.201 to 0.372) [3.3 (−7.8 to 14.4)]	.54
LDL-cholesterol, mmol/L [mg/dL]	5.35 (0.78) [207 (30)]	0.001 (−0.242 to 0.245) [0.04 (−9.4 to 9.5)]	.99
HDL-cholesterol, mmol/L [mg/dL]	1.50 (0.41) [58 (16)]	0.050 (−0.028 to 0.128) [1.9 (−1.1 to 4.9)]	.20
Triglycerides, mmol/L [mg/dL]	1.45 (0.73) [127 (64)]	0.047 (−0.229 to 0.135) [4.2 (−20.3 to 12.0)]	.60

*The baseline data represent means (SDs) of all subjects that completed the study; the treatment data represent means and 95% confidence intervals. LDL indicates low-density lipoprotein; HDL, high-density lipoprotein; and ellipses, not applicable.

Results

Twenty-five subjects completed the study and 1 subject had to be excluded from the fecal balance calculations because of incomplete intake of the marker capsules in 1 test period. The baseline characteristics and the serum lipoprotein profiles of the 25 patients are listed in Table 1.

The drug was generally well tolerated. Except for garlic odor and slight abdominal discomfort in a few cases, caused by both pills, no serious adverse events occurred. Laboratory safety parameters remained in the normal range. Compliance as measured by pill count was excellent and averaged 98.4% ± 6.3% (mean ± SD) during all phases. During active-drug treatment phase, none of the subjects had a medication intake of less than 88%.

Evaluation of the two 7-day food records showed that macronutrients, cholesterol, fiber, and alcohol were consumed similarly during both phases. Body weights remained constant during the entire course of the study (Table 2). Lipoprotein concentrations were virtually unchanged between placebo and active-drug treatment (Table 1). There was a slight increase in all lipoprotein fractions during active-drug treatment compared with placebo, none statistically significant. The post hoc calculated power of the study of 93.8% would have been able to detect differences in the primary study parameter of LDL-C of greater than or equal to – 0.429 mmol/L (– 16 mg/dL) between the 2 pills.

There were virtually no effects of garlic drug on the parameters of cholesterol metabolism (placebo vs active drug; mean [SD] values): cholesterol absorption (38.3% [10.7] vs 37.5% [10.5%], $P = .58$), cholesterol synthesis (13.4 [6.6] vs 12.7 [6.5] mg/kg of body weight per day, $P = .64$), or mevalonic acid excretion in urine (187 [66] µg/d vs 192 [66] µg/d, $P = .78$). Changes in the ratio of lathosterol to cholesterol were not statistically different during either treatment (garlic, 4.4% [24.3%]; baseline, 1.30 [0.42] µg/mg; placebo, 10.6% [21.1%]; baseline, 1.18 [0.35] µg/mg, $P = .62$). Simple linear regression analyses between changes in serum LDL-C and cholesterol absorption, cholesterol synthesis, mevalonic acid excretion, or the ratio of lathosterol to cholesterol revealed no significant correlations (cholesterol absorption, $r = 0.26$, $P = .22$; cholesterol synthe-

Table 2.—Average Daily Nutrient Intake as Assessed by 7-Day Food Records at the End of the Treatments*

	Placebo			Active Drug		
	Women	Men	All	Women	Men	All
Body weight, kg	69 (6)	80 (8)	74 (9)	70 (7)	80 (8)	74 (9)
Total energy, kJ/kg	122 (29)	151 (34)	134 (34)	126 (38)	147 (21)	134 (34)
Protein, %	15.3 (1.9)	13.5 (1.7)	14.5 (2.0)	14.3 (1.5)	14.5 (2.3)	14.4 (1.9)
Carbohydrates, %	44.0 (5.9)	44.0 (4.7)	44.0 (5.3)	46.4 (5.4)	42.5 (3.8)	44.7 (5.1)
Total fat, %	32.2 (5.1)	31.8 (5.8)	32.0 (5.3)	31.9 (3.9)	31.7 (3.9)	31.8 (3.8)
Saturated fat, %	12.6 (2.4)	12.8 (3.1)	12.7 (2.7)	13.0 (2.1)	13.2 (1.7)	13.0 (1.9)
Polyunsaturated fat, %	4.7 (1.0)	4.3 (0.6)	4.5 (0.9)	4.6 (0.9)	4.2 (0.8)	4.4 (0.9)
Alcohol, %	5.7 (5.8)	8.4 (5.1)	6.9 (5.6)	4.8 (4.8)	9.0 (5.0)	6.7 (5.2)
Fiber, g/d	26 (7)	33 (10)	29 (9)	28 (11)	31 (7)	29 (9)
Cholesterol, mg/d	342 (187)	315 (84)	330 (149)	264 (82)	337 (101)	296 (97)

