Effect of Garlic on Lipid Profile and Psychopathologic Parameters in People with Mild to Moderate Hypercholesterolemia

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Abstract

Background: The beneficial effect of 3-hydroxy-3-methylglutyaryl co-enzyme A reductase inhibitors on cardiovascular risk reduction has been clearly established. Concerns have been raised that lowering blood cholesterol by other hypolipidemic drugs or by a non-pharmacologic approach may have deleterious effects on psychopathologic parameters. Garlic is one of the most commonly used herbal remedies and is considered to have hypocholesterolemic as well as other cardioprotective properties. Its effect on psychopathologic parameters has never been reported.

Objectives: To evaluate the effect of garlic on lipid parameters and depression, impulsivity, hostility and temperament in patients with primary type 2 hyperlipidemia.

Methods: In a 16 week prospective double-blind placebo-controlled study, 33 patients with primary hypercholesterolemia and no evidence of cardiovascular disease were randomly assigned to receive either garlic or placebo. Garlic in the form of alliin 22.4 mg/day was given to 13 patients, and placebo to 20. Both groups received individual dietary counseling. The changes in lipid profile and the various psychopathologic parameters were determined at the beginning and end of the trial. The differences in lipid parameters were evaluated by Student's *t*-test. The psychological data were analyzed by one-way analysis of variance (ANOVA) with repeated measures and Neuman-Keuls test.

Results: No significant changes were observed in levels of total cholesterol, low density lipoprotein-cholesterol, high density lipoprotein-cholesterol and triglycerides, or in the psychopathologic parameters evaluated.

Conclusion: Short-term garlic therapy in adults with mild to moderate hypercholesterolemia does not affect either lipid levels or various psychopathologic parameters.

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Coronary artery disease and atherosclerosis are the leading causes of morbidity and mortality in the western world. Lowering cholesterol levels is known to be an effective preventive measure of atherosclerosis, reducing both coronary and all-cause mortality in patients with established coronary disease. However, the effect of hypocholesterolemic therapy on primary prevention of atherosclerosis is still controversial. In some trials, hypocholesterolemic drugs decreased the coronary risk, but total mortality was not reduced significantly or it even increased [1]. Therefore, the National Cholesterol Education Program recommends less aggressive measures for primary than for secondary prevention. Specifically, patients with low coronary risk should initially be managed for a few months with a dietary and non-pharmacologic approach, and only then, if low density lipoprotein-cholesterol has not reached target level, is a hypocholesterolemic drug added [2].

Concerns about untoward effects of cholesterol-lowering therapy on mortality were first raised in two primary prevention trials, the Coronary Primary Prevention Trial [3] and the Helsinki Heart Study [4]. In both, the reduction in coronary artery disease mortality expected from the hypolipidemic drug (bile acid sequestrant in the Coronary Primary Prevention Trial and gemfibrozil in the Helsinki Heart Study) was offset by an unexpected increase in non-cardiovascular death. At least part of the excessive mortality was attributed to various unnatural causes, such as suicide, depression, and car accidents. More recent prevention (primary and secondary) studies using 3-hydroxy-3-methylglutaryl co-enzyme A reductase inhibitors did not show a significant increase in non-cardiovascular mortality [5,6]. However, in none of them were psychopathologic parameters specifically investigated. Only a very few, mostly short-term studies have prospectively studied the effect of HMG CoA reductase inhibitors on psychological variables, and their results varied from no effect to deleterious effects such as aggression, guilt feelings, hostility and depression [7–10]. Some of these effects appeared late, even a year after the start of drug therapy.

A non-pharmacologic hypolipidemic therapy has been associated with increased aggressiveness in animals [11–13] and may affect cognitive function in humans [14,15]. Garlic is one of the most popular herbal remedies and is steadily gaining interest in complementary and alternative medicine practice. There is a general belief that garlic is an effective and harmless mode of lowering cholesterol. This effect has not been linked to inhibition of HMG CoA reductase and is presumably due to a different mechanism of action. Garlic has also been attributed with other protective cardiovascular effects (antihypertensive, anti-inflammatory, beneficial effects on blood rheology and coagulability), some of which may be independent of its cholesterol-lowering effect [16,17]. Reports on the effect of herbal therapy on psychologic parameters are scarce, and to the best of our knowledge there are no studies at all on garlic supplementation in this context. The aim

HMG CoA = 3-hydroxy-3-methylglutaryl co-enzyme A

of the present study was to prospectively investigate the effect of garlic, when prescribed as a dietary adjunct, on psychopathologic parameters in people with mild to moderate hypercholesterolemia.

