



The effects of garlic extract upon endothelial function, vascular inflammation, oxidative stress and insulin resistance in adults with type 2 diabetes at high cardiovascular risk. A pilot double blind randomized placebo controlled trial



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ABSTRACT

Background and aims: Endothelial dysfunction, vascular inflammation and oxidative stress have been integrally linked to the pathogenesis of both type 2 diabetes and cardiovascular disease. Aged Garlic Extract (AGE), a potent antioxidant, has been shown in previous studies to attenuate these novel risk factors in a non-diabetic population.

Aims: This study tested the hypothesis that AGE may improve endothelial function, oxidative stress, vascular inflammation and insulin resistance in high risk cardiovascular subjects with type 2 diabetes.

Methods: A double blind, placebo controlled crossover pilot study was performed in 26 subjects with type 2 diabetes who received 1200 mg of AGE or placebo daily for 4 weeks with a 4 week washout period. Plasma HsCRP was measured as a marker of inflammation. Plasma TAOS, blood GSH/GSSG and plasma LHP were measured as markers of oxidative stress/anti-oxidant defense. Insulin resistance was measured using the HOMA-IR method. Endothelial function was measured using change in the reflective index (RI) post-salbutamol using digital photoplethysmography and urinary albumin/creatinine ratio was measured as a biochemical surrogate. Measurements were taken at baseline and after intervention with AGE or placebo. **Results:** Of the 26 patients studied (male 17, female 9), age was 61 ± 8 years (mean \pm 1 SD), HbA1c $7.2 \pm 1.1\%$, BP $130/75 \pm 15.9/9.8$ mmHg, total cholesterol 4.2 ± 0.81 mmol/l, triglyceride 2.11 ± 1.51 mmol/l, and HDL cholesterol 1.04 ± 0.29 mmol/l. The majority of patients were being treated with metformin (59%), aspirin (50%) and statin (96%) therapy. 36% were treated with an ACEI. There were no changes in these therapies throughout the study.

Treatment with AGE had no significant effect upon the above metabolic parameters including insulin resistance. Treatment with AGE also had no significant effect on markers of endothelial function (plethysmography), oxidative stress (TAOS, GSH/GSSG, LHP) or inflammation (HsCRP).

Conclusion: In this group of type 2 diabetic patients at high cardiovascular risk, 4 weeks treatment with AGE did not significantly improve endothelial function, vascular inflammation, oxidative stress or insulin resistance.

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1. Introduction

Adequate treatment of the traditional risk factors for vascular disease is given equal priority to blood glucose control in patients with diabetes. This has given significant improvements in expected lifespan in type 2 diabetes. However, cardiovascular and cerebrovas-

cular diseases remain responsible for 80% of diabetes related mortality (Campbell, Newton, Patel, Jacobs, & Gapstur, 2012).

Many of the traditional risk factors share similar underlying biochemical processes such as oxidative stress, vascular inflammation and endothelial dysfunction which could explain their contribution to the complications of diabetes. Further consideration shows these processes to be present even before the development of diabetes (Lüa et al., 2009; Perticone et al., 2008; Su et al., 2008a, 2008b) and they also seem to have a fundamental role in the pathogenesis of diabetic complications (see Fig. 1). This study investigates whether treatment with an antioxidant can affect these novel risk factors in a typical diabetes outpatient population.

Conflict of interest: None of the authors have any conflict of interest.

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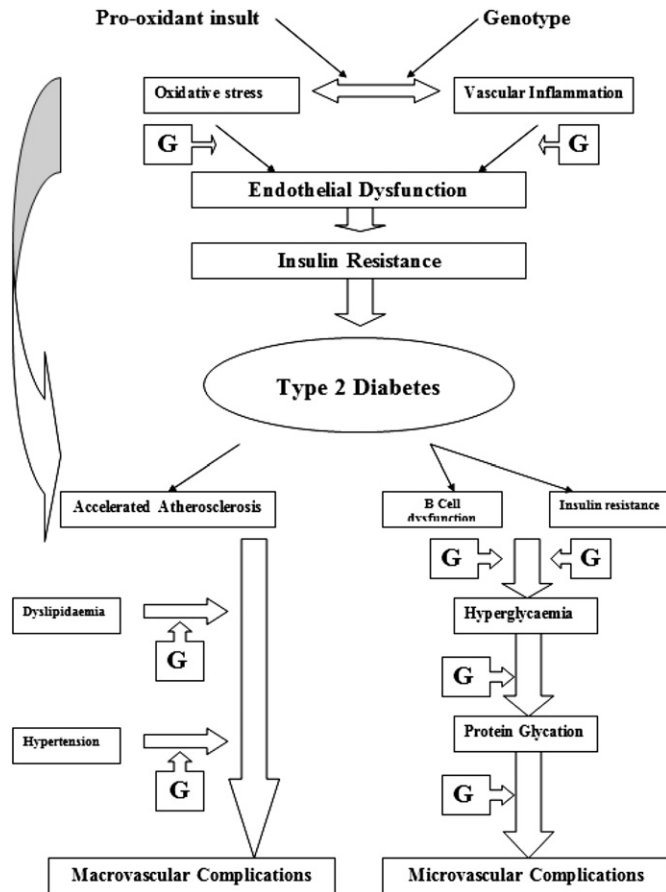


Fig. 1. Diagram to show the common soil hypothesis of the inter-relationship between oxidative stress, vascular inflammation and endothelial dysfunction in type 2 diabetes. The points at which garlic may be effective are marked with a G (Ahmad et al., 2006; Liu et al., 2007; Ried et al., 2013; Vazquez-Prieto et al., 2010; Wang et al., 2015; Williams et al., 2005).

