OBSERVATIONS

Oxidative Stress in Families of Type 1 Diabetic Patients

Further evidence

We have recently reported evidence of increased oxidative stress in nondiabetic first-degree relatives of patients with type 1 diabetes (1). Elevated circulating markers of lipid peroxidation and increased cellular fragility seemed to be associated with supposed markers of inflammation. Transition metals may promote free radical reactions. Indeed, among radical-scavenging defenses of extracellular fluids, there are proteins involved in the sequestration of transition metals. Furthermore, it has been reported that cellular-redox modification influences the activity of ion-transport systems (2–6), including sodium/hydrogen exchange (NHE), and we have found increased erythrocyte NHE activity in families of patients with type 1 diabetes (7). Because we had previously examined the plasma thiol groups and the erythrocyte antioxidant reserves in type 1 families (8), we completed our investigation of possible first-chain initiating or stimulating factors.

In these families, we searched for the contribution of extracellular antioxidants to the increased levels of oxidative stress. We also investigated the eventual relationship between oxidative stress and abnormal NHE activity. The study groups were the same type 1 diabetic patients, first-degree relatives, and control subjects previously examined (1). We selected 30 type 1 diabetic patients (mean duration 20 ± 8 years; 10 without diabetic complications, 10 with retinopathy, and 10 with nephropathy and retinopathy), 36 nondiabetic normotensive siblings, 37 parents, and three groups of healthy subjects without family history of diabetes. During the previous investigation, these patients underwent the following analyses: erythrocyte sedimentation rate analysis; blood and platelet counts (Technicon System H*1; Bayer Diagnostics, Milan, Italy); serum and urine urea, creatinine, uric acid, electrolytes, and L-gamma-glutamyl transferase measurements; and serum bilirubin, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, alkaline phosphatase; iron assays using BM/HITACHI SYSTEM 717 model) and reagents from Boehringer Mannheim (Mannheim, Germany). Serum transferrin, ceruloplasmin, and serum and urine albumin were quantified by the kinetic immunonephelometric method (Behring Institute nephelometer and reagents; Scoppitto, L'Aquila, Italy). Serum ferritin was measured by the IMX System (Abbott SpA, Divisione Roma, Italy). Serum copper was determined with a Varian SpectrAA (Varian Techtron, Victoria, Australia). Erythrocyte NHE activity was measured as previously described (7).

In comparison with the control subjects, the type 1 diabetic patients had lower levels of plasma uric acid (0.2 ± 0.1 vs. 0.3 ± 0.1 mmol/l, $P < 0.05$) and sodium (136 ± 2 vs. 140 ± 2 mEq/l, $P < 0.001$), higher levels of plasma potassium (4.2 ± 0.3 vs. 3.9 ± 0.3 mEq/l, $P < 0.001$), and an overactive erythrocyte NHE (7.06 ± 1.89 vs. 5.16 ± 1.78 mmol/l red blood cell (RBC) per h, $P < 0.01$). Urinary sodium excretion in type 1 diabetic patients nearly reached statistical significance (median 154 vs. 175 mEq/24 h, $P = 0.05$). Siblings of type 1 diabetic patients showed a lower amount of circulating sodium (139 ± 2 vs. 140 ± 2 mEq/l, $P < 0.05$) and an enhanced erythrocyte NHE activity count (8.25 ± 2.78 vs. 5.34 ± 1.75 mEq/l, $P < 0.001$). Parents differed from control subjects only in erythrocyte NHE activity (7.88 ± 2.74 vs. 6.22 ± 2.33, $P < 0.01$).

The multiple regression analysis included all of the biochemical measurements performed in these families and the assays previously reported in our study on oxidative stress. NHE activity was significantly correlated with erythrocyte glutathione (GSH) content, plasma advanced oxidation protein product (AOPP) concentration, basal plasma metal deactivator additive (MDA), basal RBC osmotic fragility, and the amount of MDA accumulated in the RBCs during a 3-h incubation under oxidative stress ($R = 0.4$, $P < 0.001$). Among the diabetic patients, plasma sodium concentration was strictly associated with plasma levels of glucose (R 0.6, $P < 0.001$), whereas among the siblings, plasma concentrations of lipoprotein(a) [Lp(a)] and fibrinogen ($R = 0.5$, $P < 0.001$) were associated.

These data, with further biochemical measurements that were performed in the same experimental session and in the same study group, complete and integrate the previous study on oxidative stress in type 1 diabetic families (1). To our knowledge, this study provides the first in vivo demonstration of a significant association between oxidative stress and NHE upregulation. We were unable to reveal any abnormalities in circulating metal ions or extracellular antioxidant defenses that could favor oxidative stress in nondiabetic relatives of type 1 patients. On the other hand, we confirmed our previous finding of a generalized increase in NHE activity, which was significantly associated with both RBC and GSH content and some markers of radical-induced damage, such as plasma AOPP, MDA, RBC osmotic fragility, and RBC MDA accumulation under oxidative stress. First, intracellular GSH content is essential in maintaining the functional integrity of NHE (2,5,6,9). Second, many ion transport pathways have been reported to be under redox control (2–6). A direct stimulatory effect of oxidative stress on NHE can be hypothesized on the basis of recent observations in hepatoma cells (6). Low concentrations of H_2O_2 activated mitogen-activated protein (MAP) kinases that stimulated NHE activity during reperfusion injury (10). Svegliati-Baroni et al. (11) gave the first demonstration in vitro of a direct stimulating effect of oxidative stress on NHE in hepatic stellate cells.

In our opinion, there are two possible mechanisms of NHE upregulation by oxidative stress: *1*) MAP kinase activation of the transport system that has a protective role for restoration of intracellular pH, such as during ischemia-reperfusion (10); and *2*) oxidative modifications of a cellular membrane cytoskeleton network that is considered a "solid-state," signaling and facilitating cross-talk among multiple signaling pathways (12). Both markers of oxidative stress and erythrocyte NHE activity were increased in all members of type 1 diabetic families (probands and nondiabetic relatives included), whereas abnormalities in circulating electrolytes were observed only in type 1 diabetic patients and their siblings, thus seeming to exclude NHE as a contributing factor. Abnormalities in electrolyte handling have been reported in type 1 diabetic patients and ascribed to the metabolic control of the disease (13). Indeed, our type 1 diabetic patients showed a striking association between plasma values of sodium and glucose (translocational hyponatremia). On the contrary, we found that plasma sodium is significantly reduced also in

nondiabetic siblings of type 1 diabetic patients and therefore correlated with plasma concentrations of Lp(a) and fibrinogen. Cases of hyponatremia have been correlated with inflammation (14) and increased plasma interleukin −6 concentration (15). These findings are consistent with our hypothesis of an association among inflammatory markers, oxidative stress, and susceptibility to type 1 diabetes. Moreover, the familiarly overactive NHE could be viewed independently as further evidence for the presence in these families of a redox disequilibrium in which oxidation seems to be dominant.

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Failure to Develop Hepatic Injury From Rosiglitazone in a Patient With a History of Troglitazone-Induced Hepatitis

The thiazolidinediones (TZDs) are an important class of antidiabetic drugs that improve glycemic control by improving sensitivity to insulin (1). The first agent in this class was troglitazone, which has been associated with idiosyncratic hepatotoxicity that included cases of liver failure, liver transplantation, and death (2,3). Troglitazone was voluntarily withdrawn from the market in the U.S. in March 2000. Two additional second-generation agents in this class remain on the market: rosiglitazone maleate (Avandia; SmithKline Beecham Pharmaceuticals) and pioglitazone (Actos; Takeda Pharmaceuticals America/Eli Lilly and Co.). Postmarketing surveillance by the manufacturers of the second-generation TZDs have shown no confirmed hepatotoxicity with either agent. Two isolated cases of drug-induced liver disease with rosiglitazone have been reported (4,5), although some debate over the strength of this association has been raised (6). We present a case of a patient with extreme insulin resistance who developed classic troglitazone-induced liver disease but showed no signs of this while on rosiglitazone.

Case report

A 36-year-old woman presented with crampy abdominal pain and evidence of jaundice. She had a 4-year history of uncomplicated type 2 diabetes, initially treated with glyburide and acarbose. Insulin was required, and she was eventually treated with 35 U of U-500 insulin twice a day. Troglitazone 400 mg/day was added in March 1997 and was increased to 800 mg/day in April 1997. Biochemical measurements of liver function were normal before initiation of troglitazone and 2 months after its start. Four months after starting troglitazone, she developed clinical evidence of jaundice, malaise, and crampy abdominal pain.

Her past medical history included an episode of gallstone-induced pancreatitis treated with endoscopic retrograde cholangiopancreatography. Her liver function tests were normal during this episode. She also had a history of modest hypercholesterolemia, obesity, and oligoamenorrhea. She was taking no other medications, including over the counter preparations. She denied any alcohol use.

When she developed clinical evidence of jaundice, troglitazone was stopped and an outpatient evaluation was undertaken. Her total and direct bilirubin levels were elevated to 127 and 100.8 μmol/l (7.5 and 5.9 mg/dl). The alanine aminotransferase (ALT) level was 2,040 mg/dl. The serum and leukocyte alkaline phosphatase levels were both normal, as were electrolytes and the blood count, including platelets. The prothrombin time and the international normalized ratio were also normal. Antibody studies were ordered. Antinuclear and anti-mitochondrial antibodies were negative. The α1 antitrypsin level was normal. The ceruloplasmin level was mildly

elevated at 61.0 mg/dl (range 20–55). A panel for hepatitis A, B, and C was nonreactive. Iron and transferrin saturation levels were normal. Her HbA_{1c} level was 7.0% (4.3–6.1).

