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ORIGINAL ARTICLE

Changes in glucose tolerance and insulin sensitivity following 2 weeks of daily cinnamon ingestion in healthy humans

Thomas P. J. Solomon · Andrew K. Blannin

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Abstract Cinnamon can improve fasting glucose in humans yet data on insulin sensitivity are limited and controversial. Eight male volunteers (aged 25 ± 1 years, body mass 76.5 ± 3.0 kg, BMI 24.0 ± 0.7 kg m^{-2}; mean ± SEM) underwent two 14-day interventions involving cinnamon or placebo supplementation (3 g day^{-1}). Placebo supplementation was continued for 5 days following this 14 day period. Oral glucose tolerance tests (OGTT) were performed on days 0, 1, 14, 16, 18, and 20. Cinnamon ingestion reduced the glucose response to OGTT on day 1 (−13.1 ± 6.3% vs. day 0; $P < 0.05$) and day 14 (−5.5 ± 8.1% vs. day 0; $P = 0.09$). Cinnamon ingestion also reduced insulin responses to OGTT on day 14 (−27.1 ± 6.2% vs. day 0; $P < 0.05$), as well as improving insulin sensitivity on day 14 (vs. day 0; $P < 0.05$). These effects were lost following cessation of cinnamon feeding. Cinnamon may improve glycaemic control and insulin sensitivity, but the effects are quickly reversed.

T. P. J. Solomon · A. K. Blannin
Exercise Metabolism Research Group,
School of Sport and Exercise Sciences,
University of Birmingham, Birmingham,
West Midlands, UK

T. P. J. Solomon (✉)
Department of Pathobiology,
Lerner Research Institute/NE4-206,
Cleveland Clinic, 9500 Euclid Avenue,
Cleveland, OH 44195, USA
e-mail: solomot@ccf.org

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Introduction

Clear positive effects of cinnamon extracts and cinnamon spice ingestion on glucose utilisation and aspects of insulin signaling have been demonstrated in vitro (Anderson et al. 2004; Jarvill-Taylor et al. 2001) and in vivo in animals (Kim et al. 2006; Qin et al. 2003), yet the in vivo human evidence is controversial (Khan et al. 2003; Mang et al. 2006; Vanschoonbeek et al. 2006). Khan et al. were the first group to demonstrate that 1, 3, and 6 g day^{-1} of cinnamon may reduce fasting plasma glucose (FPG) in patients with type 2 diabetes mellitus (T2DM), a finding confirmed with 3 g day^{-1} by Mang et al., but opposed with 1.5 g day^{-1} by Vanschoonbeek et al. In addition, there is evidence to suggest that cinnamon ingestion may have lasting effects on FPG up to 20 days post-cessation of supplementation (Khan et al. 2003). At the time of commencing this study, the work of Khan et al. was the only available study, and no evidence of long term effects of cinnamon ingestion on insulin sensitivity had been presented in humans. Previously, we presented evidence that an acute 5 g cinnamon bolus can reduce postprandial plasma glucose responses and improve insulin sensitivity for up to 12 h post-cinnamon ingestion (Solomon and Blannin 2007). The obvious progression was to establish if repeated daily ingestion of cinnamon over a prolonged period had an accumulative effect on insulin sensitivity. Cinnamon's therapeutic value would, to some extent, be influenced by the preservation of the effect following its withdrawal; therefore we also investigated the time course of insulin sensitivity changes after removal of a 2 week cinnamon feeding intervention.

Materials and methods

Following ethical approval from The School of Sport and Exercise Sciences Safety and Ethics Subcommittee, eight sedentary but otherwise healthy male volunteers, aged 25 ± 1 years, body mass 76.5 ± 3.0 kg, and BMI 24.0 ± 0.7 kg m^{-2} (mean ± SEM), were recruited from the local community. All volunteers were assessed by a general health questionnaire and provided informed written consent prior to commencing the study. A dietary record was taken for the 2 days preceding the first test, and subjects were instructed to refrain from consuming alcohol, caffeine, and cinnamon products, and from any exercise regime during the whole intervention period. The dietary record was for the purposes of diet replication prior to each trial and to ensure adequate caloric and carbohydrate intake prior to oral glucose tolerance testing (OGTT). Each subject completed two 20-day interventions in a single-blind randomised cross-over design: a control intervention (control trial) and a cinnamon intervention where cinnamon was consumed during the first 14 days (cinnamon trial). The interventions were separated by a 2 week wash-out period during which time subjects maintained their usual diet and activity habits.

