

Original Article: Treatment

Glycated haemoglobin and blood pressure-lowering effect of cinnamon in multi-ethnic Type 2 diabetic patients in the UK: a randomized, placebo-controlled, double-blind clinical trial

R. Akilen, A. Tsiami, D. Devendra* and N. Robinson

Faculty of Health and Human Science, Thames Valley University, London, UK and *Department of Investigative Sciences, Faculty of Medicine, Imperial College London and Brent Community services (National Health Service), London, UK

Accepted 30 June 2010

Abstract

Aims To determine the blood glucose lowering effect of cinnamon on HbA_{1c}, blood pressure and lipid profiles in people with type 2 diabetes.

Methods 58 type 2 diabetic patients (25 males and 33 females), aged 54.9 ± 9.8 , treated only with hypoglycemic agents and with an HbA_{1c} more than 7% were randomly assigned to receive either 2g of cinnamon or placebo daily for 12 weeks.

Results After intervention, the mean HbA_{1c} was significantly decreased ($P < 0.005$) in the cinnamon group (8.22% to 7.86%) compared with placebo group (8.55% to 8.68%). Mean systolic and diastolic blood pressures (SBP and DBP) were also significantly reduced ($P < 0.001$) after 12 weeks in the cinnamon group (SBP: 132.6 to 129.2 mmHg and DBP: 85.2 to 80.2 mmHg) compared with the placebo group (SBP: 134.5 to 134.9 mmHg and DBP: 86.8 to 86.1 mmHg). A significant reduction in fasting plasma glucose (FPG), waist circumference and body mass index (BMI) was observed at week 12 compared to baseline in the cinnamon group, however, the changes were not significant when compared to placebo group. There were no significant differences in serum lipid profiles of total cholesterol, triglycerides, HDL and LDL cholesterol neither between nor within the groups.

Conclusions Intake of 2g of cinnamon for 12 weeks significantly reduces the HbA_{1c}, SBP and DBP among poorly controlled type 2 diabetes patients. Cinnamon supplementation could be considered as an additional dietary supplement option to regulate blood glucose and blood pressure levels along with conventional medications to treat type 2 diabetes mellitus.

Diabet. Med. 27, 1159–1167 (2010)

Keywords blood pressure, cinnamon, diabetes, HbA_{1c}, lipid profiles

Abbreviations DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA_{1c}, glycated haemoglobin (A1C); MUFA, mono unsaturated fatty acids; PUFA, poly unsaturated fatty acids; SBP, systolic blood pressure; SFA, saturated fatty acids

Introduction

The incidence of late-onset diabetes is rapidly increasing in the United Kingdom as overweight and obesity are becoming more prevalent [1]. Since 1996, the number of people with diabetes has

increased from 1.4 million to 2.5 million (an average prevalence of 3.8%) [2]. By 2025, it is estimated that over 4 million people will have diabetes [2]. Globally, diabetes affects 246 million people and is expected to affect 380 million by 2025 [2]. Cinnamon bark is widely used as a spice and research has suggested that it may have useful pharmacological effects in the treatment of diabetes [3,4]. Previous human intervention trials have suggested that cinnamon can be used effectively to lower blood glucose [3,4] and cholesterol [3] levels in Type 2 diabetes

Correspondence to: Dr Rajadurai Akilen, Researcher/Lecturer in Nutrition, Faculty of Health and Human Sciences, Thames Valley University, Boston Manor Road, Brentford, TW8 9GA, UK. E-mail: rakilen22@hotmail.com

patients. In contrast, recent studies have suggested that cinnamon does not improve HbA_{1c} or blood lipid profiles in Type 2 [5,6] and Type 1 diabetes patients [7]. Our systematic review [8] of cinnamon and diabetes and meta-analysis [9] also suggested that a well-defined and adequately powered randomized controlled trial was important to further investigate the glucose-lowering potential of cinnamon among a multi-ethnic westernized population.

The potential glucose-lowering effect and pharmacological mechanisms of cinnamon have been identified *in vitro* and *in vivo* animal studies [10–15]. Cao *et al.* [12] reported that purified cinnamon extracts and cinnamon polyphenols increased insulin receptor β proteins and glucose transporter (GLUT4) proteins. These proteins are involved in the insulin signalling transduction pathway that functions in insulin receptor substrate activation and insulin-regulated glucose transportation, respectively [12]. It is well established that insulin promotes the translocation of GLUT4 from the intracellular compartment to the plasma membrane [16,17]. Therefore, the increase of GLUT4 protein by cinnamon polyphenols suggests a positive effect elicited by these compounds on the long-term regulation of glucose uptake in skeletal muscles and adipose tissues, as cinnamon polyphenol mimics insulin-like activity [10,12,15,18]. Insulin resistance has been attributed to decrease glucose transporter (GLUT4) activity, caused by inhibited insulin receptor substrate tyrosine phosphorylation [12,16,17]. The methylhydroxychalcone polymer in cinnamon also stimulates the insulin receptor substrate phosphoinositide 3-kinase pathway and up-regulates glucose uptake and glycogen synthesis activity and down-regulates glycogen synthase kinase-3 β activity [14]. Glycogen synthase kinase-3 β is involved in phosphorylation and inactivation of glycogen synthase [12,14,16].

