GYNECOLOGY

Preliminary evidence that cinnamon improves menstrual cyclicity in women with polycystic ovary syndrome: a randomized controlled trial

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OBJECTIVE: To determine the effect of cinnamon on menstrual cyclicity and metabolic dysfunction in women with polycystic ovary syndrome (PCOS).

STUDY DESIGN: In a prospective, placebo controlled, double-blinded randomized trial, 45 women with PCOS were randomized (1:1) to receive cinnamon supplements (1.5 g/d) or placebo for 6 months. Menstrual cyclicity (average cycles/month) during the 6 months study period was compared between the 2 groups using the Mann-Whitney *U* test. Changes in menstrual cyclicity and insulin resistance between baseline and the 6 month study period were compared between the 2 groups using Wilcoxon signed rank tests.

RESULTS: The 45 women were randomized, 26 women completed 3 months of the study, and 17 women completed the entire 6 months of the study. During the 6 month intervention, menstrual cycles were more frequent in patients taking cinnamon compared with patients taking placebo (median, 0.75; interquartile range, 0.5−0.83 vs median, 0.25; interquartile range, 0−0.54; $P = .0085$; Mann Whitney *U*). In patients taking cinnamon, menstrual cyclicity improved from baseline (+ 0.23 cycles/month 95% confidence interval, 0.099−0.36), yet did not improve for women taking placebo. ($P = .0076$, Wilcoxon signed rank). Samples (n = 5) of serum from the luteal phase in different patients within the cinnamon group were thawed and ovulatory progesterone levels (>3 ng/mL) confirmed. Luteal phase progesterone levels (>3 ng/mL, n = 5) confirmed ovulatory menses. Measures of insulin resistance or serum androgen levels did not change for either group.

CONCLUSION: These preliminary data suggest that cinnamon supplementation improves menstrual cyclicity and may be an effective treatment option for some women with PCOS.

Key words: cinnamon, PCOS, randomized controlled trial

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Mounting evidence has implicated insulin resistance and compensatory hyperinsulinemia in the pathogenesis of polycystic ovary syndrome (PCOS).[1] Women with PCOS have increased rates of insulin resistance compared with controls, with absolute rates of insulin resistance as high as 65% in normal weight women and 95% in obese women.[2,3] Insulin resistance as well as hyperandrogenism in women with PCOS have been implicated in the dysfunction of the hypothalamic-pituitary-ovary axis, leading to anovulation and menstrual irregularity.[4]

Insulin sensitizing agents, such as metformin and thiazolidinediones, have been used successfully to treat women with PCOS.[5] Such agents have been shown to significantly reduce insulin resistance and androgen levels as well as some inflammatory markers, improve menstrual irregularity, and improve ovulatory function in some women with PCOS.[6-8] However, thiazolidinediones have multiple safety concerns and metformin, the most widely used drug in PCOS, is often poorly tolerated because of gastrointestinal side effects of nausea (61%), vomiting (30%), and diarrhea (65%).[9,10]

Cinnamon, a commonly used spice used since biblical times, has been found to have insulin sensitizing effects in both animal and human studies.[11-13] Although the mechanism is incompletely understood, cinnamon likely increases insulin sensitivity through intermediate metabolites acting at the cellular level.[14] In vitro studies and studies using animal models have shown that polyphenol polymers isolated from cinnamon increase insulin dependent glucose metabolism by activating the insulin receptor and altering glucose transport.[15-17]

Several groups have investigated the use of cinnamon in the treatment of diabetes. In a randomized, controlled clinical trial, daily intake of 1, 3, or 6 g of oral cinnamon (cinnamomum cassia) reduced serum glucose, triglycerides, LDL cholesterol, and total cholesterol in type II diabetes patients compared with placebo.[12] In another randomized, controlled trial, 3 g of oral cinnamon

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reduced fasting glucose in poorly controlled type II diabetes patients.[18]

