Influence of Cinnamon on Glycemic Control in Individuals With Prediabetes: A Randomized Controlled Trial

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Context: The identification of adjunct safe, durable, and cost-effective approaches to reduce the progression from prediabetes to type 2 diabetes (T2D) is a clinically relevant, unmet goal. It is unknown whether cinnamon's glucose-lowering properties can be leveraged in individuals with prediabetes.

Objective: The objective of this work is to investigate the effects of cinnamon on measures of glucose homeostasis in prediabetes.

Design, Setting, Participants, and Intervention: This double-blind, placebo-controlled, clinical trial randomly assigned adult individuals meeting any criteria for prediabetes to receive cinnamon 500 mg or placebo thrice daily (n = 27/group). Participants were enrolled and followed at 2 academic centers for 12 weeks.

Main Outcome Measures: Primary outcome was the between-group difference in fasting plasma glucose (FPG) at 12 weeks from baseline. Secondary end points included the change in 2-hour PG of the oral glucose tolerance test (OGTT), and the change in the PG area under the curve (AUC) derived from the OGTT.

Results: From a similar baseline, FPG rose after 12 weeks with placebo but remained stable with cinnamon, leading to a mean between-group difference of 5 mg/dL ($P < .05$). When compared to the respective baseline, cinnamon, but not placebo, resulted in a significant decrease of the AUC PG ($P < .001$) and of the 2-hour PG of the OGTT ($P < .05$). There were no serious adverse events in either study group.

Conclusions: In individuals with prediabetes, 12 weeks of cinnamon supplementation improved FPG and glucose tolerance, with a favorable safety profile. Longer and larger studies should address cinnamon's effects on the rate of progression from prediabetes to T2D.

Diabetes affects more than 460 million adults globally [1] and is the seventh leading cause of disability worldwide [2], accounting for more than \$320 billion in health care costs in the United States alone [3]. The rise in prevalence of diabetes over the past 3 decades, primarily type 2 diabetes (T2D), has occurred at a particularly fast rate in East and South Asia [4].

Using current diagnostic criteria set forth by the American Diabetes Association [5], approximately 38% of the US population has prediabetes [6], which remains unrecognized in the vast majority of cases [7]. Prediabetes portends an annual progression to T2D ranging from 3% to 11% depending on the population [8-10]. The rate of incident T2D is higher in individuals with impaired glucose tolerance (IGT) who are also at increased risk of cardiovascular disease, as compared to patients with impaired fasting glucose (IFG) [11, 12].

As previously reviewed [13], the conversion from prediabetes to T2D can be effectively prevented using lifestyle modifications [9, 14-16], antidiabetic drugs [9, 16-19], weight loss medications [20], and metabolic surgery [21, 22]. However, such approaches to T2D prevention have several limitations. First, long-term follow-up, which is available for only a subset of interventions, demonstrates a progressive attenuation of benefits on T2D conversion rate over time [23-25]. In addition, both the cost and potential side effects (eg, weight gain with pioglitazone) can limit adherence to drugs longitudinally. Finally, up to 50% of at-risk patients will develop T2D even within the structured framework of randomized clinical trials (RCTs) [13]. Therefore, identification of efficacious, durable, safe, and cost-effective strategies for T2D prevention remains a clinically relevant unmet need, especially in low- and middle-income countries.

Complementary and alternative medicine practices, including the use of nutraceuticals, have flourished over recent decades. Based on a 2012 National Health Interview Survey, 18% of adults in the United States had used a nonvitamin, nonmineral dietary supplement during the past year [26]. Approximately one-third of patients with T2D have used complementary and alternative medicine, either alone or as adjunct, for treatment of this condition. The evidence for safety and efficacy of nutraceuticals in T2D treatment is sparse and in many instances of low quality [27, 28].

Extracts of the inner bark of the *Cinnamomum* genus ("cinnamon") of aromatic trees, commonly used as flavoring agents, have been employed since ancient times for treating arthritis and other inflammatory diseases [29], and are currently marketed as therapeutic supplements for T2D. In experimental models of diabetes, mechanisms invoked for the glucose-lowering activity of cinnamon include increased glucose transporter type 4 (GLUT4) membrane translocation [30], stimulation of postprandial levels of glucagon-like peptide-1 [31], inhibition of α-glucosidase activity [32], and antioxidant properties [33].