The randomized controlled trials reporting the glucose-lowering effect of cinnamon in Type 2 diabetes [3–6] are heterogeneous, with differences in the glucose-lowering medication, the cinnamon dose administered, duration of the trial, the number and type of participants included, baseline blood glucose, BMI and ethnicity of participants. There is a need for new therapeutic approaches to target the various aspects of Type 2 diabetes mellitus, as currently more than half of all Type 2 diabetic patients have poorly controlled glucose levels 6 years after diagnosis, irrespective of treatment used [19]. Therefore, in view of the potential side effects of conventional drugs and the safety records required for dietary supplementation, an investigation into the potential value of a herbal dietary supplement approach is timely. Given that herbal dietary supplement practices are widespread in the general population in the United Kingdom [20], the efficacy of cinnamon on glycaemic control was investigated amongst people with Type 2 diabetes mellitus. This is the first clinical trial in the United Kingdom investigating the effect of cinnamon on HbA_{1c}, blood pressure and blood lipid profiles in Type 2 diabetic patients.

Patients and methods

This study took the form of a 12-week prospective, randomized, placebo-controlled, double-blind clinical trial with two parallel groups carried out within Brent National Health Services, London, between October 2007 and January 2009. The study protocol was approved by the Brent Medical Ethics Committee (reference: 07/H0717/47; clinical trial registration: NCT00846898).

Patients included in this study were: 18 years of age or older; diagnosed with Type 2 diabetes on two consecutive FPG measurements of greater than 7 mmol/l; an HbA_{1c} \geq 7%; being treated with oral hypoglycaemic agents. Exclusion criteria included: patients treated with insulin therapy; pregnant or lactating women; already taking cinnamon or other herbal supplements with the potential use to control blood glucose levels; patients with severe health conditions such as cardiovascular disease, liver disease, kidney disease and cancer. Patients unable to read English or understand the consent form and/or the information sheet were also excluded. The appropriate inclusion and exclusion criteria ensured a homogenous group of participants to be randomized.

Subjects were recruited from three different community diabetes clinics at Brent National Health Services, London (Fig. 1). All patients were seen by dietitians at diabetes and weight management clinics and received at least two sessions of diet and lifestyle advice during the study period as for standard care. Initially, 68 eligible patients were referred by the dietitians. Only 58 agreed to randomization and provided informed consent. These patients were randomly assigned to placebo ($n = 28$) or cinnamon ($n = 30$) groups (Fig. 1). Of these patients, 55 completed the study. Two patients in the placebo group were withdrawn from the study, one at week 7 and one at week 9, because of commencement of insulin by their clinician. One patient in the cinnamon group withdrew at week 9, as he began another alternative therapy (yoga), which may have been effective, thereby acting as a confounder. These three patients were advised to discontinue study intervention and their last observations were carried forward in the analyses using the last observation carried forward method (Fig. 1).

The allocation sequence was generated using a computer-generated randomized list. Each subject was required to take 2 g (500 mg \times 4) of either starch-filled placebo capsules or cinnamon powder (*Cinnamomum cassia*) every day for 12 weeks. The 2 g of cinnamon was chosen based on the previously suggested glucose-lowering effect of 1–6 g of cinnamon per day [3]. We specifically chose starch (with 80% amylose and 20% amylopectin) for the placebo, as it may be of potential benefit in reducing postprandial glucose rise by delayed gastric emptying and has been recommended for diabetes [21]. The cinnamon and placebo capsules (500 mg) were supplied by Holland and Barrett Ltd (London, UK). The cinnamon capsule was a 100% certified natural herb (reference: HBL14020NB). The ingredients of the capsules included 100% cinnamon bark or starch powder, for both the capsule shell containing

