Influence of Caffeine on Frequency of Hypoglycemia Detected by Continuous Interstitial Glucose Monitoring System in Patients With Long-Standing Type 1 Diabetes

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OBJECTIVE — The aim of this study was to investigate the effect of caffeine (in doses equivalent to normal daily ingestion) on rates and severity of hypoglycemia in patients with long-standing type 1 diabetes to determine the relationship between caffeine, autonomic function, and hypoglycemia.

RESEARCH DESIGN AND METHODS — Using a double-blinded randomized study, we investigated the effect of caffeine versus placebo in 19 patients with long-standing type 1 diabetes using continuous glucose sensing technology and simultaneous assessment of autonomic function using Holter monitoring.

RESULTS — Caffeine reduced the duration of nocturnal hypoglycemia with a mean duration of 49 minutes (range 0–235) versus 132 (0–468) minutes ($P = 0.035$). The reduction in duration of nighttime hypoglycemia was due to a decline in the number of episodes of moderate hypoglycemia at the expense of mild hypoglycemic episodes ($P = 0.04$). There was no overall correlation between reduced heart rate variability (a marker of autonomic dysfunction) and hypoglycemic events ($r_s = 0.12$, $P = 0.62$).

CONCLUSIONS — Our results suggest that caffeine is associated with a significant reduction in nocturnal hypoglycemia. The reduction in nocturnal hypoglycemia was not linked to the concomitant rise in parasympathetic activity associated with caffeine.

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Hypoglycemia and the fear of low blood glucose levels remain rate-limiting factors in achieving normoglycemia for patients with type 1 diabetes (1). A number of irreversible factors have been implicated in increasing an individual's risk from severe hypoglycemia, including long duration of diabetes, the presence of autonomic neuropathy (2), and sleep. Recently, continuous glucose monitoring systems (CGMSs) have shown that, in adults and children with type 1 diabetes, episodes of prolonged hypoglycemia may be missed (particularly at night) if patients rely solely on warning symptoms or fingerstick blood glucose measurements (3,4).

Approaches to reducing hypoglycemia risk have included relaxation of blood glucose targets, a change in class of insulin, and the use of novel insulin delivery systems including insulin pump therapy (5). Previously, we have shown that ingestion of moderate amounts of caffeine also may be useful by augmenting the symptomatic and hormonal responses to mild hypoglycemia, allowing appropriate action to be taken before neuroglycopenia ensues (6). The benefits of regular caffeine ingestion in patients with type 1 diabetes may extend beyond its influence on hypoglycemia warning symptoms. Regular ingestion of modest amounts of caffeine also improves heart rate variability (HRV), a reproducible measure of autonomic function (7). Loss of HRV is associated with a marked increase in the risk of sudden death in both diabetic and nondiabetic populations (8,9).

The aim of this study was to examine the influence of regular ingestion of modest amounts of caffeine on the frequency of hypoglycemic episodes and to investigate the possibility of a relationship between the augmentation in nocturnal autonomic function with caffeine and frequency of nocturnal hypoglycemia, using concurrent CGMS and HRV analysis in patients with long-standing type 1 diabetes.

RESEARCH DESIGN AND METHODS

— All subjects provided written informed consent, and this study was approved by the local research ethics committee. Twenty patients with long-standing (>5 years) type 1 diabetes participated in a double-blind, randomized cross-over, placebo-controlled study examining the effects of caffeine ingestion on the frequency of hypoglycemia.

All participants were given a low-

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Abbreviations: CGMS, continuous glucose monitoring system; HRV, heart rate variability; NREM, non-rapid eye movement.

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

caffeine diet (<50 mg/day) for 2 weeks with either 250-mg caffeine capsules supplemented twice daily (equivalent to average daily caffeine intake in the U.K.) or matched placebo. Dietary advice and information sheets were provided. Both patients and investigators were blinded as to the composition of the supplemental capsules. On the last 2 days of the 2-week period, interstitial glucose levels were assessed using a CGMS (Medtronic Minimed, Minneapolis, MN) (10). Over the same 48 h, patients also underwent simultaneous assessment of HRV by continuous Holter monitoring recorded on a miniature digital recorder (Life Card, Reynolds Medical). The patients were crossed over to the alternate treatment arm and the final set of measurements was repeated at the end of an additional 2 weeks.

