Influence of Caffeine on the Frequency and Perception of Hypoglycemia in Free-Living Patients With Type 1 Diabetes

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OBJECTIVE — To examine the influence of caffeine on the frequency and perception of hypoglycemia in "free-living" patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS — A total of 34 patients with type 1 diabetes were recruited for a prospective randomized placebo-controlled double-blind study. After a lead-in phase and while adhering to a low-caffeine diet, subjects were randomized to capsules containing either 200 mg caffeine or matched placebo with crossover at 3 months. Hypoglycemic episodes were monitored throughout with capillary blood glucose readings and a symptom questionnaire. During the study, measurements of blood pressure, middle cerebral artery blood velocity (a surrogate measure of cerebral blood flow), cognitive function (via a four-choice reaction time test), HbA_{1c} levels, and lipid profiles were taken at the beginning and end of each phase.

RESULTS — Throughout the study, no changes were evident regarding glycemic control or lipid profile. The number of symptomatic episodes was greater with caffeine (1.3 vs. 0.9 episodes/week; $P < 0.03$) and was associated with more intense warning symptoms (29 vs. 26 total symptom score; $P < 0.05$). For women, caffeine ingestion caused a modest pressor response (115 vs. 110 mmHg; $P < 0.01$). Four-choice reaction time improved slightly with caffeine supplementation ($P < 0.05$).

CONCLUSIONS — Ingestion of modest amounts of caffeine enhances the intensity of hypoglycemia warning symptoms in patients with type 1 diabetes without altering the prevailing standard of glycemic control or increasing the incidence of severe hypoglycemic episodes.

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P atients with type 1 diabetes rarely achieve an ideal standard of glycemic control, largely because of the imprecision of insulin therapy, which confers a risk of postabsorptive hypoglycemia (1). The best defense against hypoglycemia is the ability to recognize warning symptoms and to take appropriate action (e.g., to consume carbohydrates in a relatively pure form). Unfortunately, up to 25% of patients with long-standing type 1 diabetes have a severely compromised ability to detect falling blood glucose levels, which places these individuals at risk for sudden and severe neuroglycopenia (2).

In healthy volunteers and patients with type 1 diabetes, acute ingestion of modest amounts of caffeine (250–400 mg, which is equivalent to 2–4 cups of drip-brewed coffee) (3) markedly enhances the intensity of warning symptoms and the usual hormonal counterregulatory response to clamped hypoglycemia under laboratory conditions (4,5). However, although the perception of hypoglycemia is augmented by prior caffeine ingestion, whether low blood glucose levels will become associated with warning symptoms if caffeine is used on a daily basis is unclear.

The aim of this study was to examine the influence of caffeine on the frequency and perception of hypoglycemia in "free-living" patients with type 1 diabetes during everyday activities and outside the laboratory environment. The supplemental dose of caffeine was almost equivalent to average consumption of caffeine in the U.K. (444 mg/day) (6).

RESEARCH DESIGN AND METHODS — A total of 39 nonsmoking patients with type 1 diabetes (Table 1) gave written consent to participate in the study, which was approved by the local hospital ethics committee. Subjects were recruited on the basis of stable glycemic control (average HbA_{1c} level of ≤10%) and absence of complications (except background retinopathy) and were taking no medications except insulin as a basal-bolus regimen of four injections each day. The study was carried out between October 1996 and September 1998. Five patients failed to complete more than two phases of the study, and their data have been excluded from further analysis.