Control trial

On day 0, volunteers arrived in the laboratory at 0800 hours following an overnight fast. An intravenous cannula (BD Venflon, Oxford, UK) was inserted into an antecubital vein and a fasting blood sample was taken. At 0830 hours subjects were instructed to ingest a 75 g bolus of dextrose (Cerestar, Manchester, UK) in 300 ml of water (OGTT). Blood samples (3 ml) were drawn from the intravenous line at $t = 0$, 30, 60, 90, and 120 min following ingestion of the drink. During the trial the cannula was kept patent with 0.9% saline (Baxter Healthcare, Northampton, UK) following each blood-letting. Blood samples were collected into sodium fluoride/potassium oxalate (for glucose determination) and non-anticoagulant (for insulin determination) tubes, centrifuged at 1,000*g* for 10 min at 4°C, and the plasma/serum fraction stored at −70°C until analysis. Volunteers returned to the laboratory for further OGTTs at 0800 hours on days 1, 14, 16, 18, and 20, having followed their diet diary. In addition, on days 0–14, subjects were given vegi-capsulated wheat flour placebo pills each containing 500 mg of wheat flour, and instructed to take six pills per day (= 3 g day^{-1}) at 2030 hours following their evening meal. Further placebo pills were given on days 15–19; again six pills were taken at 2030 hours each day.

Cinnamon trial

This period followed exactly the same protocol as the control trial. However, instead of administering placebo capsules on days 0–14, subjects were given 500 mg vegi-capsules containing cinnamon (commercially available powdered spice from the *Cinnamomum cassia* plant; Everything Cinnamon, Essex, UK). Volunteers were instructed to consume six pills (= 3 g) each day at 2030 hours, following their evening meal. At day 15 subjects consumed 6 × 500 mg wheat flour placebo capsules each evening for the remaining 5 days. Oral glucose tolerance tests followed the protocol above and blood collection proceeded in the same fashion. The dose in this study was reduced to 3 g from 5 g in our previous study (Solomon and Blannin 2007) due to potential compliance and gastrointestinal issues that may arise from ingesting 10 × 500 mg pills per day for 2 weeks. Furthermore, given the evidence that at 3 g day^{-1} Khan et al. (2003) demonstrated significant reductions in FPG after 20 days feeding (−13%), and after 40 days feeding (−18%), plus a persistent reduction 20 days after ceasing cinnamon supplementation (−13%), it was considered likely that 3 g day^{-1} would provide an effective stimulus. Measures at day 1 were included to confirm our previous findings (Solomon and Blannin 2007) and to enable comparisons to be made between single and accumulative effects of cinnamon ingestion (measures on day 1 and 14 were compared with values on day 0 to give acute and chronic effects, respectively). Measures were taken at 2-day intervals following removal of the cinnamon stimulus to investigate the time course of post-intervention recovery.

Insulin sensitivity measurement

An insulin sensitivity index (ISI_{OGTT}) was calculated based on plasma glucose and insulin responses to OGTT (Matsuda and DeFronzo 1999). FSI = fasting serum insulin, MPG = mean plasma glucose, and MSI = mean serum insulin:

$$ISI_{OGTT} = \frac{10000}{\sqrt{FPG \times FSI \times MPG \times MSI}}$$

Analytical measures

Plasma glucose concentrations were measured using a COBAS Mira Plus (ABX Diagnostics, Montpellier, France) automated analyser, by an enzymatic assay involving hexokinase and glucose-6-phosphate dehydrogenase. The intraassay C.V was 3.51%. Serum insulin concentrations were determined using a commercially available enzyme-linked immunoabsorbant assay (DRG Instruments GmbH, Germany), by a solid-phase two-site

direct sandwich technique. The intraassay C.V for insulin was 4.22%.

