Cinnamon Supplementation Does Not Improve Glycemic Control in Postmenopausal Type 2 Diabetes Patients

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ABSTRACT In vitro and in vivo animal studies have reported strong insulin-like or insulin-potentiating effects after cinnamon administration. Recently, a human intervention study showed that cinnamon supplementation (1 g/d) strongly reduced fasting blood glucose concentration (30%) and improved the blood lipid profile in patients with type 2 diabetes. The objective of this study was to investigate the effects of cinnamon supplementation on insulin sensitivity and/or glucose tolerance and blood lipid profile in patients with type 2 diabetes. Therefore, a total of 25 postmenopausal patients with type 2 diabetes (aged 62.9 ± 1.5 y, BMI 30.4 ± 0.9 kg/m^2) participated in a 6-wk intervention during which they were supplemented with either cinnamon (*Cinnamomum cassia*, 1.5 g/d) or a placebo. Before and after 2 and 6 wk of supplementation, arterialized blood samples were obtained and oral glucose tolerance tests were performed. Blood lipid profiles and multiple indices of whole-body insulin sensitivity were determined. There were no time × treatment interactions for whole-body insulin sensitivity or oral glucose tolerance. The blood lipid profile of fasting subjects did not change after cinnamon supplementation. We conclude that cinnamon supplementation (1.5 g/d) does not improve whole-body insulin sensitivity or oral glucose tolerance and does not modulate blood lipid profile in postmenopausal patients with type 2 diabetes. More research on the proposed health benefits of cinnamon supplementation is warranted before health claims should be made. J. Nutr. 136: 977–980, 2006.

KEY WORDS: • *oral glucose tolerance* • *lipid profile* • *diabetes* • *nutrition* • *insulin sensitizer*

Type 2 diabetes is the most common metabolic disease worldwide, with a prevalence estimated to rise from 171 million in 2000 to 366 million in 2030 (1). Although the cause of type 2 diabetes appears to be multifactorial, it has been firmly established that diet can play a major role in the incidence and progression of the disease (2). In addition to drug treatment, dietary interventions were shown to represent an effective tool to prevent and/or treat insulin resistance and/or type 2 diabetes (3,4).

Cinnamon is one of the spices claimed to be a natural insulin sensitizer (5,6). The insulin-sensitizing effect of cinnamon was established in in vitro cell line studies with adipocytes (6–8) as well as in in vivo animal studies (9). The bioactive compound isolated from cinnamon was first classified as a methylhydroxychalcone polymer (MHCP),[2] which acts as a mimetic of insulin (8). Qin et al. (9) reported that oral administration of MHCP in rats increased the rate of plasma glucose disposal into skeletal muscle by improving the insulin-signaling cascade through tyrosine phosphorylation of the insulin receptor substrate 1 (IRS-1). More recently, Anderson et al. (7) suggested that water-soluble polyphenolic type-A polymers were likely misidentified as MHCP in earlier studies.

The first in vivo study on cinnamon supplementation in humans was published recently (10) and gained enormous media attention. This study by Khan et al. reports a substantial reduction in fasting serum glucose concentration (18–29%) and improved blood lipid profile after 40 d of daily supplementation with only 1, 3, or 6 g of cinnamon (*Cinnamomum cassia)* in patients with type 2 diabetes. They concluded that inclusion of a relatively small amount of cinnamon in the diet of patients with type 2 diabetes likely represents a safe and effective way of reducing the risk factors for the development of co-morbidities associated with type 2 diabetes and cardiovascular disease. The study has since been quoted in numerous magazines and newspapers, and cinnamon-containing nutritional supplements are currently being released on the market.

Although Khan et al. (10) provided us with interesting and promising data, solid evidence that cinnamon supplementation effectively improves fasting blood glucose concentration and/or the lipid profile remains to be established. In their study, Khan

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[2] Abbreviations used: HbA_{1c}, glycosylated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; IRS-1, insulin receptor substrate 1; ISIcomp, index of composite whole-body insulin sensitivity; MHCP, methylhydroxychalcone polymer; OGIS, oral glucose insulin sensitivity; OGTT, oral glucose tolerance test; PI 3-kinase, phosphatidylinositol 3-kinase; PTP-1, protein tyrosine phosphatase 1.

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and co-workers do not report any dietary standardization during the intervention. Furthermore, it remains unclear why potential changes in blood insulin and/or glycosylated hemoglobin (HbA_{1c}) concentration were not included in their study design. Because indices of glucose tolerance and insulin sensitivity were not evaluated, research is warranted to assess the effects of cinnamon supplementation on glucose tolerance and/or whole-body insulin sensitivity.