This was a prospective randomized placebo-controlled double-blind study consisting of four continuous phases. Throughout phase A (baseline, 2 months duration), patients continued with their usual diets, during which 7-day food diaries were used to calculate average daily caffeine consumption. For phases B (2 months), C (3 months), and D (3 months), patients were provided with decaffeinated or caffeine-free products (e.g., tea, coffee, and carbonated soft drinks), which thus estab-

Table 1—Patient characteristics

	Subjects
Male:female ratio	22:12
Age (years)	38 ± 2
Daily caffeine consumption (mg/day)	395 ± 37
Duration of diabetes (years)	15 ± 1.7
HbA$_{1c}$ level at recruitment (%)	7.9 ± 0.2
BMI at recruitment (kg/m^2)	25.4 ± 0.5

Data are n or means ± SEM.

lished a low-caffeine diet (<15 mg/day) until the completion of the study. In addition, during phases C and D, patients were randomized to capsules containing either 200 mg caffeine twice daily or matched placebo with crossover at 3 months.

Patients were contacted directly at least once a week. Compliance was maintained by encouraging the patients to report any dietary discrepancy in addition to regular checks of study medication (including counting capsules).

Four capillary blood glucose levels were collected each day (before meals and before bedtime) using One Touch Profile Meters (Lifescan, Johnson & Johnson, High Wycombe, U.K.). Patients were also instructed to take additional measurements during suspected episodes of hypoglycemia. The hypoglycemic events recorded at the end of a phase were divided into symptomatic and biochemical hypoglycemic events. The former were defined as the development of characteristic warning symptoms with a confirmatory capillary blood glucose level (<3.5 mmol/l). The intensities of associated warning symptoms were recorded using a validated symptom questionnaire (7). Nine symptoms were assessed on a scale from 1 to 6. Symptoms were compared using total scores (i.e., including all symptoms) because previous research has shown that caffeine affects both neuroglycopenic and autonomic symptoms (5). If possible, confirmatory data were obtained from relatives and caregivers. Biochemical asymptomatic hypoglycemic events were identified by routine testing alone.

All visits to the research unit were scheduled before 10:30 A.M. after breakfast and insulin injection. During phase A, patients familiarized themselves with cognitive function testing. Thereafter, visits were made 2 days from the start of each phase and during the last 7 days of each phase. During phases C and D, subjects took a caffeine or placebo capsule 1 h before the study time. The visits lasted 1 h, and the following measurements were taken after 15 min of resting supine:

- capillary blood glucose, HbA$_{1c}$ (Behring Diagnostics, Milton Keynes, U.K.), and plasma lipid levels (Olympus AU860 autoanalyzer; Olympus Optical, Eastleigh, U.K.);
- plasma caffeine level measured using an enzyme immunoassay technique (EMIT; Behring Diagnostics) with an Olympus AU560 autoanalyzer;
- heart rate and resting blood pressure (Dinamap BP Monitor; Johnson & Johnson);
- height, weight, and BMI;
- middle cerebral artery blood velocity (V_{MCA}) measured using a transcranial Doppler technique (SciMed, Bristol, U.K.) as a surrogate measure of brain blood flow (8); and
- cognitive function measured using a four-choice reaction time test (9) calculated during a 5-min test period (during phase A and before the start of each measurement session, subjects refamiliarized themselves with the test to minimize any practice effect).

Sample size calculation was based on the effect of caffeine on changes in symptom scores reported previously (4). Primary outcomes of interest, which were highlighted during the planning stage, were frequency of hypoglycemia and effects on the intensity of warning symptoms. This two-period placebo/caffeine crossover design was analyzed by using t tests that assumed no carryover effect (10). The role of sex on the relative effect of caffeine was investigated by analysis of variance. Results are presented as means ± SEM or as the difference between the two treatment phases with 95% CIs (P < 0.05).

RESULTS — Patient details are shown in Table 1. After the introduction of a low-caffeine diet, average caffeine levels were <0.4 ± 0.1 mmol/l (P < 0.0001). With caffeine supplementation, levels averaged 2.4 ± 0.3 mmol/l 90 min after breakfast. Throughout all phases of the study, HbA$_{1c}$, plasma lipid, and body weight measurements were unaffected by caffeine status.