Statistical analysis

Data are expressed as mean ± SEM and statistical analysis was carried out with SPSS for Windows 12.0.1 (SPSS Inc., Chicago, US). Raw glucose and insulin data were tested for normality and analysed by three-way (time × day × intervention) repeated measures ANOVA. Main effects were analysed using Bonferroni post hoc tests. Raw glucose and insulin data were converted to area under the curve (AUC) values by the trapezoidal method and differences were analysed by paired *t* tests. Changes in insulin sensitivity (ISI_{OGTT}) were analysed using two-way (day × intervention) repeated measures ANOVA, and again any main effects were analysed using Bonferroni post hoc procedures. Significance was achieved when $P < 0.05$.

Results

Plasma glucose responses to OGTT

Figure 1 illustrates the glucose responses following OGTT on each day, and Fig. 2 summarises the AUC data. No significant interactions were present in the OGTT raw glucose profile data (intervention × time $P = 0.10$, day × time $P = 0.11$, intervention × day $P = 0.09$, and intervention × day × time $P = 0.13$). However, statistical analysis of AUC data comparing day 1 of the cinnamon trial to day 0 of the cinnamon trial revealed decreased AUC glucose (−13.1 ± 6.3%; Fig. 2, $P < 0.05$). A comparison between day 1 cinnamon and day 1 control revealed a significant difference in glucose responses (−13.9 ± 3.9%, $P < 0.05$). Comparing day 14 of the cinnamon trial to day 0 of the cinnamon trial showed a nonsignificant decrease (−5.5 ± 8.1%, $P = 0.09$), and a comparison between day 14 cinnamon and day 14 control also demonstrated a nonsignificant change (−12.3 ± 11.8%, $P = 0.11$). In addition, no significant differences were found between trials for fasting or 2 h OGTT glucose data ($P > 0.05$).

Serum insulin responses to OGTT

Figures 3 and 4 illustrate the insulin responses and AUC during OGTT, respectively. No significant interactions were present in the OGTT raw insulin profile data (intervention × time $P = 0.08$, day × time $P = 0.10$, intervention × day $P = 0.07$, and intervention × day × time $P = 0.12$). Again, analysis of AUC data revealed that day 14 in the cinnamon trial was significantly reduced compared to day 0 (−27.1 ± 6.2%; Fig. 4, $P < 0.05$). Area under the curve values at day 14 were also lower in the cinnamon trial than in the control trial (−22.0 ± 10.4%; Fig. 4, $P < 0.05$). No significant differences were found between trials for fasting or 2 h OGTT insulin data ($P > 0.05$).

Changes in insulin sensitivity

Figure 5 illustrates insulin sensitivity data derived from the index of Matsuda and DeFronzo (1999). Analysis showed a day × intervention interaction ($P < 0.05$). Further examination revealed that the ISI_{OGTT} at day 14 was significantly greater than at day 0 in the cinnamon trial ($P < 0.05$), and that measures on day 14 of the cinnamon trial were greater than all days in control trial ($P < 0.05$).

Discussion

Following a 3 g day^{-1} supplementation for 14 days, glucose and insulin responses to OGTT were reduced, and insulin sensitivity was improved in inactive but otherwise healthy individuals. However, these data do not show any persistent effects of prolonged cinnamon supplementation on insulin sensitivity following removal of the cinnamon stimulus. This study also confirms our previous findings that an acute bolus of cinnamon spice can reduce glucose responses to OGTT performed 12 h later (Solomon and Blannin 2007). We also demonstrate that, when considered in parallel with our previous investigation that made use of a 5 g cinnamon bolus design, in this study a 3 g bolus ingestion induces similar improvement in glucose AUC (−10 vs. −13%), therefore suggesting that doses greater than 3 g do not provide additional benefit.

