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Original Research Article

Effect of cinnamon spice on continuously monitored glycemic response in adults with prediabetes: a 4-week randomized controlled crossover trial

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A B S T R A C T

Background: Previous clinical studies showing that cinnamon spice lowers blood glucose concentrations had inconsistent results.
Objectives: To determine the effect of daily cinnamon spice supplementation in an amount commonly used for seasoning on glucose concentrations in adults with obesity and prediabetes.
Methods: Following a 2-wk run-in period of maintaining a low polyphenol/fiber diet, 18 participants with obesity and prediabetes underwent a 10-wk randomized, controlled, double-blind, crossover trial (mean age 51.1 y; mean fasting plasma glucose 102.9 mg/dL). The participants were randomly assigned to take cinnamon (4 g/d) or placebo for 4-wk, followed by a 2-wk washout period, and then crossed over to the other intervention for an additional 4-wk. Glucose changes were measured with continuous glucose monitoring. Oral glucose tolerance testing immediately following ingestion of cinnamon or placebo was performed at 4-time points to assess their acute effects both at the baseline and end of each intervention phase. Digestive symptom logs were obtained daily.
Results: There were 694 follow-up days with 66,624 glucose observations. When compared with placebo, 24-h glucose concentrations were significantly lower when cinnamon was administered [mixed-models; effect size (ES) = 0.96; 95 % confidence interval (CI): –2.9, –1.5; $P < 0.001$]. Similarly, the mean net-area-under-the-curve (netAUC) for glucose was significantly lower than for placebo when cinnamon was given (over 24 h; ES = –0.66; 95 % CI: 2501.7, 5412.1, $P = 0.01$). Cinnamon supplementation resulted in lower glucose peaks compared with placebo (Δpeak 9.56 ± 9.1 mg/dL compared with 11.73 ± 8.0 mg/dL; ES = –0.57; 95 % CI: 0.8, 3.7, $P = 0.027$). Glucose-dependent-insulinotropic-polypeptide concentrations increased during oral glucose tolerance testing + cinnamon testing (mixed-models; ES = 0.51; 95 % CI: 1.56, 100.1, $P = 0.04$), whereas triglyceride concentrations decreased (mixed-models; ES = 0.55; 95 % CI: –16.0, –1.6, $P = 0.02$). Treatment adherence was excellent in both groups (cinnamon: 97.6 ± 3.4 % compared with placebo: 97.9 ± 3.7 %; ES = –0.15; 95 % CI: –1.8, 0.2, $P = 0.5$). No differences were found in digestive symptoms (abdominal pain, borborygmi, bloating, excess flatus, and stools/day) between cinnamon and placebo groups.
Conclusions: Cinnamon, a widely available and low-cost supplement, may contribute to better glucose control when added to the diet in people who have obesity-related prediabetes.
This trial was registered at clinicaltrials.gov as NCT04342624.

Keywords: cinnamon, continuous glucose system, glycemic response, polyphenols, prediabetes

Introduction

Cinnamon contains polyphenols, which may improve glucose homeostasis, but studies of its influence on glucose changes have had mixed results [1–4]. Cinnamon's ability to affect glucose control remains uncertain. Studies have previously shown that cinnamon lowered glucose and lipid concentrations in patients with type 2 diabetes [5–8], prediabetes [9,10], and in healthy adults [11–14]. However, other studies have yielded contrary results [1–4]. Cinnamon doses in these studies were highly variable, ranging from 0.5 g up to 6 g/d, with study durations varying from 4 to 12 wk [5,7,8,10–12]. Reviews and meta-analyses suggest that supplemental cinnamon or cinnamon

Abbreviations: CGM, continuous glucose monitoring; CI, confidence interval; ES, effect size; FPG, fasting plasma glucose; GIP, glucose-dependent-insulinotropic-polypeptide; ITT, intention-to-treat; OGTT, oral glucose tolerance test; SCFA, short-chain fatty acid.

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extracts may lower blood glucose concentrations [15–22]; however, inconsistent findings of cinnamon on glycemic control from studies that had small effect sizes (ESs) or very heterogeneous results [15–22] indicate a need for further research.

We conducted a 4-wk randomized, controlled, double-blind crossover trial to evaluate the effects of cinnamon consumption on glucose changes throughout the day, as measured by continuous glucose monitoring (CGM) in participants with prediabetes and obesity. We also assessed glucose, metabolic, and hormonal responses to oral glucose tolerance tests (OGTTs) during acute administration of cinnamon and glucose using a modified OGTT protocol at 4 different time points during the study. Blood and fecal short-chain fatty acids (SCFAs) concentrations were measured by gas chromatography. We hypothesized that cinnamon spice consumption results in sustained lowering of blood glucose concentrations.

Methods

Study design

This was a total of 12-wk randomized, controlled, double-blind, crossover trial, which started with a 2-wk run-in phase (NCT04342624; Figure 1; Supplemental Table 1). Enrollment began in March 2021 and ended in September 2021, with the overall study ending in December 2021. Patients were eligible for study inclusion if they were healthy adults older than 18 y who consumed a low fiber/polyphenol diet, adults, overweight or obese [BMI in (kg/m^2) between 25–40], and had prediabetes defined as having fasting plasma glucose (FPG) between 100–125 mg/dL or hemoglobin A1c (HbA1c) concentrations between 5.7–6.4 % (39–47 mmol/mol) [23]. A comprehensive metabolic panel and HbA1c were drawn when initially screened for the study. Detailed exclusion criteria are listed in Supplemental Data 1. Participants read and signed the institutional review board-approved written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization before initiating any study-specific procedures or enrollment. The study design was carried out in accordance with the guidelines of the Human Subjects Protection Committee of the University of California, Los Angeles. Of the 19 participants who were enrolled in the study, 1 declined to participate after not tolerating the insertion of the CGM probe and was not randomly assigned (Figure 1).