During phases C and D, symptomatic episodes of hypoglycemia were more frequent with caffeine (1.3 vs. 0.9 episodes/week; difference of 0.4 episodes/week [95% CI 0.2–0.9]; P < 0.03) (Fig. 1) and were associated with more intense warning symptoms (29 vs. 26 total symptom score; difference of 3 [0.3–5.4]; P < 0.05) (Fig. 2). In contrast, the number of asymptomatic biochemical episodes (0.6 ± 0.2 and 0.7 ± 0.2 episodes/week) and the average blood glucose level recorded during a symptomatic event (2.8 ± 0.1 and 2.7 ± 0.1 mmol/l) were unaffected by the prevailing caffeine status. A total of 13 episodes of severe hypoglycemia affected four individuals taking placebo compared with 6 episodes among three patients who were taking caffeine supplements (P = 0.3). The
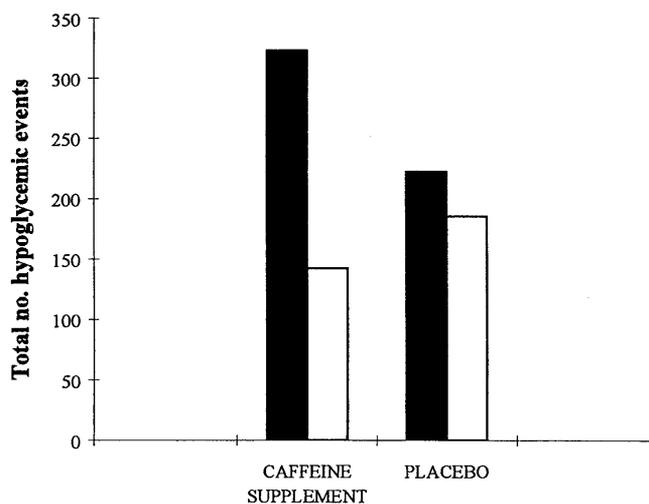

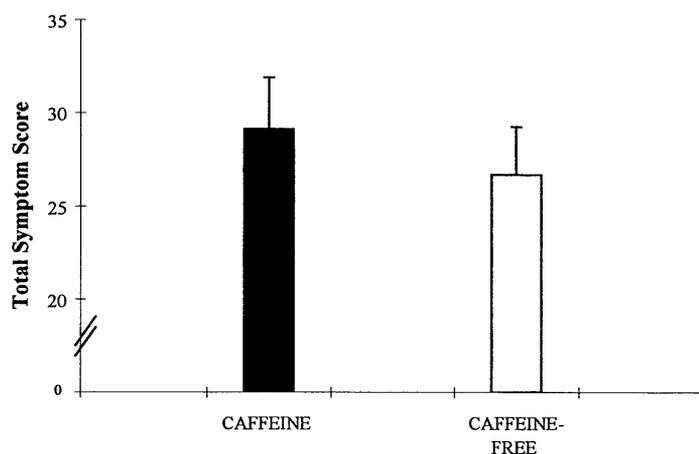Figure 1—Symptomatic hypoglycemic events. P < 0.03 caffeine vs. placebo. □, Biochemical; ■, symptomatic.

Figure 2—Influence of caffeine on intensity of warning symptoms during caffeine and placebo phases of the trial (phases C and D) P < 0.05 caffeine vs. placebo □, Biochemical; ■, symptomatic.

influence of caffeine on the frequency of hypoglycemia was strongly influenced by sex, and men were more sensitive to caffeine than women (P < 0.02).

Throughout the study, diastolic blood pressure and heart rate were not influenced by caffeine status. For men, systolic blood pressure was also unchanged by caffeine (Table 2). For women, reintroduction of caffeine caused a modest pressor response (115 vs. 110 mmHg; difference of 5 mmHg [3–8], P < 0.01). At all stages, V_{MCA} was higher in women than in men (Fig. 3). With the reintroduction of caffeine into the diet, V_{MCA} fell (P < 0.001), although this effect was sustained only in men. Four-choice reaction time tests improved slightly in both men and women with caffeine supplementation (from 0.55 to 0.54 s; difference of −0.01 s [−0.02 to −0.01]; P < 0.05).

