OBSERVATIONS

Status of Research Funded by the American Diabetes Association: Year 3

In my Presidential Address in June of 1998 (1), I proudly announced that the most recent Five Year Plan adopted by the American Diabetes Association contained the goal of allocating one of every three dollars of total public support to research awards and grants by the end of 5 years. I pledged to keep the members of the professional section apprised of our progress toward that goal. The general approach envisaged gradual increases during the first three years, with more steep increases during the final two years.

Table 1 depicts our performance from the year before the Five Year Plan went into effect through this past fiscal year.

The final two years are now upon us. Are we up to the huge challenge that remains? I'll let you know next year.

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Table 1—*Five Year Plan progress*

Fiscal year	Total public support (millions of dollars)	Amount devoted to research (millions of dollars)	%
1998	90.8	15.5	17.1
	Clock starts ticking		
1999	101.5	18.2	17.9
2000	117.8	22.4	19.0
2001	134.6	27.4	20.4
2002	—	—	—
2003	—	—	≥33?

Insulin Sensitivity Indexes From a Single Sample in Nonobese Japanese Type 2 Diabetic Patients

Comparison with minimal model analysis

Insulin resistance is important not only in obesity and diabetes but also in essential hypertension, dyslipidemia, and atherosclerotic cardiovascular disease (1). We recently demonstrated that the homeostasis model assessment for insulin resistance (HOMA-IR) proposed by Matthews et al. (2) is validated against the minimal model–derived insulin sensitivity index (MINMOD-SI) in type 2 diabetic patients (3). Although the relationship between HOMA-IR and MINIMOD-SI in these patients was statistically significant, the correlation coefficient was low ($r = 0.459$, $P = 0.021$) (3). Therefore, a more highly correlated simple index is needed to measure insulin resistance in large type 2 diabetic populations.

The major drawback of HOMA-IR is that when the glucose or insulin concentration increases, the value is overestimated. Furthermore, HOMA-IR is not linear over wide ranges of insulin sensitivity in man (4). Katz et al. (5) recently proposed the quantitative insulin sensitivity check index (QUICKI) [1/(log glucose + log insulin)] as a novel index of insulin sensitivity. They demonstrated that the correlation between the euglycemic clamp and QUICKI is significantly better than the correlation between the euglycemic clamp and HOMA-IR in 56 subjects, including diabetic patients. We proposed another three insulin sensitivity indexes based on QUICKI. To the best of our knowledge, however, the relationships between MINMOD-SI and these formulas, including QUICKI, have not been fully investigated in type 2 diabetic patients.

Twenty-five nonobese Japanese type 2 diabetic patients underwent the minimal model approach to measure insulin sensitivity index as described previously (6). Their age (mean ± SD), was 45.4 ± 11.5 years (range 26–58), and their BMI was 20.2 ± 3.0 kg/m^2 (13.5–25.3). The HbA_{1c} level was 7.2 ± 1.5% (5.1–11.3). Fasting glucose and insulin levels were 6.7 ± 1.7 mmol/l (5.0–11.9) and 4.5 ± 1.5 μU/ml (1.7–8.4), respectively. Their insulin sensitivity index was 9.0 ± 7.1 [$(\mu U/ml)^{-1}\ min^{-1}$] (range 3.2–31.3). Type 2 diabetes was diagnosed based on the criteria of the World Health Organization (7). Five patients were treated with sulfonylureas and the rest with diet alone. One might argue that the use of sulfonylureas in patients with diabetes might significantly affect the estimate of insulin resistance by HOMA, as these drugs are known to decrease fasting plasma glucose without substantially changing fasting plasma insulin (8). However, it seems unlikely because Bonora et al. (9) confirmed that in the validation studies of HOMA, the correlation of insulin sensitivity estimated by this method and that measured by the glucose clamp was not substantially different in diet- and sulfonylurea-treated type 2 diabetes.

The statistical analysis was performed with the Statview 5.0 system (Statview, Berkeley, CA). Spearman's correlation coefficient by rank was used for the analysis. $P < 0.05$ was considered as significant.

The insulin sensitivity index obtained from the minimal model approach was best correlated with 1/(log glucose × log insulin) ($r = 0.658$, $P < 0.001$), followed by 1/(insulin × log glucose) ($r = 0.615$, $P < 0.001$), 1/(glucose × log insulin) ($r = 0.596$, $P < 0.001$), QUICKI ($r = 0.521$, $P < 0.005$), and HOMA-IR ($r = 0.459$, $P = 0.021$) in our diabetic patients.

In conclusion, although the current study was performed in a limited number of patients ($n = 25$) with a relatively narrow range of insulin sensitivity (3.2–31.3 [$(\mu U/ml)^{-1}\ min^{-1}$], it can be concluded that 1/(log glucose × log insulin) is highly

correlated with the minimal model–derived insulin sensitivity in nonobese Japanese type 2 diabetic patients. Furthermore, the correlation coefficient between MINMOD-SI and 1/(log glucose × log insulin) ($r = 0.658$) was similar to that between MINMOD-SI and the insulin sensitivity index (ISI, composite) ($r = 0.677$) proposed by Matsuda and DeFronzo (3,10). Whereas the ISI (composite) requires an oral glucose tolerance test, 1/(log glucose × log insulin) can be calculated from the fasting state. Thus, 1/(log glucose × log insulin) is considered to be a simple and useful tool for the estimation of insulin resistance in nonobese Japanese type 2 diabetic patients.

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Fenofibrate Lowers Plasma Triglycerides and Increases LDL Particle Diameter in Subjects With Type 2 Diabetes

Subjects with type 2 diabetes have an increased risk of coronary artery disease (CAD). The typical dyslipidemia in type 2 diabetes consists of hypertriglyceridemia, low HDL cholesterol level, and preponderance of small, dense LDL particles. Epidemiological studies have linked all these lipid abnormalities with CAD. The Diabetes Atherosclerosis Intervention Study (DAIS) has recently reported that treatment with fenofibrate results in favorable changes in the plasma lipid profile and a significant reduction in the progression of CAD in subjects with type 2 diabetes (1). We have now determined the long-term effect of fenofibrate on LDL peak particle diameter in 46 Finnish DAIS study participants with type 2 diabetes.

The baseline characteristics in our DAIS subpopulation were similar to those in the whole cohort (2). Subjects were randomly assigned micronized 200 mg fenofibrate once daily ($n = 25$) or placebo ($n = 21$) for at least 3 years. Data obtained at randomization were used as the baseline data, and the data obtained at the final on-treatment visit were used as the on-treatment data. Biochemical analyses were performed as previously described (3). LDL peak particle diameter (LDL size) was obtained using polyacrylamide 2–10% gradient gels. Postheparin lipoprotein lipase (LPL) and hepatic lipase (HL) activities were measured as previously described (4). Posttreatment values between fenofibrate and placebo groups were compared with ANCOVA using respective baseline values as a covariate. Multivariate forward stepwise regression analysis was performed to find the determinants of the change in LDL diameter. Changes in plasma lipids and lipoproteins, HbA_{1c}, BMI, and lipase activities were used as independent variables.

LDL size, lipid and lipoprotein concentrations, LPL and HL activities, glycemic control, BMI, and sex distribution at baseline were similar in fenofibrate and placebo groups. Mean glycemic control, BMI, and HL activity did not change significantly in either group during the study. Treatment with fenofibrate was associated with significant changes in the plasma lipid profile. Specifically, LDL size was larger and plasma triglycerides, total and LDL cholesterol concentrations, and total cholesterol–to–HDL cholesterol ratio were lower in the fenofibrate group than in the placebo group at the end of the study (Table 1). The difference in HDL cholesterol concentration did not reach significance. LPL activity at the end of the study was higher in the fenofibrate group than in the placebo group.