Several RCTs in adult patients with T2D have addressed the effects of various powdered monopreparations of cinnamon, predominantly *Cinnamomum cassia*, on changes in glycated hemoglobin (HbA_{1c}), fasting plasma glucose (FPG), and lipid profile [34, 35]. The duration of these studies ranged from 4 weeks to 4 months with daily dosages of compounded cinnamon varying from 500 mg to 6000 mg. Notwithstanding significant heterogeneity in study design, the majority of RCTs demonstrated a 10% to 15% reduction in FPG from baseline whereas changes in HbA_{1c} were inconsistent and did not reach statistical significance in the aggregate [35]. Cinnamon's beneficial effects were more pronounced in drug-naive patients than as add-on therapy, and in patients with high baseline HbA_{1c} (> 8%) [34].

In individuals with prediabetes, the evidence from RCTs addressing the impact of cinnamon on glucose homeostasis is more limited. Specifically, it remains unclear whether in this population: a) cinnamon affects FPG, glucose tolerance, or both, and b) the response to cinnamon is conserved across ethnic groups.

Here, we present the results of efficacy and safety in a 2-country, placebo-controlled RCT of cinnamon treatment conducted in participants with prediabetes.

1. Materials and Methods

A. Participants

This study was a binational, double-blind, placebo-controlled RCT. Participants were recruited at Kyung Hee University Medical Center (Seoul, Republic of Korea) and the Joslin Diabetes Center (Boston, Massachusetts, US) between 2017 and 2018. The study was approved by the ethical board of Kyung Hee University Korean Medicine Hospital, (No. KOMCIRB-160318-HR-010) and the Joslin Diabetes Center (JDC) (No. 2017-15). This study was exempted from the Investigational New Drug Program by the US Food and Drug Administration. All participants provided written informed consent. Studies were conducted using Good Clinical Practice and in accordance with the Declaration of Helsinki.

Participants between ages 20 and 70 years were recruited for screening through advertisement brochures posted at the 2 enrolling clinical centers or if they had a history of dysglycemia consistent with prediabetes. Individuals met study inclusion criteria for prediabetes if they demonstrated one of the following abnormalities [5]: IFG, defined as FPG between 100 and 125 mg/dL; IGT, as demonstrated by a 2-hour PG level of 140 to 199 mg/dL based on 75-g oral glucose tolerance test (OGTT); and HbA_{1c} of 5.7% to 6.4%. Patients were excluded from screening and enrollment if they had evidence of diabetes mellitus or other significant endocrine, cardiovascular, pulmonary, renal, or liver disease, or intentional weight loss of 10 pounds (0.45 kg) or more within the past 6 months. Further exclusion criteria included pregnancy, therapy with corticosteroids, any drug or supplement with glucose-lowering activity, or any investigational drugs. The full list of exclusion criteria is available at the trial registration webpage at ClinicalTrials.gov (see "Study Funding and Oversight").

B. Study Funding and Oversight

The study was funded by a grant of the Ministry of Health and Welfare (Republic of Korea) awarded to the Korean Medicine Clinical Trial Center (K-CTC) at Kyung Hee University Medical Center as part of a collaboration with the JDC. Data and safety monitoring was conducted by an independent committee from K-CTC with periodic on-site review of study centers. The trial was registered with ClinicalTrials.gov on July 17, 2017 (NCT03219411).

C. Study Protocol

Screening procedures occurred after a minimum 8-hour overnight fast and included anthropometric measurements, HbA_{1c}, FPG, fasting insulin (FI), fasting lipid panel, comprehensive chemistry, and a standard 75-g OGTT. Eligible participants were randomly assigned 1:1 to receive cinnamon capsule 500 mg or placebo 3 times a day for 12 weeks.

Randomization was performed by a statistician using PROC PLAN of SAS 9.4 (SAS Institute Inc). To ensure a 1:1 allocation ratio of patients to cinnamon and placebo groups at each site, randomization was stratified by each site employing a random block design. All study participants and staff were blinded to treatment assignment until study completion.

The cinnamon capsules contained 300 mg of cinnamon extract (*Cinnamomum* spp) and 200 mg of *Cinnamomum burmannii* powder (Solgar Inc). The placebo, which contained cellulose (91.5%), caramel food coloring (8.4%), and cinnamon incense (0.1%) (BioFood Technology Center) did not contain any active substances. The overall appearance, weight, and organoleptic properties of cinnamon and placebo capsules were identical.