Within several months of stopping troglitazone, her symptoms had disappeared and her liver tests had normalized. Her insulin requirements increased with cessation of troglitazone and at one point, she was taking 80 U of U-500 insulin twice a day. Metformin (1 mg) twice a day was added, which decreased the insulin requirement. She requested that an additional TZD be attempted. Rosiglitazone 4 mg twice a day was initiated, with prescriptions being rewritten every 2 weeks depending on liver function tests being obtained. All liver function tests were normal up to 10 months after beginning rosiglitazone treatment.

Discussion

In this patient, the time course of hepatic dysfunction and the subsequent improvement after the use and withdrawal of troglitazone were completely consistent with drug-induced hepatotoxicity. No other viral or autoimmune causes for her hepatic dysfunction were identified. We believe that the patient experienced troglitazone-induced hepatotoxicity. At the patient's insistence, and with a fair amount of hesitancy, a second TZD was added, which to date has been very well tolerated. This suggests that there may be significant differences between the first and second generation TZDs.

There are similarities between the first and second generation TZDs. All of the agents are selective agonists of peroxisome proliferator–activated receptor (PPAR)-γ, and they all improve sensitivity to insulin, especially at the skeletal muscle level (1). Some side effects, such as fluid retention, weight gain, and changes in lipoproteins, appear to occur in all of the TZDs (9).

Differences also exist. All three available agents have different side chains, with troglitazone having a lipophilic α-tocopherol side chain. Other differences include the binding affinity, with rosiglitazone having a greater binding avidity for the PPAR-γ receptor than troglitazone (7). This allows the drug to be administered at an 80- to 100-fold lower dose than troglitazone. Rosiglitazone is predominantly metabolized by cytochrome P4502C8 and does not seem to induce this system, whereas troglitazone induces and is metabolized by cytochrome P4503A4. Although troglitazone is extensively metabolized (3% excreted in the urine), 64% of rosiglitazone is excreted in the urine (7). Troglitazone is metabolized into a quinone derivative, whereas rosiglitazone is not (8).

In clinical trials, troglitazone-induced hepatotoxicity, defined as having an ALT level greater than three times the upper limit of normal, was identified in 1.9% of 2,510 patients. Of the 4,598 patients that were included in rosiglitazone clinical trials, 0.2% of patients had an increase in ALT to three times the normal limit. An identical 0.2% of patients receiving placebo also had elevations in ALT, and the elevations in the rosiglitazone group were not clearly causally related. Two recent reports have suggested that rosiglitazone may be associated with hepatotoxicity (4,5), although one of these patients may have had an element of ischemic liver dysfunction (6), and the other patient was taking acetaminophen and zafirlukast, both of which can cause hepatitis and liver dysfunction (10).

The current recommendations for second generation TZDs include monitoring of liver function tests at baseline and every 2 months for the first year, and then periodically. While idiosyncratic responses to any drug may include adverse effects on the liver, there is currently very little evidence to suggest that hepatic dysfunction is a class effect for the second generation TZDs. Nevertheless, until the clinical experience with the second generation TZDs can match that of troglitazone, liver enzymes should be monitored regularly.

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Plasma Lipoprotein Subpopulation Distribution in Caucasian and African-American Women With Gestational Diabetes

Women who develop gestational diabetes mellitus (GDM) during their first pregnancy have a 30–50% chance of a recurrence of GDM in a subsequent pregnancy (1), and the rate of recurrence is higher in ethnic groups (2,3). The progression of GDM to type 2 diabetes later in life occurs at a rate of 26–47% (4,5), and it occurs more rapidly in ethnic groups that have a high prevalence of type 2 diabetes (4,5). We previously reported that patients with type 2 diabetes have an atherogenic lipoprotein profile that includes an abundance of small and dense

LDL and HDL particles (6). To our knowledge, there are no reports on the lipoprotein profile of patients with GDM. Therefore, we initiated this study *1*) to examine whether there are changes in the lipoproteins of GDM patients that are similar to those seen in type 2 patients and *2*) to determine whether the lipoprotein profile is affected differently in African-American women with GDM versus Caucasian women with GDM.

We recruited 18 Caucasian women (12 nondiabetic and 6 GDM women) and 17 African-American women (7 nondiabetic and 10 GDM women). The participants were classified as having GDM according to the criteria of the National Diabetes Advisory Board. The Institutional Review Board for human subject research at East Carolina University approved all protocols. Fasting plasma glucose and insulin concentrations were determined as previously described (7). Lipid concentrations and lipoprotein subpopulation distributions were determined by a nuclear magnetic resonance (NMR) spectroscopy (7).

Consistent with the results of others (8–11), we found that VLDL triglyceride levels were higher in the GDM patients than in the control subjects (1.17 vs. 0.94 mmol/l), but the HDL (1.85 vs. 1.73 mmol/l) and LDL cholesterol (3.82 vs. 4.12 mmol/l) levels were similar in the two groups. The analysis of the lipoproteins by NMR showed that, when compared with control subjects, GDM patients had higher concentrations of large VLDL (0.439 vs. 0.251 mmol/l), small LDL (1.052 vs. 0.731 mmol/l), and HDL_3 (0.763 vs. 0.692 mmol/l), but lower concentrations of large LDL (2.54 vs. 3.20 mmol/l). A comparison of the GDM patients with their respective control subjects showed that large VLDL was more abundant in the Caucasian patients than in the control subjects (0.650 vs. 0.270 mmol/l), whereas small LDL was elevated in African-American patients compared with their control subjects (0.813 vs. 0.190 mmol/l). These changes in the subpopulation distribution of the three major classes of lipoproteins are similar to those found in the patients with type 2 diabetes.

There was a more pronounced ethnic influence on the lipid concentration and the lipoprotein subpopulation distribution. The Caucasian women, as a group, had significantly higher plasma and VLDL triglyceride levels (1.26 vs. 0.825 mmol/l) and lower HDL cholesterol (1.66 vs. 1.93 mmol/l) levels than the African-American women. Koukkou et al. (11) reported that African-American women had significantly lower plasma triglyceride, total cholesterol, LDL cholesterol, and higher HDL cholesterol levels. We found similar trends for total cholesterol (5.93 vs. 6.57 mmol/l) and LDL cholesterol (3.62 vs. 4.32 mmol/l) levels that did not reach statistical significance because of the small sample size in our study. In addition, the Caucasian women had significantly smaller HDL (9.36 vs. 9.86 nm) and LDL (20.7 vs. 21.0 nm) particle diameters than the African-American women. In both cases, these elevations were seen in Caucasian control subjects compared with African-American control subjects (HDL 9.43 vs. 10.03 nm; LDL 20.73 vs. 21.20 nm), whereas differences between Caucasian GDM patients and African-American GDM patients were only seen in HDL size (9.22 vs. 9.74 nm). Thus, it appears that pregnancy with and without the complication of GDM does not affect the plasma lipid concentrations of African-American women as drastically as it effects their Caucasian counterparts.

The subpopulation distribution of the three major classes of lipoproteins also showed an ethnic influence. In comparison with the African-American women, we found that the Caucasian women, with or without GDM, had higher concentrations of large VLDL (0.397 vs. 0.273 mmol/l), small LDL (1.18 vs. 0.56 mmol/l) and HDL_3 (0.776 vs. 0.670 mmol/l), but significantly lower concentrations of HDL_2 (0.921 vs. 1.21 mmol/l). Furthermore, when compared with African-American women with GDM, Caucasian women with GDM had higher concentrations of large VLDL (0.650 vs. 0.312 mmol/l) and small LDL (1.45 vs. 0.813 mmol/l), but lower concentrations of HDL_2 (0.815 vs. 1.21). In the control group, on the other hand, Caucasian women had higher concentrations of small LDL (1.05 vs. 0.190 mmol/l) and HDL_3 (0.747 vs. 0.599 mmol/l) than the African-American women.

The results from this study show that the lipoprotein subpopulation distribution of patients with GDM was similar to that of women with type 2 diabetes. In addition, it appears that pregnancy with and without the complication of GDM has a milder effect on the plasma lipid and lipoprotein subpopulation distribution of African-American women, as a group, than that of Caucasian women, as a group. Therefore, further studies are needed to determine if these differences are maintained postpartum, and whether they affect the risk for early cardiovascular disease differently in Caucasian versus African-American women.

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Thyrotoxicosis Masked by Diabetic Ketoacidosis

A fatal complication

A 48-year-old man had been treated at our hospital for type 2 diabetes and Graves' disease. He was diagnosed with diabetic ketoacidosis (DKA) twice during previous visits. He was prescribed methimazole (10 mg/day) and insulin, but his drug compliance was poor. He had not visited our hospital since 3 September 1998, when his HbA_{1c} level was 11.6% (normal 4.3–5.8) and his thyroid function tests revealed euthyroidism. He had stopped taking medication 30 December 1998, and he was admitted to our hospital on 6 January 1999, with general fatigue, a sore throat, and excessive thirst. He appeared drowsy, and he presented with Kussmaul respirations, irregular tachycardia, dry skin, injected tonsils, and a diffuse goiter, but he had no fever or exophthalmos. Laboratory studies revealed excessive urine ketone bodies, a normal peripheral white blood cell count, a plasma glucose level of 763 mg/dl, a HbA_{1c} level of 14.6%, and a C-reactive protein level of 13.6 mg/dl (normal <0.5). Arterial blood gas analysis revealed the following: pH 7.151, P_{O_2} 120.4 mmHg, P_{CO_2} 16.7 mmHg, and HCO_3 5.6 mEq/l. Electrocardiography showed atrial fibrillation with a rate of 140 beats/min, and the chest radiograph was normal. He was diagnosed with DKA and tonsillitis.

