OBSERVATIONS

Effectiveness of Culture-Specific Diabetes Care for Surinam South Asian Patients in the Hague

A randomized controlled trial/ controlled before-and-after study

An extremely high prevalence of diabetes has been found among South Asians, especially among immigrants living in a western society (1). In the Hague, we found a high prevalence of diabetes among South Asians from Surinam (2). Because usual diabetes care had insufficient affinity with the cultural and culinary traditions of this population, a new culture-specific type of care was developed. We investigated whether this intervention led to a decrease in HbA_{1c} level, an improvement in lipid profile, or a decrease in BMI.

The intervention consisted of the referral of South Asian patients by their attending physician to a specialist diabetes nurse and a dietitian. These care providers received training to improve their knowledge of the South Asian cultural and culinary traditions. They made use of newly developed educational materials consisting of an audio-cassette containing general diabetes information recorded in the Surinam-Hindi language and two booklets, one containing general information on nutrition and another containing a carbohydrate variation list; both were based on South Asian cooking. It was expected that the advice from the dietitian would be more applicable, among other things, because of the information concerning calorie-equivalent dishes contained in the carbohydrate variation list. It was also expected that the interaction between patients and care providers would improve, resulting in improved compliance with therapy. The diabetes education provided by the nurses and dieticians consisted of intensive guidance (~4–7 visits) for 3 months, after which the patients continued to receive guidance from these care providers but with longer intervals.

The intervention study was carried out in three general practices (eight general practitioners) and an outpatient clinic. All Surinam South Asian patients known to have type 2 diabetes, with no comorbidity interfering with the interpretation of metabolic control (e.g., recent myocardial infarction or dementia), and who visited their attending physician during the first half of 1998, were included in the study.

The first part of the study was a randomized controlled trial (RCT), in which the patients were randomized based on date of birth: odd numbers (intervention patients, $n = 53$) and even numbers (waiting-list control patients, $n = 60$). The only parameter of the RCT was the difference in the change in the HbA_{1c} level immediately after the intensive guidance of the intervention patients.

After 6 months, the control patients were also given the opportunity to benefit from the new type of care. Of these 60 patients, 28 who were no longer under the control of the same physician or who could only be sent a written invitation did not participate. Together with the remaining 32 waiting-list control patients and the 53 intervention patients, 4 other patients were included in the second part of the study. This was a controlled before-and-after study (CBA), thus including 89 patients. The CBA study consisted of a pretest measurement of HbA_{1c}, BMI, and lipid profile; a measurement of HbA_{1c} and BMI immediately after the period of intensive guidance; and a second post test measurement of HbA_{1c}, BMI, and lipid profile (values known from 53–76%) 1 year later. The *t* test was used to answer the research questions.

In the RCT, the average age was 51.7 vs. 54.8 years, the male-to-female ratio was 26 of 27 vs. 31 of 29, and the initial HbA_{1c} level was 8.4 vs. 8.2% for intervention vs. control patients, respectively. A difference of 0.42% ($P = 0.02$) was found in the average change in HbA_{1c} level, in favor of the intervention patients. After controlling for differences in age, sex, and initial HbA_{1c}, the difference between groups was 0.50% ($P = 0.004$). The change was greatest in the subgroup of patients who had never previously received diabetes education. When considering only those patients with an initial HbA_{1c} level >7.5%, the difference was 0.69% (35 intervention and 35 control patients; $P = 0.003$).

In the CBA, the change in HbA_{1c} level was smaller (0.29%) because of a more modest result among the waiting-list control patients who started their participation after the completion of the RCT. BMI decreased by only 0.04 kg/m^2. One year later, this had not essentially changed. No relation was found between changes in BMI and HbA_{1c}. After 1 year, the lipid profile improved significantly; total cholesterol decreased by 0.56 mmol/l ($P < 0.0005$), total cholesterol–to–HDL ratio decreased by 0.54 mmol/l ($P = 0.001$), and triglycerides decreased by 0.34 mmol/l ($P = 0.002$).

In one general practice, for financial reasons, there was no continuity in the new type of care. Considering the data of the 19 patients of this practice with a known HbA_{1c} level 1 year later, the improvement had disappeared almost entirely. In contrast, improvement was maintained in the other three practices.

This study has shown that the development of culture-specific diabetes care can have a beneficial effect on metabolic control. It is probable that this effect is partially caused by the fact that contact was made with a group of patients that had not been contacted before. Continuity in the provision of this care appears to be crucial for a lasting effect.

With respect to the two above-mentioned possible active mechanisms, improvement in the applicability of nutritional advice should, in particular, be reflected in calorie intake. However, little improvement was found in BMI, and no relation between changes in BMI and HbA_{1c} was found. Therefore, the results suggest that the improvements in HbA_{1c} and lipid profile were mainly achieved by better interaction between care providers and patients, which may have led to better compliance, not only with regard to medication, but possibly with regard to physical activity and nutrition (e.g., a better distribution of meal times).

Effects of the intervention program are described as being particularly favorable if an important role is attributed to the nursing staff and if considerable emphasis is put on patient education (3). Both of these characteristics apply to the present intervention.

Research was restricted to only a few practice settings and a small number of care providers. This could possibly limit

the generalizability of the study results. Currently, intramural- and extramural-employed diabetes nurses and dieticians in the Hague are providing this new type of care. Further research will determine whether similar results are achieved with Surinam South Asian diabetes patients.

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Correlation Between Insulin Suppression Test and Quantitative Insulin Sensitivity Check Index in Hypertensive and Normotensive Obese Patients

Insulin resistance plays a central role in the pathophysiology of diabetes and is associated with obesity and other cardiovascular risk factors (1). In the assessment of insulin resistance, several methods have been developed. The "gold standard" hyperinsulinemic-euglycemic clamp (2) and the insulin suppression test (IST) (3) are two established methods to quantify insulin sensitivity in vivo, but neither is easily applied in large populations. Thus, it is of interest to develop simple methods to estimate insulin sensitivity that are useful for large epidemiological studies. A mathematical model derived from the so-called homeostasis model assessment (HOMA) (4) has been described as a simple and reproducible method in clinical practice. Recently, Katz et al. (5) have described a novel quantitative insulin-sensitivity check index (QUICKI) that shows a high correlation with the hyperinsulinemic-euglycemic clamp. In the present report, we studied the correlation among IST, QUICKI, and HOMA in a population of normotensive-obese (NT-OB) and hypertensive-obese (HT-OB) patients in order to determine their accuracy.

We recruited 20 obese (BMI >30 kg/m^2) male patients; 12 were NT-OB, and 8 were newly HT-OB and had never been treated before. None had previous history of metabolic disorders or were on medication with effects on insulin sensitivity. As the control group, 10 healthy (BMI <25 kg/m^2) age- and sex-matched volunteers were included. To estimate the insulin sensitivity, we first performed an IST. This test acts by suppressing endogenous insulin secretion with a sustained infusion of somatostatin. Simultaneously, exogenous crystalline insulin is infused at a constant rate to achieve a steady state of plasma insulin (SSPI), and then the resultant steady state of plasma glucose (SSPG), in response to a constant glucose infusion is determined, as we have previously described (6). The insulin sensitivity index (ISI) was calculated with the formula ISI ($dl \cdot kg^{-1} \cdot min^{-1}$) = [glucose infusion rate (mg $kg^{-1} \cdot min^{-1}$)/SSPG (mg/dl)] $\times 10^3$. The SSPG and ISI levels were considered as measures of insulin sensitivity. Furthermore, we calculated the insulin sensitivity for each subject with the QUICKI formula: $1/\log[G_0 + I_0]$, where G_0 and I_0 are fasting glucose (mmol/l) and fasting insulin (μUI/ml), respectively; and with the HOMA approach: HOMA = $g \times i/22.5$, where g is fasting glucose (mmol/l), and i is the fasting insulin (μUI/ml).

The results showed that fasting insulin concentrations were significantly greater in the HT-OB (32.5 ± 10.9 μUI/ml) and NT-OB (24.8 ± 13.7 μUI/ml) patients than in the control subjects (10.6 ± 3.3 μUI/ml; $P < 0.0001$ and $P < 0.005$, respectively). In the obese subjects, especially in the HT-OB group, the lipid profile showed a higher degree of abnormalities. In fact, serum triglyceride and total and LDL cholesterol concentrations in the NT-OB and HT-OB groups were higher than those for the control group, whereas HDL cholesterol levels were lower ($P < 0.05$ and $P < 0.0001$, respectively). Furthermore, a significant increase of total and LDL cholesterol levels and a decrease of HDL cholesterol levels were also observed in the HT-OB patients compared with the NT-OB patients ($P < 0.05$). Lastly, the uric acid levels were higher in the HT-OB group (8.5 ± 0.3 mg/dl) than in the NT-OB group (7.4 ± 0.7 mg/dl) and in the control subjects (7.0 ± 0.5 mg/dl; $P < 0.05$ and $P < 0.0001$, respectively).

The SSPG values for HT-OB (237.91 ± 41.67 mg/dl) and NT-OB (182.35 ± 49.54 mg/dl) patients were higher than those for control subjects (126.02 ± 20.7 mg/dl; $P < 0.001$ and $P < 0.05$, respectively). In the obese patients, ISI levels (25.9 ± 5.1 $dl \cdot kg^{-1} \cdot min^{-1}$ for HT-OB and 35.68 ± 11.42 $dl \cdot kg^{-1} \cdot min^{-1}$ for NT-OB) were lower than those of the control subjects (51.11 ± 9.22 $dl \cdot kg^{-1} \cdot min^{-1}$; $P < 0.001$ and $P < 0.05$, respectively). Both ISI and SSPG values showed that HT-OB patients had a greater degree of insulin resistance than NT-OB patients ($P < 0.05$). The QUICKI values (0.437 ± 0.011 for HT-OB, 0.478 ± 0.045 for NT-OB, and 0.605 ± 0.052 for control subjects) showed a gradation similar to ISI levels. In fact, QUICKI levels were lower for the HT-OB group than for the NT-OB group ($P < 0.02$) and the control subjects ($P < 0.001$). The NT-OB patients also showed QUICKI values lower than those of the control group ($P < 0.001$). The incidence of insulin resistance was determined from the ISI values attained during the IST. All patients with ISI values below the mean of the control group −2 SD were considered insulin resistant. The same criteria was used to estimate insulin resistance from QUICKI values. The analysis showed that 85.8% of the HT-OB patients and 58.5% of the NT-OB patients were insulin resistant. The calculated HOMA values were 8.79 ± 1.62 for HT-OB, 6.22 ± 2.68 for NT-OB, and 2.12 ± 0.63 for control sub-

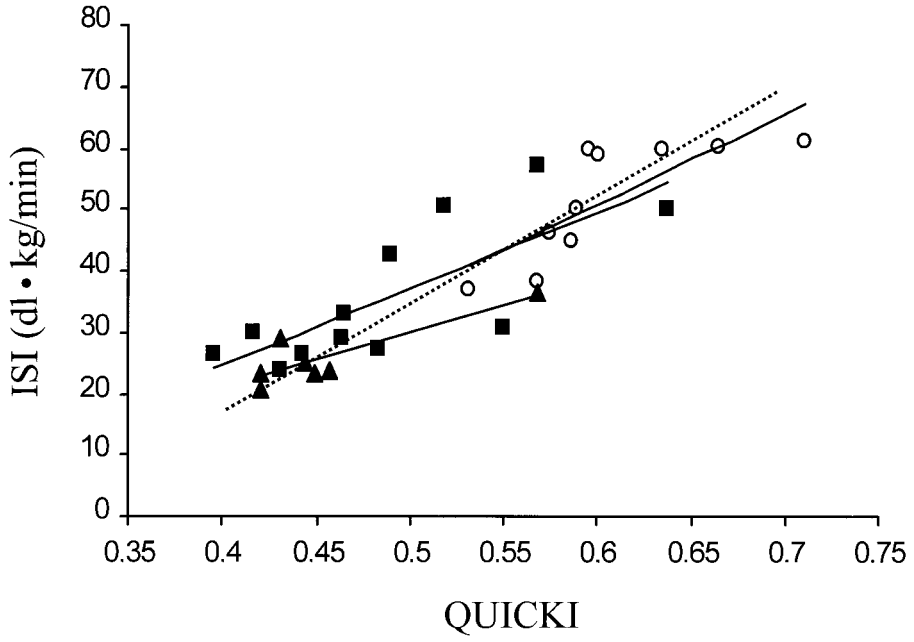

Figure 1—*Correlations between ISI and QUICKI. Indexes are plotted for 12 NT-OB subjects (■), 8 HT-OB subjects (▲), and 10 healthy control subjects (○). The dashed line represents the linear regression between ISI and QUICKI for all subjects* (r = *0.888;* P < *0.001). Linear regression lines are also shown for each subgroup:* r = *0.76,* P < *0.001 for the NT-OB group;* r = *0.86,* P < *0.001 for the HT-OB group; and* r = *0.79,* P < *0.001 for the control group.*

jects. Similar to the ISI and QUICKI, the HOMA method showed that the HT-OB patients were more insulin resistant than the NT-OB patients ($P < 0.05$) and the control subjects ($P < 0.001$). Also, the NT-OB group had higher HOMA values than the control subjects ($P < 0.001$).