Given the preliminary success of using cinnamon to treat insulin resistant diabetes and the established use of insulin sensitizing agents in the treatment of PCOS, cinnamon has been proposed as a possible alternative therapy for PCOS. In our own prospective placebo-controlled pilot study, cinnamon demonstrated significant reductions in fasting glucose and insulin resistance parameters after 8 weeks of oral cinnamon extract, 1 g per day.[19] However, the effects of cinnamon on symptoms and the metabolic dysfunction of PCOS have yet to be investigated in a large, randomized controlled trial. Accordingly, we applied to the United States Food and Drug Administration (FDA) to use cinnamon as an Investigational New Drug (IND) and have carried out a randomized, double-blinded, placebo-controlled trial investigating the effect of cinnamon on menstrual cyclicity in women with PCOS.

Materials and Methods

All study protocols and procedures were approved by the institutional review board of Columbia University. An application to use cinnamon supplements (Cinnulin PF; Integrity Nutraceuticals International, Spring Hill, TN) as an IND was submitted and accepted by the FDA (IND no. 110123). Regular reporting to the FDA and data safety monitoring board was performed as was required.

Patients aged 18-38 years meeting the Rotterdam criteria for polycystic ovary syndrome (oligomenorrhea or amenorrhea and either [1] clinical or biochemical evidence of hyperandrogenism or [2] ultrasound findings of polycystic ovaries) were recruited by print advertisement for participation in an international review board approved, registered, randomized, controlled clinical trial (NCT-01483118). Exclusion criteria were current pregnancy or lactation, current treatment of infertility, established diagnosis of diabetes mellitus, insulin sensitizing treatment within 3 months of study enrollment, hormonal treatment involving estrogen or progesterone within 3 months of study enrollment, systemic, or inhaled corticosteroid use, known hypersensitivity to cinnamon, known seizure disorder, cardiovascular disease, or cerebrovascular disease. A wide range of body mass index (20-50) was included given the anticipated patient population and the suspected mechanism of action of cinnamon through metabolic pathways.

Patients meeting inclusion and exclusion criteria were offered study participation and informed consent was established. Patients were compensated for their time and effort at each visit, after randomization. Enrolled study patients were evaluated during the early follicular phase (day 3-7) after a spontaneous or induced menses. Height, weight, and vital signs were measured and recorded. Subcutaneous fat thickness was measured by transabdominal ultrasound. Antral follicle count and ovarian volume (π/6 *transverse diameter *anterior-posterior diameter * longitudinal diameter) were measured by transvaginal ultrasound. Fasting blood samples were obtained and a 2 hour 75 g glucose tolerance test was performed with phlebotomy 30, 60, and 120 minutes after glucose ingestion.

Subjects were randomized in a 1:1 fashion to receive either cinnamon supplements (125 mg capsule, 4 capsules 3x/day =1500 mg/day) or identically appearing 1.5 cm and 0.5 cm white placebo capsules (4 capsules, 3x/day) for the 6 month study period. The 1500 mg dose was chosen based on published clinical trials in diabetic patients and our own pilot study in patients with PCOS.[11,16,17] Both the study subjects and the investigators were blinded for the duration of the study, as drug and placebo samples were labeled in code by the manufacturer (Integrity Nutraceuticals International). All patients were advised to adhere to a balanced diet of 1800 calories per day and instructed to complete a daily menstrual calendar as well as an activity log. Compliance with diet and medications and interval progress was monitored with monthly visits with the investigators. The 2 hour 75 g. glucose tolerance test was repeated at the 3 month visit. A final visit at 6 months included height and weight measurements, vital signs, repeat transabdominal and transvaginal ultrasound, and repeat 75 g glucose tolerance test.

