The Effects of Aged Garlic Extract on Coronary Artery Calcification Progression

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Abstract

Background: Aged Garlic Extract (AGE) has been shown to lower LDL, reduce the progression of coronary atherosclerosis, improve vascular function, and have a favorable effect on oxidative biomarkers. Since AGE has been shown to have several potential anti-atherosclerotic properties, including stimulation of microcirculation in peripheral arteries, it was chosen as the agent of study to evaluate its ability to inhibit progression of coronary atherosclerosis.

Objective: No study of sufficient power to date has evaluated the ability of AGE to inhibit vascular calcification, a marker of plaque formation in human coronary arteries. We sought to evaluate the ability of AGE to inhibit coronary artery calcium (CAC).

Methods: Four placebo-controlled, double-blind, randomized studies were pooled to determine whether the atherosclerotic plaque burden detected by CAC will change at a different rate under the influence of AGE as compared to placebo. 210 patients were enrolled, and 182 completed the study protocol. All participants underwent CAC scanning at baseline and at 12 months. A two-sample median test was used to compare medians of CAC progression between the garlic- and placebo-treated groups. CAC progression was also categorized into three groups (<15%, 15-20%, and >20%) prior to adjustment for age and gender.

Results: At 1 year, median CAC progression was significantly lower in the pooled AGE group (10.8, 95% Confidence Interval (CI) 0.0-30.7, n=106) than the placebo group (18.3, 95% CI 3.1-34.0, n=103; P=0.0385). There were no significant differences in individual serum cholesterol parameters or serum C-reactive protein levels between the groups. Further, after adjustment for age and gender, AGE was associated with a 1.78 fold (95% CI 0.320-0.990, P=0.046) reduction in CAC progression compared with placebo.

Conclusions: This pooled study indicates the ability of AGE to inhibit the rate of progression of coronary calcification, as compared to placebo, over 1 year independent of statin therapy or gender.

Keywords: Coronary artery disease; Garlic; Calcification

Abbreviations: AGE: Aged garlic extract; CT: Computed Tomography; CI: Confidence Interval; CAC: Coronary Artery Calcium; CAD: Coronary Artery Disease; dl: decilitre; HU: Hounsfield units; EBCT: electron beam computed tomography; LDL: low density lipoprotein; MI: Myocardial Infarction

Introduction

Several clinical reports, including meta-analyses, have revealed cholesterol-lowering effects of garlic supplementation in humans [1,2]. Such reports have increased public awareness on the potential cardiovascular benefits of garlic. Garlic and garlic extracts have been postulated to impart cardiovascular benefits through multiple mechanisms. AGE has been shown to lower low-density lipoproteins (LDLs) [3] reduce the progression of coronary atherosclerosis, improve vascular function, and have a favorable effect on oxidative biomarkers [4-6]. AGE has effects on coronary atherosclerosis by preventing smooth muscle cell transformation and proliferation, preventing entry of lipids into arterial walls and macrophages, and also directly suppressing atherosclerosis [7,8]. AGE has been shown to also have beneficial effects on arterial function by inhibiting endothelial cell damage, transforming smooth muscles cells, and inhibiting the damage of nitric oxide synthesis [9,10]. AGE helps to modulate cardiovascular risk factors by lowering blood pressure, inhibiting platelet aggregation and adhesion, lowering cholesterol, preventing LDL oxidation and smoking-induced oxidative damage [7,11,12].

Calcium deposition in the walls of coronary arteries is an active process, rather than a simple mineral precipitation in the atheromatous plaque [13]. 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 [14]. Several investigators have found a significant and direct correlation between amount of coronary calcium and amount of atherosclerosis [15-18]. Unlike other noninvasive modalities used to diagnose coronary artery disease (CAD) by focusing on physiologic consequences of coronary obstruction, CAC represents an anatomic measure of plaque burden [19]. There is general agreement that CAC provides a useful measure of atherosclerosis for population studies, and is the most predictive method for ascertaining risk in an asymptomatic cohort. It is a noninvasive procedure and a well-validated tool for examining cardiovascular diseases to measure precise quantities of coronary calcification, which is linearly correlated with the amount

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of associated atherosclerotic plaque. It has also been shown to be especially effective in quantifying trends of CAC over time [20].