Table 1—*Characteristics of the study groups*

	n	Baseline	End
LDL size (nmol/l)			
Fenofibrate group	25	25.3 ± 1.0	26.7 ± 0.7*
Placebo group	21	25.1 ± 1.3	25.9 ± 1.2
TG (mmol/l)			
Fenofibrate group	25	2.03 ± 0.60	1.30 ± 0.66†
Placebo group	21	2.16 ± 0.86	2.19 ± 1.30
TC (mmol/l)			
Fenofibrate group	25	5.61 ± 0.53	4.59 ± 0.77†
Placebo group	21	5.46 ± 0.59	5.32 ± 0.62
LDL-C, (mmol/l)			
Fenofibrate group	25	3.60 ± 0.48	2.90 ± 0.70†
Placebo group	21	3.43 ± 0.54	3.30 ± 0.59
HDL-C (mmol/l)			
Fenofibrate group	25	1.06 ± 0.17	1.09 ± 0.24
Placebo group	21	1.05 ± 0.16	1.02 ± 0.20
TC–to–HDL-C ratio			
Fenofibrate group	25	5.42 ± 0.91	4.40 ± 1.28†
Placebo group	21	5.29 ± 0.70	5.34 ± 1.03
LPL (mU/ml)			
Fenofibrate group	25	228 ± 53	247 ± 54‡
Placebo group	21	251 ± 64	211 ± 49

Data are means ± SD. HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; LPL = postheparin activity; TC, total cholesterol; TG, total trigycerides. *$P < 0.02$, †$P < 0.001$, ‡$P < 0.005$, fenofibrate group vs. placebo group at the end of the study (ANCOVA with baseline value as a covariate).

In the fenofibrate group, only change in plasma triglycerides ($r = -0.57$, $P = 0.003$) and change in HDL cholesterol ($r = 0.49$, $P = 0.012$) were significantly correlated with change in LDL diameter. Change in plasma triglycerides was, as expected, inversely correlated with change in HDL cholesterol ($r = -0.49$, $P = 0.013$). The association between change in LPL activity and change in triglycerides was of borderline significance ($r = -0.38$, $P = 0.062$). In the placebo group, only change in plasma triglycerides was significantly correlated with change in LDL diameter ($r = -0.45$, $P = 0.042$). In multivariate regression analysis, the change in plasma triglyceride concentration was the only variable to enter the model, explaining 30% of the variation of LDL size in the fenofibrate group ($P = 0.003$) and 16% in the placebo group ($P = 0.042$).

The main result of our study is that long-term treatment with fenofibrate lowers plasma triglycerides and increases LDL peak particle diameter in subjects with type 2 diabetes. Almost all subjects in the fenofibrate group had a decrease in plasma triglyceride concentration, the average decrease being 0.7 mmol/l (36%). The decrease of plasma triglycerides was strongly associated with a significant increase in LDL peak particle diameter. It is likely that the increase in LPL activity is one of the mechanisms by which fenofibrate decreases plasma trigyceride concentration (5). These results add support to the theory that LDL size and composition can be modified by changes in ambient lipoprotein concentrations and lipoprotein-modifying enzyme activities.

Cross-sectional and prospective studies have linked small, dense LDL particles and CAD (6,7). However, close connections between LDL diameter and density, triglyceride-rich lipoproteins, and HDL cholesterol have made it difficult to determine which of these variables truly has a central role in the development of atherosclerosis. DAIS has recently reported that treatment with fenofibrate reduces the angiographic progression of CAD in type 2 diabetes (1). Based on our results, the change in LDL particle distribution toward larger, probably less atherogenic particles should be included as one potential mechanism accounting for the beneficial effect of fenofibrate. Further studies are required to elucidate the clinical significance of small, dense LDL particles.

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Somatostatin Therapy in the Management of Resistant Diabetic Ketoacidosis

In the pathogenesis of type 1 diabetes, not only insulin hormone deficiency but also inappropriate secretion of counterregulatory hormones are thought to play a part. From this point of view, inhibition of counterregulatory hormones should also be evaluated in the treatment of type 1 diabetes. The cyclic tetradecapeptide hormone somatostatin was first characterized as the major physiological inhibitor of growth hormone release from the pituitary, but it has subsequently been shown to inhibit the release of many other physiologically important compounds, including insulin, glucagon, gastrin, and secretin. Diabetic ketoacidosis (DKA) is a complication of type 1 diabetes, and its management includes insulin, fluid, and electrolyte therapy. Alternative treatments have been investigated in unresponsive patients. As a inhibiting hormone of counterregulatory hormones, somatostatin may be used in the treatment of diabetic ketoacidotic coma. In this study, two diabetic ketoacidotic children who were unresponsive to standard insulin and fluid therapy are discussed; despite appropriate management of fluid and electrolytes, the patients' blood glucose levels could not be lowered, and they had no clinical improvement. We tried somatostatin infusion therapy in both of these children.

The first patient is an 8-year-old girl who was admitted to our emergency room with a history of polyuria and polydipsia during the last week. She had deep and rapid breathing, loss of consciousness, and acidosis at the time of admission. There was no particular disease in her personal or family history. On physical examination, tachicardia and Kussmaul breathing were present, and severe dehydration was observed. The Glasgow coma scale was 3, with unresponsiveness to either verbal or pain stimulus and loss of consciousness. Leukocytes were markedly increased at peripheral blood smear. Microscopic and bacteriologic examination of urine was normal, but glucose and acetone in urine were quite highly positive. The blood glucose concentration was 1,300 mg/dl. The patient was hospitalized for management of DKA.

The second patient was an 11-year-old boy who had prior complaints of polyuria and polydipsia for the previous 10 days. He was admitted with loss of consciousness, deep and rapid breathing, and acidosis. There was no particular disease in his past or family history. On physical examination, tachicardia and Kussmaul breathing were present, and severe dehydration was observed. The Glasgow coma scale was 3 at admission, with unresponsiveness to either verbal or painful stimulus and loss of consciousness. A peripheral smear revealed markedly increased leukocytes. Microscopic and bacteriologic examination of urine was normal, but glucose and acetone in urine was quite high. The blood glucose level was 1,300 mg/dl, and the other biochemical parameters were in the normal range. The patient was diagnosed as having diabetic ketoacidotic coma and hospitalized.

As the initial therapy, we started 100% oxygen inhalation by face mask and an infusion of 0.9% normal saline (10 ml/kg over 30 min), which was repeated twice. The deficit and maintenance fluids were calculated for fluid treatment (deficit fluid was calculated as the estimated percent dehydration times body weight; maintenance fluid was 60 ml/kg per 24 h in patient 1 and 50 ml/kg per 24 h in patient 2). We then added deficit fluids to 48-h maintenance fluids and replaced this volume over 48 h with 0.9% normal saline. We added 40 mmol/l potassium chloride to each liter of saline infusion. Bicarbonate was not used during the therapy. Insulin was started until shock was successfully reversed and saline/potassium rehydratation regimen was begun. Insulin therapy was started as continuos low-dose intravenous infusion (0.1 units/kg per h). Although sufficient fluid and insulin infusion was begun, the patients did not recover. The total insulin dose was increased by 25%, but in patient 1, at the 20th hour of treatment, blood glucose could not be lowered under 800 mg/dl, and she was still unconscious. In patient 2, at the 15th hour of treatment, blood glucose could not be lowered under 500 mg/dl, and he was also unconscious at that time. Meanwhile, pH was found to be 7.31 and 7.30 in patients 1 and 2, respectively. We have documented that there was no brain edema, electrolyte imbalance, or central nervous system (CNS) infection. Therapy steps were reevaluated for probable mistakes, and the therapy was found to be normal. We started continuous 3.5 μg/kg per h somatostatin asetat (250-μg ampule Stilamin; Serono) infusion. In patient 1, blood glucose dropped to 400 mg/dl, and she regained conscious 4 h after the beginning of somatostatin infusion. In patient 2, blood glucose dropped to 300 mg/dl, and he was conscious 3 h after the beginning of somatostatin infusion. When the blood glucose fell to 270 mg/dl, the infusion was changed to 0.45% saline with 5% glucose. When oral fluids were tolerated and insulin doses were decreased to <0.05 units/kg per h, the insulin infusion and fluid therapy were stopped, and we started subcutaneous insulin therapy. The patients were discharged after completion of therapy and followed-up at our outpatient clinics.