We began administering saline, insulin, antibiotics, methimazole (10 mg/day), and propranolol (30 mg/day). On 7 January he became alert and had sinus tachycardia at a rate of 110 beats/min. His temperature never exceeded 37.8°C, and his plasma glucose was under control. On 8 January, his tachycardia persisted, but he still had no fever. On admission, thyroid function tests revealed that his thyroid stimulating hormone was <0.03 μU/ml (normal 0.2–3.2), his free triiodothyronine level was 14.12 pg/ml (normal 2.9–6.0), and his free thyroxine level was 6.21 ng/dl (normal 0.78–2.10). Therefore, the administration of methimazole was increased to 30 mg/day. On 9 January, he became extremely confused and agitated. Suddenly, he lapsed into a coma and cardiopulmonary arrest. An autopsy revealed that the enlarged thyroid gland had histological findings of papillary projections of follicular cells with an increased endocytosis of colloid. The focal infiltration of the neutrophils was restricted to the alveoli contiguous to the bronchi. *Serratia marcescens* was cultured from the sputum. These findings indicated focal bronchopneumonia that was not severe enough to have been a singular cause of death. Persistent tachycardia and increased central nervous system (CNS) activity suggested that a thyrotoxic storm participated in the cause of death, although he denied fever, sweatiness, and gastrointestinal involvement.

A thyrotoxic storm is rare, but prompt diagnosis and treatment are required. The diagnosis depends on exaggerated thyrotoxic manifestations, including high fever, marked tachycardia, gastrointestinal dysfunction, and CNS involvement varying from confusion to coma (1). DKA is one of the precipitating factors, and many patients are normothermic or hypothermic even when the condition is associated with infection (2). In some cases of thyrotoxic storm with DKA, a high fever develops after the improvement of DKA (3,4). Severely uncontrolled diabetes influences the assessment of thyrotoxicosis by falsely decreasing the blood levels of thyroxine and triiodothyronine (5). DKA may obscure thyrotoxicosis and/or infection, resulting in a fatal outcome. This case emphasizes that the possibility of thyrotoxic storm should be considered as soon as possible, even when the symptoms are not so obvious in patients with DKA.

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β-Cell Autoimmunity, Genetic Susceptibility, and Progression to Type 1 Diabetes in Unaffected Schoolchildren

The current focus of the screening for individuals at risk for type 1 diabetes has moved from first-degree relatives to the general population. However, there is a shortage of data on the predictive utility of various risk markers in the background population in various countries, and predictive strategies for the general population remains open. We studied the frequency of diabetes-associated autoantibodies in a series of 3,652 unaffected Finnish schoolchildren, and determined the relationships between autoantibodies and HLA-DQB1 risk markers. In addition, all subjects were observed for progression to type 1 diabetes.

The reported frequencies of autoantibodies in the general population have varied widely. In the present study, the fre-

quencies of ICA (islet cell antibodies), GADA (GAD antibodies), IA-2A (antibodies to IA-2 protein), and IAA (insulin autoantibodies) were 2.8, 0.5, 0.6, and 0.9%, respectively. Multiple antibodies (i.e., two or more) were detected in 21 children (0.6%), and 9 children (0.25%) had three or four antibody specificities in their initial blood sample. The present cut-off limits for antibody-positivity (determined as the 99th percentile in >370 healthy control subjects) are close to the 99.5th percentile for IA-2A and GADA and the 99.0th percentile for IAA in the present series of 3,652 children. The use of different approaches for the definition of cut-off limits (1,2) resulted in somewhat higher frequencies of autoantibodies, although this did not improve the diagnostic sensitivity of any autoantibody. These data illustrate the difficulties in defining borderline positivity and in directly comparing of results from different studies, and emphasize the need for common international standards to be used in these autoantibody assays.

Our current knowledge of the relation between HLA-DQB1 risk markers and autoantibodies is mainly based on family surveys and studies on patients with type 1 diabetes. We genotyped ~600 healthy schoolchildren, including all but one of the 141 antibody-positive children. The subjects with GADA (>6.6 relative units [RU]) carried the DQB1*0302 allele [58% (CI 33–80) vs. 24% (20–29), $P = 0.002$] and the DQB1*02/0302 genotype [21% (6–46) vs. 4% (2–6), $P = 0.007$] more frequently than the antibody-negative control subjects, and carried the DQB1*0602 or *0603 allele [16% (3–40) vs. 41% (36–46), $P = 0.031$] less frequently. In addition, the subjects with moderate or high titers of GADA (≥20 RU) carried the DQA1*05-DQB1*02 haplotype more frequently than the antibody-negative control subjects [47% (CI 21–73) vs. 17% (14–21), $P = 0.010$]. The children with detectable levels of ICA carried the DQA1*05-DQB1*02 haplotype more frequently than the ICA$^-$ children [27% (18–36) vs. 17% (14–21), $P = 0.036$]. No specific associations were observed between IA-2A or IAA and DQB1 alleles or genotypes, except for a weak positive association between moderate or high levels of IA-2A (≥10 RU) and the DQB1*0302 allele [5 of 9 (56%, CI 21–86) vs. 106 of 436 (24%, CI 20–29), $P = 0.047$]. None of the nine children with three or four antibody specificities had a high-risk DQB1 genotype, whereas seven of them (78%) carried either the DQB1*0302 or the DQB1*02 risk allele. Surprisingly, three of these nine subjects had a protective genotype. Accordingly, the ongoing β-cell autoimmunity in these three subjects is probably initiated by strong environmental factors and/or is related to genetic factors other than those residing in the HLA region.

Four subjects (0.11%) progressed to type 1 diabetes over a median follow-up of 5.3 years (range 5.2–5.5). The intervals from the initial blood sampling to the diagnosis ranged from 0.9 to 4.4 years, and the age at diagnosis varied from 7.8 to 13.4 years. All progressors had multiple (more than two) antibodies in their initial blood sample, whereas none of them carried the high-risk DQB1*0302 allele. One of them carried the protective DQB1*0602, and another subject carried the DQB1*0603 allele. An intravenous glucose tolerance test was performed in these two latter subjects, and both of them had a markedly reduced first-phase insulin response for a long time before the diagnosis, as we have reported previously (3). Two subjects carried the DQA1*05-DQB1*02 haplotype, one of them being homozygous and the other also having the protective DQB1*0602 allele. One subject carried the DQB1*x/x genotype (x = other than *02, *0301, *0302, or *0602), and one carried the protective DQB1*0301/0603 genotype. These results suggest that, at least in some individuals representing the general population, HLA-DQB1 high-risk markers are not indispensable for progression to overt type 1 diabetes, and the "protective" alleles do not provide full protection against the disease. In the present series, all of the children were older than 6 years of age when initially screened, and all but one of the progressors were older than 10 years of age at diagnosis, which must be taken into account when considering the DQB1 genotype distribution in the progressors, because we previously observed an association between age and the prevalence of DQB1 risk markers in patients with type 1 diabetes (4). In addition, the number of children who have so far presented with clinical diabetes is still low, and accordingly, the genotype distribution may be a matter of chance. Furthermore, 17 (0.4%) children from the initial target population of 4,280 schoolchildren were initially excluded from the study, because they had previously been diagnosed with clinical type 1 diabetes (3). HLA-DQB1 data was available for 15 of these subjects, and only one of them carried the protective DQB1*0602 allele, whereas 6 (40%) had the DQB1*02/0302 high-risk genotype (3).

Two recent studies have proposed a two-step screening strategy for prediction of type 1 diabetes in the general population (1,5). Although autoantibodies were 100% sensitive to predict type 1 diabetes in the present series of schoolchildren, the positive predictive value of any screening strategy did not exceed 50%. The HLA-DQB1 risk markers complicated the prediction, because the two progressors with a "protective" DQB1*0602 or *0603 allele would have been classified as subjects with a low risk of progression to type 1 diabetes. The positive predictive value of ICA ≥20 Juvenile Diabetes Foundation units was 29%, and that of IA-2A and multiple antibodies was 19%, all having a disease sensitivity of 100%. The positive predictive value and sensitivity of GADA were lower (11 and 50%), because only two GADA$^+$ subjects have progressed to type 1 diabetes. On the other hand, GADA have been suggested to be related to a slower progression to clinical disease; therefore, a number of GADA$^+$ children in the present study may later progress to overt diabetes. Environmental factors and/or genetic factors other than HLA-DQB1 may also be involved in the appearance of β-cell autoimmunity in the general population, at least after the age of 6 years. With the currently available methods, the accurate assessment of the individual risk of type 1 diabetes is complicated. The present data strongly support the use of combined screening for autoantibodies, whereas further studies are needed to establish the value of current genetic risk markers in the prediction of type 1 diabetes in populations of schoolchildren.

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Type 1 Diabetes and Arterial Dysfunction in Asymptomatic Chinese Adults

Atherosclerotic disease is much less common in Chinese subjects compared with Caucasian subjects. We have previously demonstrated that traditional atherosclerosis risk factors, such as aging and smoking, have less adverse effects on arterial endothelial function and structure in Chinese subjects (1,2). Because diabetes is an important risk factor for the development of coronary heart disease, and because it is associated with endothelial dysfunction in Caucasian subjects, we studied the arterial function of Chinese adults with type 1 diabetes.

