Adiponectin Decreases Postprandially Following a Heat-Processed Meal in Individuals With Type 2 Diabetes

An effect prevented by benfotiamine and cooking method

ALIN STIRBAN, MD[1]
MONICA NEGREAN, MD[1]
BERND STRATMANN, PHD[1]
CHRISTIAN GÖTTING, PHD[1]
JULIA SALOMON[1,3]
KNUT KLEESIEK, MD[1]
DIETHELM TSCHOEPE, MD[1]

Adiponectin regulates insulin sensitivity (1), reduces the expression of endothelial adhesion molecules (2), and has anti-inflammatory effects (3). Decreased adiponectin levels accompany obesity (4) and type 2 diabetes (5), promoting insulin resistance (5) and cardiovascular disease (6,7). Data on postprandial adiponectin regulation in different populations are controversial, with studies showing no effect (8–11), increases (12,13), or decreases (14,15). Advanced glycation end products (AGEs) (16) play a major role in the development of diabetes complications (17). We have shown that dietary AGEs acutely impair endothelial function (18,19), an effect counteracted by benfotiamine (20), a transketolase activator that blocks several hyperglycemia-induced pathways, including the formation of AGEs (21). AGEs might interact with adipocytes through AGE receptors (22) and induce cellular dysfunction via generation of reactive oxygen species (23), a pathway probably responsible for the AGE-induced downregulation of leptin secretion in vitro (24).

Our study aimed at investigating the effects of a high heat–processed meal with high AGE content (HAGE) and a low heat–processed meal with low AGE content (LAGE) on postprandial adiponectin concentration. We postulated a protective effect of benfotiamine.

RESEARCH DESIGN AND METHODS

— Nineteen inpatients with type 2 diabetes (mean ± SEM age 55.2 ± 1.9 years; diabetes duration 7.3 ± 1.2 years; BMI 29.2 ± 0.8 kg/m^2; A1C 8.8 ± 0.4%; 13 male and 6 female; 4 smokers and 15 nonsmokers; 15 on oral diabetes medication alone, 2 on oral diabetes medication plus insulin, and 2 on insulin alone; 13 on angiotensin receptor blockers, 7 on hydroxymethylglutaryl-CoA reductase inhibitors; 6 on β-blockers; 6 on diuretics; 2 on calcium channel blockers; and 15 on aspirin) without cardiovascular history were investigated after approval of the institutional review board and obtainment of individual written consent.

Patients on a standard diabetes diet for the 9-day study period were studied on three occasions, following an overnight fast. Medication was withdrawn 12 h before every investigation and kept constant throughout the study. On days 4 and 6, the effects of HAGE and LAGE on postprandial adiponectin levels were studied in an investigator-blinded, randomized, crossover design (n = 10 began with HAGE and n = 9 with LAGE). Sixteen patients received benfotiamine (Milgamma, Woerwag, Germany) orally on days 7, 8 (350 mg three times a day), and 9 (1,050 mg 1 h before the repeated intake of the HAGE: HAGE plus benfotiamine).

Analyses were performed fasting (at 7:00 A.M.) as well as at 2, 4, and 6 h postprandially.

The two meals were isocaloric (580 kcal), had identical ingredients, and differed only by the temperature and time of cooking (HAGE: frying/broiling at 230°C for 20 min; LAGE: steaming/boiling at 100°C for 10 min) (18). The calculated AGE content was as follows: HAGE, 15,100 kU; LAGE, 2,750 kU (25).

Blood samples were analyzed for serum glucose, cholesterol, triglycerides, LDL and HDL cholesterol (Architect ci8200 analyzer; Abbott Diagnostics, Wiesbaden, Germany), thiobarbituric acid reactive substances (TBARS) (Alexis Biochemicals, Gruenberg, Switzerland), serum adiponectin (R&D Systems, Wiesbaden, Germany), insulin (DPC Biermann, Bad Nauheim, Germany), and serum methylglyoxal derivatives (enzyme-linked immunosorbent assay with monoclonal anti–methylglyoxal-BSA antibody [methylglyoxal3D11; Dr. Y. Al-Abed, Picower Institute, Cambridge, MA]) (26).

