Improvement of Glucose Metabolism in Patients with Impaired Glucose Tolerance or Diabetes by Long-Term Administration of a Palatinose-Based Liquid Formula as a Part of Breakfast

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Received 22 January, 2009; Accepted 17 February, 2009

Summary  A palatinose-based liquid formula (palatinose-formula), suppresses postprandial plasma glucose and insulin levels in healthy men. The objective of this study was to investigate the effects of long-term palatinose-formula ingestion on glucose metabolism in patients with impaired glucose tolerance (IGT) or type 2 diabetes. Two patients with IGT and 7 patients with type 2 diabetes participated in the palatinose-formula and dextrin-based liquid formula (dextrin-formula) loading test and long-term palatinose-formula administration study. After a 3-month control period, palatinose-formula (1046 kJ) was ingested daily by patients as a part of breakfast for 5 months. In the loading test, palatinose-formula suppressed postprandial plasma glucose and insulin levels and areas under the curve compared with those after dextrin-formula ingestion. In the long-term study, glycated hemoglobin levels (after 3 months and 5 months of treatment) and serum 8-hydroxydeoxyguanosine levels (after 5 months of treatment) were markedly decreased comparing with those at baseline. Intake of 1046 kJ palatinose-formula as a part of breakfast over a long-term period may be effective for improvement of glucose metabolism in patients with IGT or type 2 diabetes.

Key Words: palatinose, postprandial hyperglycemia, glucose metabolism, HbA₁c, 8-hydroxydeoxyguanosine

Introduction

Type 2 diabetes mellitus is a major health problem associated with excess morbidity and mortality, resulting in substantial health-care costs [1]. Treatment of type 2 diabetes has traditionally focused on control of fasting plasma glucose; in recent years, the management of postprandial hyperglycemia has been thought to be a more important target. Glycated hemoglobin (HbA₁c) levels are closely associated with postprandial glucose levels in type 2 diabetes, in comparison with fasting glucose levels [2]. Anti-hyperglycemic
therapy focused on control of postprandial glucose level has a greater impact on overall metabolic control, and thus improves long-term outcome compared with the more traditional approaches focused on fasting glucose level [3]. Postprandial hyperglycemia has been associated with increased risk of microvascular [4–6] and macrovascular [7–10] complications. In recent years, cohort studies have shown that postprandial hyperglycemia is an independent risk factor for cardiovascular disease [11–13]. In the STOP-NIDDM study, correction of postprandial hyperglycemia reduced the onset of myocardial infarction [14].

The glycemic index (GI), originally described by Jenkins et al. [15], is a ranking of carbohydrates based on their immediate effects on blood glucose levels. Epidemiologic studies demonstrated that the dietary GI would be an important factor in preventing non-insulin-dependent diabetes [16, 17]. The beneficial effects of a low-GI diet have been demonstrated over both the short- and long-term for normal subjects and patients with diabetes [18–21]. It is difficult for individuals to strictly control every meal. Therefore, if a special meal is only given once a day, it could be useful to lower the postprandial serum glucose level and improve compliance. The quality of breakfast is thought to be lower than for an isocaloric midday or evening meal [22]. Moreover, it has been reported that insulin sensitivity in individuals with diabetes fluctuated, with decreases from the night to morning and increases during the day [24].

A palatinose-based liquid formula (palatinose-formula, Inslow; Meiji Dairy Products; Tokyo, Japan) is a recently developed liquid dietary product that contains palatinose. Palatinose is a sucrose isomer found in honey [25], are metabolized by isomaltase, and less rapidly, but completely, cleaved in the intestine than sucrose [26]. Ingestion of palatinose by type 2 diabetic humans and rats resulted in a reduction in their postprandial plasma glucose and insulin levels [27, 28]. Consumption of palatinose-formula at breakfast appears to improve glycemic control by reducing postprandial plasma glucose and insulin levels after lunch (second meal effect) in healthy men [29]. However, it is not clear that the effect of continuous palatinose-formula intake at breakfast improves glucose metabolism in patients with impaired glucose tolerance (IGT) or type 2 diabetes. In this study we investigated the effects of long-term palatinose-formula ingestion as a part of breakfast on glycemic control and body composition in patients with IGT or type 2 diabetes.