We studied arterial endothelial function in 36 asymptomatic Chinese adults (age 29 ± 6 years). Of these subjects, 18 had type 1 diabetes and 18 were age- and sex-matched normoglycemic control subjects. No subjects in either group had clinical evidence of atherosclerosis, and none were taking any lipid-lowering drugs or cardiovascular medications. Arterial endothelial function was measured by the same operator, using a high-resolution B-mode ultrasound scan with regard to flow-mediated (endothelium-dependent) dilation (FMD) and glyceryl trinitrate (GTN)-induced (endothelium-independent) dilation of the brachial artery (% change of vessel diameter) (1,2).

The diabetic subjects (11 men and 7 women) were aged 29 ± 7 years; mean duration of diabetes was 7.4 ± 5.0 years (range 1.0–19.0) with a mean HbA_{1c} of 7.9 ± 1.8% (normal <6.5%). There were no significant differences between the two groups in anthropometric parameters, blood pressure, or lipid profile. The baseline flow and vessel size were similar between both groups. The diabetic group had lower FMD (6.8 ± 2.2 vs. 9.1 ± 2.0%, $P = 0.003$) and a lower GTN-induced dilation (13.9 ± 3.4 vs. 18.3 ± 4.0%, $P = 0.001$) when compared with the control subjects. In a multiple regression analysis of the two groups, diabetes was the only significant predictor for impaired FMD (model F = 3.4, $R^2 = 0.69$, $P = 0.005$), whereas vessel size ($\beta = -0.52$, $P = 0.005$), age ($\beta = -0.27$, $P = 0.04$), and diabetes ($\beta = -0.66$, $P < 0.001$) were significant predictors of GTN responses ($F = 11.6$, $R^2 = 0.49$, $P = 0.001$).

The prevalence of cardiovascular mortality in Chinese men and women is ~16-fold and ~6-fold less, respectively, compared with that in age-matched Caucasian adults. The underlying mechanism for this apparent protection in the Chinese remains unclear. This may be related to genetic and/or environmental differences. The major findings in this study were that of impaired endothelium and smooth muscle–dependent arterial dilation in asymptomatic young Chinese subjects with type 1 diabetes, similar to the findings reported in the Caucasian subjects (3). In comparison with our previous observations regarding the less deleterious effects of aging and smoking on Chinese versus Caucasian arteries (1,2), diabetes may be a more potent risk factor for vascular dysfunction in Chinese subjects.

The mechanism of diabetes-related endothelial and smooth muscle dysfunction remains unclear. It may be related to decreased baseline nitric oxide production and/or increased vascular superoxide generation. Accumulation of advanced glycosylation products in the subendothelial space and/or impaired smooth muscle responsiveness may also be contributory.

All of the subjects were free of atherosclerosis risk factors apart from diabetes, thus allowing a relatively independent assessment of diabetes-related pathophysiology in the present study. Because arterial endothelial dysfunction is an early key event in atherogenesis, the increasing prevalence of diabetes in developing countries, including China, may be associated with increased morbidity and mortality from atherosclerotic vascular events. Therefore, diabetes may be a particularly important risk factor for Chinese people.

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Lipoatrophy Associated With Lispro Insulin in Insulin Pump Therapy

An old complication, a new cause?

Lipoatrophy virtually disappeared as a cutaneous complication of insulin therapy after the introduction of recombinant human insulin. Consequently, we were surprised to observe two cases of marked lipoatrophy occurring in patients treated by lispro insulin administered by continuous subcutaneous insulin infusion (CSII).

The first case is a 10-year-old Caucasian girl diagnosed with type 1 diabetes at 4 years of age. HbA_{1c} levels had ranged between 7.8 and 8.7% (normal ≤6.3%) on two daily injections of human NPH and regular insulin (Humulin-Regular; Eli Lilly, Indianapolis, IN) with ultralente (Eli Lilly) added subsequently. Apart from mild lipohypertrophy of the biceps area, there were no cutaneous complications. At 8 years of age, increased HbA_{1c} levels and several severe hypoglycemic episodes prompted a switch to CSII (MiniMed model 507) using lispro insulin (Humulog; Eli Lilly), 35–40 U daily, 60% as basal replacement. HbA_{1c} levels fell to 6.5–7.2%, and there were no further episodes of hypoglycemia. Twelve months after commencing pump therapy, lipoatrophy was noted in the subcutaneous tissues of the anterior abdominal wall and progressed over the next few months. Treatment was changed from lispro to buffered human regular insulin (Velosulin; Novo Nordisk, Princeton, NJ). There has been no further progression of skin lesions, although the lipoatrophic areas have persisted (Fig. 1).

The second case is a 51-year-old Caucasian woman who was diagnosed with type 1 diabetes at 12 years of age and began CSII with buffered human regular insulin (Velosulin; Novo Nordisk) in 1996 (HbA_{1c} 8.1%). Previous treatment with prebreakfast injection of beef-pork NPH and regular insulin had resulted in no cutaneous complications. Ischemic heart disease, elevated LDL cholesterol, primary hypothyroidism, background of mild retinopathy, and distal sensory neuropathy were present. In 1998, treatment was changed to lispro insulin (Humulog; Eli Lilly) and HbA_{1c} levels were between 5.5 and 6.4%. In the summer of 1999, she noticed lipoatrophy in the abdomen and thigh, and her bolus doses before meals were taking longer to peak, even when bolus was administered into nonaffected areas. Examination revealed lipoatrophy involving the abdominal wall, lateral thighs, and buttocks, all of which were sites of previous insulin infusions.

These cases highlight a potential for lispro insulin to induce lipoatrophy. While CSII may have contributed to the problem, use of lispro appears to be the most important factor. No further progression in lipoatrophy was noted in either patient after the switch to buffered human regular insulin using the same MiniMed pump systems. Moreover, one author (W.V.T.) met a teenage girl at a symposium who developed lipoatrophy with lispro delivered by a Disetronic pump.

Lipoatrophy in the era of less highly purified insulins was considered to have an immunologic basis. However, Fineberg et al. (1) have reported no differences in immunogenicity between lispro and recombinant human insulin. Nevertheless, lispro has proved to be an effective substitute for human regular insulin in several cases of presumed immunogenic insulin resistance (2–4). Thus, the mechanism causing lipoatrophy in our patients is unclear.

The purpose of this letter is to alert clinicians to a potential complication of lispro insulin not previously published or reported to Eli Lilly during premarketing or postmarketing studies (J. Holcombe, personal communication). Fortunately, this adverse effect appears to be uncommon and readily managed by switching to human regular insulin. It would be important to determine whether others have observed similar problems and whether these problems are limited to CSII.

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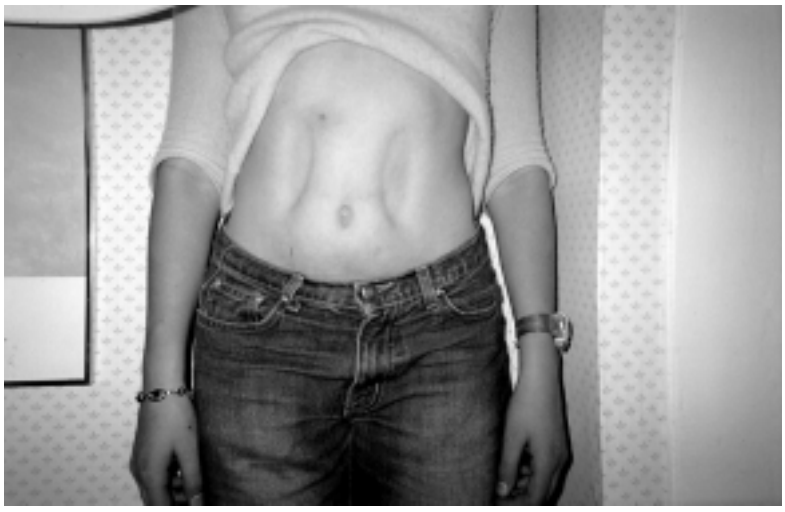

Figure 1—*Two large areas of lipoatrophy in the 10-year-old patient.*

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Clinical Evaluation of a Newly Designed Compliant Side Port Catheter for an Insulin Implantable Pump

The EVADIAC experience

Programmable implantable insulin pumps have proven to be safe and effective for achieving good metabolic control (1) and decreasing the rate of severe hypoglycemia (2). In 1994, a change in the production of insulin resulted in insulin precipitation and recurrent events of underdelivery in the MIP 2001 models (Minimed, Sylmar, CA). A new insulin variant with improved stability in delivery systems was produced in 1997 by Hoechst Marion Roussel and evaluated by the Evaluation dans le Diabete du Traitement par Implants Actifs (EVADIAC) Study Group (3). Yet, persistent underdelivery was still observed and could not be resolved by flushing procedures through the side port catheter. Difficulties in adjusting insulin dosage remained problematic. This underdelivery was explained by the fact that the forward stroke of the piston pump occurred in 2 ms with a volume of 0.5 µl, and the catheter lumen was only 0.2 mm in diameter. Thus, its compliance was too low to pass the stroke volume in 2 ms. Therefore, the manufacturer modified the catheter side port with the addition of three small titanium pillows that act as an accumulator, storing the initial impact of the hydraulic force pression of the stroke and adding compliance to the catheter system, resulting in an improved insulin delivery during bench tests.