Of the 60 screened participants, 54 were enrolled in the study, which was completed by 51 participants (39 at Kyung Hee University Medical Center and 12 at JDC) (Fig. 1A). As shown in Fig. 1B, screening was performed at visit 1, and eligible participants were randomly assigned to placebo or cinnamon within 2 weeks (visit 2). Visits 3 and 4 occurred 6 and 12 weeks after randomization, respectively. The safety follow-up (visit 5) was performed
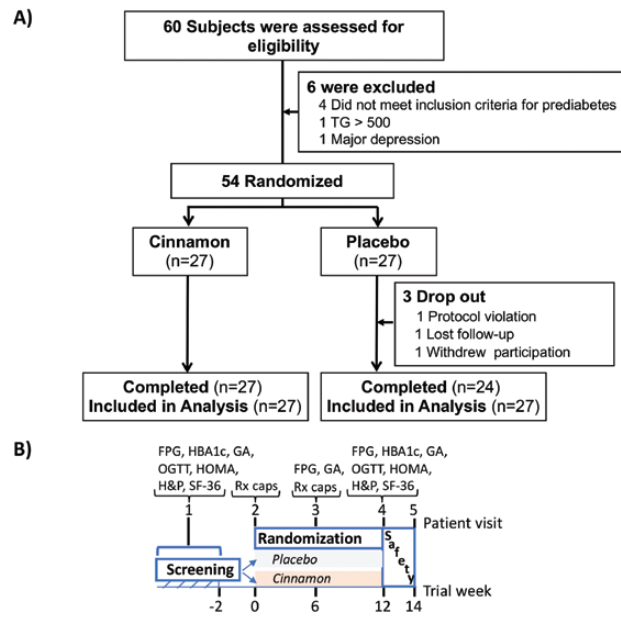
Figure 1. A, Screening, randomization, and follow-up through the 12-week treatment period. Six out of the 60 screened individuals were excluded. Three out of 27 participants randomly assigned to placebo did not complete the study. B, Study design and main assessments over the 5 patient visits. FPG, fasting plasma glucose; GA, glycated albumin; H&P, complete history and physical exam; HBA$_{1c}$, glycated hemoglobin; HOMA, Homeostatic Model Assessment, HOMA-IR and HOMA-B; IR, insulin resistance; OGTT, oral glucose tolerance test; Rx caps, dispensing of placebo or cinnamon capsules; SF-36, 36-Item Short Form Survey.

1 to 2 weeks after visit 4. Compliance with capsule administration was assessed at visit 3 and visit 4 by counting capsules returned by the patient, if any, and self-reported adherence to the thrice-daily regimen.

D. Primary and Secondary End Points

The primary outcome measure was the between-group difference in FPG at 12 weeks from baseline. Prespecified efficacy secondary end points included the change at 6 weeks from baseline in FPG; the change at 12 weeks from baseline in PG at the 2-hour time point of the OGTT; and the change at 12 weeks from baseline in the area under the curve (AUC) of PG derived from the OGTT. Other relevant measure of glucose homeostasis included HbA$_{1c}$, glycated albumin (GA), homeostatic model assessment for insulin resistance (HOMA-IR), which was calculated as FI (μU/mL) $\times$ FPG (mg/dL)/405, and (HOMA)–β-cell function (HOMA-B) percentage, which was calculated as $360 \times$ FI (μU/mL)/FPG (mg/dL) $-$ 63. Finally, a quality of life indicator test was completed using the 36-Item Short Form Survey.

E. Statistical Analysis

Statistical analyses were conducted using SPSS for Windows, version 21.0. Data are expressed as mean $\pm$ SD unless otherwise specified. The study was powered for detection of clinically significant differences in the primary end point of change in FPG. Briefly, the protocol was designed with the plan to enroll 60 participants with an expected 10% dropout, which would provide 90% power to detect a between-treatment difference in FPG means of 9 mg/dL with an SD of 10 mg/dL, with type 1 error of 0.05.

Primary and secondary outcomes were analyzed principally using an intent-to-treat approach, unless otherwise noted. The t test (or Mann-Whitney test) and the chi-square test (or Fisher exact test) were used to compare general characteristics within groups, and between the cinnamon and placebo groups. To adjust for potential between-groups differences

in PG at baseline, analysis of covariance was used to compare changes in FPG, and AUC and PG at all time points of the OGTT. Statistical tests were 2-sided with a significance level of α equal to .05.