Randomization

Randomization was performed by the study statistician after subjects met all eligibility criteria and completed baseline evaluations. Subjects were randomly assigned to 1 of 2 capsules (A or B) containing cinnamon or placebo. The randomization used a permuted block design with a random block size of 4.

Intervention

In this randomized, controlled, double-blind, crossover trial, participants started with a 2-wk run-in phase by consuming a low polyphenol *beige diet* (included foods typically beige in color and rich in simple carbohydrates and were asked to avoid any cinnamon or cinnamon products; Supplemental Table 2). This diet was maintained for the entire 12 wk of the study. After the 2-wk run-in phase, the participants were randomly assigned to ingest cinnamon (16 capsules-4 g/d) or placebo for 4 wk, followed by a 2-wk washout phase, then crossed over to the other intervention for an additional 4 wk (allocation ratio 1:1). Three-day food intake records were obtained during the screening process and at subsequent clinical visits. Patient eligibility for the study was determined during screening by assessing the participants' dietary habits and compliance with the low fiber/polyphenol diet, which was based on the analysis of their 3-d food records and consultations with a dietitian. Participants were given a low fiber/polyphenol diet handout providing nutritional guidance about the diet that was maintained for the study duration. Cinnamon (C. burmannii - Indonesian cinnamon) was administered in 250 mg capsules. Participants took 8 capsules with breakfast and 8 capsules with dinner (16 capsules or 4 g/d). Participants took the same number of placebo capsules that contained 250 mg of maltodextrin and were identical such that the participants could not tell the difference between them. The chemical profile of the cinnamon powder used in this study was analyzed and found to contain 3.64 ± 0.04 mg/g of coumarin, 1.02 ± 0.01 mg/g of cinnamic acid, and 29.03 ± 0.15 mg/g cinnamaldehyde (coumarin: 0.17 mg/kg body weight, cinnamic acid is 0.054 mg/kg body weight, and cinnamaldehyde is 1.55 mg/kg body weight; Supplemental Data 2). Capsules were compounded by Tele-Travel Services (Thousand Oaks, CA). The study was double-blinded, with neither the participants nor the researchers knowing if the participants received cinnamon or placebo. Glucose monitoring was performed by use of a flash system device (FreeStyle Libre Pro; Abbott Diabetes Care, Alameda, CA). Validation of the flash

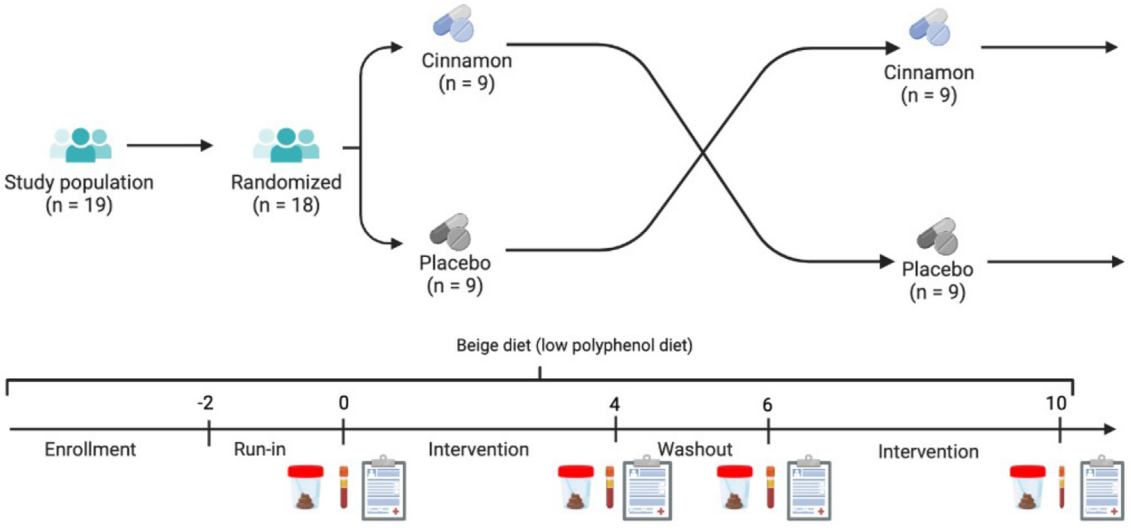

FIGURE 1. Participant flow chart for the crossover study design.

system device's accuracy can be found in Supplemental Data 3. The device was reapplied every 2 wk during the study (Figure 1: weeks 0, 2, 6, 8; Supplemental Data 3). Each participant recorded their cinnamon/placebo capsule intake in a diary. A weekly medication dispenser was provided to assist subjects in managing their daily capsule intake. At the end of the study, the remaining capsules were counted, and compliance was calculated. Compliance was defined as having consumed 75 % or more of the capsules. Participants also recorded digestive symptoms (abdominal pain, borborygmi, bloating, excess flatus, number of stools/day) daily throughout the study.