The EVADIAC Group designed a study protocol to investigate the effect of this new side port catheter on the stability of insulin delivery and to assess the clinical improvement of the catheter compliance. After the approval of an ethical committee, 40 type 1 diabetic patients, currently implanted, were consecutively enrolled for a new implantation with the Minimed implantable pump MMT 2001 and the modified side port catheter MMT 4027 (Minimed). The patients were seen every 45 days to refill the pump reservoirs, to examine the accuracy of the insulin delivery system, to measure the HbA_{1c} levels, and to check for adverse events. The main end point was the accuracy of insulin infusion (% error), calculated from the ratio of the difference between the programmed and the actual infused insulin volume on programmed insulin delivery.

Throughout the study, 40 patients were followed for 450 days, with clinical visits every 45 days (10 refill procedures). The HbA_{1c} levels remained stable at 7.70 ± 0.98% (mean ± SD). The mean percent error was negative at the first 2 refills and then remained nonsignificantly modified between 8.31 ± 7.3% at the 6th refill and 10.4 ± 11.8% at the 10th refill (NS). Thus, during the 450 days of follow-up, the infusion accuracy remained acceptable under the percent error threshold of 15%, previously defined as a level of unacceptable dysfunction. During the same period, the number of insulin units actually infused per dose plateaued at 46 ± 20 U/kg at the 6th refill and 55 ± 21 U/kg at the 10th refill (NS). Thus, the indexes of good pump delivery throughout the catheter appeared constant and stable over the course of observation.

During this observation period, eight adverse events occurred between the 9th and the 14th month (16 of 100 patient-years). These events included one catheter encapsulation, one catheter obstruction, and six catheter/pump-related underdeliveries, all solved by pump NaOH rinse, catheter flushing procedures, or catheter surgical clearance (for the catheter encapsulation). Several of these adverse events were similar to those observed before 1994 (4).

After 450 days of follow-up in 40 patients, we concluded that modified side port catheters with titanium pillows restore the expected infusion accuracy of implantable pump systems without increasing device complications. The new system appears to be safe and effective. Due to the combined new insulin variant from Hoechst (3) and modified side port catheter by Minimed, the implantable insulin infusion system has returned to its state observed before the change in insulin production (4). Accordingly, our results need long-term confirmation, examined while continuing to refill pump reservoirs at 90-day intervals, as should be allowed by reservoir capacity.

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Efficacy of Tibetan Medicine as an Adjunct in the Treatment of Type 2 Diabetes

Diabetes is the most frequently seen chronic disease in Tibetan medical clinics (1). Ancient texts of Tibetan medicine outline the successful management of diabetes (2). However, there is a paucity of systematic research studies using modern scientific tools to evaluate the efficacy of Tibetan medicine. Therefore, we undertook a study to assess the efficacy of Tibetan medicine when combined with a diet and exercise regimen compared with a diet and exercise regimen alone in controlling the blood glucose and glycated hemoglobin (GHb) in newly diagnosed or untreated type 2 diabetes.

A total of 200 newly diagnosed or untreated type 2 diabetic patients, who were eligible and consented to participate in the trial, were recruited from two branch clinics of the Tibetan Medical and Astrological Institute (TMAI), the Bangalore Branch Clinic in South India and the New Delhi Branch Clinic in north India, from April 1997 to April 2000. The subjects were aged 30–65 years, with a fasting venous plasma glucose (FPG) value between 140 and 250 mg/dl and a postprandial plasma glucose (PPG) value of ≥200 mg/dl. The subjects were willing to follow dietary and lifestyle guidelines. Patients who had an FPG >250 mg/dl, who had a BMI <19 kg/m^2, or who were insulin dependent, were not included in the study. The other criteria for exclusion were hypertension, heart disease, kidney failure, pregnancy, a period of lactation <6 months, history of a blackout episode, or any complaint of vision loss.

At each center, all of the 200 subjects, 136 men and 64 women, were randomized into two groups, the treatment group and the control group. The treatment group was treated with Tibetan medication in the form of powder or pills, as prescribed by a practitioner of Tibetan medicine, in addition to the modification of diet and lifestyle recommended by the American Diabetes Association (3). At least two of four Tibetan medicines (Kyura-6, Aru-18, Yungwa-4, and Sugmel-19) were administered based on each patient's age, sex, personality, pulse, and urine characteristics. Subjects in the control group were treated only with the dietary and lifestyle modification. The study was not blind, and the subjects gave their informed consent. The TMAI Ethics Committee approved the study.

A predesigned proforma was created for each patient. FPG, 2-h PPG, and GHb levels were estimated at baseline, 12 weeks, and 24 weeks. Of the 200 subjects, 136 patients completed 12 weeks of follow-up and 112 patients completed 24 weeks of follow-up. The age, sex, BMI, FPG, PPG, serum cholesterol, serum triglycerides, serum HDL, and GHb of the subjects who withdrew at 12 and 24 weeks were similar in both groups at the baseline. Therefore, an intention-to-treat analysis was performed. A Student's *t* test was used to compare the mean values between the two groups. χ^2 test was applied to assess the association between the two groups and the other categorical variables. The STATA 6.0 intercooled version (STATA, Houston, Texas) was used to analyze data.

The treatment and control groups were comparable with regard to age, sex , blood pressure, body weight, BMI, serum creatinine, and urine albuminuria. However, despite randomization, the treatment group had worse symptoms, including significantly higher FPG and PPG values (178.2 ± 34.1 and 284.4 ± 65.3 mg/dl vs. 166.4 ± 35.5 and 260.2 ± 71.1 mg/dl, $P < 0.05$), as

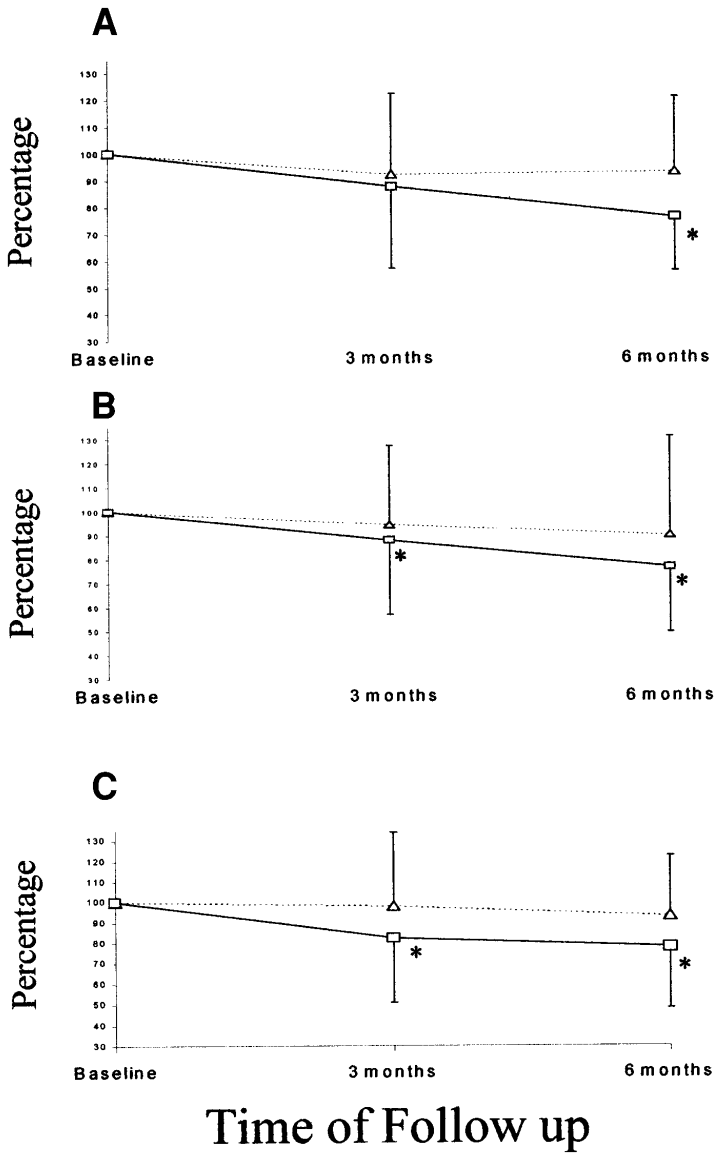

Figure 1—*Change in fasting plasma glucose (A), postprandial plasma glucose (B), and GHb (C), after treatment with Tibetan medicine. △, Control; □, treatment.* *P < *0.05.*

well as a higher GHb value (9.4 ± 3.0 vs. 8.5 ± 2.3%, $P < 0.01$), indicating poorer glycemic control at the start of the study in the treatment group. The treatment group also had a higher serum cholesterol level.

The percentage change in the levels of these parameters was calculated from the baseline of the treatment group, because the baseline plasma glucose values were different between the two groups (Fig. 1). Fasting blood glucose levels decreased by 12.2 ± 30.5% at 12 weeks and by 23.4 ± 20.0% at 24 weeks in the treatment group compared with 7.4 ± 30 and 6.4 ± 27.7% in the control group ($t = 0.94$, $P = 0.35$ at 12 weeks; $t = 3.76$, $P = 0.0003$ at 24 weeks). The PPG measurement was significantly lower in the treatment group at 12 and 24 weeks (decrease of 18.0 ± 31.2 and 23.4 ± 27.1%) compared with the control group (decrease of 5.5 ± 32.9 and 10.0 ± 41.2%) ($t = 2.21$, $P = 0.02$ at 12 weeks; $t = 1.98$, $P = 0.05$ at 24 weeks). At 12 weeks, the percentage decrease in the GHb levels was 1.9 ± 35.8% in the control group compared with 17.5 ± 31.3% in the treatment group ($t = 2.58$, $P = 0.011$). At 24 weeks, the decrease in GHb was 21.8 ± 30.1% in the treatment group compared with 6.7 ± 29.3% in the control group ($t = 2.44$, $P = 0.02$). There was no significant change in body weight, blood pressure, or serum lipids in either group.

