

OBSERVATIONS

Association Between Vitamin D Receptor Genotype and Age of Onset in Juvenile Japanese Patients With Type 1 Diabetes

1,25-dihydroxyvitamin D₃ [1,25(OH)₂D₃] not only regulates calcium metabolism but also modulates the immune system. Some reports have suggested that 1,25(OH)₂D₃ helps to prevent the development of type 1 diabetes. The association between the vitamin D receptor (VDR) genotype and susceptibility to type 1 diabetes has been examined, but a definitive conclusion has not yet been reached (1,2). We examined the VDR genotype in juvenile Japanese patients with type 1 diabetes.

A total of 108 diabetic patients (41 boys and 67 girls, age of onset 0.4–18 years with a median age of 8.9) and 120 nonrelated nondiabetic subjects were studied. Three polymorphic restriction fragment–length polymorphisms (RFLPs), i.e., Fok I, ApaI, and TaqI, were genotyped by PCR-RFLP method. The genotype or allele frequencies were compared statistically by the χ^2 test. The significance of differences in each genotype for the age of onset was tested with the Mann-Whitney *U* test.

Among the patients, the FF (*n* = 50) and tt (*n* = 5) genotypes were found relatively frequently, and aa (*n* = 46) was infrequent compared with those in control subjects, but these differences were not statistically significant (*P* = 0.14, 0.18, and 0.38 for FF, tt, and aa genotypes, respectively). There was also no significant difference in the allele frequency of each polymorphism, although the incidence of the F allele tended to be higher in the diabetic patients (*P* = 0.051). Concerning the age of onset of diabetes, patients with the ff genotype (*n* = 12, median 5.2 years, range 1.7–11.0) were significantly younger at onset than those with FF (*n* = 50, 9.7 years, 0.4–15.9, *P* = 0.01) or Ff (*n* = 46, 8.9 years, 0.9–18.0, *P* = 0.03). No significant

association was observed between the TaqI or ApaI genotype and the age of onset.

The ff genotype has been reported to be associated with a lower expression of VDR mRNA and reduced inhibition of phytohemagglutinin-stimulated growth of peripheral blood mononuclear cells. Thus, the Fok I genotype may influence the rate of the progression of insulinitis by modifying the autoimmune process, which may have led to the significant difference in the age of onset. The relatively high frequency of the F allele in diabetic patients, which has also been found in Japanese adult diabetic patients (2), is apparently inconsistent with this observation. A possible explanation is that the impact of Fok I polymorphism may not be strong enough to prevent the progression of autoimmune insulinitis into overt diabetes and thus does not influence susceptibility to the disease itself.

In conclusion, VDR gene polymorphism does not appear to have a strong enough impact to clearly influence susceptibility to the disease itself, but Fok I polymorphism might influence the age of onset of diabetes in juvenile Japanese diabetic patients.

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The Cost of Self-Monitoring of Blood Glucose Is an Important Factor Limiting Glycemic Control in Diabetic Patients

Maintenance of near normoglycemia can delay or prevent microvascular complications, but it cannot be carried out without a program of patient education, including self-monitoring of blood glucose (SMBG) (1,2). Motivation toward SMBG depends on several ill-defined factors, and there is no consensus on the effectiveness of SMBG in diabetes management (3–6).

We undertook a single-blinded, control-matched, longitudinal study of patients with insulin-requiring diabetes (*n* = 62) to examine barriers to SMBG and determine whether eliminating the cost barrier would increase SMBG frequency and glycemic control. Eligibility criteria were insulin treatment with at least two injections/day for at least 1 year (1), HbA_{1c} >120% of upper limit of normal (2), and recent diabetes education (3). The patients completed questionnaires reporting their habitual SMBG frequency, perceived barriers to SMBG, monthly income, and any private health insurance plans to verify coverage for glucometer reagents. They were randomly assigned in a patient-blinded fashion to two groups of 31 patients each, matched for age, sex, education, income, private health insurance coverage, diabetes type, diabetes duration, number of years on insulin, habitual SMBG frequency, random blood glucose, HbA_{1c}, and number of daily insulin injections. They were asked to participate in the study over a period of 12 months, with second monthly visits to the research nurse, and they were instructed in the use of the glucometer DEX (Bayer, Etobicoke, Canada), but they were not

given any information on how frequently they should self-monitor. A glucometer and 50 strips were supplied to one group of patients (control or C group), who were instructed to purchase additional strips as needed. A glucometer and 100 strips/month were given to the second group (no-cost or NC group). At each visit, random blood glucose and HbA_{1c} were measured, familiarity with the glucometer was checked, and the glucometer memory was downloaded using a computer software program (WinGlucofacts; Bayer, Elkhart, IN). No feedback was provided to the patient. Because of the small number of patients and the similar representation of diabetes types in both groups, the data were combined for statistical analysis.

At entry, patients indicated that they were not self-monitoring more often because testing was not convenient (47%), strips were too expensive (31%), they could feel their own blood glucose without testing (21%), testing was too painful (14%), or testing did not help (10%). Totals of 16 and 25 patients in the C and NC groups, respectively, completed the study (dropout rates of 48 and 19%, respectively). At the end of the study, the remaining patients indicated that testing was not convenient (29%), they could feel their own blood glucose without testing (20%), testing was too painful (17%), strips were too expensive (10%), or testing did not help (7%). The stated reasons were not significantly different between groups.

Glucometer-recorded SMBG frequency increased with time and was higher in the NC than in the C group (2.0 ± 0.2 vs. 1.4 ± 0.1 during the first 4 months, $P < 0.05$). Insulin dose increased ~ 1.5 -fold in the C group (58.5 ± 6.9 to 75.1 ± 12.1 unit/day, $P < 0.05$) but not in the NC group (52.5 ± 3.0 to 52.6 ± 3.4 units/day). HbA_{1c} initially decreased in both groups and then increased in the C group, and final HbA_{1c} was lower in the NC than in the C group (8.7 ± 0.3 vs. $9.9 \pm 1.1\%$, $P < 0.01$). Average blood glucose at the end of the study was also lower in the NC than in the C group (205.2 ± 10.6 vs. 252.0 ± 39.6 mg/dl, $P < 0.05$).

Thus, although inconvenience was the main reported barrier to SMBG, cost was an important factor, perhaps explaining the higher dropout rate in the C than in the NC group. The simple strategy of

supplying free strips increased compliance with SMBG and enhanced diabetes self-management. Overall, patients who were given free strips had lower HbA_{1c} and average blood glucose and insulin doses versus control subjects.

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Association Between Plasma Thrombin-Activatable Fibrinolysis Inhibitor Levels and Activated Protein C in Normotensive Type 2 Diabetic Patients

Hypofibrinolysis is a common finding in patients with diabetes and a risk factor for the occurrence of micro- and macroangiopathy (1–3). Recently, a new potent inhibitor of fibrinolysis, the thrombin-activatable fibrinolysis inhibitor (TAFI) was isolated from human plasma (4). It has been reported that the plasma levels of TAFI are increased in diabetic patients, and it may play an important role in the mechanism of hypofibrinolysis observed in these patients (5).

Activated protein C (APC) is a serine protease that inhibits thrombin formation by proteolytically inactivating factors Va and VIIIa and by stimulating fibrinolysis (6,7). Thrombin stimulates the conversion of TAFI in its active form. APC may indirectly promote fibrinolysis by inhibiting thrombin generation and by inhibiting the action of plasminogen activator inhibitor-1 (7,8). Both TAFI and APC are regulated by thrombin-thrombomodulin complex on the plasma membrane of endothelium (6). This mechanism appears to be important for controlling the balance between coagulation and fibrinolysis in diabetic patients. In the present study, we investigated the plasma levels of TAFI and its relationship with APC in normotensive type 2 diabetic patients.

Forty normotensive (<140/90 mmHg) nonobese type 2 diabetic patients (28 men and 12 women, aged 54.7 ± 1.8 years [means \pm SE], BMI 22.5 ± 0.4 kg/m², diabetes duration 9.1 ± 1.1 years, systolic blood pressure 129.1 ± 2.1 mmHg, diastolic blood pressure 77.0 ± 1.6 mmHg, fasting blood glucose levels 8.59 ± 0.32 mmol/l, and HbA_{1c} $9.1 \pm 0.3\%$) with normal hepatic function and without any medication that may influence blood coagulation profile were enrolled in the present study. There were 30 patients with normoalbuminuria (albumin excretion rate 8.6 ± 0.6 μ g/min) and 10 with microalbuminuria (47.6 ± 6.9

μg/min). No patient had cardiovascular autonomic neuropathy. Twenty six patients were being treated with diet therapy alone, 14 with oral hypoglycemic agents, but none with thiazolidine. Twenty age-matched nonobese healthy individuals (16 men and 4 women) were used as control subjects.

The plasma levels of TAFI were measured using a commercially available EIA kit (TAFI-EIA; Kordia Laboratory Supplies, Leiden, the Netherlands) (5). APC-PCI complex, a marker of ongoing protein C (PC) activation, was measured by enzyme-linked immunoassay as described (9). PC antigen was measured by solid-phase immunoassay as described (9). Total protein S (PS), which is a cofactor for activation of PC, was measured as reported (9). The plasma levels of the thrombin-antithrombin complex (TAT) were measured by EIA method as described (9). The plasma levels of D-dimer (DD) were measured by a commercial EIA kit (D-dimer test-F; Kokusai-Shiyaku, Kobe, Japan).