Patients and Methods

Patients

Thirty-nine patients with primary hypercholesterolemia were recruited from the outpatient Hyperlipidemia Clinic of the Rabin Medical Center. Primary hypercholesterolemia was defined as an LDL-cholesterol level of 130–190 mg/dl after at least 4 weeks of generalized dietary modification. Other entry criteria were age 18–80 years, no previous cardiovascular disease, triglyceride level <400 mg/dl, and no intake of any hypolipidemic drugs for at least 6 weeks prior to the study. Excluded were patients with diabetes mellitus, serum creatinine level >2 mg/dl, serum liver transaminase level above the upper normal range, nephrotic syndrome, uncontrolled hypothyroidism, marked obesity (body mass index >32 kg/m^2), history of alcoholism or psychiatric disturbances, malignancy diagnosed during the previous 3 years, and concomitant therapy with any drug that may affect the lipid profile. The study was approved by the local Ethics Committee, and each participant signed an informed consent form.

Protocol

A 16 week, double-blind, randomized, placebo-controlled design was used. At the baseline visit (week 0), physical examination was performed and serum levels of lipid profile, glucose, creatinine kinase and liver transaminase were checked. Participants were then randomly assigned to receive two tablets twice a day of either garlic powder (Inodiel, Arkopharma, France) (each tablet containing 5,600 g alliin) or a matched placebo. At this meeting, the patients were also given individually targeted dietary recommendations by a clinical dietitian, according to the American Heart Association step I guidelines. Daily intake of total cholesterol was reduced to <300 mg, saturated fatty acid to <10%, monounsaturated fatty acid to 10–15%, polyunsaturated fatty acid to <10%, carbohydrates to 50–60%, and protein to 10–20% of total caloric intake adjusted to the desired weight. The patients were seen after 2 weeks for dietary reinforcement and at 6, 10 and 16 weeks for blood tests, recording of dietary adherence, and further reinforcement. At each visit, drug compliance was determined by a pill count and adverse effects were recorded. Dietary compliance was qualified by a personal interview on a scale of 1 (poor) to 5 (excellent).

Methods

Serum lipid profile (total cholesterol, HDL-cholesterol, triglyceride) as well as other biochemical parameters were determined after a 12 hour overnight fast by standard methods. LDL-cholesterol level was calculated according to the Friedewald formula [18]. Psychological status was determined at the first and last visit by the following self-report questionnaires, all of which are considered sensitive and reliable:

- The Beck Depression Inventory [19], which evaluates the level of depression on the basis of affective, behavioral, cognitive and somatic symptoms and reflects continuous changes over time.
- The Buss-Durkee Hostility Inventory [20], which evaluates aggression according to four sub-scales: direct and indirect assault, irritability and negativism.
- The Impulse Control Scale [21], which evaluates impulsivity and comprises 15 items rated on a 3 point scale.
- The questionnaire of Strealu et al. [22], which evaluates temperament according to three sub-scales: reactivity, mobility and inhibition.

Statistical analysis

The difference in lipid parameters between the first and last visit was statistically evaluated with Student's *t*-test for independent variables (for differences between groups) and for paired observation (for differences within groups). The psychological data were analyzed by one-way analysis of variance with repeated measures and Neuman-Keuls test. Significance level for all statistical tests was $P < 0.05$. The correlation among the various emotional parameters was determined by product-movement correlations.