The overall correlation between QUICKI and ISI was very high ($r = 0.888$; $P < 0.001$). Similar values were obtained for each individual group ($r = 0.86$ for HT-OB patients, $P < 0.001$; $r = 0.76$ for NT-OB subjects, $P < 0.001$; and $r = 0.79$ for control subjects, $P < 0.001$) (Fig. 1). Next, we compared SSPG with QUICKI and found a large overall negative correlation between them ($r = -0.81$; $P < 0.001$), due to the fact that SSPG is an index of insulin resistance and increases when the insulin sensitivity decreases. As expected, the overall correlation between HOMA and QUICKI was very high ($r = -0.91$; $P < 0.001$). In contrast, the overall correlation between HOMA and ISI was significantly smaller ($r = -0.69$) than that between ISI and QUICKI ($r = 0.888$; $P < 0.05$).

The results of the present study clearly show that obese patients with hypertension have a higher incidence of insulin resistance (85.8%) than obese patients without hypertension (58.5%), as estimated from SSPG and ISI data. Similar results were obtained using QUICKI: insulin sensitivity was lowest in the HT-OB group, intermediate in the NT-OB group, and highest in the control group. In our patients, we have not found differences in the incidence of insulin resistance assessed by IST or QUICKI. However, there seems to be a gradation in the severity of the insulin resistance present in obese patients, leading finally to the coexistence of hypertension. In fact, it is well known that insulin resistance is present in most hypertensive patients with obesity. Another major cardiovascular risk factor associated with obesity is an abnormal plasma lipid profile (7). We observed that for the obese patients, the lipid profile closely followed the changes in the insulin sensitivity. Lastly, the uric acid levels in the HT-OB patients confirm that hyperuricemia is an inherent component of the metabolic syndrome.

On the other hand, we found that the overall correlation between QUICKI and ISI was very high ($r = 0.888$; $P < 0.001$). As expected, in our study, we also found a very high correlation between HOMA and both QUICKI and ISI. Nevertheless, the correlation between QUICKI and ISI was significantly higher than the correlation between HOMA and ISI. Katz et al. (5) have recently reported that the correlation between QUICKI and hyperinsulinemic-euglycemic clamp measurements of insulin sensitivity was significantly better than the correlation between the minimal-model sensitivity index and glucose clamp. These results suggest that QUICKI contains additional independent information about insulin sensitivity that is not captured by the minimal-model approach. Based on the observed correlations between QUICKI and the hyperinsulinemic-euglycemic glucose clamp and between QUICKI and the ISI, QUICKI may be considered as a very good, inexpensive, and simple tool to estimate insulin sensitivity in a large population with, in particular, a clustering of cardiovascular risk factors.

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The Insulin Analog Aspart: A Safe Alternative in Insulin Allergy

The introduction of human recombinant insulin has considerably lowered, but not eliminated, adverse reactions to insulin administration. Several reports indicate that human recombinant insulin can also induce IgE- and non–IgE-mediated local or systemic reactions (1–2). However, in most patients with allergy to human recombinant insulin, insulin lispro—a genetically engineered insulin analog (Humalog; Lilly, Indianapolis, IN)—is well tolerated and can be safely used (3–5). Although the main immunogenic insulin epitopes remain unchanged in the lispro molecule, it has been suggested that this analog has reduced immunogenicity because of its rapid dissociation in monomers (6).

Here we report the case of cutaneous hypersensitivity to human insulin, successfully treated with the human insulin analog aspart (NovoRapid; Novo Nordisk, Bagsværd, Denmark). This rapid-acting insulin analog is produced by recombinant technology that replaces the proline at position 28 on the β-chain of insulin with negatively charged aspartic acid. Insulin aspart exists as examers that rapidly dissociate into monomers and dimers after the subcutaneous injection (7); therefore, it should be less immunogenic than human recombinant insulin.

A 45-year-old man was referred to our division for the management of uncontrolled diabetes. Type 2 diabetes had been diagnosed 2 years before and was treated with glyburide and metformin. Recently, non-Hodgkin's lymphoma was diagnosed, and a combination chemotherapy was started. The use of glucocorticoids worsened glycemic control, and two daily injections of premixed human insulin (30% regular and 70% intermediate-acting) were prescribed. After a few days, the patient noticed local wheal and flare reactions immediately after the injection at the injection site. The flare reached a diameter of 3–5 cm and was followed by an indurated lesion that lasted for 3–5 days. Treatment with cetirizine (10 mg daily) provided relief from pruritus. No previous history of atopy was known. Serum total IgE was 3.1 kU/l (UniCAP; Pharmacia, Uppsala, Sweden). The search for insulin-specific IgE antibodies in the serum was positive (0.7 kU/l, class I, UniCAP); conversely, no latex-specific IgE could be detected. Skin prick tests were performed with several human recombinant insulins at commercial concentrations, using saline solution and histamine as negative and positive controls. The skin tests with Humulin R, Humulin I, Humulin 30/70 (Lilly), Actrapid, Protaphane, and Actraphane 30/70 (Novo Nordisk) were positive, with an immediate wheal and flare reaction that cleared up within 40 min. The skin prick test for insulin lispro (Humalog by Lilly) was weakly positive, whereas the skin prick test with insulin aspart (NovoRapid; Novo Nordisk) was negative. To confirm the results of skin prick tests, in vitro basophil histamine release was evaluated after challenge with different types of insulin. Leukocyte suspensions, prepared by dextran sedimentation of peripheral venous blood and containing 7×10^4 basophils/ml, were incubated with different insulins (final concentration 5 units/ml for all types) and polyclonal goat IgG anti-IgE (final concentration 10 μg/ml; Sigma Chemical, St. Louis, MO) as a control. After incubation for 40 min at 37°C, the reaction was stopped by the addition of ice-cold buffer solution and centrifugation. The supernatants were assayed for histamine concentration by a commercially available radioimmunoassay (Immunotech, Marseille, France). Net histamine release was calculated as the percentage of total histamine content, after subtraction of spontaneous release. A 5% net release cutoff value was used. Insulin analogs (Humalog and NovoRapid) did not induce any significant histamine release (<1%), whereas a histamine release >5% was found after stimulation with Humulin I, Protaphane, and Actraphane 30/70 (6.9, 5.4, and 5.5%, respectively). Humulin R and Actrapid provoked a weak and nonsignificant in vitro histamine release (3%).

Because the results of the skin prick tests and in vitro basophil histamine release suggested that insulin aspart could be tolerated, we decided to start this type of insulin, which was administered in three premeal doses. The patient tolerated subcutaneous insulin aspart without any evidence of allergy. Subsequently, metformin was added at 1.0 g daily in two divided doses.

Several case reports suggest that insulin lispro may be an option in treating patients with insulin allergy. Our report indicates that the insulin analog aspart can be considered as an alternative treatment in patients with allergic reactions to human recombinant insulin.

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IAA/GAD-Positive Offspring of Diabetic Parents Have a Different Seasonality in Month of Birth Than Antibody-Negative Offspring

Nowadays, it is agreed that childhood type 1 diabetes is a progressively developing disease in which the clinical unmasking is usually triggered by an infectious (viral) disease, oftentimes during the yearly viral epidemic in autumn and winter (1). The timing of the onset of the autoimmune process and its initiating factor(s) are uncertain and controversial. One of the proposed mechanisms is that viruses damage the pancreatic β-cells and trigger the autoimmune process (2), which, by subsequent destruction at a loss of 70–80% of β-cells, causes the clinical disease.

Epidemiological studies performed by Z.L. and I.A. in recent years in Israel (3), Sardinia (4), Slovenia (6), and parts of Germany (7) have revealed that children and adolescents who developed type 1 diabetes at various ages have a statistically significant different pattern in their seasonality of month of birth from that found in the total live births for the respective country. Children who developed diabetes had an excess birth rate in spring and summer months compared with an evenly distributed birth rate in the general population. It was proposed that in pregnancies starting in autumn and early winter, periods of the yearly viral epidemics, the mother transmits to the fetus β-cell pathogenic viruses, which in genetically susceptible individuals initiate the autoimmune process.

To test this hypothesis, the seasonality of the month of birth of 61 offspring of type 1 diabetic parents (mothers and/or fathers) who were found to be IAA/GAD-positive were compared with 1,754 offspring without antibodies. All of the babies from the German BABYDIAB Study were tested within the first year of life, and testing was repeated at 2, 5, 8, and 11 years (8). The data of the children in the two groups were divided into the four 3-month seasonal periods of the year, which were compared using Student's *t* test between the pooled means (±SD) for each seasonal block.

The month of birth of the antibody-positive offspring showed a significantly different month of birth pattern ($P < 0.03$), which peaked between June and September, from the antibody-negative offspring.

The present findings strengthen the previous epidemiological observations that children who develop autoimmune diabetes have a different seasonality pattern than the general population (3–7) and fit the viral etiology theory (2). Recently, further support is provided by the findings of Lonnrot et al. (9) who sampled sera every 6 months from 765 originally nondiabetic siblings of type 1 diabetic children and found that 22% (11 of 49) of those who subsequently developed the clinical disease had enterovirus RNA in their sera compared with 2% (2 of 105) of control subjects. At clinical manifestation, all of the children were negative for enterovirus RNA.

In conclusion, the present observations support the hypothesis that the autoimmune process begins in utero or in the perinatal period in many children and adolescents who develop type 1 diabetes.