This study was perhaps underpowered to detect significant interactions between time, day and trial in raw glucose and insulin concentrations following OGTT. Power calculations, with power set at 0.8 and alpha at 0.05, reveal that based on the effect size in this study, investigating twenty subjects should be sufficient to detect statistically significant changes in a future experiment. This suggests that, with more subjects, significant differences in glucose responses at day 14 may arise, and therefore a more powerful study may increase the potential value of cinnamon as a therapeutic. Nevertheless significant reductions in insulin AUC data and improvements in insulin sensitivity were detected after 14 days of cinnamon supplementation; illustrating that prolonged cinnamon supplementation may be useful for improving insulin sensitivity. However, these findings should not be directly extrapolated to insulin resistant populations (obese/T2DM) as these data were obtained in healthy individuals. Despite this, our

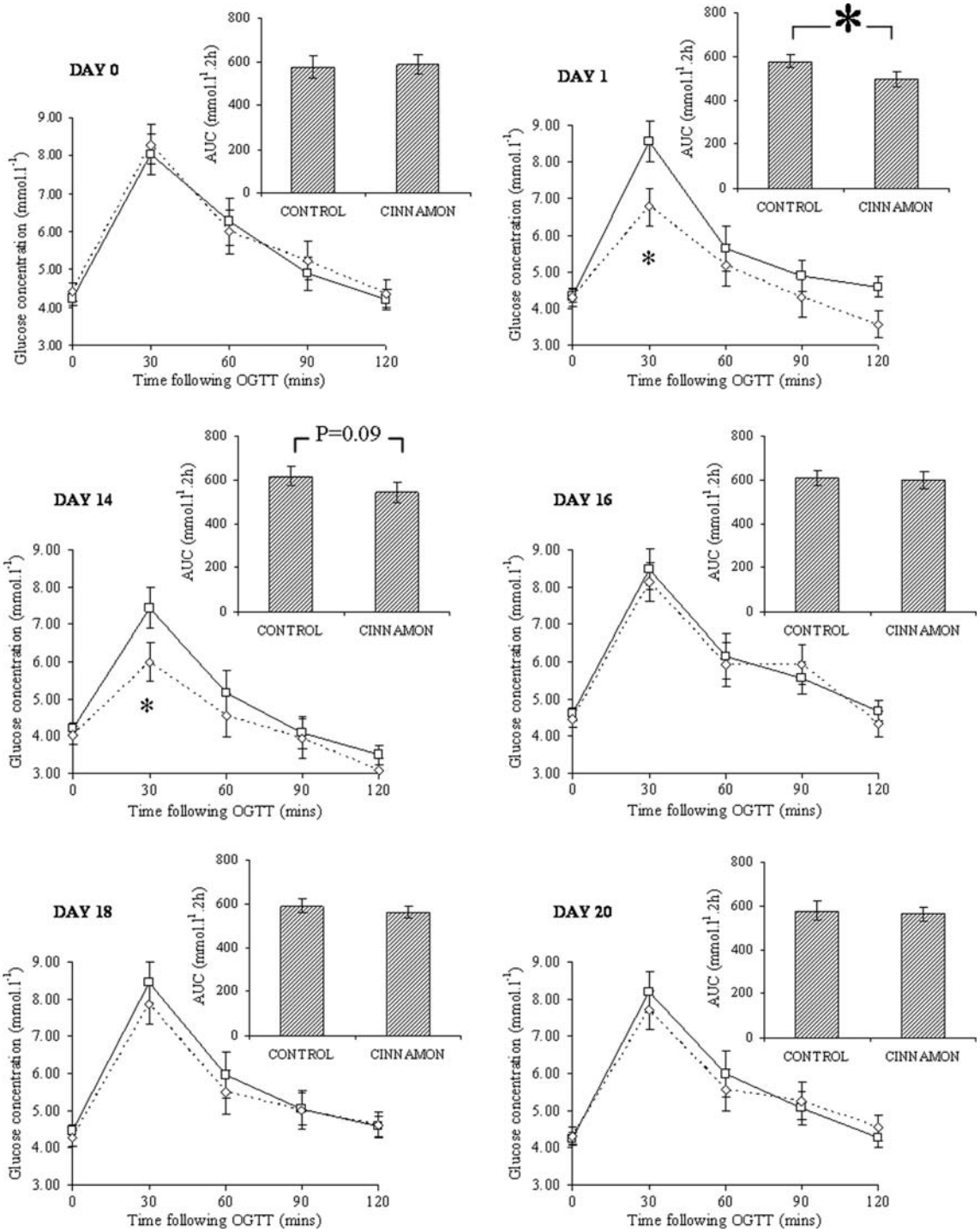

Fig. 1 Glucose concentration profiles following OGTT during each intervention period. OGTTs were undertaken at days 0, 1, 14, 16, 18, and 20 during the intervention period. *Bold lines* represent the control trial, where 3 g of placebo was administered each day. *Dashed lines* represent the cinnamon trial, where 3 g of cinnamon spice was administered each day until day 14, from when 3 g of placebo where given until the end of the 20-day intervention. Glucose concentrations at $t = 30$ mins on day 1 and 14 were significantly lower in the cinnamon trial than in