Aged Garlic Extract (AGE) is prepared by storing sliced raw garlic in 15–20% ethanol solution for 20 months at room temperature. It is administered either in liquid form or capsules. It has been shown to be a potent antioxidant (Imai et al., 1994) and has beneficial effects on markers of oxidative stress (Dillon et al., 2002), inflammation (Budoff et al., 2009) and endothelial function (Weiss et al., 2006) in vitro or animal models. AGE has been used in previous human studies and has been shown to be safe (Nakagawa et al., 1984).

2. Methods

2.1. Subjects

26 subjects with type 2 diabetes who were deemed to be at high cardiovascular risk (deemed to be at 30% risk of a cardiovascular event within the next 10 years using a prediction algorithm (Wilson et al., 1998)) were recruited between 2007 and 2009. All subjects gave written informed consent. The Hampshire and Isle of Wight Research Ethics Committee gave their approval for this study.

The inclusion criteria included type 2 diabetes patients aged between 18 and 70 years, who were not treated with insulin. Exclusion criteria included established cardiovascular or cerebrovascular disease and treatment with insulin or warfarin (Table 1).

2.2. Protocol

Physical examination was undertaken and baseline measurements taken (BMI and BP). An ECG was also performed to exclude occult ischaemic heart disease. Baseline fasting investigations included

Table 1
Baseline subject characteristics.

Mean age	Mean duration of diabetes	% of smokers	Male	Mean BMI	Mean baseline HbA1c
49.8 years	4.9 years	25	72%	32	7.2%

measurements of plasma lipids (total cholesterol, high density lipoprotein cholesterol and triglyceride) serum urea and serum electrolytes, liver function tests and INR. Glycemic control was measured using HbA1c and fructosamine. Measurements were also made of insulin resistance, endothelial function, vascular inflammation and oxidative stress as described below.

Once baseline assessments had been concluded, the subjects were given either Aged Garlic Extract (kyolic) or a placebo. Double blind, randomized allocation of the placebo or garlic treatment was undertaken. Subjects took 4 capsules per day (1200 mg) for 4 weeks. There was then a 4 week washout period and then the subjects entered the crossover arm (see Fig. 2). Compliance levels were monitored with a tablet count at the end of each 4 week treatment period.

2.3. Photoplethysmography

Digital photoplethysmography is a non-invasive measurement of vasoactive endothelial function. Measurements were made to determine the digital volume waveform [DVW] using the photoplethysmography apparatus (Micro Medical Pulse Trace, Rochester, Kent, UK). This technique was previously described and validated in diabetic and non-diabetic populations by Chowienczyk et al. (1999). This technique has also been validated against macrovascular brachial FMD (Rambaran et al., 2008).

Each subject had the probe attached to an index finger for 20 minutes, resting supine, before measurements were taken. Digital pulse wave readings were taken at baseline and the software calculated reflective index (RI). This was then repeated following administration of a sublingual 500 mcg dose of GTN. GTN is an endothelium-independent vasodilator and thus acted as a control. These readings were then repeated following inhaled salbutamol (an endothelium dependent vasodilator). Three readings were taken at baseline and an average taken. Readings were taken at 3 and 5 minutes. A washout period of 20 minutes was allowed after which another reading was taken to confirm the return to baseline. Inhaled salbutamol (400 mcg) was administered using a standardized technique via a spacer device, and readings taken at 10, 12 and 15 minutes. An average of the readings was taken.

2.4. Assays

Metabolic markers including fasting glucose, insulin, HOMA-IR, fructosamine, lipid profile (total cholesterol, HDL cholesterol and triglycerides), liver function tests, urea and electrolytes were also measured at each visit.

HbA1c was measured by HPLC (Menarini Diagnostics, Wokingham, UK). Plasma total cholesterol concentration was measured by esterase and oxidase conversion (Advia 1650, Bayer Diagnostics, Newbury, UK) and HDL cholesterol and plasma triglyceride concentration by enzymatic determination (Advia 1650, Bayer Diagnostics, Newbury, UK). The intra-assay coefficient of variation of these assays was <2%.

Samples taken for HsCRP and oxidative stress markers were separated and frozen to -80°C at the date of collection. The assays were then run in single batches.

2.5. Insulin Resistance

Plasma insulin and fasting plasma glucose were collected at the beginning of each visit in each of the subjects. These were repeated at 5 minute intervals to give a total of 3 pairs of results and the average

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