Significance of Garlic and Its Constituents in Cancer and Cardiovascular Disease

Aged Garlic Extract Retards Progression of Coronary Artery Calcification[1,2]

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ABSTRACT Prospective epidemiologic studies have identified several risk factors for heart disease, and most can be the target of risk reduction interventions. The most widely recognized risk factors for atherosclerotic cardiovascular disease (ASCVD) include age, gender, cigarette smoking, sedentary lifestyle, elevated LDL, reduced HDL, hypertension, and diabetes. The consistency of associations between these factors and ASCVD risk across populations is substantial. Our understanding of the pathogenesis and etiology of coronary ASCVD, as well as its clinical implications, has grown tremendously over the past 20 y. The role garlic might play in treating ASCVD has been postulated for many years, but until recently no studies on garlic's ability to inhibit the atherosclerotic process have been reported. A pilot study evaluating coronary artery calcification and the effect of garlic therapy in a group of patients who were also on statin therapy suggested incremental benefits. The implications of this study must be put in context of the potential importance of early atherosclerosis detection and prevention. J. Nutr. 136: 741S–744S, 2006.

KEY WORDS: • *aged garlic extract* • *atherosclerosis* • *cardiovascular* • *electron beam tomography* • *calcification*

Calcification and atherosclerosis. Calcium deposition in the walls of coronary arteries is an active process, rather than a simple mineral precipitation in the atheromatous plaque (1). Calcification has been shown to be an early feature of atherosclerotic plaque formation, beginning with fatty-streak formation and continuing throughout the natural history of the plaque (2). In 1959, Blankenhorn reported an association between coronary calcification (CC)[4] and atherosclerotic cardiovascular disease (ASCVD) at autopsy (3). Since then, at least 6 other autopsy studies involving >2500 hearts, have confirmed these initial findings. Several investigators have found a significant correlation between amount of coronary calcium and amount of atherosclerosis. These investigators used measurements of plaque volume rather than stenoses, and demonstrated, through the results of autopsies, that there was a consistent and direct relation between calcium and plaque volume (4–6). Similarly, in vivo studies have demonstrated a linear relationship between CC and ASCVD plaque burden (7,8). Recently Mintz et al. (9) evaluated patients using intravascular ultrasound and electron beam tomography and found a strong relationship between calcification and plaque burden.

Electron beam computed tomography. There has been great interest in the development of noninvasive imaging techniques to detect the presence or absence of atherosclerosis. One approach that has recently gained particular attention, and is being used in several NIH studies of subclinical atherosclerosis, is CC as measured by electron beam computed tomography (EBCT). As opposed to other noninvasive modalities to diagnose coronary artery disease (CAD) by focusing on physiologic consequences of coronary obstruction, coronary calcium represents an anatomic measure of plaque burden (10). There is general agreement that CC as measured by EBCT provides a useful measure of atherosclerosis for population studies. It is noninvasive and readily applicable for routine use; it demonstrates sufficient accuracy and reproducibility, and it correlates with angiographic or pathologic evidence of CAD.

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[4] Abbreviations used: AGE, aged garlic extract; ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CC, coronary calcification; EBCT, electron beam computed tomography.

The presence of CC is nearly 100% specific for atheromatous coronary plaque. Because both obstructive and nonobstructive lesions have calcification present in the intima, CC is not specific to obstructive disease (11). Studies have demonstrated a direct relationship between coronary-artery calcium as measured by EBCT and histologic (12,13) and in vivo intravascular ultrasound (14) measures of atheromatous plaque. In a multicenter study, it has been demonstrated that CC by EBCT correlates well with angiographic stenosis (15), with progressively higher scores found in nonobstructive, and 1-, 2- and 3-vessel obstructive CAD. Guerci et al. (16) demonstrated a strong correlation between the square root of the total EBCT calcium score and maximum percent luminal coronary stenoses in a small group of asymptomatic patients undergoing diagnostic coronary angiography. Rumberger (17) analyzed studies of symptomatic patients and demonstrated calcium scores with 90% specificities for variable degrees of angiographic stenosis. Thus, in both symptomatic and asymptomatic populations, correlative studies have demonstrated a relationship between the CC score and the severity of underlying disease.