F. Safety Analysis

Frequency and severity of adverse events (AEs), including serious AEs, were recorded and rated as mild, moderate, or severe. In addition, we monitored clinically relevant changes in vital signs and physical examination, and laboratory safety indicators such as complete blood cell count, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, and creatinine levels.

G. Assessments

OGTTs were performed in the morning after an overnight fast and PG levels were measured at baseline and then at 30, 60, 90, and 120 minutes after glucose administration using a YSI 2300 Stat Plus device (Xylem Inc). Within the plasma glucose range of 75 to 250 mg/dL, the intra-assay and interassay coefficients of variation were 0.9% and 1.5%, respectively. PG, and serum insulin and lipoprotein levels were measured in samples collected at baseline, and after 6 and 12 weeks of randomization at an accredited clinical chemistry laboratory at Kyung Hee University Hospital and JDC. GA was measured using a commercially available kit in serum samples at baseline, and at the 6- and 12-week time point (Lucica GA-L assay; Asahi Kasei Pharma Corporation). Total protein carbonylation was quantitated in serum samples (50 µL), according to the manufacturer's instructions (Sigma-Aldrich; catalog No. MAK094). Serum proteins carbonyl groups were derivatized with 2,4-dinitrophenyl (DNP)-hydrazine (DNPH) to form stable protein-DNP adducts followed by detection by fluorometry (375 nm). Carbonyl content (nanomoles, nmol) was calculated as absorbance/6.364 × 100 (6.364 = extinction coefficient), then normalized by microliter (µL) of serum. Only samples collected in participants enrolled at JDC were available for this post hoc analysis.

2. Results

A. Participant Characteristics

A total of 54 individuals meeting the criteria for prediabetes [5] were enrolled at 2 sites and randomly assigned to placebo (n = 27) or cinnamon (n = 27). The 12-week study period was completed by all participants in the cinnamon group and 24/27 participants enrolled in the placebo group (Fig. 1A). Baseline characteristics were well matched in the 2 groups (Table 1) with the exception of body mass index, which was higher in the group randomly assigned to cinnamon. Also, triglycerides' mean at baseline was higher in the placebo group owing to relatively elevated levels in 3 participants, who however did not meet the statistical definition of outliers. The proportion of participants with IFG, IGT, and IFG/IGT was comparable in the cinnamon (22%, 18%, and 48%, respectively) and placebo groups (20%, 13%, and 58%, respectively). Three participants in the cinnamon group and 2 in the placebo group were enrolled solely based on the HbA$_{1c}$ criterion. Adherence to the thrice-daily capsule regimen was greater than 90% in both treatment groups and study centers.

B. Efficacy

FPG levels were similar at enrollment in the placebo and cinnamon groups (110 ± 11 vs 109 ± 12 mg/dL, respectively) and were not different after 6 weeks of treatment in either group (109 ± 11 with placebo vs 108 ± 13 mg/dL with cinnamon). Conversely, the assessment at 12 weeks (visit 4) showed that FPG had increased from baseline by an average of

Table 1.   Characteristics of participants at baseline[a]