The present study investigated the proposed health benefits of cinnamon use in patients with type 2 diabetes. Therefore, a standardized 6-wk placebo-controlled intervention study was performed in 25 postmenopausal patients with type 2 diabetes. In this study, we assessed the effects of 2 and 6 wk of cinnamon supplementation (*Cinnamomum cassia*, 1.5 g/d) on fasting blood glucose, insulin, and HbA_{1c} concentrations, indices of oral glucose tolerance and whole-body insulin sensitivity, and fasting blood lipid profiles.

SUBJECTS AND METHODS

Subjects. A total of 25 postmenopausal women diagnosed with type 2 diabetes were selected to participate in this study. Type 2 diabetes was verified by an oral glucose tolerance test (OGTT) according to the criteria set by the WHO in 1999 (11). Exclusion criteria were impaired liver or renal function, cardiovascular disease, and exogenous insulin therapy. All subjects were using either oral blood glucose–lowering agents (sulfonylurea derivatives with or without metformin derivatives, $n = 14$; thiazolidinediones with or without metformin derivatives, $n = 6$; metformin derivatives only, $n = 3$) or diet only ($n = 4$). All subjects were stable because medication had not been modified over the last 3 mo. Subjects were assigned to a control ($n = 13$) or placebo group ($n = 12$), matched for age, BMI, years since diagnosis with type 2 diabetes, fasting blood glucose concentration, and medication (**Table 1**). The nature and risks of the experimental procedures were explained to the subjects, after which their written informed consent was obtained. The study was approved by the Medical Ethical Committee of the Academic Hospital Maastricht and performed at the Maastricht University.

Screening. Before inclusion in the study, an OGTT was performed in all subjects. After an overnight fast, subjects arrived at the laboratory at 0800. A blood sample was collected, which was followed by the ingestion of 75 g glucose dissolved in 250 mL water ($t = 0$ min). Subjects were given maximum of 3 min to ingest the glucose-containing beverage. After 120 min, a second blood sample was obtained. Plasma glucose concentrations were measured to verify the type 2 diabetes state.

TABLE 1

Baseline characteristics of postmenopausal patients with type 2 diabetes[1,2]

n	Placebo 13	Cinnamon 12
Age, *y*	64 ± 2	62 ± 2
Body weight, *kg*	82.2 ± 4.0	85.4 ± 3.6
Height, *m*	1.65 ± 0.02	1.67 ± 0.02
BMI, *kg/m²*	30.1 ± 1.4	30.7 ± 1.1
Fasting plasma glucose, *mmol/L*	8.28 ± 0.33	8.37 ± 0.59
Fasting plasma insulin, *pmol/L*	111.0 ± 15.5	110.1 ± 13.0
HbA_{1c}, *%*	7.1 ± 0.2	7.4 ± 0.3
HOMA-IR	6.01 ± 1.03	6.21 ± 1.12
ISIcomp	34.1 ± 3.8	34.5 ± 5.8
Time since diagnosis, *y*	7.1 ± 1.6	7.6 ± 1.4

[1] Values are means ± SEM. The groups did not differ for any variable, $P > 0.05$.

[2] Insulin sensitivity was estimated using HOMA-IR (12) and ISIcomp (13).

Study design and dietary intervention. Subjects were studied over a 6- to 7-wk period in a double-blind, placebo-controlled trial at least 2 wk after the screening. Whole-body insulin sensitivity or oral glucose tolerance were estimated by performing an OGTT before (wk 0) and after 2 (wk 2) and 6 wk (wk 6) of supplementation with either 1500 mg/d cinnamon (*Cinnamomum cassia*, Verstegen) or 1500 mg/d placebo (wheat flour, Verstegen). In addition, HbA_{1c} and blood lipid profiles were determined in blood samples from fasting subjects collected before and after 2 and 6 wk of supplementation. After the initial test, subjects received prepackaged amounts of capsules containing either cinnamon or placebo and were instructed to ingest 1 capsule (500 mg) at each main meal (breakfast, lunch and dinner). Capsules were prepared by the local pharmacy and could not be distinguished by color, scent, or taste. Nontransparent packages of capsules were prepared by a technician and provided to each subject by the experimenter. Compliance was monitored by counting the unconsumed capsules of the surplus of capsules provided by personal contact on a weekly basis.

