Influence of Mulberry Leaf Extract on the Blood Glucose and Breath Hydrogen Response to Ingestion of 75 g Sucrose by Type 2 Diabetic and Control Subjects

Mitchell Mudra, ba[1]
Nacide Ercan-Fang, md[1,2]
Litao Zhong, md, phd[3]
Julie Furne, bs[1]
Michael Levitt, md[1,2]

In Asia, type 2 diabetes is treated with mulberry leaf. Studies supporting this usage include the demonstration that mulberry leaf *1*) reduced blood glucose in normal rats (1) and rats with diabetes induced by streptozotocin (2) or alloxan (3), *2*) reduced fasting blood glucose and A1C concentrations in 12 subjects with type 2 diabetes (4), and *3*) relative to glybenclamide therapy, reduced fasting blood glucose, serum lipids, and lipid peroxidation indicators in subjects with type 2 diabetes (5). In the present study, we determined whether co-ingestion of mulberry extract with 75 g sucrose influenced the blood glucose response and sucrose absorption of type 2 diabetic and control subjects.

RESEARCH DESIGN AND METHODS

— Participants included 10 healthy control subjects (aged 24–61 years) and 10 type 2 diabetic subjects without complications who were receiving oral hypoglycemic agents (aged 59–75 years; glycohemoglobin 7.1 ± 0.9% [normal <6.2%]). The study was approved by the Minneapolis VA Medical Center Human Studies Committee. Mulberry leaf extract was provided by NatureGen (San Diego, CA). Placebo (red dye #40 and caramel) was similar in color and taste to the mulberry.

At 8 a.m., subjects randomly ingested mulberry extract (1 g) or placebo plus 75 g sucrose in 500 ml hot water. The test was repeated in 1 week with the opposite treatment. Medications (except acarbose) were allowed. Hourly breath samples for H_2 measurements (6) were obtained for 8 h. Blood glucose was assessed via finger stick (AccuCheck; Roche Diagnostics, Indianapolis, IN) before and at intervals over 120 min after sucrose ingestion in control subjects and additionally at 180 and 240 min in type 2 diabetic subjects. A low H_2–producing lunch was provided after completion of glucose measurements. On the test day, subjects kept a diary of severity of abdominal and other symptoms rated on a linear scale (0 = none through 4 = severe) (7).

Calculations and statistics. Because blood glucose concentrations often declined below baseline after 120 min, the significance of differences of blood glucose increases between extract and placebo was determined by ANOVA of values obtained over the initial 120 min. The statistical model included treatment and time as repeated measures and the interactions of treatment and time. The influence of treatment on breath H_2 was determined from differences between areas under the curves for 8 h (two-tailed paired *t* test). Sucrose malabsorption was estimated from breath H_2 concentrations (8).

RESULTS

— Compared with placebo, co-ingestion of mulberry produced significant reductions in blood glucose increases for the initial 120 min of the study (Fig. 1). The mean ± SD increases in glucose for mulberry versus placebo over this period were 15 ± 18 vs. 22 ± 33 mg/dl ($P = 0.005$) for control subjects and 42 ± 28 vs. 54 ± 46 mg/dl ($P = 0.002$) for type 2 diabetic subjects. Placebo was associated with greater glucose declines below fasting at the tail end of the study (Fig. 1). The peak-to-trough difference in blood glucose concentration was significantly ($P < 0.001$) less for mulberry versus placebo for both groups.

Breath H_2 concentration was greater ($P < 0.01$) in the mulberry versus the placebo treatment for both subject groups. Sucrose malabsorption with the extract was estimated to be 12 and 16 g for the control and diabetic subjects, respectively. There was no significant difference in severity for any symptom between mulberry- and placebo-treated subjects; 3 of 20 subjects receiving mulberry or placebo reported mild gas and/or bloating.

CONCLUSIONS

— The co-ingestion of mulberry extract with 75 g sucrose significantly reduced the increase in blood glucose observed over the initial 120 min of testing in control and type 2 diabetic subjects (Fig. 1). Blood glucose declines at the tail end of the study were less with extract. Thus, peak-to-trough fluctuations in blood glucose were markedly reduced by mulberry ingestion.

The mulberry-induced reduction in blood glucose presumably reflects the ability of mulberry to inhibit intestinal sucrase (9). The increased H_2 observed with mulberry indicates that this supplement induced sucrose malabsorption.