	Placebo	Cinnamon	
n	27	27	
Age, y	54.1 ± 8.0	50.4 ± 11.5	
Sex (M:F)	16:8	12:15	
Race[b]			
White	4	4	
Asian	19	23	
African American	1	0	
Weight, kg	69.8 ± 11.4	77.7 ± 20.9	
BMI, kg/m^2	25.5 ± 3.3	28.2 ± 5.0	[e]
SBP, mm Hg	125 ± 10	127 ± 11	
DBP, mm Hg	75 ± 7	77 ± 9	
FPG, mg/dL	110 ± 11.5	109 ± 12.4	
Glycated albumin, %	13.9 ± 1.2	13.8 ± 2.0	
HbA$_{1c}$, %	5.7 ± 0.4	6.0 ± 0.5	
OGTT, min			
0	105 ± 12	111 ± 12	
30	185 ± 23	171 ± 34	
60	211 ± 40	202 ± 38	
90	208 ± 45	194 ± 43	
120	174 ± 55	169 ± 55	
AUC	22 330 ± 4090	21 389 ± 3858	
Insulin, μIU/mL	12.7 ± 4.4	11.7 ± 7.1	
HOMA-IR[c]	3.17 ± 1.17	3.21 ± 2.09	
HOMA-B %[d]	92.4 ± 40.8	91.4 ± 50.6	
Total cholesterol, mg/dL	194 ± 37	180 ± 39	
Triglycerides, mg/dL	170 ± 95	109 ± 53	[f]
HDL, mg/dL	45 ± 11	52 ± 13	
LDL cholesterol, mg/dL	129 ± 33	113 ± 37	
Total protein, g/dL	7.3 ± 0.5	7.4 ± 0.5	
ALT, U/L	25 ± 11	27 ± 21	
AST, U/L	24 ± 5	25 ± 10	
γ-GT, U/L	36 ± 29	36 ± 40	
BUN, mg/dL	16 ± 4	15 ± 3	
Creatinine, mg/dL	0.8 ± 0.2	0.7 ± 0.2	
Uric acid, mg/dL	5.9 ± 1.4	5.3 ± 1.2	
Creatinine kinase, U/L	146 ± 114	118 ± 41	
Alkaline phosphatase, IU/L	71 ± 23	69 ± 18	
WBC, 10^9/L	5.4 ± 1.2	6.0 ± 1.4	
RBC, 10^{12}/L	4.6 ± 0.4	4.6 ± 0.4	
Hemoglobin, g/dL	14 ± 1	14 ± 1	
Hematocrit, %	42 ± 3	41 ± 3	
Platelets, 10^9/L	243 ± 33	235 ± 68	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the curve; BMI, body mass index; BUN, blood urea nitrogen; DBP, diastolic blood pressure; F, female; FPG, fasting plasma glucose; HbA$_{1c}$, glycated hemoglobin; HDL, high-density lipoprotein; HOMA, homeostatic model assessment; IR, insulin resistance; LDL, low-density lipoprotein; M, male; OGTT, oral glucose tolerance test; RBC, red blood cells; SBP, systolic blood pressure; WBC, white blood cells.

[a]Plus-minus values are means ± SD.
[b]Race was self-reported.
[c]HOMA-IR or [d]β-cell function (HOMA-B) were calculated as described in "Materials and Methods."
[e]P less than .5.
[f]P less than .01.

4.5 ± 6 mg/dL with placebo treatment without any significant difference in the cinnamon group, resulting in a statistically significant between-group mean difference of approximately 5 mg/dL (114 ± 8 vs 108 ± 11; $P < .01$; Table 2). Although the present study was not powered to detect outcome differences between the 2 study centers, a similar trend in FPG was noted in participants independently randomly assigned at K-CTC and JDC.

With regard to prespecified secondary end points, cinnamon resulted in a significant reduction in the AUC of PG during the OGTT from baseline to 12 weeks (21 389 ± 3858, baseline vs 19 946 ± 4070 mg/dL/120 min, 12 weeks; $P < .05$) whereas no change was observed in the placebo group (Fig. 2A). Also, cinnamon but not placebo resulted in a significant decrease in PG at the 2-hour time point of the OGTT, from baseline to 12 weeks (–20 ± 27 mg/dL; Fig. 2B; $P < .01$ for between-group difference).

Analysis of HOMA-B showed an increase from baseline to 12 weeks in the cinnamon group (20.1 ± 36.8%, Table 2; $P < .01$), but not with placebo, with a 32% between-group difference at the end of the study period. HOMA-B measurements were comparable at baseline (92 ± 40.8% for placebo and 91.4 ± 50.6% for cinnamon, Table 1). In contrast, cinnamon supplementation had no effect on HOMA-IR (Table 2).

In addition, we observed improvements in long-term measures of glucose levels routinely used in clinical practice. Cinnamon treatment was associated with a modest drop in HbA_{1c} at 12 weeks (–0.13 ± 0.25% from 5.98 ± 0.49% at baseline), with a 0.2% between-group mean difference (Table 2; $P < .01$). Similarly, randomization to cinnamon was accompanied by a between-group difference of 0.7% in GA at 12 weeks ($P < .01$), which was primarily accounted for by a decrease of 0.45 ± 0.6% from baseline with cinnamon (Table 2). In keeping with the results for FPG, changes in GA—a marker of glucose levels over 3 weeks—were not observed at 6 weeks in either group.