Postprandial changes were assessed by two-way ANOVA for repeated measurements followed by a two-tailed paired t test with Bonferroni's correction for multiple testing. We measured the area under the curve and the area under the curve change (area under the curve of values minus baseline). Data are means ± SEM unless otherwise indicated. The level of significance was P = 0.05.

RESULTS

— Plasma adiponectin decreased significantly only 2 h after HAGE (Fig. 1*A*). The area under the curve change was −2041 ± 753 (HAGE), 33 ± 1,070 (LAGE), and 840 ± 824 (HAGE plus benfotiamine) ng/ml × h.

Fasting glucose was comparable be-

From the [1]Diabetes Center, Heart and Diabetes Center NRW, Ruhr-University Bochum, Bad Oeynhausen, Germany; the [2]Institute for Laboratory and Transfusion Medicine, Heart and Diabetes Center NRW, Ruhr-University Bochum, Bad Oeynhausen, Germany; and the [3]University of Applied Sciences, Muenster, Germany.

Address correspondence and reprint requests to Dr. Diethelm Tschoepe, Heart and Diabetes Center NRW, Georgstrasse 11, 32545 Bad Oeynhausen, Germany. E-mail: dtschoepe@hdz-nrw.de.

Received for publication 13 March 2007 and accepted in revised form 10 July 2007.

Published ahead of print at http://care.diabetesjournals.org on 13 July 2007. DOI: 10.2337/dc07-0302. Clinical trial reg. no. NCT00437008, clinicaltrials.gov.

Abbreviations: AGE, advanced glycation end product; HAGE, high AGE content; LAGE, low AGE content; TBARS, thiobarbituric acid reactive substances.