Serum levels of insulin, total testosterone (T), dehydroepiandrosterone sulfate (DHEA-S), and sex-hormone binding globulin (SHBG) were measured with chemiluminescence assays using Immulite (Diagnostic Products Corporation, Los Angeles, CA). Baseline data from the study subjects (insulin resistance and androgen profiles) were compared with established controls from our previously published studies and reference values.[20-23]

The primary study outcome was menstrual cyclicity, approximated in the study by menstrual frequency, (number menses/number months observed) during the study period. Secondary outcomes were change in menstrual cyclicity from reported baseline cyclicity, change in insulin sensitivity indices (homeostasis model of insulin resistance [HOMA-IR], Quantitative Insulin Sensitivity Check Index [QUICK-I]), change in glucose response (area under the curve, trapezoidal method), change in serum androgen and SHBG levels, change in weight, change in subcutaneous fat measurements, and change in ovarian volume.

The Mann-Whitney *U* test was used to compare the number of menstrual cycles during the study period between the patients taking cinnamon and placebo. Wilcoxon signed-rank tests were used to compare all variables between baseline and at study completion in both the cinnamon and placebo groups. The target sample size was 40, powered to detect a 40% increase in menstrual cycle frequency with a type II error of 0.20 and a type I error of 0.05.

Results

Study enrollment began in Aug. 2011 and was terminated in Sept. 2012 because of expiration of the study drug and matched placebo in March 2013. Sixty-three women were screened and 45 patients were enrolled in the clinical trial (Figure 1). Twenty-three women were randomized to receive cinnamon and 22 women were randomized to

FIGURE 1
Flowchart

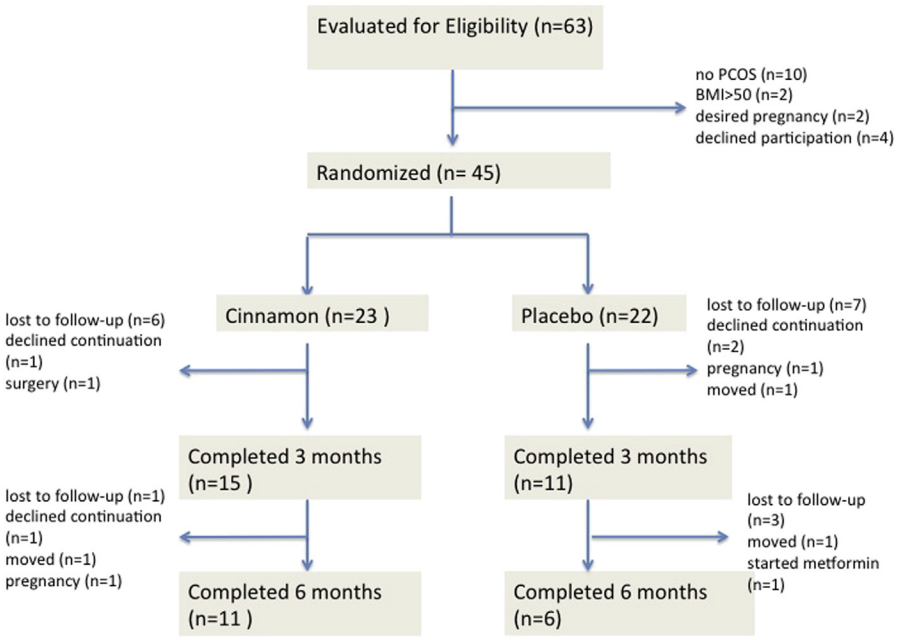


Diagram of patient recruitment, enrollment, and completion of the randomized controlled trial.

Kort. Effect of cinnamon in women with PCOS. Am J Obstet Gynecol 2014.

receive placebo. Race and ethnic groups were diverse and well matched between groups, including nonHispanic black (total, n = 18), nonHispanic white (n = 8), Hispanic (n = 16), Asian (n = 1), other (n = 2).

