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Aged Garlic Extract Reduces Low Attenuation Plaque in Coronary Arteries of Patients with Metabolic Syndrome in a Prospective Randomized Double-Blind Study

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Abstract

Background: Although several previous studies have demonstrated that aged garlic extract (AGE) inhibits the progression of coronary artery calcification, its effect on noncalcified plaque (NCP) has been unclear.

Objective: This study investigated whether AGE reduces coronary plaque volume measured by cardiac computed tomography angiography (CCTA) in patients with metabolic syndrome (MetS).

Methods: Fifty-five patients with MetS (mean ± SD age: 58.7 ± 6.7 y; 71% men) were prospectively assigned to consume 2400 mg AGE/d (27 patients) or placebo (28 patients) orally. Both groups underwent CCTA at baseline and follow-up 35 ± 41 d apart. Coronary plaque volume, including total plaque volume (TPV), dense calcium (DC), NCP, and low-attenuation plaque (LAP), were measured based upon predefined intensity cutoff values. Multivariable linear regression analysis, adjusted for age, gender, number of risk factors, hyperlipidemia medications, history of coronary artery disease, scan interval time, and baseline %TPV, was performed to examine whether AGE affected each plaque change.

Results: The %LAP change was significantly reduced in the AGE group compared with the placebo group (−1.5% ± 2.3% compared with 0.2% ± 2.0%, P = 0.0049). In contrast, no difference was observed in %TPV change (0.3% ± 3.3% compared with 1.6% ± 3.0%, P = 0.13), %NCP change (0.2% ± 3.3% compared with 1.4% ± 2.9%, P = 0.14), and %DC change (0.2% ± 1.4%, compared with 0.2% ± 1.7%, P = 0.99). Multivariable linear regression analysis found a beneficial effect of AGE on %LAP regression (β: −1.61; 95% CI: −2.79, −0.43; P = 0.008).

Conclusions: This study indicates that the %LAP change was significantly greater in the AGE group than in the placebo group. Further studies are needed to evaluate whether AGE has the ability to stabilize vulnerable plaque and decrease adverse cardiovascular events. This trial was registered at clinicaltrials.gov as NCT01534910.


Keywords: garlic, atherosclerosis, progression, cardiac ct, randomized trial

Introduction

Metabolic syndrome (MetS) is a constellation of metabolic abnormalities that includes features of obesity, hypertension, hyperlipidemia, and impaired glucose tolerance. Approximately 20% of the US population is diagnosed with MetS (1). MetS is associated with subclinical cardiovascular disease; nearly one-half of patients diagnosed with coronary artery disease (CAD) are also diagnosed with MetS (2, 3). For this condition, the Adult Treatment Panel III recommends adopting a healthy lifestyle and also effectively managing each cardiovascular disease risk factor through the use of clinically established medications such as aspirin, angiotensin-converting enzyme inhibitors, and statins (4). Furthermore, dietary therapy also has an important role for prevention of the progression atherosclerosis. Recent studies have shown that diet therapy such as the Mediterranean diet has a beneficial effect on cardiovascular disease (5). In addition, dietary supplements such as garlic extract have been known to have a positive effect on cardiovascular disease risk factors, including blood pressure, cholesterol, and endothelial function (6, 7). Our group has shown through the use of noncontrast cardiac computed tomography (CT) that aged garlic extract (AGE) helped slow progression of coronary artery calcium (8, 9).

Cardiac computed tomography angiography (CCTA) is a noninvasive tool that evaluates the heart and coronary arteries with the use of contrast-enhanced computed tomography technology. The high spatial and temporal resolution of CCTA permits not
only detection of coronary artery anatomic stenosis but also coronary plaque composition with a high degree of diagnostic accuracy. The diagnostic accuracy and feasibility of this technique is illustrated in many previous studies (10–12). Although previous studies have demonstrated that noncalcified plaque (NCP) has an important role in acute coronary events (13, 14), the effect of AGE on NCP is unclear. This current study investigates whether AGE reduces plaque volume, including NCP measured by CCTA in patients with MetS.