Defining an episode of hypoglycemia

On each day trace obtained from the CGMS, hypoglycemia was defined according to the following criteria (11). Four consecutive readings of ≤63 mg/dl are required. The first reading ≤63 mg/dl is the start of the hypoglycemic episode. The hypoglycemic episode ends when there are at least four consecutive readings >63 mg/dl. The first reading >63 mg/dl is the end of the episode. The episode is prolonged if it lasts more than 2 h.

During an episode, if the sensor value is ≥63 mg/dl for one to three readings and then falls below 63 mg/dl, the whole episode is counted as one hypoglycemic episode, including the small period >63 mg/dl. A moderate hypoglycemic event occurs when interstitial glucose levels are ≤53 mg/dl for at least four consecutive readings. During a mild episode, if glucose levels fall to ≤53 mg/dl for four or more consecutive readings, the whole episode is classified as moderate. Severe hypoglycemia is defined as an event requiring external help.

The definition of interstitial hypoglycemia in terms of glycemic thresholds (mild and moderate) is based on the level at which there is activation of the counterregulatory hormone cascade and onset of neuroglycopenic symptoms, respectively (12).

Assessment of autonomic dysfunction

Patients had no clinical evidence of overt autonomic dysfunction from history or physical examination. All were screened by 12-lead electrocardiogram, echocardiography, and treadmill exercise testing. Exclusion criteria included the presence of atrial fibrillation, left bundle-branch block, evidence of left ventricular systolic impairment (<50%), or exercise-induced ischemia (ST depression ≥1 mm at ≥85% maximum predicted heart rate during or after exercise using the Bruce protocol). All patients had time-domain analyses of HRV performed on 24-h ambulatory electrocardiogram monitoring (7).

Statistical analysis

CGMS data were downloaded to a Microsoft Excel spreadsheet. Only data from days with a mean absolute error of <28% with at least three calibration points per day were accepted. Data not fulfilling strict validity criteria were discarded. Hypoglycemia was defined as a sensor value ≤63 mg/dl for at least four consecutive sensor values (20 min). An episode was deemed to have ended when the sensor showed four consecutive readings of ≥63 mg/dl. Number, severity, and duration of hypoglycemic episodes were recorded. Time periods were also divided into day (0800–2400) and night (2400–0800).

Statistical analysis was performed through SPSS 11 for Windows. In the assessment of HRV, for each individual at the end of each phase of the study, the hourly counts of RR (interval between subsequent QRS complexes) over 50 ms for the 48-h period were summarized by calculating the area under the curve. These summary statistics were then used for the data analysis. HRV and average glucose are assumed to be normally distributed by the Kolmogorov-Smirnov Z statistic ($P > 0.05$). Average glucose has been summarized using means and SDs and compared between caffeine and placebo phases of the study using the paired *t* test.

The number of hypoglycemic episodes and changes in the number of episodes between caffeine and placebo phases of the study did not appear to be normally distributed and were summarized using medians and ranges; changes were tested using the Wilcoxon test. The association between HRV and number of hypoglycemic episodes was summarized using Spearman's correlation coefficient. All tests were two tailed and used a 5% critical *P* value.

Table 1—*Participant characteristics*

n	19
Male (*n*)	9
Age (years)	44.3 ± 9.2
Duration of diabetes (years)	19.2 ± 10.4
Heart rate (bpm)	79 ± 8
Systolic/diastolic blood pressure (mmHg)	125 ± 14/73 ± 7
HbA_{1c} (%)	8.4 ± 1.1
Microalbuminuria (albumin-to-creatinine ratio)	0.4 (0.1–3.8)
Retinopathy	5 (26)
Sensory neuropathy	2 (11)
Antihypertensives*	5 (26)
Hypoglycemia unawareness	12 (63)

Data are means ± SD, mean (range), or *n* (%). *ACE inhibitor or angiotensin receptor blocker.

