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Aged garlic extract reduces left ventricular myocardial mass in patients with diabetes: A prospective randomized controlled double-blind study

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Abstract. Increased left ventricular myocardial mass (LVM) is a well known prognostic marker of poor cardiac outcomes. Decreases in LVM have been shown to decrease the cardiovascular risk. Aged garlic extract (AGE) has been shown to have an overall favorable effect on cardiac health; however, to the best of our knowledge, no study to date has specifically examined its effects on left ventricular mass. This study investigated whether AGE can affect LVM measured by cardiac computed tomography angiography (CCTA) in patients with diabetes mellitus (DM). This is a double-blind, placebo controlled randomized trial. In total, 65 participants with DM with a mean age of 58 years were prospectively assigned to consume 2,400 mg AGE/day or the placebo orally. Both groups underwent CCTA at baseline and follow-up at 1 year apart. LVM was measured using automated software. The baseline characteristics did not differ between the AGE and placebo groups. There was a trend towards a significant reduction in LVM at follow-up as compared to baseline in the AGE group (119.30±34.77 vs. 121.0±34.70, P=0.059). No change was observed in LVM in the placebo group at 1-year follow-up as compared to baseline (124.6±37.33 vs. 124.6±35.13, P=0.9). On the whole, this study indicated that AGE may decrease or stabilize LVM. Further studies however, with a larger sample size and longer follow-up times are required to evaluate the effects of AGE on hypertension and LVM.

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Introduction

Left ventricular hypertrophy (LVH) is a relatively common cardiomyopathy. The prevalence of LVH in the general population has been estimated at 12.9-16% for males and 9.1-19% for females (1,2). The prevalence increases markedly with age (1), the diagnosis of hypertension (3) and the diagnosis of diabetes (4). LVH and increased left ventricular mass (LVM) is furthermore a known predictor of poor cardiovascular outcomes, including sudden cardiac death (5), ventricular arrhythmias (6), and heart failure (7). However, LVH appears to be somewhat reversible, with studies demonstrating a decreased left ventricular myocardial mass (LVM) with a reduction in blood pressure (8), as well as exercise and weight loss (9). Importantly, reductions in LVM appear to reduce risk of poor cardiovascular outcomes in several studies (10).

Aged garlic extract (AGE) is a supplement with several known medicinal qualities. As regards cardiovascular health, garlic supplementation has been shown to lower total cholesterol levels (11), blood pressure (12) and to prevent oxidative DNA damage in essential hypertension (13). AGE has also been shown to attenuate the progression of coronary atherosclerosis, improve vascular function and exert favorable effects on oxidative biomarkers (14,15). However, to the best of our knowledge, no studies available to date have examined the effects of AGE on LVM. Thus, the present placebo-controlled randomized double blinded study, examined the effects of AGE on LVM in subjects with diabetes mellitus (DM) using serial contrasted coronary CT scans.

Subjects and methods

Study design. The present study is a single center randomized, placebo-controlled, double-blind comparison of AGE (2,400 mg daily) compared to matching placebo capsules (ClinicalTrials.gov ID: NCT01534910). As previously described (15), AGE (Kyolic), provided by Wakunaga of America, 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 a low temperature.

Table I. Baseline characteristics of the study subjects by treatment arm.