### Experimental Procedures

#### Liquid formulas

Palatinose-formula was prepared by partially replacing dextrin in the dextrin-based liquid formula (dextrin-formula) with 55.7% palatinose. The detailed composition is shown in Table 1; it included palatinose, dextrin, xylitol, dietary fiber, and mixed carbohydrates. The protein, fat, and carbohydrate % of energy were 20.0%, 29.7%, and 50.3%, respectively. The control formula was a dextrin-formula that also contained sucrose; the protein, fat, and carbohydrate % of energy were 14.0%, 31.0%, and 55.0%, respectively (Table 1).

#### Subjects and study design

The study was performed after obtaining written informed consent from all patients, and was approved by the Ethics Committee of the University of Tokushima. The protocol conformed to the Helsinki Declaration. Two patients with impaired glucose tolerance (IGT) (2 females) and 7 patients with type 2 diabetes (3 males and 4 females) participated in

| Characteristics                        | Values |
|----------------------------------------|--------|
| Impaired glucose tolerance (male/female)| 0/2    |
| Type 2 diabetes mellitus (male/female) | 3/4    |
| Age (years)                            | 63.4 ± 3.0 |
| Body weight (kg)                       | 63.8 ± 2.5 |
| Body mass index (kg/m²)                | 25.0 ± 0.8 |
| Body fat ratio (%)                     | 28.2 ± 2.2 |
| Fasting plasma glucose (mmol/L)        | 7.76 ± 0.45 |
| Fasting insulin (pmol/L)               | 32.4 ± 3.0 |
| HbA1c (%)                              | 6.60 ± 0.24 |
| Triacylglycerol (mmol/L)               | 2.37 ± 0.40 |
| Total cholesterol (mmol/L)             | 5.46 ± 0.29 |
| HDL cholesterol (mmol/L)               | 1.36 ± 0.13 |

Values are means ± SE, n = 9.
this study. Their clinical characteristics at study entry are shown in Table 2. Patients with abnormal renal, hepatic, or thyroid function were excluded. Five patients were medicated with sulfonylurea or phenylalanine derivative and 4 patients were only received nutritional consultation. All patients maintained any current therapies throughout the study period, with no dosing changes. Prior to the beginning of the long-term palatinose-formula administration study, each patient underwent a palatinose-formula and dextrin-formula loading test.

Loading test

The loading test had a crossover design, with a one-week washout period between dosing episodes. Each patient consumed both palatinose-formula (250 ml; 1046 kJ) and dextrin-formula (250 ml; 1046 kJ). The patients came to the University of Tokushima at 0830 h after a 12-h overnight fast. Patients completely consumed the liquid formula within a 5-min period. Peripheral venous blood samples were collected at times 0 (before ingestion), and 30, 60, 90, 120, and 180 min after ingestion of the formula. Blood samples were used for analysis of plasma glucose and insulin concentration.

Long-term study

The long-term study was carried out after a 3-month control period (from Month -3 to Month 0). The first month of the control period (from Month -3 to Month -2) was established to determine individual patient energy intake. Each patient’s energy intake and dietary habits were determined from daily dietary records. Patients received individual counseling on dietary food intake and were recommended to reach a goal of a stable and reasonable energy intake. A 2-month control period (from Month -2 to Month 0) was arranged after the patients’ quantity of energy intake was stabilized. After the control period, patients ingested palatinose-formula for 5 months (test period). During the test period, patients were instructed to maintain the quantity of total energy intake and substituted a palatinose-formula dose for 1046 kJ of their breakfast. The total energy of the breakfast in the test period was fixed to the control period (from Month -2 to Month 0) quantity based on each patient’s dietary record. Patients were asked to maintain a constant lifestyle and keep a dietary record to be completed during the 3 days prior to each scheduled visit to the University of Tokushima. Visits were scheduled at Month -3, Month -2 (control period), and at Month 0 (baseline), 3, and 5 for collection of fasting blood samples, body composition measurement, and to hand in their previous 3-day’s dietary records. Blood samples were used for analysis of fasting plasma glucose, fasting insulin, HbA1c, total cholesterol, HDL cholesterol, triacylglycerol, adiponectin and 8-hydroxydeoxyguanosine (8-OHdG) concentrations. A dietician calculated the quantity of intake energy from each patient’s dietary records and determined the mean value for the 3 days leading up to the scheduled clinic visit.