control (paired t test, $P < 0.05$). The *insert graph* on each day represents total area under the glucose curve (*AUC*) for each OGTT. Glucose AUC was decreased at day 1 in the cinnamon intervention compared to control. *Asterisk* represents significant differences at $P < 0.05$. Glucose AUC at day 14 indicated a nonsignificant trend towards improved glucose responses in the cinnamon trial ($P = 0.09$). *Data* represents mean ± SEM

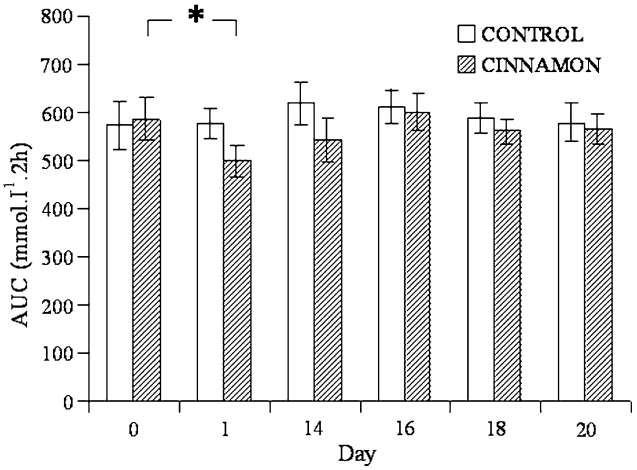

Fig. 2 Summary of the area under the OGTT glucose curve on each study day. OGTTs were undertaken at days 0, 1, 14, 16, 18, and 20. Control (*white bars*) represents 3 g of placebo administered each day. Cinnamon (*shaded bars*) represents 3 g of cinnamon administered each day until day 14. Analysis of area under the glucose curve following OGTT revealed intervention × day interaction analysis comparing day 1 to day 0 did demonstrate reduced area under the curve in the cinnamon trial (*Asterisk* indicates $P < 0.05$). Day 14 versus day 0 indicated a nonsignificant trend towards improved glucose responses in the cinnamon trial ($P = 0.09$). No differences within the control trial were found ($P > 0.05$). *Data* represents mean ± SEM

volunteers, although lean (BMI = 24 kg m^{-2}), did undertake less than the recommended physical activity guidelines. Inactivity is a cardiovascular disease risk factor (Barnard and Wen 1994) and a key factor in determining progression along the insulin sensitivity continuum (Eriksson et al. 1999; Holloszy et al. 1986; Lindstrom et al. 2003). Thus, our study cohort do not exhibit optimal insulin sensitivity.