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

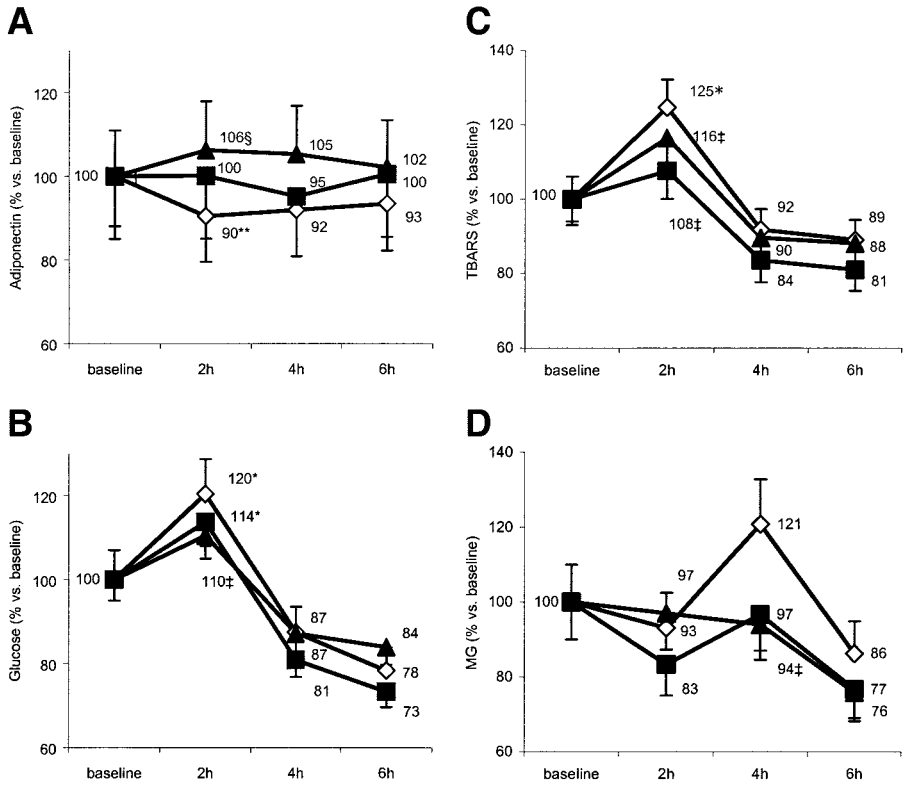

Figure 1—*Baseline values (HAGE, ◇; LAGE, ■; and HAGE plus benfotiamine, ▲; respectively) for adiponectin (4,102 ± 543, 3,856 ± 399, and 3,360 ± 512 ng/ml), TBARS (7.3 ± 0.3, 7.9 ± 0.4, and 6.7 ± 0.2 nmol/ml), and methylglyoxal (2.9 ± 0.3, 3.0 ± 0.3, and 3.3 ± 0.5 nmol/ml). *P < 0.05 vs. baseline; **P < 0.01 vs. baseline; ‡P < 0.05 vs. HAGE; and §P = 0.061 vs. HAGE.*

fore HAGE and LAGE and decreased after benfotiamine (143 ± 7, 146 ± 8, and 124 ± 4 mg/dl, respectively.) Postprandial glucose (2 h) was significantly reduced by benfotiamine (Fig. 1*B*).

The HAGE induced an increase in TBARS at 2 h, an effect significantly reduced after LAGE and by benfotiamine (Fig. 1*C*). The HAGE-induced increase in methylglyoxal at 4 h was prevented by benfotiamine (Fig. 1*D*). There was no difference between days in fasting and postprandial values of the following parameters: plasma insulin; triglycerides; and total, LDL, and HDL cholesterol (data not shown).

CONCLUSIONS — The main findings of our study are that a real-life, AGE-rich, high heat–processed meal transiently decreases postprandial adiponectin levels in individuals with poorly controlled type 2 diabetes, an effect prevented both by changing the cooking method and by pretreatment with benfotiamine. Adiponectin decreased significantly only 2 h following the HAGE and not after LAGE. Because both meals had identical ingredients and differed only by the cooking method, we suggest that postprandial adiponectin regulation is influenced not only by food composition (15) but also by cooking method.

Adipocyte dysfunction occurs under conditions of oxidative stress (27) and increased AGE concentration (24), resulting in decreased adipokine secretion (24). After HAGE, we found a significant increase in oxidative stress and AGEs and suggest that these pathomechanisms are responsible for the adiponectin decrease. Moreover, we found a significant correlation between changes in TBARS and adiponectin at 2 h following HAGE ($r = -0.530$; $P < 0.05$).

Three-day benfotiamine therapy reduced fasting TBARS and postprandial methylglyoxal and TBARS, paralleled by a reversal of postprandial adiponectin decrease. We have previously shown that benfotiamine prevents postprandial increase in oxidative stress, AGEs (20), and endothelial dysfunction. We suggest that similar mechanisms reduce postprandial adipocyte stress, thus preventing adiponectin decrease.

Adiponectin closely mirrors insulin sensitivity. Its postprandial decrease might induce transient impairment of insulin sensitivity, thus worsening postprandial hyperglycemia. Benfotiamine pretreatment significantly reduced postprandial hyperglycemia, despite similar postprandial insulin levels. This suggests improved postprandial insulin sensitivity, a finding in line with the preserved adiponectin levels. Metabolic effects of thiamine have previously been postulated in certain populations (28) but questioned in others (29). We suggest that in type 2 diabetes, benfotiamine exerts metabolic effects by reducing oxidative stress and AGEs, thus lowering adipocyte stress and preserving adiponectin levels.

Limitations of the study

We cannot exclude that thermal-induced inactivation of vitamins and antioxidants (30) or generation of other toxic compounds (31) potentiated the effects of oxidative stress and AGEs. Still, the main messages of our study, that cooking method and benfotiamine preserve postprandial adiponectin regulation, remain unaltered.

Acknowledgments— We acknowledge Prof. Helen Vlassara and Dr. Jaime Uribarri (Mount Sinai School of Medicine, Division of Diabetes and Aging, New York City, NY) for their valuable assistance.