Methods

Study population and randomization. The present study was a placebo-controlled double-blind study (NCT01534910). Seventy-two patients were enrolled and underwent CCTA. The Investigational Review Board of the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center approved this research project. All patients signed informed written consent forms after careful explanation and review of protocol. Eligible participants were 40–75 y of age who had at least 2 components of MetS as defined by the Adult Treatment Panel III Clinical Identification of MetS (including impaired fasting glucose >110 mg/dl, treated hypertension or systolic blood pressure >130 mm Hg or diastolic blood pressure >85 mm Hg, TGs >150 mg/dl, LDL cholesterol <35 mg/dl for men or <40 mg/dl for women, abdominal obesity as defined as waist circumference >40 inches (1.02 meters) for men or >35 inches (0.89 meters) for women) . Glucose and cholesterol were assayed from serum with the use of an Abbott autoanalyzer.

1 Published in a supplement to The Journal of Nutrition. Presented at the conference “2014 International Garlic Symposium: Role of Garlic in Cardiovascular Disease Prevention, Metabolic Syndrome, and Immunology,” held 4–6 March 2014 at St. Regis Monarch Beach Resort in Dana Point, CA. This supplement is dedicated to the memory of our dear colleague and friend John A Milner. His commitment to good science and his voice for nutrition are remembered and sorely missed. The symposium was sponsored by the University of California, Los Angeles School of Medicine and the University of Florida and co-sponsored by the American Botanical Council; the American Herbal Products Association; the ASN; the Japanese Society for Food Factors; the Japan Society for Bioscience, Biotechnology, and Agrochemistry; the Japan Society of Nutrition and Food Science; and the Natural Products Association. The symposium was supported by Agencias Motta S.A.; Bionam; Ecolntraviticos; Healthy U 2000 Ltd.; Magna; Manavittva Bbva; Maxima Pharma; Medica Nord A.S.; Nature’s Farm Pte. Ltd.; Nature Valley V.L.L.; Organic Health Ltd.; Oy Valiosavinto Ab; Purity Life Health Products L.P.; PT Nutriprima Jayasakti; Vitoce Health Ltd.; Vitate Natural Nutrition; Sanofi Consumer Health Care; Wakunaga Pharmaceutical Co., Ltd.; and Wakunaga of America Co., Ltd. The Chair of the conference and Scientific Program Coordinator for a supplement publication was Matthew J Budoff, Harbor-UCLA Medical Center, Torrance, CA. Scientific Program Coordinator disclosures: MJ Budoff has been awarded research grants from Wakunaga of America Co., Ltd., and received an honorarium for serving as Vice-Chair of the conference. Vice-Chair and Supplement Coordinator for the supplement publication was Susan S Percival, Unversity of Florida, Gainesville, FL. Supplement Coordinator disclosures: SS Percival has been awarded research grants from Wakunaga of America Co., Ltd., and received an honorarium for serving as Vice-Chair of the conference. Publication costs for this supplement were defrayed in part by the payment of page charges. This publication must therefore be hereby marked “advertisement” in accordance with 18 USC section 1734 solely to indicate this fact. The opinions expressed in this publication are those of the authors and are not attributable to the sponsors or the publisher, Editor, or Editorial Board of The Journal of Nutrition.

2 While the study was funded by Wakunaga of America Co., Ltd., the authors are solely responsible for the design, all study analyses, the drafting and editing of the paper and its final contents.

3 Author disclosures: S Matsumoto, R Nakashiki, D Li, A Alani, P Rezaeian, S Prabhu, J Abraham, MA Fahmy, C Dailing, F Flores, S Hamal, and A Broersen, no conflicts of interest. PH Kitalai is employed by Medis Medical Imaging Systems and has a research appointment at the Leiden University Medical Center. MJ Budoff receives funding from Wakunaga of America Co., Ltd.

4 Abbreviations used: AGE, aged garlic extract; CAD, coronary artery disease; CCTA, cardiac computed tomography angiography; CT, computed tomography; DC, dense calcium; LAP, low-attenuation plaque; MetS, metabolic syndrome; NCP, noncalcified plaque; TPV, total plaque volume.

