Caffeine Impairs Glucose Metabolism in Type 2 Diabetes

JAMES D. LANE, PHD
CHRISTINA E. BARKAUSKAS, AB
RICHARD S. SURWIT, PHD
MARK N. FEINGLOS, MD

Caffeine is a widely used drug despite evidence that it has deleterious consequences for health, including diabetes (1). In 1967, a study reported that drinking two cups of instant coffee significantly impaired glucose tolerance in a small group of men with "maturity-onset diabetes" (2). Recent studies showed that caffeine acutely decreased insulin sensitivity in young, nondiabetic adults (3–5). This study tested how oral caffeine affects carbohydrate metabolism in patients with type 2 diabetes, for whom decreases in insulin sensitivity might result in exaggerated hyperglycemic responses to glucose and other carbohydrates, which would aggravate the glycemic dysregulation found in the disease. We tested the effects of caffeine on fasting glucose and insulin levels and on glucose and insulin responses to a mixed-meal tolerance test (MMTT).

RESEARCH DESIGN AND METHODS

— The research protocol, approved by the medical center's Institutional Review Board, employed a double-blind, placebo-controlled, cross-over design. The study group comprised of 14 habitual coffee drinkers (11 men and 3 women, age 61 ± 9 years [means ± SD]), who had at least a 6-month history of type 2 diabetes. Based on self-reports, daily caffeine intake from all beverages averaged 526 ± 144 mg/day. Mean fasting plasma glucose was 7.5 ± 1.6 mmol/l. Three of the subjects managed diabetes with diet and exercise, and the remainder also used oral agents. None required exogenous insulin therapy. They were free of major medical disorders, were nonsmokers, and used no psychotropic medications known to affect glucose metabolism. The subjects completed informed consent before testing.

Caffeine and placebo treatments. Caffeine and placebo treatments were administered in identical gelatin capsules containing either 125 mg anhydrous caffeine plus dextrose filler or dextrose alone. The total caffeine dose (375 mg) was given on a divided schedule as described below. The order of the treatments was counterbalanced.

Procedures. Informed consent and screening data were collected at an appointment before testing. The subjects also completed a 7-day diary of caffeinated beverage consumption, recording the serving size and time of day for each caffeinated beverage. They were studied on two different mornings within a 2-week period, following overnight fast and caffeine abstinence. The subjects took prescribed diabetes medications according to their usual treatment regimen. A forearm vein was cannulated for nontraumatic blood sampling. After 30 min quiet rest, baseline fasting blood samples were drawn. The subject ingested 250 mg caffeine or placebo in two capsules with water. After a 60-min interval for caffeine absorption, a second set of fasting blood samples was drawn. Subjects then ingested an additional 125 mg caffeine or placebo (intended to maintain drug levels) and consumed a commercial liquid meal (Boost) that contained 75 g carbohydrate to begin the MMTT. Additional blood samples were drawn 1 and 2 h after the meal. The subject remained sedentary throughout the MMTT and relaxed while reading or watching television. Blood samples were centrifuged, and plasma was frozen for later assay of glucose and insulin. Plasma glucose levels were measured using a Beckman Glucose Analyzer II, and plasma insulin levels were measured by a double-antibody radioimmunoassay (Linco Research, St. Charles, MO).

Statistical methods and calculations. The caffeine effects on fasting measures were tested by comparing the postdrug fasting levels with a repeated-measures ANCOVA, including predrug fasting levels as a covariate to control for within-subject variations in the initial level. To test the effects on responses to the MMTT, we calculated the incremental areas under the MMTT 2-h time curves ($AUC_{2\,h}$) for glucose and insulin with the trapezoidal rule, using the postdrug fasting value and the values 1 and 2 h after the meal. Incremental areas were compared by a repeated-measures ANOVA. Data are presented as means ± SE, unless otherwise specified, and $P < 0.05$ was considered statistically significant.

RESULTS

— The concentration-time curves for plasma glucose or insulin levels are shown in Fig. 1. The curves illustrate that caffeine produced increases in both glucose and insulin during the MMTT in these type 2 diabetic subjects.

Caffeine did not affect the fasting levels of plasma, glucose, or insulin compared with placebo ($P > 0.10$). However, comparisons of the $AUC_{2\,h}$ values demonstrated significant caffeine effects for both plasma glucose ($P = 0.04$) and plasma insulin ($P = 0.01$) responses to the MMTT. The average glucose $AUC_{2\,h}$ after caffeine administration (3.87 ± 0.30 $mmol \cdot l^{-1} \cdot 2\ h^{-1}$) was 21% larger than the $AUC_{2\,h}$ after placebo (3.2 ± 0.36 $mmol \cdot l^{-1} \cdot 2\ h^{-1}$). The average insulin $AUC_{2\,h}$ in the caffeine condition (66.73 ± 10.49 $\mu U \cdot ml^{-1} \cdot 2\ h^{-1}$) was 48% larger than that in the placebo condition (45.17 ± 5.98 $\mu U \cdot ml^{-1} \cdot 2\ h^{-1}$).

CONCLUSIONS

— Acute administration of caffeine impaired postprandial glucose metabolism in these diabetic patients. In contrast to nondiabetic subjects (3–5), our subjects demonstrated exaggerations of both glucose and insulin re-

From the Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, North Carolina.

Address correspondence and reprint requests to James D. Lane, PhD, P.O. Box 3830, Duke University Medical Center, Durham, NC 27710-0001. E-mail: james.lane@duke.edu.

Received for publication 20 April 2004 and accepted in revised form 23 April 2004.

Abbreviations: AUC, area under the curve; MMTT, mixed-meal tolerance test.