Somatostatin analogs have been used in the treatment of neuroendocrine tumors, vipomas, carcinoid tumors, congenital microvillus atrophy, AIDS-associated diarrhea, gastrointestinal system bleeding, dawn phenomena, and short–small bowel syndrome. The use of somatostatin in type 1 diabetes is not a new phenomenon. Somatostatins have been successfully used in the treatment of diabetes-associated autonomic neuropathy, and they have also been shown to decrease the requirements for insulin (1,2). This effect is via inhibition of ketogenesis and decreasing secretion of glucagon (3). In the literature, there are limited studies about somatostatin use in DKA. It was used in unresponsive and glucagonoma-caused diabetic ketoacidotic coma (4), and it was also used prophylactically in the short term for patients at risk of DKA (3). Yun et al. (5) compared insulin with somatostatin analogs and insulin therapy in DKA. The improvement in hyperglycemia and acidosis was not different, but in the somatostatin-added group, improvement in ketonuria was achieved earlier. The authors concluded that somatostatin analogs were not effective in manifest DKA to control acidosis and hyperglycemia. In a study by Greco et al. (6), acidosis improved earlier when somatostatin analogs were added to insulin therapy. The two presented case subjects reported no benefit, although they had appropriate insulin and fluid therapy.

Their biochemical and neurological improvements were delayed, and cerebral edema, hypoglycemia, hypopotassemia, CNS, or any other infections were excluded.

We added somatostatin therapy to inhibit ketogenesis and decrease glucagon secretion. After somatostatin infusion, hyperglycemia improved in both patients, and they were clinically well. Blood glucose levels declined in both patients, and they regained consciousness. Acidosis was also improved a short time after somatostatin therapy.

In conclusion, for patients who do not respond well to standard DKA treatment, somatostatin may be added to the therapy. Counterregulatory hormones may be as effective as insulin in the treatment of DKA. More data and further randomized controlled studies are necessary to expand our findings.

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Validation of a Case Definition for Foot Complications Among Hospitalized Patients With Diabetes

Lower extremity ulcers (LEU) and amputations (LEA) as well as other foot complications are a serious preventable problem among patients with diabetes. To establish a hospital-based surveillance system for foot complications and to initiate quality improvement efforts to prevent future complications, we used a case definition developed by Harrington et al. (1). The authors developed this definition as part of a cost analysis study of foot complications among Medicare beneficiaries. The case definition utilizes ICD-9-CM diagnosis codes and Current Procedural Terminology, version 4 (CPT-4), procedural codes to identify patients with diabetes having a LEU, LEA, or other foot complications. First, patients with diabetes were identified based on hospitalization diagnoses. Then, the subgroup of patients with ICD-9-CM diagnoses of CPT-4 procedure codes for possible foot complications were identified. The ICD-9-CM diagnoses included LEU; carbuncle or furuncle of the foot; cellulitus of abscess of the toe or foot; gangrene; infectious myositis; unspecified myalgia or myositis; osteomyelitis; amputation or resection of the foot, ankle, leg, or knee and above; and late amputation stump complication. The CPT-4 procedures included simple repair of a superficial wound; debridement; lower extremity radiographic techniques; angioscopy; arteriography; angiography; lower extremity CAT or MRI scanning; incision or excision of the foot; Unna's boot application; and amputation or resection of the foot, ankle, leg, or knee and above. The validity of this case definition, to our knowledge, has not been established. This report describes the adaptation of this case definition using hospitalization discharge data and an evaluation of its validity.

Patients hospitalized with diabetes (ICD-9-CM codes 250, 250.0–250.9, 251.0, and 362.01–362.02) at two hospitals in Missoula, Montana (the Saint Patrick Hospital and Health Sciences Center and the Community Medical Center), in 1999–2000 were identified. The subset of patients with potential foot complications based on diagnosis and procedure codes was then identified using the same definition as Harrington et al. We added ICD-9-CM codes for Charcot disease (ICD-9-CM 94.0 and 713.5) and revascularization or bypass surgery (ICD-9-CM 38.08, 38.09, 38.48, and 38.49) as part of the case definition to increase the sensitivity. The medical records of hospitalized patients with diabetes and foot complications were then reviewed to confirm that these cases were correctly classified. A systematic sample (4%) of medical records of patients with diabetes but without foot complications listed was also reviewed to confirm the absence of obvious foot problems.

A total of 3,596 hospitalizations were identified, and 157 (4.4%) had ≥1 foot problem coded as a discharge diagnosis or procedure code. Of these hospitalizations, 58% were men, and the mean age was 65 years. The majority of the discharge diagnoses were LEU (42%), LEA (36%), and cellulitus or abscess of the toe or foot (26%). Fewer discharges listed diagnoses such as LEA complication (8%), revascularization (6%), Charcot disease (5%), gangrene (4%), and infectious myositis (2%). None of the patients had discharge diagnoses for other local infections of the skin and subcutaneous tissue or for a carbuncle or furuncle of the toe or foot. Of the 157 hospitalizations for foot problems, 137 (87%) were confirmed to have ≥1 foot complication based on the medical record review, 10 (6%) had no foot complication listed, and 10 (6%) records were not available for review. Of the 10 cases with no confirmed foot complication, 4 had a history of foot complications but no current problem, 2 had ulcers on other regions of the body, 1 had a femoral bypass with no foot complication, 1 had sepsis not related to the foot, and 1 had a lower extremity clot with no other foot complications. Of the medical records of patients with diabetes but with no foot complications included in the diagnoses or procedural codes, 2 of 131 (1.5%) had a foot problem documented in the medical record (both foot ulcers). Overall, the values for sensitivity, specificity, predictive value pos-

itive, and predictive value negative of the adapted case definition were 0.99, 0.93, 0.93, and 0.98, respectively.

Our findings suggest that the methods developed by Harrington et al. as well as our adapted case definition are valid in terms of accuracy and reliability. The incorporation of diagnosis codes for Charcot disease was useful in that this condition was present among patients hospitalized with diabetes and foot complications. The incorporation of revascularization procedure codes as part of the case definition did not increase the number of false-positive cases. Overall, these case definitions can be useful not only for cost analysis studies as conducted by Harrington et al., but also for hospital-based surveillance for foot complications to initiate quality improvement efforts to prevent future foot complications.

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Impairment of the Auditory Brainstem Function in Diabetic Neuropathy

Diabetes may alter both the peripheral and the central nerve function, but the peripheral manifestations of diabetic neuropathy are more frequently discussed in the literature than the impairment of the central nervous system. Delay of the evoked potentials in the central pathways has been reported in diabetic patients (1), but the exact pathophysiology of these alterations is still unclear (2). The aims of our study were to characterize the afferent brainstem function by detection of the auditory-evoked potentials in patients with long-standing type 1 diabetes and to analyze possible connections between the central neural dysfunction and the autonomic and peripheral sensory neuropathies.

We enrolled 12 patients with long-standing type 1 diabetes who had normal hearing (age [mean ± SD] 42.1 ± 14.8 years, duration of diabetes 23 ± 8.9 years, BMI 26.8 ± 4.6 kgm^2). The quantitative characteristics of the brainstem function were evaluated by the detection of auditory-evoked potentials (3). This procedure consists of the analysis of seven electrical waves generated along the nerve tracts of the auditory system after the delivery of an audible click of short duration via an earphone. The latencies and the interpeak latencies of five waves (I-V) were determined in this study. The presence of cardiovascular autonomic neuropathy was investigated by means of the five standard cardiovascular reflex tests (4), and a score (scale 0–10) was used to express the severity of the overall autonomic disorder (5). Three of these tests (the heart rate response to breathing, the 30/15 ratio, and the Valsalva ratio) evaluate mainly the parasympathetic function, whereas the systolic blood pressure response to standing up and the diastolic pressure change to a sustained handgrip predominantly allow an assessment of the sympathetic integrity. The peripheral sensory nerve function was characterized by evaluation of current perception thresholds (CPTs) with a neuroselective diagnostic stimulator (Neurotron, Baltimore, MD), which permits transcutaneous testing at three sinusoidal frequencies (2 kHz, 250 Hz, and 5 Hz) of electrical stimulus (6). Median and peroneal nerves (digital branches) were studied.