*The data represent means (SDs). Macronutrients are presented as percentage of total energy intake.

sis, $r = 0.17$, $P = .43$; mevalonic acid excretion, $r = 0.11$, $P = .61$; ratio of lathosterol to cholesterol, $r = 0.05$, $P = .81$).

Comment

We evaluated the effects of a commercially available garlic preparation using a double-blind, randomized, placebo-controlled study design. No changes in serum lipoprotein levels in patients with moderate hypercholesterolemia were found. Although 2 meta-analyses and a recent study had shown small but significant effects of garlic on serum lipoprotein levels,[3,4,11] there were 2 other well-designed studies that found no influence.[7,9] Thus, the overall evidence for a positive effect of garlic on serum lipid levels is questionable.

We have addressed some new questions yet to be elucidated during treatment with garlic preparations. During trials with lipid-lowering substances, it is important to exclude changes in body weight or dietary habits, especially total calories, fat, and cholesterol content of the diet.

Earlier studies were often criticized for dosage, duration of treatment, and baseline cholesterol values. Most studies used dried garlic powder preparations in doses from 600 to 900 mg/d, the equivalent of 1.8 to 2.7 g/d of fresh garlic. Nonpowder preparations, however, seem according to the literature to have a stronger lipid-lowering effect than powder preparations, although their effects showed also a greater heterogeneity.[4] Few studies have used steam-distilled garlic oils or oil-macerated garlic.[20] These preparations contain only polysulfides and other volatile thioallyls. Based on comparisons of the content of active ingredients, the dosage of our study medication would be relatively high. The duration of treatment is assumed to be sufficient to document changes in serum lipoproteins. To circumvent the notion that garlic lowers only elevated cholesterol levels,[21] our baseline levels were high enough (cholesterol, 7.53 ± 0.75 mmol/L [291 ± 29 mg/dL] and LDL-C, 5.35 ± 0.78 mmol/L [207 ± 30 mg/dL]). Although the effects of garlic on serum lipoprotein levels have been studied extensively, very little is known about its possible mechanism of action. In vitro data in rat hepatocytes suggest that allicin and ajoene inhibit cholesterol synthesis at various steps or inhibit acetate uptake into liver cells, respectively.[22,23] Validated in vivo methods for measurement of cholesterol synthesis in humans include the sterol balance technique, the determination of mevalonic acid in 24-hour urine, and the measurement of sterol precursors in serum.[24] It has been shown that the ratio of the cholesterol precursor lathosterol to cholesterol in serum is a reliable indicator of cholesterol synthesis because it closely reflects the activity of hepatic 3-hydroxy-3-methylglutaryl coenzyme A reductase.[18] In this study an influence of garlic on cholesterol synthesis, based on determinations of 3 indicators, could be excluded. Furthermore, it could be shown that absorption of cholesterol was not affected by garlic. On the basis of these findings, it can be concluded that cholesterol metabolism at multiple metabolic sites is not influenced by garlic at least with the pharmaceutical formulation used in this study. Moreover, individual changes in the effect of garlic on LDL-C concentrations did not correlate with any of the parameters of cholesterol metabolism, so that the conjecture of possible specific effects that are overridden by counterbalancing effects seems to be excluded.

Based on a meta-analysis from 1994, the total patient experience in randomized trials amounted to only 1365 individuals until then. This is a surprisingly low number, assuming that garlic may be effective in reducing elevated lipid levels without harmful side effects. Based on the results of the present study, however, there is no evidence to recommend garlic therapy for lowering serum lipid levels.

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