The Effect of Cinnamon on A1C Among Adolescents With Type 1 Diabetes

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OBJECTIVE — The purpose of this study was to determine the effect of cinnamon on glycemic control in adolescents with type 1 diabetes.

RESEARCH DESIGN AND METHODS — Using a prospective, double-blind, placebo-controlled design, 72 adolescent type 1 diabetic subjects were treated in an outpatient setting with cinnamon (1 g/day) or an equivalent-appearing placebo for 90 days. A1C, total daily insulin intake, and adverse events were recorded and compared between groups.

RESULTS — There were no significant differences in final A1C (8.8 vs. 8.7, $P = 0.88$), change in A1C (0.3 vs. 0.0, $P = 0.13$), total daily insulin intake, or number of hypoglycemic episodes between the cinnamon and placebo arms.

CONCLUSIONS — Cinnamon is not effective for improving glycemic control in adolescents with type 1 diabetes.

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Basic scientists and clinical researchers have been investigating the possibility that cinnamon improves glycemic control in patients with diabetes. Anderson et al. (1) suggested that doubly linked, water-soluble A-type polymers, possibly misidentified earlier as methylhydroxychalcone polymers (2), are the active compounds. Several in vitro investigations reported the insulin-sensitizing effect of cinnamon (1–4). Using a rat model, Qin et al. (5) postulated that cinnamon acts by "[potentiating] the insulin-stimulated tyrosine phosphorylation of IR-β [insulin receptor-β] and IRS-1 [insulin receptor substrate-1] and the IRS-1 association with PI [phosphoinositol] 3-kinase." Jarvill-Taylor et al. (2) observed that when cinnamon and insulin were combined in vitro, the effect was greater than was expected, implying a synergistic relationship. Additionally, Kim et al. (6) proposed that cinnamon acts by increasing endogenous insulin production, rather than by a target-based mechanism.

Previous research has suggested that cinnamon may be effective for improving glycemic control in type 2 diabetic subjects (7–9). Khan et al. (7) compared fasting serum glucose levels in 60 type 2 diabetic subjects taking daily cinnamon or placebo for 40 days (1, 3, or 6 g cinnamon versus a equivalent-appearing placebo). At all three doses, subjects taking cinnamon had a statistically significant decrease in fasting serum glucose level (from a mean of 236 to 175 mg/dl), not observed with the placebo. Mang et al. (8) and Vanschoonbeek et al. (10) both conducted randomized, controlled trials evaluating cinnamon in adults with type 2 diabetes. Neither group observed a change in lipids or A1C, but Mang et al. reported a significant decrease in fasting glucose.

Widespread achievement of therapeutic glycemic targets remains an elusive goal for type 1 diabetic subjects (11). This is particularly true for adolescent patients because of physiological changes, such as increased insulin resistance, as well as psychosocial issues (12–14). Bryden et al. (15) reported that A1C increases consistently throughout adolescence, from 9.4% at age 13 years to 11% at age 19 years.

To date, no researchers have investigated the effect of cinnamon on type 1 diabetic subjects. However, the potential benefit of adding enteral diabetes medications to insulin in this population has been previously demonstrated (16–18). If the addition of a simple, natural pill taken once a day can significantly improve glycemic control, particularly in adolescents, the clinical implications would be substantial.

RESEARCH DESIGN AND METHODS

— The primary objective of this study was to determine the effect of cinnamon on glycemic control among adolescents with type 1 diabetes. The study was prospective, randomized, double-blind, and placebo controlled. It was approved by the Dartmouth Committee for the Protection of Human Subjects. Patients were recruited at the Dartmouth-Hitchcock Medical Center (DHMC) endocrinology clinic and at the Hitchcock Clinic in Manchester, New Hampshire. DHMC is a tertiary care academic medical center in Lebanon, New Hampshire, with regional clinics and affiliates across the state. Approximately 250 pediatric diabetic patients are followed at DHMC, and another 300 are seen in the Manchester Clinic.