Previous studies have reported that when used alone or in conjunction with sulfonylureas, traditional Chinese medicine decreases the fasting and postprandial blood glucose levels in diabetic patients (4,5). Chinese medicine has been reported to improve the symptoms of diabetes and insulin and glucose blood levels (5). However, there are no published reports in English medical literature regarding the effectiveness of Tibetan medicine in the treatment of diabetes. We report a significant improvement in glycemic control with the use of Tibetan medicine in patients with a recent onset of type 2 diabetes compared with patients treated only with diet and exercise. The improvement in glycemic control was observed at 3 and 6 months after the start of the treatment. We have not measured insulin or C-peptide levels in our patients.

One of the limitations of this study was a high drop-out rate during follow-up. However, the characteristics of the subjects who dropped out from the two groups were similar and therefore should not alter the conclusions. Further evaluation of the Tibetan medical system in patients with diabetes will require blinded placebo controlled trials and comparisons of this system with other available oral hypoglycemic agents.

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COMMENTS AND RESPONSES

Acknowledgments

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Therapeutic Benefits of ACE Inhibitors and Other Antihypertensive Drugs in Patients With Type 2 Diabetes

Recently, Pahor et al. (1) presented a meta-analysis based on four studies assessing whether ACE inhibitors are superior to alternative agents for the prevention of cardiovascular events in patients with hypertension and type 2 diabetes. The four eligible trials were as follows: *1*) the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET), *2*) the Appropriate Blood Pressure Control in Diabetes Trial (ABCD), *3*) the Captopril

Prevention Project (CAPPP), and *4*) the U.K. Prospective Diabetes Study (UKPDS) (2–5). FACET's study lasted only 2.8 years, whereas the other studies lasted 5, 6.1, and 8.4 years, respectively. All of the trials were blind except for FACET. The primary end points of FACET were serum lipids and glucose metabolism, whereas the primary end point of the ABCD trial was the rate of decline in creatinine clearance. Neither of these two studies were powered for cardiovascular end points, only for the primary end points mentioned above. The CAPPP study, based on 10,985 hypertensive patients, showed that captopril and conventional antihypertensive treatments did not differ in efficacy in the prevention of cardiovascular morbidity and mortality. However, the subanalysis of the 572 diabetic patients (5.2%) showed a significantly better cardiovascular outcome for ACE inhibition versus alternative treatments. The UKPDS fulfilled all of the ideal criteria for conducting a cardiovascular end point trial of blood pressure lowering in hypertensive type 2 diabetic patients (n = 758); the study was double-blind, and randomized, powered for cardiovascular end points, included the largest number of patients, had the longest observation period (8.4 years), and consequently had the largest number of cardiovascular events. Actually, the number of events in the UKPDS study was greater than the combined event rate of the three studies mentioned previously, which deal with acute myocardial infarction (MI) and the cardiovascular end point combined and death. Despite these findings, Pahor et al. (1) claim that the UKPDS should be excluded from the meta-analysis because a test of heterogeneity revealed the study as a potential outlier. In other words, the test revealed that the UKPDS results were different from the results of the three studies previously mentioned, which all suffer from various flaws in relation to the study design, as previously discussed.

The ABCD trial originally reported 5 MI cases treated with ACE inhibition and 25 MI cases treated with nisoldipine. However, these figures were corrected by the principal investigator of the ABCD trial, Robert Schrier, in his state-of-the-art lecture at the American Society of Nephrology 6 November 1999 in Miami, FL. The correct figures were presented as 9 MI cases in the ACE inhibitor group and 27 MI cases in the nisoldipine group. The relative risk (95% CI) for MI quoted in the Pahor et al. analysis (1) was 0.73 (0.54–0.99). Applying these corrected values will now give the following numbers of acute MI, stroke, cardiovascular events, and all causes of mortality from ACE-inhibitors versus other antihypertensive drugs: 90 vs. 111, 56 vs. 58, 170 vs. 190, and 109 vs. 108, respectively. Therefore, none of the reported differences in cardiovascular events and mortality are significant; the differences are only borderline significant.

Aggressive blood pressure lowering in hypertensive diabetic patients is recommended. However, a reduction in blood pressure to a level <130/85 mmHg is unlikely to be achieved by monotherapy in most patients, as demonstrated in several recent trials carried out in hypertensive patients, including the four studies mentioned above. Consequently, we suggested that the combination of ACE inhibitors with other first-line drugs, such as calcium channel blockers, diuretics, and β-blockers, is a rational choice for treatment of hypertensive diabetic patients.

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Meta-analysis of Hypertension Trials in Diabetic Patients

Response to Parving and Rossing

Methodological and statistical reasons may explain why the U.K. Prospective Diabetes Study (UKPDS) was considered an outlier when compared with the other reviewed studies. Study design, report, and conduct weaknesses limit the conclusions of the UKPDS (1). Several of these weaknesses have been discussed in published articles (2,3). These weaknesses are as follows: *1*) the UKPDS hypertension study was not blind, but open label; *2*) the dosing regimens for captopril may not have been adequate (captopril was given twice per day; for the treatment of hypertension captopril should be given three times per day [4]); *3*) the trial was not powered to detect differences in drug effects on cardiovascular events; *4*) none of the blood pressure goals in the tight blood pressure control group (150/85 mmHg) or in the less tight blood pressure control group (initially 200/105 mmHg and recently 180/105 mmHg) are currently recommended according to U.S. or U.K. guidelines for the treatment of hypertension in patients with or without diabetes (5,6); *5*) in the less tight blood pressure control group the first-line agent was furosemide, a diuretic not recommended for treatment of hypertension, according to the current guidelines (5,6); and *6*) patients randomized to atenolol were significantly more likely to dropout of the trial than those randomized to captopril (35 vs. 22%, $P < 0.0001$), which may have created biased results.

These weaknesses may have obscured potentially important differences between captopril and atenolol and limited the possible generalizations of the potential benefits of more intense blood pressure control. The current recommended blood pressure target of <130/85 mmHg in patients with diabetes relies solely on observational data (5,7), not on definitive evidence from randomized controlled trials. It is not known whether a blood pressure target of <130/85 mmHg can be

Table 1—*Cardiovascular outcomes in the ACE-inhibitors group and other-drugs group in combined analyses of ABCD, CAPPP, and FACET*

	ACE inhibitors	Other drugs	Odds ratio (95% CI)	*z*	Overall effect (*P*)	Heterogeneity (*P*)
n	733	689	—	—	—	—
Acute MI	29	65	0.41 (0.27–0.63)	4.13	<0.001	0.25
Stroke	35	41	0.77 (0.48–1.22)	1.12	0.3	0.32
Combined cardiovascular events	73	117	0.55 (0.40–0.74)	3.88	<0.001	0.95
Mortality	35	50	0.63 (0.40-0.97)	2.08	0.04	0.65

Data are *n* unless otherwise indicated.

achieved safely in the majority of diabetic patients with hypertension. It remains to be established whether the more favorable outcomes in the tight blood pressure control group of the UKPDS are explained by better blood pressure control, the type of first-line drug being used (furosemide versus captopril or atenolol), chance, or any combination of these factors.

As described in previous reports, the Appropriate Blood Pressure Control in Diabetes (ABCD) study was conducted double-blind (8), whereas the Captopril Prevention Project (CAPPP) (9), the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) (10), and the UKPDS (1) were all conducted open label. None of the individual trials were adequately powered to assess effects on the risk of major cardiovascular events in diabetic patients with hypertension. The updated number of events in the nisoldipine and enalapril groups of ABCD were 27 and 9 for acute myocardial infarction (MI), 11 and 7 for stroke, 8 and 10 for heart failure, and 18 and 14 for all-cause mortality (M.P., personal communication with Dr. R. Estacio). We have estimated the number of combined cardiovascular events (47 in the nisoldipine and 29 in the enalapril group) by adding the number of new MI events and heart failure events to the previously reported number of combined events. In an analyses of the four trials combined with these new data, the odds ratio for ACE inhibitors versus other treatments (95% CI) was 0.72 (0.54–0.96) for acute MI, 0.87 (0.59–1.27) for stroke, 0.81 (0.64–1.01) for cardiovascular events, and 0.90 (0.68–1.20) for all-cause mortality. The tests for heterogeneity were significant for the outcomes of acute MI and cardiovascular events when the data from the UKPDS were combined with the data from the other three trials ($P < 0.001$ for both outcomes), but the outcomes were not significant when the UKPDS was excluded from the meta-analysis, suggesting that the results of the UKPDS were different from the results of the other three trials. It cannot be assessed whether such heterogeneity was due to the many weaknesses of the UKPDS, the therapeutic equivalence of captopril and atenolol, or chance. Whether atenolol is equivalent to captopril for the treatment of diabetic patients with hypertension remains a question.