The literature investigating long term cinnamon supplementation indicates increased glucose utilisation and increased activity of insulin signaling intermediates in mice (Kim et al. 2006) and rats (Qin et al. 2003), reversal of fructose-induced insulin resistance in rats (Qin et al. 2004), and improved fasting glycaemia and lipids in humans (Khan et al. 2003; Mang et al. 2006). A recent placebo-controlled study showed no effect of a 1.5 g day^{-1} cinnamon intervention in postmenopausal T2DM patients (Vanschoonbeek et al. 2006). This study had a superior design compared to the experiments of Khan et al. (2003) and Mang et al. (2006) with strict pharmaceutical, dietary and exercise restrictions, but used only female subjects, and a relatively low dose, which might possibly account for their null finding. Our data indicates improved insulin sensitivity in a healthy cohort but with no changes in fasting glycaemia. Mang et al. (2006) demonstrated that large improvements in FPG are only likely in cases of very poor glycaemic control. Our subjects' fasting glycaemia was within the normal reference range, and therefore further improvements are improbable. The presence of a persistent effect of cinnamon on glycaemic control seen in Khan's data is useful with regards to cost-benefit analysis, and patient compliance, such that constantly ongoing supplementation is not necessary, and failure to take a dose does not reverse all previous benefits. However, our current data fails to show any persistent effects on insulin sensitivity following cessation of cinnamon supplementation. These differences could be due to an inadequate time period of cinnamon ingestion in comparison to other long term cinnamon studies (20 vs. >40 days); or indeed due to the superior insulin sensitivity exhibited by our subjects in contrast to those used in previous investigations. Furthermore, the OGTT glucose AUC data suggest that the effects of cinnamon may diminish with continuous supplementation. Insulin AUC data however, was decreased by the accumulative effects of 14 days cinnamon feeding, yet these effects were quickly lost within 2 days of ceasing cinnamon intake. It appears that the effects on postprandial glucose responses are rapid, whereas there is a delayed effect on insulin responses and insulin sensitivity. These mechanisms warrant further attention by investigating glucose uptake at the cellular level, intracellular insulin signaling cascades, and transcriptional and translational regulation of genes and proteins involved in glucose metabolism. One in vitro experimental study showed increased insulin receptor autophosphorylation and reduced glycogen synthase kinase-3β (GSK-3β) activity with cinnamon in adipocytes (Imparl-Radosevich et al. 1998), and Qin et al. (2003) has shown cinnamon-induced increases in skeletal muscle IRS-1 tyrosine phosphorylation and PI3K association in rats. Another study by Qin et al. (2004) demonstrated that endothelial nitric oxide synthase (eNOS) inhibition prevents the effects of cinnamon in insulin resistant rats, suggesting a mechanism involving nitric oxide (NO), a signaling moiety implicated with insulin resistance (Kashyap et al. 2005; Monti et al. 2003). Cinnamon may activate similar mechanisms in humans, but further work is required. In addition, it is possible that reductions in postprandial glucose responses during periods of cinnamon feeding may be due to a reduction in gastric emptying or intestinal absorption. No investigation exists that examines the gastrointestinal effects of cinnamon; again, further work in this area is warranted.

These findings indicate that in a lean but sedentary male population, long term cinnamon supplementation can improve insulin sensitivity but that the effects are rapidly reversed in the post-stimulus period. Despite the strong in vitro and in vivo animal evidence, the rather conflicting human findings confuse the clinical therapeutic value of cinnamon, particularly when compared to the large impact of pharmaceutical, dietary and exercise interventions on