CONCLUSIONS — In clinical practice, hypoglycemia is usually defined as the blood glucose level that, if not corrected, leads to the development of characteristic warning symptoms and impairment of higher cerebral functions. In this study, free-living type 1 diabetic patients reported a 44% increase in the number of mild hypoglycemic episodes associated with more intense warning symptoms when caffeine was included in their diets. This was not associated with any adverse effect on diabetes control or plasma lipid levels. Although subjects experienced fewer severe hypolgycemic episodes during caffeine use, these episodes were too infrequent for useful statistical comparison.

These findings support previous laboratory-based work in which acute ingestion

of caffeine (in doses equivalent to that in 2–4 cups of drip-brewed coffee) markedly enhanced the symptomatic and sympathoadrenal responses to clamped hypoglycemia in healthy volunteers and patients with type 1 diabetes (4,5). These effects of caffeine may relate to uncoupling of brain blood flow and glucose utilization via antagonism of adenosine receptors (11). Ingestion of caffeine acutely reduces brain blood flow while simultaneously augmenting brain glucose utilization by enhancing firing of cortical neurons (12,13). Therefore, caffeine ingestion may increase an individual's sensitivity to neuroglycopenia through the combined influence of reducing substrate delivery and simultaneously increasing brain glucose metabolism. As a corollary, increasing cerebral blood flow

(and thus substrate delivery) at the onset of acute hypoglycemia attenuates both the counterregulatory hormonal responses to and the perception of hypoglycemia (14). The reduction in V_{MCA} after caffeine ingestion has been reported previously (4) and correlates with changes in cerebral blood flow as measured by xenon inhalation (4,15). Thus, although not directly measured, changes in V_{MCA} are likely to represent alterations in substrate delivery.

Caffeine supplementation did not alter HbA_{1c} or plasma lipid levels. The variable effects of caffeine on glucose tolerance reported previously may be partly explained by the prevailing caffeine status of enrolled subjects (16,17). Giving a single dose of 200 mg to a caffeine-naive individual (has not recently consumed caffeine) will modestly elevate blood glucose levels 3-4 h after a glucose load without any effect on fasting levels or insulin concentration (18). Others have reported a strong positive correlation between coffee consumption and cholesterol levels (19), although this discrepancy may be partly explained by the method of preparing coffee (20). Under normal circumstances, habitual caffeine consumption causes a much smaller pressor response to caffeine than placebo does, but the effect is not completely eliminated (21). The rise in blood pressure seen in the present study was comparatively modest (systolic blood pressure only) but may be clinically significant, especially in subjects who are already at increased risk for ischemic heart disease.

Table 2—Changes in blood pressure and heart rate throughout the study showing the mean difference between the caffeine and placebo supplementation

	Baseline	Average caffeine diet	Average low-caffeine diet	Difference
Systolic blood pressure (mmHg)				
All subjects	124 ± 3	124 ± 3	121 ± 3	3 (1 to 4)
Male subjects	130 ± 4	130 ± 4	128 ± 4	2 (−1 to 2)
Female subjects	113 ± 4	115 ± 4	110 ± 4	5 (2 to 7)
Diastolic blood pressure (mmHg)				
All subjects	68 ± 2	69 ± 2	68 ± 2	1 (0 to 2)
Male subjects	69 ± 3	69 ± 2	68 ± 2	1 (−2 to 2)
Female subjects	66 ± 3	67 ± 3	68 ± 2	1 (−1 to 2)
Heart rate				
All subjects	71 ± 1	72 ± 2	69 ± 2	0 (−2 to 2)
Male subjects	67 ± 2	67 ± 3	67 ± 2	1 (−3 to 4)
Female subjects	76 ± 2	72 ± 3	73 ± 3	−1 (−4 to 2)