Results

The patient characteristics are shown in Table 1. Most of the participants did not use other drugs. Two patients (one in each group) had hypertension that was treated by felodipine, and four women (all in the placebo group) were receiving conjugated estrogen (n=2), ranitidine (n=1) or aldetronate (n=1). Six patients were excluded from the final analysis, one (study group) because of a failure to comply with follow-up, and another 5 (4 study group, 1 control) because of a failure to properly complete the psychological questionnaires at the last visit. Ages ranged from 38 to 68 years; about one-third of the participants were less than 50 years old, with almost equal division between the groups.

In each group, adherence to the diet was graded as 3 (good) or more in one-third of the participants. Overall, there was a small, non-significant change in weight. Drug compliance was >90% in both groups. No adverse biochemical effects were noted, and there were only a few subjective complaints, equally distributed between the groups.

The change in lipid profile is demonstrated in Table 2. A slight decrease in total and LDL-cholesterol, more pronounced during the first 10 weeks of the study, was noted in both groups. There was also a minor decrease in HDL-cholesterol. The change in triglyceride level was highly variable. None of these differences reached

Table 1. Patients' characteristics

	Garlic		Placebo	
	Week 0	Week 16	Week 0	Week 16
No. of patients	18	13	21	20
Male/female	8/10	6/7	9/12	9/11
Weight (kg)	69.3 ± 11.8	67.1 ± 11.6	70.1 ± 8.4	68.1 ± 8.1
Age (yrs)	52.4 ± 7.5	–	54.7 ± 7.5	–

Weight and age given as mean ± SD

LDL = low density lipoprotein
HDL = high density lipoprotein

Table 2. Change in lipid profile

	Garlic: Lipid profile (mg/dl) (% difference from baseline)					Placebo: Lipid profile (mg/dl) (% difference from baseline)				
Week	No. of patients	Total cholesterol	LDL-cholesterol	Triglycerides	HDL-cholesterol	No. of patients	Total cholesterol	LDL-cholesterol	Triglycerides	HDL-cholesterol
0	18	262.6 ±25.3	172.7 ±18.8	179.5 ±69.6	54.0 ±11.9	21	275.4 ±23.9	186.6±16.8	169.6 ±70.7	54.9±15.8
4	17	243.9 ±37.1	157.9 ±25.3	186.5 ±85.7	48.8 ±10.8	21	257.4 ±30.7	170.9±25.7	182.9 ±92.8	50.0±13.4
		(-7.2 ±10.5)	(-8.1 ±15.3)	(3.4 ±23.1)	(-9.2 ±9.3)		(-6.3 ±10.2)	(-8.2±13.1)	(13.3±85.0)	(-5.0 ±4.6)
10	17	248.6 ±36.6	161.3 ±22.3	189.2 ±82.7	49.5±9.6	21	256.5 ±31.1	169.3±24.3	120.1 ±72.3)	51.2±12.5
		(-5.4 ±9.3)	(-6.3 ±11.5)	(7.0 ±26.1)	(-7.4 ±7.8)		(-6.8 ±8.5)	(-8.9±12.4)	(-29.2±53.4)	(-5.7 ±9.5)
16	13	259.6 ±38.6	171.0 ±28.3	231.4 ±13.9	49.8±13.3	20	267.7 ±29.6	182.0±23.5	157.9 ±44.3	54.0±11.9)
		(-0.7 ±9.9)	(-0.1 ±14.7)	(30.1±53.3)	(-7.7 ±10.7)		(-2.8 ±11.2)	(-2.7±15.1)	(-6.9 ±29.0)	(-0.2 ±9.8)

All values are mean ± SD.

Table 3 Changes in psychopathologic parameters

		Garlic group		Placebo group		
Parameter		Week 0 (n=20)	Week 16 (n=13)	Week 0 (n=21)	Week 16 (n=20)	F
Depression		6.56±8.02	7.65±8.65	6.56±8.02	5.21±6.04	2.06 (NS)
Impulsivity		3.27±0.28	3.26±0.28	3.12±0.24	3.17±0.21	1.03 (NS)
Hostility						
Direct assault		1.77±0.21	1.76±0.27	1.71±0.21	1.68±0.24	0.89 (NS)
Indirect assault		1.52±0.22	1.52±0.17	1.53±0.16	1.49±0.17	0.51 (NS)
Irritability		1.62±0.21	1.61±0.23	1.60±0.17	1.62±0.18	0.24 (NS)
Negativism		1.72±0.32	1.71±0.28	1.74±0.25	1.71±0.28	0.10 (NS)
Temperament	Reactivity	1.23±0.18	1.29±0.16	1.29±0.19	1.23±0.17	6.9 (NS)
	Mobility	1.34±0.11	1.30±0.9	1.34±0.13	1.31±0.14	0.11 (NS)
	Inhibition	1.30±0.14	1.32±0.1	1.31±0.1	1.33±0.1	1.52 (NS)