RESULTS — Patient details are shown in Table 1. CGMS data were available for 19 subjects. One set of data was invalid because of poor correlation between paired sensor and fingerstick values (mean absolute error of 33%). There was no difference in mean glycemic control between the groups over the 48 h of CGMS analysis (146 ± 47 mg/dl on caffeine vs. 144 ± 38 mg/dl on placebo, $P = 0.94$).

Over the 2-week study period, there were no reported severe hypoglycemic events. Overall, interstitial hypoglycemia was less frequent in those taking caffeine ($P = 0.044$). When patients were awake, the duration of interstitial hypoglycemia (<63 mg/dl) was similar with caffeine and placebo, but, in contrast, hypoglycemia was reduced at night during treatment with caffeine (49 [range 0–235] minutes vs. 132 [0–468], $P = 0.035$). The reduction in nocturnal hypoglycemia was as a consequence of a fall in the number of moderate episodes defined as an interstitial glucose level <53 mg/dl for 20 min or more (0.6 vs. 0.1 hypoglycemic events on caffeine, $P = 0.011$) (Table 2).

Ten patients did not suffer from any episode of hypoglycemia during the CGMS assessment phase of the study. Of the patients with interstitial hypoglycemia, moderate hypoglycemic episodes were less frequent in eight subjects during the caffeine treatment, although one subject had more episodes of interstitial hypoglycemia with caffeine ($P = 0.003$).

As noted previously, in this sample, ingestion of caffeine was associated with improvement in HRV (7). Although caffeine ingestion was associated with a

Table 2—*Diurnal influence of caffeine on frequency and rates of hypoglycemia*

	Total time hypoglycemic per 24 h (min)	Daytime hypoglycemia (min)	Mild nocturnal hypoglycemic events	Moderate nocturnal hypoglycemic events	Prolonged nocturnal hypoglycemic events	Nocturnal hypoglycemia (min)
Caffeine	90 (0–380)	47 (0–160)	0.13 (0–2)	0.13 (0–1)	0.16 (0–1)	49 (0–235)
Placebo	195 (0–570)	63 (0–235)	0.13 (0–1)	0.61 (0–3)	0.39 (0–1)	132 (0–468)
P value	0.044	0.51	0.71	0.011	0.053	0.035

Data are means (range) or *n* (%). *P* values were determined by the Wilcoxon test.

marked increase in HRV, particularly at night, we could find no correlation between HRV and the frequency of hypoglycemia ($r_s = 0.12$, $P = 0.62$). Similarly, there was no correlation between the increase in HRV at night with caffeine and the reduction in nocturnal hypoglycemia with caffeine ($r_s = -0.18$, $P = 0.47$).

CONCLUSIONS — Despite modern intensive treatment regimens, hypoglycemia continues to be an important problem for patients with type 1 diabetes (13,14). Previously we have shown that ingestion of modest amounts of caffeine (equivalent to three to four cups of drip-brewed coffee each day) augments the symptomatic and hormonal responses to hypoglycemia in healthy volunteers (15) and patients with type 1 diabetes (6). The beneficial effect of caffeine on hypoglycemia risk is independent of a change in glycemic control (16). Here, using continuous interstitial glucose monitoring, we have shown that caffeine may also be beneficial by reducing the frequency of moderate episodes (<53 mg/dl) of hypoglycemia occurring at night.

The consequences of prolonged unrecognized nocturnal hypoglycemia are not known, but it is recognized that recurrent episodes of hypoglycemia can cause loss of warning symptoms and defective glucose counterregulation during subsequent episodes in which glucose levels fall below normal (17). Therefore, it can be postulated that the caffeine-associated reduction in moderate hypoglycemic episodes occurring during sleep seen here may be beneficial by reducing the risk of next day hypoglycemia unawareness with the corollary of less asymptomatic hypoglycemia. In this study, we showed a tendency toward less daytime hypoglycemia, although this did not reach statistical significance (Fig. 1). However, the caffeine-associated reduction in "antecedent" nocturnal hypoglycemia seen in this study may explain the augmentation in the symptomatic and hormonal responses to mild daytime hypoglycemia described previously (6).

Using a validated tool for analysis of CGMS data allows breakdown of the number and time of hypoglycemic events during the day and night (11). Examination of the various hypoglycemic episodes generates a number of statistical tests, potentially increasing the chance of spuriously identifying a significant difference. Conversely, that three of the four variables examining nocturnal hypoglycemia were significant or nearly significant is reassuring.