Oral glucose tolerance testing following cinnamon or placebo ingestion

OGTT was performed at 4-time points (Figure 1; Supplemental Table 1): *1*) baseline (time period #0- after the 2-wk run-in phase), *2*) time period #4- after the first 4-wk intervention period, *3*) time period #6- following the 2-wk washout time period, *4*) time period #10- after the second 4-wk intervention period. On each testing day, subjects were evaluated at the University of California, Los Angeles Center for Human Nutrition following an 8–12 h fast. An indwelling catheter was inserted into a forearm vein, and a baseline (0 h) fasting blood sample was collected. Between blood draws, the catheter was flushed with saline through it for the entire experiment to prevent clothing or blockages. A trained nurse was responsible for the entire OGTT procedure. She was responsible for ensuring that the cannula remained patent, collecting blood samples at the correct time intervals, and addressing any complications that may arise. The subjects then ingested 75 g of glucose cola within a 5-min time period along with 8 capsules (2 g) of cinnamon or placebo. Blood samples (10 mL) were drawn every 30 min for 3 h. Glucose, insulin, C-peptide, glucagon, glucose-dependent-insulinotropic-polypeptide (GIP), Glucagon-like Peptide-1, and triglyceride concentrations (Supplemental Data 4) were measured. A stool sample was collected the day before each visit (4 visit days; Supplemental Table 1; Supplemental Data 5). Weight, body composition, and systolic and diastolic blood pressure were measured after participants arrived at the Center for Human Nutrition at each visit after resting for 15 min (Supplemental Table 1). Percent body fat, fat mass, lean body mass, total body water, and basal metabolic rate were measured using bioelectrical impedance (BIA310e; Biodynamics Corporation, Tanita-BC418 body-fat analyzer; Tanita Corporation) [7]. Blood and fecal SCFA content were analyzed by gas chromatography. The concentrations of serum and fecal acetic, propionic, butyric, isobutyric, valeric, and isovaleric acids were quantified. Additional information regarding gut microbiome and serum and fecal SCFA analysis are found in Supplemental Data 5.

Statistical analysis

The primary objective of this trial was to assess the effect of 4 g/d of cinnamon spice supplementation on continuous glycemic response in participants who had obesity and prediabetes. The primary outcome was the continuously measured glucose concentrations. Secondary outcomes included the effects of cinnamon on *1*) the glycemic response to an OGTT, *2*) anthropometric parameters and body composition, and *3*) SCFA and the microbiome. The primary analytic approach was per protocol, and an intention-to-treat (ITT) approach was assessed as a sensitivity analysis. Missing data were modeled using multiple imputations, assuming observations were missing completely at random (Supplemental Figure 1) [24]. Sample size estimation was based on a prior study where 3 g/d ingestion of cinnamon for 40 d resulted in a reduction of fasting serum glucose from 11.4 ± 1.2 mmol/L to 9.4 ± 1.1 mmol/L [5]. Based on these results, 14 participants would be needed to achieve 80 % power, and 18 participants would be needed for 90 % power to detect a significant reduction in fasting glucose concentrations of 2 mmol/L with a 2-sided significance level of 0.05 [5]. Recalculation of study power based on our sample size ($n = 18$) and anticipating a reduction in glucose of 2 mmol/L and a 2-sided significance level of 0.05 yielded a study power of 93.8 % [5]. Continuous variables were presented as mean ± SD unless specified otherwise. Categorical variables were expressed as percentages with IQRs. Baseline characteristics were presented for the entire study population. Participants were seen in the clinic every 2 wk for the placement of CGM sensors. These visits occurred in the morning, at ~08:00. CGM data for each individual were collected and organized into daily segments (24 h - from around 08:00 to 08:00). To establish the start time for each day, we calculated the mean time of day the glucose sensor was applied for each person (start time ranged between 07:30 and 08:30). We excluded days that were not representative of normal daily activity, such as days when OGTT was performed and the first 24 h after applying the sensor. We calculated the mean glucose concentrations (every 15 min/d) for each participant for the 2 interventions (cinnamon or placebo). Eventually, we had a day with 96 glucose mean observations (every 15 min) for each intervention. Glucose concentrations were reported as changing relative to the initial glucose measurement. CGM data processing was performed by an analyst blinded to the intervention (HZ). Statistical analysis was performed by an unblinded investigator. Glucose changes were assessed by calculation of the glucose AUC using the net incremental AUC method (netAUC) [25–27]. NetAUC calculation includes the areas below a curve, both above and below the level of fasting time periods. The netAUC can result in values <0 since it is calculated as positive and negative blood glucose increments. Within-subject differences were determined by estimating the mean net incremental area under the 24-h glucose-time curve [25–27] and tested for statistical significance using Wilcoxon Signed rank testing. Individual glycemic-response parameters were also determined: peak glucose height, peak start time, time to glucose peak, and mean peak duration. Peak values were determined from the difference of the highest measurement relative to the mean glucose concentration for the corresponding time period. Statistical significance between cinnamon and placebo glycemic responses was determined by Wilcoxon Signed rank testing. Mixed-model analysis was used to evaluate the difference between cinnamon and placebo CGM trajectories (the pattern of serial glucose readings taken at different time points), taking into account within and between-subject differences. Mixed-model analysis was performed, treating subjects as random effects (within-subject test) with the intervention as a fixed effect (between-subject factor) and the outcome being the glucose concentration. Additional adjustments for potential confounders were added to the model (sex, age, and FPG at baseline/ HbA1c at baseline/systolic or diastolic blood pressure). Mixed-model analysis was also used in the OGTT analysis (every 30 min over 3 h after glucose load). Exploratory analysis comparing differences between various time points during OGTT used Bonferroni correction for multiple comparisons. Additionally, we assessed insulin sensitivity with the OGTT test using the Matsuda Index: [10,000 /$\sqrt{}$(FPG x fasting plasma insulin) X (mean glucose OGTT x mean insulin OGTT)] [28]. Differences between cinnamon and placebo effects on serum and fecal SCFA, anthropometric, and body composition measurements were evaluated by the