The most powerful information regarding the utility of the EBCT calcium score relates to its prognostic ability regarding cardiovascular events. The greatest potential for coronary calcium detection is as a marker of coronary heart disease risk. A number of large studies have reported that the presence of CC is an independent predictor of coronary heart disease risk after controlling for coronary heart disease risk factors (18–21). In all studies to date, the extent of CC was an independent and incremental estimator of coronary events over and above age, gender, and traditional cardiovascular risk factors. These studies demonstrate that persons with significant CC (scores >100) have a 10- to 20-fold greater risk of future coronary events. Published guidelines state that "[t]he resulting calcium score is an important parameter to detect asymptomatic individuals at high risk for future CVD [cardiovascular disease] events, independent of the traditional risk factors" (22). Numerous professional organizations, including the National Cholesterol Education Panel, American Heart Association, American College of Cardiology, and European Society of Cardiology, in both guidelines and expert consensus documents, have extended the recommendation for its use in clinically selected intermediate coronary heart disease risk patients (e.g., those with a 10–20% Framingham 10-y risk estimate) to refine clinical risk prediction (23–27).

EBCT calcium scanning has achieved a substantial degree of standardization, allowing for use in randomized trials and across centers. It possesses an ease of implementation sufficient to make it applicable to population-based and multicenter studies of ASCVD. The reproducibility of calcium measurements is essential to assess progression or regression of disease and to conduct longitudinal studies. EBCT inter-scan, inter- and intraobserver variability has been extensively studied, with reproducibility varying from moderate (28) to excellent (29–31) (r = 0.96–0.99). With excellent inter- and intraobserver variability (~1–3%), this test can measure plaque burden and follow atherosclerosis over time. Using new gating algorithms, EBCT inter-scan variability has been shown to be ~11% (32). Furthermore, with its ability to estimate total plaque burden, the tool has been demonstrated to be ideal for measuring the progression, stabilization, or regression of coronary plaque noninvasively.

Several studies have demonstrated a decrease in EBCT-measured calcium volume in patients treated with statin drugs (33). Callister enrolled 149 patients with hypercholesterolemia who underwent 2 EBCT scans after a minimum of 12 mo. Sixty percent of the subjects, having achieved LDL reductions to <120 mg/dL, showed EBCT stabilization (regression or no increase) of coronary atherosclerosis compared with subjects whose LDL cholesterol was not reduced to <120 mg/dL ($P <$ 0.001). A second study followed 274 patients with various cardiovascular risk factors who were scanned twice at least 1 y apart. Of 123 patients with hyperlipidemia, 61 were on statin therapy, and 62 reported no therapy. Those patients reporting use of a statin had an annual progression rate of 16%, compared with a 39% annual increase in the EBCT score for the untreated group ($P < 0.01$) (34). In large studies of progression, annual changes in calcium scores measured by EBCT predict the progression of CAD; EBCT-measured progression of CC ([>]15% per year) is associated with a 13-fold greater risk of cardiac events (35,36).

Garlic and atherosclerosis. Several clinical reports, including meta-analyses, have revealed cholesterol-lowering effects of garlic supplementation in humans (37,38). Such reports have strongly affected public awareness of the cholesterol-lowering effect of garlic. Recent studies of aged garlic extract (AGE) have shown it to be a modulator of multiple cardiovascular risk factors (39), such as blood pressure, platelet aggregation and adhesion, total cholesterol, LDL, HDL, LDL oxidation, smoking-caused oxidative damages, and directly suppressed atherosclerosis (40–43). In addition, AGE has been demonstrated to improve endothelial function (44), inhibit endothelial cell damage, and transform smooth muscle cells (45). This suggests that AGE may have an effect on controlling arterial function through inhibiting the damage of nitric oxide synthesis (46). Thus, garlic and extracts have been postulated to impart cardiovascular benefits through multiple mechanisms.

