OBSERVATIONS

The Role of Dobutamine Stress Echocardiography in Detecting Severe Coronary Artery Disease in Asymptomatic at High Risk Type 2 Diabetic Patients

In type 2 diabetes, coronary artery disease (CAD), the major cause of mortality, is often diagnosed late because of silent myocardial ischemia (MI) (1). Asymptomatic type 2 diabetic patients, particularly those with additional atherogenic factors predisposing to a more severe coronary risk (i.e., those "at high risk") have to be, therefore, screened for CAD (2). Exercise electrocardiogram (ECG) is the most utilized screening test; however, several type 2 diabetic patients cannot exercise because of amputations or claudicatio and, as a whole, exercise ECG is not applicable also because of fatigue, dizzines, and hypertensive response in 30% of "at high risk" type 2 diabetic patients (3). Whatever the reason for exercise inability, these patients have a higher mortality rate (4) and they particularly deserve, therefore, to be screened for CAD (2).

This study aimed to evaluate the accuracy of dobutamine stress echocardiography (DSE) in detecting severe CAD in asymptomatic "at high risk" type 2 diabetic patients who were unable to exercise. In asymptomatic type 2 diabetic patients, DSE shows a 100% positive predictive value (5), but its negative predictive value is unknown. "At high risk" was defined as peripheral vascular disease (lumen stenosis ≥40% at ultrasound Doppler) and/or two or more of the following: family history of MI before 65 years of age, albumin excretion rate (AER) >20 μg/min, hypertension (>140/90 mmHg, or antihypertensive treatment), dyslipidemia (LDL cholesterol >13.3 mmol/l, HDL cholesterol <0.9 mmol/l, or <1.1 mmol/l in male or female, triglycerides >2.26 mmol/l, or antidyslipidemic treatment), and currently smoking. Exclusion criteria were symptoms or resting ECG signs of MI, age >70 years, and severe disease with poor prognosis.

Accuracy of DSE was measured against coronary angiography (CA), defined as positive if severe coronary stenosis (SCS) (≥70% lumen reduction) was observed.

DSE and CA were independently interpreted by two "blind" investigators. According to the Helsinki Declaration, all patients gave informed consent for this study.

A total of 56 consecutive patients were recruited, but DSE was not applicable/diagnostic in 21 (37%) because of either poor transthoracic window ($n = 12$, 21%) or submaximal stress ($n = 9$, 16%). CA was performed in the remaining 35 patients (16 males and 19 females, aged 63 ± 6 years, BMI 30 ± 5 kg/m^2, diabetes duration 15 ± 8 years, HbA_{1c} 8.5 ± 2%). Of these, 72% had peripheral vascular disease, 60% family history of MI, 46% increased AER, 75% hypertension, 85% dyslipidemia, and 65% were smokers. Of the 35 patients, 19 (54%) showed SCS, 7 (20%) showed three-vessel, 6 (17%) showed two-vessel, and 6 (17%) showed one-vessel disease. No significant differences in clinical and metabolic features were observed between patients with or without SCS. Although not an aim of our study, these data indicate a high prevalence (54%) of severe CAD in asymptomatic "at high risk" type 2 diabetic patients unable to exercise. Of the 19 patients with SCS, 4 (all with three-vessel disease) were DSE positive (true positive) and 15 were DSE negative (false negative). Of the 16 patients with no SCS, 1 was DSE positive (false positive) and 15 DSE negative (true negative). Overall, DSE accuracy was 54% (i.e., sensitivity = 21% and specificity = 94%). Positive and negative predictive values were 80 and 50%, respectively.

In conclusion, our data indicate a very poor sensitivity and negative predictive value of DSE in detecting severe CAD in "at high risk " type 2 diabetic patients unable to exercise.