References

1. Beltowski J: Adiponectin and resistin: new hormones of white adipose tissue. *Med Sci Monit* 9:RA55-RA61, 2003
2. Ouchi N, Kihara S, Arita Y, Maeda K, Kuriyama H, Okamoto Y, Hotta K, Nishida M, Takahashi M, Nakamura T, Yamashita S, Funahashi T, Matsuzawa Y: Novel modulator for endothelial adhesion molecules: adipocyte-derived plasma protein adiponectin. *Circulation* 100: 2473–2476, 1999
3. Fantuzzi G: Adipose tissue, adipokines, and inflammation. *J Allergy Clin Immunol* 115:911–919, 2005
4. Osei K, Gaillard T, Cook C, Kaplow J, Bullock M, Schuster D: Discrepancies in the regulation of plasma adiponectin and TNF-alpha levels and adipose tissue gene expression in obese African Americans with glucose intolerance: a pilot study using rosiglitazone. *Ethn Dis* 15:641–648, 2005
5. Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K: Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. *J Clin Invest* 116:1784–1792, 2006
6. Funahashi T, Nakamura T, Shimomura I,

Maeda K, Kuriyama H, Takahashi M, Arita Y, Kihara S, Matsuzawa Y: Role of adipocytokines on the pathogenesis of atherosclerosis in visceral obesity. *Intern Med* 38:202–206, 1999
7. Matsuzawa Y, Funahashi T, Nakamura T: Molecular mechanism of metabolic syndrome: contribution of adipocytokines adipocyte-derived bioactive substances. *Ann N Y Acad Sci* 892:146–154, 1999
8. Greenfield JR, Samaras K, Hayward CS, Chisholm DJ, Campbell LV: Beneficial postprandial effect of a small amount of alcohol on diabetes and cardiovascular risk factors: modification by insulin resistance. *J Clin Endocrinol Metab* 90: 661–672, 2005
9. Imbeault P, Pomerleau M, Harper ME, Doucet E: Unchanged fasting and postprandial adiponectin levels following a 4-day caloric restriction in young healthy men. *Clin Endocrinol (Oxf)* 60:429–433, 2004
10. Peake PW, Kriketos AD, Denyer GS, Campbell LV, Charlesworth JA: The postprandial response of adiponectin to a high-fat meal in normal and insulin-resistant subjects. *Int J Obes Relat Metab Disord* 27:657–662, 2003
11. English PJ, Coughlin SR, Hayden K, Malik IA, Wilding JPH: Response: postprandial adiponectin revisited (Letter). *Obes Res* 12:1032–1034, 2004
12. English PJ, Coughlin SR, Hayden K, Malik IA, Wilding JP: Plasma adiponectin increases postprandially in obese, but not in lean, subjects. *Obes Res* 11:839–844, 2003
13. Musso G, Gambino R, Durazzo M, Biroli G, Carello M, Faga E, Pacini G, De MF, Rabbione L, Premoli A, Cassader M, Pagano G: Adipokines in NASH: postprandial lipid metabolism as a link between adiponectin and liver disease. *Hepatology* 42:1175–1183, 2005
14. Caixas A, Gimenez-Palop O, Gimenez-Perez G, Potau N, Berlanga E, Gonzalez-Glemente JM, Arroyo J, Laferrere B, Mauricio D: Postprandial adiponectin levels are unlikely to contribute to the pathogenesis of obesity in Prader-Willi syndrome. *Horm Res* 65:39–45, 2006
15. Esposito K, Nappo F, Giugliano F, Di PC, Ciotola M, Barbieri M, Paolisso G, Giugliano D: Meal modulation of circulating interleukin 18 and adiponectin concentrations in healthy subjects and in patients with type 2 diabetes mellitus. *Am J Clin Nutr* 78:1135–1140, 2003
16. Tan KC, Chow WS, Ai VH, Metz C, Bucala R, Lam KS: Advanced glycation end products and endothelial dysfunction in type 2 diabetes. *Diabetes Care* 25:1055–1059, 2002