The ratio between the plasma concentrations of DD and TAT complex (DD/TAT), an index of fibrinolytic activity, was significantly decreased in diabetic patients compared with healthy subjects (15.3 ± 1.3 vs. 26.5 ± 2.2 , $P < 0.05$). The plasma levels of TAFI were significantly higher (139.1 ± 10.3 vs. $99.5 \pm 4.9\%$, $P < 0.05$) in diabetic patients than in normal subjects. The plasma levels of APC-PCI were significantly higher (3.36 ± 0.28 vs. 2.17 ± 0.48 pmol/l, $P < 0.05$) in diabetic patients than in normal subjects. The plasma levels of TAFI were positively and significantly correlated with the plasma levels of APC-PCI ($r = 0.53$, $P < 0.001$) in diabetic patients. There was significant correlation between the plasma levels of TAFI and PS in diabetic patients ($r = 0.50$, $P < 0.005$). There was no significant correlation between TAFI and PC antigen levels ($r = 0.04$).

The thrombomodulin-thrombin complex formed on the plasma membrane of endothelium exerts anticoagulant activity by catalyzing the conversion of PC to activated APC, which inhibits activation of blood coagulation (6,7). On the other hand, this thrombomodulin-thrombin complex may also promote coagulation by activating TAFI (6). Activated TAFI inhibits fibrinolysis by removing COOH-terminal lysine residues from

fibrin. Lysine residues are high affinity binding sites for plasminogen, which is a precursor of plasmin, the key serine protease for fibrinolysis (10). In the present study, the DD/TAT ratio was significantly decreased in diabetic patients compared with healthy control subjects, suggesting the occurrence of hypofibrinolysis in diabetes. This decrease in fibrinolytic activity may be related to the increase in the plasma levels of TAFI.

Interestingly, the circulating levels of TAFI were significantly correlated with those of APC-PCI complex, a marker of APC generation. It has been reported that APC improves decrease of fibrinolytic activity induced by TAFI in vitro (11,12). The fact that circulating levels of TAFI and APC-PCI complex are significantly correlated suggests that APC may promote fibrinolysis in diabetic patients by modulating the action of TAFI. However, the significant decrease of DD/TAT in diabetic patients compared with control subjects suggests that APC may not be sufficient for suppressing the decrease in fibrinolytic activity in diabetes.

This insufficient activity of APC may be due to an imbalance between the thrombomodulin-mediated activity of both TAFI and PC in favor of the former. In brief, PC activation may be important for the regulation of TAFI-induced hypofibrinolysis in diabetes.

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Metabolic Syndrome in American Indians

The National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP III]) recently proposed a formal definition of the metabolic

(insulin resistance) syndrome (1). For the purposes of ATP III, metabolic syndrome is present when ≥ 3 of the following determinations are present: waist circumference >102 or >88 cm in men and women, respectively; triglycerides ≥ 150 mg/dl; HDL cholesterol <40 or <50 mg/dl in men and women, respectively; blood pressure $\geq 130/\geq 85$ mmHg; and fasting glucose ≥ 110 mg/dl.

Data from the Third National Health and Nutrition Examination Survey (NHANES III) show that among U.S. adults ≥ 20 years of age, metabolic syndrome is present in 23.8, 21.6, and 31.9% of whites, blacks, and Hispanics, respectively (2). NHANES III does not include data for American Indians. The baseline examination of the Strong Heart Study (SHS), a longitudinal, population-based study of cardiovascular disease (CVD) and CVD risk factors in 4,549 American Indians, was concurrent with NHANES III. Therefore, SHS data provide a unique opportunity to contrast the dramatic ethnic differences in prevalence of metabolic syndrome between American Indians and other ethnic groups in the U.S. The prevalence of metabolic syndrome in SHS men aged 45–49 years was 43.6% compared with 20.0% among all men in NHANES III, a prevalence ratio of 2.18. The prevalence of metabolic syndrome in SHS women in the same age group was 56.7% compared with 23.1% among NHANES III women, a ratio of 2.45.

Ethnic differences in prevalence of metabolic syndrome between SHS men and NHANES III men diminished with age, resulting in similar prevalence rates in the 60–69 and 70–74 age groups ($\sim 43\%$ for both SHS and men in both age groups). In contrast, the prevalence of metabolic syndrome in SHS women was considerably higher than that in NHANES III women, even in the older-aged participants. In the 60–69 and 70–74 age groups, the prevalence ratio contrasting SHS women to NHANES III women was 1.56. The overall prevalence of metabolic syndrome was 55.2% in SHS participants aged 45–74 years.

The lack of increase in metabolic syndrome with age in SHS men may reflect maintenance of a traditional lifestyle among men of older generations and/or selective mortality among less healthy older men. The high prevalence of metabolic syndrome among older SHS women may reflect relatively better survival with

CVD risk factors and/or earlier adoption of a sedentary lifestyle. Metabolic syndrome among American Indians is likely a combination of genetics (3) and environmental factors, such as low physical activity and obesity. The high prevalence of metabolic syndrome in American Indians may, in part, explain the rapidly increasing rates of CVD in this population (4). Additional efforts are needed to achieve desirable practice patterns that are sufficient to meet the needs of people with metabolic syndrome. This is especially pressing for American Indians, in whom the high prevalence of metabolic syndrome and increasing CVD rates underscore the need for effective treatment of risk factors.

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Fasting Hyperglycemia Predicts the Magnitude of Postprandial Hyperglycemia

Implications for diabetes therapy

Postprandial blood glucose is a strong predictor of HbA_{1c} levels and cardiovascular mortality (1–3). The treatment of postprandial hyperglycemia has become prominent with the recent availability of oral hypoglycemic agents that specifically target the postmeal glucose rise. The aim of this study was to examine the relationship between the fasting blood glucose level and the magnitude of the postprandial glucose rise in type 2 diabetes. Specifically, if the fasting blood glucose level is a determinant of the postprandial glucose excursion, then correction of fasting hyperglycemia should precede attempts at limiting postprandial hyperglycemia.

All results are expressed as means \pm SD. A total of 21 subjects (11 men and 10 women) with non-insulin-requiring type 2 diabetes and average glycemic control (HbA_{1c} $7.3 \pm 1.4\%$) were recruited. The subjects were aged 59.4 ± 11.1 years, were moderately obese (BMI 31.3 ± 5.5 kg/m²), and had been diagnosed with diabetes for 8.7 ± 8.8 years. Two of the patients were treated with diet and exercise alone, and the remaining 19 were taking one or two oral hypoglycemic agents for diabetes control ($n = 13$ for sulfonylureas, $n = 6$ for metformin, and $n = 3$ for thiazolidinediones).

Subjects were admitted overnight to the General Clinical Research Center for stabilization. At 2200, subjects ate a 5-kcal/kg American Diabetes Association (ADA) snack and then fasted until morning. The volunteers' diabetes medications were withheld on the morning of the study. Between 0800 and 0815, the subjects ate a standardized 8-kcal/kg ADA breakfast. The breakfast was prepared in the metabolic kitchen and consisted of an English muffin, bacon, a scrambled egg, and a noncaffeinated beverage. Blood was drawn for analysis at -0.05 , 0, 0.5, 1, 2, 3, and 4 h relative to the test meal. Plasma

glucose was analyzed using the glucose oxidase method. The glucose excursion at each time point was expressed as the change from the fasting plasma glucose level. Area under the curve (AUC) for the glucose excursion was calculated using the linear trapezoidal rule. The relationship between the fasting plasma glucose level and the postprandial glucose excursions was analyzed using linear regression.

The average fasting plasma glucose was 7.4 ± 2.4 mmol/l (135 ± 43 mg/dl), with a range of 4.3–14.3 mmol/l (78–259 mg/dl). The fasting plasma glucose level was strongly correlated with the 30-min ($r = 0.86$, $P < 0.001$), 1-h ($r = 0.9$, $P < 0.001$), 2-h ($r = 0.89$, $P < 0.001$), 3-h ($r = 0.84$, $P < 0.001$), and 4-h ($r = 0.89$, $P < 0.001$) absolute postmeal plasma glucose levels and with the integrated AUC ($r = 0.93$, $P < 0.001$) for the absolute postmeal plasma glucose levels (not baseline corrected). Furthermore, the fasting plasma glucose level had a strong positive correlation with the 1-h ($r = 0.55$, $P = 0.01$), 2-h ($r = 0.7$, $P < 0.001$), 3-h ($r = 0.59$, $P = 0.005$), and 4-h ($r = 0.6$, $P = 0.004$) glucose excursions from baseline. Overall, the correlation between the fasting plasma glucose and the AUC for the postprandial glucose excursion was highly significant ($r = 0.71$, $P < 0.001$).

We conclude that the fasting plasma glucose level predicts the degree of postmeal hyperglycemia and the magnitude of the postmeal glucose excursion from baseline. It is not surprising that the uncorrected postmeal glucose levels are strongly related to the premeal baseline glucose concentration. However, the observation that the prandial glycemic excursion from baseline is predicted by the fasting plasma glucose level is more relevant to decisions regarding diabetes therapy. The premeal glucose concentration accounts for 50% of the variability in the postmeal glucose rise in subjects with non-insulin-requiring diabetes. The remaining variability in glycemic responses after a standardized meal could be explained by relatively fixed factors, such as the renal threshold for glycosuria, endogenous insulin reserves, and the gastric emptying time.