Furthermore, it was appropriate not to combine the UKPDS data with the data of the other trials because of the substantial heterogeneity generated by the inclusion of the UKPDS. Thus, only the data from the ABCD study, the CAPPP, and the FACET were included in the final meta-analytic calculations. When the data from the ABCD study, the CAPPP, and the FACET were combined, the patients randomized to an ACE inhibitor had a significantly lower risk of acute MI, cardiovascular events, and all-cause mortality than those randomized to an alternative treatment (Table 1). There were no such differences for the outcome of stroke. The revised data from the ABCD study did not change the conclusions of our meta-analysis (11).

Several recent comparative trials in hypertension have shown important differences in cardiovascular outcomes according to the type of drug administered, despite the minimal differences in blood pressure lowering. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial , doxazosin was inferior to chlorthalidone (12). In a meta-analysis of nine trials with ~120,000 person-years of follow-up, calcium channel blockers were inferior to other drugs (13). In the present meta-analysis, ACE inhibitors appear to provide a special advantage in addition to blood pressure control when compared with the alternative agents tested. These data suggest that other mechanisms, possibly including the modulation of fibrinolysis, may be important in determining the therapeutic effects of antihypertensive drugs. Recently, the Fosinopril versus Amlodipine Comparative Treatments Study, a double-blind randomized controlled trial of 96 diabetic patients with hypertension, has shown that fosinopril resulted in a significantly (20%) lower level of plasminogen activator inhibitor 1 compared with amlodipine over 4 weeks of treatment (14). In brief, the available evidence suggests that the manner in which blood pressure is lowered is important. The advantages of more intense blood-pressure lowering here yet to be demonstrated in randomized controlled trials. While the present meta-analysis should not be considered conclusive, it seems beneficial to prefer an ACE inhibitor as a first-line agent when treating hypertension in diabetic patients.

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Environmental Factors and Type 1 Diabetes

In the July 2000 issue of *Diabetes Care*, Hummel et al. (1) reported a 2-year follow-up of the German BABYDIAB Study. Indeed, the BABYDIAB Study is an interesting and comparably large prospective study that follows infants of mothers or fathers with type 1 diabetes. So far, 10 children have developed diabetes and an additional 21 have developed islet cell antibodies. In the present article, Hummel et al. (2) attempted to study the possible effects of environmental risk factors, such as breast-feeding and vaccination, as well as measles, mumps, and rubella infections, to determine the likelihood of genetically susceptible children to develop diabetes or β-cell autoimmunity, as mirrored by islet autoantibodies. The authors found no significant effect of breast-feeding prevalence, duration of vaccinations, or reported childhood viral infections, and they concluded that these environmental factors are unlikely to have a major causal influence on initiating islet autoimmunity in genetically susceptible children. Nevertheless, it is important to identify what is meant by the expression "major." Does it relate to relative or absolute risk, to the attributable proportion, or to the total number of type 1 diabetes cases (only a small fraction of which occur in first-degree family members)? The magnitude of risk considered to be important and the basis for this consideration should be defined when designing any study. Moreover, it should lead to a comprehensive power calculation that would establish the possibility of the study to detect such effects.

For example, the meta-analysis by Gerstein et al. (3), which is cited by Hummel et al. and was based on thousands of cases and controls, indeed showed a rather small overall effect in terms of relative risk (odds ratio [OR] 1.63, 95% CI 1.22–2.17). In populations with a low breast-feeding frequency and duration, the attributable proportion of cases and the total number due to this specific factor might still be of significance. In populations with a high compliance to vaccination programs, the number of cases due to this factor could be considered to be of major importance if identified as having a risk exposure with an OR of 1.5–2.0.

When applying a power calculation test for cohort studies with internal comparisons (4) on breast-feeding data presented by Hummel et al., the number of expected events (i.e., clinical diabetes or autoantibody appearance) necessary to detect a relative risk of 1.5 would be estimated as 156 cases among the nonexposed children, given that the proportion of exposed (e.g., no breast-feeding) to nonexposed is 1:4 and the desired power is 80%, ($P < 0.05$). However, the expected number of events (under the null hypothesis) of independent component analysis positivity in the report by Hummel et al. was ~25. Eight cases of clinical diabetes were among the unexposed (breast-fed) children, which suggests a very low power to detect a risk increase of 1.5. With this sample size, only risk increases of ~5–10 times would be detectable. With 16% of bacillus Calmette-Guerin-vaccinated individuals, approximately the same high probability of missing a risk increase would be expected. As for the diphtheria and tetanus toxoids and pertussis vaccine -vaccination, to which almost all the children in the cohort were exposed, even extremely large effects would remain undetected. In addition, for measles, mumps, and rubella vaccines and exposure to measles, mumps, or rubella infections the study gives no meaningful assessment of risk, because of the very low power.

For the study of a complex disease like type 1 diabetes, which requires the consideration of large numbers of risk genes and environmental factors, much larger studies are needed for estimating possible effects. In general, case-control studies are preferable in studying low-prevalence diseases because they allow enough power to effectively estimate low relative risks and to identify exposure interactions and confounding effects in multivariate analyses. The problems with potential disease-dependent biases in case-control studies certainly must be recognized, but not overestimated, because they can be avoided by using a prerecorded hospital or register data. The lower sensitivity/specificity of exposure estimates often experienced in retrospective studies and unrelated to disease, will only lead to more conservative risk estimates, and can be readily compen-

sated for by larger study populations (5). Indeed, prospective cohort studies now taking place in different parts of the world may be important for the assessment of the predictive value of immune markers at different ages before clinical onset of type 1 diabetes and for the presentation of viral antibodies. Even for these purposes, though, larger studies are preferable.

A meaningful assessment of the impact of potential environmental risks on study populations is of interest for understanding the mechanisms of type 1 diabetes and for developing preventive strategies. However, despite the prospective design, Hummel et al.'s study on the children of mothers or fathers with type 1 diabetes is insufficient. Conclusive negative results cannot be attained until studies with substantially larger populations are conducted.

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Response to Dahlquist

Environmental factors and type 1 diabetes

There are important differences between the prospective studies from birth and the case-control studies of type 1 diabetes. First, the prospective studies have been performed on subjects who have relatives with type 1 diabetes and, therefore, have the so-called familial type 1 diabetes, a minority of all type 1 diabetes cases. None of the case-control studies have examined risk factors in individuals having a relative with the disease. A second difference is that prospective studies examine the relationship between environmental factors and the development of islet autoimmunity. This is very important because *1*) most of the environmental factors examined (breast-feeding, introduction of cow's milk, vaccinations, etc.) are likely to have causative effects early in life and *2*) as we have previously shown, islet autoantibodies appear early in life; type 1 diabetes, on the other hand, can manifest at any age (1). Case-control studies can only relate environmental factors to endpoint disease; therefore, unlike these prospective studies, case-control studies cannot distinguish between environmental factors that could be primary or secondary in the disease process. Hence, the accumulation of data from these comparatively few labor-intensive prospective studies from birth is fundamental in the identification of factors that may trigger autoimmunity.

As pointed out by Dahlquist (2), the question of power calculations remains crucial to determining associations between environmental factors and disease. Although the power calculations presented by Dahlquist are empirically correct, they fail to take into consideration the actual data from the BABYDIAB cohort. The motivation for our conclusion, that there was no major effect of breast-feeding duration and islet autoimmunity in the offspring of mothers with type 1 diabetes, was that breast-feeding duration in children developing islet autoimmunity tended to be longer, rather than shorter, than those remaining autoantibody-negative (median exclusive breast-feeding duration 8 vs. 4 weeks). Indeed, the odds ratio for developing antibodies in children not breast-fed versus those breast-fed was 0.5 (i.e., autoantibodies were twice as frequent in breast-fed children) with an upper CI of 1.4, suggesting that even if considerably more children were studied, finding an association similar to that reported by Gerstein (3) [odds ratio of 1.63 (95% CI 1.22–2.17)] would be highly unlikely. Nevertheless, this can only be verified with more data. In addition, the prospective studies should be encouraged to perform the type of meta-analyses reported for case-control studies. Moreover, because the validity of meta-analyses is dependent on an unbiased representation, reporting the data is necessary even if no associations are found (4). Undoubtedly, a study the size of the German BABYDIAB study, which found an association between one of the environmental factors and the appearance of islet autoimmunity, would be published in a high-impact journal. This is true for many of the published case-control studies in which the study populations were often small.

The second issue raised by Dahlquist relates to the definition of what constitutes a major effect. Again, we acknowledge that an association reported by Gerstein for cow's milk may be considerable in certain circumstances. However, we would like to stress that the issue of these environmental factors listed as causative agents has gone beyond the types of associations observed by Gerstein et al. Several studies on antibodies to cow's milk proteins report a markedly increased prevalence of such antibodies in patients compared with control subjects; for example, bovine serum albumin antibodies were reported in 100% of patients vs. 0% of control subjects (5). Even when allowing for agents that are more selective with particular HLA genotypes or more persistent in subjects who develop type 1 diabetes, such major differences are not supported by our study, Diabetes Autoimmunity Study in the Young (6), or the Australian BABYDIAB Study (7). We cannot exclude effects from each of the environmental factors presented; however, through the examination of autoimmunity from birth, we cannot attribute them major causative roles in the pathogenesis of type 1 diabetes.

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Efficacy of Octreotide in the Therapy of Severe Nonproliferative and Early Proliferative Diabetic Retinopathy: A Randomized Controlled Study

Response to Grant et al.