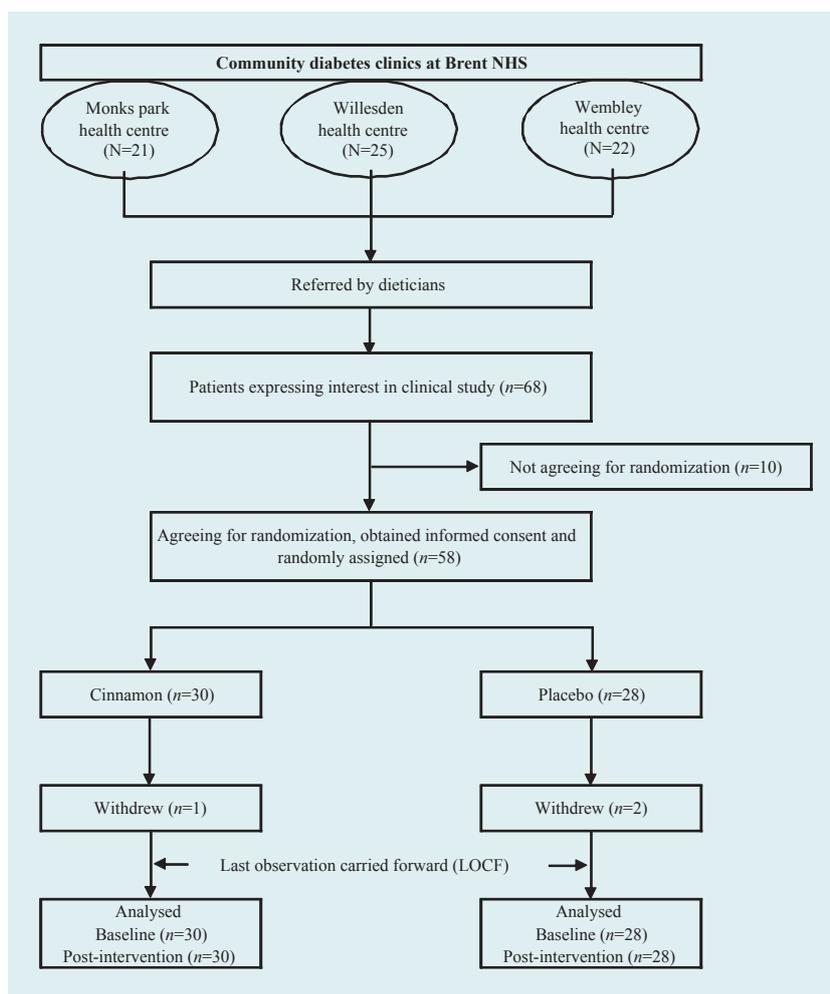


FIGURE 1 The recruitment and randomization of participants for a randomized controlled trial based on consolidated standards of reporting clinical trial (CONSORT) guidelines.

hydroxypropyl methylcellulose and anti-caking agents of silicone dioxide, magnesium stearate and stearic acid. No impurities or traces were mixed with the capsules during synthesis, formulation and production procedures. The quality and purity of both cinnamon and placebo capsules were certified by the manufacturer.

Subjects were instructed to take one capsule with breakfast, two with lunch and one with dinner. Double blinding of this trial was ensured by use of matching colour, size and smell of the placebo and cinnamon. Capsules were packaged in non-transparent black plastic bottles and coded A or B. To ensure that the characteristic cinnamon aroma was present for the placebo capsules, cinnamon powder was placed under the lid of the placebo bottles. The capsules were sealed independently in serially numbered containers of equal appearance and weight (allocation concealment). The investigator and clinicians involved in the clinical trial at different sites received sealed bottles of capsules (A and B) for distribution and were unaware which were active and placebo during the 12 weeks of the

intervention period. Compliance was monitored by capsule count at weeks 6 and 12. Finally, a post-intervention compliance questionnaire was used to collect information pertaining to compliance about capsule counts, tolerability and safety. A tolerability score of $\geq 80\%$ was considered as excellent. To ensure that the study was properly double blinded, the patients were asked post-intervention (by questionnaire) whether they were aware of the type of capsule they were taking (Table 1).

Data collection

At baseline (week 0), all participants were requested to complete a structured questionnaire (validated and pretested) reporting socio-demographic characteristics and lifestyle characteristics (such as smoking habits, consumption of alcohol, physical activity and dietary habits). The physical activity behaviour of patients was self reported. Participants also answered questions regarding time since diagnosis of diabetes, type of treatment for diabetes, other diagnosed medical conditions (such as

Table 1 Characteristics of the study participants at baseline ($n = 58$)