The strength of this study is that participants had a wide range of fasting blood glucose levels with HbA_{1c} values close to targets recommended by the ADA. The subjects enrolled in this study were taking standard oral hypoglycemic agents, in-

cluding sulfonylureas, metformin, and thiazolidinediones, until the morning of the study and were tested after a standardized meal. Our results extend a recently published study that employed non-standardized meals and variable medications (4). In that study, the investigators found a weaker correlation between the fasting and absolute postbreakfast glucose levels ($r = 0.64$, $P < 0.01$). A small number of studies have shown equivalent reductions in HbA_{1c} regardless of whether treatments were used to specifically correct fasting or postprandial hyperglycemia (5–7). The outcomes of these studies suggest a carry over beneficial effect on premeal glucose levels when postmeal and nocturnal hyperglycemia is reduced with meal-based therapies. To date, no published studies have compared the glycemic response to a standardized meal in subjects with type 2 diabetes where each subject was studied at varying levels of fasting glucose.

The importance of the current study to health care providers is that it shows that the postmeal glucose excursion is directly related to overnight fasting blood glucose concentration. Data from this study suggest that, in order to improve overall glycemic control, fasting hyperglycemia should be corrected before starting specific treatment for postprandial hyperglycemia in subjects with non-insulin-requiring type 2 diabetes. Because correction of fasting hyperglycemia may be easier to achieve (in some patients) than correction of postprandial hyperglycemia, this strategy may result in improved overall glycemic control at reduced medication cost.

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Dysfunction of Active Transport of Blood-Retinal Barrier in Patients With Clinically Significant Macular Edema in Type 2 Diabetes

Diabetic macular edema (DME), which causes retinal thickening, is a main cause of visual impairment in patients with diabetes (1,2). The important pathophysiology of DME is the loss of retinal capillary pericytes, resulting in increased vascular permeability of the blood-retinal barrier (BRB) (3). However,

there is only one report about the active transport of the BRB in patients with DME (4). The aim of this study was to evaluate the active transport of the BRB in patients with clinically significant diabetic macular edema (CSME) (5) in type 2 diabetes using differential vitreous fluorophotometry (DVF).

We studied six eyes of six patients with type 2 diabetes with CSME (age range 53–70 years, mean 63 years), five eyes of five patients with type 2 diabetes without CSME (age range 64–73 years, mean 69 years), and seven eyes of seven normal subjects (age range 58–66 years, mean 62 years). Informed consent was obtained from all subjects. All procedures adhered to the tenets of the Declaration of Helsinki. The eyes were diagnosed based on the findings of a best-corrected visual acuity, slit-lamp biomicroscopy, indirect ophthalmoscopy, fundus photography, and fluorescein angiography (5).

Fluorescein (F) and fluorescein monoglucuronide (FG) concentrations in the vitreous were determined using DVF modified Fluorotron Master (OcuMetrics, Mountain View, CA). The fluorescence readings were converted to F and FG concentrations using the methods of McLaren et al. (6). DVF was performed 120 min after intravenous injection of 14 mg/kg sodium fluorescein. The F/FG ratio, a good indicator of the estimated active transport of the BRB, was calculated based on the concentration of F and FG in the vitreous obtained by DVF (7). If the active transport of the BRB is low, the F/FG ratio increases. We compared the F/FG ratio in the three groups using one-way ANOVA and Scheffe's test.

The F/FG ratio in the control subjects, the patients without CSME, and the patients with CSME were 0.42 ± 0.32 (0.13–0.95), 0.50 ± 0.34 (0.10–0.80), and 2.84 ± 1.20 (1.13–4.12), respectively. The F/FG ratio was markedly higher in the patients with CSME than in the control subjects ($P = 0.0001$) and in the patients without CSME ($P = 0.0004$).

This result indicates directly and clinically the active transport dysfunction of the BRB in the patients with CSME. We reported the abnormal inward permeability of the retina caused by BRB breakdown in patients without CSME with diabetes using vitreous fluorophotometry (8). However, in the present study, the active transport of the BRB was normal in the patients without CSME. Dysfunctional

active transport of the BRB may not be found until DME develops. The abnormality of the active transport of the BRB may be a pathogenic mechanism of DME. The pharmacologic normalization of the active transport of the BRB may be the future treatment of DME.

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Necrobiosis Lipodica Is a Clinical Feature of Maturity-Onset Diabetes of the Young

Necrobiosis lipodica (NL) is a recognized feature of diabetes affecting 0.3–1.2% of patients (1,2). It presents with elevated, erythematous lesions (usually on the shins), which typically become atrophic in the center over time. It is most commonly seen in patients with type 1 diabetes, but 7–30% of diabetic patients with NL have type 2 diabetes (1–3). This gives a prevalence of NL of 6.5% in patients with type 1 diabetes and 0.4% in patients with type 2 diabetes. Numerous underlying mechanisms have been proposed, including vascular dysfunction, autoimmunity, and genetic factors (4).

Maturity-onset diabetes of the young (MODY) is a subtype of non-insulin-dependent diabetes characterized by a young age of onset (usually before 25 years), autosomal dominant inheritance, and β -cell dysfunction. Mutations in five genes have been found to cause MODY: glucokinase, hepatocyte nuclear factor (HNF)-1 α , HNF-4 α , HNF-1 β , and insulin promoter factor-1 (5). Two family members from a Chinese family with an HNF-1 α mutation have been described with diabetes and NL (6). There have been no studies looking at the prevalence and course of NL in MODY.

We reviewed the records of 178 patients from 108 families referred to Exeter fitting the clinical criteria for MODY (diagnosis <25 years and three-generation history of diabetes with autosomal dominant inheritance). If evidence of a rash was noted, further details were collected from the patient and clinical records.

Five patients (three female) from five families had a rash typical of NL (confirmed on biopsy in one patient), giving a prevalence of 2.8%. The mean age of onset of NL was 19 years (range 15–25 years). Onset varied between 3 years before and 5 years after diagnosis of diabetes. The diagnosis of NL led directly to the diagnosis of diabetes in two patients. Patients had good glycemic control, and no

other diabetic complications were present at diagnosis of NL. In two patients the rash resolved within 1 year, whereas there has been no improvement for the other three patients (17–43 years after diagnosis). Mutations in the HNF-1 α gene have been found by direct sequencing in three patients (P291fsinsC, R159Q, and R54X), one patient declined genetic testing, and in the fifth patient direct sequencing of the full coding region and minimal promoter of the HNF-1 α and HNF-4 α genes has failed to identify a mutation.

We have shown that NL is a feature of MODY in 2.8% of patients, a prevalence lower than that seen in type 1 diabetes (6.5%) and higher than that found in type 2 diabetes (0.4%) (1–4). This higher prevalence of NL in MODY compared with type 2 diabetes may be caused by selection bias in a well-characterized group.

The MODY patients described here developed NL early in their disease course, often before diagnosis of diabetes; their glycemic control was good, and other diabetic complications were not present. This is in contrast with other reports that have suggested an association with microvascular complications (7,8). The finding of NL in this monogenic form of diabetes makes a specific etiology related to a type of diabetes, such as autoimmunity, unlikely.

We conclude that NL is a feature of diabetes due to MODY. If NL is found in a young nonobese diabetic patient, a diagnosis of MODY as well as type 1 diabetes should be considered, especially in the presence of a family history.

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Atorvastatin, Diabetic Dyslipidemia, and Cognitive Functioning

Cognitive functioning is reduced in patients with type 2 diabetes as compared with age-matched patients without diabetes (1). In particular, verbal memory and complex information processing are affected in patients with diabetes, which has an impact on daily functioning (2). The severity of cognitive dysfunction in patients with diabetes presumably results from an interaction be-

tween risk factors for macro- and microvascular disease (3). Previous studies suggest a positive association between indexes of cognitive impairment and elevation of plasma triglyceride level (4,5). The effect of lowering serum triglyceride levels by gemfibrozil on cognitive functioning has been investigated in elderly hypertriglyceridemic patients (11 of the 44 patients had diabetes). Lowering triglyceride levels appeared beneficial to cerebral perfusion and cognitive performance after 4–6 months (6). Therefore, we studied in the Diabetes Atorvastatin Lipid Intervention (DALI) study (7), the effect of atorvastatin on diabetic dyslipidemia and cognitive functioning. Thirty patients with diabetes, aged 45–75 years, with fasting triglycerides between 1.5 and 6.0 mmol/l and total cholesterol levels between 4.0 and 8.0 mmol/l, and without ischemic heart and cerebrovascular disease were included. Patients received placebo ($n = 8$), 10 mg atorvastatin ($n = 7$), or 80 mg atorvastatin ($n = 11$) during 30 weeks. Two patients withdrew before the end of the study for personal reasons, and two patients withdrew because of protocol violation. Fasting lipids and neuropsychological tests were assessed at baseline and after 30 weeks. The neuropsychological test-battery was composed in line with the findings of previous studies with comparable groups (1). Orientation and auditory-verbal memory were tested, as well as attention, psychomotor speed, and executive functioning. Furthermore, we estimated premorbid intelligence with the Dutch version of the National Adult Reading Test (NLV). Baseline characteristics, lipids, and neuropsychological tests results did not differ between the intervention groups. The mean HbA_{1c} was $8.1 \pm 1.0\%$, and the diabetes duration was 8.9 ± 5.9 years. Atorvastatin 10 and 80 mg respectively reduced plasma triglyceride by 19 and 39%, total cholesterol by 27 and 42%, and LDL cholesterol by 36 and 56%. The baseline results of the auditory-verbal memory test were below mean (i.e., ≥ 1 SD) in 71% of the study population, in comparison with the normative data (8). The baseline results on the other neuropsychological tests did not differ from a nondiabetic population. The verbal memory test (CVLT) improved 24% (a mean of seven extra words) after 30 weeks of treatment with atorvastatin 80 mg. In the atorvastatin 10 mg group, the CVLT

improved only 8% (a mean of two extra words), and in the placebo group, no effect was observed. Verbal memory improvement correlated with an increase in HDL cholesterol ($r = 0.67$, $P < 0.05$), a reduction in LDL cholesterol ($r = -0.34$, $P < 0.05$), and a reduction in triglycerides ($r = -0.34$, $P = 0.07$) after adjustment for age, baseline HDL cholesterol, LDL cholesterol, triglycerides, and verbal memory in the entire population. Atorvastatin did not affect psychomotor speed, attention, and executive functioning.