All pills were prepared in advance by the University of California San Francisco Investigational Pharmacy. Pills contained either 1 g cinnamon or an equivalent appearing amount of lactose. Pills were packaged in standard pill bottles and labeled with an expiration date. Each pill bottle was assigned a randomly determined study number before being distributed to subjects. Although both cinnamon and placebo pills appeared identical, it is possible

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Abbreviations: DHMC, Dartmouth-Hitchcock Medical Center.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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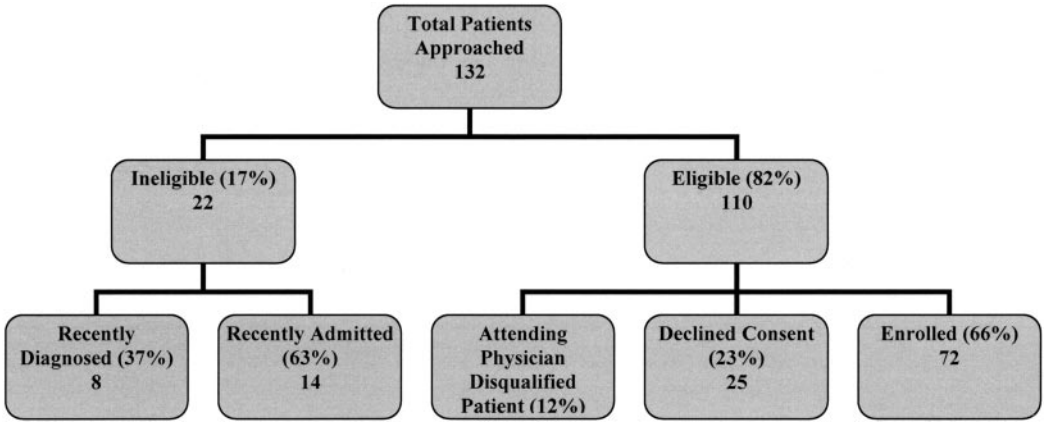

Figure 1—*Flow diagram of eligible patients.*

that some of the participants could discern differences between the two types of capsules.

Patients were selected for the study on the basis of the following inclusion criteria: *1*) diagnosis of type 1 diabetes for ≥18 months before enrollment, *2*) aged 13–18 years at the time of enrollment, *3*) presentation to the clinic for routine care, *4*) no hospital admissions for medical or psychiatric reasons in the 12 months before enrollment, *5*) ability to be accessed by phone, and *6*) not pregnant. Informed consent was obtained from a parent or legal guardian with assent from the patient. At the time of enrollment, patients received a 3-month supply of cinnamon or placebo. Patients were instructed to choose a time of day that would be most convenient and take the pill consistently at that time. Subjects were given phone numbers and e-mail addresses of the investigators and instructed to call with any questions or concerns. Patients were also asked to keep a log of their total daily insulin dose during the course of the study. The research team did not suggest any alterations in other aspects of the subject's medical care, diet, or exercise. A member of the research team called each participant every 2 weeks during the study to assess adherence to the study protocol, to collect data on the subjects' current insulin dosing, and to determine possible adverse events. Specific adverse events elicited included hypoglycemic episodes, recent illnesses, or other adverse health changes the participants believed to be relevant.

A1C levels, already planned as part of subjects' regular diabetes care, were obtained from medical records at the time of enrollment and ~90 days later. Three months after enrollment, subjects returned to the clinic at which time insulin logs were collected. Compliance was measured by a pill count performed at that time.

Statistical analyses

Baseline characteristics are reported as means ± SD and proportions and were compared between the cinnamon and placebo arms using unpaired *t* tests and χ^2 tests. The primary end point, A1C at 3 months, as well as the change in A1C, was compared between study arms using an unpaired *t* test. Total daily insulin, available as a repeated measure for up to 3 months, was compared between the study arms using a mixed-effects model with random subject intercept. The ratio of carbohydrates to insulin dose was compared between the study arms using an unpaired *t* test. The number of hypoglycemic events (glucose <80 mg/dl) was compared using Poisson regression with robust SEs to estimate a rate ratio (an offset equal to number of 2-week intervals for which a hypoglycemia count was available for each subject was used). R software was used (19).

Sample size calculations were used to determine that study completion of 64 subjects (32 per arm) would be sufficient to have power of 80% to detect a reduction in A1C at 3 months of 0.5, based on an SD of 0.7 for change in A1C over 3 months and type I error of 5%. Anticipating a dropout rate of 10% over 3 months, a total of 72 subjects were enrolled and randomized.

RESULTS — During the study period, 132 patients were approached for enrollment, of whom 110 were ultimately found to be eligible. Of the eligible patients, 25 declined consent and 13 were disqualified at the discretion of the treating physician, most often because of a perceived inability to comply with the study protocol or concern about current diabetes management (Fig. 1). Of the 72 patients who began the protocol, 15 did not complete 90 days of medication.

There were no significant differences in demographic variables between groups (Table 1). Because adolescence is a period of rapid growth, height, weight, and BMI characteristics are presented as *z* scores, rather than actual values. A basal/bolus insulin regimen was used for all patients.