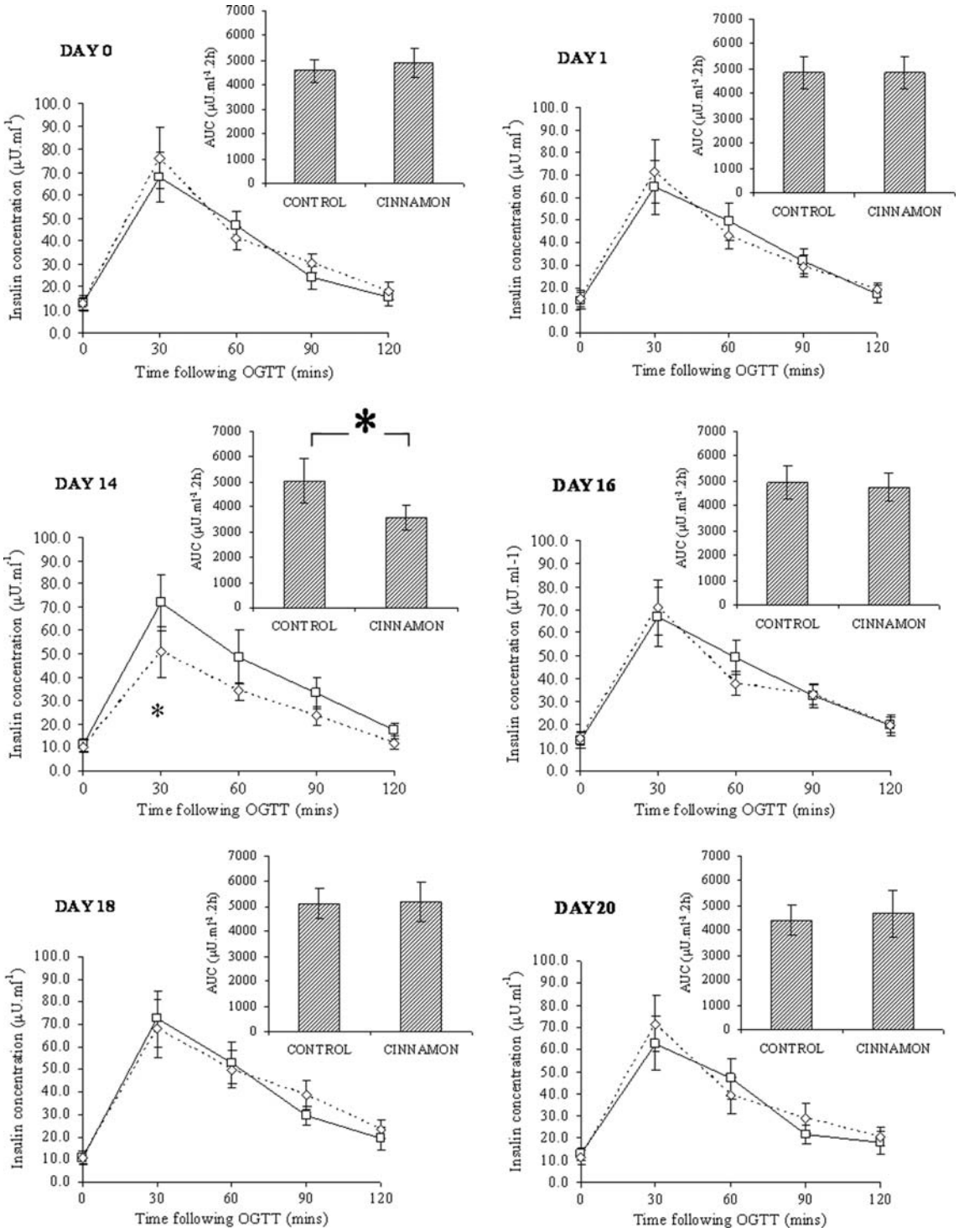

Fig. 3 Insulin concentration profiles following OGTT during each intervention period. OGTTs were undertaken at days 0, 1, 14, 16, 18, and 20 during the intervention period. *Bold lines* represent the control trial, where 3 g of placebo was administered each day. *Dashed lines* represent the cinnamon trial, where 3 g of cinnamon spice was administered each day until day 14, from when 3 g of placebo where given until the end of the 20 day intervention. Insulin concentrations at $t = 30$ mins on day 14 were significantly lower in the cinnamon trial than in control (paired t test, $P < 0.05$). The *insert graph* on each day represents total area under the insulin curve for each OGTT. Insulin AUC was decreased at day 14 in the cinnamon intervention compared to control. *Asterisk* represents significant differences at $P < 0.05$. *Data* represents mean ± SEM