5 To whom correspondence should be addressed. E-mail: mbdoff@labiomed.org.

6 S of 6S Supplement

8 Abbreviations used: AGE, aged garlic extract; CAD, coronary artery disease; CT, computed tomography; DC, dense calcium; LAP, low-attenuation plaque; MetS, metabolic syndrome; NCP, noncalcified plaque; TPV, total plaque volume.

10 Although previous studies have demonstrated that noncalcified plaque (NCP) has an important role in acute coronary events (13, 14), the effect of AGE on NCP is unclear. This current study investigates whether AGE reduces plaque volume, including NCP measured by CCTA in patients with MetS.

13 Statistical analysis. Continuous variables were expressed as means ± SDs. Comparisons of all parameters between the AGE and placebo groups were made with the use of Student’s t test. Categoric variables were expressed as counts and percentages and a χ² test was used for comparisons between the placebo and AGE groups. To correct for differences in baseline values, we performed multiple linear regression analysis. By multivariable linear regression analysis, we examined
whether AGE is associated with plaque regression of %LAP, %TAP, %NCP, and %DC, after adjusting for age, gender, number of risk factors, hyperlipidemia medications, history of known CAD, scan interval time, and baseline %TPV. A value of \( P < 0.05 \) was considered statistically significant. All statistical analyses were performed with the use of SAS software (version 9.3).

**Results**

**Baseline characteristics.** From June 2012 through December 2012, 72 patients were enrolled and randomly assigned to placebo or AGE groups. Patients were maintained on current medications such as aspirin, hypertensive, or hyperlipidemia medication, and did not change medications during the study period. Participants were followed for a mean \( \pm SD \) of 354 \( \pm 41 \) d (range: 250–461 d). As of October 2013, 15 patients were unable to undergo a follow-up visit. We also excluded 2 patients with coronary artery bypass graft from the analysis because of imaging artifacts from excessive DC in their vessels. Ultimately, this gave us a total of 587 segments from 55 patients (mean 11 \( \pm \) 3 segments; range: 2–15 segments per patient) to analyze for this study (Figure 1).

**Plaque characteristics at baseline and follow-up, and the change among placebo and AGE groups.** The baseline data at entry into this study are presented in Table 1. The 2 groups had similar demographic characteristics. However, baseline %TPV and %DC were significantly higher in the placebo group than in the AGE group, whereas %LAP was lower in the placebo group (Table 2). The change in value of each plaque over 1 y in the placebo and AGE groups is shown in Table 2. The %LAP change was significantly reduced in the AGE group compared with the placebo group. However, no significant difference was seen in %TPV, %NCP, or %DC. A CCTA case example is presented in Figure 2. By multivariable linear regression analysis adjusting for age, gender, number of risk factors, hyperlipidemia medications, history of known CAD, scan interval time, and baseline %TPV, a beneficial effect from AGE was observed with respect to LAP regression, but not for %TPV, %NCP, or %DC (Table 2).

**Discussion**

The current study demonstrates that, in patients with MetS, %LAP change was significantly greater in the AGE group than in the placebo group after 1 y of treatment. This result is consistent with the previous study that showed the beneficial effect of AGE on atherosclerosis.

In general, atherosclerosis starts with the accumulation of oxidized LDL within the intima. Lipoprotein attracts macrophages, which are transformed into foam cells after phagocytosing these pools of lipids. These foam cells eventually undergo necrosis, which forms a necrotic core within the intima. In addition, pathologic studies with the use of invasive coronary angiography have shown that the culprit lesion of acute coronary syndrome likely has a lipid-rich necrotic core, which is covered by a thin fibrous cap (14, 20).

CCTA is a noninvasive modality with excellent diagnostic accuracy in identifying the presence, extent, and severity of CAD, as well as coronary plaque characteristics (11, 21).