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Increased Platelet and Erythrocyte External Cell Membrane Phosphatidylserine in Type 1 Diabetes and Microalbuminuria

The cosegregation of traditional risk factors, such as smoking, hypertension, dyslipidemia, and hyperglycemia, per se do not fully account for the excessive cardiovascular risk in diabetes (1,2), thus suggesting that there are other contributory factors. Diabetes is associated with several defects of coagulation

Table 1—*External cell membrane phosphatidylserine and scramblase in platelets and erythrocytes in HC, DM, and DM-MA patients*

	HC	DM	DM-MA
Phosphatidylserine			
Platelet	59 (0–277)	319 (154–1,067)*	977 (391–2,139)†‡
Erythrocyte	29 (0–156)	198 (117–367)*	552 (146–921)†§
Scramblase			
Platelet	294 (131–960)	1,780 (1023–3,073)*	2,137 (847–6,928)*
Erythrocyte	121 (0–259)	600 (316–861)†	1,105 (436–1,937)†‖

Data are median (range). *$P < 0.01$ compared with HC; †$P < 0.001$ compared with HC; ‡$P = 0.04$ compared with DM; §$P < 0.001$ compared with DM; ‖$P < 0.01$ compared with DM. HC, healthy control subjects; DM, type 1 diabetic subjects without macrovascular disease; DM-MA, type 1 diabetic subjects with microalbuminuria.

and fibrinolysis that predispose to a thrombogenic tendency (3–5). Phospholipids are distributed asymmetrically between the inner and outer leaflets of the normal cell membrane lipid bilayer (6), with the cholinephospholipids (phosphatidylcholine and phosphatidylsphingomyelin) predominantly in the external leaflet and the aminophospholipids (phosphatidylserine [PS] and phosphatidylethanolamine) located internally. This equilibrium can be disrupted by activation of the calcium-dependent scramblase enzyme (6). PS is a potent activator of thrombin and other clotting factors (6), thus promoting a procoagulant environment that may increase the risk of cardiovascular disease. Therefore, we investigated whether there is an increase in PS in the outer leaflet of the lipid bilayer of erythrocyte and platelet cell membranes in type 1 diabetic patients and whether this is associated with changes in the appearance of scramblase.

Consent for the study was obtained from 13 healthy control (HC) subjects; 11 normoalbuminuric type 1 diabetic patients of ≥15 years diabetes duration without macrovascular disease (DM subjects); and 18 type 1 diabetic patients with microalbuminuria, defined as a urine albumin-to-creatinine ratio (ACR) >2.5 mg/mmol in males and >3.5 mg/mmol in females on at least three occasions, of which two were consecutive and at least 6 months apart, without macrovascular disease (DM-MA subjects). There were no significant differences in age, sex distribution, and smoking status between HC, DM, and DM-MA subjects. Furthermore, DM and DM-MA subjects were well matched for retinopathy, neuropathy, blood pressure (BP), BMI, and lipid and metabolic control. Venous blood was collected into acid-citrate-dextrose and then centrifuged at 120*g* for 15 min at 15°C to obtain platelet-rich plasma and erythrocytes. These were used to determine the median number of external PS molecules and their within-subject variance (intracoefficient of variation) by using the binding of the cell membrane–impermeant annexin V-fluorescein isothiocyanate (FITC) conjugate (Beckman-Coulter, Paris) and quantified by a fluorescence-activated cell-scanner (Becton-Dickinson FACScan supporting Lysis II software) (7,8). The number of external scramblase molecules on platelets and erythrocytes were measured by fluorescence-activated cell scanning using a rabbit anti-scramblase antibody (directed to the extracellular COOH-terminal domain) and FITC–anti-rabbit IgG. Differences between groups were compared by the Mann-Whitney *U* test and corrected for multiple comparisons by a Bonferroni correction factor.

The results clearly show that the PS molecules per cell in the external leaflet of the cell membrane lipid bilayer of circulating platelets and erythrocytes were higher in DM subjects than in HC subjects (Table 1). Furthermore, the externalized PS was further increased in cells from DM-MA subjects (Table 1). Although increases in total cell membrane PS have previously been reported in type 1 diabetes (9), this is the first investigation of the appearance of PS in the outer leaflet of the lipid bilayer. The increased expression of PS on blood cells is likely to be an important contributor to the elevated cardiovascular risk in type 1 diabetic patients. This is supported by the even higher levels of PS on the exterior of blood cells from patients with microalbuminuria who have a higher risk of cardiovascular disease than patients without microalbuminuria (10).

The lipid bilayer enzyme scramblase, which can externalize PS when activated, was also increased in platelets and erythrocytes from DM subjects, with further increases in DM-MA subjects (Table 1). This suggests that scramblase may be involved in the increased externalized PS on cells from the diabetic subjects. This was further supported by the positive correlation between the number of external cell membrane PS and scramblase molecules in erythrocytes ($r_{sp} = 0.774$; $P < 0.001$), and platelets ($r_{sp} = 0.715$; $P < 0.01$) from all subjects. However, there were no significant correlations within each subject group. There were no significant relations among HbA_{1c}, BP, ACR, BMI, or plasma lipids and outer-leaflet PS or scramblase, which suggested that the abnormality in the latter was not a simple reflection of glycemic control or renal function.

Although the median values for platelet and erythrocyte PS were increased in DM subjects, the percentage of variance in the cells within each subject was similar to that of HC subjects (59 [31–88] vs. 61 [51–87] and 62 [49–88] vs. 63 [55–91], respectively), suggesting that in DM subjects, the cells were able to control their external levels of PS but did so at a new increased steady state level. In contrast, the variance in externalized PS in the cell populations from DM-MA subjects was markedly increased (110 [76–178] and 111 [72–192], $P < 0.01$), suggesting that these cells not only had increased levels of external PS, but that their control mechanisms were impaired. Therefore, the results suggest that platelets and erythrocytes from DM-MA subjects not only had increased external PS with the accompanying thrombogenic tendency, but that the cells also had a loss of control of phospholipid asymmetry and would be at much greater risk of a catastrophic breakdown.

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Epididymitis Caused by *Candida glabrata*

A novel infection in diabetic patients?

Visceral candidiasis is uncommon in patients with type 2 diabetes (1). Here, we discuss the sixth known case report of fungal epididymitis in a diabetic patient and only the second one caused by *Candida glabrata*. Two cases of epididymitis caused by *C. glabrata* have been described in nondiabetic patients, one in an HIV-positive individual (2), and the other in a permanently catheterized patient (3).

An 81-year-old male type 2 diabetic patient who was on a twice-daily insulin regimen was admitted for intermittent fever and confusion over the previous 2 days. Past history revealed a stroke 2 years earlier that led to permanent urinary catheterization, along with several short courses of oral antibiotics. No information about his previous diabetes control was available. Physical examination showed fever (37.8°C), tachycardia of 100 beats per min, and a warm, enlarged, erythematous, indurated, and tender left hemiscroteum. Laboratory tests showed normochromic and normocytic anemia (hematocrit 31.7%), leukocytosis (17,800/μl), hyperglycemia (363 mg/dl), and hypercreatinemia (1.9 mg/dl). Scrotal ultrasound revealed a solid, heterogenous mass with increased vascularization over the left testis, whereas the right testis was normal. Budding yeast forms were recognized on urine microscopy, and urine culture yielded 5×10^5 CFU/cm^3 of *C. glabrata*.

The patient was started on a fluconazole 200-mg i.v. b.i.d., and, due to persistence of clinical symptoms, 3 days later he underwent a left epididymo-orchiectomy, abscess drainage, and surgical excision of tunica vaginalis and of the overlying skin and dartos muscle. Histology showed cavitary abscess and acute inflammation in the epididymis that extended to the overlying skin layers without involving the testis. Numerous pseudohyphae were present on the wall of the abscess staining that were positive for *p*-aminosalicylic acid (PAS).

Culture of the pus on Saboureau's medium yielded *C. glabrata*. Identification and sensitivity testing of antifungals were performed as described elsewhere (3). *C. glabrata* was of intermediate susceptibility to fluconazole and susceptible to other antifungals. After surgical excision, the patient was continued on the intravenous regimen for 7 days. When discharged, the patient was placed on an oral fluconazole 200-mg b.i.d. for 10 additional days. Three months later, the patient remained without any relapse.

A Medline search from 1966 to 2000 revealed five cases of fungal epididymitis connected to type 2 diabetes (5–9) that shared several common characteristics with the present case. Permanent catheterization and former antibiotic consumption are the main predisposing factors. Infection occuring by *C. albicans* or *C. glabrata* and involving one or both epididymes may or may not be accompanied by involvement of the testis and by abscess formation. Diagnosis is based on the recognition of fungi, either in histology, in cultures of the draining pus, or in both. Because urine cultures always yield the fungi, this indicates retrograde spread as the responsible mechanism that involves the epididymes. Treatment consists of surgical drainage accompanied by the administration of antifungal agents, mainly fluconazole for 10–30 days, even if the isolated species is of intermediate susceptibility to fluconazole, as in the present case report.

In conclusion, although this occurance is rare, any diabetic patient with inflammation of the scrotum and former consumption of antibiotics should bear in mind the possibility of developing fungal epididymitis.

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Study of the −429 T/C and −374 T/A Receptor For Advanced Glycation End Products Promoter Polymorphisms in Diabetic and Nondiabetic Subjects With Macrovascular Disease

The receptor for advanced glycation end products (RAGE) has been implicated in the development of vascular complications of diabetes by both in vitro and in vivo studies (1). The most compelling evidence demonstrated that blocking of AGE/RAGE binding prevented atherosclerotic development in animal models (2). It is plausible that genetic differences in the RAGE gene could alter expression and function to affect disease development. In previous studies, we have identified a number of potentially functional polymorphisms: Gly82Ser in the AGE-binding domain (3) and two common promoter polymorphisms at positions −429 and −374 (4). The Gly82Ser polymorphism was not found to relate to micro- or macrovascular disease of diabetes in a number of other studies. However, we reported an association between the −429 polymorphism and retinopathy (4). The relation between genotype at the RAGE promoter and macrovascular disease is unknown.

Therefore, we screened the −429 T/C and −374 T/A polymorphisms in 157 type 2 diabetic subjects with ischemic heart disease (IHD) (107 without myocardial infarction [MI] vs. 51 with MI), 390 nondiabetic subjects with IHD (230 without MI vs. 160 with MI), and 199 control subjects with no personal or family history of diabetes or IHD. Patients with IHD were diagnosed by coronary angiography as having >50% stenosis in at least two coronary vessels. Type 2 diabetes was diagnosed according to World Health Organization criteria. Polymerase chain reaction/restriction fragment–length polymorphism genotyping was performed as previously described (4).

There were no differences in allele frequencies between diabetic subjects with (−429 T 81%, C 19%; −374 T 83%, A 17%) or without (−429 T 83%, C 17%; −374 T 81%, A 19%) macrovascular disease, nor were there any differences between these subjects and control subjects (−429 T 81%, C 18%; −374 T 80%, A 20%) ($P > 0.05$). In the nondiabetic subjects, no difference was found between subjects with (−429 T 84%, C 16%; −374 T 78%, A 22%) or without (−429 T 81%, C 19%; −374 T 80%, A 20%) MI.

In conclusion, our results demonstrate that in these groups of subjects, no association exists between either the −429 or −374 RAGE promoter polymorphisms and macrovascular disease. Previous functional studies on these polymorphisms indicated an influence on RAGE levels; taken together with the demonstrated role of RAGE in human and animal models of vascular disease, this suggests that an association with vascular disease may be seen, especially in diabetic individuals. These polymorphisms may therefore make either little or no detectable contribution to macrovascular disease or demonstrate the limitations of gene association studies by representing a type II statistical error. As such, larger numbers are required to establish whether these polymorphisms have a causative role in the pathogenesis of vascular disease, demonstrating the possible limitation of gene association studies in case control populations.

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Comparative Trial Between Insulin Glargine and NPH Insulin in Children and Adolescents With Type 1 Diabetes

Studies such as the Diabetes Control and Complications Trial have shown that, as in adult patients, intensive diabetes management in adolescent patients results in better glycemic control and delays the onset and slows the progression of vascular and neurological complications (1). However, a cross-sectional multinational study showed that less than one-third of the children and adolescents who underwent treatment for diabetes had adequate metabolic control (2). Providing a constant supply of basal insulin that mimics that of healthy individuals is an essential aspect of maintaining tight glycemic control in patients with type 1 diabetes. The traditional NPH insulin and ultralente basal insulin formulations do not provide a constant and reliable 24-h basal insulin supply because their duration of action is too short, and unwanted peaks of action in the night can cause nocturnal hypoglycemia (3). This is of particular relevance in children and adolescents, who are more prone to hypoglycemic episodes (4,5).