Positive correlations were observed between the autonomic score and the lengths of the latencies of of waves III and V (Table 1). In accordance with this finding, there was a negative relationship between the results of three heart rate tests (the heart rate response to deep breathing, the 30/15 ratio, and the Valsalva ra-

Table 1—*Correlations between cardiovascular reflex tests and latency intervals of auditory-evoked brainstem potentials*

Correlated parameters	Correlation coefficient	*P*
Autonomic score and latency of wave III	0.6149	<0.05
Heart rate response to breathing and latency of wave III	−0.6450	<0.001
30/15 ratio and latency of wave III	−0.5904	<0.01
Valsalva ratio and latency of wave III	−0.5015	<0.05
Autonomic score and latency of wave V	0.4979	<0.05
Heart rate response to breathing and latency of wave V	−0.4982	<0.01
30/15 ratio and latency of wave V	−0.5932	<0.01
Valsalva ratio and latency of wave V	−0.4802	<0.05
Autonomic score and interpeak latency I-III	0.5414	<0.01
Heart rate response to breathing and interpeak latency I-III	−0.5544	<0.01
30/15 ratio and interpeak latency I-III	−0.5111	<0.05
Autonomic score and interpeak latency I-V	0.4891	<0.05
Heart rate response to breathing and interpeak latency I-V	−0.4621	<0.05
30/15 ratio and interpeak latency I-V	−0.5434	<0.05

tio) and the prolongation of the latencies of waves III and V. Neither the systolic blood pressure response to standing nor the sustained handgrip test showed any significant correlation with the prolongation of the evoked potentials. Pronounced abnormalities of waves III and V were also recorded during the analysis of the interpeak latencies of the brainstem potentials. Positive correlations were demonstrated between the autonomic score and the interpeak latencies I-III and I-V. The heart rate response to deep breathing and the 30/15 ratio correlated negatively with the interpeak latencies I-III and I-V. These two heart rate tests are considered the most sensitive procedures for autonomic function (4). No significant correlations were found between the other three cardiovascular reflex tests and the interpeak latencies. The higher CPT values obtained at 2,000 and 250 Hz at the peroneal nerve correlated positively with the latencies of waves III (both $P < 0.05$) and V (both $P < 0.01$).

As a novel finding, wave III and V latencies were associated with cardiovascular autonomic and peripheral sensory nerve dysfunctions, which are progressive forms of diabetic neuropathy. The parasympathetic nerve dysfunction characterized mainly by the three heart rate tests develops earlier in the course of diabetes. The higher CPT values obtained at 2,000 and 250 Hz indicate large sensory nerve fiber damage, which usually precedes small fiber neuropathy (5). These abnormalities are commonly seen first in the lower extremities. In our study, the impairment of the three heart rate tests and the degree of large sensory nerve dysfunction correlated with the wave III and V latencies. These data may suggest that the abnormalities of waves III and V indicating an impairment of the auditory brainstem function should be regarded as early central manifestations of diabetic neuropathy.

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Plasma Homocysteine Is not Increased in Microalbuminuric Patients With Type 2 Diabetes Without Clinical Cardiovascular Disease

Although mild hyperhomocysteinemia (MHH) has been considered as an independent risk factor for cardiovascular disease (CVD) (1,2), some investigators have cast doubts about this statement (2–4). Subjects with type 2 diabetes and microalbuminuria (MA) are particularly at risk of developing CVD. In these subjects, there is some controversy as to whether total plasma homocysteine (tHcy) levels are increased (5–7) or not (8–11). Usually, these studies, which include subjects with and without CVD, do not take into account this variable when analyzing their results. It is well known that there is a positive relationship between the presence of CVD and MA (12). In addition, CVD itself is associated with MHH (1,2). We hypothesized that studies that found an increase in tHcy levels in subjects with MA did not take into account the presence of a preexisting CVD as a confounding variable. Therefore, as subjects with type 2 diabetes and MA have a higher prevalence of preexisisting CVD, higher values of tHcy could be expected as a result of CVD and not because of MA.

To test this hypothesis, we studied 93 subjects with type 2 diabetes (55 with normoalbuminuria and 38 with MA) and 86 nondiabetic control subjects matched for age and sex, all of whom were recruited at a primary care center. The exclusion criteria were: age <35 or >85 years, serum creatinine >1.4 mg/dl, uncontrolled hypertension (systolic >160 mmHg and/or diastolic >95 mmHg), congestive heart failure, major invalidating disease, pregnancy, hypothyroidism, preexisting clinical CVD (including coronary heart disease, stroke, or peripheral vascular disease), use of oral drugs that could have elevated tHcy in the previous 3 months (notably drugs for dyslipemia and metformin), or macroalbuminuria (urinary albumin excretion rate [UAER] ≥200 ugr/min). The following data were collected for each subject: age, sex, duration of type 2 diabetes, BMI, and blood pressure. Blood pressure was measured twice via the right arm after 10 min rest in the supine position by a trained staff member using a standard manometer. Hypertension was defined as blood pressure ≥140/90 mmHg or being under antihypertensive treatment. After an overnight fast, blood was drawn and analyzed for fasting plasma glucose, HbA_{1c}, serum creatinine, total cholesterol, triglycerides, HDL cholesterol, thyroid-stimulating hormone, serum vitamin B_{12}, serum folate, and tHcy. Information about alcohol intake and smoking habits was obtained through a questionnaire. During 3 months, subjects collected triplicate 24-h urine samples, which were analyzed for UAER and urinary creatinine excretion rate. MA was diagnosed when the geometric mean of the three values of UAER was between 20 and 200 μg/min. Otherwise, subjects were classified as nor-

moalbuminuric (<20 μg/min) or macroalbuminuric (≥200 μg/min). Estimated creatinine clearance was calculated by the Cockroft-Gault formula (13). Retinopathy was assessed by a consultant ophthalmologist. In the statistical analysis, skewed variables were logarithmically transformed to reduce kurtosis.

There were no differences between the subjects with type 2 diabetes and control subjects with respect to age (66.0 ± 11.5 vs. 65.4 ± 12.8 years, $P = 0.74$), sex (49.5 vs. 50.0% of women, $P = 0.94$), and the other variables evaluated, except for fasting plasma glucose (151.9 ± 61.7 vs. 100.8 ± 14.0 mg/dl, $P = 0.00$), HbA_{1c} (6.3 ± 1.4 vs. 5.0 + 0.6%, $P = 0.00$), and UAER (39.9 ± 33.6 vs. 4.3 ± 3.6 μg/min, $P = 0.00$). All subjects had serum vitamin B_{12} and folate concentrations within the reference range. No significant differences were found in relation to tHcy levels between type 2 diabetic and control subjects (7.4 ± 2.6 vs. 7.3 ± 2.8 μmol/l, $P = 0.81$). There were no differences between type 2 diabetic subjects with and without MA in relation to sex (47.4 vs. 50.9% of women, respectively), age (66.4 ± 10.5 vs. 65.8 ± 10.5 years), BMI (27.4 ± 4.7 vs. 28.4 ± 4.8 kg/m^2), alcohol intake >20 g/day (10.5 vs. 10%), percentage of current smokers (15.8 vs. 27.3%), prevalence of diabetic retinopathy (21.1 vs. 10.9%), fasting plasma glucose (155.2 ± 66.0 vs. 149.7 ± 53.1 mg/dl), total cholesterol (223.0 ± 41.1 vs. 217.1 ± 38.0 mg/dl), triglycerides (134.1 ± 71.7 vs. 141.1 ± 91.9 mg/dl), HDL cholesterol (46.6 ± 13.3 vs. 47.7 ± 15.3 mg/dl), LDL cholesterol (149.6.2 ± 42.4 vs. 140.4 ± 34.2 mg/dl), creatinine (0.95 ± 0.19 vs. 0.95 ± 0.17 mg/dl), creatinine clearance (79.0 ± 25.3 vs. 88.2 ± 26.2 ml/min), UAER (57.9 ± 30.5 vs. 10.6 ± 5.3 μgr/min), serum folate (9.2 ± 3.4 vs. 9.7 ± 7.3 ng/ml), serum vitamin B_{12} (431 ± 228 vs. 427 ± 210 pg/ml), tHcy (7.3 ± 2.8 vs. 7.4 ± 2.4 μmol/l), and percentage of subjects with MHH (31.6 vs. 25.5%). However, subjects with MA had a longer duration of the disease (12.2 ± 8.7 vs. 8.2 ± 9.5 years, $P = 0.04$), a higher prevalence of hypertension (65.8 vs. 41.8%, $P = 0.01$), and higher HbA_{1c} levels (6.7 ± 1.5 vs. 6.0 ± 1.2 mg/dl, $P = 0.00$). In the control group, the 75th percentile of the tHcy values distribution was ≥8.2 umol/l. This cutoff value was used to classify subjects with type 2 diabetes as having MHH. A total of 14 subjects with normoalbuminuria (25.5%) and 12 with MA (31.6%) had MHH, but the differences were not statistically significant. In the whole group of subjects with type 2 diabetes, we found higher tHcy values in male as compared with female subjects (8.0 ± 2.9 vs. 6.4 ± 2.0 μmol/l, $P = 0.02$). We also found a significant positive correlation (Pearson's correlation coefficient) between Log tHcy and age ($r = 0.25$, $P = 0.02$) and a significant negative correlation between Log tHcy and both serum folate ($r = -0.23$, $P = 0.03$) and serum B_{12} vitamin ($r = -0.24$, $P = 0.03$). No significant correlation was found between Log UAER and Log tHcy ($r = 0.15$, $P = 0.17$). By stepwise logistic regression analysis, serum folate (negative relationship, $P = 0.01$) and serum creatinine (positive relationship, $P = 0.01$), but not UAER, emerged as the independent variables related to MHH in subjects with type 2 diabetes. Additional preliminary data in a reduced group of 22 subjects with type 2 diabetes and CVD (aged 67.6 ± 9.2 years, sex 50.0% of women, 10.7 ± 6.9 years of duration of type 2 diabetes, 45.5% of them with MA, 68.1% hypertensive, and 40.9% with MHH) supported our hypothesis. This subgroup of patients had higher values of tHcy than subjects with MA but without CVD (8.5 ± 2.5 vs. 7.3 ± 2.8 μmol/l, $P = 0.05$).