During the experimental period, the subjects maintained their normal dietary and physical activity pattern and all medication was continued. All subjects excluded food products containing cinnamon from their diet and refrained from heavy physical exercise training and/or labor for at least 3 d before each OGTT. Dietary food intake records were obtained for 2 d before the first OGTT. These were used to standardize dietary intake before the other OGTT trials. Food intake was recorded and details on energy intake and macronutrient composition of the diet before each of the 3 OGTT trials were compared. In addition, all subjects were fed the same standardized meal the evening before each of the trials (44 kJ/kg body mass; 60% of energy as carbohydrate, 28% of energy as fat, and 12% of energy as protein). All medication was continued as usual, with the last dose of medication taken before 2200 on the evening before the trials.

Examination procedures. After an overnight fast, subjects arrived at the laboratory at 0800 h. A Teflon catheter (Baxter Quick Cath Dupont) was inserted into a dorsal hand vein. Before the collection of arterialized blood samples, the hand was enclosed for 15 min in a hot-box at a temperature of 60°C. Arterialized blood samples provide a more accurate measure of circulating blood metabolite concentrations because they prevent confounding via local changes in blood flow or metabolic activity in the arm. After collection of the first blood sample, 75 g glucose was ingested. Thereafter, arterialized blood samples were collected every 30 min until $t = 120$ min.

Biochemical measurements. Blood (10 mL) was collected in EDTA-containing tubes and immediately centrifuged at 1000 × *g* for 10 min at 4°C. Aliquots of plasma were immediately frozen in liquid nitrogen and stored at −80°C until analysis. Glucose concentrations (Uni Kit III, La Roche) were analyzed with COBAS FARA semi-automatic analyzer (Roche). Insulin was analyzed by RIA (Linco Human Insulin RIA Kit). Reagents to determine plasma triacylglycerol, HDL, LDL, and total cholesterol were from ABX Diagnostics. HbA_{1c} content was analyzed using a blood sample from a fasting subject (3 mL, EDTA) by HPLC (Bio-Rad Variant II).

Insulin sensitivity/oral glucose tolerance. Parameters of insulin sensitivity and/or glucose tolerance were calculated on the basis of fasting blood parameters [the homeostasis model assessment of insulin resistance (HOMA-IR)] and/or the OGTT. The HOMA-IR index was calculated as the product of fasting plasma glucose (mmol/L) and insulin (mU/L) concentrations divided by 22.5 (12). The index of composite whole-body insulin sensitivity (ISIcomp) was calculated using all 5 plasma glucose (mmol/L) and insulin (mU/L) concentrations collected at 0, 30, 60, 90, and 120 min after glucose intake in a 2-h OGTT (13); the oral glucose insulin sensitivity (OGIS) was calculated as described by Mari et al. (14).

Statistics. Data are expressed as means ± SEM. For non-time-dependent variables, a Mann-Whitney U test was applied. Power analyses revealed that sample size was sufficient to detect <50% of the effects described earlier by Khan et al. (10). For multiple comparisons, data were analyzed using a 2-way repeated-measures ANOVA with treatment and time as the 2 factors. When significant time × treatment interactions were found, subgroups were analyzed further and changes in time within each group were checked using a 1-way repeated-measures ANOVA. Statistical significance was set at

$P < 0.05$. All calculations were performed using the Statistical Package for the Social Sciences 12.0 (SPSS).

RESULTS

Baseline characteristics did not differ between the 2 intervention groups of the study population (Table 1). Energy intake and macronutrient composition of the diet did not differ between groups at baseline and did not change in the placebo or cinnamon group during the intervention period. The recorded mean energy intake in the entire population was 76.8 ± 4.0 kJ/kg body mass, with 50.6 ± 1.0% of energy as carbohydrates, 30.6 ± 1.0% of energy as fat, and 16.8 ± 0.6% of energy as protein. Alcohol consumption was negligible during the intervention period.

Before supplementation, plasma HbA_{1c} and fasting glucose and insulin concentrations did not differ between the groups (**Table 2**). During the intervention period, there were no time × treatment interactions for plasma HbA_{1c}, fasting glucose, or insulin concentrations.

Before supplementation, the groups did not differ in fasting plasma triacylglycerol, LDL, HDL, and total cholesterol concentrations (Table 2). There were no time × treatment interactions for fasting blood lipid concentrations during the intervention period.

Before supplementation, insulin resistance and sensitivity indices did not differ between the groups (**Table 3**). During the intervention period, there were no time × treatment interactions for HOMA-IR, ISIcomp, or OGIS.