A new long-acting insulin analog has been developed using recombinant DNA technology. Insulin glargine differs from human insulin by the addition of two additional arginines on the COOH terminus of the B-chain and the replacement of an asparagine residue with glycine on the A-chain (6). The resulting molecule has a peakless, prolonged time-action profile and can be used once daily. These features enable insulin glargine to provide sufficient basal insulin over 24 h when used in a basal-bolus regimen while limiting the incidence of hypoglycemic, particularly nocturnal hypoglycemic, episodes (7). The objective of this study was to compare the metabolic effect and safety of insulin glargine with NPH insulin in children and adolescents with type 1 diabetes.

In a multicenter open-label randomized study, 349 patients with type 1 diabetes, aged 5–16 years, who were using at least three daily preprandial injections of normal insulin and who had an HbA_{1c} value of <12%, were treated for 6 months. Patients received insulin glargine once daily (at bedtime), irrespective of their prior regimen (174 patients), whereas the regimen for patients receiving NPH insulin was either once (at bedtime in 114 patients) or twice daily (in the morning and at bedtime in 61 patients), based on their prior treatment regimen. Titration of the bedtime dose of insulin was related to fasting blood glucose (FBG), with a target of 4.4–8.8 mmol/l. Regular insulin was injected before meals according to the habits of the patients. Insulin glargine and NPH insulin treatment groups had a similar distribution in terms of sex, age (11.8 ± 2 vs. 11.5 ± 2 years), BMI (18.8 ± 2 vs. 18.9 ± 2 kg/m^2), ethnic group, puberty stage (preadolescent 32.8 vs. 35.4%; and adolescent 67.2 vs. 64.6%), and age at onset of diabetes (7.4 ± 3.17 vs. 7.4 ± 3.31 years).

The primary efficacy measure was mean change from baseline in GHb levels, which was determined by analysis of covariance (ANCOVA). The difference in mean change from baseline between insulin glargine and NPH insulin was estimated using adjusted means together with the associated SE and 95% CI from the ANCOVA model. The secondary efficacy measures were mean change in FBG levels from baseline (analyzed by ANCOVA) and incidence of hypoglycemia (compared between treatment groups using rank analysis of variance). Hypoglycemia was catergorized as either symptomatic (with clinical symptoms that could be confirmed by blood glucose levels <2.8 mmol/l) or asymptomatic (any event with a confirmed blood glucose level <2.8 mmol/l but without any symptoms). Severe hypoglycemia was defined as an event with symptoms consistent with hypoglycemia in which the patient required assistance from another person and which was associated with a blood glucose level <2.8 mmol/l or prompt recovery after oral carbohydrate or intravenous glucose or glucagon administration (8).

There was no difference between insulin glargine and NPH insulin in terms of change in GHb from baseline to end point (0.28 ± 0.09% vs. 0.27 ± 0.09%, P = 0.93). However, FBG decreased more from baseline to end point in the insulin glargine group (−1.29 mmol/l) than in the NPH insulin group (−0.68 mmol/l; P = 0.02). At end point, a higher percentage of insulin glargine–treated patients (43.9%) than NPH insulin–treated patients (39.0%) reached the target range of 4.4–8.8 mmol/l. These improved FBG levels could be due to the extended time-action profile of insulin glargine.

During the entire study period, the percentage of subjects reporting at least one episode of symptomatic hypoglycemia was similar for insulin glargine and NPH insulin treatment (78.9 and 79.3%, respectively); however, fewer patients in the insulin glargine versus the NPH insulin group reported severe hypoglycemia (23.0 vs. 28.6%, respectively; P = 0.22, Cochran-Mantel-Haenszel test) and severe nocturnal hypoglycemia (12.6 vs. 17.7%, respectively; P = 0.19), although these differences were not statistically significant.

Both insulin glargine and NPH insulin treatments were well tolerated. Of note, injection site reactions, categorized as adverse events of special interest, were evenly distributed between the insulin glargine and NPH insulin groups (9.2 vs. 8.6%, respectively). Serious adverse events were observed more often in the NPH insulin group than in the insulin glargine group (13.7 vs. 5.8%, respectively; P < 0.02, Fisher's exact test).

In conclusion, a once-daily subcutaneous dose of insulin glargine provides glycemic control that is at least as effective as once- or twice-daily NPH insulin in children and adolescents with type 1 diabetes, with significantly lower FBG levels and a trend toward fewer episodes of severe hypoglycemia and nocturnal hypoglycemia.

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APPENDIX

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Evaluation of Light Exercise in the Treatment of Gestational Diabetes

The metabolic goal of therapy in gestational diabetes (GD) is to maintain euglycemia, and when it is not achieved with diet alone, insulin therapy is added (1). Physical training has both acute and long-term effects on insulin sensitivity, insulin secretion, and glucose metabolism in both nondiabetic and diabetic subjects (2), and the benefit of training has also been shown in patients with GD, where controlled training achieves euglycemia with no need for insulin treatment (3). Nevertheless, physical exercise of moderate intensity has been associated with uterine contractions unless performed with the arms (4).

The clinical observation that light postprandial exercise in patients with GD was useful in decreasing blood glucose (BG) prompted this controlled crossover study, which had the aim of assessing the magnitude of its effect in women with GD.

A total of 20 non–exercise-trained women with GD (Third Workshop-Conference on Gestational Diabetes Mellitus criteria) were studied after diagnosis on two different days (3–7 days apart, first day regime randomly allocated). The study began between 8:00 A.M. and 9:00 A.M., and capillary blood glucose (CBG) was measured (Hemocue, Angelholm, Sweden) during fasting and 1 and 2 h after a standard breakfast consisting of 20 g of carbohydrates. On the control day, the women remained seated throughout the observation period, and in the study day, they walked self-paced on a flat surface in the first hour after breakfast and remained seated during the second hour. The mean age (means ± SD) was 33.5 ± 4.6 years, the gestational age was 30.7 ± 5.5 weeks, and the weight was 69.6 ± 9.4 kg. For data analysis, the *t* test for paired data was used (variables normally distributed).

We found significant differences (control day versus study day) in 1-h postprandial BG (6.02 ± 0.78 vs. 5.35 ± 0.69 mmol/l, $P = 0.001$), 1-h postprandial heart rate (82 ± 9 vs. 91 ± 10 bpm, $P = 0.002$), and 1-h BG excursion (1.79 ± 0.6 vs. 1.07 ± 0.68 mmol/l, $P < 0.001$), whereas no differences were observed in fasting and 2-h postprandial BG, basal and 2-h postprandial heart rate, or basal and 1- and 2-h postprandial blood pressure. There was a trend toward a higher effect of exercise in 1-h postprandial BG in those women with higher levels on the control day ($r = 0.43$, $P = 0.058$). No untoward effect was observed.

We have shown that light postprandial exercise decreases postprandial BG excursion in women with GD, and this has been achieved with very light exercise (2.52 km in 1 h, 9 bpm increase in heart rate). We conclude that in addition to the benefits of physical training on blood glucose control, women with GD could benefit from light postprandial exercise and potentially avoid or delay insulin therapy. In clinical practice, light postprandial exercise could translate into avoiding rest at that time.

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Preventing Type 2 Diabetes

Perceptions about risk and prevention in a population-based sample of adults ≥45 years of age

Type 2 diabetes is increasing in the U.S. and constitutes a major public health problem (1). Preventing the onset of diabetes through lifestyle changes, such as improved diet, increased physical activity, and weight control, in individuals at risk presents an attractive public health opportunity. Recently, a randomized controlled clinical trial from Finland showed a 58% decrease in the incidence of type 2 diabetes when lifestyle interventions were conducted in high-risk subjects (2). Similar studies comparing lifestyle interventions and pharmacological therapies to prevent type 2 diabetes are currently underway (3). However, implementing diabetes prevention interventions in the general population will be challenging.

From November 2000 through January 2001, the Montana Department of Public Health and Human Services conducted a random-digit household telephone survey of people ≥45 years of age living in two rural counties in Montana. Respondents were asked if they had ever been told by a physician that they had diabetes (including gestational diabetes), if they had a family history of diabetes (sister, brother, or parents), and if they had ever been told they had high cholesterol and/or high blood pressure. Respondents with a previous diagnosis of diabetes (except gestational diabetes) were excluded. The remaining respondents were asked, "Do you think you are at risk for diabetes?," "Do you think that you can prevent getting diabetes?," and "Has a doctor or other health professional ever told you that you may be at risk for developing diabetes?" BMI was calculated based on self-reported height and weight. Respondents with a BMI ≥25.0 were defined as overweight, and respondents with a BMI ≥30.0 were defined as obese. Risk factors, including age ≥45 years, family history of diabetes, history of gestational diabetes, being overweight, history of high blood pressure, and history of high cholesterol, were categorized for each respondent. Hypertension and a history of high cholesterol were used to indicate a possible association with the insulin resistance/metabolic syndrome. Pearson's χ^2 tests were used to assess associations among perceived risk for diabetes, perceived ability to prevent diabetes, and medical advice regarding diabetes risk. Logistic regression analyses were conducted to identify independent variables associated with these responses. Odds ratios (ORs) and 95% CIs were calculated.

A total of 605 people were reached by telephone, and 29 (4.8%) of these reported that they had diagnosed diabetes and were excluded from the analyses. Of the total respondents, 571 (94.4%) reported that they did not currently have diabetes. In addition, five (0.8%) women reported a history of gestational diabetes only and were included in the analyses. Among those with no current diagnosis of diabetes, the majority of respondents were female (60%) and the mean age was 60 years (maximum age 97 years). Altogether, 38% reported a family history of diabetes, 49% had a BMI ≥25.0, 26% reported having high blood pressure, and 28% reported having high cholesterol.

Also, 22% of the respondents considered themselves at risk for diabetes, 71% did not consider themselves at risk, and 7% were unsure; 60% thought they could prevent diabetes, 17% did not, and 23% were unsure. Only 10% of the respondents reported receiving medical advice regarding diabetes risk.

The probability of considering oneself at risk for diabetes was higher among

Table 1—*Characteristics and risk factors among respondents ≥ 45 years of age who consider themselves at risk for diabetes, perceive that they can prevent getting diabetes, and have received medical advice regarding diabetes risk*

	Consider self at risk for diabetes	Can prevent getting diabetes	Received medical advice regarding diabetes risk
Total (N = 576)	22 (129)	60 (347)	10 (55)
Age (years)			
45–64 (n = 390)	26 (101)*	63 (246)*	10 (39)
≥65 (n = 186)	15 (28)	54 (101)	9 (10)
Sex			
Men (n = 232)	18 (42)	57 (131)	6 (14)
Women (n = 344)	25 (87)*	63 (216)	12 (41)*
BMI			
Obese (n = 83)	41 (34)*	66 (55)	21 (17)*
Overweight (n = 199)	29 (58)	56 (111)	10 (19)
Not overweight (n = 264)	9 (23)	63 (165)	6 (16)
High blood pressure			
Yes (n = 151)	33 (49)*	52 (79)	14 (21)*
No/unknown (n = 425)	19 (80)	63 (268)*	8 (34)
High cholesterol			
Yes (n = 163)	27 (44)	49 (79)	9 (14)
No/unknown (n = 413)	21 (85)	65 (268)*	10 (41)
Family history of diabetes			
Yes (n = 217)	42 (92)*	55 (119)	20 (43)*
No/unknown (n = 359)	10 (37)	64 (228)*	3 (12)
Number of risk factors for diabetes			
1 (n = 117)	3 (4)	66 (77)	1 (1)
2 (n = 213)	13 (27)	67 (142)	7 (15)
3–6 (n = 246)	40 (98)*	52 (128)*	16 (39)*

Data are % (n) of subjects in each risk category who answered "Yes." *$P < 0.05$. Numbers may not total 576 due to missing data.

respondents who were 45–64 years of age, female, and obese and who had high blood pressure and a family history of diabetes (Table 1). People aged 45–64 years were also more likely than older respondents to feel that they could prevent diabetes. Those with high blood pressure, high cholesterol, and a family history of diabetes were less likely to feel that they could prevent diabetes. Women, obese respondents, those with high blood pressure, and those with a family history of diabetes were more likely than others to have received medical advice from a health professional regarding diabetes risk.