Characteristic	Placebo (n=29)	Active (n=36)	P-value
Age, (mean ± SD), years	58.7±11.4	59.4±11.2	0.808
BMI (mean ± SD), kg/m^2	30.8±6.0	30.0±5.6	0.567
Sex, male, n (%)	21 (72)	18 (50)	0.067
Race, Hispanic, n (%)	9 (31)	14 (39)	0.284
Hypertension, n (%)	15 (52)	23 (64)	0.323
Taking anti-hypertensive medication, n (%)	15 (52)	23 (64)	0.323
Hyperlipidemia, n (%)	24 (83%)	33 (92%)	0.277
Taking anti-hyperlipidemia medication, n (%)	24 (83%)	33 (92%)	0.277
Family history of heart disease, n (%)	14 (48%)	11 (31%)	0.144
Post-menopausal, n (%)	7 (24%)	13 (36%)	0.299
Previous smoker, n (%)	11 (38%)	15 (42%)	0.760
Present smoker, n (%)	5 (17%)	2 (6%)	0.131
Taking aspirin, n (%)	21 (72%)	21 (58%)	0.238
SBP (mean ± SD), mmHg	126.59±15.55	131.0±18.35	0.307
DBP (mean ± SD), mmHg	76.86±9.57	79.11±9.59	0.350
Heart rate (mean ± SD), mmHg	71.07±12.91	69.11±9.09	0.493
Adiponectin (mean ± SD), µg/dl	10.01±11.01	9.22±5.75	0.872
HDL cholesterol (mean ± SD), mg/dl	40.10±12.56	40.11±11.14	0.293
LDL cholesterol calculated (mean ± SD), mg/dl	72.55±33.10	66.56±27.34	0.695
non-LDL cholesterol (mean ± SD), mg/dl	100.17±42.76	89.97±29.31	0.757
Total cholesterol (mean ± SD), mg/dl	140.28±45.35	130.08±29.75	0.872
hsCRP (mean ± SD), mg/l	3.47±3.90	2.26±2.15	0.933
Interleukin 6 (mean ± SD), ng/ml	2.37±1.89	2.60±4.52	0.504
Lp-PLA2 (mean ± SD), ng/ml	41.17±15.04	36.47±13.14	0.695
Oxidized LDL (mean ± SD), U/l	28.69±10.60	24.97±8.07	0.923
Triglycerides (mean ± SD), mg/dl	138.76±79.38	116.92±54.47	0.807

SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; hsCRP, high sensitivity C-reactive protein; Lp-PLA2, lipoprotein-associated phospholipase A2.

The AGE used in this trial contained 305 g extracted solids/L. The finished product used in this clinical study was commercially available. The participants were assigned to AGE or placebo in a double-blinded manner, using numbered containers assigned to a computer-generated randomization chart by a nurse coordinator. The subjects were observed on therapy for 52 weeks. The subjects had study-related visits quarterly (at 13, 26, 29 and 52 weeks) where they were assessed for compliance and adverse events.

Imaging and laboratory data. Laboratory data, including complete blood count, chemistry panel, hemoglobin A1c levels and inflammatory biomarkers were collected at weeks 1, 26 and 52. At baseline and week 52, the subjects underwent non-contrast CT and coronary CT angiography using a 64-slice multi-detector scanner. Sublingual nitroglycerin or nitroglycerin spray 0.4 mg was administered prior to the scan. Prescan beta-blockers were also administered to achieve a resting heart rate of <60 beats/min. Quantitative data analyses were performed using automated methods on a workstation and software (AW 4.6; GE Medical Systems) that used a Hounsfield unit-based endocardial border detection technique. Images were reconstructed with a slice thickness of 1.25 mm. LVM was also simultaneously calculated automatically. The mid-diastolic phases were chosen for measurement of LVM. The user acquiring the measurements was blind to participant characteristics and randomization status of each subject. The use of contrast CT for the measurement of chamber size and LVM has been validated in previous studies (16,17).

Patient population. The patients were males and females aged 30-75 years with known DM (defined as hemoglobin A1c levels, >6.5%; fasting blood sugar levels, >125 mg/dl; and/or taking anti-diabetes medications) with a coronary calcium score of >20 at baseline and who consented to the study design. This study was approved by the local IRB (Los Angeles Biomedical research Center). Notable exclusion criteria included a known allergy to AGE, a body weight >350 pounds, bleeding disorders, a history of known coronary artery disease (CAD), any malignancy within the past 5 years and serum creatinine levels >1.4 mg/dl.

Statistical analysis. Demographic and clinical characteristics were determined at the baseline time point and

Table II. Left ventricular mass by treatment arm.

	Baseline		Follow-up		Within group change	Between group change
Group	LVM (mean ± SD)	P-value[a]	LVM (mean ± SD)	P-value[b]	P-value[c]	P-value[d]
Active (n=36)	121.00±34.7	0.69	119.30±34.77	0.542	0.0593	0.300
Placebo (n=29)	124.60±37.33		124.60±35.13		0.9764	

[a]P-value for comparison of LVM between treatment arms at baseline time point; [b]P-value for comparison of LVM between treatment arms at follow-up time point; [c]P-value for change in LVM within each group across baseline and follow-up time points; [d]P-value for difference in change in LVM between treatment arms across baseline and follow-up time points. LVM, left ventricular myocardial mass.

compared by randomization status. A Student's t-test or Chi-square test was used to assess the differences in all baseline parameters. Continuous variables are expressed as the means ± SD, while categorical variables are stated as counts and percentages. For the primary outcome (change in left ventricular mass over time), an analysis of variance (ANOVA) model with Tukey's post hoc test was used to compare the treatment arm versus placebo. Analyses was performed on an intention-to-treat basis. SAS software (version 9.4; SAS Institute, Inc.) was used to carry out all statistical analyses.

