Original Article

Lipid-Lowering Effects of Time-Released Garlic Powder Tablets in Double-Blinded Placebo-Controlled Randomized Study

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***Aim*: Clinical investigations of the effects of garlic preparations in hypercholesterolemia have demonstrated somewhat controversial results. These discrepancies may be due to the differences of the composition of garlic preparations and the biological response they may induce. The study was undertaken to test the hypothesis that garlic powder tablets with a prolonged mode of action promise potent biological effects.**

***Methods*: The lipid-lowering effects of time-released garlic powder tablets, Allicor (600 mg daily), were investigated in a double-blinded placebo-controlled randomized study in 42 men aged 35–70 with mild hypercholesterolemia.**

***Results*: Allicor treatment resulted in a moderate but statistically significant decrease in total cholesterol level that was observed after 8 and 12 weeks of active treatment. By the end of the study, total cholesterol in Allicor-treated patients had fallen by 7.6% ($p=0.004$) as compared to the level at randomization, and was 11.5% lower than the placebo group ($p=0.005$). LDL cholesterol in Allicor-treated patients fell by 11.8% ($p=0.002$) and 13.8% ($p=0.009$), respectively. HDL cholesterol also increased significantly after 8 and 12 weeks of treatment. By the end of the study, HDL cholesterol in Allicor-treated patients had increased by 11.5% ($p=0.013$).**

***Conclusion*: The obtained results are in good agreement with trials that have demonstrated the cardioprotective action of garlic preparations and may be due to the use of a time-released form of garlic powder tablets that provides a prolonged biological effect.**

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Key words; Hypercholesterolemia, Garlic, Allicor, Placebo-controlled trial

Introduction

Atherosclerosis is a complex disease that develops due to many risk factors, including alterations in plasma lipid and lipoprotein levels, blood pressure regulation, platelet function, clotting factors, arterial smooth muscle cell metabolism, etc.[1)]. Among all risk factors of atherosclerosis, dyslipidemia is thought to be the most potent that greatly increases the risk of cardiovascular diseases[2, 3)]. The increased level of cholesterol in blood is an acknowledged major risk factor for cardiovascular disease and death in both men and women. The lipid hypothesis, formulated more than 25 years ago, proposed that reduction of plasma cholesterol would lead to a fall in coronary disease[4)]. Dietary therapy is the first step in the treatment of hyperlipidemia. The medicinal use of garlic (Allium sativum) dates back thousands of years, and it is still included in the traditional medicine of many cultures. Historically, there has been great interest in the role of garlic in reducing cardiovascular risk factors, but there was little scientific support for its therapeutic and

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pharmacologic properties until recently, when the antiatherosclerotic and cardiovascular-protective effects of garlic were extensively evaluated. Evidence from numerous studies demonstrates that garlic can bring about the normalization of plasma lipids, along with the enhancement of fibrinolytic activity, inhibition of platelet aggregation and reduction of blood pressure[5-8], however, contradictory results have also emerged, in part as a result of methodological shortcomings, the use of different garlic preparations or inadequate duration of the studies[9]. Many garlic-based products are presently on the market. They can be generally classified into four groups, i.e., garlic essential oil, garlic oil macerate, garlic powder and garlic extract. The manufacturing process can markedly influence the composition of garlic product. thus, the biological activity of different preparations may vary greatly. As compared to other garlic preparations, dehydrated garlic powder is thought to retain the same ingredients as raw garlic, both water-soluble and organic-soluble, although the proportions and amounts of various constituents may differ significantly. This study was performed to evaluate the lipid-lowering potency of a new garlic-based formulation, namely, time-released garlic powder tablets, in mildly hyperlipidemic men. We supposed that this form of garlic tablets would promise more potent pharmacological effects.

Subjects and Methods

Study Subjects

This study was a randomized double-blinded placebo-controlled clinical trial of 42 outpatient mildly hypercholesterolemic men aged from 35 to 70 years. The participants included in the study had not received lipid-lowering drugs for at least 3 months prior to the recruitment and had no diseases demanding continuous administration of beta-blockers, calcium antagonists, nitrates, sugar-lowering drugs or diuretics. The patients had a total plasma cholesterol level 5.8–7.0 mmol/L, LDL cholesterol level 3.5–4.6 mmol/L, and HDL cholesterol 0.65–1.95 mmol/L. Before randomization, there was an 8-week acclimatization period consisting of 4-week with a hypolipidemic diet and a 4-week hypolipidemic diet plus placebo (1 tablet twice a day) treatment. After the acclimatization period, the study participants were randomized either to time-released garlic powder tablets, Allicor (INAT-Farma, Russia), 600 mg daily (1 tablet twice a day), or placebo for 12 weeks. Both placebo and Allicor were coated tablets that appended identical with respect to outlook, taste and smell. To obtain equal distribution over the treatment groups and to enable statistical tests of effect, randomization was stratified according to age, total and LDL cholesterol level, fasting glucose level, systolic and diastolic blood pressure, smoking history, family history, body mass index, alcohol consumption and cardiovascular history at the baseline. Regular alcohol consumers and abusers were not included in the study. The baseline data on clinical and demographic characteristics of study participants at randomization are presented in **Table 1**. All participants received similar dietary and behavioral recommendations and followed the hypolipidemic diet through the study.