TABLE 1
Baseline characteristics

Index	Cinnamon	Placebo	Difference
Age (y), mean (range)	26.95 (18–34)	27.86 (18–38)	NS
BMI (kg/m^2), mean, SD	33.0 ± 5.6	31.4 ± 6.0	NS
Waist circumference (cm), mean, SD	97.0 ± 12.9	93.1 ± 19.4	NS
Hip circumference (cm), mean, SD	112.2 ± 1.1	112.3 ± 21.4	NS
Average SQ fat (cm), mean, SD	3.7 ± 0.82	3.9 ± 1.0	NS
HOMA-IR, mean, SD	2.8 ± 1.4[a]	2.5 ± 0.93[a]	NS
QUICK-I	0.34 ± 0.029[b]	0.35 ± 0.044[b]	NS
Total T (ng/dL), mean	52.2 ± 26.2[c]	62.0 ± 46.3[c]	NS
DHEA-S (μg/mL), mean	1.81 ± 0.71[d]	1.91 ± 1.02[d]	NS
SHBG (nmol/L), mean	31.3 ± 18.2[e]	36.7 ± 16.0 [e]	NS

BMI, body mass index; *DHEA-S*, dehydroepiandrosterone sulfate; *HOMA-IR*, homeostasis model of insulin resistance; *NS*, not significant; *PCOS*, polycystic ovary syndrome; *QUICK-I*, Quantitative Insulin Sensitivity Check Index; *SHBG*, sex hormone binding globulin; *SQ*, subcutaneous.

[a] Increased compared with historical nonPCOS controls - HOMA-IR = 1.6 (1.2-2.1)[22]; [b] Eecreased compared with historical nonPCOS controls - QUICK-I = 0.358 ± 0.02[21]; [c] Elevated compared with historical nonPCOS controls – Total T = 31 ± 11 ng/dL[20]; [d] Similar to nonPCOS control – DHEA-S 1.8 ± 0.5 μg/mL[20]; [e] Lower than established values in premenopausal women –51 ± 16 nmol/L)[23]

Kort. Effect of cinnamon in women with PCOS. Am J Obstet Gynecol 2014.

Of the 45 women enrolled in the trial, 26 patients completed 3 months of intervention and 17 patients completed 6 months of intervention. Reasons for patient dropout included loss to follow-up, pregnancy, surgery, moving, and starting insulin sensitizing with medication. The complete enrollment flowsheet can be found in Figure 1.

Baseline clinical characteristics, insulin resistance, subcutaneous fat measurement, and serum androgen levels may be found in Table 1. Menstrual data was collected for a total of 51 months for the cinnamon group and 47 months for the placebo group. Baseline menstrual cyclicity (average number of cycles/month) was comparable between the cinnamon and placebo groups (mean, standard deviation, 0.42 ± 0.16 vs 0.47 ± 0.21). Measures of insulin resistance and serum androgen levels were comparable between groups and elevated compared with historical controls.

Adverse events included headache (4 patients), heartburn symptoms (2 patients), menstrual cramps (2 patients), and nausea with diarrhea (1 patient). All adverse events resolved during the study period and no serious adverse events were reported.

During the 6 month intervention, menstrual cyclicity (number of cycles/month) was more frequent in women taking cinnamon compared with women assigned to placebo (median, 0.75; interquartile range, 0.5–0.83 vs median, 0.25; interquartile range, 0–0.54; P = .0085; Mann Whitney U; Table 2, Figure 2). Menstrual cyclicity significantly improved from baseline (P = .0076, Wilcoxon matched pairs signed rank test) in women taking cinnamon, yet did not improve in women on placebo (P = .145, Wilcoxon matched pairs signed rank test). Samples (n = 5) of serum from different patients within the cinnamon group determined to be in the luteal phase (bleeding within 12 days of blood draw) were thawed and ovulatory progesterone levels (>3 ng/mL) were confirmed.