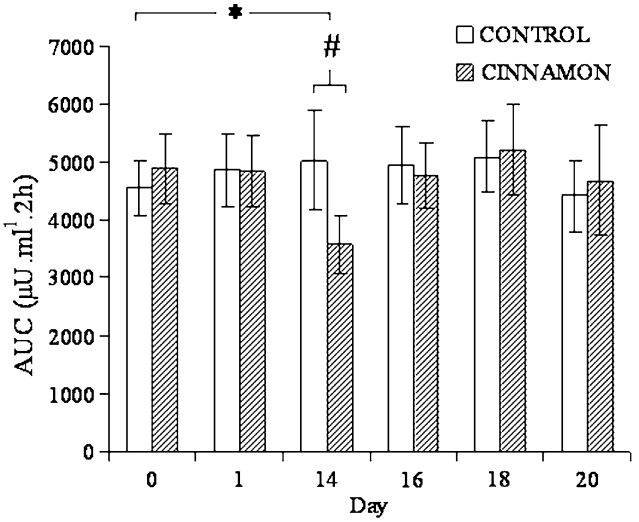

Fig. 4 Area under the serum insulin response curve to OGTT on each study day. OGTTs were undertaken at days 0, 1, 14, 16, 18, and 20. Control (*white bars*) represents 3 g of placebo administered each day. Cinnamon (*shaded bars*) represents 3 g of cinnamon administered each day until day 14. Analysis of area under the insulin curve following OGTT revealed an intervention × day interaction ($P < 0.05$). Further analysis indicated that measures at day 14 in the cinnamon trial were significantly lower than baseline (*Asterisk* indicates $P < 0.05$) and all other days ($P < 0.05$), and also that the AUC data at day 14 in the cinnamon trial was significantly lower than in the control trial (*Hash* indicates $P < 0.05$). *Data* represents mean ± SEM

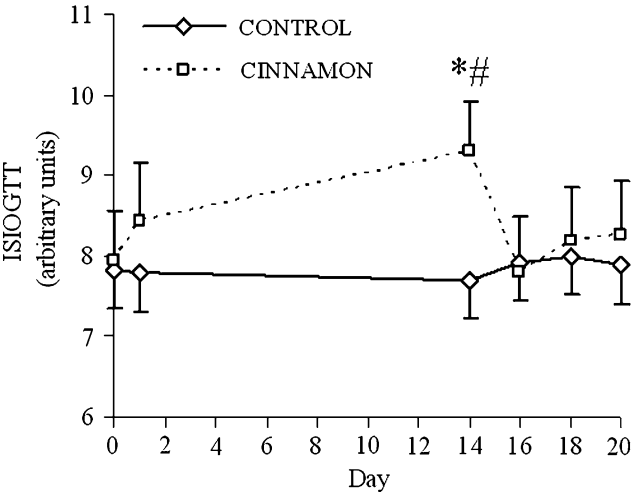

Fig. 5 Changes in insulin sensitivity during each intervention period. OGTTs were undertaken at days 0, 1, 14, 16, 18, and 20. The trials follow the same legend as previous figures. Analysis of insulin sensitivity (Matsuda and DeFronzo 1999) revealed a day × intervention interaction ($P < 0.05$) where day 14 was increased compared to day 0 in the cinnamon trial (*Asterisk* indicates $P < 0.05$), as well as being significantly greater than all days in the control trial (*Hash* indicates $P < 0.05$). *Data* represents mean ± SEM

insulin sensitivity and diabetes prognosis in epidemiological studies (Orchard et al. 2005). However, the increasing prevalence of obesity and diabetes suggests alternative therapeutic avenues should perhaps be explored. Further investigation of the long term effects of cinnamon on insulin sensitivity and intramuscular insulin signaling pathways in humans is required, so that conclusions as to its potential clinical application can be made.

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