Including age ≥45 years as a risk factor, 20% of respondents had one factor suggesting high risk for diabetes, 37% had two factors, and 43% had three to six factors. Although people with three or more factors were more likely than people with fewer than three risk factors to consider themselves at risk for diabetes ($P < 0.001$), people with three or more risk factors were less likely to feel that they could prevent diabetes ($P = 0.002$) (Table 1). However, respondents with three or more risk factors were more likely than those with fewer risk factors to recall having received medical advice from a health care professional regarding diabetes risk ($P < 0.001$).

After adjusting for multiple factors, younger age (OR 2.59 [95% CI 1.51–4.46]), high blood pressure (1.93 [1.16–3.23]), family history of diabetes (6.65 [4.17–10.61]), and being overweight (3.81 [2.34–6.20]) were independently associated with respondents considering themselves at risk for diabetes. Men were less likely than women to consider themselves at risk (0.53 [0.33–0.87]). Respondents with high blood pressure (0.80 [0.35–0.79]), high cholesterol (0.52 [0.34–0.78]), and a family history of diabetes (0.65 [0.45–0.93]) were less likely to feel they could prevent diabetes. Those with a family history of diabetes (6.42 [3.27–12.62]) and those who were overweight (2.28 [1.22–4.29]) were more likely to report having received medical advice regarding diabetes risk. Men, however, were less likely than women to recall medical advice regarding diabetes risk (0.46 [0.23–0.90]).

People must perceive that they are at risk for type 2 diabetes and believe that diabetes can be prevented before they will initiate and maintain positive diet and exercise behaviors or prophylactic medication. In this survey, people reporting multiple risk factors for diabetes were less likely to perceive that diabetes was preventable than those with fewer risk factors. Although a family history of diabetes was most strongly associated with an individual's perceived risk, those with a positive family history were less likely than others to believe that diabetes was preventable. Of particular interest is the finding that few respondents reported receiving medical advice from health professionals regarding diabetes risk. It is likely that more respondents in our study were at risk for diabetes than those who could recall receiving medical advice concerning their personal risk for diabetes. Although this study was conducted in two predominantly white, western, U.S. rural counties and has the limitations inherent in any telephone survey, the data have important implications. Our study suggests that widespread translation of the findings of type 2 diabetes prevention trials will require changing the beliefs about primary prevention in those at the highest risk for diabetes and aggressively promoting diabetes prevention in medical practice.

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Human Insulin Analog Insulin Aspart Does Not Cause Insulin Allergy

Human insulin is beneficial for most diabetic patients for whom insulin therapy is indispensable. However, some patients suffer from insulin allergy. Insulin allergies are immunologic reactions to exogenous insulin, which cause local or systemic symptoms. Here we report that insulin aspart, a human insulin analog, alleviated local and generalized insulin allergy in the absence of anti-allergic agents in a Japanese patient.

A 59-year-old woman (60 kg body wt, BMI 24.4 kg/m^2) with bronchial asthma was admitted to our hospital in December 2000 for the treatment of uncontrolled diabetes. She was first diagnosed as having type 2 diabetes in 1996 and started on treatment with oral hypoglycemic agents. However, hyperglycemia was difficult to control, and treatment with human insulin was started in July 1999. After subcutaneous injection of human regular insulin, she developed a skin rash, itching, and slight stridor. Although she had been treated with anti-allergic drugs (anatomize 75 mg, chlorpheniramine maltase 6 mg per day) along with

regular/NPH insulin, her allergic reaction to insulin continued. The percentage of eosinophils in the peripheral white blood cell count was 9.8% (normal <7%). On further examination, she also showed a high level of total IgE (2,368 IU/ml; normal range <270 IU/ml) and human insulin–specific IgE in RAST (radioallergosorbent test; 8.04 AU/ml; normal range <0.34). Drug-induced lymphocyte stimulation tests for regular and NPH insulin were negative.

The patient demonstrated both local and generalized allergic reactions to different kinds of human insulin, including human regular insulin, NPH insulin, and crystalline zinc-insulin suspension, not only after systemic injection but also after intradermal test. She also demonstrated similar allergic reactions to bovine and porcine insulin. There was no evidence of allergic reactions to concomitant materials or any preservatives. To test the possibility of treating the patient with insulin analogs, we examined skin reactions to the two rapid-acting insulin analogs aspart (B28Asp human insulin) and lispro (B28Lys-B29Pro human insulin). Although insulin lispro also caused localized allergic reactions, insulin aspart alone did not induce local or systemic allergic reactions. Moreover, during the 6 months after the start of treatment with insulin aspart, diabetic control was improved, as shown by a reduction in HbA_{1c} values from 8.9 to 7.6%. Although total IgE was not changed (from 2,368 to 2,254 IU/ml), the level of human insulin–specific IgE in RAST was significantly reduced from 8.04 to 4.37 AU/ml.

Insulin aspart is a new rapid-acting human insulin analog. It is characterized with rapid uptake, higher insulin peak, and rapid decline. The B26-B30 region is not particularly critical for insulin receptor recognition and has been a preferred site for structural modifications aimed at modifying the pharmacokinetic profile of the insulin molecule. In human insulin–transgenic mice, antibodies against insulin were not elicited by injection of B28Asp insulin (insulin aspart), in comparison with other analogs (1). It appears that insulin aspart had a reduced antigenicity. This is supported by the fact that no allergic reaction was induced in our patient when injected with insulin aspart. Although it was not found in this case, insulin lispro has also been reported to not induce insulin allergy (2). Taken together, the data suggest that position B28 may be a common immunogenic epitope in insulin allergy. Therefore, the modification of insulin at position B28 allows not only acceleration of the rate of absorption from injection sites but also suppression of insulin allergy.

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COMMENTS AND RESPONSES

Misleading Algorithm for Management of Adult Patients With Diabetic Ketoacidosis

We were initially pleased to see the technical review and position statement on management of hyperglycemic crises in the January issue of *Diabetes Care* (1,2), believing that this could serve as an excellent educational resource for house staff, until we read the algorithm for treatment of adult diabetic ketoacidosis (DKA), which was presented in both articles. The final recommendation reads, "After resolution of DKA, follow blood glucose (BG) every 4 h and give sliding scale regular insulin SC [subcutaneous] in 5 unit increments for every 50 mg/dl increase in BG above 150 mg/dl for up to 20 units for BG of ≥300 mg/dl." Although the text of both papers comments on the need to overlap SC insulin with intravenous insulin, the algorithm does not address this. In fact, a physician following this algorithm could very well stop the insulin infusion when the blood glucose is 140 mg/dl, withhold insulin therapy (as the "sliding scale" implies) from a patient known to be prone to ketosis, and not check another blood glucose until 4 h later. Even if the blood glucose at discontinuation of the insulin infusion is >150 mg/dl (which the algorithm suggests it should be, for reasons unclear to us), there is no reason to think that 5 units of SC regular insulin for a 4-h period will be sufficient in every patient. Interestingly, the algorithm for treatment of DKA in children is more appropriate, suggesting the institution of mixed short- and intermediate-acting insulin therapy based on the patient's body weight. In our experience, we have also found it easier to continue the insulin infusion overnight and transition to SC insulin at breakfast. Although this approach may not be suitable for every patient, in most cases it seems to work well.

We are also very concerned with the term "sliding scale." We work very hard to explain to house staff that the term is misleading, and we prefer to use "supplemental insulin" instead to drive home the physiological relationship between basal and mealtime insulin requirements. The term "sliding scale" invariably leads to patients being given only short-acting insulin intermittently in response to an already elevated BG and having their insulin withheld at lower BG levels, which clearly is not suitable for most situations.

Because there is no scientific rationale for the recommendation to treat adult ketosis-prone patients with sliding scale insulin only and, in fact, logic would suggest that this could be harmful, we feel that this algorithm should be amended to be more in keeping with what is recommended in the text of these articles.

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Response to Kirkman and Juneja and Lorber

Drs. Kirkman and Juneja (1) are correct in pointing out the discrepancies between the text and the algorithm figures for post hyperglycemic crises management in our articles on hyperglycemic crises (2,3). We regret the confusion surrounding this issue and have corrected this omission in Figs. 1 and 2, as described below.

As stated in the text, as soon as the patient is able to tolerate fluids and/or meals, we recommend treatment with a multidose regimen of short- and intermediate/long–acting insulin after resolution of the hyperglycemic crisis. To maintain adequate plasma insulin levels and prevent recurrence of diabetic ketoacidosis (DKA) and/or hyperglycemia, subcutaneous (SC) insulin should be given 1–2 h before the insulin infusion is discontinued.

After the resolution of DKA or hyperosmolar hyperglycemic state (HHS), some patients may be unable to take oral nourishment. While NPO (not eating), they should receive intravenous (IV) insulin infusion or be temporarily treated every 4 h with SC regular insulin based on blood glucose levels. SC regular insulin is given in 5-unit increments for every 50 mg/dl increase in blood glucose above 150 mg/dl for up to 20 units for a blood glucose of 300 mg/dl. In our experience, the above dosage of insulin every 4 h, while the patient is NPO and receiving glucose and insulin, has not resulted in hypoglycemia or relapse of hyperglycemia and/or ketoacidosis. It should be emphasized that such a step is only temporary and is by no means a replacement for intermediate/long–acting insulin along with multiple-dose regular insulin. This statement was omitted in Figs. 1 and 2 of the position paper (2) and Figs. 4 and 5 in the technical review (3). The figures will be modified as follows for DKA and HHS:

> Check electrolytes, BUN [blood urea nitrogen], creatinine and glucose every 2–4 h until stable. After resolution of DKA, if the patient is NPO, continue IV insulin and supplement with SC regular insulin as needed. When the patient can eat, initiate a multidose insulin regimen and adjust as needed [see text for details]. Continue IV insulin infusion for 1–2 h after SC insulin is begun to ensure adequate plasma insulin levels. Continue to look for precipitating cause(s).

> Check electrolytes, BUN, creatinine and glucose every 2–4 h until stable. After resolution of HHS, if the patient is NPO, continue intravenous insulin and supplement with SC regular insulin as needed [see text]. When the patient can eat, initiate SC insulin or previous treatment regimen and assess metabolic control. Continue to look for precipitating cause(s).

In the second letter, Dr. Lorber (4) expresses his concern that sliding scale insulin is reactive rather than proactive and that it fails to account for individual variability in insulin sensitivity. We believe that the use of continuous fixed sliding scale insulin as monotherapy should be discouraged; however, the transient use of supplemental regular insulin alone or in combination with long-acting insulin is effective in the recovery phase of hyperglycemic crises (5,6). A different issue is the use of sliding scale insulin for the routine management of diabetes, which has been a subject of controversy in the literature. Historically, the term "sliding scale insulin" has evoked concerns by clinicians regarding the risk of hypoglycemia and hyperglycemia that may result from a lack of attention to daily blood glucose patterns. Obviously, any insulin regimen requires frequent assessments and adjustments; therefore, using a fixed sliding scale as the only treatment to control blood glucose is counterproductive.