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Severe Hypoglycemia From Clarithromycin-Sulfonylurea Drug Interaction

We report two cases of severe hypoglycemia occurring in elderly men with type 2 diabetes who were prescribed clarithromycin for respiratory infections. Both individuals had well-controlled diabetes and mild to moderately impaired renal function. Both individuals were prescribed clarithromycin in identical dosages and both developed severe hypoglycemia within 48 h of starting the antibiotic. Although many drugs have been reported to interact with

sulfonylureas causing hypoglycemia, the interaction between clarithromycin and a sulfonylurea has not been previously reported. We discuss the suspected mechanism for this potentially severe reaction which is of concern in the treatment of elderly patients with type 2 diabetes.

Case 1

An 82-year-old white male with a 4-month history of type 2 diabetes was treated with diet and glyburide 5 mg daily. His blood glucose readings were in the low 100s (mg/dl). His comorbidities included atherosclerotic heart disease, hypertension, mild chronic renal failure with a creatinine of 1.6 mg/dl, emphysema, and bladder cancer. In a local emergency department (ED), he was diagnosed with "bronchitis" and prescribed clarithromycin, 1,000 mg daily. He became unresponsive with an Accucheck reading of 24 mg/dl, 48 h after starting clarithromycin. Administration of intravenous glucose in the ED resolved the problem. However, 12 h later, he again was found unresponsive. A chemstrip glucose test, administered by the paramedics, was in the 0–30 mg/dl range. Intravenous glucose resolved the problem a second time. There were no further episodes after stopping the sulfonylurea.

Case 2

A 72-year-old white male with type 2 diabetes of >10 years' duration was treated with diet and glipizide 15 mg daily. His most recently measured HbA_{1c} was 6.1%. His comorbidities included atherosclerotic heart disease, hypertension, and chronic renal failure with creatinine in the mid-3s (mg/dl). In a local urgent care center he was diagnosed with "bronchitis" and prescribed clarithromycin 1,000 mg daily. He was brought to the emergency department (ED) in a stupor 48 h after starting clarithromycin. His Accucheck reading was 20. Admission to the hospital and continuous intravenous glucose resolved the stupor. There were no further episodes after ceasing sulfonylurea therapy.

Common features of both cases included type 2 diabetes treated with diet and a sulfonylurea, age >70 years, male sex, and renal insufficiency. Common comorbidities included hypertension, atherosclerotic heart disease, and mildly low albumin levels. Both men were given identical clarithromycin dosages, and both experienced profound mental status changes 48 h after initiating the antibiotic.

Drug-induced hypoglycemia in elderly patients with type 2 diabetes is a major clinical concern. Several reviews have addressed this problem, and three general mechanisms have been implicated. First, hypoglycemia can be induced by a single hypoglycemic agent such as a sulfonylurea. Second, two or more hypoglycemic drugs can induce hypoglycemia. Specific examples known to cause hypoglycemia include a sulfonylurea plus insulin, a sulfonylurea and salicylates, and a sulfonylurea or insulin mixed with alcohol. Third, multiple drug-drug interactions have been reported to potentiate the effect of sulfonylureas. These include anti-inflammatory agents, sulfa antibiotics, bishydroxycoumarin, and antidepressants. Other agents such as propranolol and tetracyclines have been reported to potentiate the hypoglycemic effects of insulin (1).

All the sulfonylurea agents stimulate insulin release from pancreatic islet cells. The sulfonylurea agents with the longest half-lives cause the most problems and risk of hypoglycemia. Chlorpropamide has the longest half-life and has been reported to cause substantial hypoglycemia. Of the newer second-generation agents, glyburide has been reported to cause hypoglycemia more often than glipizide. Sulfonylurea-induced hypoglycemia can be particularly problematic in patients with impaired renal or hepatic function (2).

Various risk factors have been analyzed when looking at sulfonylurea-induced hypoglycemia. These include age >60 years, renal dysfunction, alcohol ingestion, sepsis, intentional overdose, and liver cirrhosis. The most common cause for sulfonylurea-induced hypoglycemia is an interaction between two medications (2).