Baseline characteristics	Cinnamon ($n = 30$)	Placebo ($n = 28$)	<i>P</i>
Age (years)	54.90 ± 10.14	54.43 ± 12.53	0.877
Sex			
Males	11 (36.6)	15 (53.6)	
Females	19 (63.4)	13 (46.4)	0.291
BMI (kg/m^2)	33.36 ± 4.20	32.13 ± 8.31	0.150
Time since diagnosis of Type 2 diabetes (years)	5.76 ± 4.93	5.84 ± 4.23	0.946
Number of capsules remaining (capsule count after 12 weeks)	1.50 ± 1.52	1.75 ± 2.03	0.596
Tolerability scores			
Excellent (> 80%)	21 (70)	18 (64)	
Good (65–80%)	8 (27)	9 (32)	
Acceptable (50–65%)	1 (3)	1 (4)	0.1686
Awareness of the type of capsules received			
I received cinnamon capsules	24 (80)	23 (82)	
I received placebo capsules	6 (20)	3 (11)	
I don't know what capsule I received	0 (3)	2 (7)	0.135
Ethnicity			
White (British/Irish/others)	6 (60)	4 (40)	
Asian/Asian British (Indians/Pakistani/Bangladeshi/others)	17 (51.5)	16 (48.5)	
Black/Black British (African/Caribbean/others)	7 (46.7)	8 (53.3)	0.179
Blood pressure or cholesterol-lowering medication			
Anti-hypertensive only	4 (13)	9 (32)	
Statins only	8 (27)	4 (14)	
Both anti-hypertensive and statins	5 (17)	2 (7)	
None of both	13 (43)	13 (46)	0.214
Glucose-lowering medication			
Metformin	24 (80)	20 (71)	
Sulphonylureas	2 (7)	5 (8)	
Both metformin and sulphonylureas	4 (13)	3 (11)	0.422
Diagnosed medical conditions of hypertension or dyslipidaemia			
Hypertension	6 (20)	11 (39)	
Dyslipidaemia	7 (23)	2 (7)	
Both hypertension and dyslipidaemia	7 (23)	7 (25)	
None	10 (33)	8 (29)	0.221
Alcohol consumption			
Yes	13 (45)	10 (36)	
No	16 (55)	18 (64)	0.592
Habits of smoking			
Never smoked	26 (90)	26 (93)	
I used to smoke	2 (7)	0 (0)	
I smoke daily	1 (3)	2 (7)	0.314
Compared with last year; physical activity this year			
More physical activity	8 (28)	8 (29)	
About the same	14 (48)	10 (36)	
Less physical activity	7 (24)	10 (36)	0.555
Level of exercise			
Hardly any	6 (21)	10 (36)	
Light	13 (45)	8 (29)	
Moderate	10 (34)	8 (29)	
Heavy	0 (0)	2 (7)	0.222
Patient referral/recruitment centres			
Monks Park Health Centre	9 (30)	10 (36)	
Willesden Health Centre	11 (37)	8 (28)	
Wembley Health Centre	10 (33)	10 (36)	0.206

Data presented as mean ± sd and n (%).

$P > 0.05$ (χ^2 -test) shows that there were no statistically significant difference observed between the cinnamon and placebo groups in terms of age, sex, time since diagnosis of diabetes, tolerability scores of cinnamon capsules, ethnicity, blood pressure and cholesterol-lowering medications, glucose-lowering medication, diagnosed medical conditions of hypertension and dyslipidaemia, alcohol consumption, habits of smoking and physical activity behaviours of the participants at baseline.

Patients recruited from each health centre were equally randomized in to cinnamon and placebo groups.

hypertension and dyslipidaemia) and related treatment (Table 1). Subjects were requested to complete a 3-day diet diary at baseline and post-intervention, which was used to analyse total energy intake from carbohydrates, proteins and fats (Table 3).

Height, weight and waist circumference (anthropometrics) were measured at baseline (week 0) and post-intervention (week 12) and BMI was calculated accordingly. Height was measured in centimetres while the subject stood erect and barefooted on a stadiometer with a movable headpiece. Weight was measured in kilograms by using a calibrated scale, in light clothes and no shoes. BMI was calculated by weight in kilograms divided

by the square of height in meters; kg/m^2). Waist circumference was measured in centimetres at the minimum circumference between the iliac crests and lower ribs by using a flexible tape while the subject stood erect with relaxed abdominal muscles. Systolic and diastolic blood pressure were measured three times on the left arm, with the subject in a sitting position, and were measured a second time, after 5 min rest using an aneroid sphygmomanometer and stethoscope. The average of the last two measurements was used as the blood pressure. Hypertension was defined as a systolic blood pressure of 140 mmHg or above, a diastolic blood pressure of 90 mmHg or above, or both [26,27]. The HbA_{1c} , fasting plasma glucose and serum

Table 2 The effect of cinnamon on glycaemic indicators, serum lipid profiles, BMI and systolic and diastolic blood pressures at baseline and post-intervention ($n = 58$)