Some previous studies have evaluated the relationship between MA and tHcy levels in subjects with type 2 diabetes. Some of these studies have found a positive relationship between MA and tHcy values (5–7), but this finding has not been confirmed by others (8–11). The majority of these studies are cross-sectional and have not adjusted their results according to the presence of CVD. Uncontrolled confounding variables must always be considered as a possible noncausal explanation for any observed association between tHcy levels and MA. Therefore, if an association between tHcy and MA is found, it is mandatory to adjust for the presence of CVD before concluding that an association between tHcy and MA exists. This adjustment is very important, especially if we take into account that in some of the above-mentioned studies (5), ~30% of subjects with type 2 diabetes have CVD as compared with an absence of CVD in the control group. In conclusion, the present findings suggest that in type 2 diabetic subjects with MA but without clinical CVD, there is no association between MA and tHcy levels.

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Lipohypertrophy in Young Patients With Type 1 Diabetes

Abnormal injection sites may complicate insulin treatment in type 1 diabetic patients, leading to delayed insulin absorption (1). The aim of this study was to document the prevalence of lipohypertrophy in young patients treated with modern insulin regimens and devices and to assess parameters influencing its development.

The injection sites of 282 children and adolescents (160 boys and 122 girls, median age 12.3 years [range 2.1–23.8]) with diabetes (duration 3.7 years [0.1–18.8]) were prospectively evaluated during outpatient clinic visits between 1 January and 31 March 2001. Findings were graded as followed: grade 0 = no changes; grade 1 = visible hypertrophy of fat tissue but palpably normal consistency; grade 2 = massive thickening of fat tissue with higher consistency; and grade 3 = lipoatrophy. HbA_{1c}, needle length, use of syringes, pen, or pump, number of daily injections, and insulin preparations were documented. All patients received human insulin from diabetes onset. They were taught and asked to rotate their injection sites after every injection according to a scheme (left, right thigh and/or left, right abdominal area). Data were analyzed using the Statistical Package for the Social Sciences (SPSS 9.0). Differences between the groups were calculated by the χ^2 test for categorical variables and the Mann-Whitney *U* test or Kruskal-Wallis test for two or more continuous variables, respectively. Data are presented as median (range).

A total of 135 (47.8%) of 282 patients had lipohypertrophy, 147 had no lipohypertrophy, and none had lipoatrophy at their insulin injection sites. Eighty-three patients (29.4%) had changes according to grade 1, and fifty-two (18.4%) had massive lipohypertrophy (grade 2). Patients with lipohypertrophy had significantly higher HbA_{1c} values (8.5% [5.1–13.3] vs. 8.7% [5.7–14.3] vs. 9.3% [5.3–16.1], $P < 0.05$, grade 0 vs. grade 1 vs. grade 2, respectively), more daily insulin injections (three [2–5] vs. four [2–6] vs. four [2–5], $P < 0.001$), and longer diabetes duration (3.0 years [0.1–18.8] vs. 4.1 years [0.3–17.3] vs. 4.3 years [0.5–13.9], $P < 0.001$) than those without abnormalities at injection sites. Pen usage was associated with lipohypertrophy ($P = 0.003$). However, there was no association between lipohypertrophy at injection sites and length of needle (≤6, 8, or 12.7 mm) used by the patients ($P = 0.176$).

These data extend previous findings in adults (2) and underline that lipohypertrophy is a very frequent problem in young patients with diabetes associated with poor glycemic control. Although a cause for these lesions is not known, the predisposing conditions are trauma to the skin and subcutaneous tissue repeated over time in the presence of insulin. Because modern insulin treatments require numerous daily injections, the results of this study highlight the need of repeated and intensive education of patients about adequate injection techniques and the necessity for routine change of the injection sites.

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Continuous Subcutaneous Insulin Infusion to Resolve an Allergy to Human Insulin

Insulin allergy has increasingly decreased with the use of human recombinant insulin and is now reported in <1% of diabetic patients treated with insulin (1,2). Different methods have been used in the treatment of insulin allergy, such as the use of oral antihistaminics, the addition of glucocorticoids to insulin, the change to lispro insulin, which has proven to be less allergenic in several cases (3), as well as different models of desensitization. We report a patient with generalized allergy to insulin who was successfully treated with a continuous subcutaneous insulin infusion system.

A 43-year-old man (weight 65 kg, BMI 21.9 kg/m^2) was diagnosed as having type 1 diabetes in October of 1998. He had no other diseases and no history of any allergy. He began treatment with human insulin (regular and NPH). Shortly after initiating treatment, he developed a local reaction at the injection site (pruritus, erythema, and swelling) 15–20 min after the injection, which subsided within 1–2 h. This reaction appeared 4–5 times a week and was tolerated without treatment. In June 2000, he developed a sys-

temic reaction 5 min after insulin injection (generalized urticaria), which resolved with an H1 antihistamine. In July 2000, he used lispro insulin sporadically, and the same reaction ensued. Systemic reaction reappeared on two other occasions in September and December 2000. In January 2001, he was admitted to our hospital to evaluate a possible insulin allergy. Physical examination was normal. Leukocytes were within the normal range (6.10 × 109/l), but there was eosinophilia (0.73 × 109/l). Total IgE was 20.1 KU/l (n <100). The specific human insulin IgE antibody (CAP-SYSTEM; Pharmacia, Upssala, Sweden) was 123 KU/l (n <0.35). Skin-prick tests (5 UI/ml) were performed with human insulin and insulin lispro, as well as with additives of insulin preparations (protamine, paraben, metacresol, phenol, zinc, and isophane) using the Novo Insulin Allergy Kit (Novo Nordisk). The patient tested positive for all types of insulin and negative for additives and was thus diagnosed with insulin allergy. Because the local reactions were moderate and he had not received previous treatment, daily oral antihistamine therapy (mizolastine) was initiated. During the first week with mizolastine, the local reaction improved, but it reappeared with every injection during the second week. At the beginning of February 2001, systemic reaction recurred (generalized urticaria with facial and periorbital angioedema), coinciding with an omission of the mizolastine. Because of the increase in the intensity of the local reaction, despite the antihistaminic, treatment with an insulin pump with insulin lispro was started to achieve insulin tolerance by continuous insulin infusion. This therapy schedule involved a basal line (0.7 IU/h for 2–8 h, 0.3 IU/h for 8–13 h, 0.6 IU/h for 13–18 h, 0.8 IU/h for 18–21 h, and 0.6 IU/h for 21–22 h) and an additional bolus (6IU before breakfast, 5IU before lunch, and 6IU before dinner). The allergic reaction immediately disappeared, and optimal metabolic control was achieved. Skin-prick tests remained positive 3 months later, although the patient remained clinically asymptomatic.