Analytic methods

Body composition with respect to lean and fat mass was determined using a bioelectrical impedance analysis method (In Body 3.0; MP JAPAN, Tokyo, Japan). Plasma samples were kept at −20°C until analyzed. Plasma glucose concentration was measured by using a glucose oxidase-based autoanalyzer. Serum insulin concentration was measured by a standard radioimmunoassay. The total incremental area under the curve (AUC) for plasma glucose and insulin were calculated for a 180-min period after ingestion of each liquid formula. The insulin resistance index was calculated using the homeostasis model assessment for insulin resistance (HOMA-IR = fasting insulin (μU/ml) × fasting glucose (mmol/L) / 22.5).

HbA1c concentration was determined by high-performance liquid chromatography; serum triglyceride, total cholesterol, and HDL cholesterol concentrations were determined by enzymatic techniques using a Hitachi Model 736 autoanalyzer (Mito, Japan). Serum adiponectin concentrations were measured by human adiponectin ELISA kit (Otsuka Pharmaceutical Co, Ltd, Tokyo, Japan). Serum 8-OHdG concentrations were measured by high sensitive 8-OHdG ELISA kit (Japan Institute for the Control of Aging, Nikken SEIL Co., Ltd. Fukuroi; Shizuoka, Japan).

Statistical analyses

Data are presented as mean ± standard error of the mean (SE). The loading test was analyzed using Student’s t test for paired comparisons. The long-term study was analyzed using Wilcoxon matched-pairs signed-rank test. All statistical analyses were performed with Stat View for Windows, version 5.0 (SAS Institute; Cary, NC).

Results

Loading test

The effects of palatinose-formula administration on postprandial glucose and insulin levels were confirmed in patients with IGT and type 2 diabetes. Postprandial plasma glucose concentrations after palatinose-formula loading were significantly lower than those after dextrin-formula loading at 30 min (p<0.01), 60 min (p<0.01), and 90 min (p<0.01) post-dosing (Fig. 1A). Postprandial insulin after palatinose-formula loading were lower than those after dextrin-formula loading at 30 min, 60 min, and 90 min post-dosing, but were not significantly different (Fig. 1B). Plasma glucose and insulin incremental AUCs after palatinose-formula loading were significantly lower than those after dextrin-formula loading (p<0.05; Fig. 1C, D).
During the long-term study, two subjects withdrew due to conflicts of schedule and health problems unrelated to the study, and one subject was excluded from analysis due to poor compliance. Therefore, all long-term study data were analyzed and are presented for the six subjects (IGT; 2 females, type 2 diabetes; 1 male and 3 females) who completed the study. Serious side effects such as anemia, renal, or hepatic disorders did not appear during this study.

Daily intake of total energy at Month -2 decreased from that determined at the Month -3 visit, but there was no change in the daily total energy intake over subsequent control and test period. Macronutrients and dietary fiber intake from the control period to the test period did not change (Table 3).

Anthropometric and laboratory parameters from the beginning of control period (Month -3) to the end of the test period (Month 5) are shown in Table 4. Body weight, body mass index, and serum triacylglycerol concentration significantly decreased during the control period (possibly due to the nutritional consultation and subsequent dietary changes). No significant changes were observed in any other parameter during the control period. In the experimental period, no significant changes were observed in body weight, body mass index, body fat ratio, fasting plasma glucose, fasting insulin, triacylglycerol, total cholesterol, or HDL cholesterol levels. However, with intake of 1046 kJ palatinose-formula as a part of breakfast, HbA1c and 8-OHdG levels were significantly decreased at the Month 3 and Month 5 evaluations. HOMA-IR slightly decreased.