Within the combined pool of participants with IGT and IFG/IGT at baseline, 4 out of 18 in the cinnamon group vs 1 out of 18 with placebo had normalization of the 2-hour PG during OGTT to levels less than 140 mg/dL. Also, within the group of participants with an HbA_{1c} of 5.7% to 6.4% at baseline, 7 out of 14 in the cinnamon group vs 1 out of 10 with placebo had reductions to levels of less than 5.7% at the end of the 12-week randomization period (χ^2 [1, N = 24] = 4.02, $P < .05$). None of the participants with baseline an HbA_{1c} of 5.7% to 6.4%, in either group, progressed to an HbA_{1c} greater than 6.5%. Although the present study was not designed to assess remission of prediabetes, these preliminary findings suggest that cinnamon treatment could result in recategorization of a number of people with prediabetes to the nonprediabetic population.

Weight, blood pressure, complete blood count, and measures of liver and kidney function were not affected by cinnamon or placebo.

With regard to health-related quality of life measures, none of the 36-Item Short Form Survey components (ie, Physical Component and Mental Component) was changed after 12 weeks on either placebo or cinnamon, from baseline measurements that were comparable between groups.

Table 2.   Changes between baseline and 12 weeks[a]

	Placebo	Cinnamon	
FPG, mg/dL	4.2 ± 6.6	–0.7 ± 6.7	[e]
Glycated albumin, %	0.3 ± 0.6	–0.5 ± 0.6	[f]
HbA_{1c}, %	0.1 ± 0.2	–0.1 ± 0.3	[e]
Insulin, µIU/mL	–0.7 ± 5.7	2.2 ± 3.5	[d]
HOMA-IR[b]	–0.1 ± 1.6	0.5 ± 1.0	
HOMA-B %[c]	–13.2 ± 40	20.1 ± 36.8	[e]

Abbreviations: FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; HOMA, homeostatic model assessment; IR, insulin resistance.

[a]Plus-minus values are means ± SD.

[b]HOMA-IR or [c]β-cell function (HOMA-B) were calculated as described in "Materials and Methods."

[d]P less than .5.

[e]P less than .01.
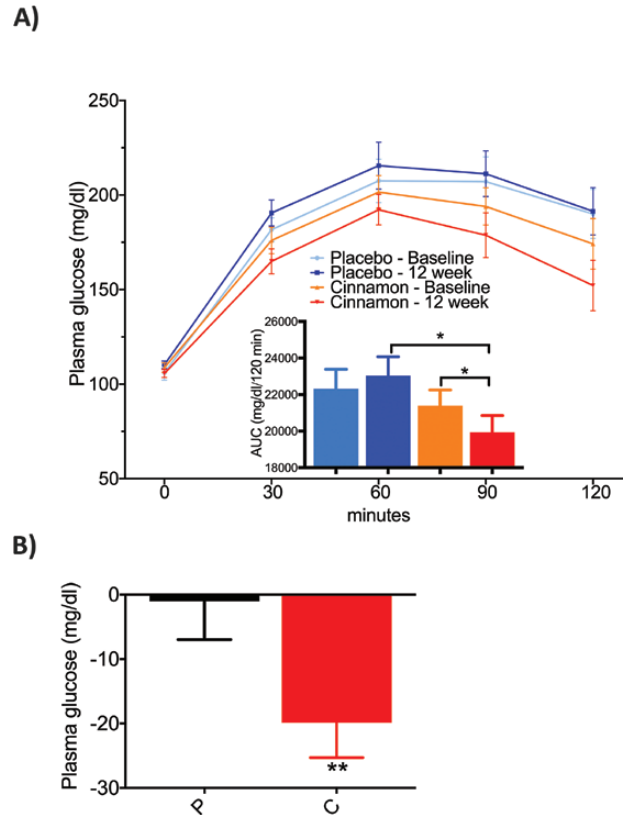
[f]P less than .001.

Figure 2. Change in A, overall plasma glucose (PG) profile, and B, 2-hour plasma glucose of the oral glucose tolerance test (OGTT), from baseline to 12 weeks. A, PG profile and corresponding area under the curve (AUC, inset) of the OGTT, at baseline and after 12 weeks, on placebo and cinnamon. B, Mean PG change at 2-hour time point from respective baseline OGTT (0) to OGTT at 12 weeks with placebo (P) and cinnamon (C). Data are presented as mean ± SEM. Between-group differences were analyzed by analysis of covariance. Within-group differences were analyzed by paired t test. *P less than .05; **P less than .01; ***P less than .001.