Another criticism is that a sliding scale insulin regimen simply "chases" the blood glucose rather than prevents hyperglycemia through the use of a proactive insulin plan. The latter statement is without supported evidence. On the contrary, the benefit of an insulin bolus preprandially based on a flexible schedule using rapid-acting insulin either via an insulin pump or injection has been well demonstrated (7–9); however, a static dose of insulin has resulted in very poor glucose control. The current use of sliding scale insulin incorporates a more sophisticated approach to optimizing blood glucose control that considers not only the ambient blood glucose level but also the variables that will affect the blood glucose level over the next 1–4 h. Therefore, the intent of a flexible sliding scale is one that varies depending on content of meal, time of day, premeal blood glucose, etc. This, however, does not remove the responsibility from the clinician or the patient for acting on consistent pre- or postprandial elevations in blood glucose levels.

A flexible regimen may be the most important approach in controlling postprandial peaks in blood glucose. Therefore, it behooves us to look carefully at the subject of "sliding scale" insulin before summarily dismissing it as a harmful intervention. Whatever term we choose to use, the use of a sliding scale or supplemental insulin algorithm is an invaluable tool in the management and education of the patient requiring insulin for glucose control.

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What Is the Real Contribution of Fasting Plasma Glucose and Postprandial Glucose in Predicting HbA_{1c} and Overall Blood Glucose Control?

We read with interest the consensus statement of the American Diabetes Association on postprandial blood glucose published in the April 2001 issue of *Diabetes Care* (1). We are concerned about the following consensus position in that report regarding the relation among postprandial glucose (PPG), fasting plasma glucose (FPG), and HbA_{1c}: "In summary, there are insufficient data to determine accurately the relative contribution of the FPG and PPG to HbA_{1c}. It appears that FPG is somewhat better than PPG in predicting HbA_{1c}, especially in type 2 diabetes." Absolute FPG is not a reliable tool for management of type 2 diabetes. Trovati et al. (2) evaluated whether a fasting blood glucose <6.7 mmol/l can predict overall blood glucose control in 287 type 2 diabetic patients. They found that 56% of the subjects had PPG values >8.9 mmol/l or <4.4 mmol/l, and that HbA_{1c} was not correlated with fasting blood glucose concentrations. Conversely, the same authors pointed out that fasting hyperglycemia does not exclude the occurrence of low glucose values throughout the day in both diet-treated and drug-treated type 2 diabetic patients (3). Thus, FPG alone is not predictive enough of the overall control in type 2 diabetes.

Bouma et al. (4) showed in 1,020 type 2 diabetic patients that HbA_{1c} is difficult to predict from FPG values: only 66% of the patients with HbA_{1c} <7.0% were identified by FPG values <7.8 mmol/l. HbA_{1c} is difficult to predict from FPG values, and predicting HbA_{1c} changes from FPG changes is even more difficult. Finally, Avignon et al. (5) demonstrated in 66 type 2 diabetic patients that postlunch (2:00 P.M.) and extended postlunch (5:00 P.M.) plasma glucose (PG) correlated significantly and independently with HbA_{1c}, but that prebreakfast PG and prelunch PG did not. Moreover, postlunch PG and extended postlunch PG demonstrated better sensitivity, specificity, and positive predictive value in predicting poor glycemic control than prebreakfast PG or prelunch PG. In summary, published data don't support the conclusion that FPG is somewhat better than PPG in predicting HbA_{1c}, especially in type 2 diabetes.

We think that in a period in which the idea of evidence-based medicine is maturing and is better defined, one shouldn't undervalue the results of these studies (some of which were published in this journal), which were conducted with a large number of patients.

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Sliding Scale Insulin

I was surprised and disappointed to see a recommendation for "sliding scale insulin" treatment in Figs. 1 and 2 of the otherwise excellent position statement "Hyperglycemic Crises in Patients with Diabetes Mellitus" (1). I carefully read the text of the article and the accompanying technical review (2), searching in vain for some justification for this recommendation.

I then turned to the literature and performed a Medline search from 1987 to 2000 using the words "sliding scale insulin." The overwhelming consensus in the literature (3–14) is that sliding scale insulin is neither efficient nor effective. Sliding scale insulin is an historical artifact dating back to the days of urine testing. As pointedly outlined by Gill and MacFarlane (10), sliding scale is illogical in that it responds to hyperglycemia after it has happened, rather than preventing it, and the sliding scale depends on the clearly inaccurate assumption that insulin sensitivity is uniform among all patients.

In my experience, the major deficit of

sliding scale insulin is that it allows the house officer to write an arbitrary insulin regimen and leave the patient's diabetes management in the hands of floor nursing staff. This is a prescription for hypoglycemia and recurrent diabetic ketoacidosis.

Sliding scale insulin should be discouraged, not endorsed, by the American Diabetes Association.

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Idiopathic Type 1 Diabetes?

The study by Piñero-Piloña et al. entitled "Idiopathic Type 1 Diabetes in Dallas, Texas: A 5-Year Experience" (1) reports on the features of 80 patients who present with diabetic ketoacidosis, the absence of islet cell antibodies, insulin autoantibodies, and GAD antibodies, or HLA antigens associated with type 1 diabetes. The authors then describe the phenotypic characteristics of 54 patients who had follow-up data. When the study began, the patients had a mean age of 34.8 years and a mean BMI of 31.6 kg/m^2 and had lost 12.8 kg body wt. All of the subjects reported type 2 diabetes in first-degree relatives, and 35 had acanthosis nigricans. At follow-up 5 years later, 21 were treated with oral agents or diet and the remainder with insulin. Of the subjects, 65% were of African origin, 30% were Hispanic, and the remainder were Native American. Piñero-Piloña et al. (1) state that "[i]diopathic type 1 diabetes has been described mostly in African-Americans but also in individuals from other ethnic groups," citing among others a study (2) concerning diabetic ketoacidosis in Apache Indians who clearly had type 2 diabetes.

Idiopathic type 1 diabetes is defined as diabetes not associated with autoantibodies but for which insulin treatment is required for survival, although an absolute requirement for insulin replacement therapy and ketoacidosis may be episodic (3). Thus, it is unclear why the authors believed that all of these subjects had idiopathic type 1 diabetes. Because 40% of the subjects were no longer being treated with insulin after 5 years, and only 5 of the 21 on oral agents and 4 of the 33 on insulin had a second episode of ketoacidosis, the evidence presented strongly suggests that the majority did not have type 1 diabetes. Unfortunately, the authors did not provide data on insulin or C-peptide levels after the initial acute episode of diabetic ketoacidosis; such data might have helped to differentiate between patients with type 1 diabetes and those with type 2 diabetes.

It is well established that adolescents and young adults with type 2 diabetes often develop ketoacidosis, which may be the event that leads to diagnosis (2,4). The characteristics (viz., high level of obesity, history of type 2 diabetes, occurrence of acanthosis nigricans in >60%, and lack of true insulin dependency) of the group of patients in the study by Piñero-Piloña et al. (1) do not, as the authors claim, indicate idiopathic type 1 diabetes, but instead clearly indicate that the majority of these patients had type 2 diabetes. Although some of the patients might have idiopathic type 1 diabetes, the title of the study as well as its interpretation and discussion are extremely misleading, causing the reader to believe it to describe the clinical characteristics of a series of patients with documented idiopathic type 1 diabetes. We believe that the majority of the patients described in this study have type 2 diabetes rather than idiopathic type 1 diabetes.

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Idiopathic Type 1 Diabetes in Dallas

In this issue of *Diabetes Care*, the letter by Bennett et al. (1) in response to our study (2) points out a huge problem that we wished to previously identify. The problem is "the importance of a name" (3). Dr. Bennett and his colleagues (1), who are respected epidemiologists, considered our study subjects to have type 2 diabetes, whereas we determined that they met the diagnostic criteria for idiopathic type 1 diabetes.

According to the report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (4), idiopathic type 1 diabetes is described as follows: "This form of diabetes is strongly inherited, lacks immunological evidence for β-cell autoimmunity, and is not HLA associated. An absolute requirement for insulin replacement therapy in affected patients may come and go." Even in "typical" type 1 diabetes, the absolute requirement for insulin "to preserve life" is not always 100%, especially early in the course of the illness. This so-called "honeymoon period" is probably longer for individuals with idiopathic type 1 diabetes. We strongly feel that our patients have idiopathic type 1 diabetes. They all presented with unprovoked ketoacidosis and had none of the associated HLA haplotypes or markers of β-cell autoimmunity commonly seen in individuals with immune-mediated type 1 diabetes. All had a strong family history for what is called type 2 diabetes. In sum, all of these components meet the diagnostic criteria for idiopathic type 1 diabetes. Decisions on the classification for each individual with diabetes must be clinical and are often difficult.

We also disagree with the statement by Bennett et al. (1) that "[i]t is well established that adolescents and young adults with type 2 diabetes often develop ketoacidosis, which may be the event that leads to diagnosis." The study by Umpierrez et al. (5), which they used in support of this statement, actually describes individuals with idiopathic type 1 diabetes. With respect to the report by Wilson et al. (6) in Apache Indians, we may have been incorrect in including such patients as examples of idiopathic type 1 diabetes. It is difficult to tell from reading the article (6) exactly how many of those patients developed ketoacidosis in the absence of any precipitating factor (infection, alcohol, etc). There is no question that developing ketoacidosis in association with external stressors, such as infection or alcohol abuse, is not unusual in type 2 diabetes, and we have no argument with that statement. It is interesting to note that we had three Native Americans in our study population, so it is possible that some of the patients described by Wilson et al. (6) actually did have idiopathic type 1 diabetes.

It is our belief that idiopathic type 1 diabetes is very common in minority populations in urban areas. What sets this type of diabetes apart from the typical case of type 2 diabetes is the development of spontaneous ketoacidosis. According to the Expert Committee's report (4), in type 2 diabetes, "Ketoacidosis seldom occurs spontaneously; when seen, it usually arises in association with the stress of another illness such as infection." All of our subjects presented with ketoacidosis that was not associated with other stressors. As was noted above, that was probably not the case with all of the patients reported by Wilson et al. (6).

The purpose of our study was not to argue over names, although we feel that we are justified in saying that this group of individuals did in fact meet the Expert Committee's definition of idiopathic type 1 diabetes. More importantly, we wanted to make the clinical recommendation that, when individuals who seem to be at risk for type 2 diabetes (i.e., are older, are obese, and have acanthosis nigricans) present with unprovoked ketosis or ketoacidosis, the appropriate long-term therapy is insulin. What name we attach to such individuals is probably unimportant.

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Education Level and Clustering of Clinical Characteristics of Metabolic Syndrome

An association between low education level and an increased risk of metabolic syndrome was recently reported among middle-aged women from Sweden (1). Because the statistics of cardiovascular mortality in Hungary—in sharp contrast to other countries (2)—are discouraging (3), and because metabolic syndrome can contribute to accelerated atherosclerosis (4), it is considered worthwhile to screen subjects to detect early signs of metabolic syndrome in our country. We performed a mass screening to evaluate the clinical features of metabolic syndrome in northwest Hungary (5), and the cohort proved to be large enough to allow subgroup analysis to assess the relationship between education level and clinical characteristics of metabolic syndrome.