Wilcoxon Signed rank test. Analysis of covariance model was used to evaluate the differences in body composition and anthropometric adjusted for age, sex, and baseline measurements. Potential carryover effects from the first phase treatment allocation were minimized with the 2-wk washout period that should have been sufficiently long for the cinnamon effect to be depleted [4]. The washout period in our study is consistent with previous publications that employed a washout period of 7–20 d (2,5,6). The risk of potential carryover effects was evaluated by the interaction of the intervention order and the treatment in repeated mixed-models [29]. Effect size was calculated as Eta-squared (η^2). Statistical significance was assumed if the 2-sided $P < 0.05$. Statistical analysis was performed using IBM SPSS Statistics, version 29.0 software. Graphs were constructed using GraphPad Prism 9 by Dotmatics. Further detailed statistical analysis is presented in Supplemental Data 6.

Results

Baseline characteristics

The baseline characteristics of all participants are shown in Table 1. There were 13 females (72 %), the mean ± SD age was 51.1 ± 10.4 y, and the mean weight was 84.6 ± 15.8 kg (BMI: 31.5 ± 4.3). The mean FPG concentration was 102.9 ± 13.6 mg/dL, with a mean HbA1c of 5.9 ± 0.4 % (41.1 ± 4.3 mmol/mol). Baseline parameters were similarly distributed among the participants who started first with cinnamon or a placebo.

CGM

There was a total of 694 follow-up days with 66,624 glucose observations (every 15 min). Three participants were excluded because of missing glucose observations from 1 of the interventions. The glucose trajectories over 24 h after cinnamon spice supplementation and placebo administration are presented in Figure 2. The characteristics of the continuous glucose measures are shown in Supplemental Table 3. Cinnamon supplementation resulted in lower glucose peaks (Δ = 9.56 ± 9.1 mg/dL) compared with placebo [Δ = 11.73 ± 8.0 mg/dL; ES = –0.57, 95 % confidence interval (CI): 0.8, 3.7, $P = 0.027$] (Figure 2). Cinnamon consumption reduced mean netAUC over 24 h compared with placebo (cinnamon: –1265.2 ± 9027.3 mg/dL * min compared with placebo: 1914.6 ± 9223.4 mg/dL * min, ES = –0.66, 95 % CI: 2501.7, 5412.1, $P = 0.01$). The overall repeated glucose concentrations over 24 h were significantly lower at all time points in the cinnamon intervention compared with the placebo (ES = 0.96, 95 % CI: –2.9, –1.5, $P < 0.001$). The mean starting peak time, the time to peak, and the mean duration of the peaks were not significantly different between the interventions ($P > 0.05$; Supplemental Table 3). The difference in the glucose trajectories between cinnamon and placebo remained strongly significant after adjusting for age, sex, and HbA1c at baseline/FPG at baseline/systolic or diastolic blood pressure at baseline performed in multivariable repeated measurement models ($P < 0.001$). The potential for the carryover effect of cinnamon from the initial to the final time period was evaluated by testing for an interaction between treatments, and the order of intervention allocation was not statistically significant ($P = 0.5$). Individual continuous blood glucose concentrations are presented in Supplemental Figure 2. ITT analysis showed similar results between the imputed results and the perprotocol data. The ITT analysis can be found in Supplemental Figure 1. Sensitivity analysis exploring continuous glucose trajectories after cinnamon ingestion compared with placebo, excluding participants number 2, 5, 12, and 15, was similar to the perprotocol analysis (Supplemental Figure 3).

Oral glucose tolerance testing

OGTT administered at baseline and following cinnamon or placebo ingestion are presented in Figure 3. Cinnamon supplementation led to a statistically significant increase in the GIP AUC-180 min

TABLE 1
Baseline characteristics of the study participants ($n = 18$)[1]