We performed a placebo-controlled, double-blind, randomized pilot study to determine whether the atherosclerotic plaque burden detected by electron beam tomography will change at a different rate under the influence of AGE as compared with a placebo (47). Twenty-three high-risk patients were enrolled, and 19 (14 men, 5 women, with a mean age of 59.9 ± 10.5 y) completed the 1-y study protocol. Subjects received 4 mL of AGE (1200 mg) or the equivalent amount of placebo. All patients were on, and maintained, a stable course of statin therapy and aspirin during the course of the study. Of the 19 patients who completed the study protocol, 9 were randomized to AGE, and 10 to placebo. *S*-allyl cysteine, one of the active compounds of AGE, was measured in the blood as a compliance marker. *S*-allyl cysteine serum measurement is currently the only reliable human compliance marker used for studies involving garlic consumption, since it is detectable and quantitatively increases in the blood after oral intake of garlic capsules (48).

The mean change and absolute difference in the calcium score (volumetric method) for the AGE group was 7.5 ± 9.4% and 45.2 ± 57.2 over the year, respectively. The placebo group exhibited a mean increase in calcium scores of 22.2 ± 18.5% and 129.0 ± 102.1, significantly greater than the treated cohort ($P = 0.046$ and 0.045, respectively). All patients in this study were on statin therapy; thus the improvement seen under the influence of garlic suggests incremental benefit to statin therapy in this small study. The study shows that patients on placebo (with statin baseline therapy) progressed at a rate of 22.2% per y, while the addition of AGE reduced progression to 7.5%. Calcium scores did not correlate with measures of glutathione and lipid peroxidation at entry. Lipid peroxidation significantly decreased at follow-up period in both groups. Although the homocysteine changes did not achieve significance in this small study, there was a favorable trend.

Changes in baseline values over 1 y as observed under the influence of both AGE and placebo are shown in **Table 1**.

TABLE 1

Changes in values over one year under the influence of therapies[1]

	AGE (n = 9)	Placebo (n = 10)	P
Volume calcium score	45.2 ± 57.2	129.0 ± 102.1	0.0445
% Change (volume)	7.5 ± 9.4	22.2 ± 18.5	0.0464
Agatston calcium score	71.1 ± 95.8	151.6 ± 126.5	0.1401
% Change, Agatston	11.5 ± 16.8	21.1 ± 18.9	0.2628
Lipid peroxidase	−0.28 ± 0.20	−0.20 ± 0.10	0.2787
GSH,[2] micrograms/ 10^{10}RBC	−0.9 ± 108.0	−26.4 ± 102.7	0.6056
White blood count	−0.2 ± 1.90	−0.95 ± 1.85	0.3960
Hematocrit	−2.02 ± 3.02	−3.25 ± 2.58	0.3522
Platelet	3.2 ± 17.4	1.8 ± 42.6	0.9269
Sodium	3.33 ± 3.12	1.8 ± 6.65	0.5365
Potassium	−0.01 ± 1.15	−0.15 ± 0.64	0.7464
Glucose	14.3 ± 55.1	13.3 ± 50.8	0.9666
Creatinine	0.00 ± 0.00	0.01 ± 0.14	0.9152
AST[3]	1.89 ± 7.85	−4.6 ± 15.0	0.2620
Alkaline phosphatase	4.0 ± 12.1	−10.1 ± 25.2	0.1452
ALT[4]	0.11 ± 7.25	−2.6 ± 13.0	0.5876
Total cholesterol	7.0 ± 21.8	12.8 ± 25.9	0.6065
HDL	3.0 ± 10.6	−1.3 ± 13.8	0.4611
Cholesterol/HDL	−0.15 ± 1.04	0.79 ± 1.13	0.0763
LDL	−3.2 ± 16.2	21.9 ± 39.4	0.0932
Triglycerides	8.3 ± 42.6	29.5 ± 95.7	0.5500
Homocysteine	−1.77 ± 9.85	5.77 ± 7.75	0.0798
C-reactive protein	−0.10 ± 0.22	−0.13 ± 0.27	0.8464

[1] Values are means ± SD.
[2] GSH, glutathione.
[3] AST, aspartate aminotransferase.
[4] ALT, alanine aminotransferase.