Progression of calcified lesions in the wall of the coronary artery has been investigated as an active process of atherosclerosis, dependent upon multiple variables [21]. Since AGE has been shown to have several potential anti-atherosclerotic properties, including stimulation of microcirculation in peripheral arteries, it was chosen as the agent of study to evaluate its ability to inhibit progression of coronary atherosclerosis. Previous studies have shown that the progression of CAC, defined as clinically significant when the rate of change exceeds 15% per year based upon clinical outcomes studies, may provide incremental prognostic information beyond that provided by the baseline calcium score itself. Primarily, CAC progression has been shown to be the strongest predictor of cardiac events [22,23]. Raggi et al. suggested that continued accumulation of CAC in asymptomatic individuals is associated with increased risk of MI. CAC not only provides information regarding cardiovascular risk, but it can also be used to track progression of atherosclerosis over time [24-28].

It has been suggested that a synergistic effect exists between statin therapy and AGE in retarding progression of CAC. For example, in one observational study using non-contrast CT, 123 persons with hypercholesterolemia were followed [29]. This study showed that patients on placebo (with statin baseline therapy) progressed at a rate of 22.2% per year, and the addition of AGE reduced CAC progression to 7.5%, a reduction of over 66%. These results were supported by another study that found that patients given AGE demonstrated a significant slowing of the accumulation of coronary artery calcification. The difference in progression was significant, whether measured by absolute plaque volume or percent change. This was found to be complementary to the effects of statin therapy [30].

This study seeks to determine the rate of atherosclerotic plaque burden detected by CT under the influence of AGE or placebo, and the effectiveness of AGE in inducing regression or slowing progression in patients with established atherosclerosis.

Materials and Methods

Cohort/dataset

The present study is a combined analysis of four placebo-controlled, double-blinded studies that followed the same protocols. In total, all four studies combine to involve 210 patients with known coronary artery disease. The Investigational Review Board of Los Angeles Biomedical Research Institute at Harbor-UCLA approved this research project. All the patients signed informed written consent after careful explanation and review of the protocol. The patients were well matched for age, gender, statin use and cardiac risk factors. Inclusion criteria were known coronary artery disease or high risk for coronary artery disease, with a 10-year Framingham risk of developing coronary artery disease of >20%. Patients underwent CAC and blood testing at baseline, were randomized to AGE or placebo in a double-blinded manner. Patients were followed for compliance measures, blood pressure, and safety monitoring and blood samples. Repeat CAC was performed at the conclusion of the trial at 1 year of follow-up.

Aged garlic extract (AGE) and its administration

Aged Garlic Extract (AGE, Kyolic®), provided by Wakunaga of America Co., Ltd. (Mission Viejo, CA), was formulated by soaking sliced raw garlic in aqueous ethanol for up to 20 months at room temperature. The extract was then filtered and concentrated at low temperature. The AGE used in this trial contained 305 g/L of extracted solids. The liquid extract used in this study was identical to the liquid formulation available commercially.

After obtaining consent, each patient was seen at baseline for interview, physical examination and baseline blood tests. Baseline examination included screening for coronary disease utilizing non-contrast CT, as well as demographic and coronary risk factor measures (including biochemical markers). All participants were educated on a low-cholesterol diet at entry to the study by the nurse coordinator. A physical examination was performed by the study physician. Baseline information regarding risk factors for atherosclerotic cardiovascular disease (cigarette smoking status, systemic hypertension, family history of premature atherosclerosis, menopausal and hormone replacement status in women, sedentary lifestyle, current medications, chest pain questionnaire and measures of obesity) was determined by interview and measurement of cardiovascular risk factors, including blood pressure, fasting lipids, fasting blood sugar, homocysteine and ultra-sensitive C reactive protein. The patients were questioned quarterly as to their garlic intake from food sources, including allium vegetables and nutritional supplements, and instructed to avoid any direct form of garlic supplementation. Each subject had blood drawn after a 12-h fast. In all subjects, a blood sample of approximately 30 mL was drawn from an arm vein by the phlebotomist. The sample was centrifuged and the serum separated. Samples were stored at 70°C. Participants were instructed to self-administer the AGE or placebo. The dose of AGE for each of the four studies were as follows: 1) AGE Liquid: 4 mL/day; 1200mg AGE; 2) Kyolic 108 (AGE with B-Vitamins): 4 capsules/day: 1000 mg AGE powder; 3) Kyolic 110 (AGE with CoQ10): 4 caps/day: 1200 mg AGE powder; 4) AGE: 4 capsules/day: 1200 mg AGE powder.