	Entire sample size $n = 18$	Intervention 1 order * ($n = 9$)	Intervention 2 order † ($n = 9$)
Age, y	51.1 ± 10.4	50.0 ± 7.0	52.2 ± 13.4
Females (%)	13 (72 %)	7 (78 %)	6 (67 %)
Hispanic population (%)	8 (44 %)	4 (44 %)	4 (44 %)
Race			
White (%)	7 (39 %)	3 (33 %)	4 (44 %)
Black or African American (%)	4 (22 %)	2 (22 %)	2 (22 %)
Asian (%)	2 (11 %)	1 (11 %)	1 (11 %)
Multi-race (%)	4 (22 %)	3 (33 %)	1 (11 %)
Pacific Islander (%)	1 (6 %)	0 (0 %)	1 (11 %)
Weight (kg)	84.6 ± 15.8	84.5 ± 15.5	84.7 ± 17.1
BMI (kg/m^2)	31.5 ± 4.3	31.7 ± 4.3	31.3 ± 4.5
Fasting plasma glucose (mg/dL)	102.9 ± 13.6	98.4 ± 8.1	107.4 ± 16.8
HbA1c			
%	5.9 ± 0.4	5.8 ± 0.4	6.1 ± 0.4
mmol/mol	41.1 ± 4.3	39.5 ± 3.8	42.8 ± 4.3
Systolic blood pressure (mm Hg)	123.0 ± 14.9	118.8 ± 12.5	127.2 ± 16.6
Diastolic blood pressure(mm Hg)	75.6 ± 10.1	76.0 ± 11.9	75.2 ± 8.7
Pulse (bpm)	72.2 ± 9.5	74.1 ± 8.9	70.3 ± 10.3
FFM (kg)	51.3 ± 11.6	50.4 ± 10.3	52.2 ± 13.4
BMR (kcal)	1565.6 ± 333.5	1542.3 ± 293.5	1588.9 ± 386.0
%Fat	39.5 ± 5.6	40.1 ± 6.4	38.9 ± 5.0

BMI, body mass index; BMR, basal metabolic rate; FFM, fat-free mass; SD, standard deviation; HbA1c, Hemoglobin A1c.
[1] Values are presented as mean ± SD for continuous variables or percent for nominal parameters.
* Phase 1 started with placebo.
† Phase 2 started with Cinnamon.

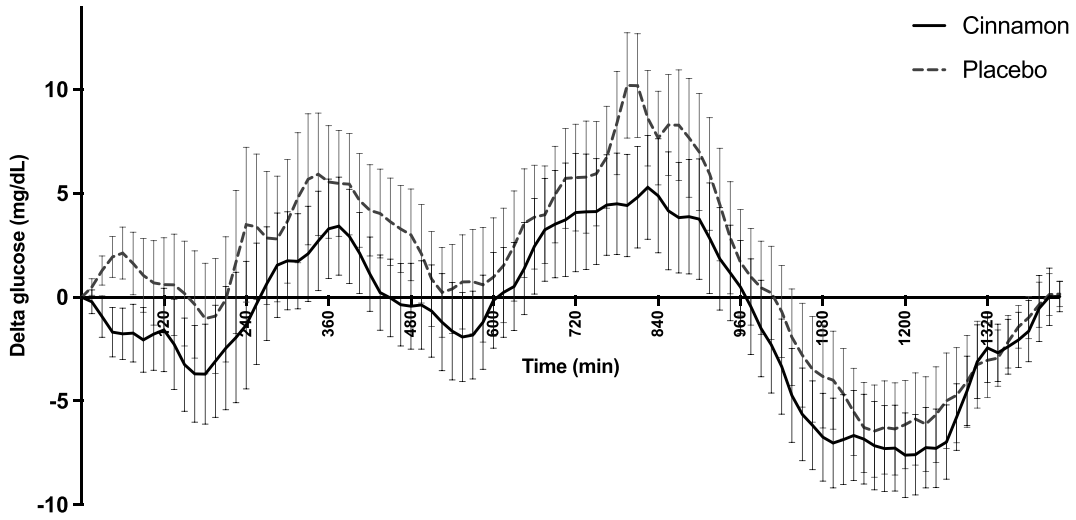

FIGURE 2. Continuous glucose trajectory after cinnamon compared with placebo intake over 24 h. The overall repeated glucose concentrations for 24 h were consistently and significantly lower in the cinnamon intervention compared with the placebo after 4 wk for each intervention [mixed-models; effect size (ES) = 0.96; 95 % CI: –2.9, –1.5, $P < 0.001$]. Differences were analyzed by mixed-model regression as a within-subject test (subjects were used as the random effect) and the intervention as a between-subject factor, with the primary outcome being the glucose concentration. The mean 24-h netAUC was significantly lower in the cinnamon compared with the placebo (ES = –0.66; 95 % CI: 2501.7, 5412.1, $P = 0.01$). Cinnamon supplementation resulted in lower glucose peaks compared with placebo (ES = –0.57; 95 % CI: 0.8, 3.7, $P = 0.027$). Within subjects differences were analyzed by the Wilcoxon Signed rank test. CI, confidence interval; netAUC, net area under curve.