**TABLE 1 Baseline characteristics of study population**

<table>
<thead>
<tr>
<th></th>
<th>Placebo ((n = 28))</th>
<th>AGE ((n = 27))</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>58.7 (\pm 6.7)</td>
<td>56.8 (\pm 7.4)</td>
<td>0.32</td>
</tr>
<tr>
<td>Male</td>
<td>21 (75.0)</td>
<td>19 (70.4)</td>
<td>0.70</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13 (46.4)</td>
<td>12 (44.4)</td>
<td>0.88</td>
</tr>
<tr>
<td>Taking antihypertensive medicine</td>
<td>9 (32.1)</td>
<td>6 (22.2)</td>
<td>0.41</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>13 (46.4)</td>
<td>9 (33.3)</td>
<td>0.32</td>
</tr>
<tr>
<td>Taking antihyperlipidemia medicine</td>
<td>8 (28.6)</td>
<td>7 (25.9)</td>
<td>0.83</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>11 (39.3)</td>
<td>7 (25.9)</td>
<td>0.29</td>
</tr>
<tr>
<td>Known CAD</td>
<td>2 (7.1)</td>
<td>0 (0)</td>
<td>0.16</td>
</tr>
<tr>
<td>Scan period, mo</td>
<td>11.7 (\pm 1.6)</td>
<td>11.5 (\pm 1.1)</td>
<td>0.68</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>131 (\pm 2)</td>
<td>132 (\pm 2)</td>
<td>0.75</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>77 (\pm 2)</td>
<td>81 (\pm 2)</td>
<td>0.19</td>
</tr>
<tr>
<td>Serum LDL cholesterol, mg/dL</td>
<td>124 (\pm 43)</td>
<td>131 (\pm 29)</td>
<td>0.95</td>
</tr>
<tr>
<td>Serum HDL cholesterol, mg/dL</td>
<td>58 (\pm 14)</td>
<td>58 (\pm 18)</td>
<td>0.92</td>
</tr>
<tr>
<td>Serum TGs, mg/dL</td>
<td>142 (\pm 71)</td>
<td>139 (\pm 91)</td>
<td>0.91</td>
</tr>
<tr>
<td>Serum glucose, mg/dL</td>
<td>100 (\pm 3)</td>
<td>101 (\pm 3)</td>
<td>0.77</td>
</tr>
<tr>
<td>Framingham risk scores, %</td>
<td>17 (\pm 2)</td>
<td>18 (\pm 2)</td>
<td>0.77</td>
</tr>
</tbody>
</table>

\(1\) Values are means \(\pm SDs\) or \(n\) (\%): AGE, aged garlic extract; CAD, coronary artery disease.
Motoyama et al. (13) used CCTA to define plaque features that likely lead to acute coronary syndrome, such as positively dilated coronary arteries, voluminous plaque, and large LAP content (necrotic core). Although statins have been shown to reduce LAP in previous findings (22, 23), this study indicates that AGE has the ability to stabilize atherosclerosis by reducing the amount of LAP in a manner similar to that of statin therapy.

The mechanism by which garlic affects the atherosclerotic process, however, still remains unclear. Nonetheless, previous reports support several complex mechanisms of garlic metabolites that contribute to the suppression of atherosclerosis. For example, a garlic supplement with high concentrations of S-allyl-cysteine have been shown to have a cholesterol-lowering effect (24, 25). γ-Glutamylcysteine—a component of garlic—also has the ability to decrease blood pressure by modulating nitric oxide and endothelia synthesis (26, 27). Furthermore, the anti-inflammatory effect of garlic was also reported. Specifically, AGE therapy led to a decrease in CD36 expression on foam cells and oxidized LDL uptake in macrophages (28).

Our laboratory previously has shown the possibility that AGE has an antioxidative effect through the observation of autoantibodies to malondialdehyde LDL and oxidized phospholipids on

### TABLE 2
Change in each percentage plaque volume after 345 ± 41 d of placebo compared with AGE (2400 mg/d) treatment in adult patients with MetS1