Variables	Intervention	Cinnamon ($n = 30$)		Placebo ($n = 28$)		<i>P</i>
		Mean \pm SD	CI for mean	Mean \pm sd	CI for mean	
HbA_{1c} (%)	Baseline	8.22 \pm 1.16	(7.80–8.63)	8.55 \pm 1.82	(7.84–9.26)	0.809
	Post-intervention	7.86 \pm 1.42	(7.33–8.39)	8.68 \pm 1.83	(7.97–9.39)	0.029
	Changes (Δ)	0.36 \pm 0.90	(0.01–0.69)	–0.12 \pm 0.82	(–0.44–0.19)	0.002
Fasting plasma glucose (mmol/l)	Baseline	8.82 \pm 3.45	(7.53–10.11)	8.77 \pm 2.59	(7.76–9.78)	0.641
	Post-intervention	8.04 \pm 3.10	(6.88–9.20)	8.74 \pm 3.11	(7.53–9.95)	0.318
	Changes (Δ)	0.78 \pm 1.86	(0.08–1.48)	0.03 \pm 1.82	(0.002–0.73)	0.888
HDL cholesterol (mmol/l)	Baseline	1.18 \pm 0.29	(1.06–1.28)	1.16 \pm 0.19	(1.08–1.23)	0.764
	Post-intervention	1.21 \pm 0.31	(1.08–1.32)	1.14 \pm 0.21	(1.05–1.22)	0.360
	Changes (Δ)	–0.03 \pm 0.13	(–0.08–0.02)	0.02 \pm 1.13	(–0.03–0.06)	0.257
LDL cholesterol (mmol/l)	Baseline	2.47 \pm 0.96	(2.11–2.83)	2.27 \pm 0.75	(1.93–2.52)	0.284
	Post-intervention	2.52 \pm 1.00	(2.06–2.85)	2.34 \pm 0.78	(2.01–2.66)	0.648
	Changes (Δ)	–0.04 \pm 0.72	(–0.32–0.23)	–0.07 \pm 0.35	(–0.21–0.07)	0.740
Serum triglycerides (mmol/l)	Baseline	1.65 \pm 0.93	(1.28–1.97)	1.48 \pm 1.04	(1.11–1.91)	0.427
	Post-intervention	1.60 \pm 0.83	(1.28–1.91)	1.66 \pm 1.16	(1.20–2.12)	0.774
	Changes (Δ)	0.05 \pm 0.45	(–0.55–0.48)	–0.18 \pm 0.53	(–0.39–0.03)	0.509
Total cholesterol (mmol/l)	Baseline	4.31 \pm 1.07	(3.91–4.71)	4.10 \pm 0.87	(3.76–4.44)	0.420
	Post-intervention	4.34 \pm 1.09	(3.93–4.75)	4.25 \pm 1.05	(3.84–4.66)	0.743
	Changes (Δ)	–0.03 \pm 0.82	(–0.33–0.27)	–0.15 \pm 0.52	(–0.35–0.38)	0.844
Body weight (kg)	Baseline	87.60 \pm 17.51	(81.1–94.1)	87.52 \pm 20.24	(79.7–95.3)	0.989
	Post-intervention	84.70 \pm 16.43	(78.5–90.8)	87.02 \pm 18.88	(79.7–94.3)	0.618
	Changes (Δ)	2.90 \pm 2.33	(2.02–3.76)	0.50 \pm 1.92	(0.01–1.24)	0.183
Waist circumference (cm)	Baseline	106.36 \pm 11.89	(101.9–110.8)	105.09 \pm 13.40	(99.8–110.2)	0.704
	Post-intervention	103.94 \pm 10.80	(99.9–107.9)	104.48 \pm 12.85	(99.5–109.4)	0.860
	Changes (Δ)	2.42 \pm 2.01	(1.67–3.17)	0.61 \pm 3.40	(0.08–1.92)	0.354
BMI (kg/m^2)	Baseline	33.36 \pm 4.20	(31.8–34.9)	32.13 \pm 8.30	(28.9–35.4)	0.150
	Post-intervention	32.30 \pm 3.87	(30.9–33.8)	31.94 \pm 7.76	(28.9–34.9)	0.418
	Changes (Δ)	1.06 \pm 0.80	(0.75–1.35)	0.19 \pm 0.75	(0.01–0.47)	0.096
Systolic blood pressure (mmHg)	Baseline	133 \pm 8.6	(129–136)	134 \pm 10.9	(129–139)	0.654
	Post-intervention	129 \pm 7.9	(126–132)	135 \pm 9.2	(131–139)	0.011
	Changes (Δ)	4 \pm 1.77	(3.9–4.3)	–1 \pm 3.95	(–2.1–1.2)	< 0.001
Diastolic blood pressure (mmHg)	Baseline	85 \pm 6.45	(83–88)	87 \pm 8.82	(83–90)	0.473
	Post-intervention	81 \pm 5.80	(78–83)	86 \pm 8.08	(83–89)	0.008
	Changes (Δ)	4 \pm 4.25	(3.1–6.3)	1 \pm 4.32	(–1.1–2.5)	< 0.001

Data presented as mean \pm SD and 95% CI for mean.