Table 1. Baseline data on clinical and demographic characteristics of study participants

Variable	Allicor (n=23)	Placebo (n=19)
Age, years	51.7 ± 2.0	51.7 ± 2.5
Body mass index, kg/m^2	26.6 ± 0.5	27.0 ± 0.7
Total cholesterol, mmol/L	6.97 ± 0.20	7.04 ± 0.18
LDL cholesterol, mmol/L	5.00 ± 0.17	4.93 ± 0.18
HDL cholesterol, mmol/L	1.06 ± 0.07	1.20 ± 0.09
Triacylglycerols, mmol/L	2.00 ± 0.26	2.25 ± 0.20
Fasting glucose, mmol/L	4.71 ± 0.12	4.31 ± 0.20
Systolic BP, mm Hg	129.3 ± 4.6	128.6 ± 4.1
Diastolic BP, mm Hg	82.2 ± 2.3	83.7 ± 2.3
Current smokers, n (%)	9 (39)	7 (37)
History of angina, n (%)	10 (43)	8 (42)
History of myocardial infarction, n (%)	6 (26)	5 (26)
Family history, n (%)	5 (22)	4 (21)

Measurements of Biochemical Markers

Venous blood for lipid analysis was taken after overnight fasting at the baseline, after 4 weeks of dietary treatment, at randomization, and after 4, 8 and 12 weeks of the placebo-controlled treatment phase. To obtain serum, the blood was incubated for 1 h at 37℃ and centrifuged for 15 min at 1,500 g. Cholesterol and triacylglycerol levels were measured using commercial enzymatic kits (Boehringer Mannheim GmbH, Germany). Serum HDL cholesterol concentrations were measured after precipitation with magnesium chloride phosphotungstic acid reagent (Boehringer Mannheim GmbH, Germany). Serum LDL cholesterol was calculated as the difference between total cholesterol and the sum of HDL cholesterol and 1/2.3 triacylglycerols.

Statistical Analyses

Results are expressed in terms of the means and

Table 2. Changes in general clinical parameters during the study

Time	Allicor	Placebo
Systolic BP, mm Hg		
Randomization	143.4 ± 1.5	140.3 ± 1.8
12 weeks	136.8 ± 1.2*	139.4 ± 1.5
Diastolic BP, mm Hg		
Randomization	88.8 ± 0.9	87.9 ± 1.1
12 weeks	83.8 ± 0.7*	85.9 ± 1.0
White blood cells, $*10^9$/L		
Randomization	5.97 ± 0.15	6.08 ± 0.32
12 weeks	6.06 ± 0.14	5.88 ± 0.13
Hemoglobin, g/L		
Randomization	134.9 ± 1.0	128.9 ± 1.9
12 weeks	135.1 ± 1.0	127.4 ± 2.4
Erythrocyte sedimentation rate, mm/h		
Randomization	10.3 ± 0.5	8.3 ± 0.5
12 weeks	10.8 ± 0.6	9.1 ± 0.2
Alanine transaminase, mmol/L		
Randomization	22.1 ± 2.1	23.3 ± 1.9
12 weeks	25.5 ± 4.3	26.1 ± 3.0
Aspartate aminotransferase, mmol/L		
Randomization	18.5 ± 1.8	17.3 ± 1.2
12 weeks	19.0 ± 2.1	18.1 ± 1.9

*, significant difference from the level at randomization, paired samples *t*-test, $p < 0.05$.