After randomization, participants returned at 3, 6, 9 and 12 months to have measures of biochemical serum markers and to assess compliance with medication. Bottles were collected and unused portions were measured and noted. At the 12-month visit, participant underwent repeat CAC scanning to assess for progression or regression of atherosclerosis.

Non-contrast computed tomography

CAC scanning was performed with an E-Speed electron beam scanner (EBCT) (GE-Imatron, South San Francisco, Calif., USA) or Volume CT (64-detector, GE Healthcare, Milwaukee WI). The coronary arteries were imaged with 30–40 contiguous 3 mm slices during mid-diastole using ECG-triggering during a 15 second breath hold. Total radiation exposure using this technique was <1 rad per patient. CAC was considered present in a coronary artery when a density of >130 Hounsfield units (HUs) was detected in ≥ 3 contiguous pixels (>1 mm²) overlying that coronary artery and was quantified using the described Agatston scoring method [31]. The total Agatston score was determined by summing the scores obtained for each lesion. Second, the calcium score was determined using the volumetric score by the method of isotropic interpolation [32,33]. All voxels with a value greater than 130 Hounsfield units were defined as the calcified lesion. A total score by the Agatston and volumetric methods was determined by summing individual lesion scores for each of four anatomic sites (left main, left anterior descending, circumflex, and right coronary arteries). CAC progression was defined as annual CAC progression >15% [34].

A single experienced investigator, blinded to clinical status of the participant and temporal relation of the scans, interpreted all studies on a commercially available software package (Neo Imagery Technologies, City of Industry, CA).
Statistical methods

All analyses were performed on the pooled data from the 4 placebo-controlled, double-blind, randomized studies. To compare the progression of CAC score between the groups of AGE and placebo, the percent change of CAC score per year was calculated as the annualized relative changes in the calcium score. The data was first analyzed using the Shapiro-Wilk normality test. Continuous variables were presented as mean ± SD or median (quartile 1, quartile 3), and categorical variables were presented as frequency (percentage). For variables with normal distributions, Student t test was used to determine the statistical significance between AGE and placebo groups. For the variables failing the normality test, statistical significance between groups was determined by nonparametric median test. Chi-square test was used to assess differences between groups of AGE and placebo for categorical variables. Unadjusted and adjusted ordinal logistic regression was performed to examine the relationship between the progression of CAC score (<15%, 15-50%, and ≥50%) and treatment groups (AGE vs. placebo). All statistical tests were two-tailed, with a P value < 0.05 considered statistically significant. All statistical analyses were performed using SAS software (SAS Institute, Cary, NC).

Results

Overall, we included 210 patients in the study. The median annual percent CAC score progression was significantly lower in the AGE group (10.8, 95% CI: 0.0-30.7, n=107) than the placebo group (18.3, 95% CI: 3.1-34.0, n=103) with a p-value of 0.0325 (Table 1). There were no significant differences in clinical risk factors between the treatment groups. However, adjustment for age and gender partially attenuated the finding between the annual percent progression of CAC score (<15%, 15-50%, and ≥50%) and treatment groups (AGE vs. placebo). All statistical tests were two-tailed, with a P value < 0.05 considered statistically significant. All statistical analyses were performed using SAS software (SAS Institute, Cary, NC).

Discussion

Non-contrast CT was utilized to measure calcium deposits within the coronary artery tree and have been shown to be highly predictive of future CV events. CAC deposits are influenced by lipid-lowering therapy and the rate of progression reflects the process of atherosclerosis [21,29].

Prior studies have shown progression of atherosclerosis is slowed under the influence of statin therapy. For example, in an observational study using CAC, 123 people with hypercholesterolemia were followed [29]. The participants reporting use of a statin (n=60) had an annual rate of progression of 15% compared with 39% annual increase in CAC score for the 62 persons in the placebo group (P=0.001).