C. Exploratory Studies

Because of the previously reported effects of cinnamon supplementation on circulating markers of oxidative stress [33], we tested the level of serum carbonylation—a form of oxidation characterized by the introduction of carbon monoxide into a substrate—before and after 12 weeks of placebo or cinnamon. This post hoc analysis was performed using remaining samples that were available at only 1 of the 2 study centers. Serum protein carbonylation was comparable in the 2 groups at baseline, and was reduced by cinnamon treatment (3.3 ± 0.43, baseline vs 2.2 ± 0.47, 12 weeks; n = 6/group; $P < .01$) but not by placebo treatment (3.2 ± 0.36, baseline vs 3.1± 0.37, 12 weeks; n = 6/group) (Fig. 3A). In addition, the reduction of carbonylation closely correlated with the change in the 2-hour PG during OGTT (R^2 = 0.87; $P < .01$) (Fig. 3B), suggesting a potential link between the cinnamon-mediated effects on glucose homeostasis and oxidative stress.

D. Safety

The rate of any AEs was comparable in participants taking cinnamon, 29.2% (8/27), and placebo, 29.2% (7/24). No serious AEs were reported in either group; all AEs were rated mild with the exception of nausea and vomiting in 2 patients on placebo that were moderate. All AEs were self-limiting and were deemed unlikely to be related to the study treatment.
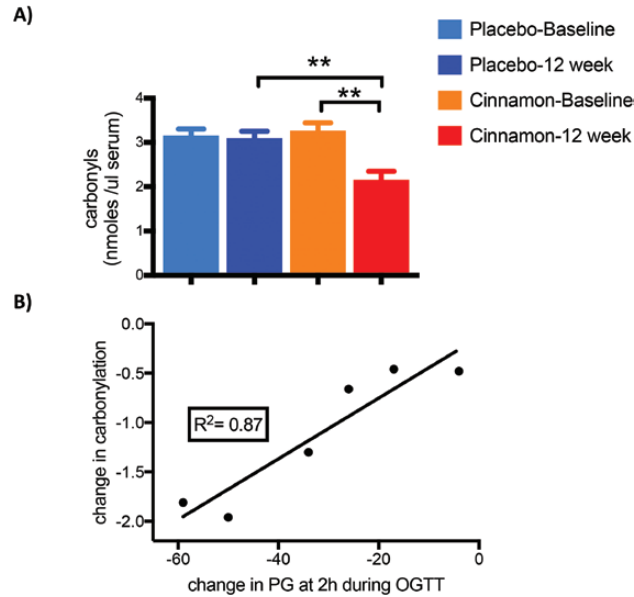
Figure 3. A, Serum protein carbonylation, and B, correlation of changes in carbonylation and in 2-hour plasma glucose (PG) during oral glucose tolerance test (OGTT). A, Total protein serum carbonylation at baseline and after 12 weeks on placebo or cinnamon. Levels of carbonyls were reduced from baseline by cinnamon but not by placebo. Samples were available and analyzed from participants enrolled at 1 of the 2 study centers. Data are presented as mean ± SEM (n = 6/group; **P < .01). B, Correlation between the change in serum carbonyls and the decrease in PG at 2-hour time point of the OGTT in the cinnamon group (R^2 = 0.87; **P < .01).

No clinically relevant changes in vital signs, physical exam, or laboratory tests results were observed in either group.

3. Discussion

This RCT of individuals with prediabetes showed that treatment with cinnamon 500 mg thrice daily resulted in a statistically significant between-group mean difference in FPG of approximately 5 mg/dL at 12 weeks, which was the primary outcome measure of the study. No change in FPG was noted at 6 weeks, which was 1 of the 3 prespecified secondary end points.

Our data are consistent and extend the results of the study by Roussel et al [33], which demonstrated a decrease in FPG with 500 mg daily of Cinnulin (aqueous extract of *C cassia*) in a small group of participants with IFG. Similar to our trial, effects on FPG were observed after 12 weeks of supplementation, but not at 6 weeks. Of note, our larger study enrolled participants meeting any of the criteria for prediabetes [5], thus expanding the relevance of these findings to a larger population.