For patients completing the study and undergoing the 6 month 75 g glucose tolerance test, insulin resistance did not significantly change for either patients taking cinnamon or patients taking

TABLE 2
Menstrual cyclicity

Menstrual cyclicity	Cinnamon	Placebo	*P* value
Baseline (no. of cycles/month), median (IQR)	0.42 (0.33–0.63)	0.42 (0.29–0.68)	.7 (NS)[a]
Study period (no. of cycles/month), median (IQR)	0.75 (0.5–0.83)	0.25 (0–0.54)	.0085[a]
Change during study, ± cycles/month (95% CI)	+ 0.23 (0.099–0.36)	−0.13 (−0.46 to 0.065)	.0076[b]

CI, confidence interval; *IQR*, interquartile range; *NS*, not significant.

[a] Mann-Whitney *U* test; [b] Wilcoxon matched pairs signed rank.

Kort. Effect of cinnamon in women with PCOS. Am J Obstet Gynecol 2014.

placebo. Measures of insulin sensitivity (HOMA-IR, QUICK-I, and glucose area under curve) may be found in Table 3.

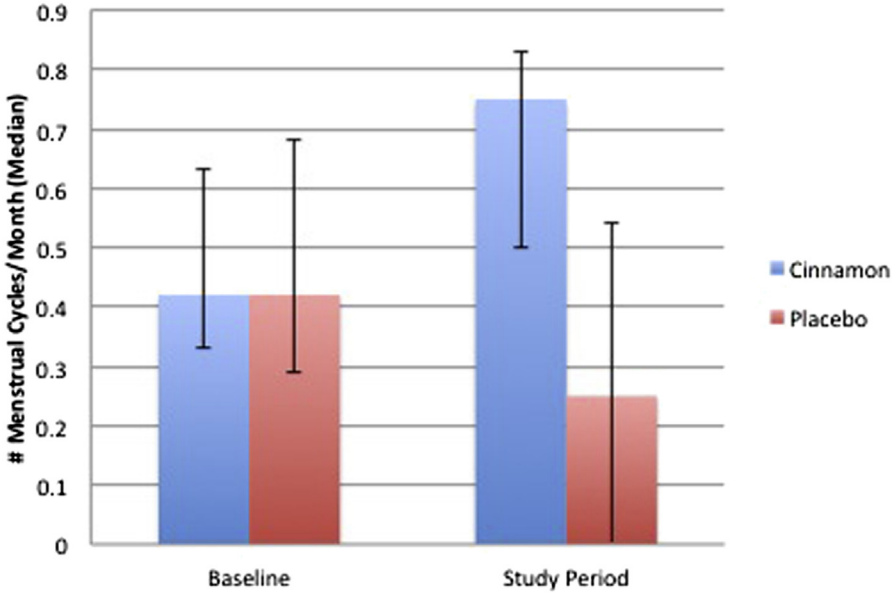
Serum androgen and SHBG levels did not significantly change over the study period in either group. Total testosterone levels remained mildly elevated in both the cinnamon (study completion value 41.0 ng/dL) and placebo groups (49.7 ng/dL). Weight, subcutaneous fat thickness, and ovarian volume did not significantly change in either the cinnamon or placebo group that completed the 6 month study.

Comment

The above study is the first randomized, double-blinded, controlled trial investigating the effect of cinnamon on menstrual cyclicity in women with PCOS. During the 6 months study period, women receiving cinnamon treatment showed significant improvements in menstrual cyclicity, whereas patients receiving placebo did not. Sampling of luteal phase serum progesterone, sonographic visualization of corpora lutea, and pregnancy all support that reported bleeding resulted from ovulatory cycles, rather than merely changes in menstrual flow.