All variables were found to be similar ($P > 0.05$) at baseline between the cinnamon and placebo groups. At post-intervention (week 12), there was a significant difference ($P < 0.05$) in HbA_{1c} , systolic and diastolic blood pressures between the cinnamon and placebo groups. Similarly, the changes (Δ) in HbA_{1c} , systolic and diastolic blood pressures were also statistically significant ($P < 0.05$) between the cinnamon and placebo group. At post-intervention, the mean HbA_{1c} , fasting plasma glucose, body weight, waist circumference, BMI, systolic and diastolic blood pressures in the cinnamon group were significantly ($P < 0.05$) low compared with baseline. However, the changes (Δ) in fasting plasma glucose, body weight, BMI, waist circumference and serum lipid profiles in the cinnamon group were not significantly ($P > 0.05$) different from the placebo group.

lipid profiles were measured as part of the patient's diabetes standard care in Brent NHS, London. HbA_{1c} was assessed by high-performance liquid chromatography, which is able to separate haemoglobins in whole blood samples. (G8 Best Practice Guide Version 1.0; Tosoh Bioscience, London, UK). An enzymatic rate assay method (Abbott kit insert assay; Abbott Laboratories, London, UK) was used to measure serum total cholesterol, triglycerides and HDL cholesterol levels. LDL cholesterol was calculated using the Friedwald equation [LDL cholesterol = total cholesterol - HDL cholesterol - (triglycerides)/2.2]. Hexokinase/glucose-6-phosphate dehydrogenase was used to assess fasting plasma glucose levels.

Statistical analysis

SPSS version 15.0 (SPSS Inc., Chicago, IL, USA) was used to analyse the data. The Kolmogorov–Smirnov test was used to assess whether the data were normally distributed. If the Kolmogorov–Smirnov test is highly significant ($P < 0.05$), this indicates that the distributions are not normal (skewed). Owing to the skewed distribution of the variables of BMI, fasting plasma glucose, dietary carbohydrate, fat, protein, sodium, fibre and serum triglyceride concentrations (at baseline and post-intervention), the Mann–Whitney U -test was applied for detection of intergroup differences and the Wilcoxon test used for intragroup differences for this variable. If data were normally distributed, parametric tests (paired and independent t -tests) were used to compare means within and between groups respectively. ANCOVA was used to measure the effect of covariates on the independent variables of cinnamon or placebo. Data are shown as mean \pm SD and n (%). P -values < 0.05 were considered statistically significant. The total energy intake

from the 3-day diet diary was analysed by diet plan 6 (Forestfield Software, Horsham, West Sussex, UK). Post-hoc tests for the Kruskal–Wallis (H-test) and Jonckheere's (J) test were also performed to demonstrate the effect of cinnamon on HbA_{1c}. The χ^2 -test was used to compare the data from the questionnaire; i.e. the socio-demographic and lifestyle characteristics of the participants in the cinnamon and placebo groups (Table 1).

Results

The baseline characteristics of the participants are shown in Table 1. The age and sex distribution were found to be similar between the groups. There were no significant differences in demographic and lifestyle variables between the groups (Table 1). Furthermore, this study had a minimum dropout rate, which is a fairly reliable indicator of treatment acceptability/tolerability. No side effects were reported because of cinnamon intervention; one patient reported mild gastric upset for 2 days in the placebo group. No subjects reported any changes in their hypertensive or dyslipidaemia medications or usual physical activity levels during the course of the study.

The mean post-intervention HbA_{1c} among patients in the cinnamon group was significantly different from that in the placebo group (7.86 vs. 8.68, $P = 0.029$) (Table 2). The mean change (Δ) in HbA_{1c} was also statistically significant between the groups (cinnamon Δ HbA_{1c} -0.36 ; placebo Δ HbA_{1c} 0.12 ; $P = 0.002$). There were no statistically significant differences observed at post-intervention between groups in terms of fasting plasma glucose, BMI, weight, waist circumference and lipid profiles. However, a significant reduction in fasting plasma glucose, BMI, weight and waist circumference was observed in

Table 3 Dietary analysis of total calorie intake from carbohydrates, fats and proteins at baseline and post-intervention ($n = 58$)

Variables	Cinnamon ($n = 30$)		Placebo ($n = 28$)	
	Baseline	Post-intervention	Baseline	Post-intervention
Total energy intake (kcal/day)	1863 \pm 270	1818 \pm 192	1844 \pm 228	1843 \pm 235
% carbohydrates (kcal/day)	47.7 \pm 7.2	47.2 \pm 9.4	47.0 \pm 6.9	48.5 \pm 6.0
% starch (kcal/day)	33.4 \pm 5.6	34.5 \pm 6.8	35.8 \pm 6.3	36.2 \pm 6.9
% sugar (kcal/day)	12.6 \pm 3.9	11.9 \pm 4.5	10.9 \pm 4.1	10.9 \pm 4.7
% total protein (kcal/day)	13.9 \pm 3.2	13.5 \pm 2.7	14.6 \pm 2.7	14.1 \pm 2.9
% total fats (kcal/day)	38.1 \pm 6.6	37.8 \pm 7.1	38.3 \pm 5.8	37.2 \pm 5.4
% SFA (kcal/day)	10.5 \pm 4.4	10.6 \pm 4.9	10.0 \pm 3.9	9.7 \pm 4.6
% PUFA (kcal/day)	7.8 \pm 2.8	7.5 \pm 2.9	7.3 \pm 2.6	7.6 \pm 2.7
% MUFA (kcal/day)	11.1 \pm 3.3	10.7 \pm 3.5	10.4 \pm 3.4	10.1 \pm 3.3
% trans-fats (kcal/day)	0.4 \pm 0.6	0.2 \pm 0.4	0.5 \pm 0.6	0.4 \pm 0.4
Sodium (mg/day)	4312 \pm 1794	4243 \pm 1487	4497 \pm 1425	4678 \pm 3862
Fibre (g/day)	6.1 \pm 1.7	6.1 \pm 2.5	6.1 \pm 2.2	6.2 \pm 2.1