There has been controversy as to the relationship between autonomic dysfunction and the development of hypoglycemia unawareness. Most studies have suggested that peripheral autonomic neuropathy is not associated with an increased risk of severe hypoglycemia (14, 18–20), although central autonomic dysfunction may be important (21). We also found no relationship between the presence of autonomic dysfunction and hypoglycemia detected by the CGMS. Nevertheless, defects in HRV are associated with markedly increased risk of sudden death and premature mortality in diabetic and nondiabetic populations (8). Therefore, it is noteworthy that caffeine ingestion also improved HRV as well as reduced episodes of nocturnal hypoglycemia.

It is possible that caffeine may reduce more moderate hypoglycemia by uncoupling brain blood flow and glucose utilization via antagonism of adenosine receptors (22), simultaneously attenuating brain glucose supply (reduced cerebral blood flow) while increasing glucose demand, resulting in relative neuroglycopenia and earlier release of counterregulatory hormones. This could prevent a further fall in interstitial glucose levels.

Alternatively, caffeine may act through an alteration in sleep pattern. Adenosine has been implicated in the physiological regulation of sleep, and caffeine, an adenosine-receptor antagonist, reduces non-

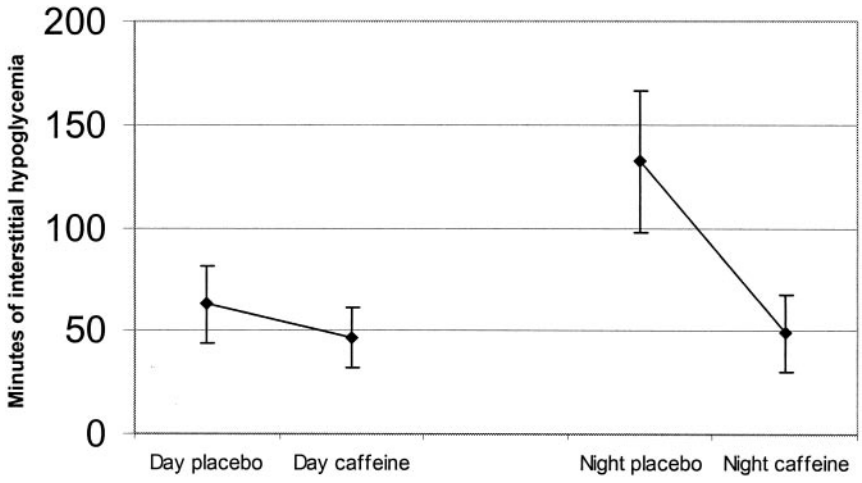

Figure 1—*Diurnal variation in time spent hypoglycemic (interstitial glucose <63 mg/dl) comparing caffeine and placebo. Error bars indicate the CIs of the means.*

rapid eye movement (NREM) sleep (23). In turn, NREM sleep is associated with an attenuated counterregulatory response to hypoglycemia (24). Therefore, it could be hypothesized that caffeine reduces the time spent in NREM sleep, lessening the period during which counterregulatory responses are suppressed. This may protect against prolonged hypoglycemia and could explain our findings of fewer and shorter moderate nocturnal hypoglycemic episodes in those on caffeine.

Despite the alteration in phases of sleep seen with caffeine (25), there is no evidence to suggest any negative consequences such as any change in behavior or mood (26). Average levels of caffeine consumption (in doses similar to those used in this study) have largely positive effects on behavior and quality of life (27).