To summarize, in this small cohort of hyperlipidemic patients with type 2 diabetes who were treated with atorvastatin, verbal memory improvement was associated with improvement of the diabetic dyslipidemia profile. Low- and high-dose atorvastatin had no significant effect on cognitive functioning.

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Rosiglitazone in Combination With Glimepiride Plus Metformin in Type 2 Diabetic Patients

Type 2 diabetic patients are often treated with a combination of antidiabetic agents. The need to use drugs with different and complementary mechanisms of action frequently arises in daily clinical practice. There are several reasons to do this; namely, the disease itself is progressive, with deterioration of glycemic control over time, and monotherapeutic attempts to achieve and maintain glycemic control often fail in the long run (1,2).

Some patients do not accept insulin treatment because of the fear of needles and injections, the fear that the complications of diabetes are caused by insulin, and other false beliefs, and are willing to take as many antidiabetic pills the doctor is prepared to prescribe.

The combination of a sulfonylurea with metformin is commonly used in clinical practice. But when this potent combination is no longer able to provide acceptable glycemic control, the addition of an antidiabetic drug with a different mode of action may lead to improved metabolic control.

The peroxisome proliferator-activated receptor- γ (PPAR- γ) agonist rosiglitazone has been shown to produce significant improvement in glycemic control when administered to patients who were inadequately controlled on the combination of glibenclamide and metformin (3). Similar findings were obtained in a trial with troglitazone, the first member of the thiazolidinedione class of antidiabetic agents. In a

double-blind placebo-controlled trial, the addition of troglitazone in a therapeutic regimen of sulfonylurea and metformin in inadequately controlled type 2 diabetic patients led to significant improvement in glycemic control (4). The trial was completed before troglitazone was taken off the market because of hepatotoxicity.

We examined the efficacy of rosiglitazone when added to a therapeutic regimen of glimepiride and metformin in type 2 diabetic patients.

A total of 38 Greek diabetic patients inadequately controlled on maximum doses of glimepiride (6 mg/day) and metformin (2,550 mg/day) were given rosiglitazone. There were 20 men and 18 women, the mean age was 58.6 ± 8.1 (mean \pm SD), diabetes duration was 10.5 ± 6 years, and BMI was 31 ± 4.8 kg/m². The patients were divided into two groups. In the first group (19 patients), the dose of rosiglitazone was 4 mg/day, whereas in the second group (19 patients), the dose was 8 mg/day.

HbA_{1c} levels were measured by high-performance liquid chromatography. Paired *t* testing was used for statistical analysis, and $P < 0.05$ was considered significant. Twenty weeks after the addition of rosiglitazone there was a statistically significant decrease in HbA_{1c} levels in both groups.

In the first group of patients, the average HbA_{1c} before the treatment modification was $8.9 \pm 1.1\%$ and baseline fasting plasma glucose (FPG) was 10.7 ± 2.2 mmol/l. After the treatment modification HbA_{1c} was $7.8 \pm 0.9\%$ ($P < 0.001$) and FPG 8.9 ± 1.2 mmol/l ($P < 0.0001$). In the second group, the average baseline HbA_{1c} was $9 \pm 1.1\%$ and the baseline FPG was 10.8 ± 2.3 mmol/l. After the treatment modification, HbA_{1c} was 7.6 ± 0.8 ($P < 0.0001$) and FPG was 7.9 ± 1 mmol/l ($P < 0.0001$).

The treatment with rosiglitazone was well tolerated. Hypoglycemia was the most frequent side effect in both patient groups (18.6% at 4 mg/day and 28% at 8 mg/day). The dose of glimepiride and/or metformin was reduced in patients with hypoglycemic episodes, and the reduction proved to be effective in avoiding hypoglycemic reactions. Mean body weight increased in both rosiglitazone groups (4.2 kg at 4 mg/day and 4.6 kg at 8 mg/day).

Rosiglitazone treatment has rarely

been associated with severe liver reactions (5–7). No symptoms or signs of liver disease were observed, and no change in liver function tests was noted in the patients in our treatment groups for the 20-week period of follow-up.

Our findings are in accordance with those of other investigators who found that in inadequately controlled type 2 diabetic patients, on treatment with a sulfonylurea and metformin, the addition of rosiglitazone produces significant improvement in glycemic control and is safe and well tolerated (3).

Given the analogous results obtained with troglitazone, it is very possible that this is a class effect of thiazolidinediones and not a specific action of rosiglitazone. However, a major issue is whether hepatotoxicity is a class characteristic of all thiazolidinediones related at least partly to the activation of PPAR- γ receptors, or whether it is unique to troglitazone and thus spares newer glitazones, such as rosiglitazone and pioglitazone.

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Preobesity in World Health Organization Classification Involves the Metabolic Syndrome in Japanese

Obesity has increased at an alarming rate throughout the world and has been regarded as a global epidemic disease in light of its close association with a cluster of cardiovascular risk factors, including hypertension, dyslipidemia, and hyperglycemia. This clustering of metabolic disorders is known as the metabolic syndrome, which is associated with insulin resistance (1). BMI is an estimate of total body fat mass and is probably the most useful scale to define obesity. Obesity has been defined as a BMI >30.0 kg/m² in World Health Organization (WHO) classification (2), but this does not take into account the morbidity and mortality associated with more modest degrees of overweight. A significant increase in risk of death from cardiovascular disease was found for all BMIs of >25.0 kg/m² in women and >26.5 kg/m² in men in a prospective study conducted in the U.S. (3). The relation between BMI up to 30.0 kg/m² and the relative risk of several chronic conditions caused by excess body fat, including type 2 diabetes, hypertension, coronary heart disease, and cholelithiasis, appears to be approximately linear (4). In Japan and most other Asian countries, a pronounced increase in the prevalence of overweight and obesity has been observed during the past two decades (5). Although the Japanese are often considered to be nonobese com-

pared with Caucasians, because of the differences in the prevalence of obesity and BMI distribution, the clustering of cardiovascular risk factors is thought to occur in this relatively lean population as well.

To investigate whether an increment in body weight increases the risk of metabolic complications in the Japanese, we studied the relation of a graded classification of obesity using BMI values based on the WHO classification to components of the metabolic syndrome, including the levels of fasting plasma glucose (FPG), total cholesterol (TC), triglycerides (TGs), high-density lipoprotein cholesterol (HDL-C), blood pressure, and uric acid. In a population-based cross-sectional study of 1,559 healthy adults (1,169 men, 390 women) aged 35–60 years who underwent annual health examinations in 1998, we classified the subjects into four groups: underweight (BMI <18.5 kg/m², $n = 113$), normal (18.5–24.9 kg/m², $n = 1,086$), preobese (25.0–29.9 kg/m², $n = 323$), and class I obese (30.0–34.9 kg/m², $n = 37$) based on the WHO classification (Table 1). Venous blood was sampled after an overnight fast for routine laboratory investigations. Comparisons between groups were performed with Bonferroni's multiple comparison test. In our study the prevalence of BMI ≥ 25.0 kg/m² was 23.1%, and that of BMI ≥ 30 kg/m² was 2.4%. All but one of the components were significantly higher (only HDL-C was lower) for the preobese group compared with the normal group ($P < 0.001$). These components were also higher for the normal group than for the underweight group, except for TGs ($P < 0.01$). No statistically significant differences were observed among any of the parameters except for systolic blood pressure in the preobese and class I obese groups, whereas there were differences in all of the parameters besides TC ($P = 0.09$) between class I obese and normal groups ($P < 0.05$) (Table 1). This means that a significant increase in all of the components of the metabolic syndrome was recognized in preobesity defined as BMI 25.0–29.9 kg/m² in the WHO classification. However, no BMI-related differences in FPG, TC, TGs, HDL-C, diastolic blood pressure, and uric acid were observed between preobesity and class I obesity. Therefore, abnormalities in these parameters seem to reach a plateau before the BMI reaches 30.0 kg/m², although this

Table 1—Metabolic parameters by grade of obesity defined by a WHO expert committee

BMI (kg/m ²)	WHO classification	n	FPG (mg/dl)	TC (mg/dl)	TG (mg/dl)	HDL-C (mg/dl)	Systolic BP (mmHg)	Diastolic BP (mmHg)	Uric acid (mg/dl)
<18.5	Underweight	113	88 ± 11	178 ± 28	79 ± 24	62 ± 14	118 ± 13	70 ± 10	4.8 ± 1.2
18.5–24.9	Normal	1,086	92 ± 15*	196 ± 33*	113 ± 77	56 ± 13*	122 ± 14*	73 ± 10*	5.3 ± 1.4*
25.0–29.9	Preobese	323	96 ± 14†	207 ± 34†	167 ± 111†	48 ± 9.8†	128 ± 13†	78 ± 10†	6.0 ± 1.3†
30.0–34.9	Class I obese	37	98 ± 18	205 ± 38	179 ± 122	47 ± 8.4	133 ± 12‡	81 ± 10	6.5 ± 1.5

Values are means ± SD. *P < 0.01 (versus underweight); †P < 0.001 (versus normal); ‡P < 0.01 (versus preobese). BP, blood pressure.

finding should be confirmed in a larger population study.