To date, two cases of allergy to human insulin treated with an insulin pump have been reported (1,2). In one case, previous desensitization with human insulin injected every 2 h failed. In the other case, desensitization was achieved with an insulin pump. In our case, the insulin allergy was successfully treated with the insulin pump at therapeutic doses without previous desensitization. Continuous basal infusion may therefore induce tolerance of additional doses of preprandial insulin, despite these doses being similar to those that previously produced allergic reaction upon subcutaneous injection. Thus, the insulin pump may be useful as an alternative treatment in insulin allergy.

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T-Cell–Mediated Autoimmunity May Be Involved in Fulminant Type 1 Diabetes

According to the new classification of diabetes by the American Diabetes Association (1,2), type 1B diabetes is considered to be "idiopathic," i.e., of unknown origin. However, the existence of type 1B diabetes itself has not yet been defined. Recently, a subtype of type 1B diabetes, so-called "fulminant" type 1 diabetes, has been proposed (3). This type of type 1 diabetes is characterized by the following criteria: *1*) no detectable "islet-associated" autoantibody; *2*) regardless of diabetic ketoacidosis, near-normal HbA_{1c} levels, suggesting extremely acute onset; and *3*) high levels of pancreatic exocrine enzymes. On pancreatic biopsy in this type of type 1 diabetes, no insulitis is found, although infiltration of T-cells in exocrine tissue is observed. On the other hand, Tanaka et al. (4) reported that, at autopsy, clear CD8-dominant insulitis was found in a patient who died of diabetic ketoacidosis with no islet-associated autoantibody and a low HbA_{1c} level. Therefore, it has not yet been concluded whether T-cell–mediated autoimmunity is involved in this type of diabetes. Because the majority of type 1 diabetes is considered to be caused by cellular immunity, assessment of antigen-specific T-cell reactivity is obviously necessary. However, probably because of the very low frequency of pancreatic β-cell antigen-specific lymphocytes in the periphery, a system to assess islet-associated antigen-specific T-cell reactivity has not yet been established. Recently, we reported that the level of serum interferon (IFN)-inducible protein-10 (IP-10), an important chemokine inducing migration of activated T-cells to local lesions, was significantly elevated in type 1 diabetes and that the serum IP-10 level positively correlated with the number of GAD-reactive IFN-γ–producing $CD4^+$ cells in autoimmune-related type 1 diabetes (5). Therefore, the measurement of these markers, serum IP-10 level, and GAD-reactive IFN-γ–producing $CD4^+$ cells was considered to be useful to assess whether T-cell–mediated autoimmunity is involved in fulminant type 1 diabetes. We recently encountered a 33-year-old man who was considered to have so-called "fulminant" type 1 diabetes, characterized by diabetic ketosis (plasma glucose 23.9 mmol/l, urine ketone bodies 4^+), low HbA_{1c} (5.8%, normal range <5.4%), negative GAD antibody (detection limit <0.4 u/ml, 100% sensitivity and specificity of the assay in the GAD antibody proficiency test) (Immunology of Diabetes Workshop, Lab Identification no. 305), negative IA-2 (insulinoma-associated protein-2) antibody (detection limit <0.75 u/ml) (M. Powell, S. Chen, H. Tanaka, M. Masuda, C. Beer, B. Rees Smith, J. Farmaniak; unpublished observations), and elevated pancreatic exocrine enzymes (elastase-1 567 ng/ml, trypsin 739 ng/ml).

Probably because the patient visited our hospital in a very early phase, he had not yet developed an acidosis; his bicarbonate level was 22.9 mEq/l. Although thyroid-associated autoantibodies, such as thyroid peroxidase antibody and thyroglobulin antibody, were negative, a high level of serum IP-10 (296 pg/ml, mean 38.2 in healthy subjects) was observed, and GAD-reactive IFN-γ–producing $CD4^+$ cells were detected in peripheral blood in this case (55 of 50,000 $CD4^+$ cells; mean 8 of 50,000 $CD4^+$ cells in healthy subjects). Glucagon-stimulated C-peptide level was low (0.7 ng/ml), and HLA A24, which is considered to be related to total β-cell destruction (6), was detected. Other HLA types include A33, B7, B62, Cw7, Cw3, DQ1, DQ3, DR1, and DR6. Therefore, intensive insulin treatment was started immediately after admission (total 31 units/day at discharge). Previously, it has been reported that $CD4^+$ cells are rarely observed in the islet lesion of fulminant type 1 diabetes at autopsy (4); therefore, the finding of GAD-reactive IFN-γ–producing $CD4^+$ cells in peripheral blood in this type of diabetes is of importance. This case suggests the involvement of T-cell–mediated autoimmunity in fulminant type 1 diabetes, and this type of diabetes should not be diagnosed as type 1B diabetes based on the negativity of islet-associated autoantibody. We propose that more discussion and accumulation of cases are essential to conclude whether autoimmunity is involved in this type of diabetes.

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Increased Risk of Diabetes in First-Degree Relatives of Young-Onset Type 2 Diabetic Patients Compared With Relatives of Those Diagnosed Later

We were pleased to see an article focusing on the features of young-onset type 2 diabetes (YT2D), which is diagnosed between 18 and 44 years of age (1). The importance of studying this group is illustrated by reports of rapid increases in the prevalence of diabetes in young adults in both the U.S. (2) and U.K. (3).

We describe another feature of YT2D subjects not highlighted in the study by Hillier and Pedula (1): the increased rate of diabetes in first-degree relatives. Patients with YT2D may present earlier because of a greater genetic predisposition. We hypothesized that the risk of diabetes for relatives of patients with YT2D would be higher than the risk to relatives of those diagnosed later.

To test this hypothesis, we surveyed the family history of diabetes in 4,770 patients with type 2 diabetes (99% U.K. Caucasian) in Devon, U.K. Patients were defined as type 2 diabetic if they had been diagnosed at >25 years of age and were not treated with insulin for a year after diagnosis. Family history of diabetes was compared in those diagnosed before (n = 568) or after (n = 4,202) 45 years of age. Despite the YT2D subjects being younger at the time of sampling (median age 53 vs. 72 years, $P < 0.001$), the prevalence of diabetes was higher in the parents of young-onset patients. An affected mother or father was reported in 26.9 and 15.1% of the YT2D group, respectively, compared with 15.2 and 7.6% of those diagnosed at >45 years of age ($P < 0.001$ for both). Biparental diabetes was also significantly increased (2.5 vs. 0.6%, $P < 0.001$) in the YT2D group. The rates of diabetes in siblings (21.0 vs. 21.2%, $P = 0.91$) and children (3.7 vs. 4.6%, $P = 0.35$) were similar in the two groups, suggesting that young age of diabetes onset clusters in these families. Similar ages of onset among affected family members have been previously observed in Mexican-American and Jewish populations (4,5).

To eliminate the effects of present age and sex on the prevalence of diabetes in relatives, 344 patients diagnosed before 45 years of age were individually matched with patients diagnosed after 45 years of age for these factors (median age of group 59.5 years, 66% male). The prevalence of diabetes in siblings was nonsignificantly higher when the proband was diagnosed before 45 years of age (23.6 vs. 16.9%, $P = 0.075$). The higher rate in parents (35.8 vs. 25.5%, $P = 0.03$) was confirmed. These results support a 40% increased relative risk of diabetes in relatives of YT2D compared with relatives of later-onset subjects.

We conclude that first-degree relatives of young-onset type 2 patients (diagnosed at <45 years of age) have a higher rate of diabetes when compared with relatives of diabetic patients diagnosed after 45 years of age. YT2D clusters in families; therefore, parents and siblings who will still be comparatively young are at high risk. Because this is most marked in parents, particularly mothers, nondiabetic parents should be screened when their child is first diagnosed with YT2D and on an annual basis thereafter. Parents and siblings of YT2D are an important group for all screening programs for diabetes.

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COMMENTS AND RESPONSES

Newly Diagnosed Type 2 Diabetic Population in Belgium

We read with interest the article by Hillier and Pedula (1). The authors stated that, so far, no study has evaluated baseline metabolic profiles in a newly diagnosed type 2 diabetic population. However, in Belgium a few years ago, a registration of newly diagnosed people with type 2 diabetes was performed in a network of ~130 sentinel general practices throughout the country. Due to lack of inscription lists by the family physician in our liberal health care system, the free choice of physician within primary, secondary, and tertiary health care and the dissemination of parts of the medical file over the various health care providers that resulted, it was not easy to collect basic population data about sickness and health. Therefore, this method of registration by volunteering family physicians is the only validated (2,3) method to gather at least some epidemiological primary care figures in Belgium.