DISCUSSION

The present study shows that 6 wk of cinnamon supplementation (*Cinnamomum cassia,* 1.5 g/d) does not improve fasting plasma glucose or insulin concentrations, whole-body oral glucose tolerance, or blood lipid profiles in postmenopausal patients with type 2 diabetes.

Khan et al. (5) were the first to report that cinnamon enhances glucose uptake in a rat epididymal fat cell assay. Thereafter, others confirmed the insulin-potentiating properties of cinnamon on glucose uptake (6) and on glycogen production in 3T3-L1 adipocytes (8). A possible mechanism by which cinnamon potentiates insulin signaling was defined by Imparl-Radosevich et al. (15). In their in vitro study, they reported that a cinnamon extract stimulates autophosphorylation of the insulin receptor kinase domain and inhibits protein tyrosine phosphatase (PTP)-1, thereby relieving the PTP-1–induced inhibition of the insulin receptor activity.

The purified bioactive compound from cinnamon was first classified as a methylhydroxychalcone polymer (MHCP), which stimulated insulin-like cellular responses in 3T3-L1 adipocytes (8). Qin et al. (9) showed that oral administration of MHCP increased glucose disposal in vivo in rat skeletal muscle. This was attributed to enhanced tyrosine phosphorylation of the insulin receptor substrate 1 (IRS-1) and increased IRS-1/PI 3-kinase association. Qin et al. (9) did not assess the direct effect of cinnamon on the activation of PI 3-kinase, but tyrosine phosphorylation of IRS-1 leads to the binding of PI 3-kinase (16) and correlates closely with PI 3-kinase activation (17). Therefore, they concluded that MHCP induces changes in tyrosine phosphorylation of IRS-1, which improve PI 3-kinase activation and subsequent glucose uptake. More recently, Anderson et al. (7) reported that water-soluble polyphenolic type-A polymers increased the in vitro insulin-dependent breakdown of radiolabeled glucose to carbon dioxide in rat epididymal adipocytes. The authors proposed that these type-A polymers could likely have been misidentified as MHCP in earlier studies.

Recently, Khan et al. (10) presented the first data on the effects of cinnamon supplementation in vivo in humans. In their study, 10 patients with type 2 diabetes (aged 52.2 ± 6.3 y) consumed 1, 3, or 6 g of cinnamon or placebo daily for a period of 40 d. Cinnamon consumption led to a major reduction in fasting serum glucose (18–29%), triacylglycerol (23–30%), LDL (7–27%), and total cholesterol (12–26%) concentrations in each of the cinnamon supplementation trials. Consequently, the authors concluded that small amounts of cinnamon likely represent a safe and effective means to reduce the risk factors for the development of co-morbidities associated with type 2 diabetes. Presently, cinnamon-containing nutritional supplements are being released on the market, claiming health benefits for patients with type 2 diabetes.

In the present study, we investigated the effects of short- and long-term cinnamon use (1.5 g/d) on oral glucose tolerance, whole-body insulin sensitivity, and the blood lipid profile. We performed glucose and insulin analyses on arterialized blood samples collected in repeated OGTT trials under strict dietary standardization. In blood samples from fasting subjects, we also measured HbA_{1c} concentration as an indicator of blood glucose homeostasis (18) and triacylglycerol, LDL, HDL, and total cholesterol concentrations. Cinnamon use did not affect fasting glucose concentrations, HbA_{1c}, or the HOMA-IR index as measures of glucose homeostasis and/or insulin sensitivity (Tables 2–3). Other, more contemporary indices of oral glucose tolerance and whole-body insulin sensitivity (OGIS and

TABLE 2

Effect of cinnamon supplementation on plasma biochemistry in fasting, postmenopausal patients with type 2 diabetes[1]

	Placebo			Cinnamon		
	Before	2 wk	6 wk	Before	2 wk	6 wk
Plasma glucose, *mmol/L*	8.28 ± 0.33	8.11 ± 0.31	8.07 ± 0.36	8.37 ± 0.59	8.37 ± 0.64	7.91 ± 0.71
Plasma insulin, *pmol/L*	111.0 ± 15.5	104.3 ± 13.9	104.9 ± 16.2	110.1 ± 13.0	103.5 ± 12.1	106.4 ± 13.2
HbA_{1c}, %	7.1 ± 0.2	7.1 ± 0.3	7.2 ± 0.2	7.4 ± 0.3	7.4 ± 0.3	7.5 ± 0.3
Total cholesterol, *mmol/L*	4.91 ± 0.30	4.80 ± 0.29	4.66 ± 0.31	5.05 ± 0.15	4.90 ± 0.16	4.81 ± 0.19
LDL cholesterol, *mmol/L*	3.04 ± 0.25	2.91 ± 0.24	2.77 ± 0.24	3.06 ± 0.15	2.92 ± 0.14	2.85 ± 0.16
HDL cholesterol, *mmol/L*	1.29 ± 0.11	1.32 ± 0.10	1.29 ± 0.09	1.42 ± 0.09	1.39 ± 0.10	1.41 ± 0.09
Triacylglycerol, *mmol/L*	1.28 ± 0.14	1.24 ± 0.09	1.32 ± 0.18	1.25 ± 0.17	1.30 ± 0.17	1.20 ± 0.13