Fig. 1. Change in plasma glucose (A) and insulin (B) concentrations after patients consumed palatinose-formula (open circle) or dextrin-formula (closed circle). Incremental AUC for plasma glucose (C) and insulin (D) levels are shown for subjects after they consumed palatinose-formula or dextrin-formula. Values are means ± SE, n = 9. * Difference between palatinose-formula and dextrin-formula at that time point, $p<0.05$. ** Difference between palatinose-formula and dextrin-formula at that time point, $p<0.01$. 
and adiponectin slightly increased by palatinose-formula ingestion, although these changes were not statistically significant.

**Discussion**

In this study, postprandial glucose and insulin levels after the ingestion of palatinose-formula diet were significantly lower than those after the ingestion of dextrin-formula diet in patients with IGT or type 2 diabetes, as previously observed in rats and healthy human subjects [29, 30]. Since energy amounts during the control and experimental periods were unchanged, it is conceivable that the decrease in HbA1c and 8-OHdG concentrations is due to the effect of the long-term (5-month) ingestion of palatinose-formula as a part of breakfast in these patients with IGT or type 2 diabetes.

There are evidences of the beneficial effects to glycemic control of a low-GI diet in type 2 diabetes [18, 19, 21, 31], but there are few reports of the glycemic effects of a low-GI breakfast alone. Golay et al. found that switching from a standard cereal (cornflakes) to slow-release starch cereal (muesli) at breakfast for only 2 weeks improved carbohydrate metabolism and reduced insulin requirements in the insulin-treated type 2 diabetic patients [32]. In addition, it has been suggested that the low-glycemic-index foods consumed during the first meal improved glucose tolerance after the second meal, so-called “second meal effect” [33, 34]. In this study, long-term ingestion of palatinose-formula diet as a part of breakfast decreased HbA1c concentration. In addition, decreased in HOMA-IR and increased in serum adiponectin level suggested that insulin sensitivity may also be ameliorated by long-term ingestion of palatinose formula. We previously reported that long-term ingestion of palatinose-formula over the long-term reduced visceral fat accumulation, improved insulin sensitivity in comparison with dextrin-formula [30], and increased adipocyte adiponectin gene expression in rats [35]. Adiponectin plays a role in glucose metabolism and plasma adiponectin level is
positively correlated with insulin sensitivity [36–38]. These data suggest that long-term ingestion of palatinose-formula diet can improve glucose tolerance, probably due to the second meal effect.

In contrast, fasting plasma glucose levels did not change in this study. Avignon et al. suggested that postprandial hyperglycemia reflects better glycemic control than does fasting plasma glucose in patients with type 2 diabetes [2]. Additionally, lowering postprandial plasma glucose optimized overall glycemic control, thus improving long-term outcomes when compared with simply lowering fasting plasma glucose [3].

Serum 8-OHdG concentration after five months of treatment was also significantly reduced by palatinose-formula ingestion. Patients with type 1 and 2 diabetes have significantly higher 8-OHdG concentrations than do control subjects [39, 40]. Since 8-OHdG concentration was correlated with HbA1c concentration [40, 41], reduced 8-OHdG reflected improvement of glycemic control by palatinose-formula ingestion. It is known that 8-OHdG can serve as a sensitive biomarker of oxidative DNA damage [42]. In a previous study, glucose fluctuations during postprandial periods exhibited a more specific triggering effect on oxidative stress than chronic sustained hyperglycemia in type 2 diabetes [43]. Oxidative stress triggers micro- and macrovascular complications [44]. Because ingesting palatinose-formula suppressed the postprandial glucose fluctuations, it might also reduce production of oxidative stress.