Table 3. The dynamic of lipid changes during the placebo-controlled phase of the study

Time	Allicor	Placebo
Total cholesterol, mmol/L		
Randomization	6.97 ± 0.20	7.04 ± 0.18
4 weeks	6.87 ± 0.26	6.78 ± 0.22*
8 weeks	6.54 ± 0.24*	6.98 ± 0.23
12 weeks	6.41 ± 0.22*#	7.24 ± 0.18
Triacylglycerols, mmol/L		
Randomization	2.00 ± 0.26	2.25 ± 0.20
4 weeks	1.98 ± 0.30	2.11 ± 0.26
8 weeks	1.89 ± 0.24	2.01 ± 0.22
12 weeks	1.91 ± 0.21	2.06 ± 0.22
HDL cholesterol, mmol/L		
Randomization	1.06 ± 0.07	1.20 ± 0.09
4 weeks	1.13 ± 0.07	1.12 ± 0.09*
8 weeks	1.16 ± 0.08*	1.07 ± 0.10
12 weeks	1.17 ± 0.09*	1.16 ± 0.10
LDL cholesterol, mmol/L		
Randomization	5.00 ± 0.17	4.93 ± 0.18
4 weeks	4.84 ± 0.20	4.71 ± 0.18*
8 weeks	4.52 ± 0.21*	5.00 ± 0.20
12 weeks	4.37 ± 0.20*#	5.07 ± 0.16

*, significant difference from the level at randomization, paired samples *t*-test, $p < 0.05$; #, significant difference from placebo, independent samples *t*-test, $p < 0.05$.

S.E.M. Significance of differences was evaluated using the SPSS 10.1.7 statistical program package (SPSS Inc., USA) and defined at the 0.05 level of confidence. After examination of variable distribution, between-group comparisons of changes in lipid parameters were made using one-way ANOVA. Within-group effect assessments of changes in lipid levels from baseline to the mean of follow-up measurements were analyzed by Wilcoxon statistics and paired two-tailed *t*-test.

Results

At the baseline, the study participants were characterized by elevated total and LDL cholesterol levels, i.e. were mildly hypercholesterolemic. After the acclimatization phase when patients stayed on the hypolipidemic diet for 4 weeks and on the hypolipidemic diet plus placebo for an additional 4 weeks, a moderate but statistically insignificant decrease in total and LDL cholesterol was observed; at the same time, no significant changes occurred in HDL cholesterol and triacylglycerol levels. At randomization, groups totally comparable by biochemical, clinical and demographic variables were formed (**Table 1**). There were no side effects during the study period. Changes in general clinical parameters measured within the study protocol are slown in **Table 2**.

The results of the study demonstrate a significant difference between changes in lipid parameters occurring in Allicor-treated patients and placeborecipients with respect to total cholesterol ($p = 0.003$), LDL cholesterol ($p = 0.002$), and HDL cholesterol ($p = 0.034$), but not in triacylglycerols ($p = 0.201$). Allicor treatment resulted in a moderate but statistically significant decrease in the total cholesterol level that was observed 8 and 12 weeks after the placebo-controlled phase, but not after the first 4 weeks of treatment (**Table 3**). By the end of the study, total cholesterol in Allicor-treated patients had fallen by 7.6 ± 2.4%, $p = 0.004$ (95% CI: 2.7, 12.5), as compared to the level at randomization, and was 11.5% lower than the placebo group ($p = 0.003$). The same dynamic of changes was observed for LDL cholesterol levels. By the end of the study, LDL cholesterol in Allicor-treated patients had fallen by 11.8 ± 4.5%, $p = 0.002$ (95% CI: 4.5, 19.1), as compared to the level at randomization, and was 13.8% lower than the placebo

group ($p=0.002$). In placebo recipients, the changes in total and LDL cholesterol during the placebo-controlled phase did not reach statistical significance.

Allicor treatment also resulted in a significant increase in HDL cholesterol that was observed 8 weeks after placebo-controlled phase and maintained up to the end of the 12-week follow-up. By the end of the study, HDL cholesterol in Allicor-treated patients had increased by 11.5 ± 3.8%, $p=0.013$ (95% CI: 3.5, 19.4), as compared to the level at randomization. In placebo recipients, there were no significant changes in HDL cholesterol during the placebo-controlled phase.

Serum triacylglycerols fell both in Allicor-treated patients and placebo recipients by 7.7 ± 9.0% (CI: − 26.3, 10.9) and 7.8 ± 6.0% (CI: − 5.1, 20.6), respectively, but these changes did not reach statistical significance.

Discussion

The results of the present double-masked placebo-controlled randomized study demonstrate that time-released garlic powder tablets slow beneficial effects on blood lipid levels in mildly hyperlipidemic patients, namely, lower total and LDL cholesterol and increased HDL cholesterol.