The reduction of blood glucose at early time points but higher values at later time points with mulberry would yield relatively minor alterations in A1C. However, factors other than A1C concentrations may play a role in the microvascular complications of diabetes (10,11). Brownlee (12) proposed that generation of reactive oxygen species is the common pathway responsible for diabetes complications, and glucose fluctuations are associated with

From the [1]Minneapolis VA Medical Center Research Service, Minneapolis, Minnesota; the [2]Department of Medicine, University of Minnesota, Minneapolis, Minnesota; and [3]NatureGen, Inc., San Diego, California.
Address correspondence and reprint requests to Michael Levitt, MD, Research Office, Minneapolis VAMC, 1 Veterans Dr., Minneapolis, MN 55414. E-mail: levit015@umn.edu.
Received for publication 13 October 2006 and accepted in revised form 3 February 2007.
Published ahead of print at http://care.diabetesjournals.org on 15 February 2007. DOI: 10.2337/dc06-2120.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

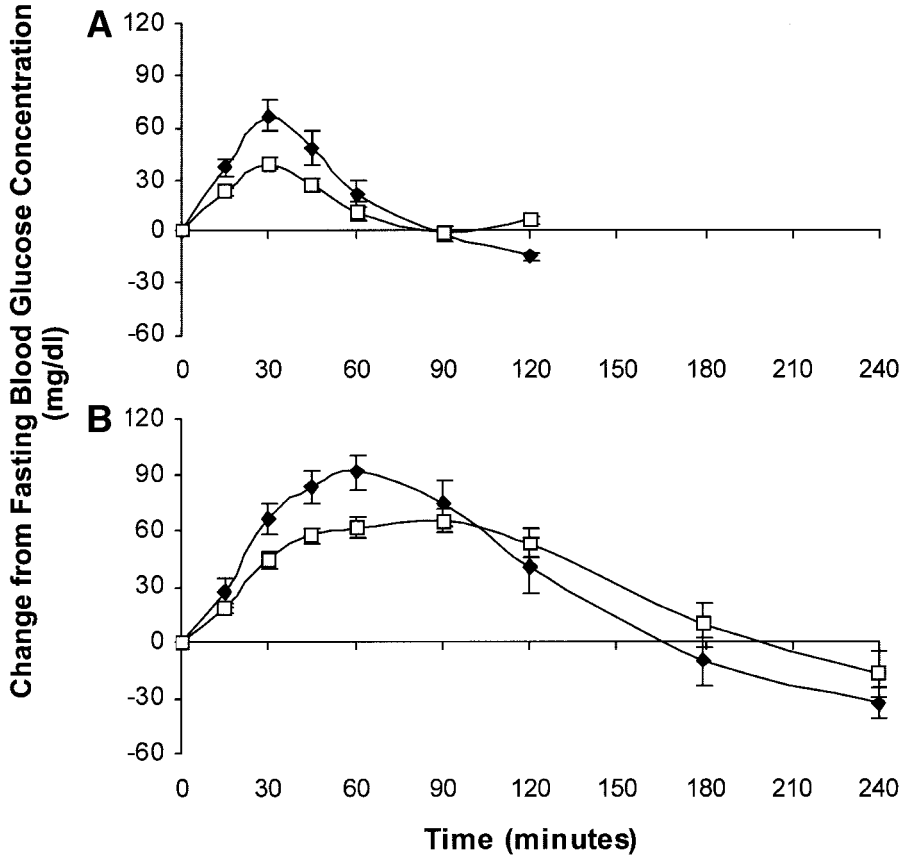

Figure 1—*Changes in blood glucose concentration from the fasting concentration of 10 healthy control subjects* (A) *and 10 type 2 diabetic subjects* (B) *after ingestion of 75 g sucrose with 1.0 g mulberry leaf extract* (□) *or placebo* (◆). *The difference between mulberry and placebo over the first 120 min of the study, determined by ANOVA, was highly significant for control* ($P = 0.005$) *and diabetic* ($P = 0.002$) *subjects.*

increased markers of oxidative injury (13). Thus, reductions in blood glucose fluctuation with mulberry extract might reduce diabetes complications despite minor reduction of A1C.

Two drugs (acarbose and miglitol) that inhibit carbohydrate digestion produce modest reductions in fasting blood glucose and A1C (14) and slow progression of glucose intolerance to overt diabetes (15). Use of these drugs has been limited by associated bloating, gas, and diarrhea (16). These symptoms were not significantly increased by mulberry extract; however, convincing evidence of lesser side effects will require studies with extract ingested with each major meal.

Some individuals prefer an herbal over a pharmaceutical preparation, and such individuals might find mulberry extract more acceptable and better tolerated than acarbose or miglitol. In addition, mulberry extract contains compounds such as fagomine, which induces insulin secretion (17), and antioxidants that putatively reduce lipid peroxidation (5,18,19).

While mulberry leaf is considered safe as a drug and a foodstuff in Asia (20), the extract contains multiple constituents, increasing the potential for idiosyncratic reactions. While unlikely, such reactions can be excluded only after extensive, monitored use of the extract.