Cinnamon treatment also exerted beneficial effects on several other end points. OGTT results showed a significant drop of the PG at 2 hours and of the overall AUC of PG profile after 12 weeks of cinnamon, but not placebo, thus indicating an improvement in glucose tolerance. Our findings are in keeping with previous studies showing that cinnamon extract induces membrane translocation of GLUT4 in 3T3-L1 adipocytes and partial correction of glucose intolerance in a rat model of T2D [30]. The significant decrease in the AUC of PG suggests that reductions in HbA_{1c} and GA with cinnamon, discussed as follows, result in part from lessening of postprandial hyperglycemia.

Although the lack of information on insulin concentrations during the OGTT prevents any statement regarding the effect of cinnamon on insulin release in response to a glucose load, cinnamon-treated participants displayed higher FI levels and an ample increase

in HOMA-B percentage at 12 weeks when compared to the respective baseline (Table 2). Notwithstanding limitations of static models [36], our findings point to an effect of cinnamon on β-cell function that should be further investigated with more mechanistic studies. In this context, ingestion of rice pudding with 3 g of cinnamon (*C cassia*) in healthy participants resulted in a higher peak of glucagon-like peptide-1, when compared to the meal without cinnamon [31].

The correlation between the lowering in the AUC of PG during the OGTT and the reduction in serum protein carbonylation is intriguing. Mohanty and colleagues first reported an increase in reactive oxygen species in polymorphonuclear cells of normal individuals following a glucose challenge [37]; also, fiber intake blunted reactive oxygen species production induced by a high-fat, high-calorie diet in mononuclear cells, in parallel with an increase in insulin secretion [38]. Finally, orange juice reduced markers of oxidative stress induced by a high-fat, high-calorie meal in polymorphonuclear cells of healthy participants [39]. In this view, our exploratory studies suggest that a reduction in serum protein carbonylation could be a marker both for cinnamon's metabolic effects and its antioxidant activity.

Furthermore, cinnamon had a significant impact on long-term indexes of dysglycemia, including a between-group difference of –0.2% in HbA_{1c} and –0.7% in GA at 12 weeks. The concordant trend of HbA_{1c} and GA is noteworthy because participants in the cinnamon group had a small reduction in hemoglobin, which could be a caveat when interpreting HbA_{1c} [40]. Within a population with prediabetes, relatively small changes in HbA_{1c} can be clinically meaningful. The EPIC-Norfolk study estimated that 10% of total mortality could be prevented by lowering HbA_{1c} by 0.2% [41], from a baseline of 5.0% to 6.9% that overlaps the HbA_{1c} range in our trial (ie, 5.7%-6.0%).

Cinnamon was overall well tolerated with mild AEs reported in 29% of participants, with a frequency nearly identical to the placebo group and without any prevailing pattern in the frequency of specific AEs.

Our study has several strengths. First, this is the largest RCT testing the effects of cinnamon on glucose homeostasis in participants with prediabetes, along a spectrum of abnormalities (IFG, IGT, or both). Although our trial was not powered to compare the extent of changes between the 2 study centers, the overall trend on relevant end points appeared comparable in participants enrolled at K-CTC (all of self-reported Asian ethnicity) and at JDC (primarily white). More targeted, powered studies will be required to assess whether age and/or sex are factors that modify the response to cinnamon on metabolic outcomes.

Second, the study protocol had a 'light-touch' approach, without any recommendation for structured lifestyle interventions beyond general counseling at the time of enrollment. Although this experimental design could also be construed as a limitation, it allows the better isolation of the effect of cinnamon from superimposed investigator-mandated lifestyle modifications.

Third, the correlation between the reduction in serum protein carbonylation and in PG at 2 hours of the OGTT lends initial support to the use of total carbonylation as a marker of the effect of cinnamon on glucose tolerance.

This trial also has certain limitations. The relatively short duration does not allow us to draw conclusions regarding the durability of cinnamon's effects or the rate of progression from prediabetes to T2D. Also, the potential emergence of tachyphylaxis, noted with certain mainstay diabetes drugs [42], has to be evaluated rigorously. In addition, the present study was not powered to discriminate differences in the response to cinnamon between participants with IFG vs IGT. Finally, our experimental design did not directly aim to clarify the mechanism(s) of action of cinnamon, which should be investigated in future studies.

In conclusion, treatment with cinnamon for 12 weeks, compared to placebo, resulted in favorable changes in measures of glucose homeostasis in a representative population of participants with prediabetes. These findings should set the foundation for a longer and larger RCT that directly addresses the impact of cinnamon on incident T2D and/or remission of prediabetes.

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Additional Information

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