Data of 651 patients were registered in two consecutive years, 1997 and 1998. After diagnosis of a new patient with type 2 diabetes, the participating family physician ticked a weekly registration form and sent it postfree to the scientific institute for inclusion. Two weeks later, the registering physician received a follow-up questionnaire about the method of diagnosis (1), different patient characteristics (biochemical parameters, diabetes risk factors, and possible early complications) (2), and the management suggested by the physician (treatment initiated for diabetes and possible associated pathology, referral to other health care workers, or possible hospitalization) (3).

The results of this study (4) were submitted for publication. It seems very interesting to compare at least some remarkable similarities despite the different study designs.

A total of 608 individuals met the inclusion criteria: 48 (7.9%) were "early onset" (<45 years of age), and 560 (92.1%) were "usual onset" (≥45 years of age). In comparison with the study of Hillier and Pedula (1), both Belgian onset groups were less obese, but the average BMI was significantly higher for early type 2 diabetes than for usual diabetes (Table 1). An inverse linear relation (Fig. 1) could not be found, possibly because of the small numbers in the early-onset groups. Average BMI varied from 28.6 kg/m^2 in the 66- to 71-year age group to 33.3 kg/m^2 in the 41- to 45-year age group. In the oldest age group, the average BMI was 29.6 kg/m^2. In both onset groups, the prevalence of hypertension at the time of diagnosis was less in the Belgian diabetic population as compared with the American population. The differences between the early- and usual-onset groups were also significant in Belgium.

In our database, there were more women in the early-onset group (56.3%) compared with the usual-onset group (42.1%). HbA_{1c} was inclined to be higher in the early-onset group, but the difference was not significant; the same results were found for total cholesterol and serum triglycerides.

Despite the disadvantages of our health care system to perform high-quality preventive medicine, Belgian diabetic subjects have a lower risk profile than American diabetic subjects, perhaps resulting from a healthier lifestyle and an earlier time of diagnosis.

We also have data regarding the medical management immediately after diagnosis. No differences can be mentioned between the early- and usual-onset groups. Nearly all newly diagnosed diabetic patients receive food advice from their family physicians. However, not many family doctors actively refer their patients to a dietitian. A recent study in Flanders (Gent and Antwerp) revealed that only 4% of family doctors systematically refer all their patients to the dietitian, whereas 7% never do so. Im-

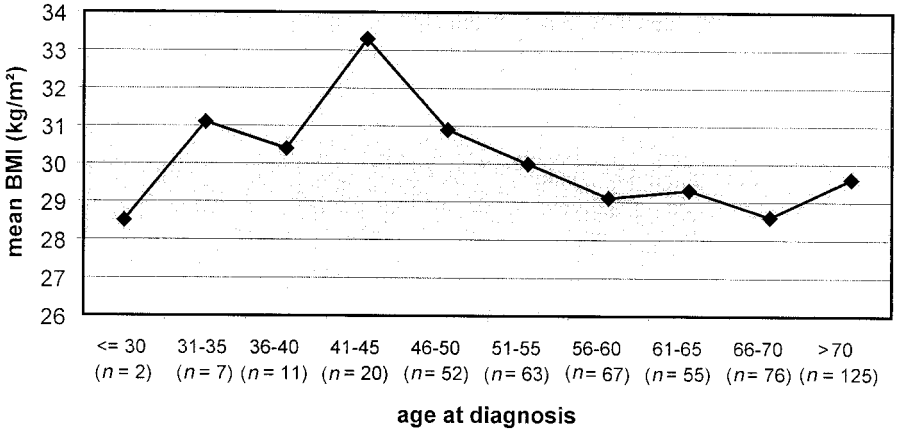

Figure 1—*Relation of mean BMI (kg/m^2) amd age at diagnosis among subjects with newly diagnosed type 2 diabetes in Belgium.*

Table 1—*Comparison of characteristics at diagnosis with early and usual type 2 diabetes*

	Early onset	Usual onset	*P*
n	48	560	
BMI (kg/m^2)	32.0 ± 7.5	29.4 ± 5.0	<0.005
Sex (% female)	56.3	42.1	NS
HbA_{1c} (%)	8.2 ± 3.1	8.2 ± 2.5	NS
Total cholesterol (mg/dl)	244.0 ± 59.8	244.0 ± 54.6	NS
Triglycerides (mg/dl)	275.8 ± 172.7	275.8 ± 179.3	NS
Hypertension (%)	29.5	51.5	<0.005
Diet prescription (%)	97.7	97.8	NS
Biguanides (%)	30.0	30.0	NS
Sulfonylurea (%)	44.2	40.4	NS
Referral to diabetologist (%)	31.0	11.0	0.006

Data are means ± SD or %. Hypertension is defined as systolic blood pressure >130 mmHg or diastolic blood pressure >85 mmHg. NS, not significant.

portant pressure points for optimal collaboration are lack of clearly defined tasks on the one hand and lack of refunding for dietary advice on the other (5). Although obesity is more frequent in the early-onset group, we found no differences in the prescription rate for metformin, the first choice for obese diabetic patients (6). We also found that young people with type 2 diabetes are significantly more referred to the diabetologist at the time of diagnosis than older patients.

The representativeness of both the sentinel physicians and sentinel population, with respect to the whole population, remains an important pressure point in this kind of epidemiological analysis. Although the registering physicians are representative of the whole Belgian population of physicians for age and sex, it is not possible to extrapolate the medical practice of family doctors in Belgium. Due to the voluntary nature of participation in the network, random selection of the participants is impossible because the physicians with the greatest motivation answer the call. Registration is done by the physician himself based on his medical file; therefore, the results could be presented rather euphemistically because the data on the follow-up questionnaire probably come closer to the expected guideline level rather than the actual data in the medical record. However, the voluntary nature of the registration and the anonymity of the registering physicians reduce this possible bias. So far, we consider that extrapolation from the sentinel population to the total population is possible.

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Response to Jungheim and Koschinsky

In a recent letter of observation, Jungheim and Koschinsky (1) reported on their findings about a risky delay of hypoglycemia detection by glucose monitoring at the arm. Given the possible significant implications of their findings, we repeated their experiment in our own clinical unit in an institutional review board (IRB)-approved study. We would hereby like to report on our results with 10 patients (4 women, 6 men, 6 type 1 diabetic, and 4 type 2 diabetic subjects; age [mean ± SD] 49 ± 14 years, mean disease duration: 50 ± 14 years). During an oral glucose tolerance test (OGTT) phase, results obtained from the arm with no rubbing (Soft-Sense; Abbott Medisense) were lower than the results obtained with our reference method (Super GL; Mueller Apparatebau) from the fingertip, but the differences were clinically acceptable. However, during an intravenous intervention phase, the results from the arm nicely tracked the results obtained from the fingertip. There was no potential risk for overlooking development of a hypo-

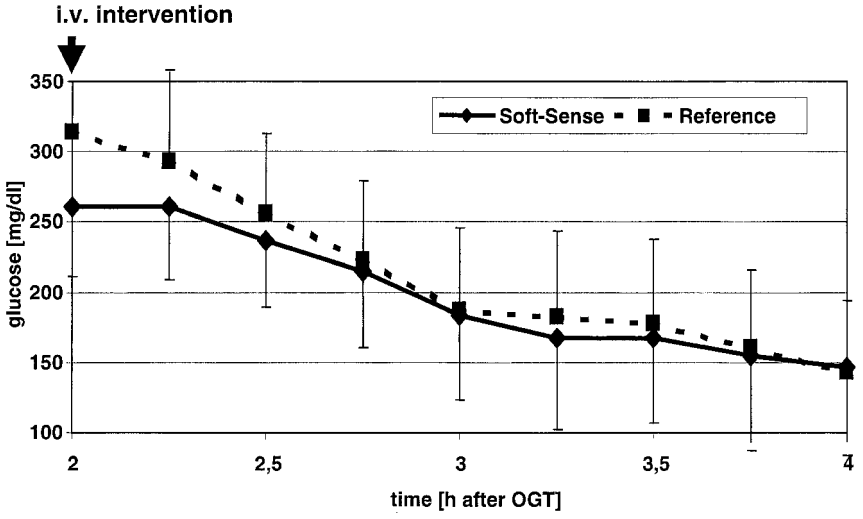

Figure 1—*Drop of blood glucose in 10 patients after intravenous insulin intervention during an OGTT experiment (reference: Super GL, glucose oxidase method).*

glycemic episode in any of the experiments, even in the two cases where we reached glucose levels <70 mg/dl (Fig. 1).