There are, however, limitations to the study. In patients with long-standing type 1 diabetes, the physiological and hormonal responses to hypoglycemia are defective compared with those in individuals with a shorter duration of diabetes. We did not measure these responses to hypoglycemia here. Although there is increasing experience with the CGMS system for detection of hypoglycemia, the relationship between interstitial glucose levels measured from the anterior abdominal wall and cerebral interstitial levels is unknown. Furthermore, in nondiabetic individuals, the CGMS may overestimate the duration of hypoglycemia as there seems to be a time lag between sensor-measured interstitial and peripheral blood glucose levels during recovery from hypoglycemia (28). Overestimation of nocturnal hypoglycemia in patients with tightly controlled type 1 diabetes has also been reported (29). However, in more customary populations where capillary glucose sensor calibration was more widely dispersed, accurate prediction of hypoglycemia with the CGMS has been demonstrated (30,31). The effects of caffeine on measurement of interstitial glucose are unknown. Caffeine is known to alter cerebral blood flow, blood pressure, and heart rate (16) and may influence CGMS analysis of hypoglycemia. However, it is reassuring there was no significant difference in mean interstitial glucose between caffeine and placebo throughout the 48-h period of analysis.

As impaired function of the autonomic nervous system carries a poor prognosis and our observations that short-term caffeine use improves HRV in patients with type 1 diabetes, it remains to be determined whether this translates into a reduction in risk of premature cardiac events in at-risk populations, such as individuals with type 1 diabetes. Nevertheless, the suggested beneficial effects seen here may indicate a role for caffeine in reducing nocturnal hypoglycemia.

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References

1. Pramming S, Thorsteinsson B, Bendtson I, Binder C: Symptomatic hypoglycemia in 411 type 1 diabetic patients. *Diabet Med* 8:217–222, 1991
2. Stephenson JM, Kempler P, Perin PC, Fuller JH: Is autonomic neuropathy a risk factor for severe hypoglycaemia? The EURODIAB IDDM Complications Study. *Diabetologia* 39:1372–1376, 1996
3. Sachedina N, Pickup JC: Performance assessment of the Medtronic-MiniMed Continuous Glucose Monitoring System and its use for measurement of glycaemic control in type 1 diabetic subjects. *Diabet Med* 20:1012–1015, 2003
4. Amin R, Ross K, Acerini CL, Edge JA, Warner J, Dunger DB: Hypoglycemia prevalence in prepubertal children with type 1 diabetes on standard insulin regimen: use of continuous glucose monitoring system. *Diabetes Care* 26:662–667, 2003
5. Bode BW, Steed RD, Davidson PC: Reduction in severe hypoglycemia with long-term continuous subcutaneous insulin infusion in type I diabetes. *Diabetes Care* 19:324–327, 1996
6. Debrah K, Sherwin RS, Murphy J, Kerr D: Effect of caffeine on recognition of and physiological responses to hypoglycemia in insulin-dependent diabetes. *Lancet* 347:19–24, 1996
7. Richardson T, Rozkovec A, Thomas P, Ryder J, Kerr D: Influence of caffeine on heart rate variability in patients with long-standing type 1 diabetes. *Diabetes Care* 27:1127–1131, 2004
8. Villareal RP, Liu BC, Massumi A: Heart rate variability and cardiovascular mortality. *Curr Atheroscler Rep* 4:120–127, 2002
9. Lombardi F, Makikallio TH, Myerburg RJ, Huikuri HV: Sudden cardiac death: role of heart rate variability to identify patients at risk. *Cardiovasc Res* 50:210–217, 2001
10. Bode BW, Gross TM, Thornton KR: Continuous glucose monitoring used to adjust diabetes therapy improves glycosylated hemoglobin: a pilot study. *Diabetes Res* 46:183–190, 1999
11. Choudary P, Emery C, Davies C, Malik R, Allen K, Mills K, Richardson T, McLaughlin D, McLaren M, Tilly I, Heller SR. Development of a robust method to identify episodes of clinically relevant hypoglycemia using the MiniMed Medtronic continuous glucose monitoring system. *Diabetes Metab* 29:2250–2255A, 2003
12. Fanelli C, Pampanelli S, Epifano L, Rambotti AM, Ciofetta M, Moda F, Di Vincenzo A, Annibale B, Lepore M, Lalli C: Relative roles of insulin and hypoglycemia on induction of neuroendocrine responses to, symptoms of, and deterioration of cognitive function in hypoglycemia in male and female humans. *Diabetologia* 37:797–807, 1994
13. The DCCT Research Group: Hypoglycemia in the Diabetes Control and Complications Trial. *Diabetes* 46:271–286, 1997
14. The DCCT Research Group: Epidemiology of severe hypoglycemia in the Diabetes Control and Complications Trial. *Am J Med* 90:450–459, 1991
15. Kerr D, Sherwin RS, Pavalkis F, Fayad PB, Sikorski L, Rife F, Tamborlane WV, During MJ: Effect of caffeine on the recognition of and responses to hypoglycemia in humans. *Ann Intern Med* 119:799–804, 1993
16. Watson JM, Jenkins EJ, Hamilton P, Lunt MJ, Kerr D: Influence of caffeine on the frequency and perception of hypoglycemia in free-living patients with type 1 diabetes. *Diabetes Care* 23:455–459, 2000
17. Heller SR, Cryer PE: Reduced neuroendocrine and symptomatic responses to subsequent hypoglycemia after1 episode of hypoglycemia in nondiabetic humans. *Diabetes* 40:223–226, 1991
18. Polinsky RJ, Kopin IJ, Ebert MH, Weise V: The adrenal medullary response to hypoglycemia in patients with orthostatic hypotension. *J Clin Endocrinol Metab* 51: 1401–1406, 1980
19. Bjork E, Palmer M, Shvarcz E, Berne C: Incidence of severe hypoglycemia in an unselected population of patients with insulin-treated diabetes mellitus, with special reference to autonomic neuropathy. *Diabetes Nutr Metab* 4:303–309, 1990
20. Ryder RE, Owens DR, Hayes TM, Ghatei MA, Bloom SR: Unawareness of hypoglycemia and inadequate hypoglycemic counterregulation: no causal relation with diabetic autonomic neuropathy. *BMJ* 301: 783–787, 1990
21. Evans SB, Wilkinson CW, Gronbeck P, Bennett JL, Taborsky GJ Jr, Figlewicz DP: Inactivation of the PVN during hypoglycemia partially simulates hypoglycemia-associated autonomic failure. *Am J Physiol*