With respect to the primary prevention of atherosclerotic diseases, normalization of blood lipids seems to be an effective way to reduce the risk of cardiovascular events[10, 11]. The scientific evidence in support of cholesterol-lowering therapy is incontrovertible. Questions remain that are related mostly to what and how treatment should be applied. From this point of view, the use of natural agents for atherosclerosis prevention is preferable, since it offers the possibility of long-term intervention that is safe and inexpensive. Some risk categories, such as mildly hyperlipidemic patients, are usually poorly motivated to take powerful lipid-lowering drugs like statins, but may easily trust agents of natural origin with a mild biological effect.

Several epidemiologic studies have indicated that certain diets with high garlic consumption are associated with a low risk of cardiovascular disease[12]. These studies demonstrated significant reductions in blood cholesterol and triglyceride levels after garlic ingestion[9, 13, 14].

Several clinical trials using commercially available garlic preparations have been conducted, and most of these used dried garlic powder. The majority of these studies demonstrated the lipid-lowering effects of garlic; some also showed a significant decrease in serum triglyceride levels[6, 15-17].

However, contradictory results exist that do not allow a conclusion on the beneficiary role of garlic-based preparations in the improvement of cardiovascular risk via normalization of blood lipids. Simons *et al*. demonstrated no significant effect of garlic powder tablets on plasma lipids in subjects with mild-to-moderate hypercholesterolemia[18]. The results of another study showed that dried garlic powder was less effective in reducing total cholesterol than had been suggested by previous meta-analyses[19, 20]. Issaacsohn *et al*. demonstrated that 12-week administration of garlic powder pills (Kwai) was ineffective in lowering cholesterol levels in patients with hypercholesterolemia[21]. It was shown by Berthold at al. that steam-distilled garlic oil preparation had no influence on serum lipoproteins[22].

The marked discrepancies rising from different clinical trials may be explained by the interference of several factors, such as a lack of consistency among studies in relation to dosage, standardization of garlic-based preparations and duration of treatment. It is known that allicin, a biologically active substance from garlic that is supposed to possess an antiatherosclerotic effect, is unstable and is very poorly absorbed on ingestion[23]. In addition, secondary compounds and metabolites that are formed in the body after the ingestion of garlic have not been well studied with respect to their lipid-lowering and antiatherosclerotic potency[24]. The manufacturing process can also markedly influence the composition of garlic products, and the proportions and amounts of various biologically active constituents may differ significantly[25, 26].

The results of our study are in good coincidence with trials that have demonstrated cardioprotective effects of garlic-based preparations, although the daily dosage of 600 mg was markedly lower than is usually used. These results seem to be due mostly to the use of the time-released form of garlic powder tablets that provides a prolonged biological effect. One tablet of a commercially available garlic-based dietary supplement "Allicor" contains 150 or 300 mg of dried garlic powder standardized to 1.3% allicin, and 300 mg tablets were used in this study. The technology of Allicor manufacturing implies a "slow-release" approach, and the prolonged effect of a single dose of Allicor that lasts for 8−12 hours and exceeds that of ordinary garlic powder tablets on blood serum atherogenicity and plasma fibrinolytic activity has been demonstrated[27-29].

Evidence obtained from this randomized placebo-controlled trial supports the suggestion that garlic has potential in the prevention and control of cardiovascular disorders due to its lipid-lowering mechanisms, which may strictly depend on the formulation

of the garlic preparation and duration of the biological effect. However, in spite of the beneficial results of our study, further controlled clinical trials with standardized preparations and known and established active constituents are required to estimate the usefulness of this remarkable botanical in reducing or preventing cardiovascular disease.