Because this study was carried out with a limited number of subjects, further study with larger populations should be initiated to support our findings. In conclusion, we suggest that long-term ingestion of palatinose-formula as a part of breakfast is effective in improving glycemic control for patients with IGT or type 2 diabetes.

Acknowledgments

This work was supported by Meiji Dairies Corporation, Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology in Japan (for H.A., E.T.), and from the 21st Century COE Program, Human Nutritional Science on Stress Control in The University of Tokushima Graduate School Tokushima, Japan. We are grateful to Kazusa Sato for her excellent technical assistance and enthusiastic support in the preparation of this manuscript.

Abbreviations

palatinose-formula, palatinose-based liquid formula; dextrin-formula, dextrin-based liquid formula; IGT, impaired glucose tolerance; HbA1c, glycated hemoglobin; 8-OHdG, 8-hydroxydeoxyguanosine; HOMA-IR, homeostasis model assessment for insulin resistance; BMI, body mass index; AUC, area under the curve; HDL, high density lipoprotein.

References

[1] Harris, M.I.: Diabetes in America: epidemiology and scope of the problem. Diabetes Care, 21 Suppl 3, C11–C14, 1998.
[2] Avignon, A., Radauceanu, A., and 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.
[3] Bastyr, E.J.3rd, Stuart, C.A., Brodows, R.G., Schwartz, S., Graf, C.J., Zagar, A., and Robertson, K.E.: Therapy focused on lowering postprandial glucose, not fasting glucose, may be superior for lowering HbA1c. IOEZ Study Group. Diabetes Care, 23, 1236–1241, 2000.
[4] de Veciana, M., Major, C.A., Morgan, M.A., Asrat, T., Toohey, J.S., Lien, J.M., and Evans, A.T.: Postprandial versus preprandial blood glucose monitoring in women with gestational diabetes mellitus requiring insulin therapy. N. Engl. J. Med., 333, 1237–1241, 1995.
[5] McCance, D.R., Hanson, R.L., Charles, M.A., Jacobsson, L.T., Pettitt, D.J., Bennett, P.H., and Knowler, W.C.: Comparison of tests for glycated haemoglobin and fasting and two hour plasma glucose concentrations as diagnostic methods for diabetes. BMJ, 308, 1323–1328, 1994.
[6] Engelsing, M.M., Thompson, T.J., Herman, W.H., Boyle, J.P., Aubert, R.E., Kenny, S.J., Badran, A., Sous, E.S., and Ali, M.A.: Comparison of fasting and 2-hour glucose and HbA1c levels for diagnosing diabetes. Diagnostic criteria and performance revisited. Diabetes Care, 20, 785–791, 1997.
[7] Lowe, L.P., Liu, K., Greenland, P., Metzger, B.E., Dyer, A.R., and Stamler, J.: Diabetes, asymptomatic hyperglycemia, and 22-year mortality in black and white men. The Chicago Heart Association Detection Project in Industry Study. Diabetes Care, 20, 163–169, 1997.
[8] Donahue, R.P., Abbott, R.D., Reed, D.M., and Yano, K.: Postchallenge glucose concentration and coronary heart disease in men of Japanese ancestry. Honolulu Heart Program. Diabetes, 36, 689–692, 1987.
[9] Hanefeld, M., Fischer, S., Julius, U., Schulze, J., Schwanebeck, U., Schmechel, H., Ziegelasch, H.J., and 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.
[10] Balkau, B., Shipley, M., Jarrett, R.J., Pyörälä, K., Pyörälä, M., Forhan, A., and Eschwege, E.: High blood glucose concentration is a risk factor for mortality in middle-aged nondiabetic men. 20-year follow-up in the Whitehall Study, the Paris Prospective Study, and the Helsinki Policemen Study. Diabetes Care, 21, 360–367, 1998.
[11] DECODE Study Group, the European Diabetes Epidemiology Group: Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. Arch. Intern. Med., 121, 397–405, 2001.
[12] Nakagami, T.; DECODA Study Group: Hyperglycaemia and mortality from all causes and from cardiovascular disease in J. Clin. Biochem. Nutr.
five populations of Asian origin. Diabetologia, 47, 385–394, 2004.