Thus, 1) the risk of metabolic syndrome is significantly related to the degree of obesity, 2) underweight appears to be more preventive against the metabolic syndrome than normal weight, and 3) preobesity in the WHO classification involves increased cardiovascular risk factors for the Japanese. Therefore, a lower BMI at 25.0 kg/m² should be used for the Japanese population to estimate the prevalence of obesity and to identify the high-risk groups for cardiovascular disease. Racial differences should thus be taken into account when defining obesity, and we propose a BMI of 25.0 kg/m² as the optimal cutoff point for obesity in Japanese and presumably other Asian populations.

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Prevalence of Metabolic Syndrome Among HIV Patients

Recently published observations (1) suggest that among HIV-positive patients treated with highly active antiretroviral therapy (HAART), the incidence of cardiovascular diseases is increased. Until now, no specific risk factors have been identified except for those related to behavior or metabolic abnormalities. So far, a sum of metabolic abnormalities have frequently been reported among these patients, including increased lipid levels, abnormal fat distribution, elevated blood pressure, and disturbance in glucose metabolism (2). Studies designed to identify subclinical atherosclerosis in HIV-infected patients on HAART have been inconclusive. Numerous modalities, including carotid intimal thickness measurement, brachial reactivity, and electron beam computed tomography, have shown varying results; at this time, it is unclear what the results mean. The metabolic syndrome is a cluster of risk factors (disturbance in glucose metabolism, central obesity, hypertension, and dyslipidemia) caused by insulin resistance (3,4). Metabolic syndrome is considered a powerful independent risk factor for cardiovascular morbidity and mortality (4). Insulin resistance is frequent among HIV patients on HAART (5), but there are no data about the prevalence of the metabolic syndrome in these patients.

We evaluated the prevalence of the metabolic syndrome in a large cohort of HIV patients on HAART. We studied 553 patients (321 men, 232 women) with a mean age of 37.1 ± 7.3 years (range 20–61). Metabolic syndrome has been defined according to criteria released by the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults III (3). In particular, HIV patients with three or more of the following risk factors were defined as having the metabolic syndrome: 1) high fasting glucose (≥6.1 mmol/l), 2) central obesity (waist circumference >102 cm in men and >88 cm in women), 3) hypertension (≥130/85 mmHg), 4) hypertriglyceridemia (≥1.69 mmol/l), and 5) low HDL (<1.04 mmol/l in men and <1.29 mmol/l in women) (3).

Among HIV patients, 133 (24.0%) showed high fasting glucose or antidiabetes medication use, 209 (37.8%) had central obesity, 234 (42.3%) showed hypertension, 328 (59.3%) showed hypertriglyceridemia, and 290 (52.4%) showed low HDL. One single risk factor was present in 108 (19.5%) patients, two in 95 (17.2%), three in 146 (26.4%), four in 67 (12.1%), and five in 38 (6.9%). Of the subjects, 99 (17.9%) showed no risk factors. We found that 251 patients had the metabolic syndrome (at least three risk factors), leading to a prevalence of 45.4%. This prevalence was more than twofold that reported recently by Ford et al. (6) in the general population and was even higher than that observed in subjects older than 60 years (6). Although we are referring to two different populations (Italian HIV patients and American adults), the difference in the prevalence of metabolic syndrome between a cohort of HIV patients on HAART and the general population appears to be very remarkable.

Our data show that among HIV pa-

tients, the prevalence of metabolic syndrome is impressively high, considering the mean age of our sample population; this finding could explain why HIV patients may have an increased risk for cardiovascular disease. Despite the improvement of prognosis related to HIV infection due to the effect of antiretroviral therapy, an increase of cardiovascular morbidity and mortality should be expected. In the years to come, cardiovascular diseases may become important clinical problems for HIV-infected patients, mainly because the cluster of risk factors defining the metabolic syndrome increases cardiovascular risk more than each single component (4). On this basis, a close monitoring of cardiovascular risk factors and their aggressive treatment in HIV patients to reduce cardiovascular-related morbidity and mortality appear necessary.

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Effect of Losartan on Plasma C-Reactive Protein in Type 2 Diabetic Patients With Microalbuminuria

Recent data suggest that the renin-angiotensin system may participate in inflammatory responses and that angiotensin II is a proinflammatory mediator in renal damage (1). An association between C-reactive protein (CRP), a sensitive marker of inflammation, and urinary albumin excretion in the microalbuminuric range has been reported in nondiabetic as well as type 2 diabetic subjects in the Insulin Resistance Atherosclerosis Study (2). Angiotensin II type 1 (AT₁) receptor antagonists have been shown to have a renal protective effect and to reduce proteinuria in type 2 diabetic patients with either microalbuminuria or overt nephropathy (3–5); therefore, we investigated whether the beneficial effects of these agents are partly mediated through an anti-inflammatory action as a result of angiotensin II blockade. We did this by evaluating the effect of losartan on plasma CRP levels in a group of type 2 diabetic patients with microalbuminuria.

Concentration of CRP was measured from stored plasma samples from a previous 6-month randomized double-blind placebo-controlled study investigating the effect of losartan (50 mg daily) on endothelial function in 80 type 2 diabetic patients with microalbuminuria. A full description of the design and methods has been published (6). Plasma CRP levels were measured at baseline and 6 months after treatment, and 80 nondiabetic control subjects matched for age, sex, BMI, and smoking status were recruited to establish a reference range for CRP. High-

sensitivity CRP (hs-CRP) was measured by a particle-enhanced immunoturbidimetric assay (Roche Diagnostics, Mannheim, Germany) using anti-CRP mouse monoclonal antibodies coupled to latex microparticles. Urinary mean albumin excretion rate (MAER) was determined from two consecutive 12-h overnight urine collections. Statistical analyses were performed using logarithmically transformed data because of their skewed distribution. Within-group comparisons were analyzed by paired *t* tests, and between-group comparisons were analyzed by two-sample *t* tests.

At baseline, the diabetic patients had significantly higher plasma hs-CRP levels (median [interquartile range]) than the nondiabetic control subjects (1.58 [0.71–3.25] vs. 0.86 [0.42–2.16] mg/l, respectively; *P* < 0.01). There were no significant differences in MAER in the losartan- and placebo-treated groups at the beginning of the study. Within-group analysis showed that treatment with losartan reduced MAER (baseline vs. 6 months: 70.8 [41.8–112.6] vs. 54.5 [27.6–85.9] μ g/min, respectively; *P* = 0.007), whereas an increase in MAER was observed in the placebo group (53.0 [38.4–102.6] vs. 78.5 [40.5–141.0] μ g/min, respectively; *P* = 0.02). As a result, the losartan-treated group had significantly lower MAER than the placebo-treated group at 6 months (*P* = 0.04). No differences were found in plasma hs-CRP between the losartan- and the placebo-treated groups at baseline (1.61 [0.93–3.39] vs. 1.44 [0.54–2.79] mg/l, respectively) or at 6 months (1.74 [0.98–2.92] vs. 1.46 [0.69–3.49] mg/l, respectively).

In conclusion, type 2 diabetic patients with microalbuminuria have elevated plasma CRP levels. Losartan significantly reduces the degree of microalbuminuria in these patients, but the lowering of urinary albumin excretion by AT₁ receptor antagonist is not associated with any changes in plasma hs-CRP concentration. Our data would suggest that losartan, at a dose sufficient to reduce microalbuminuria, does not have a significant anti-inflammatory effect.

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COMMENTS AND RESPONSES

The Value of Self-Monitoring of Blood Glucose

The issues surrounding self-monitoring of blood glucose (SMBG) are interesting and complex. Recently published American Diabetes Association (ADA) Position

Statements (1–3) encourage the use of SMBG in all diabetic patients and urge governments and other payers to meet the cost. Until 6 months ago, however, reliable data to support these views in patients with type 2 diabetes have not been available.

At first sight, the recent report by Franciosi et al. (4) appears to make conclusions contrary to the ADA Position Statements, but closer examination reveals this not to be the case. Franciosi studied 2,855 patients with type 2 diabetes recruited from 204 different centers. Different methodologies for HbA_{1c} measurement were adjusted for mathematically, whereas statistical methods were used for adjusting between different treatment regimes and for between-center variability (the latter accounting for 27% of the differences in the results between groups). In non-insulin-treated patients, Franciosi et al. found that there was a nonsignificant 0.2% increase in HbA_{1c} levels between no SMBG and infrequent (<1/week) SMBG testing, with a further increase of 0.3% in HbA_{1c} levels in patients who tested at least daily.

However, the study was not designed to determine the causality of these differences. The authors state that “a higher frequency of SMBG was related to higher HbA_{1c} levels, thus suggesting that patients with poor metabolic control have a greater tendency to self monitor.”