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Baseline (%)</th>
<th>Follow-up (%)</th>
<th>Δ (%)</th>
<th>β (SE)</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPV</td>
<td>28</td>
<td>28.4 ± 6.5</td>
<td>36.4 ± 6.6</td>
<td>8.0</td>
<td>0.77</td>
<td>1.98, -0.46</td>
<td>0.17</td>
</tr>
<tr>
<td>Placebo</td>
<td>28</td>
<td>28.4 ± 6.5</td>
<td>36.4 ± 6.6</td>
<td>8.0</td>
<td>0.77</td>
<td>1.98, -0.46</td>
<td>0.17</td>
</tr>
<tr>
<td>AGE</td>
<td>27</td>
<td>27.1 ± 6.3</td>
<td>34.9 ± 6.4</td>
<td>7.8</td>
<td>0.78</td>
<td>1.99, -0.45</td>
<td>0.16</td>
</tr>
<tr>
<td>NCP</td>
<td>28</td>
<td>28.4 ± 6.5</td>
<td>36.4 ± 6.6</td>
<td>8.0</td>
<td>0.77</td>
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<td>0.16</td>
</tr>
<tr>
<td>LAP</td>
<td>28</td>
<td>28.4 ± 6.5</td>
<td>36.4 ± 6.6</td>
<td>8.0</td>
<td>0.77</td>
<td>1.98, -0.46</td>
<td>0.17</td>
</tr>
<tr>
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<td>7.8</td>
<td>0.78</td>
<td>1.99, -0.45</td>
<td>0.16</td>
</tr>
<tr>
<td>DC</td>
<td>28</td>
<td>28.4 ± 6.5</td>
<td>36.4 ± 6.6</td>
<td>8.0</td>
<td>0.77</td>
<td>1.98, -0.46</td>
<td>0.17</td>
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<tr>
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</table>

1 Values are means ± SDs. Models were adjusted for age, gender, number of risk factors, antihyperlipidemia medications, known CAD, scan interval, and baseline %TPV. a,bDifferent from placebo: aP < 0.05; bP < 0.01. AGE, aged garlic extract; CAD, coronary artery disease; DC, dense calcium; LAP, low-attenuation plaque; MetS, metabolic syndrome; NCP, noncalcified plaque; TPV, total plaque volume.

### FIGURE 2
Representative example automated plaque quantification analysis. The lumen border contours and vessel wall borders are assessed and eccentric noncalcified plaque is observed. CT, computed tomography; VCT, volume computed tomography.
apolipoprotein B-100 particles, which are markers of oxidation (9). This is congruent with previous studies that indicate that garlic has an inhibitory effect on LDL oxidation (29). Together these findings validate that AGE exhibits an antiatherosclerotic effect. Additional research is necessary to examine whether AGE is associated with the reduction of future cardiac events.

Limitations. The present study has several limitations. First, this relatively small sample size and short-term follow-up study did not have enough power to show the significant differences in TPV, NCP, and DC. Second, patients were under different therapies. For example, with respect to hyperlipidemia, some patients used varying medications and different doses. Because of our small sample size, a separate analysis by different hyperlipidemia medications was not performed. Third, plaque volume, including %TPV, %LAP, and %DC, was significantly different at baseline between the 2 groups. Therefore, we operated a multivariable linear regression analysis including baseline %TPV (%DC and %LAP were represented by %TPV). Finally, although we evaluated individual plaque volume with the use of semiautomated plaque quantification software, we still cannot exclude the possibility of reading error and variability, especially in the images with excess noise or motion artifact. However, we evaluated 13 randomly selected patients undergoing CCTA in our group to evaluate interobserver variability. We reported excellent interobserver variability in assessing each plaque volume (30).

Conclusion

This study indicates that the %LAP change was significantly greater in the AGE group than in the placebo group. Further studies are needed to evaluate whether AGE has the ability to stabilize vulnerable plaque and to decrease adverse cardiovascular events.

Acknowledgments

MJB conceived of and designed the study; SP, JA, MAF, FF, and SH generated the clinical data; AA, PR, SP, JA, MAF, CD, FF, and SH collected the patient information; SM, RN, DL, AA, and MJB analyzed and/or interpreted the data; AA, PR, SP, JA, MAF, CD, FF, and SH collected the patient information; SM, RN, DL, AA, and MJB drafted or revised the manuscript. All authors read and approved the final version of the manuscript.

References


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