References

1. Miyahara C, Miyazawa M, Satoh S, Sakai A, Mizusaki S: Inhibitory effects of mulberry leaf extract on postprandial hyperglycemia in normal rats. *J Nutr Sci Vitaminol* 50:161–164, 2004
2. Chen F, Nakashima N, Kimura I, Kimura M: Hypoglycemic activity and mechanisms of extracts from mulberry leaves (folium mori) and cortex mori radicis in streptozotocin-induced diabetic mice. *Yakugaku Zasshi* 115:476–482, 1995
3. Ye F, Shen ZF, Qiao FX, Zhao DY, Xie MZ: Experimental treatment of complications in alloxan diabetic rats with alpha-glucosidase inhibitor from the Chinese medicinal herb ramulus mori. *Yao Xue Xue Bao* 37:108–112, 2002
4. Murata K, Yatsunami K, Mizukami O, Toriumi Y, Hoshino G, Kamei T: Effects of propolis and mulberry leaf extract on type 2 diabetes. *Focus Alternat Complement Ther* 8:4524–525, 2003
5. Andallu B, Suryakantham V, Srikanthi BL, Reddy GK: Effect of mulberry (Morus indica L.) therapy on plasma and erythrocyte membrane lipids in patients with type 2 diabetes. *Clin Chim Acta* 314:47–53, 2001
6. Strocchi A, Corazza G, Ellis CJ, Gasbarrini G, Levitt MD: Detection of malabsorption of low doses of carbohydrate: accuracy of various breath H_2 criteria. *Gastroenterology* 105:1404–1410, 1993
7. Suarez Fl, Zummaraga LM, Furne JK, Levitt MD: Nutritional supplements used in weight reduction programs increase intestinal gas in persons who malaborb lactose. *J Am Diet Association* 101:1147–1152, 2001
8. Zhong L, Furne JK, Levitt MD: An extract of black, green and mulberry teas causes malabsorption of carbohydrate but not triacylglycerol in health controls. *J Clin Nutr* 84:551–555, 2006
9. Oku T, Yamada M, Nakamura M, Sadamori N, Nakamura S: Inhibitory effects of extractives from leaves of Morus alba on human and rat small intestinal disaccharidase activity. *Br J Nutr* 95:933–938, 2006
10. U.K. Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. *Lancet* 352:837–853, 1998
11. Brownlee M, Hirsch IB: Glycemic variability: a hemoglobin A_{1c}-independent risk factor for diabetic complications. *JAMA* 295:1707–1708, 2006
12. Brownlee M: The pathphysiology of diabetic complications: a unifying mechanism. *Diabetes* 54:1615–1625, 2005
13. Monnier L, Mas E, Ginet C, Michael F, Villon L, Cristol JP, Colette C: Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *JAMA* 295:1681–1687, 2006
14. Hanefeld M, Fischer S, Schulze J, Spengler M, Wargenau M, Schollberg K, Fucker K: Therapeutic potentials of acarbose as first line drug in NIDDM insufficiently treated with diet alone. *Diabetes Care* 14: 732–737, 1991
15. Chiasson JL, Gomis R, Hanefeld M, Josse RG, Karasik A, Laakso M: The STOP-NIDDM trial: an international study on the efficacy of an α-glucosidase inhibitor to prevent type 2 diabetes in a population with impaired glucose tolerance rationale,

design, and preliminary screening data. *Diabetes Care* 21:1720–1725, 1998
16. Balfour JA, McTavish D: Acarbose: an update of its pharmacology and therapeutic use in diabetes mellitus. *Drugs* 46:1025–1054, 1993
17. Taniguchi S, Asano N, Tomino F, Miwa I: Potentiation of glucose-induced insulin secretion by fagomine, a pseudo-sugar isolated from mulberry leaves. *Horm Metab Res* 30:679–683, 1998
18. Enkhamaa B, Shiwaku K, Katsube T, Kitajima K, Anuurad E, Yamasaki M, Yamane Y: Mulberry (*Morus alba* L.) leaves and their major flavonol queretin 3-(6-malonylglucoside) attenuate atherosclerotic lesion development in LDL receptor-deficient mice. *J Nutr* 135:729–734, 2005
19. Varadacharylul AB: Antioxidant role of mulberry (*Morus indica* L. cv. Anantha) leaves in streptozotocin-diabetic rats. *Clin Chim Acta* 348:215–218, 2004
20. Srivastava S, Kapoor R, Thathola A, Srivastava RP: Mulberry (*Morus alba*) leaves as human food: a new dimension of sericulture. *Int J Food Sci & Nutr* 54:411–416, 2003