[1] Values are means ± SEM, $n = 13$ (placebo group) or 12 (cinnamon group). There were no time × treatment interactions for any variable, $P > 0.05$.

TABLE 3

Effect of cinnamon supplementation on whole-body insulin resistance/sensitivity indices in postmenopausal patients with type 2 diabetes[1]

	Placebo			Cinnamon		
	Before	2 wk	6 wk	Before	2 wk	6 wk
HOMA-IR	6.01 ± 1.03	5.48 ± 0.83	5.60 ± 1.05	6.21 ± 1.12	5.95 ± 1.18	5.82 ± 1.27
ISIcomp	34.1 ± 3.8	34.4 ± 3.5	38.0 ± 4.7	34.5 ± 5.8	35.3 ± 6.2	36.5 ± 5.7
OGIS	270 ± 10	270 ± 10	288 ± 12	291 ± 16	291 ± 19	313 ± 18

[1] Values are means ± SEM, $n = 13$ (placebo group) or 12 (cinnamon group). There were no time × treatment interactions for any variable, $P > 0.05$.

ISIcomp) were not affected by cinnamon use in these patients (Table 3). In line with these observations, cinnamon use did not affect blood lipid profiles. We conclude that cinnamon supplementation (1.5 g/d) does not improve oral glucose tolerance or whole-body insulin sensitivity in patients with type 2 diabetes.

Cinnamomum is a large genus, and the exact chemical composition of the cinnamon was shown to differ among different species and geographic sources (19). Therefore, we applied a daily supplementation dose of 1.5 g powdered *Cinnamomum cassia* in our study; this is the same cinnamon genius as that administered by Khan et al. (10) but in a 50% higher dose than their lowest effective dose. Differences in the administered dosage of cinnamon could not account for the apparent discrepant findings between the 2 studies. Our cinnamon was generated from the whole bark of Indonesian cinnamon trees and manufactured in a standard production process (Verstegen). Moreover, due to the continuing discussion about the identity of the proposed bioactive component(s) of cinnamon (7,8), a comparison based on the content of a certain substance is impossible. Furthermore, it should be noted that Anderson and co-workers compared several samples of cinnamon differing in geographic source (Indonesia, China, Vietnam) and commercial preparation (ground, bulk bark) for insulin-enhancing biological activity using the epididymal fat cell assay (7). They reported that the insulin-like activities of different species/samples of cinnamon tested were of similar magnitude. Nonetheless, differences in geographic source and preparation of the cinnamon should not be overlooked as potential sources of variability.

Differences between the 2 studies could be attributed to the inclusion of only women in the present study and the type of medication that was used by the patients. Although Khan et al. (10) selected subjects using only sulfonylurea derivatives, we selected a group of patients using commonly prescribed combinations of oral blood glucose–lowering agents (sulfonylureas derivatives, metformin, and/or thiazolidinediones). In addition, there were apparent differences in the baseline values of fasting glucose and triglycerides between the subjects participating in the 2 studies. Baseline values for fasting glucose and triglycerides were higher in the cohort described by Khan et al. (>11.4 and > 2.25 mmol/L, respectively) compared with our study population (8.3 and 1.26 mmol/L, respectively). These differences and the lack of nutritional standardization in the study by Khan et al. could likely be responsible for the discrepant findings in the 2 studies.

In conclusion, cinnamon supplementation (*Cinnamomum cassia,* 1.5 g/d) does not improve fasting blood glucose, oral glucose tolerance, or measures of whole-body insulin sensitivity in overweight, postmenopausal patients with type 2 diabetes. Furthermore, cinnamon supplementation does not modulate the blood lipid profile in these patients. Therefore, we conclude that the proposed health benefits of cinnamon supplementation in patients with type 2 diabetes should be regarded as not yet proven.

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