17. Vlassara H, Uribarri J: Glycoxidation and diabetic complications: modern lessons and a warning? *Rev Endocr Metab Disord* 5:181–188, 2004
18. Negrean M, Stirban A, Stratmann B, Gawlowski T, Horstmann T, Gotting C, Kleesiek K, Mueller-Roesel M, Koschinsky T, Uribarri J, Vlassara H, Tschoepe D: Effects of low- and high-advanced glycation endproduct meals on macro- and microvascular endothelial function and oxidative stress in patients with type 2 diabetes mellitus. *Am J Clin Nutr* 85:1236–1243, 2007
19. Uribarri J, Stirban A, Sander D, Cai W, Negrean M, Buenting CE, Koschinsky T, Vlassara H: Single oral challenge by advanced glycation end products acutely impairs endothelial function in diabetic and nondiabetic subjects. *Diabetes Care* 30:2579–2582, 2007
20. Stirban A, Negrean M, Stratmann B, Gawlowski T, Horstmann T, Götting C, Kleesiek K, Mueller-Roesel M, Koschinsky T, Uribarri J, Vlassara H, Tschoepe D: Benfotiamine prevents macro- and microvascular endothelial dysfunction and oxidative stress following a meal rich in advanced glycation end products in individuals with type 2 diabetes. *Diabetes Care* 29:2064–2071, 2006
21. Hammes HP, Du X, Edelstein D, Taguchi T, Matsumura T, Ju Q, Lin J, Bierhaus A, Nawroth P, Hannak D, Neumaier M, Bergfeld R, Giardino I, Brownlee M: Benfotiamine blocks three major pathways of hyperglycemic damage and prevents experimental diabetic retinopathy. *Nat Med* 9:294–299, 2003
22. Kuniyasu A, Ohgami N, Hayashi S, Miyazaki A, Horiuchi S, Nakayama H: CD36-mediated endocytic uptake of advanced glycation end products (AGE) in mouse 3T3–L1 and human subcutaneous adipocytes. *FEBS Lett* 537:85–90, 2003
23. Uchida Y, Ohba K, Yoshioka T, Irie K, Muraki T, Maru Y: Cellular carbonyl stress enhances the expression of plasminogen activator inhibitor-1 in rat white adipocytes via reactive oxygen species-dependent pathway. *J Biol Chem* 279:4075–4083, 2004
24. Unno Y, Sakai M, Sakamoto Y, Kuniyasu A, Nakayama H, Nagai R, Horiuchi S: Advanced glycation end products-modified proteins and oxidized LDL mediate down-regulation of leptin in mouse adipocytes via CD36. *Biochem Biophys Res Commun* 325:151–156, 2004
25. Goldberg T, Cai W, Peppa M, Dardaine V, Baliga BS, Uribarri J, Vlassara H: Advanced glycoxidation end products in commonly consumed foods. *J Am Diet Assoc* 104:1287–1291, 2004
26. Oya T, Hattori N, Mizuno Y, Miyata S, Maeda S, Osawa T, Uchida K: Methylglyoxal modification of protein: chemical and immunochemical characterization of methylglyoxal-arginine adducts. *J Biol Chem* 26:18492–18502, 1999
27. Fridlyand LE, Philipson LH: Reactive species and early manifestation of insulin resistance in type 2 diabetes. *Diabetes Obes Metab* 8:136–145, 2006
28. Valerio G, Franzese A, Poggi V, Tenore A: Long-term follow-up of diabetes in two patients with thiamine-responsive megaloblastic anemia syndrome. *Diabetes Care* 21:38–41, 1998
29. Valerio G, Franzese A, Poggi V, Patrini C, Laforenza U, Tenore A: Lipophilic thiamine treatment in long-standing insulin-dependent diabetes mellitus. *Acta Diabetol* 36:73–76, 1999
30. Klopotek Y, Otto K, Bohm V: Processing strawberries to different products alters contents of vitamin C, total phenolics, total anthocyanins, and antioxidant capacity. *J Agric Food Chem* 53:5640–5646, 2005
31. Elvevoll EO, Osterud B.: Impact of processing on nutritional quality of marine food items. *Forum Nutr* 56:337–340, 2003