I read with interest the article by Grant et al. (1) regarding the effects of octreotide on severe nonproliferative and early proliferative diabetic retinopathy. However, I have a few observations and questions for Grant et al. First, I noticed that the baseline Early Treatment of Diabetic Retinopathy Study (ETDRS) scores of the two groups were not compared. Did these two groups have baseline ETDRS scores that were not significantly different? The results of the study cannot be interpreted without the knowledge of the baseline ETDRS scores of the two groups. In addition, it appears that the photos were not judged by a reading center, as is traditional for most diabetic retinopathy studies. Also, there is no comment regarding the potentially confounding ocular factors, such as cataract extraction or yttrium:aluminum:garnet (YAG) laser capsulotomy, that might cause the diabetic retinopathy to progress independently of glycemic control (2). Finally, I noticed that all of the patients in the octreotide treatment group had a decrease in HbA_{1c} levels, averaging 1.2%. In the control group, however, the average HbA_{1c} level of the group remained essentially unchanged throughout the study, and in some subjects, HbA_{1c} actually increased during the study. At the end of the study, the mean HbA_{1c} in the treatment group was 7.1%, whereas in the control group it was 8.3%. This discrepancy is similar to the difference in HbA_{1c} levels between the conventional and the more intense treatment groups in the U.K. Prospective Diabetes Study, in which the end point of needing retinal laser was decreased by 29% in patients with more intensive control and lower HbA_{1c} levels (3). Because Grant et al.'s study was open label, it was possible that patients receiving study drugs were more motivated to be vigilant about their diabetes control than those who were treated conventionally. Therefore, we may actually be seeing an epi-phenomenon in which the difference in the need for panretinal photocoagulation between the treatment and control groups was actually due to the improved glycemic control in the treatment group. It is not clear from this study whether improved glycemic control is attributable to octreotide or to patient-initiated measures.

The use of octreotide to inhibit IGF-1 and its effects on diabetic retinopathy is an interesting and promising avenue of therapy. I look forward to the results of ongoing randomized clinical trials that use a reading center and are conducted in a prospective, masked fashion. The authors of this study appropriately noted that their results only suggest that the use of octreotide may be helpful in delaying the progression of retinopathy. However, this report does not support the use of octreotide for diabetic retinopathy outside the context of a randomized, prospective, controlled, masked clinical trial.

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K.M.G. has been a paid investigator for Novartis.

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Efficacy of Octreotide in the Therapy of Severe Nonproliferative and Early Proliferative Diabetic Retinopathy: A Randomized Controlled Study

Response to Gehrs

We appreciate both Dr. Gehrs' (1) careful examination of our study (2) on the efficacy of octreotide in the therapy of severe nonproliferative and early proliferative diabetic retinopathy and the opportunity to respond to her thoughtful comments. In response to her question concerning the baseline scores, the control group and octreotide-treated group baseline Early Treatment of Diabetic Retinopathy Study (ETDRS) scores were not different, with mean (± SD) values of 51.6 ± 4.0 for control and 51.6 ± 4.8 for treated groups. Although a reading center was not used in this pilot study, each retinal specialist used identical criteria for determining when patients reached high risk proliferative diabetic retinopathy, as defined by an ETDRS score of 71. As detailed in our article, the ETDRS score was based on ocular examinations and stereoscopic photographs using standard photographic fields and angiography as needed. There is no reason to believe that the treatment influenced the decision to laser, because the three retina specialists were masked from the study treatment. Patients were specifically

instructed not to discuss medications with anyone except the endocrinologist.

Regarding potential confounding factors, no cataract extractions or yttrium: aluminum:garnet laser capsulotomies were performed on the participants during the study. We acknowledge that cataract extractions have been associated with a 20–30% incidence in the advancement of retinopathy (3,4). There are many older uncontrolled retrospective reports of diabetic retinopathy progression after surgical techniques of intracapsular or extracapsular cataract extraction. More importantly, there are also prospective studies using the phacoemulsification technique that indicate no significant advancement of diabetic retinopathy (5). Dr. Gehrs is correct in stating that cataract extraction has also been associated with increasing macular edema and decreasing visual acuity (6), but these were not the end points we used in our study.

Improved glycemic control has been noted in patients receiving octreotide. Octreotide blocks the effect of counter-regulatory hormones such as growth hormone, glucagon, and cortisol, resulting in decreased blood glucose fluctuations and thus facilitating the regulation of blood glucose. However, we do not believe that the beneficial effect observed in the octreotide-treated patients was a result of improved control. As discussed in our report, an earlier study using octreotide alone, without concomitant thyroxine, also resulted in improved glycemic control with mean HbA_{1c} levels of 6.4 ± 0.9% in octreotide–treated patients versus mean values of 8.1 ± 1.8% in conventionally managed patients (7). In this previous study, the octreotide-treated patients and the conventionally-treated patients had an identical incidence of panretinal photocoagulation. Thus, improved glycemic control in our current study cannot explain the efficacy of octreotide therapy. In addition, there are studies suggesting that quickly bringing patients under tight control may actually worsen retinopathy acutely; this effect, however, disappears with a longer duration of tight control (8).

As Dr. Gehrs indicated (1), these results suggest a promising therapeutic approach for treating diabetic retinopathy. However, routine use of octreotide in patients with the progressive vision-threatening disease cannot be recommended until results from ongoing more definitive trials become available.

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4-g Monofilament Is Clinically Useful for Detecting Diabetic Peripheral Neuropathy

The American Diabetes Association recommends the use of the 10-g Semmes-Weinstein monofilament for the early identification of diabetic patients at risk for foot ulceration (1). However, this 10-g monofilament can only detect advanced diabetic peripheral neuropathy (DPN). Thus, we evaluated whether other monofilaments could be useful for the detection of early DPN with high sensitivity and high specificity, and compared the results of monofilament tests with the results of microneurography.

We recruited 65 patients (aged 61.0 ± 1.3 years, diabetes duration 9.8 ± 1.0 years [range 1–35]) with type 2 diabetes to participate in this study. Of these patients, 24 were treated with oral hypoglycemic agents, 32 were treated with insulin, and 9 were kept on a controlled diet only. In addition, 19 patients had background retinopathy, 2 had proliferative retinopathy, and 21 had microalbuminuria (>30 mg/day) defined as diabetic nephropathy. Patients with at least two of the following criteria were diagnosed with DNP: *1*) numbness in the toes, *2*) loss of ankle jerk, and *3*) decreased vibratory sensation assessed by a 128-Hz tuning fork (<10 s). Participants were tested for their ability to sense three kinds of Semmes-Weinstein monofilament, with target forces of 2, 4, and 10 g, respectively, at three sites of the foot: the great toe, the plantar aspect of the first metatarsal, and the plantar aspect of the fifth metatarsal (2,3). Individual cut off monofilament was defined as the lowest target force to sense. Microneurography was performed as previously described (4).

The sensitivity and specificity of the 2-g monofilament in the detection of DPN were 0.48 and 0.86, respectively. On the other hand, the corresponding values for the 4-g monofilament, 0.85 and 0.73, respectively, were quite close to those for the 10-g monofilament (0.88 and 0.68, respectively). Thus, we concluded that the 4-g monofilament was clinically useful for detecting DPN. Participants were divided into two groups based on a cut off target force: the 2-g monofilament group (group A, n = 52) and the 4- and 10-g monofila-

ments group (group B, $n = 13$). The maximal nerve velocity of group B was significantly lower than that of group A (50.4 ± 1.5 vs. 57.3 ± 0.6 m/s, $P < 0.0001$). The amplitude of group B was also significantly lower than that of group A (119.9 ± 31.8 vs. 184.1 ± 11.5 μV, $P < 0.05$).

The 10-g monofilament has typically been considered the easiest tool to use for detecting the loss of protective sensation (5,6). However, the 10-g monofilament is only capable of detecting severe DPN, and there is no information on the usefulness of other monofilaments for detecting early DPN. Consistent with studies on microneurography, our data show that the 4-g monofilament is clinically useful in the detection of relatively early DPN. Although the sensitivity and specificity of the 4-g monofilament were not sufficient for detecting DPN, this monofilament might be the easiest to apply to the entire diabetic population when factors such as cost, ease of application, and portability are taken into consideration. Because the number of participants was limited, further study is needed to clarify the usefulness of the 4-g monofilament for detecting early DPN.

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4-g Monofilament Is Clinically Useful for the Detection of Diabetic Peripheral Neuropathy

We agree with Nagai et al. (1) that the Semmes-Weinstein 10-g monofilament detects severe rather than mild diabetic peripheral neuropathy. However, the choice of monofilament to be used in clinical practice is based on its intended purpose. In our work, we were keen to detect patients at high risk of ulceration, whereas Nagai et al. were seeking an instrument that would detect neuropathy at an earlier stage. Our rationale for selecting the 10-g monofilament was to detect very high-risk patients so that limited resources of diabetes education and podiatry could be used for those who are most at risk of neuropathic ulceration. Another point emphasized in our article (2) was that even for a monofilament of any given strength, sensitivity and specificity for the detection of neuropathy can be varied according to the number of sites and the criteria for abnormalities.

We fail to see from the data provided by Nagai et al. (1) any evidence to substantiate the claim that the 4-g monofilament is better than the 10-g monofilament. Furthermore, we do not see any justification for the claim that the "4-g monofilament is the easiest to apply when factors such as cost, ease of application, and portability are taken into account."

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Errata

Savage S, Estacio RO, Jeffers B, Schrier RW: Urinary albumin excretion as a predictor of diabetic retinopathy, neuropathy, and cardiovascular disease in NIDDM. *Diabetes Care* 19:1243–1248, 1996

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In the lists of authors of the above articles, the degree PhD was appended to Barrett Jeffers's name in error. He should have been listed as Barrett Jeffers, MS.