13. Tominaga, M., Eguchi, H., Manaka, H., Igarashi, K., Kato, T., and Sekikawa, A.: Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose. The Funagata Diabetes Study. Diabetes Care, 22, 920–924, 1999.

14. Chiasson, J.L., Ros, R.G., Gomis, R., Hanefeld, M., Karasik, A., and Laakso, M.: STOP-NIDDM Trial Research Group.: Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. JAMA, 290, 486–494, 2003.

15. Jenkins, D.J., Wolever, T.M., Taylor, R.H., Barker, H., Fielden, H., Baldwin, J.M., Bowling, A.C., Newman, H.C., Jenkins, A.L., and Goff, D.V.: Glycemic index of foods: a physiological basis for carbohydrate exchange. Am. J. Clin. Nutr., 34, 362–366, 1981.

16. Salmerón, J., Ascherio, A., Rimm, E.B., Colditz, G.A., Spiegelman, D., Jenkins, D.J., Stampfer, M.J., Wing, A.L., and Willett, W.C.: Dietary fiber, glycemic load, and risk of NIDDM in men. Diabetes Care, 20, 545–550, 1997.

17. Meyer, K.A., Kushi, L.H., Jacobs, D.R. Jr., Slavin, J., Salmerón, J., Ascherio, A., Rimm, E.B., Colditz, G.A., Brand, J.C., Colagiuri, S., Crossman, S., Allen, A., Roberts, V., Vol. 45, No. 2, 2009

18. Järvi, A.E., Karlström, B.E., Granfeldt, Y.E., Björck, I.E., Fontvieille, A.M., Rizkalla, S.W., Penfornis, A., Acosta, M., Nestler, J.E., Gebhart, S.S., and Blackard, W.G.: Failure of Tominaga, M., Eguchi, H., Manaka, H., Igarashi, K., Kato,

19. Kasaoka, N., Ezaki, O., Akanuma, Y., Gavrilova, O., Vinson, C., Reitman, M.L., Kagechika, H., Shudo, K., Yoda, M., Nakano, Y., Tobe, K., Nagai, R., Kimura, S., Tomita, M., Yamamoto, H., Taketani, Y., Doi, T., and Takeda, E.: Effects of a palatinose-based liquid diet (Inslow®) on glycemic control and the second-meal effect in healthy men. Metabolism, 56, 115–121, 2007.

20. Tominaga, M., Eguchi, H., Manaka, H., Igarashi, K., Kato,

21. Arai, H., Mizuno, A., Sasaki, H., Matsuura, M., Okumura, H., Yamamoto, H., Taketani, Y., Doi, T., and Takeda, E.: Effect of a novel palatinose-based liquid balanced formula (MHN-01) on glucose and lipid metabolism in male Sprague-Dawley rats after short- and long-term ingestion. Metabo-

22. Arai, H., Mizuno, A., Sasaki, H., Matsuura, M., Taketani, Y., Doi, T., and Takeda, E.: Effect of a novel palatinose-based liquid balanced formula (MHN-01) on glucose and lipid metabolism in male Sprague-Dawley rats after short- and long-term ingestion. Metabolism, 53, 977–983, 2004.

23. Jenkins, D.J., Wolever, T.M., Vuksan, V., Jenkins, A.L., Buckley, G.C., Wong, G.S., and Josse, R.G.: Beneficial effect of a low glycaemic index diet in type 2 diabetes. Diabet. Med., 9, 451–458, 1992.

24. Golay, A., Koebernik, B., Bloise, D., Assal, J.P., and Würsch, P.: The effect of muesli or cornflakes at breakfast on carbohydrate metabolism in type 2 diabetic patients. Diabetes Res. Clin. Pract., 15, 135–141, 1992.