Unfortunately, a mechanism for the positive effect of cinnamon on menstrual cyclicity was not identified in our study group. The suspected mechanism, improvement in insulin sensitivity, was not appreciated. This is in contrast to several studies that have shown cinnamon to improve insulin sensitivity in a variety of patient populations. In the first randomized, controlled trial, cinnamon at different dosages (1 g, 3 g, 6 g) decreased mean fasting glucose (18-29%) in patients with type 2 diabetes.[12] Improvements were seen as early as 20 days after supplementation, with a slight dose response and a lasting effect after stopping supplementation. In another randomized, controlled trial involving type II diabetes patients, 3 g of daily cinnamon over 4 months improved fasting glucose by a mean of 18 mg/dL, yet had no effect on hemoglobin A1C levels.[18] Serum insulin levels, and thus measurements of insulin resistance, were not reported in either trial, thus making comparisons to our study difficult. However, in our own previous pilot study, we reported improved insulin sensitivity in patients with PCOS taking 1 g of cinnamon daily (QUICK-I, +7.7%; HOMA-IR, −44.5%).[19] Although it was surprising that we did not find statistical changes in insulin/glucose parameters after cinnamon, the women who were randomized to cinnamon and completed the trial had higher HOMA and lower QUICK-I (suggesting more insulin resistance), compared with the group randomized to placebo treatment. Indeed the participants in the placebo group who completed the trial had normal insulin resistance parameters (Table 3), although the group as a whole was similar to the cinnamon group at trial initiation (Table 1) This may suggest that although we could not demonstrate changes, women receiving cinnamon had a greater chance for improvement of insulin resistance with

FIGURE 2
Menstrual cyclicity



Bar chart illustrating the change in menstrual cyclicity in both the cinnamon and placebo groups. Error bars indicate interquartile range.

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TABLE 3
Insulin resistance

	Cinnamon (n = 11)		Placebo (n = 6)	
Index	**Baseline**	**6 months**	**Baseline**	**6 months**
HOMA-IR, median (IQR)	2.3 (1.4–2.8)	2.5 (0.97–3.3)	1.8 (0.71–3.3)	1.2 (0.78–2.6)
QUICK-I, median (IQR)	0.34 (0.33–0.36)	0.33 (0.32–0.39)	0.35 (0.32–0.41)	0.37 (0.33–0.40)
AUC, median (IQR, mg/dL[a] min)	16,485 (13,995–18,964)	16,515 (15,068–20,190)	13,298 (11,993–15,285)	15,420 (14,468–17,798)

AUC, area under the curve; *HOMA-IR*, homeostasis model of insulin resistance; *IQR*, interquartile range; *QUICK-I*, Quantitative Insulin Sensitivity Check Index.

Kort. Effect of cinnamon in women with PCOS. Am J Obstet Gynecol 2014.

treatment over time. Along these lines, fasting blood measurements of glucose and insulin may not be sensitive enough to detect subtle changes in insulin resistance at the tissue or cellular level, and particularly with small numbers of participants.

Other mechanisms, such as altered serum androgens or altered size and content of fat mass, may also be involved, yet differences could not be identified in the 6 month time period with our sample size.

Adverse events in our trial were not common and no serious adverse events were reported. This is consistent with published data, showing minimal adverse events and no increase when compared with placebo in comparative trials.[24]

The biggest concern with our trial was the high drop out rate of patients during the 6 month study period. The recruitment period lasted over a year and we were not able to continue because of expiration of the study drug and placebo. Although some patients encountered situations excluding them from further participation (pregnancy, surgery), the majority of patients who dropped out were either lost to follow-up or declined further participation. Many possible factors may be involved in this drop out rate, including the large geography of our catchment area, required monthly follow-up visits, compensation rates, required daily menstrual diary, and recommended 1800 calorie dietary restriction using a daily intake diary. Nevertheless, this drop out rate is typical of trials in women with PCOS not trying to conceive. Our data are extremely similar to other clinical trials, where a drop out rate of close to 50% is not unexpected.[25,26] However, given the high drop out rate, this study should be considered a pilot study for future investigations.

In summary, our data suggest that cinnamon supplementation may be a useful adjunct in the treatment of menstrual dysfunction in women with PCOS. Further work to confirm these results and shed light on the mechanism(s) of action is still needed. ■

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