Contrary to the implication of the concluding sentence of the abstract, this paper presents no data to detract from the extension of SMBG to patients with non-insulin-treated type 2 diabetes.

A few months earlier, Karter et al. (5) published the results of a 24,312-patient study performed by Kaiser Permanente. In contrast to the study by Franciosi et al., in this study all patients were health maintenance organization members following the same treatment protocols and had HbA_{1c} levels that did not need adjustment. They were randomized by design into treatment groups before statistical analysis. Treatment groups were type 1 diabetic patients ($n = 1,159$), insulin-treated type 2 diabetic patients ($n = 5,552$), type 2 diabetic patients on oral treatments ($n = 12,786$), and type 2 diabetic patients using dietary measures only ($n = 4,815$). In addition to these study size and design benefits, Karter et al. also had a control group of 24,302 patients

who could not be included in the main study.

Within each treatment group, Karter et al. found clinically significant decreases of 0.7% in HbA_{1c} levels in patients who used daily SMBG compared with patients who did not perform SMBG. Comparison with the control cohort confirmed the results, and the study conclusions remained consistent and significant for each treatment group.

Karter et al. provide good data to support ADA Position Statements to promote the use of SMBG in all diabetic patients, regardless of diagnosis or treatment, and one of the conclusions of Franciosi et al. should remain the goal for all diabetic patients: “Our findings suggest that self-monitoring of blood glucose can have an important role in improving metabolic control if it is an integral part of a wider educational strategy devoted to the promotion of patient autonomy.”

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Self-Monitoring of Blood Glucose Can Be Effective in Type 2 Diabetes Only If It Serves a Clearly Identified Purpose

Response to Court

The use of self-monitoring of blood glucose (SMBG) in type 2 diabetic patients is still a matter of debate, as documented by the letter from Dr. Court (1). Despite its recommendation for all diabetic patients by the American Diabetes Association, the evidence supporting its effectiveness in improving glycemic control is questionable. A recent meta-analysis of all randomized trials on this topic failed to show any benefit for patients practicing SMBG (2). Previous observational studies were also unable to document a relation between frequency of SMBG and metabolic control (3).

From this point of view, the results from Karter et al. (4) are the first to show, in a highly homogeneous setting, a positive association between SMBG practice and metabolic control, irrespective of the treatment. These data are not confirmed by our results (5) or those from the recently published third National Health and Nutrition Examination Survey (NHANES III) (6). We believe that the large number of centers involved in our study, as well as in the national sample of the NANHES III, represent a strength rather than a limitation because they provide a true picture of diabetes care, which is without any doubt much more heterogeneous than that described in the article by Karter et al.

To take into account the inter- and intracenter variability, we applied appropriate multilevel models, thus adjusting for the correlation between observations relative to patients enrolled by the same center. The comparability of HbA_{1c} levels was made possible by widely accepted mathematical transformations; in previous analyses, we have shown that HbA_{1c} levels in the very same population were strongly associated with physicians' be-

liefs, as well as with known clinical correlates (7).

We agree that our study does not exclude the possible benefit of SMBG in type 2 diabetes; on the contrary, it clearly shows that SMBG can be associated with better metabolic control in those patients able to self-adjust insulin doses, thus stressing the crucial role played by patient education. On the other hand, when the information deriving from SMBG cannot be readily used by the patient or in the absence of clear guidelines on the actions to be undertaken in the presence of high blood glucose levels in individuals not treated with insulin, this practice can be related to psychological harm and feelings of powerlessness, as our data clearly show.

We believe that a deeper knowledge of the features of diabetes care in the Kaiser Permanente Medical Care Program of Northern California, which made SMBG so successful in determining lower HbA_{1c} levels (even in those patients treated with diet alone), would be of great interest in understanding the transferability of these results in other, more heterogeneous, clinical settings.

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Evidence-Based Nutritional Recommendations for the Treatment and Prevention of Diabetes and Related Complications

A European perspective

We read with interest the revised 2002 Clinical Practice Recommendations as they relate to nutrition therapy for diabetes (1) as well as the associated Technical Review (2). We would strongly endorse the need to individualize this component of treatment because advice is indeed necessary regarding other aspects of lifestyle, oral hypoglycemic agents, and insulin. However, we question some of the recommendations regarding dietary carbohydrates.

The need for evidence-based guidelines in all aspects of medical management is universally recognized. Unfortunately, with regard to nutritional recommendations, there are no randomized-controlled clinical trials with morbidity and mortality as end points. These are regarded as the ultimate type of evidence on which to make recommendations. We therefore have to use less conclusive approaches to study, including several different epidemiological methods and studies of dietary

manipulations on surrogate end points known to be related to morbidity and mortality. This inevitably leads to subjective interpretation regarding the quality of studies because it is clearly inappropriate to simply count the numbers of investigations pointing in one direction or another. Furthermore, there is need to determine the emphasis that should be given to one type of evidence compared with another. We suggest that meticulously conducted and controlled human studies of people with diabetes that involve dietary manipulations over a period of weeks or months and that acknowledge clinically relevant end points should provide the most powerful level of evidence, especially when the findings are compatible with epidemiological data. It is also important to consider the manner in which recommendations are likely to be interpreted by health professionals and patients.

With these considerations in mind, we express concern regarding two aspects of the recommendations regarding carbohydrates. The recommendations that the "total amount of carbohydrate in meals or snacks is more important than the source or type" and that "as sucrose does not increase glycemia to a greater extent than isocaloric amounts of starch, sucrose and sucrose-containing foods do not need to be restricted by people with diabetes" (A-level evidence) (1) are in our opinion not backed by convincing evidence and are open to misrepresentation. The first recommendation regarding carbohydrate (also based on A-level evidence) indicates that "foods containing carbohydrate from whole grains, fruits, vegetables and low fat milk should be included in a healthy diet," but provides no indication that these are the most desirable choices (1). Thus, despite the caveat based on "expert consensus" that "sucrose and sucrose-containing foods should be eaten in the context of a healthy diet," it appears, according to this set of recommendations, that it is perfectly acceptable for the bulk of dietary carbohydrate to be derived from highly refined (processed) starchy foods, foods rich in sucrose, and other sugars or sucrose. We know of no medium or long-term studies in which such a dietary practice has been shown to be compatible with good glycemic control and optimum levels of risk factors for the complications of diabetes. Indeed, most of the well-controlled studies in which sucrose has been shown to be an acceptable

component of the diabetic dietary prescription have included modest intakes of sucrose eaten with meals as part of a high-fiber diet, with the sucrose displacing other fiber-depleted carbohydrate-containing foods (3,4). Such a recommendation also has the potential to increase the energy density of the diet, surely an undesirable step when obesity rates are escalating out of control in all age groups. The latter is especially remarkable in the young age groups, considering that calories from fluids have been shown to satisfy less than solid food (5). A high intake of sugary beverages has been convincingly shown to be related to subsequent risk of obesity in children (6). The potential for misinterpretation has already been clearly demonstrated by a news item in the *British Medical Journal* (7) that describes the new recommendations under the headline "U.S. relaxes sugar ban for people with diabetes"

Under the heading of B-level evidence is the statement that "there is insufficient evidence of long-term benefit to recommend the use of low-glycemic index diets as a primary strategy in food/meal planning" (1) and that there is no need to recommend that people with diabetes consume a greater amount of fiber than other Americans. There is impressive evidence from carefully controlled studies that diets containing low-glycemic index foods (8) or foods high in fiber (9) are associated with appreciably improved levels of several measures of carbohydrate metabolism and cardiovascular risk factors. These studies confirm a substantial body of earlier research and suggest that these two characteristics of carbohydrate-containing foods may independently influence glycemic control, insulin levels, and lipoprotein-mediated risk of cardiovascular disease (10–12). There is also recent epidemiological evidence that a high intake of dietary fiber improves glycemic control and reduces the risk of ketoacidosis in type 1 diabetes (13). The Food and Agriculture Organization/World Health Organization Expert Consultation on Carbohydrates endorsed the use of glycemic index as a means of determining optimum carbohydrate-containing foods (14).

Thus, we believe that there is a convincing evidence base to advise that although sucrose and other added sugars may be included in moderation in the diets of people with diabetes, the bulk of

dietary carbohydrate should be derived from foods with a low glycemic index and/or foods that are rich in soluble fiber. Such a recommendation permits the choice of foods from a wide range of fruits, vegetables, and whole-grain cereals and, although processed starchy foods are not excluded, they are not regarded as equivalent to these food choices. The European recommendations for people with diabetes that include such advice (15) will be updated to include the evidence base from which they were derived.

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Response to the Diabetes Nutrition Study Group of the European Association for the Study of Diabetes

We welcome the European perspective, although we do not completely share it. We agree with the statement of Mann et al. (1) that “meticulously conducted and controlled human studies of people with diabetes that involve dietary manipulations over a period of weeks or months. . . provide the most powerful evidence.” However, we take issue with several concerns they express. First, we take issue with the statement that it is important to consider how recommendations are likely to be interpreted by health professionals and patients. Second, we continue to believe that the total amount of carbohydrate is more important than the source or type. Third, we continue to believe that sucrose does not need to be restricted, relative to other carbohydrates, because of concern about aggravating hyperglycemia.