Originally, the aim of the screening procedure was to identify subjects with hyperinsulinemia (serum fasting insulin >15 μU/ml and/or postchallenge insulin >45 μU/ml at 120 min after 75 g glucose) because hyperinsulinemia is one of the characteristic features of metabolic syndrome and can contribute to accelerated cardiovascular events (6). In our screening procedure, subjects of both sexes (aged 20–65 years) were referred to our

Table 1—*Clinical and laboratory findings according to the education level in subjects exhibiting at least one of the inclusion criteria (obesity, elevated waist-to-hip ratio, hypertension, positive family history) for screening hyperinsulinemia* (n = *1,002*)

	Education level		
	Low	Middle	High
n	337	493	172
F/M [*n* (%)]	223*/114* (66.2/33.8)	281/212 (57.0/43.0)	86/86 (50.0/50.0)
Age of subjects (years)	46.4 ± 7.9	45.4 ± 7.2	46.2 ± 6.7
BMI (kg/m^2)	32.97 ± 5.46*	31.53 ± 5.46	30.37 ± 4.97
Hypertension	277† (82.2)	386 (78.3)	123 (71.5)
Positive family history	302 (89.6)	449 (91.1)	157 (91.3)
Hyperinsulinemia	178 (53.0)	250 (51.0)	84 (48.8)
Glucose intolerance (IGT/diabetes)	47/28 (14.0/8.3)	69/50 (14.1/10.2)	20/13 (11.6/7.6)
Fasting blood glucose (mmol/l)	6.47 ± 3.13	5.62 ± 2.00	6.35 ± 3.09
Fasting plasma insulin (μU/ml)	14.6 ± 9.7	14.1 ± 10.2	12.6 ± 7.4
HOMA	3.70 ± 2.69	3.61 ± 3.00	3.19 ± 2.20
Postprandial plasma insulin (μU/ml)	56.2 ± 65.2	57.3 ± 63.6	54.9 ± 65.7
Serum total cholesterol (mmol/l)	6.00 ± 1.28	6.11 ± 1.31	6.01 ± 1.28
Serum triglycerides (mmol/l)	2.50 ± 2.53	2.58 ± 2.29	2.64 ± 2.24
Serum LDL cholesterol (mmol/l)	3.74 ± 1.12	3.81 ± 1.14	3.71 ± 1.21
Serum HDL cholesterol (mmol/l)	1.19 ± 0.33	1.19 ± 0.33	1.17 ± 0.34
Serum uric acid (μmol/l)	260 ± 89	256 ± 86	262 ± 81

Data are means ± SD or absolute numbers (%). Statistical analysis was made by analysis of variance and χ^2. HOMA, homeostasis model assessment test. HOMA = plasma fasting glucose × fasting insulin/22.5. *$P < 0.001$ vs. high education level; †$P < 0.05$ vs. high education level.

center by general practitioners, and at least one of the following clinical characteristics was applied for inclusion: hypertension (subjects with actual blood pressure ≥140/90 mmHg [mean of three consecutive values] or with antihypertensive treatment irrespective of actual blood pressure measurement); obesity (BMI >30.0 kg/m^2); elevated waist-to-hip ratio (WHR; >0.85 in women and >0.90 in men); or positive family history of diabetes, obesity, hypertension, or cardiovascular events. Known diabetic patients were excluded from the study. Anthropometric data and blood pressure values were registered, fasting blood samples were taken, and an oral glucose tolerance test with 75 g glucose was performed. Subjects were classified according to the categories of glucose intolerance (World Health Organization criteria) based on postchallenge 120-min glucose values, and normo- and hyperinsulinemia were based on the plasma insulin values measured. Education levels (low: primary school; middle: high school; high: university) of screened subjects were assessed by questionnaires.

In the total cohort (n = 1,002; 590 women and 412 men), the prevalence of women with lower education level was significantly higher than that of women with high education level, and, in addition, the prevalence of men with lower education level was significantly lower than that of men with high education level. Although the ages of the subjects in the subgroups were comparable, both BMI and the prevalence of hypertension were significantly higher in subjects with low education level compared with those with high education level. The laboratory data and the prevalence of hyperinsulinemia (total 51.3%), different categories of glucose intolerance (total prevalence of impaired glucose tolerance [IGT] = 13.6%; diabetes = 9.1%), and positive family history (total 90.6%) did not differ significantly in subgroups classified according to education level (Table 1). A further analysis regarding sex and education level indicated that women with low education level (n = 223) had significantly higher values (means ± SD) for BMI (32.96 ± 5.79 kg/m^2) as well as elevated WHR (0.87 ± 0.06) compared with women with middle education level (n = 281; BMI: 31.35 ± 5.52 kg/m^2; WHR: 0.85 ± 0.07; $P < 0.001$) or high education level (n = 86; BMI: 30.40 ± 5.45 kg/m^2; WHR: 0.83 ± 0.07). Men with low education level (n = 114) had significantly higher BMI (32.98 ± 4.79 kg/m^2) and elevated WHR (0.97 ± 0.07) compared with men with high education level (n = 86; BMI: 30.35 ± 4.46 kg/m^2, $P <$ 0.001; WHR: 0.95 ± 0.08, $P < 0.05$). Laboratory findings did not differ significantly in subgroups classified according to sex and education level (data not shown).

In summary, a clustering of the clinical features of metabolic syndrome (higher BMI and elevated WHR as well as higher prevalence rate of hypertension) proved to be associated with lower education level in a large cohort of subjects, particularly women in Hungary. Our results are in accordance with others (1,7, 8), suggesting that this association could be considered irrespective of the country. Therefore, subjects with low education level and a clustering of clinical characteristics of metabolic syndrome should have priority in efforts aimed at preventing cardiovascular complications. Undoubtedly, lifestyle modification, even in childhood (9), and drug therapy at a later stage (when necessary) should be considered in these subjects.

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Cardiovascular Risk in Diabetes

A story of missed opportunities?

We commend the Veterans Administration for implementing a clinical trial of the impact of glucose control on cardiovascular complications in patients with type 2 diabetes (1). Among people with diabetes, cardiovascular disease (CVD) is the leading cause of death (2); 27% have CVD, and an additional 71% have CVD risk factors (3). However, the burden of CVD can be substantially reduced by improving metabolic control, including that of glucose, lipids, blood pressure, and coagulation parameters (4). Published data from national surveys enable us to evaluate the current level and control of CVD risk factors among people with diabetes in the U.S.

In regard to glucose control, 37% of people with diabetes had HbA_{1c} >8.0% according to the Third National Health and Nutrition Examination Survey (NHANES III) (5). Although the majority (73%) were taking either insulin or oral agents, 51% of those on insulin, 42% of those on oral agents only, and 15% of those on diet only had HbA_{1c} >8%.

Among individuals with diabetes, 97% had at least one lipid abnormality (NHANES III) (6). Overall, 33% had LDL between 100 and 130 mg/dl, and 56% had LDL ≥130 mg/dl. Of diabetic individuals, 32% followed some type of treatment for high cholesterol, but only 9% were taking a lipid-lowering medication. Among those treated, only 1% had LDL <100 mg/dl, and 61% had LDL ≥130 mg/dl.

The prevalence of elevated blood pressure (≥130/85 mmHg or on antihypertensive medication) was 71% among U.S. people with diabetes (NHANES III) (7). Among those with elevated blood pressure, only 57% were on prescription medication.

Although nearly every U.S. adult with diabetes is eligible for aspirin treatment (3,4), aspirin was used by only 20% of diabetic individuals overall, 37% of whom had CVD, and 13% of whom had CVD risk factors (NHANES III) (3). Other risk factors in people with diabetes were also inadequate. Of people with diabetes, 26–34% had microalbuminuria (≥30 μg/ml) (NHANES III) (3,8), 34–54% were obese (BMI ≥30 kg/m^2) (NHANES III) (8), 31% were sedentary, 35% were somewhat active, only 34% were regularly active according to the National Health Interview Survey (NHIS) (9), and 18–27% were smokers (NHIS and NHANES III) (8,10).

In conclusion, national data in the U.S. point to suboptimal control of CVD risk factors and substantial missed opportunities for awareness, treatment, and control of these risk factors in the diabetic population. Although the prevalence of CVD risk factors is higher among people with diabetes, the use of treatments for many CVD risk factors is not more prevalent among the diabetic population. In fact, CVD mortality for the U.S. diabetic population has not declined as much as it has for the nondiabetic population (2). Reduction in CVD mortality in the general population is a major achievement in recent decades, but people with diabetes deserve similar improvement. We look forward to seeing the results of the Veterans Affairs Diabetes Trial. We hope this trial will encourage future trials that will examine how control of other CVD risk factors (such as lipid levels, blood pressure, and coagulation parameters) may reduce morbidity and mortality associated with CVD among people with diabetes.

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Half-Shoes for Off-Loading Diabetic Plantar Ulcers

The first randomized clinical trial on different modes of off-load diabetic foot wounds by Armstrong et al. (1) was long awaited. The total contact cast (TCC) turned out to be better than a removable cast walker (RCW) or a half-shoe for the off-loading of neuorpathic plantar ulcers that were not "on the heel, rear foot, or area other than the plantar aspect of the foot" (1).

Unfortunately, the authors failed to indicate whether the type of half-shoe (Darco, Huntington, WV) used was one with extended "support surface all the way under the foot [. . .]. [S]uch a shoe does not relieve the forefoot completely [. . .] and should not be confused" (2) with a true half-shoe, according to Barouk (2–4). Forefoot plantar ulcers will be completely off-loaded with a Barouk-type half-shoe (Ipos, Niagara Falls, NY) but probably not with a Darco half-shoe.

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Response to Chantelau

We greatly appreciate the commentary offered by our esteemed colleague Dr. Chantelau (1) and the opportunity to make a response. As he correctly points out, the modality used in this project was not the Barouk-type device but rather the Darco device. His point is well taken. In our anecdotal experiences, both modalities have positive and negative attributes with respect to their ability to off-load the plantar aspect of the forefoot—issues related to postural/ambulatory stability and compliance. Clearly, the Barouk device deserves the same sort of practical clinical testing as the Darco device, and we look forward to further studies that will take up this challenge.

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Acute Hyperglycemia and Autonomic Function

We read with interest the study by Lefrandt et al. (1) in which they analyzed the association between baroreflex sensitivity (BRS) and blood glucose levels in healthy subjects. They observed a negative relationship between BRS and glucose levels that was independent from other risk factors and that had no glycemic thresholds. Some years ago, we evaluated the effects of acute hyperglycemia (15 mmol/l) on autonomic function in 12 healthy male volunteers (2). Heart rate variations during the squatting maneuver (3) were significantly reduced in hyperglycemic condition, suggesting a reduced baroreflex activation. The ratio between the baseline R-R interval and the longest R-R interval during squatting (SqT vagal) represents the bradicardia secondary to baroreflex activation triggered by the raised arterial pressure after squatting. The ratio between the baseline R-R interval and the shortest R-R interval during standing up from squatting is a measure of the tachicardia after the increased sympathetic drive brought about by the fall in blood pressure (SqT sympathetic). Exogenous glutathione (600 mg as an intravenous bolus followed by a 5-mg/min infusion) completely prevented the baroreflex alterations, suggesting the mediation of hyperglycemia-induced free radical generation (4).

Among the possible mechanisms, Lefrandt et al. (1) hypothesized that high normal glucose levels may influence signal transmission through the neuronal pathway of the baroreflex arc, affecting the cardiac autonomic function at the myocyte level or diminishing normal endothelium function. A unifying link across these mechanisms might be the increased free radical generation evoked by high glucose. First, one of the earliest known events after exposure of cells to free radicals is the impairment of Na^+-K^+ ATPase, which may reduce nervous conduction velocity (5). Second, increased free radical generation is able to raise cytosolic free calcium at the myocyte level (6). Last, free radicals quench nitric oxide (NO), diminishing NO availability (7). On the other hand, all of these findings

are observed, both in vitro and in vivo, with glucose concentrations that are well above those reported as being in the high normal glucose range (maximum 7 mmol/l). We ignore if, at this glucose concentration, the pathogenetic mechanisms are the same as those hypothesized during acute hyperglycemia (15 mmol/l).