Results

A total of 65 diabetic patients successfully completed the 1-year study and received a baseline and follow-up CT, including 29 patients in the placebo arm and 36 patients in the active treatment (AGE) arm. The baseline characteristics were similar between the 2 groups (Table I). The average age in the placebo group was 58.7 years and 59.4 years in treatment group (P=0.808). A higher number of subjects in the placebo group were male (72% of patients vs. 50% in the treatment arm), although this was not statistically significant (P=0.067). Body mass index (BMI) was similar between the groups (30.8 vs. 30.0 kg/m^2, P=0.567). The subjects in both groups were generally at a high cardiovascular risk with hypertension being 52% in the placebo arm and 64% in the treatment arm (P=0.323); and hyperlipidemia being 83% in the placebo arm vs. 92% in the treatment arm (P=0.277). The cholesterol levels and inflammatory marker levels measured were similar between groups. All patients were diabetic as per the study protocol. All the patient baseline characteristics are presented in Table I.

The baseline mean LVM was similar between groups (121.0 g in treatment arm vs. 124.0 g in the placebo arm, P=0.69). At follow-up scans, the mean LVM in the treatment arm decreased to 119 g (1.65% decrease) and the mean LVM in the placebo arm was similar at 124.6 g (0.48% increase). The decrease in LVM in the treatment arm trended towards statistical significance (P=0.059). The change in LVM in the placebo arm was not statistically significant (P=0.97). The mean difference in absolute change between the groups was not statistically significant (-1.68 g in the treatment arm vs. 0.04 g in the placebo arm, P=0.30) (Table II).

Discussion

In the present study, a trend towards a decreased LVM was observed in patients undergoing 1 year of treatment with AGE, with a reduction of mass of 1.65%. The same trend was not observed in the placebo arm, in which the LVM was essentially unaltered following 1 year of placebo therapy (increased by 0.48%). These results suggest an effect of AGE in reducing LVM; however, studies with larger sample sizes are warranted to confirm these findings.

AGE is known to decrease blood pressure (12,18) which in turn, is known to reduce left ventricular mass (8). A reduction in blood pressure may indeed be the mechanism behind the observed effects. AGE may also have a direct effect on cardiomyocytes that has yet to be determined. AGE has also been demonstrated to improve endothelial function, which may reduce afterload and stress on the myocardium (19). Finally, AGE reduces inflammation and this in turn my improve myocardial mass and induce regression (20).

This study has several limitations. Firstly, the sample size was small, and may not have been powerful enough to detect a statistically significant effect of AGE on LVM. Second, it was only a 1-year study, and it may take a longer period of time to observe the full effects of AGE on myocardial mass changes. Third, the population cohort was predominantly male and Hispanic, which limits generalizability. Future research is required in order to include similar trials with larger sample sizes and longer duration in order to better understand the trend observed in the current study.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article or are available from the corresponding author on reasonable request.

Authors' contributions

EH was invovled in the conception and design of the study and in the writing of the manuscript. KS was invovled in the design of the study, and in data collection and the editing of the manuscript. AK was invovled in the design of the study, and in stastical analysis and the editing of the manuscript. LC was invovled in the conception and design of the study, and in data collection, manuscript supervision, and in the editing of the manuscript. DB was invovled in data collection and in the editing of the manuscript. SSM was invovled in data collection and in the editing of the manuscript. RN was invovled in the conception and design of the study, data collection, manuscript supervision and in the editing of the manuscript. SA was invovled in data collection and in the editing of the manuscript. EJ was invovled in the conception and design of the study, and in data collection, manuscript supervision and in the editing of the manuscript. CS was invovled in the design of the study, data collection and in the editing of the manuscript. FF was invovled in the design of the study, data collection, and in the editing of the manuscript. SH was involved in the design of the study and in the editing of the manuscript. SS was invovled in the design of the study, data collection and in the editing of the manuscript. AJ was invovled in the design of the study and in the editing of the manuscript. BC was invovled in the design of the study and in the editing of the manuscript. GT was invovled in the design of the study and in the editing of the manuscript. MJB was involved in the conception and design of the study, data collection, manuscript supervision and in the editing of the manuscript.

Ethics approval and consent to participate

This study was approved by the local IRB (Los Angeles Biomedical research Center). All patients provided signed and written informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

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