concentrations compared with baseline (AUC baseline: 31885.1 ± 15594.7, AUC end, following 4 wk: 43592.9 ± 25863.1, ES = –0.47, 95 % CI: 1005.0, 23692, $P = 0.048$). GIP after 4 wk of cinnamon was significantly increased relative to baseline (mixed-models; ES = 0.51, 95 % CI: 1.56, 100.1, $P = 0.04$). Glucagon concentrations following the cinnamon intervention were significantly lower as compared with the placebo (mixed-models; ES = 0.66, 95 % CI: 2.0, 10.9, $P = 0.005$). Mixed-model analysis found that cinnamon supplementation statistically significantly decreased triglyceride concentrations as compared with baseline (mixed-models; ES = 0.55, 95 % CI: –16.0, –1.6, $P = 0.02$). We did not identify this difference with netAUC. AUC has less statistical power to detect differences than mixed-model analysis because the information is lost when individual data points and the time in which they occur are averaged together as an AUC. The differences in glucagon, GIP, and triglyceride changes remained significant following adjustments for baseline and changed body composition (body weight, fat-free mass, or fat percentage). Numerical results for pre and post-OGTT are shown in Supplemental Table 4. The Matsuda Index showed no differences in insulin sensitivity between baseline and the end of each intervention [medians (IQR): cinnamon baseline: 0.04 (0.02–0.06); cinnamon end: 0.04 (0.02–0.08); $P = 0.4$; placebo baseline: 0.05 (0.02–0.09); placebo end: 0.04 (0.03–0.08); $P = 0.8$). Additional results related to the microbiome, SCFAs, and anthropometric and body composition measurements are presented in Supplemental Data 7 and Supplemental Figures 4–10.

Digestive symptoms and adherence rate

There were no significant differences in capsule ingestion adherence of cinnamon compared with placebo (cinnamon: 97.6 ± 3.4 %, placebo: 97.9 ± 3.7 %, ES = –0.15, 95 % CI: –1.8, 0.2, $P = 0.5$). There were no differences in digestive symptoms (abdominal pain, borborygmi, bloating, excess flatus, and number of stools/day) between cinnamon and placebo supplementation with time as compared with baseline ($P > 0.05$ for all; Supplemental Figure 11).

Discussion

In this 4-wk randomized, controlled, double-blind, crossover trial, 4 g daily of cinnamon supplementation lowered glucose concentrations during CGM relative to placebo. Compliance with treatment administration was excellent, and there were no digestive side effects. Postprandial GIP was increased, and triglyceride concentrations decreased in response to an oral glucose load after 4 wk of cinnamon supplementation. Cinnamon was encapsulated in this research study to achieve accurate dosing, blinding, and compliance. In practice, the 4 g cinnamon doses used in this study, which equate to the contents of a typical sugar packet, can easily be incorporated into foods.

Cinnamon lowered glucose concentrations as measured with 24-h CGM, but there was no effect on glucose when measured by OGTT performed at the end of the 4-wk study period. Our OGTT findings were similar to a previous study that showed that cinnamon did not affect postprandial glucose and insulin concentrations [30]. OGTT testing has less than optimal reliability, accuracy, and reproducibility [31]. Because it measures glucose over long time periods, 24-interstitial glucose monitoring may be superior to OGTT in detecting dysglycemia in impaired glucose tolerance [32,33]. CGM is a powerful tool that has the principal advantage of capturing glucose fluctuations (short-term glycemic variability) [34,35]. Our study may differ from those that did not find an effect of cinnamon on glucose concentrations because we employed 24-h CGM, which is a more sensitive measure of glucose changes than other methods.

Although prior studies have documented cinnamon's beneficial effect on fasting triglyceride concentrations [5,15], its influence on postprandial triglycerides has not been previously reported. Postprandial hypertriglyceridemia has been associated with an increased risk of cardiovascular events, and reducing elevated concentrations of postprandial triglycerides may reduce the risk of coronary artery disease [36–38]. Our study found that adding cinnamon to the diet may reduce overall postprandial triglyceride concentrations. However, triglyceride concentrations fluctuated during the OGTT in our study,