25. Jenkins, D.J., Wolever, T.M., Taylor, R.H., Griffiths, C., Krzeminiska, K., Lawrie, J.A., Bennett, C.M., Goff, D.V., Sarson, D.L., and Bloom, S.R.: Slow release dietary carbohydrate improves second meal tolerance. Am. J. Clin. Nutr., 35, 1339–1346, 1982.

26. Wolfer, T.M., Jenkins, D.J., Ocana, A.M., Rao, V.A., and Collier, G.R.: Second-meal effect: low-glycemic-index foods eaten at dinner improve subsequent breakfast glycemic response. Am. J. Clin. Nutr., 48, 1041–1047, 1988.

27. Matsuo, K., Arai, H., Muto, K., Fukaya, M., Sato, T., Mizuno, A., Sakuma, M., Yamanaka-Okumura, H., Sasaki, H., Yamamoto, H., Taketani, Y., Doi, T., and Takeda, E.: The anto-obesity effect of palatinose-based formula Inslow® is likely due to an increase in the hepatic PPAR-α and adipocyte PPAR-γ gene expressions. J. Clin. Biochem. Nutr., 40, 234–241, 2007.

28. Yamauchi, T., Kamon, J., Waki, H., Ishii, K., Kubota, N., Hara, K., Mori, Y., Ide, T., Murakami, K., Tsuboyama-Kasao, N., Ezaki, O., Akanuma, Y., Gavrilo, O., Vinson, C., Reitman, M.L., Kagoshima, H., Shudo, K., Yoda, M., Nakano, Y., Tobe, K., Nagai, R., Kinura, S., Tomita, M., Froghol, P., and Kadowaki, T.: The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. Nat. Med., 7, 941–946, 2001.

29. Yamauchi, T., Kamon, J., Minokoshi, Y., Ito, Y., Waki, H., Uchida, S., Yamashita, S., Noda, M., Kita, S., Ueki, K., Eto, K., Akanuma, Y., Froghol, P., Foufelle, F., Ferre, P., Carling,
D., Kimura, S., Nagai, R., Kahn, B.B., and Kadowaki, T.: Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. *Nat. Med.*, **8**, 1288–1295, 2002.

[38] Weyer, C., Funahashi, T., Tanaka, S., Hotta, K., Matsuzawa, Y., Pratley, R.E., and Tataranni, P.A.: Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. *J. Clin. Endocrinol. Metab.*, **86**, 1930–1935, 2001.

[39] Dandona, P., Thusu, K., Cook, S., Snyder, B., Makowski, J., Armstrong, D., and Nicotera, T.: Oxidative damage to DNA in diabetes mellitus. *Lancet*, **347**, 444–445, 1996.

[40] Hinokio, Y., Suzuki, S., Hirai, M., Chiba, M., Hirai, A., and Toyota, T.: Oxidative DNA damage in diabetes mellitus: its association with diabetic complications. *Diabetologia*, **42**, 150–152, 1999.

[41] Leinonen, J., Lehtimäki, T., Toyokuni, S., Okada, K., Tanaka, T., Hiia, H., Ochi, H., Laippala, P., Rantalaiho, V., Wirta, O., Pasternack, A., and Alho, H.: New biomarker evidence of oxidative DNA damage in patients with non-insulin-dependent diabetes mellitus. *FEBS Lett.*, **417**, 150–152, 1997.

[42] Loft, S., Fischer-Nielsen, A., Jeding, I.B., Vistisen, K., and Poulsen, H.E.: 8-Hydroxydeoxyguanosine as a urinary biomarker of oxidative DNA damage. *J. Toxicol. Environ. Health*, **40**, 391–404, 1993.

[43] Monnier, L., Mas, E., Ginet, C., Michel, F., Villon, L., Cristol, J.P., and 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.

[44] Giugliano, D., Ceriello, A., and Paolisso, G.: Oxidative stress and diabetic vascular complications. *Diabetes Care*, **19**, 257–267, 1996.