All patients were taking a stable dose of statin and aspirin throughout the study. There were no significant changes in cholesterol parameters, homocysteine or C-reactive protein between the groups, although there was a trend toward improvement of cholesterol parameters and homocysteine (P = 0.07–0.09 for these measures, Table 1). There was also a trend (not significant) toward decreasing cholesterol/HDL ratios (P = 0.076).

Conclusion. Electron beam tomography is a noninvasive procedure and a well-validated tool for examining cardiovascular diseases, to measure precise quantity of CC, which is linearly correlated with the amount of associated atherosclerotic plaque, and track atherosclerotic plaque over time. Because AGE has been shown to have several potential anti-atherosclerotic properties, it was chosen as the agent of study to evaluate its ability to inhibit progression of coronary atherosclerosis. The exact mechanism by which garlic and AGE may inhibit atherosclerosis is still unknown. Campbell et al. (40) found a direct effect of AGE on atherosclerosis using both molecular techniques in vitro and in vivo models. The possible mechanisms by which garlic can inhibit coronary plaque formation are listed in **Table 2**. In general, intimal-cell hyperplasia followed by fatty streaks develops before arterial calcification. AGE may exert anti-atherogenic effects through inhibition of both smooth-muscle phenotypic change and proliferation and on lipid accumulation in the artery wall and into the macrophage. In addition, inhibiting damage of the endothelial cells and transforming smooth muscle cells as shown in the several studies using AGE suggest that AGE may have an effect of controlling arterial function and improving endothelial function through inhibiting the damage of nitric oxide synthesis. Data suggests garlic may increase glutathione levels and protection of endothelial cells by reducing oxidant stress, especially LDL oxidation, a recognized risk factor in cardiovascular disease (49).

It is of special interest that garlic was not given as an alternative, but rather in addition to statin drugs. Despite the small study size, patients given AGE demonstrated a significant slowing of the accumulation of coronary artery calcification during this randomized, placebo-controlled trial. The difference in progression was significant, whether measured by absolute plaque volume or percent change (**Fig. 1**). This was found to be complementary to the effects of statin therapy. This effect of AGE may be related with the reduction of multiple risk factors in cardiovascular diseases, such as homocysteine, LDL, LDL oxidation, blood coagulations, and others. Larger studies will be needed to validate this finding and to derive the mechanism by which garlic may provide cardiovascular benefit.

TABLE 2

Possible mechanisms by which garlic may inhibit atherosclerosis

Inhibition of stenosis caused by damage induced by balloon catheterization (in vivo)
Inhibition of cell transformation and cell growth in the smooth muscle cells (in vitro)
Inhibition of lipid accumulation into macrophage (foam cells) (in vitro)
Inhibition of LDL oxidation-caused endothelial cell damage in artery (in vitro)
Inhibition of LDL oxidation-induced free radical generation from damaged endothelial cells in artery (in vitro)
Inhibition of glutathione depletion from the endothelial cells (in vitro)
Activation of cNOS (in vitro)
Increase of Nitrous Oxide metabolites; cNOS activation (in vivo)
Lowering of cholesterol, raising of HDL cholesterol
Lowering blood pressure
Reduction of homocysteine
Improvement of endothelium function (in vivo)

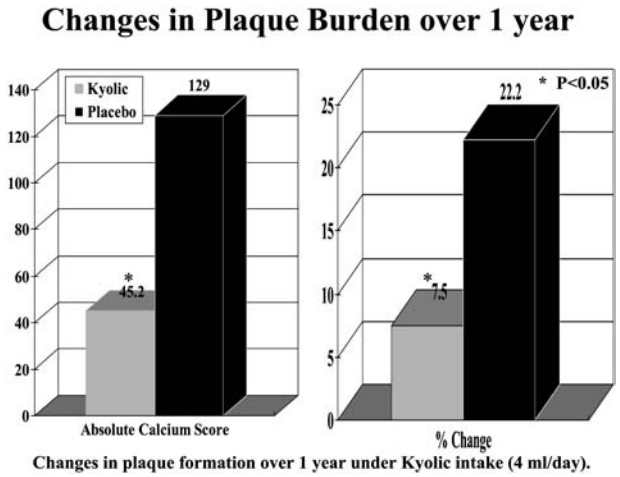

FIGURE 1 Changes in plaque burden over 1 y.

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