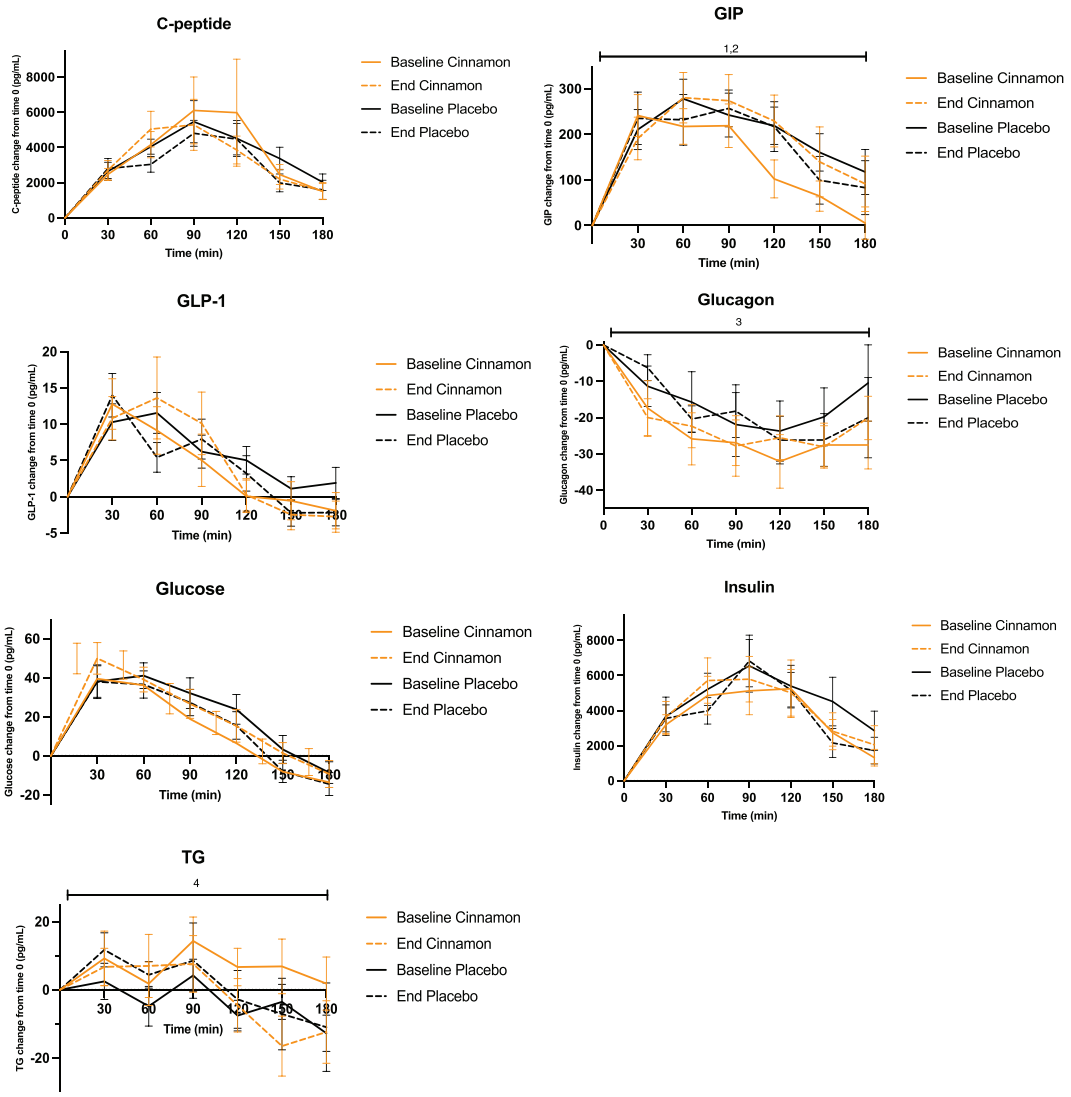

FIGURE 3. OGTT response curves over 4 wk for each intervention. Statistical comparisons between AUCs were evaluated by the Wilcoxon Signed rank test. Differences in the trajectories were analyzed by mixed-model regression with subjects used as the random effect, and the intervention or the time (baseline compared with the following 4 wk) served as a between-subject test. Bonferroni correction for multiple testing was used to adjust the statistical significance threshold for comparisons of measures obtained at several time points during the OGTT. AUC, area under the curve; GIP, glucose-dependent-insulinotropic-polypeptide; GLP-1, Glucagon-like Peptide-1; OGTT, oral glucose tolerance test; TG, triglycerides. [1]The cinnamon supplementation led to a significant increase in the GIP AUC-180 min concentrations after 4 wk of intervention compared with baseline [AUC baseline: 31885.1 ± 15594.7, AUC end: 43592.9 ± 25863.1, effect size (ES) = –0.47, 95 % CI: 1005.0, 23,692, $P = 0.048$]. [2]The GIP trajectories (the baseline compared with end-4 wk) were significantly different in the cinnamon intervention (mixed-models; ES = 0.51; 95 % CI: 1.56, 100.1, $P = 0.04$). [3]The cinnamon trajectories of the glucagon concentrations were significantly different as compared with the placebo trajectories over 4 wk for each intervention (mixed-models; ES = 0.66; 95 % CI: 2.0, 10.9, $P = 0.005$). [4]The cinnamon intervention, the baseline triglyceride trajectory was significantly different as compared with the trajectory at the end of the intervention (following 4 wk) (mixed-models; ES = 0.55; 95 % CI: –16.0, –1.6), $P = 0.02$).

showing increments and decrements. Triglyceride reduction in response to OGTT likely results from insulin-mediated inhibition of lipolysis, down-regulation of hepatic VLDL secretion [39,40], and upregulation of triglyceride clearance from the circulation by lipoprotein lipase and remnant receptors [41,42]. In addition, we observed that GIP concentrations were increased after 4 wk of cinnamon intake. GIP, an incretin produced in the intestinal mucosa, increases insulin concentrations in a glucose-dependent manner while also promoting β-cell proliferation and survival [43–46]. GIP stimulates adipocyte lipoprotein lipase activity, resulting in hydrolysis of circulating triglycerides [47,48]. However, the increased triglycerides after a glucose load might be caused by insulin resistance with reduced hepatic fatty acid oxidation, causing triglycerides to increase rather than decrease after a glucose load [39,40]. The presence of obesity and prediabetes among the participants in our study may potentially explain the fluctuations observed in triglyceride concentrations.

This glucose-lowering effect of cinnamon may be explained by unique compounds and high polyphenol content in cinnamon. Cinnamon contains cinnamaldehyde, proanthocyanidins, coumarin, catechins, trans-cinnamic acid, and flavones [49–53]. Polyphenols improve insulin sensitivity by activating the insulin receptor through several mechanisms, including increased auto-phosphorylation of the insulin receptor, increased glucose transporter-4 receptor synthesis and activation, possess an anti-inflammatory effect, which may act beneficially

in diabetes, and increased hepatic glycogen synthesis [9,15–17,51,54]. However, the specific bioactive compounds in cinnamon responsible for these effects remain unknown.