One patient in the cinnamon arm developed hives and discontinued the study. It was later determined that this patient had a family history of allergy to cinnamon. A patient in the placebo arm withdrew because of stomach aches, possibly attributable to lactose intolerance. A third patient, also in the placebo arm, reported frequent illnesses while enrolled and declined to continue in the study. One patient in the cinnamon arm had a hypoglycemic seizure and withdrew. This incident occurred the day after the subject enrolled in the study. One patient in the cinnamon group withdrew from the study without stating a reason. Four participants in the cinnamon group and four in the placebo group were lost to follow-up. One patient in the placebo group and one patient in the cinnamon group were unable to swallow the pills.

Based on intention-to-treat analysis, the mean final A1C among patients in the cinnamon arm was not significantly different from that in the placebo group (8.8 vs. 8.7, $P = 0.88$) (Table 2 and Fig. 2). The mean change in A1C was also not statistically significant between groups (cinnamon ΔA1C 0.3, placebo ΔA1C 0.0; $P = 0.13$) There were no statistically sig-

Table 1—*Study population characteristics*

	Cinnamon	Placebo	*P* value
n	28	29	
Age (years)	14.7 ± 1.4	15.2 ± 1.7	0.20
Sex			0.90
Male	13 (46)	13 (45)	
Female	14 (54)	15 (55)	
Height (*Z* score)	0.22 ± 0.96	0.19 ± 1.17	0.91
Weight (*Z* score)	0.88 ± 0.78	0.74 ± 0.84	0.51
BMI (*Z* score)	0.77 ± 0.73	0.78 ± 0.63	0.98
Time since type 1 diabetes diagnosis (years)	7.1 ± 4.6	6.1 ± 5.6	0.39
Treatment modality			
Insulin pump (%)	10 (36)	121 (41)	0.66
Injections (%)	18 (64)	17 (59)	

Data are means ± SD or *n* (%).

nificant differences observed between groups in terms of daily use of insulin (cinnamon patients used 2.9 more units of insulin per day [95% CI −5.8 to 11.6], $P = 0.51$, adjusted for insulin dose at baseline). Patients in the cinnamon arm had 39% more self-reported hypoglycemic episodes (<80 mg/dl [−13 to 123%]) than those in the placebo arm, but this value did not reach statistical significance ($P = 0.17$).

CONCLUSIONS — To our knowledge, this was the first study to evaluate the effect of cinnamon on glycemic control in type 1 diabetes. We chose to study adolescents because we believed that this age-group was particularly at risk and had the most to gain from the intervention. The results did not demonstrate any benefit of cinnamon in this patient population. In addition, the directionality of the results is somewhat surprising. In essentially all outcomes (A1C, total daily dose, number of hypoglycemic episodes, and weight change), the trend favored the placebo group, although did not achieve statistical significance.

The mechanistic differences between type 1 and type 2 diabetes, i.e., the lack of endogenous insulin production in the former, is one possible explanation for the negative result. Kim et al. (6) was the first to suggest that cinnamon may act by stimulating endogenous insulin production. If this were true, it would explain our result. However, this contention does not fit well with the majority of published research, which instead suggests a mechanism focused on the insulin receptor. Both the cinnamon group and the placebo group used similar amounts of insulin per day and had similar sensitivity to injected insulin. This finding suggests that whatever effect insulin has on glucose uptake in type 2 diabetic subjects is not present in those with type 1 diabetes. If cinnamon either increased the effect of insulin or independently aided glucose uptake, we would have expected to see a drop in total insulin intake in the cinnamon arm compared with the placebo arm. Likewise, we would have expected a decrease in the amount of insulin the cinnamon group needed to cover ingested carbohydrates. These changes would be expected independent of changes in A1C.

Although Khan et al. (7) reported a benefit of cinnamon in fasting serum glucose levels in type 2 diabetic subjects, another possible explanation for our negative result is that cinnamon is actually ineffective in type 1 and type 2 diabetes. Vanschoonbeek et al. (10) and Mang et al. (8) have both failed to find any effect on A1C in type 2 diabetic subjects, although the latter group demonstrated an effect on fasting glucose. Because A1C remains the most important long-term predictor of complications in both type 1 and type 2 diabetes, the effect of any intervention on A1C is critical in determining its clinical usefulness. Perhaps the reported benefit of cinnamon on fasting glucose but negligible effect on A1C can best be explained by the relatively small contribution fasting glucose makes to A1C. Given the current evidence, we question whether the initial optimism surrounding the clinical importance of cinnamon remains warranted.