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Relation Between Autonomic Function and Blood Glucose in the Nondiabetic Range

We agree with Marfella et al. (1) that increased free radical generation could very well be a common denominator of the mechanisms by which elevations in blood glucose influence baroreflex sensitivity (BRS) in healthy subjects, as we have proposed (2). Free radicals influence Na^+-K^+-ATPase enzyme activity and intracytosolic free Ca^{2+} content at the cellular level as well as endothelial function in the broader perspective. The importance of nitric oxide (NO) availability for a baroreflex-induced cardiovascular response to changes in blood pressure has recently been underscored by a study showing that inhibition of NO synthase by N(G)-monomethyl-L-arginine reduced the changes in heart rate variability (HRV) and BRS, in contrast to an equivalent rise in blood pressure induced by phenylephrine (3). Moreover, diminished NO availability has been reported in a clinical study of patients with several stages of autonomic neuropathy (4). Increasing evidence thus shows that autonomic function strongly depends on cardiac and vascular (endothelial) function and does not simply reflect autonomic nerve function per se, a concept that needs further investigation in evaluating modern measurements of autonomic function (i.e., HRV and BRS). As proposed by Marfella et al. (1), the effects of increased free radical generation on cardiac and vascular function fit into this concept and might explain the inverse relation between blood glucose and BRS.

Finally, the relation between hyperglycemia and diminished autonomic function has been well demonstrated in both controlled clinical studies (5) and large population studies (6). However, we agree with Marfella et al. (1) that it is not yet clear whether the putative mechanisms explaining the relation between blood glucose and autonomic function in the nondiabetic range are the same in hyperglycemia, and the answer to this is certainly awaiting newer studies.

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HbA_{1c} Measurements Do Not Improve the Detection of Type 2 Diabetes in a Randomly Selected Population

Perry et al. (1) compared the sensitivity of fasting plasma glucose (FPG) concentrations and HbA_{1c} levels to diagnose diabetes in high-risk subjects

whose 2-h glucose concentrations on an oral glucose tolerance test (OGTT) exceeded 11.1 mmol/l (200 mg/dl) and therefore met the OGTT criterion for diabetes (2). A total of 950 subjects with the following high-risk parameters were recruited: *1*) obesity (BMI ≥24 kg/m^2), *2*) a family history of diabetes, and *3*) individuals who had been told that they had "a touch of sugar," "borderline diabetes," or "glucose intolerance." Of these subjects, 244 had FPG concentrations between 5.5 and 8.0 mmol/l (99 and 144 mg/dl) and underwent an OGTT. Of the 121 subjects with OGTT-diagnosed diabetes, 101 had complete data that also included FPG and HbA_{1c} values; 45% had an FPG concentration of ≥7.0 mmol/l, whereas 62% had an HbA_{1c} level exceeding the upper limit of normal (ULN) for the assay used (6.1%). The authors concluded that in a high-risk population with FPG concentrations between 5.5 and 8.0 mmol/l (99 and 144 mg/dl), an elevated HbA_{1c} level was more sensitive in diagnosing diabetes than an FPG concentration ≥7.0 mmol/l (126 mg/dl), the FPG criterion for the diagnosis (2). They appropriately raised the question of whether this conclusion was justified in more general populations.

We have attempted to answer this question in the randomly selected population evaluated in the Third National Health and Nutrition Examination Survey (NHANES III). NHANES III is a national health survey that includes historical, physical, and laboratory examination of subjects selected through a stratified multistage probability-cluster sampling design. Minorities were oversampled, and the results were weighted to provide data representative of the U.S. population. Subjects in NHANES III who met the following criteria were identified using STATA 6.0 (STATA, College Station, TX), in accordance with the method described by Harris et al. (3): *1*) between 40 and 74 years of age, *2*) no known history of diabetes (other than gestational diabetes), and *3*) fasting, 2-h 75-g postglucose load and HbA_{1c} measurements taken after an appropriate overnight fast.

Of the 2,836 subjects in NHANES III who met these criteria, 261 had a 2-h postglucose value ≥11.1 mmol/l (200 mg/dl), 51% had an FPG concentration ≥7.0 mmol/l (126 mg/dl; a very similar percentage to Perry's high-risk group), and 49% had an HbA_{1c} level exceeding the ULN for the assay used (6.1%). We have previously shown in the NHANES III population that 70% of those with 2-h values between 11.1 and 13.3 mmol/l (200 and 239 mg/dl) had normal HbA_{1c} levels, whereas 60% with 2-h values ≥13.3 mmol/l (240 mg/dl) had elevated HbA_{1c} levels (4). Therefore, we tested the hypothesis that HbA_{1c} levels might be more sensitive than FPG concentrations in diagnosing diabetes in the 150 NHANES III subjects with 2-h postglucose values ≥13.3 mmol/l (240 mg/dl). As expected, the proportion with elevated FPG and HbA_{1c} values was higher in this group. However, the hypothesis was still not supported, because 74% had FPG concentrations ≥7.0 mmol/l (126 mg/dl) and only 59% had elevated HbA_{1c} levels.

Perhaps the difference in the sensitivities of the FPG and HbA_{1c} values in diagnosing diabetes in a high-risk population versus a randomly selected one is not surprising. In the high-risk group, 50% (121 of 244) had 2-h values on the OGTT that met the criterion for the diagnosis of diabetes (2), whereas only 9% (261 of 2,836) of the randomly selected NHANES III population had values in this range. Because postprandial (rather than fasting) hyperglycemia characterizes early diabetes, it is likely that members of the high-risk group who suspected that they may have had diabetes had higher postprandial glucose concentrations (and therefore higher HbA_{1c} levels) than people from the randomly selected population.

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Gestational Diabetes, Birth Weight, Sex Ratio, and Cesarian Section

Knights et al. (1) reported on the sexes of the offspring of 216 women with gestational diabetes (GDM) and 216 control subjects without GDM, all of whom underwent cesarian section. The sex ratio (proportion male) for the control offspring was significantly higher than that for the offspring of the GDM women. The birth weights and gestational ages of the offspring from the two groups of women showed no appreciable differences, even when offspring sex was controlled. These authors claimed that their data do not support the suggestion that the high sex ratio generally associated with cesarian section is due to the greater weight of male fetuses. They asserted that although the male babies were heavier than the female babies in both groups of women, the male babies of the women with GDM had the same mean birth weight as the male babies of the control women.

I suggest that they misinterpreted their data; there can be no reasonable doubt that one cause of the high sex ratio associated with cesarian section is that male babies are bigger, on the average, and consequently are associated with failure to progress at delivery (2). The rationale of this practice is that cesarian section is associated with lower injury rates in large infants than are forceps, vacuum, or spontaneous vaginal delivery (3).

I suggest that the high sex ratio gen-

erally associated with cesarian section is due to strong selection for fetal weight. If I am correct, this sex ratio is a statistical artifact of the circumstance that weight is one criterion for cesarian section. In 1993, the sex ratios of U.S. live births in the weight ranges of 3,000, 3,500, 4,000, 4,500, and ≥5,000 g were 0.482, 0.554, 0.626, 0.679, and 0.703, respectively (4). So, the higher the birth weight criterion for cesarian section, the higher the sex ratio associated with cesarian section. In contrast, GDM women *1*) have heavier infants on the average (5), and *2*) are more weakly selected for fetal weight (in the sense that a higher proportion of these women are sectioned) (3).

These features would result in roughly the same mean birth weight in the GDM women and control subjects but a lower sex ratio in the GDM cases. In short, cesarian section subjects control women to strong selection on an average birth weight distribution, whereas cesarian section subjects GDM patients to weaker selection on a high mean birth weight distribution. If I am correct, these circumstances explain the features of their data, which mystified Knights et al. (1).

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Brain Natriuretic Peptide as a Potential Marker of Diastolic Dysfunction in Type 2 Diabetes

In the January issue of *Diabetes Care*, Poirier et al. (1) reported on the prevalence of left ventricular diastolic dysfunction (LVDD), as determined by echocardiography in 46 middle-aged men with well-controlled type 2 diabetes. Remarkably, they found a prevalence of LVDD as high as 60%. Although this needs to be replicated with studies of much larger sample sizes, they nevertheless illustrated the importance of identifying pseudonormal patterns of ventricular filling, which have been underestimated by previous studies using Doppler assessment of transmitral flow velocity, to help diagnose early or subclinical LVDD (1). As elucidated by the excellent editorial of Gustafsson and Hildebrandt (2), the prognostic implication and possibility for intervention remain unknown and warrant further studies before early echographic screening in diabetic patients can be justified. We speculate that a potential marker of diastolic dysfunction in diabetic cardiomyopathy may help in the selection of high-risk diabetic patients for early cardiological assessment.

The natriuretic peptide family (including atrial, brain, and type C natriuertic peptide) plays a key role in the homeostasis of intravascular fluid balance and in the maintenance of cardiovascular hemodynamics (3). Originally isolated from porcine brain tissue (4), brain natriuretic peptide (BNP) is a vasodilator produced by cardiac myocytes in the ventricles and is degraded by neural endopeptidase. Along with atrial natriuretic peptide (ANP), BNP has effects on natriuresis, diuresis, and inhibition of the renin-angiotensin-aldosterone system, all of which contribute to the modulation and control of cardiovascular hemodynamics (5). There is growing evidence that BNP may be a marker of advanced heart failure (5,6). More importantly, it may also be a marker of early heart failure as manifested by isolated diastolic dysfunction (7) or diastolic dysfunction in association with hypertension (8). The underlying pathophysiology for elevated BNP levels in diastolic heart failure is not fully understood. However, it is likely that BNP production is increased as a compensatory response to diminish preload (vasodilatation) and postload (natriuresis and diuresis), thereby improving cardiac contractility. This is supported by the observation that infusion of BNP in patients with diastolic dysfunction improves hemodynamic response in isolated diastolic heart failure (9).

Although elevation of BNP in cardiac failure is not specific to disease states, BNP may be a useful tool in diabetic patients with microalbuminuria. This is supported by the study of Poirier et al. (1), in which there was a greater incidence of microalbuminuric patients in the group with abnormal ventricular relaxation pattern (15 of 28 [54%]) compared with the group with normal diastolic function (6 of 18 [33%]) (1). Furthermore, it has recently been shown by Yano et al. (10) that BNP is elevated in type 2 diabetic patients with microalbuminuria compared with those with normoalbuminuria. In their study, all microalbuminuric patients were normotensive, suggesting that any potential elevation of blood pressure commonly associated with microalbuminuria may have been compensated by the increased BNP level through its action on natriuresis and vasodilatation. Hence, it is at least physiologically plausible that increased circulating BNP concentrations in the presence of microalbuminuria may be a useful marker for early diastolic dysfunction in diabetic patients. Unlike ANP levels, which can be increased by acute hyperglycemia, circulating BNP concentrations have been shown to be unaffected by an elevated glucose level (11), making it more suitable for screening in diabetic patients. Further research will be required to determine the potential value of BNP in selecting microalbuminuric diabetic patients for further cardiological assessment.

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Erratum

Pisabarro R, Recalde A, Chaftare Y: High incidence of maternal transmission of diabetes in obese Uruguayan children (Letter). *Diabetes Care* 24:1303, 2001

Sentence 3 of the fourth paragraph of the above letter was omitted. The correct text of the paragraph is shown here:

> A total of 17% of the children were classified as OW and 9% as OB. No differences in BMI were found between sexes at the age interval studied. Of the OB group, 9% had a diabetic mother diagnosed by a physician. All of the mothers in the OB group had type 2 diabetes, 1% of the mothers in the NW and OW groups had type 1 diabetes, and no differences were found between diabetic and nondiabetic fathers. This maternal transmission of type 2 diabetes was addressed in a recent study (4).