Data presented as mean \pm sd.

Total energy intake of carbohydrates, proteins and fats were calculated from 3-day diet diary. There were no significant differences ($P > 0.05$) in total energy intakes including carbohydrates, fats, proteins, sodium/salt and fibre intake within and/or between the cinnamon and placebo groups at baseline and post-intervention.

MUFA, mono-unsaturated fatty acids; PUFA, poly-unsaturated fatty acids; SFA, saturated fatty acids.

the cinnamon group at post-intervention compared with baseline (Table 2). The post-hoc test demonstrated that HbA_{1c} was significantly ($P = 0.029$) affected by cinnamon intake (Kruskal–Wallis H-test = 4.76). Additionally, Jonckheere's test (J) revealed a significant trend in the data: as more cinnamon was consumed, the median HbA_{1c} decreased ($J = 560$, $Z = -2.18$, $r = -0.04$). Furthermore, the HbA_{1c} level at baseline showed a significant correlation with the decrease of HbA_{1c} ($r = 0.567$, $P = 0.008$). This positive correlation between baseline HbA_{1c} and the significant decrease of HbA_{1c} in our study demonstrated that subjects with poor glycaemic control may benefit more from cinnamon. ANCOVA suggests that there was no possible influence on the change in body weight ($P = 0.383$) or BMI ($P = 0.298$) and total energy intake ($P = 0.791$) on the improvement of HbA_{1c}. The mean post-intervention systolic blood pressure and diastolic blood pressure among patients in the cinnamon group was also significantly different from that in the placebo group (systolic blood pressure 129 vs. 135, $P = 0.011$; diastolic blood pressure 81 vs. 86, $P = 0.008$) (Table 2). The mean change (Δ) in systolic blood pressure and diastolic blood pressure was also statistically significant between the groups (cinnamon Δ systolic blood pressure -4 ; placebo Δ systolic blood pressure 1, $P < 0.001$; cinnamon Δ diastolic blood pressure -4 ; placebo Δ diastolic blood pressure -1 , $P < 0.001$) (Table 2). According to our blood pressure measurements, at baseline 53% ($n = 31$) of the subjects were hypertensive (cinnamon = 13 and placebo = 18). Interestingly, after 12 weeks of intervention, approximately 22% ($n = 13$) of the subjects were hypertensive (cinnamon = 8 and placebo = 5).

The total energy intake from carbohydrates, fats and proteins and intake of salt was found to be similar ($P > 0.05$) at baseline and post-intervention between the cinnamon and placebo groups (Table 3).

Discussion

This is the first clinical trial in the United Kingdom in a multi-ethnic population that has confirmed beneficial effects of 2 g cinnamon on HbA_{1c} and blood pressure in Type 2 diabetes patients. One of the main reasons for the significant reduction of HbA_{1c} in our study could be attributed to the administration of 2 g of cinnamon. Previously suggested mechanisms of action of cinnamon include delayed gastric emptying [22], increased glycogen synthesis by activating glycogen synthase and inhibiting glycogen synthase kinase 3 β , and reduced glucose absorption in the small intestine through increased glucosidase enzymes and inhibition of intestinal ATPase [10,23]. Furthermore, the baseline HbA_{1c}% (8.38 ± 1.49) in our study shows that patients had elevated glycaemic levels. Therefore, we suspect that the therapeutic effect of cinnamon may depend upon the subjects' baseline HbA_{1c} level; it could be more effective among patients with elevated HbA_{1c}. The post-hoc analysis of the results of previous human intervention trials [4–6] also demonstrates that in well-controlled Type 2 diabetic patients

(HbA_{1c} < 7%), the effects of cinnamon on HbA_{1c} may be minimized.

We designed the study based on the minimal required duration of HbA_{1c} change (i.e. 8–12 weeks) and on previous studies. It would be very useful to look at the sustainability (beyond 12 weeks) of the effects of cinnamon, which we would like to do in the future. Measuring HbA_{1c} represents an 8- to 12-week (2- to 3-month) average of blood glucose concentrations [24].