Another potential explanation for the glucose-lowering effect of cinnamon is the impact on the population of intestinal microbiota. Our previous in vitro study demonstrated that cinnamon and other spices strongly influenced bacterial growth by enhancing the growth of Bifidobacterium spp and Lactobacillus spp, with inhibitory activity against selected Ruminococcus species, Fusobacterium strains and selected Clostridium spp [55]. One prior study in healthy participants showed that daily consumption of a spice mix resulted in a significant reduction in Firmicutes abundance and a trend of enrichment in Bacteroidetes compared with placebo [56]. In the current study, we found that changes in the alpha diversity index Shannon during intervention were significantly different between cinnamon and placebo. The relative abundance of *Terrisporobacter* and *Dialister* was reduced, but *Methanobrevibacter* was increased by cinnamon compared with placebo. Energy restriction for weight reduction has been associated with the reduction of Terrisporobacter [57]. A positive correlation has been reported between the prevalence of Dialister and elevated HbA1c concentrations in prediabetic patients [58]. Methanobrevibacter, a methanogenic microorganism, poses a risk factor for obesity because of its influence on the extraction of calories from dietary carbohydrates [59]. Whether the effects of cinnamon on Terrisporobacter, Dialister, and Methanobrevibacter contribute to the improvement in glucose profile requires further investigation.

Cinnamon is a commonly used spice produced from the dried inner tree bark of several species within the Cinnamomum genus. The genus has 250 different species, but only 4 are commercially cultivated to produce the cinnamon spice. One of these is C. burmannii, or Indonesian cinnamon, which was used in our study. Cinnamon has a long history of use as a culinary spice, food preservative, anti-bacterial, and anti-inflammatory agent [60–62]. The composition of cinnamon also varies across species. Cinnamaldehyde, proanthocyanidin, and especially coumarin concentrations were found in C. burmannii [52]. In addition, C. burmannii was previously found to have 1 of the highest amounts of polyphenols (618 μg/mg Gallic acid equivalent) [53]. Cinnamon has had traditional use for glucose lowering, and it continues to be investigated for its potential in glycemic control for individuals with overweight and obesity with prediabetes and diabetes [50].

Our study has limitations. We included individuals with obesity and prediabetes such that our findings may not generalize to individuals with lesser degrees of glucose intolerance or insulin resistance. The small number of participants studied may not be population representative of all individuals with prediabetes and obesity. However, the relatively small sample did provide sufficient statistical power to detect a significant difference between cinnamon and placebo interventions in nearly 700 repeated days of observations in a crossover design. The study's relatively short duration only examined the acute effects of cinnamon. Our results do not necessarily reflect the chronic effects of this spice on glucose homeostasis. The short duration was necessary to successfully conduct this complicated study that was dependent on a high degree of patient cooperation. We did not monitor participants' daily dietary intake and physical activity records during the intervention period, but we did assess adherence to the beige diet with 3-d food records. It is possible that participant behavior differed between time periods, but this is not likely given the relatively short duration of the entire study. Although there was a washout period between the 2 treatments, cinnamon's ½ life is unidentified, so the optimal washout duration is unknown. Thus, there was the possibility of a carryover effect from the first to the second treatment phase. To minimize this risk, we used a washout time period duration of 2-wk that was used in prior studies field [12,13,30]. No statistical adjustment was made in an effort to control for potential carryover effects; however, they were unlikely because there was no interaction between the cinnamon effect and time. We did not perform a safety evaluation of liver toxicity in our study. The daily dose of cinnamon in our study (coumarin: 0.17 mg/kg body weight) was slightly greater than the Tolerable Daily Intake for coumarin (0.1 mg/kg body weight [63,64]). We did not believe a safety evaluation was necessary because the European Food Safety Authority's has concluded that there are no safety concerns for cinnamon ingestion exceeding 3 times the Tolerable Daily Intake of coumarin for as long as 1–2 wk [65]. We did not measure phenolic metabolites in blood or urine. There was a risk of imprecise measurement of continuous glucose concentrations. We did not adjust for testing of multiple secondary outcomes. For that reason, the secondary outcomes should be considered exploratory.

Study strengths included its randomized controlled crossover and double-blind design, using placebo capsules. The excellent compliance rate for capsule intake was similar for both cinnamon and placebo. There was a good participant retention rate, with no dropouts from the randomization phase. Our study is novel in that we evaluated cinnamon's effect on glucose excursions using CGM in addition to OGTT co-administered with cinnamon or placebo at 4-time points during the study. We also determined the effects of cinnamon on the microbiome, SCFA, and body composition. Finally, we studied the effects of a 4 g/d cinnamon dose in contrast to previous studies that administered either 1–2 g/d or 6 g/d.

In conclusion, our study suggests that adding cinnamon, a substance naturally rich in polyphenols, to daily diets may have beneficial glycemic effects in prediabetes.

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Dr. Poon had been the pharmacist for compounding multiple dietary supplements for clinical trial studies at the University of California, Los Angeles Center for Human Nutrition.

Author contributions

The authors' responsibilities were as follows – HZ and JY: the guarantors of this work and, as such, had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. All authors reviewed and edited the manuscript, and all authors: read and approved the final manuscript.

Conflict of interest

The authors report no conflicts of interest.

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Data availability

Data described in the manuscript, code book, and analytic code will be made available upon request pending.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2024.01.008.

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