The differences between our data and the observations from Jungheim and Koschinsky may be due to differences in *1*) the experimental design, e.g., how extreme and artificial the experimental conditions were; *2*) the testing device; *3*) the patient populations; and *4*) the methodology, including how the skin was prepared and how the blood was collected.

It also has to be considered that the artificial design chosen by Jungheim and Koschinsky does not match with the daily treatment situation, and it is rather unlikely that such rapid glucose decreases occur when not induced by intravenous insulin treatment. Therefore, in another IRB-approved study using the same devices, we explored the performance of alternative site testing in a regular treatment situation with preprandial insulin treatment before a standardized test meal (66 g carbohydrate) in 10 patients with type 1 diabetes (6 women, 4 men, age 35 ± 11 years, mean disease duration 13 ± 13 years). In a randomized crossover setting, they either received an appropriately calculated dose of regular human insulin 20–30 min before the meal or only 25% of this dose on the other experimental day. The arm measurements were not different from the fingertip measurements in both treatment arms, even in the phase of glucose increase after an insufficient insulin dose (Fig. 2).

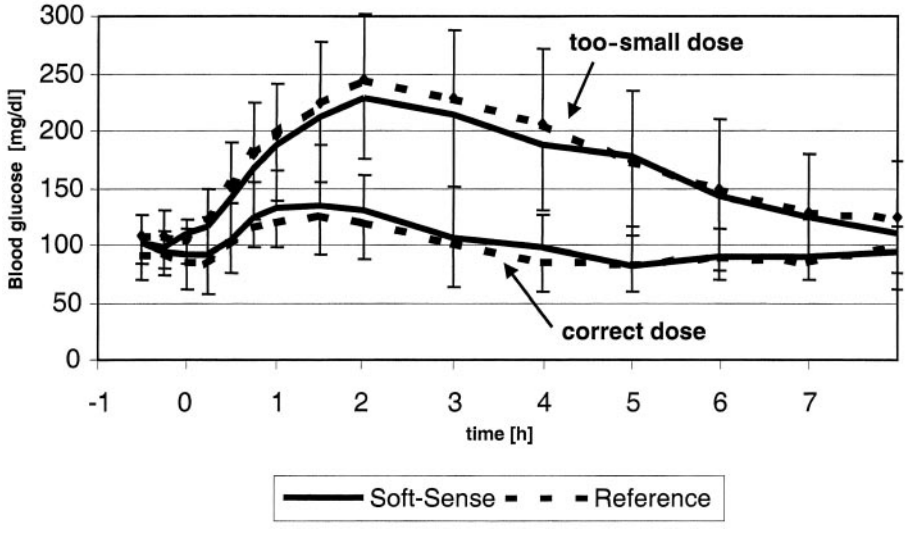

Figure 2—*Glucose excursions after a standardized meal (66 g carbohydrate content) in 10 patients with a correct insulin dose and a too-low insulin dose (25% of correct dose), respectively.*

Because our data and those of other studies (2) suggest good performance of the Soft-Sense meter regarding accuracy and precision in daily practice, we consider this device to be a suitable alternative option for virtually pain-free glucose monitoring in daily practice. If confirmation of an alternative site test is desired, the user can always simply perform a finger test with the same device. Furthermore, more practical studies will be required to establish whether patient groups or circumstances exist where alternative site testing should not be performed.

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Response to the Letter by Pfützner and Forst

Pfützner and Forst (1) report that they found no significant blood glucose (BG) differences between the arm and finger during *1*) BG decrease induced by intravenous insulin injection, and *2*) BG increase and decrease induced

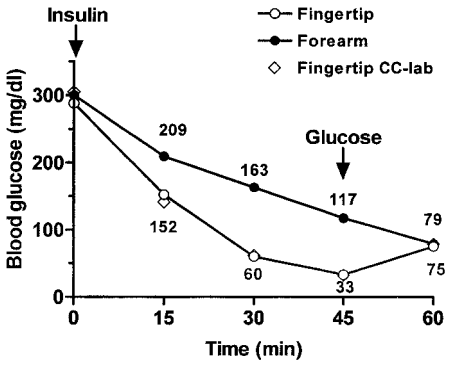

Figure 1—*BG profiles of a patient with diabetes. BG samples from the forearm and the fingertip were analyzed by the Soft-Sense glucose monitor. BG changes were induced with 75 g oral glucose and followed by intravenous insulin injection (t = 0). At hypoglycemia, oral glucose was administered. For validation, additional BG samples from the fingertip were analyzed by a clinical chemistry laboratory (CC-Lab) method.*

by a standardized meal in combination with subcutaneous insulin injection.

As previously suggested by Pfützner and Forst, the observed differences between our data and their observations are caused by differences in experimental design. Our study protocol aimed at rapid BG decreases and achieved a mean BG change at the finger (averaged over total decline) of 3 mg · dl^{-1} · min^{-1}. Hypoglycemic values at the finger were reached faster after insulin injection. This velocity has not been repeated by Pfützner and Forst, as their mean rate of BG decline did not exceed 2 mg · dl^{-} · min^{-1} during the first hour after insulin injection and fell below 1 mg · dl^{-1} · min^{-1} during the second hour after insulin injection. Hypoglycemic values <60 mg/dl were not reached at all (Fig. 1 of Pfützner and Forst).

The same applies to the BG data in Pfützner and Forst's Fig. 2, as these BG values declined at a mean rate <0.5 mg · dl^{-1} · min^{-1} from the second until the eighth hour after subcutaneous insulin injection. These results are well in agreement with our own observations that the chance of observing clinically relevant BG differences are very low if mean BG change rates (averaged over at least 45–60 min) are <2 mg · dl^{-1} · min^{-1} (2). Applying our original study protocol, we have provided evidence that the described BG differences between the arm and finger can be observed with the Soft-Sense device (Fig. 1) (used by Pfützner and Forst), as well as with other BG devices approved for alternative-site testing. We conclude that the data provided by Pfützner and Forst do not sufficiently address the question of the effects of rapid BG changes on BG differences between the finger and alternate skin sites such as the arm. Therefore, their data do not support their unrestricted statement that Soft-Sense would be a suitable alternative option, as far as rapid BG changes are concerned, for glucose monitoring in daily practice.

Concerning the likelihood of rapid BG changes >2 mg · dl^{-1} · min^{-1} in daily life, it is well known from continuous glucose monitoring studies, particularly in insulin-treated patients with type 1 diabetes, that such rapid BG changes can occur and often go unrecognized by patients (3,4). Based on our studies with 17 diabetic patients on subcutaneous continuous glucose monitoring up to 72 h/patient (4), an average 7% of all BG changes have been >2 mg · dl^{-1} · min^{-1} (maximum 5.7). Therefore, our study design does match daily treatment situations and is so far realistic, not artificial.

Our study was designed to examine whether potential clinical risks can be associated with alternative-site monitoring at the forearm and, if such risks exist, to estimate the potential severity of the risks. A standardized experimental protocol was therefore used. Exact determination of the probability and severity of the described potential hazard is an important task originating from our findings. Keeping the probability of rapid BG changes in mind, we feel that experimental studies per se, even if they are designed to mimic daily life (as done by Pfützner and Forst), are an inadequate tool to exclude the relevance of our findings in daily life. We would suggest proving clinical significance under real daily life conditions in population-based field studies that include samples taken at times of presumed rapid BG change. Such a study has been performed and presented to the U.S. Federal Drug Administration (5). The results of this study support our concern that clinically relevant BG differences occur under daily life conditions, as BG differences between fingertip and forearm exceeding even 100 mg/dl were observed. Therefore, our preliminary clinical recommendations remain unchanged. This is supported by essentially identical recommendations of the Clinical Chemistry and Clinical Toxicology Devices Panel of the Medical Devices Advisory Committee Panel to the U.S. Food and Drug Administration (6).

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