All scores are given as mean ± SD.
NS = not significant.

statistical significance within or between groups. Similar results were obtained on intention-to-treat analysis of all 39 patients who participated in the study (data not shown). In none of the psychological parameters investigated was a statistically significant difference observed between baseline and end-of-study values [Table 3].

Discussion

Many studies, mostly short term, have investigated the hypolipidemic effect of garlic. Results were conflicting, ranging from a non-detectable to a statistically significant hypocholesterolemic effect [23,24]. These differences may be attributable to various causes, such as differences in study design (not all were randomized, double-blind placebo-controlled) and in characteristics of the participants (especially with regard to lipid profile, dietary modification, and compliance). Another possible confounder is the type of garlic preparation used (aged garlic extracts, dehydrated powdered garlic, steam-distilled garlic oil), which could yield different amounts of the active compound. The cholesterol-lowering effect of garlic is attributed to the bioavailability of allicin and its derivatives. In our short-term, randomized, double-blind placebo-controlled study, we used the odorless precursor, alliin, which is converted by the enzyme alliinase to the sulfur-containing active component allicin. The daily dose employed (22,400 g, alliin expected to yield 13,440 g of allicin) as well as the form of garlic chosen is considered sufficient to induce a hypolipidemic effect. We did not observe any significant difference in lipid profile between the garlic and placebo-treated groups. Our results are in accordance with the meta-analysis by Stevinson et al. [25] of 13 randomized double-blind placebo-controlled trials using various doses and various garlic preparations, which failed to find a significant reduction in total cholesterol. The slight decrease in total and LDL-cholesterol noted in our study in both groups during the early stage of the study was attenuated later, probably owing to a drop in dietary adherence towards the end of the study. The slight non-significant decrease (between the groups and within each group) that was noted in HDL-cholesterol level may be attributed to the dietary modification recommended to the participants. Since most of the participants were already following a hypolipidemic diet, the lack of significant difference in the lipid profile in the placebo group is not unexpected.

Because of the importance of a possible association of hypocholesterolemic drug therapy with adverse psychopathologic effects, especially in people whose coronary risk is not high, the initial approach to primary prevention is non-pharmacologic and based on dietary and lifestyle modifications. Though animal studies have shown that a low cholesterol diet increases aggression [11–13], dietary modifications in humans have not generally been associated with an untoward effect on psychological parameters [9,10]. However, Wing and colleagues [14] and Weidner et al. [15] noted possible effects on cognitive function. In our placebo group, treated only with a dietary approach, we did not observe significant psychological changes. Similarly, in our garlic-treated patients, we did not observe any significant effect of garlic on depression, impulsivity, hostility or temperament. Since, to the best of our knowledge this is the first study looking at the effect of garlic on psychopathologic parameters,

further confirmation of our finding will reassure that garlic therapy is psychologically harmless.

Our study has several limitations. The small sample size and relatively high drop-out rate, especially in the garlic group, reduced the statistical power. Because of the lack of a significant change in serum lipid level between the two groups, differentiating the cholesterol (or other lipid)-lowering effect (if it exists) of garlic from its effect on psychological function was impossible. Furthermore, some reports suggest that some psychological effects may be observed only after a longer duration than our study allowed [9,15]. Thus, our conclusion that garlic consumption does not have untoward effects should be taken with caution. More long-term studies with garlic as well as other more powerful hypolipidemic drugs, and a larger number of patients, are recommended. With regard to the public's growing interest in complementary medicine and the belief that garlic reduces some cardiovascular risk factors, its effect on coronary risk as well as on psychological parameters warrants further investigation.

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