This study had several limitations. It is possible, but unlikely, that subjects received an inadequate dose of cinnamon. The dose for this study was based on the previously demonstrated benefit of 1 g/day (7). Perhaps, although sufficient for type 2 diabetic subjects, this is an inadequate dose for those with type 1 diabetes. Vanschoonbeek et al. (10) used 1.5 g/day and failed to demonstrate a benefit, whereas Mang et al. (8) used 3 g/day and did demonstrate improvement in fasting glucose. However, according to the data Khan et al. (7) presented, both 1 g/day and higher doses were effective. Given the directionality of our results, it is possible that a higher dose of cinnamon could have actually resulted in a statistically significant benefit for the placebo group.

It is also possible that participants were not given cinnamon for a long enough duration. Because 90 days is less than the full 120-day lifespan of red blood cells, perhaps this shorter duration contributed to a false-negative result. However, we believe that 90 days is a sufficient time in which to demonstrate an effect and also point out that these results are consistent with other recent observations (8,10).

In summary, this study provides evidence that cinnamon is not effective in improving glycemic control in adoles-

Table 2—*Study variables*

	Cinnamon	Placebo	*P* value
A1C at baseline	8.4 ± 1.3	8.7 ± 1.3	0.49
A1C post-intervention	8.8 ± 1.6	8.7 ± 1.4	0.88
A1C change	0.3 ± 0.9	0.0 ± 0.6	0.13
Baseline insulin sensitivity (g CHO/unit insulin)	9.0 ± 3.2*	9.7 ± 3.3†	0.33
Postintervention insulin sensitivity (g CHO/unit insulin)	8.8 ± 3.0*	8.8 ± 2.4†	0.97
Change in insulin sensitivity (g CHO/unit insulin)	−0.2	−0.9	0.19
Weight (*Z* score) postintervention	0.91 ± 0.77	0.73 ± 0.84	0.40
Weight change (*Z* score)	0.030 ± 0.20	−0.010 ± 0.23	0.48
Hypoglycemic episodes/14 days (mg/dl <80)	3.0 ± 0.6	2.3 ± 0.4	0.17

Data are means ± SD. *Based on 22 of 28 subjects with 3-month insulin sensitivity data. †Based on 26 of 29 subjects with 3-month insulin sensitivity data. CHO, carbohydrates.

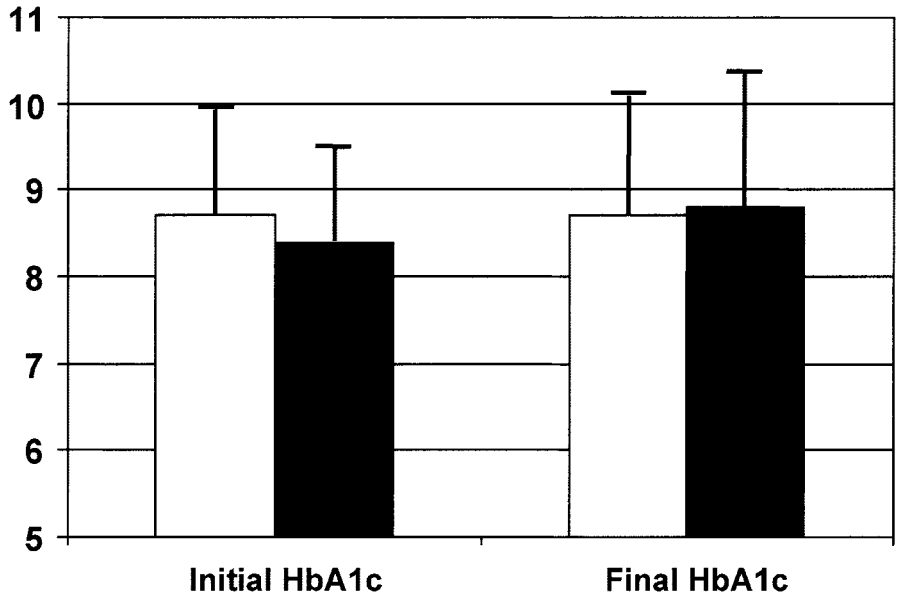

Figure 2—*A1C between groups.* □*, placebo;* ■*, cinnamon.*

cents with type 1 diabetes. Coupled with other recent research, our failure to demonstrate any effect on A1C, insulin sensitivity, or total daily insulin dose introduces significant doubt regarding the efficacy of cinnamon in diabetic subjects.

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