The randomized controlled trials on the glucose-lowering potency of cinnamon in the past few years have demonstrated conflicting results [3–6]. Ziegenfuss *et al.* [25] reported an 8.4% reduction in fasting plasma glucose in subjects with mean baseline fasting plasma glucose of 6.46 mmol/l treated with 10 g of cinnamon daily for 12 weeks. This illustrates that an even higher cinnamon dose can bring about a significant reduction in blood glucose ($P < 0.01$) in subjects with lower baseline fasting plasma glucose and suggests a possible relationship between baseline fasting plasma glucose, dose of cinnamon and reduction in glycaemic levels. However, the tolerability and compliance of a high dose of cinnamon along with glucose-lowering medication is uncertain and needs to be investigated further. Therefore, it remains unclear whether the effects of cinnamon are because of the dosage or the duration of the study, or related to the baseline glycaemic levels, and further studies are important to address these issues.

According to the current guidelines recommended for the treatment of diabetes, normal or near normal blood pressure with a systolic blood pressure of < 130 mmHg and a diastolic blood pressure of < 80 mmHg should be achieved [26,27]. Therefore, patients with elevated baseline blood pressure ($\sim 134/86$ mmHg) in our study demonstrate that improvements in systolic blood pressure and diastolic blood pressure may found with higher baseline values. This again suggests that subjects with a higher baseline blood pressure level may benefit more from cinnamon intake. Additionally, attainment of better glycaemic control may also improve blood pressure. Results from the study by Ziegenfuss *et al.* [25] also demonstrate that the effect of cinnamon on blood pressure was greater with higher baseline systolic blood pressure. The results of studies in animals have also proposed that cinnamon has the ability to regulate blood pressure levels through peripheral vasodilatation [28]. However, the exact blood pressure-lowering mechanism of cinnamon is still unknown and further studies needs to elucidate this issue. None of the previous human trials reported a beneficial effect of cinnamon on blood pressure. The ANCOVA demonstrates that there was no possible influence of the change in body weight ($P = 0.348$), HbA_{1c} ($P = 0.591$), total energy intake ($P = 0.568$) or sodium intake ($P = 0.189$) on changes in systolic and diastolic blood pressures. Most importantly, when evaluating the effect of sodium on systolic and diastolic blood pressures separately, the intake of low or high sodium did not significantly change our results in either group. Therefore, we believe cinnamon is independently associated with blood pressure levels.

There were no significant changes regarding the lipid profiles between the groups at baseline and post-intervention. Insulin

resistance leads to the overproduction of very low density lipoproteins and to a reduction of lipoprotein lipase activity, thereby resulting in dyslipidaemia [4]. We therefore suspect that the significant decrease in HbA_{1c} in our study may be enough to induce an improvement in the serum lipid profiles. Furthermore, the baseline lipid profiles in our study show a normal or near normal level (Table 2) and therefore the effect of cinnamon on lipid profiles may be minimal.

There were no changes regarding the total energy intake (calories from macronutrients and sodium) after the intervention compared with baseline in both groups. This may be because all participants received diet and lifestyle advice from dieticians at least twice during the study period. The excellent acceptability and tolerability of cinnamon and minimum dropout rate were the main strengths in this study. Despite the strengths of this randomized controlled trial study design; there are some important limitations that may jeopardize the internal and external validity of this study. Subjects were not stratified by age or gender or type of glucose-lowering medication or time since diagnosis of diabetes. Participants in this study were treated with sulphonylurea and metformin, and these medications have different pharmacological effects. Therefore, stratifying subjects based on the type of drugs they used could be considered in future studies. Although *Cinnamomum cassia* species was administered in this study, the precise consideration of the purity of cinnamon, the chemical composition or active ingredients and the potency of derivatives of cinnamon may be influenced by the age of the cinnamon plant, the geographical location, the season of harvest, the method of drying and the crude preparation. The use of a standardized method could eliminate this bias.

In summary, the administration of cinnamon (2 g/day for 12 weeks), along with regular medications for Type 2 diabetes, significantly reduced HbA_{1c} and systolic and diastolic blood pressures compared with a placebo group. The 2-g dose of cinnamon administered in our study was safe and well tolerated over the 12 weeks of treatment. The sustainability and durability of the effect of cinnamon has not been tested, nor has its long-term tolerability and safety, both of which will need to be determined. However, the short-term effects of the use of cinnamon for patients with Type 2 diabetes look promising.

Competing interests

Nothing to declare.

Acknowledgements

This study was supported by the following: Thames Valley University UK; Jeffrey Kelson Diabetes and Endocrine Centre, Central Middlesex Hospital London; Brent NHS London; Department of Dietetics, Brent National Health Services, London; Research and Development Office, Brent National Health Services, London and Holland and Barrett Ltd, UK.

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