It was an initial determination of the American Diabetes Association Task Force that it was our task to write, as accurately as possible, evidence-based nutrition principles and recommendations. The implementation of these principles and recommendations was to be determined by health professionals in their individualized nutrition counseling with patients. Furthermore, we concluded that patients have the right to read and know

accurate nutrition information. With this information, it is then their right to make decisions about their own food choices. Too often in the past, health professionals have taken a parental approach, such as “do this because it is good for you,” or a “food police” approach, such as “don’t eat sugar.” These approaches have not led to successful outcomes. Table 1 outlines this well.

With respect to amount and source of carbohydrate, we stand behind our original recommendation. However, as stated in our response to Wolever (2), our recommendation about the amount of carbohydrate might be more clear if it were changed to say the total amount of “available” carbohydrate is more important than the source or the type. In type 1 diabetic subjects, the amount of carbohydrate in test meals influenced the amount of insulin necessary to control glycemia, whereas glycemic index, fiber content, and caloric content did not (3).

With regard to the concern about sucrose, it is clearly stated in our introduction that “basic to the nutrition recommendations is the underlying concern for optimal nutrition through healthy food choices and an active lifestyle” (4). The section on sucrose, as noted by Mann et al. (1), also states that “sucrose and sucrose-containing foods should be eaten in the context of a healthy diet” (4,5). Mann et al. states that they know of no medium or long-term studies where the practice of focusing on total carbohydrate was shown to be compatible with good glycemic control. Please note that, in the 20 studies quoted, when total carbohydrate came from a variety of

Table 1—Comparison of traditional and empowerment viewpoints regarding diabetes medical nutrition therapy

Traditional viewpoint	Patient-centered viewpoint
Food choices affect physical health, including diabetes management.	Food choices affect psychosocial quality of life as well as physical health.
The professional is the expert in nutrition and is therefore in charge of developing a meal plan based on assessed needs.	The professional is the expert in nutrition, and patients are the experts about themselves and their life circumstances.
The focus is on metabolic goals, such as weight and blood glucose levels. The professional provides instruction on an appropriate meal plan and teaches clients how to follow it.	Desired metabolic outcomes shape behavior change plans but are not in themselves behaviors that clients can control. The focus is on behavioral goals, i.e., specific action steps that clients can control.
The professional feels effective and successful when clients follow nutrition recommendations.	The professional teaches behavior change skills so clients can achieve their own nutritional goals. The professional feels effective and successful when clients become skilled at making informed choices and solving problems.

From Maryniuk MD: Counseling and education strategies for improved adherence to nutrition therapy. In *American Diabetes Association Guide to Medical Nutrition Therapy for Diabetes*. Alexandria, VA, American Diabetes Association, 1999, p. 369

starches or starches plus sucrose, the sucrose intake represented approximate usual intake, and only Peterson et al. (6) made an attempt to use sucrose with fiber-containing foods. In most of the studies, rigorous control of the nutrients under study was established by providing meals to subjects. One of the studies provided 23% and another 30% of energy from sucrose. Two of the studies lasted 28 days. If the total carbohydrate intake was kept similar, the responses were also similar. Was the European perspective that both sucrose and starch should be restricted in the diabetic diet because both aggravate hyperglycemia generated with these studies in mind? If so, does this not affirm the concept that the total amount of carbohydrate is more important than the source or type?

The headline "U.S. relaxes sugar ban for people with diabetes," which appeared in the *British Medical Journal* (7), surprised us. The relaxation of the restriction on sucrose was nothing new, having been recommended in 1994 (8).

With regard to the statement by Mann et al. (1) that a "high intake of sugary beverages has been convincingly shown to be related to subsequent risk of obesity in children," we would call attention to another study (9) in which added sugars were found to be relatively unimportant when it came to overall diet quality in individuals between 2 and 19 years of age.

With regard to the glycemic index, the study by Jarvi et al. (10) did find benefit, but as noted in the previous reply to the letter by Irwin (11), other studies (4) have not confirmed long-term benefit from low-glycemic index diets. One study is not "impressive evidence." The same applies to fiber. Whereas some intervention studies have reported benefit (12,13), others have not (14–16). Moreover, the study by Chandalia et al. (13), which compared 24 g fiber with 50 g fiber, would support our statement that it "appears that ingestion of large amounts of fiber is necessary to confer metabolic benefits. It is unclear whether the palatability and gastrointestinal side effects of fiber in this amount would be acceptable to most people" (5,6). The control arm of the study used 24 g dietary fiber and had no beneficial effects on glucose, lipid, or insulin levels. This amount of fiber is clearly at the upper end of usual intake for most Americans and would, by itself, require major lifestyle changes for most

Americans to achieve. The 50-g dietary fiber diet included two servings of oatmeal (15 g carbohydrate/serving), six slices of whole wheat bread, six to seven servings of fruit (15 g carbohydrate/serving), and three servings of vegetables (15 g carbohydrate/serving). For many individuals, this type of food plan would require very dramatic changes in eating habits.

In conclusion, we stand behind our original recommendations, as we believe they are evidence based.

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Insulin Resistance After Renal Transplantation

Hjelmsaeth et al. (1) have validated the use of seven oral glucose tolerance test (OGTT)-derived insulin sensitivity indexes against the euglycemic-hyperinsulinemic clamp technique in a Caucasian renal transplant population. We agree with the authors that the avail-

ability of more cost- and time-efficient surrogate estimates of insulin sensitivity than the euglycemic-hyperinsulinemic clamp would greatly benefit the design of future epidemiological studies investigating the role of insulin resistance in the extremely high incidence of diabetes and cardiovascular disease in renal transplant recipients (2,3). The authors found all seven insulin sensitivity indexes to correlate significantly with the euglycemic clamp. They concluded that an insulin sensitivity index based on glucose and insulin serum concentrations 2 h after the glucose challenge from the OGTT suffices best in renal transplant recipients. However, the routine performance of OGTTs to assess insulin sensitivity in renal transplant recipients is cumbersome, time-consuming, and frequently impossible in busy outpatient practices. McAuley et al. (4) recently suggested an insulin sensitivity index based on fasting serum insulin and triglyceride concentrations ($\text{Exp}[2.63 - 0.28\ln(\text{insulin}) - 0.3\ln(\text{TG})]$) as a better predictor of insulin sensitivity than homeostasis model assessment (HOMA) in the general population. Insulin sensitivity indexes based on fasting parameters alone don't have the drawback of interference with outpatient practices. For this reason, it would have been very interesting if the authors had included this insulin sensitivity index in their analyses to assess whether this measure correlates better with the results from the euglycemic-hyperinsulinemic clamp than with HOMA or even the insulin sensitivity indexes derived from the 2-h glucose and insulin concentrations of the OGTT.

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Insulin Resistance After Renal Transplantation

Response to de Vries and Bakker

We think that the question raised by de Vries and Bakker (1) in regard to our study (2) is appropriate. It is important to find the most convenient and adequate method to estimate insulin resistance (IR) in transplant recipients without necessarily carrying out an oral glucose tolerance test. Also, because the IR observed in transplant recipients is a common side effect of treatment with prednisolone, this issue is probably of interest for most physicians.

Accordingly, we have validated the insulin sensitivity index (ISI) suggested by McAuley et al. (3), based on fasting serum insulin and triglycerides (TG) ($\text{ISI}_{\text{McAULEY}} = \text{Exp}[2.63 - 0.28 \times \ln(\text{insulin}) - 0.31 \times \ln(\text{TG})]$), against the results from our glucose clamp studies. The equation proposed by McAuley et al. correlated significantly and reasonably well with the clamp-derived ISI (Spearman's correlation; $r = 0.43, P = 0.004$) (Table 1). This is superior to the results

from the other ISIs based on either fasting insulin (insulin resistance index [IRI]: IRI_{INSO} ; $r = -0.32$) or fasting glucose and insulin (IRI_{HOMA} ; $r = -0.30$) (4).

In addition, we calculated the correlation between our clamp results and the Quantitative Insulin Sensitivity Check Index: $\text{ISI}_{\text{QUICKI}} = 1/[\log I_0 + \log G_0]$, where I_0 is the fasting insulin ($\mu\text{U/ml}$) and G_0 is the fasting glucose (mg/dl) (5). This equation also correlated significantly with the clamp-derived ISI ($r = 0.30, P = 0.049$) similar to the IRI_{INSO} and the IRI_{HOMA} .

We therefore suggest that the $\text{ISI}_{\text{McAULEY}}$ is the most appropriate formula to use when estimating insulin action in steroid-treated patients when fasting insulin, glucose, and triglyceride concentrations are known. However, our previously proposed formula ($\text{ISI}_{\text{TX}} = 0.208 - 0.0032 \times \text{BMI} - 0.0000645 \times \text{Ins}_{120} - 0.00375 \times \text{Gluc}_{120}$) remains superior to other known estimates of insulin action when the 2-h glucose and insulin concentrations are available.

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Table 1—Correlation of $\text{ISI}_{\text{CLAMP}}$ to surrogate measures of insulin sensitivity and insulin resistance

		Spearman's correlation (r)
$\text{IRI}_{\text{INS120}}$	2-h Insulin	-0.45*
$\text{IRI}_{\text{AUCGI}}$	AUC glucose/AUC insulin	-0.44*
$\text{ISI}_{\text{MATSUDA}}$	Composite index	0.41*
ISI_{TX}	Modified Stumvoll index	0.58†
IRI_{INSO}	Fasting insulin	-0.32‡
IRI_{HOMA}	Homeostasis model assessment	-0.30‡
$\text{ISI}_{\text{QUICKI}}$	Quantitative insulin sensitivity check index	0.30‡
$\text{ISI}_{\text{McAULEY}}$		0.43*

* $P < 0.01$; † $P < 0.001$; ‡ $P < 0.05$. AUC, area under curve.