Both glyburide and glipizide are well absorbed and are 90–99% protein bound. Glyburide and glipizide are extensively metabolized by the cytochrome P450 system in the liver—the principal enzyme seems to be CYP2C9 (3). Glyburide has weakly active metabolites, whereas the metabolites of glipizide are inactive. Glyburide is ~50% excreted through feces and the remainder is renally excreted. Reduced renal function delays clearance of the parent drug and its metabolites. Glipizide and its metabolites are predominately excreted in the urine with less enteric excretion than glyburide. (4) The half-life of glipizide is ~7 h, and the half-life of glyburide is ~10 h. Both have durations of action between 12 and 24 h in the normal host.

Clarithromycin is well absorbed from the gastrointestinal tract. It is 40–70% protein bound and has first-pass hepatic metabolism, being converted to 14-OH clarithromycin. Clarithromycin inhibits intestinal *p*-glycoprotein as well as cytochrome CYP3A4.

Mechanisms of drug-drug interactions include one drug binding another, displacement from protein binding sites, alteration of drug metabolism, or alteration of drug excretion. Alterations of drug metabolism account for the majority of clinically relevant interactions (5). In these cases, we postulate that clarithromycin may have displaced glipizide and glyburide from protein binding sites, thereby increasing the unbound, or free, portion of the drug. It is unlikely that clarithromycin reduced metabolism of glipizide and glyburide because of the isoenzymes involved with drug metabolism. Decreased renal clearance may have also played a role in these cases. Although clarithromycin inhibits intestinal *p*-glycoprotein, we do not think this was the mechanism in these two cases, as secretion of glipizide or glyburide into the gut is not a major route of clearance of these two agents.

We conclude that clarithromycin should be cautiously prescribed to type 2 diabetic patients with mild renal impairment who are taking sulfonylurea medications.

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Impairment of Visual Evoked Potentials

An early central manifestation of diabetic neuropathy?

Impairment of the central nervous system is a frequent complication of diabetes (1), but its clinical importance is still underestimated. The exact pathophysiology of the central nervous dysfunction is not clear, but it seems to be multifactorial, involving vascular and metabolic factors, similar to the pathogenesis of diabetic peripheral neuropathy (1). Earlier studies revealed new data on the central manifestations of diabetes but did not permit a comprehensive comparative analysis of the peripheral and central neuronal dysfunctions (2,3).

We recently observed significant correlations between the impairment of the auditory evoked potentials and the severity of autonomic and peripheral sensory neuropathy in type 1 diabetes (4). In addition to the detection of the auditory evoked potentials, evaluation of the visual evoked potentials furnishes another diagnostic tool for the assessment of functional anomalies of the cerebral function, even at an early stage of the pathogenetic process (2). The aim of this study was to demonstrate the possible associations between the latencies of visual evoked potentials and the severity of the cardiovascular autonomic and peripheral sensory dysfunctions in type 1 diabetes.

In the study, 12 middle-aged patients with longstanding type 1 diabetes were enrolled, 5 males and 7 females with a mean (±SD) age of 46.3 ± 14.9 years , a mean duration of diabetes of 24.1 ± 9.4 years, and a mean BMI of 27 ± 4.1 kg/m^2. Patients with proliferative retinopathy, impaired visual acuity, or neuronal dysfunction of nondiabetic origin were excluded from the study.