However, another study showed that patients on placebo (with statin baseline therapy) progressed at a rate of 22.2% per year, and the addition of AGE reduced progression to 7.5%, a reduction of over 66% [4]. Despite the small study size, patients given AGE demonstrated a significant decrease in CAC accumulation during this randomized, placebo-controlled trial. The difference in progression was significant, whether measured by absolute plaque volume or percent change. This was found to be irrespective of the effects of statin therapy and gender.

Prior studies have shown that the progression of CAC, defined as clinically significant when the rate of change exceeds 15% per year, may provide incremental prognostic information beyond that provided by the baseline calcium score itself [22,23]. One study suggested that continued accumulation of CAC in asymptomatic individuals is associated with increased risk of MI; a change in volume score of ≥ 15% was recorded in 42 of 45 individuals who suffered an MI [22]. Furthermore, Taylor et al., in the sub-study of the Prospective Army Coronary Calcium project, have shown that among middle-aged healthy men with CAC, an increasing extent of non-calcified atherosclerosis was strongly associated with CAC progression during a 4-year period [35].

The exact mechanism by which garlic and AGE may inhibit atherosclerosis is still unknown. Campbell, Lau, and other researchers found a direct effect of AGE on atherosclerosis using both in vitro and in vivo models [9,10,36]. 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 [36]. 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.

| Table 1: Clinical Risk Factor Distribution by Treatment Group. |
| --- |
| **Age, years** | Total (n = 210, 100%) | Placebo (n = 103, 49.0%) | AGE Treatment (n = 107, 51.0%) | P-value |
| **Female, n (%)** | 36 (18.1) | 18 (17.5) | 20 (18.7) | 0.81 |
| **Statin, n (%)** | 76 (45.5) | 40 (50.0) | 36 (41.4) | 0.26 |
| **CACs Progression Ratio** | 15.6 (9.9, 32.8) | 18.3 (3.1, 34.0) | 10.8 (0.0, 31.6) | 0.0325* |

There is no significant difference between the treatment groups with regard to age, gender, or statin use. Data presented as Median (Quartile 1, Quartile 3), p-value from median test.

| Table 2: Pooled CAC Progression by AGE and Statin Treatment Groups. |
| --- |
| **No AGE/ Statin** (n = 36) | **AGE / No Statin** (n = 46) | **AGE / Statin** (n = 31) | P-value |
| **CACs Progression Ratio** | 12.8 (0.7, 27.9) | 11.1 (0.0, 34.7) | 15.6 (5.6, 31.6) | 0.94 |

Statin therapy does not have an appreciable influence on CAC progression. Data presented as Median (Quartile 1, Quartile 3), p-value from median test.

| Table 3: Pooled CAC Progression Distribution by Gender. |
| --- |
| **Female** (n = 35) | **Male** (n = 148) | P-value |
| **CACs Progression Ratio** | 8.9 (0.0, 29.4) | 16.4 (4.0, 33.2) | 0.20 |

Gender does not influence CAC progression. Data presented as Median (Quartile 1, Quartile 3), p-value from median test.
function through inhibiting the damage of nitric oxide synthesis [10,30]. Data suggest garlic may increase glutathione levels and protection of endothelial cells by reducing oxidant stress, especially LDL oxidation, a recognized risk factor in cardiovascular disease [13].

There are other postulated benefits of garlic that may have played a role. We have previously demonstrated that homocysteine level is a factor in progression of CAC [37], Yeh et al. showed a significant reduction of homocysteine levels by AGE administration in animals. Since AGE contains many sulfur compounds and homocysteine is a metabolite of methionine, a sulfur-containing amino acid, there may be a possible relationship between homocysteine metabolism and AGE.

Our prior studies [4,5,38,39] were limited by their relatively small size. This current study possesses sufficient power to demonstrate a definitive inverse relationship between AGE and CAC progression irrespective of statin therapy and gender. The patients given AGE exhibited a significant slowing of the accumulation of CAC as compared to placebo during this randomized, double-blind, placebo-controlled trial.

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