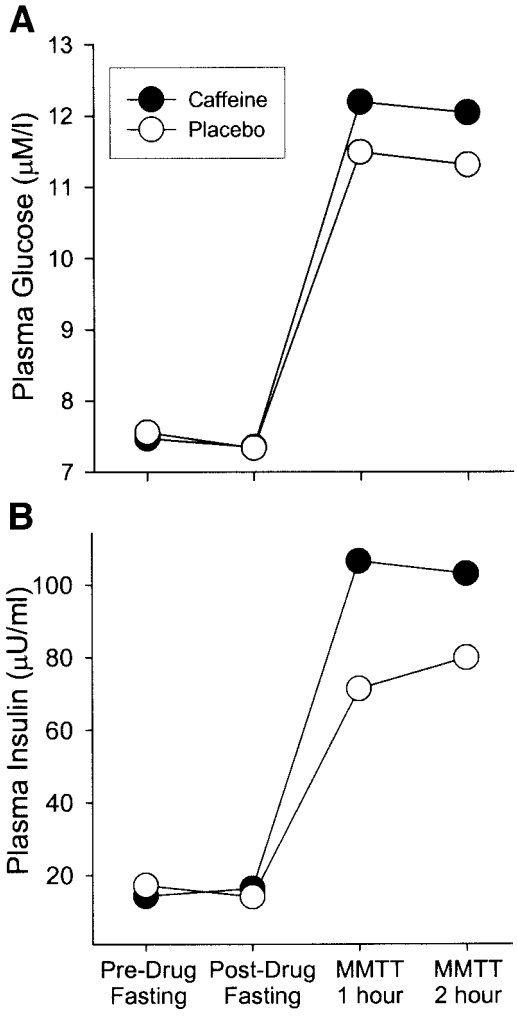

Figure 1—*Effects of caffeine versus placebo on plasma glucose* (A) *and insulin* (B) *time curves while fasting and during the 2-h MMTT.* ●, *caffeine;* ○, *placebo.*

sponses when caffeine was ingested with carbohydrates. Such effects could have implications for the clinical management of type 2 diabetes.

Caffeine only affected postprandial responses. Mealtime hyperglycemia may be a more accurate predictor of HbA_{1c} (6) and cardiovascular mortality (7,8) than fasting hyperglycemia. Strategies for controlling postprandial glucose metabolism are gaining importance in diabetes management. Caffeine abstinence may have beneficial effects that compare favorably with oral agents used to control postprandial glucose. Acute abstention reduced glucose increases following the mixed meal by 21%, which compares favorably to the 30% reductions observed in clinical trials of acarbose (9) and the short-acting insulin secretagogue nateglinide (10). If the results of this acute study extrapolate to chronic abstinence, quitting caffeine could be beneficial.

These results are limited by a small sample size. Furthermore, the study tested the effects of caffeine only and not the effects of coffee or tea. Both beverages contain numerous organic compounds, some of which might augment or offset the effects of caffeine (11). Despite these limitations, our results raise concerns about the potential hazards of caffeine for patients with type 2 diabetes and possibly for individuals who are glucose intolerant or "pre-diabetic." Repeated exaggerations of postprandial glucose, resulting from daily consumption of caffeinated beverages with meals, could produce higher average glucose levels that increase the risk of diabetes complications.

References

1. James JE: *Caffeine and Health*. New York, Academic Press, 1991
2. Jankelson OM, Beaser SB, Howard FM, Mayer J: Effect of coffee on glucose tolerance and circulating insulin in men with maturity-onset diabetes. *Lancet* 1:527–529, 1967
3. Graham TE, Sathasivam P, Rowland M, Marko N, Greer F, Battram D: Caffeine ingestion elevates plasma insulin response in humans during an oral glucose tolerance test. *Can J Physiol Pharmacol* 79: 559–565, 2001
4. Greer F, Hudson R, Ross R, Graham T: Caffeine ingestion decreases glucose disposal during a hyperinsulinemic-euglycemic clamp in sedentary humans. *Diabetes* 50:2349–2354, 2001
5. Keijzers GB, De Galan BE, Tack CJ, Smits P: Caffeine can decrease insulin sensitivity in humans. *Diabetes Care* 25:364–369, 2002
6. Avignon A, Radauceanu A, Monnier L: Nonfasting plasma glucose is a better marker of diabetic control than fasting plasma glucose in type 2 diabetes. *Diabetes Care* 20:1822–1826, 1997
7. The DECODE Study Group, European Diabetes Epidemiology Group: Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria: Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe. *Lancet* 354:617–621, 1999
8. Hanefeld M, Fischer S, Julius U, Schulze J, Schwanebeck U, Schmechel H, Ziegelasch HJ, Lindner J: Risk factors for myocardial infarction and death in newly detected NIDDM: the Diabetes Intervention Study, 11-year follow-up. *Diabetologia* 39:1577–1583, 1996
9. Chiasson JL, Josse RG, Hunt JA, Palmason C, Rodger NW, Ross SA, Ryan EA, Tan MH, Wolever TM: The efficacy of acarbose in the treatment of patients with non-insulin-dependent diabetes mellitus: a multicenter controlled clinical trial. *Ann Intern Med* 121:928–935, 1994
10. Carroll MF, Izard A, Riboni K, Burge MR, Schade DS: Control of postprandial hyperglycemia: optimal use of short-acting insulin secretagogues. *Diabetes Care* 25: 2147–2152, 2002
11. Johnston KL, Clifford MN, Morgan LM: Coffee acutely modifies gastrointestinal hormone secretion and glucose tolerance in humans: glycemic effects of chlorogenic acid and caffeine. *Am J Clin Nut* 78: 728–733, 2003