The visual evoked potentials were recorded from an active electrode placed over the occipital region, with a reference electrode at the left ear (5). Monocular, pattern-reversal checkboard stimulation was used with a frequency of 1.8 Hz. Two measurements were performed for both eyes, and the visual function was evaluated via the latency of the major positive component of the potentials P100. The five standard cardiovascular reflex tests were applied to assess autonomic function (6). Heart rate tests (the heart rate response to deep breathing, the 30:15 ratio, and the Valsalva ratio) mainly reflect the parasympathethic function, while evaluation of the systolic blood pressure responses to standing and the diastolic pressure changes in response to a sustained handgrip primarily allow the assessment of sympathetic integrity. The results of each of the five tests were scored as 0 (normal), 1 (borderline), or 2 (abnormal). A final score was calculated (range 0–10) to express the severity of the overall autonomic disorder. The peripheral sensory nerve function was characterized by evaluation of the current perception thresholds (CPTs), with a neuroselective diagnostic stimulator (Neurotron, Baltimore, MD), which permits transcutaneous testing (7) at three sinusoidal frequencies of electrical stimulus (2 kHz, 250 Hz, and 5 Hz). Median and peroneal nerves (digital branches) were studied. Significant positive correlations were found between the autonomic score and the lengths of the latencies of the P100 waves of the right and left eyes (Table 1). Further analyses revealed a negative relationship between the results of the three heart rate tests (the heart rate response to deep breathing, the 30:15 ratio, and the Valsalva ratio) and the prolongation of the P100 latencies for both eyes. The systolic blood pressure response to both standing and sustained handgrip test did not display any significant correlation with the abnormal latencies of the P100 potentials. The impaired sensory nerve function manifested in high CPT values at stimulation frequencies 2,000, 250, and 5 Hz, which reflects hypesthesia at the peroneal nerve, correlated positively with the P100 latencies of the right and left eyes. The CPT values of the median nerve did not correlate with the abnormal central visual function.

The parasympathetic nerve dysfunction, characterized mainly by means of heart rate tests, develops earlier in the course of diabetes (6), and sensory neuropathy affects the lower limbs predominantly. The impairment of visual pathways is considered an early sign among the electrophysiological visual function alterations (8). It is still unclear as to whether there are similarities between the altered central and peripheral neuronal manifestations of diabetic neuropathy. In our study, the prolongation of the P100 latencies of the visually evoked

Table 1—*Correlations between neuropathy parameters and P100 latency intervals of visual evoked potentials*

Correlated parameters	Correlation coefficient	*P*
Right eyes		
Autonomic score and P100 latency	0.6042	<0.01
Heart rate response to breathing and P100 latency	−0.4359	<0.05
Valsalva ratio and P100 latency	−0.5464	<0.01
30:15 ratio and P100 latency	−0.4523	<0.05
CPT at 2,000 Hz on peroneal nerve and P100 latency	0.5021	<0.05
CPT at 250 Hz on peroneal nerve and P100 latency	0.5627	<0.01
CPT at 5 Hz on peroneal nerve and P100 latency	0.5819	<0.01
Left eyes		
Autonomic score and P100 latency	0.5721	<0.01
Heart rate response to breathing and P100 latency	−0.4617	<0.05
Valsalva ratio and P100 latency	−0.5456	<0.01
30:15 ratio and P100 latency	−0.5948	<0.01
CPT at 2,000 Hz on peroneal nerve and P100 latency	0.6246	<0.01
CPT at 250 Hz on peroneal nerve and P100 latency	0.6715	<0.001
CPT at 5 Hz on peroneal nerve and P100 latency	0.7056	<0.001

potentials for both eyes was associated with parasympathetic autonomic neuropathy and the hypesthetic form of lower-limb sensory neuropathy. These data are consistent with our previous findings from an assessment of the autonomic and the sensory neuropathy and auditory brainstem function in patients with type 1 diabetes, and may suggest that an impairment of visual evoked potentials should be regarded as an early central manifestation of diabetic neuropathy.

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Do Latent Autoimmune Diabetes of the Adult (LADA) Patients Require Insulin at Diagnosis?

Response to Pozzilli and Di Mario

In the August 2001 issue of *Diabetes Care*, Paolo Pozzilli and Umberto Di Mario (1) present their current opinion about the definition, characterization, and potential prevention of latent autoimmune diabetes in adults (LADA). We read their article with great interest, especially as it concerns different treatments of patients with LADA. Because 10–15% of adult diabetic patients may have autoimmune diabetes, management in this group seems to be a very important question. Yet, we do not fully concur with Pozzilli and Di Mario's conclusion that LADA does not require insulin at diagnosis. In our experience, treatment with insulin at the onset of the disease (when the autoimmune background is proven) is of special clinical benefit (2).

There is strong evidence that LADA is an autoimmune form of diabetes. Shimada et al. (3) have reported their findings of T-cell insulitis in an anti–GAD-positive 65-year-old patient with diabetes and residual β-cell function. The latter is assumed to be similar to type 1 diabetes, with genetic susceptibility and presence of autoimmune markers.