Regul Integr Comp Physiol 284:R57–R65, 2003
22. Laurienti PJ, Field AS, Burdette JH, Maldjian JA, Yen YF, Moody DM: Relationship between caffeine-induced changes in resting cerebral perfusion and blood oxygenation level-dependent signal. *AJNR Am J Neuroradiol* 24:1607–1611, 2003
23. Landolt HP, Werth E, Borbely AA, Dijk DJ: Caffeine intake (200 mg) in the morning affects human sleep and EEG power spectra at night. *Brain Res* 675:67–74, 1995
24. Jones TW, Porter P, Sherwin RS, Davis EA, O'Leary P, Frazer F, Byrne G, Stick S, Tamborlane WV: Decreased epinephrine responses to hypoglycemia during sleep. *N Engl J Med* 338:1657–1662, 1998
25. Landolt HP, Dijk DJ, Gaus SE, Borbely AA: Caffeine reduces low-frequency delta activity in the human sleep EEG. *Neuropsychopharmacology* 12:229–238, 1995
26. Nawrot P, Jordan S, Eastwood J, Rotstein J, Hugenholtz A, Feeley M: Effects of caffeine on human health. *Food Addit Contam* 20:1–30, 2003
27. Smith A: Effects of caffeine on human behavior. *Food Chem Toxicol* 40:1243–1255, 2002
28. Cheyne E, Kerr D: Making 'sense' of diabetes: using a continuous glucose sensor in clinical practice. *Diabetes Metab Res Rev* 18 (Suppl. 1):S43–S48, 2002
29. McGowan K, Thomas W, Moran A: Spurious reporting of nocturnal hypoglycemia by CGMS in patients with tightly controlled type 1 diabetes. *Diabetes Care* 25:1499–1503, 2002
30. Caplin NJ, O'Leary P, Bulsara M, Davis EA, Jones TW: Subcutaneous glucose sensor values closely parallel blood glucose during insulin-induced hypoglycaemia. *Diabet Med* 20:238–241, 2003
31. Monsod TP, Flanagan DE, Rife F, Saenz R, Caprio S, Sherwin RS, Tamborlane WV: Do sensor glucose levels accurately predict plasma glucose concentrations during hypoglycemia and hyperinsulinemia? *Diabetes Care* 25:889–893, 2002