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New Dietary Guidelines From the American Diabetes Association

The new Dietary Guidelines from the American Diabetes Association (ADA) provide no support for the use of the glycemic index in the management of diabetes. However, it should be made clear to the ADA's membership that the ADA's position is at odds with recent reviews and recommendations from authorities that have evaluated the same evidence. Specifically:

1) The United Nations World Health Organization and the Food and Agriculture Organization recommend in their 1997 expert consultation report on Carbohydrates in Human Nutrition that when looking at carbohydrate-containing foods, the glycemic index should "be used to compare foods of similar composition within food groups" (1).

2) The European Association for the Study of Diabetes Nutrition Group recommend in their 1999 revision of guidelines for the management of patients with diabetes that: "Foods with a low glycemic index (e.g., legumes, oats, pasta, par-boiled rice, certain raw fruits) should be substituted when possible for those with a high glycemic index since they may help to improve glycemic control and lipid levels" (2).

3) The Dietary Guidelines for Older Australians (1999) specifically recommend the consumption of lower glycemic index cereal-based foods: "Eat plenty of cereals, breads and pastas—preferably high-fiber foods and those with a lower glycemic index" (3).

4) Recommendations for the use of glycemic index in meal planning are also outlined by Diabetes Australia (<http://www.diabetesaustralia.com.au>), the Juvenile Diabetes Research Foundation Australia (<http://jdrf.org.au>), and the International Diabetes Institute in Melbourne (<http://www.diabetes.com.au>).

In Australia, people with diabetes have benefited from the general acknowledgment among health professionals that the glycemic index is one tool among many that can be used in diabetes management. The glycemic index is already familiar to many consumers. We recently conducted a random telephone survey of Australian grocery buyers and found that nearly 30% of respondents were aware of the glycemic index, and after the glycemic index was explained, 71% stated they would be likely to use the glycemic index in food purchase decisions. A member survey by Diabetes Australia in 2000 found that two in three respondents would like to see the glycemic index stated in nutrition panels.

This awareness has stimulated the introduction of a glycemic index symbol program for food labels. The program is run by a nonprofit company formed as a partnership between Diabetes Australia, the Juvenile Diabetes Research Foundation, and the University of Sydney. The aim is to promote consumer awareness and understanding of glycemic index as an important guide for food purchase decisions. Carbohydrate-containing foods that have been properly glycemic index tested (tested in vivo according to published methodology) are licensed to carry an easily recognizable symbol on their labels. Foods must meet several nutrition

criteria for their food group. The license fees are used to fund educational activities about the glycemic index and to support the research and education undertaken by our member organizations.

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Response to Irwin

The American Diabetes Association nutrition principles and recommendations (1,2) do acknowledge that a number of factors influence the glycemic response to food, including the amount of carbohydrate, type of sugar, nature of the starch, cooking and food processing, particle size, food structure, and other food components (fat and natural substances that slow digestion) as well as the fasting and preprandial glucose concentrations, severity of glucose intolerance, and the second meal or lente effect (1). The question that the task force asked was, is there evidence that chronic consumption of low-glycemic index foods will contribute to improved glycemia in people with diabetes? The concern being that if another layer of complexity (glycemic index) is to be added to food/meal planning guide-

Table 1—Type 1 diabetes: low-glycemic index diets compared with high-glycemic index diets in studies lasting 2 weeks or longer (5 studies, 48 subjects)

Endpoint	Low GI significantly better than high GI	No significant difference
HbA _{1c}	0	4 [n = 40] (3,4,6,7)
Fructosamine	3 [n = 27] (3,5,6)	1 [n = 9] (7)
Fasting plasma glucose	0	3 [n = 27] (3,5,6)

Data are n. Numbers in parenthesis refer to the reference list. GI, glycemic index.

lines, there should be clear evidence of benefit.

To answer this question, all studies comparing low- and high-glycemic index diets for 2 weeks or longer were reviewed. As can be seen from Tables 1 and 2, the number of studies is limited. Moreover, the design and implementation of several of these studies is subject to criticism, and in none of the studies was the effect of the diets on postprandial glucose concentrations reported.

Clearly, longer and larger studies are needed to evaluate the utility of glycemic indexing. Until such studies are available, use of low-glycemic index diets is not, in our judgment, evidenced based. Recommendations by other organizations do not change this. We do acknowledge that some individuals might benefit from low-glycemic index diets. However, a decision to use such a diet should be an individual one made in consultation with a nutrition counselor.

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American Diabetes Association Evidence-Based Nutrition Principles and Recommendations Are Not Based on Evidence

I am disappointed with the American Diabetes Association's Position statement: Evidence-Based Nutrition Principles and Recommendations for the Treatment and Prevention of Diabetes and Related Complications (1) and technical review of the same title (2). The recommendations are not

Table 2—Type 2 diabetes: low-glycemic index diets compared with high-glycemic index diets in studies lasting 2 weeks or longer (10 studies, 174 subjects)

Endpoint	Low GI significantly better than high GI	No significant difference
HbA _{1c}	1 [n = 16] (9)	5 [n = 92] (4, 6, 8, 13, 15)
Fructosamine	3 [n = 41] (10,11,14)	3 [n = 54] (8, 12, 13)
Fasting plasma glucose	0	9 [n = 162] (6, 8–15)

Data are n. Numbers in parenthesis refer to the reference list. GI, glycemic index.

based on evidence. There is no explanation of the methods used for searching the literature and selecting papers for inclusion, nor any indication of the criteria used to grade the evidence (3). The sections in the technical review dealing with carbohydrate contain several errors, but space does not allow me to deal with all of the issues. I will focus just on the following recommendation: "With regard to the glycemic effects of carbohydrates, the total amount of carbohydrate in meals or snacks is more important than the source or type."

The technical review indicates that dietary carbohydrates consist of monosaccharides, disaccharides, polyols, oligosaccharides, polysaccharides, and fiber, and it includes discussion about using correct terminology when referring to dietary carbohydrate. Presumably, therefore, the authors understood the meaning of the term "carbohydrate," and used it intentionally. There are no qualifications. Thus, it can be presumed that amount is always more important than source or type of carbohydrate without exception. This carries a great deal of weight because it is said to be based on A-level evidence, the highest possible level of evidence and supposedly virtually indisputable.

I will not dwell on the fact that this is not based on any evidence. No data comparing the relative effects of different amounts versus different sources of carbohydrate was considered, and a large amount of evidence against it was ignored. I want to point out that nonglycemic carbohydrates will not raise blood glucose, no matter how much is consumed. Thus, sometimes, source is more important than amount. By denying this, the recommendation may harm people with diabetes.

More and more carbohydrates with little or no effect on blood glucose, such as polyols, fructo-oligosaccharides, and resistant starch, are appearing in the food supply. Some foods contain most of their carbohydrate in this form. For example, chocolate bars containing over 90% of their carbohydrate as lactitol have been promoted at the annual meeting of the Canadian Diabetes Association for several years. Lactitol is not absorbed (4,5) and, therefore, presumably has no effect on blood glucose. If a person with type 1 diabetes based preprandial insulin dose primarily on the amount of carbohydrate, as recommended, too much insulin might be taken before consuming a snack or

meal containing predominantly nonglycemic carbohydrates, and an unexpected hypoglycemic episode might result.

Perhaps I am over-reacting, but I would like to know why the authors made this recommendation and who will be responsible if someone is injured because of it?

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Response to Wolever

We thank M.S. Wolever (1) for his letter asking about the process used to develop the American Diabetes Association (ADA) nutrition principles and recommendations. As with all ADA technical reviews and position statements, the process is determined by the ADA as outlined in the ADA Clinical

Practice Recommendations 2002 introduction (2), which is used for all new and revised ADA position statements. Members of the task force reviewed the literature with emphasis on research published since the last nutrition review completed in 1994. After completion of the technical review nutrition principles (3), nutrition recommendations were developed and classified according to the system outlined by the ADA for position statements (4).

In regard to the concern that "nonglycemic carbohydrates" will not raise blood glucose, you make an important point. Carbohydrates such as fiber and sugar alcohols have minimal effects on blood glucose. In the recommendation that total amount of carbohydrate in meals or snacks is more important than the source or type, it is implied that the carbohydrate is digested and absorbable. Thus, fiber should not be considered, and sugar alcohols should be considered at a reduced level because of their partial absorption. Perhaps this should have been stated rather than implied. The recommendation would be clearer if it were changed to state that the total amount of "available" carbohydrate in meals or snacks is more important than the source or type.

Your biggest concern appeared to be that a person eating a chocolate bar sweetened with the polyol lactitol might be confused as to the amount of available carbohydrate and administer too much insulin. However, you might presume that the lactitol-sweetened chocolate bar was selected because the person wanted the reduced sugar and caloric intake and would take this into account. Consultation with a dietitian would be useful to clear up any confusion in this regard.

Incidentally, in other polyol-sweetened foods, such as ice cream or cookies, the difference in the total amount of carbohydrate in the alcohol-sweetened foods, compared with foods sweetened with sucrose, is small, even when the amount of sugar alcohol is subtracted from the total carbohydrate.

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