Data are means ± SEM or means (95% CIs). *P < 0.05 caffeine vs. low-caffeine status.
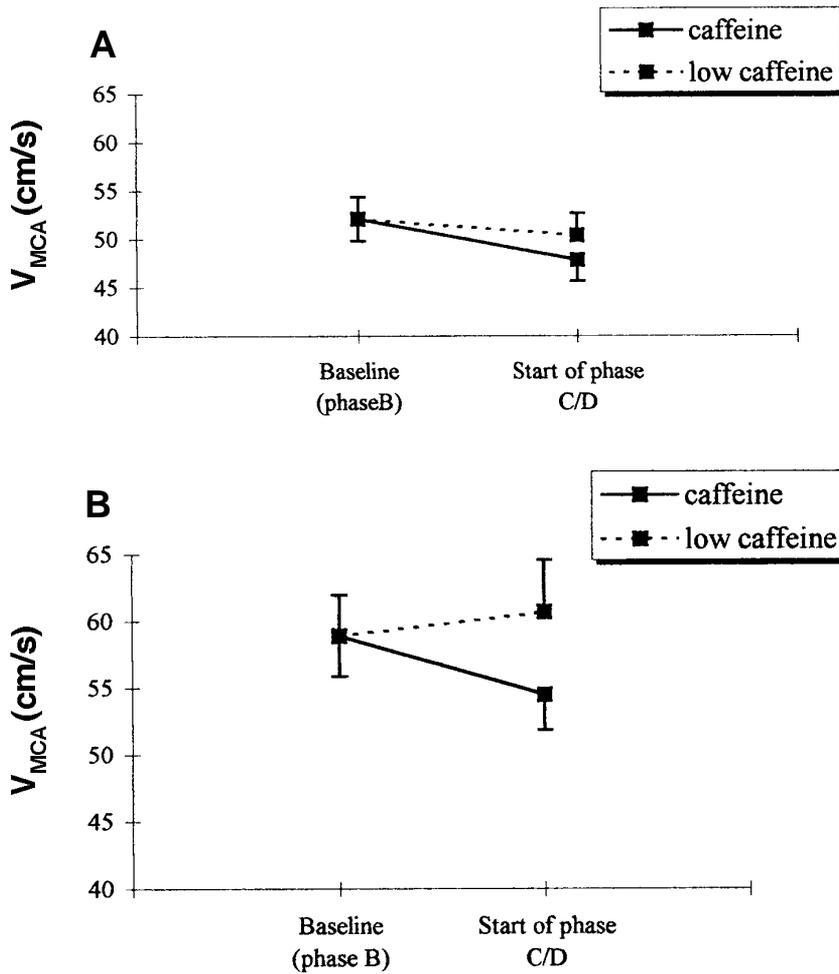
A

B

Figure 3—Change in middle cerebral artery blood velocity during caffeine and placebo supplementation compared with baseline. Male patients (*A*) and female patients (*B*).

The effect of caffeine on hypoglycemia frequency was influenced by sex and affected men to a greater degree than women. In general, low blood glucose levels are better tolerated by women (22). The effect of caffeine on memory tasks is also influenced by sex (23). In the present study, reaction time improved slightly with regular caffeine use in all subjects. A recent review of the effect of caffeine on intellectual performance concluded that the purported positive effects of caffeine on cognition result from increased arousal and suppression of boredom with repetitive tasks rather than from a direct effect on cognitive performances (11).

In summary, ingestion of modest amounts of caffeine enhances the intensity of hypoglycemic warning symptoms in patients with type 1 diabetes without altering their standard of glycemic control. As a consequence, the number of mild hypoglycemic episodes increases. Although this may be viewed as problematic, the enhancement of early warning symptoms allows an individual to be alerted to impending hypoglycemia early enough to be able to act on it. Alternatively, given that caffeine did not reduce the number of asymptomatic events and that symptomatic episodes were more frequent with caffeine, caffeine may be viewed as increasing the risk for severe hypoglycemia (24), but, fortunately, our study did not show evidence of this.

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