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References

1) Kannel WB, Neaton JD, Wentworth D, Thomas HE, Stamler J, Hulley SB, Kjelsberg MO: Overall and coronary heart disease mortality rates in relation to major risk factors in 325,348 men screened for the MRFIT. Multiple Risk Factor Intervention Trial. Am Heart J, 1986; 112:825-836
2) Donnell CJ, Kannel WB: Cardiovascular risks of hypertension: lessons from observational studies. J Hypertens Suppl, 1998; 16:3-7
3) Anderson KM, Odell PM, Wilson PW, Kannel WB: Cardiovascular disease risk profiles. Am Heart J, 1991; 121:293-298
4) Kannel WB, Castelli WP, Gordon T: Cholesterol in the prediction of atherosclerotic disease. New perspectives based on the Framingham study. Ann Intern Med, 1979; 90:85-91
5) Bordia AK, Joshi HK, Sanadhya YK, Bhu N: Effect of essential oil of garlic on serum fibrinolytic activity in patients with coronary artery disease. Atherosclerosis, 1977; 28:155-159
6) Lau B, Lam F, Wang-Chen R: Effect of odor-modified garlic preparation on blood lipids. Nutr Res, 1987; 7:139-149
7) Harenberg J, Giese C, Zimmermann R: Effect of dried garlic on blood coagulation, fibrinolysis, platelet aggregation and serum cholesterol levels in patients with hyperlipoproteinemia. Atherosclerosis, 1988; 74:247-249
8) Phelps S, Harris WS: Garlic supplementation and lipoprotein oxidation susceptibility. Lipids, 1993; 28:475-477
9) Rahman K: Historical perspective on garlic and cardiovascular disease. J Nutr, 2001; 131:977S-979S
10) Shepherd J, Barter P: Lipid-lowering -- translating evidence into benefits. Atheroscler Suppl, 2002; 2:1-3
11) Shepherd J: A tale of two trials: The West of Scotland Coronary Prevention Study and the Texas Coronary Atherosclerosis Prevention Study. Atherosclerosis, 1998; 139:223-229
12) Stavric B: Role of chemopreventers in human diet. Clin Biochem, 1994; 27:319-332
13) Agarwal KC: Therapeutic actions of garlic constituents. Med Res Rev, 1996; 16:111-124
14) Ali M, Thompson M: Consumption of a garlic clove a day could be beneficial in preventing thrombosis. Prostaglandins Leukot Essent Fatty Acids, 1995; 53:211-212
15) Reuter HD, Koch HP, Lawson LD: Therapeutic effects of garlic and its preparations. In: Koch HP, Lawson LD, eds. Garlic. London, UK, Williams and Wilkins, 1996; 135-162
16) Steiner M, Khan AH, Holbert D, Lin RI: A double-blind crossover study in moderately hypercholesterolemic men that compared the effect of aged garlic extract and placebo administration on blood lipids. Am J Clin Nutr, 1996; 64:866-870
17) Morcos NC: Modulation of lipid profile by fish oil and garlic combination. J Natl Med Assoc, 1997; 89:673-678
18) Simons LA, Balasubramaniam S, von Konigsmark M, Parfitt A, Simons J, Peters W: On the effect of garlic on plasma lipids and lipoproteins in mild hypercholesterolaemia. Atherosclerosis, 1995; 113:219-225
19) Silagy C, Neil A: Garlic as a lipid lowering agent--a meta-analysis. J R Coll Physicians Lond, 1994; 28:39-45
20) Neil HA, Silagy CA, Lancaster T, Hodgeman J, Vos K, Moore JW, Jones L, Cahill J, Fowler GH: Garlic powder in the treatment of moderate hyperlipidaemia: a controlled trial and meta-analysis. J R Coll Physicians Lond, 1996; 30:329-334
21) Isaacsohn JL, Moser M, Stein EA, Dudley K, Davey JA, Liskov E, Black HR: Garlic powder and plasma lipids and lipoproteins: a multicenter, randomized, placebo-controlled trial. Arch Intern Med, 1998; 158:1189-1194
22) Berthold HK, Sudhop T: Garlic preparations for prevention of atherosclerosis. Curr Opin Lipidol, 1998; 9:565-569
23) Lawson LD, Ransom DK, Hughes BG: Inhibition of whole blood platelet-aggregation by compounds in garlic clove extracts and commercial garlic products. Thromb Res, 1992; 65:141-156
24) Newall CA, Anderson LA, and Phillipson JD: Garlic. In: Newall CA, Anderson LA, Phillipson JD, eds. Herbal Medicines - A Guide for Health Care Professionals. Cambridge, UK: University Press, 1995; 129-133
25) Iberl B, Winkler G, Müller B, Knobloch K: Quantitative Determination of Allicin and Alliin from Garlic by HPLC*. Planta Med, 1990; 56:320-326
26) Amagase H, Petesch BL, Matsuura H, Kasuga S, Itakura Y: Intake of garlic and its bioactive components. J Nutr, 2001; 131:955S-962S
27) Orekhov AN, Tertov VV, Sobenin IA, Pivovarova EM: Direct anti-atherosclerosis-related effects of garlic. Ann Med, 1995; 27:63-65
28) Orekhov AN: New prospects for the treatment of atherosclerosis: garlic preparations. Ter Arkh, 1998; 70:75-78
29) Andrianova IV, Ionova VG, Demina EG, Shabalina AA, Karabasova IaA, Liutova LI, Povorinskaia TE, Orekhov AN: Use of allikor for the normalization of fibrinolysis and hemostasis in patients with chronic cerebrovascular diseases. Klin Med (Mosk), 2001; 79:55-58