In NOD mice and BB rat models, subcutaneous or oral administration of insulin can prevent the onset of diabetes (4,5). Such insulin administration is thought to provide a form of β-cell "rest," protecting them from destruction. Insulin is also considered to be an immunomodulator. It increases production of Th^2 profile cytokines in peripheral blood in subjects at high risk and in newly diagnosed type 1 diabetic patients (6).

A 1996 report suggests that insulin therapy may also help in preventing C-peptide secretion in LADA patients, and that such patients appear to lose expression of islet cell antibodies faster than patients treated with oral hypoglycemic drugs (7). Furthermore, treatment of LADA patients with hypoglycemic drugs was not satisfactory, and they showed insulin dependency quicker than patients with type 2 diabetes (8,9). Finally, some anti-GAD65 antibodies recognize patients with risk for insulin requirement (10). Earlier treatment of diabetes with insulin may improve their quality of life, thus potentially saving β-cell function and perhaps lessening the risk of long-term microvascular complications. Because the use of insulin as a preventive agent is still under investigation (11), the discussion about management of LADA patients still remains open.

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Pediatric Use of Insulin Pumps: Longer Infusion Site Lifetime With NovoLog

Insulin aspart (Novolog) and insulin lispro (Humalog) are rapid-acting insulin analogs suitable for mealtime use in an intensive insulin therapy regimen of multiple daily injections (MDIs). Insulin analogs administered just before meals improve postprandial glycemic control as compared with regular human insulin administered 30 min before meals (1,2). These rapid-acting analogs are soluble insulins and are effective in continuous subcutaneous insulin infusion (CSII) (3,4).

Case history

P.L. is a 12-year-old male with a 4-year history of type 1 diabetes. Initial treatment with a mixed-split regimen of NPH insulin and insulin lispro in MDI therapy was reasonably well accepted, given the necessity of lifestyle modifications (patient was then 9 years old). However, P.L. had to follow a meal-snack schedule to minimize hypoglycemic episodes related to the duration of NPH insulin. HbA_{1c} was maintained at 8.1% during this time.

After 4 months of MDI therapy, P.L. initiated CSII therapy with insulin lispro administered by a Disetronic Pump. After 6 months of CSII therapy, P.L. had remarkable improvements in perceived lifestyle: freely adjusted eating schedule, freedom from previously required snacks, notably fewer hypoglycemic episodes, and reduced HbA_{1c} to 5.4%. However, his blood glucose became more difficult to control and his insulin requirements progressively increased, perhaps related to leaving a "honeymoon phase" of his evolving type 1 diabetes. His response to therapy showed a pattern that was related to the infusion site duration.

- Day 1: P.L. was exquisitely sensitive to boluses and minor basal rate dosage changes.
- Day 2: There was less sensitivity to minor dosage changes.
- Day 3: The infusion site showed signs of erythema and swelling, and P.L. experienced mild hyperglycemia, conditions requiring a new infusion site. The same insulin dose could not be maintained over the 3-day cycle without an increased frequency of hypoglycemic episodes on day 1 followed by an increased frequency of unacceptable hyperglycemia on day 3.

A partial solution was to change the infusion site every 1.5–2 days. During this period of increased treatment difficulties, his HbA_{1c} was maintained at 6.2%.

After another 8.5 months, P.L.'s family visited the Insulin Pumpers Web site. They learned that other patients were adding Velosulin (buffered regular insulin) to insulin lispro to increase site duration in CSII. When they used a ratio of 1:4 (Velosulin:lispro), P.L.'s infusion sites consistently lasted up to 3 days. This practice was continued for 2.5 years, during which P.L.'s average HbA_{1c} was 7.2%.

In July 2001 P.L. started using insulin aspart in his pump. His HbA_{1c} has since been maintained at ≤7%. In June 2002, his HbA_{1c} was 6.2%. The infusion site has been changed every 4–5 days (only when the insulin cartridge is empty).

Although the mechanism for improved infusion site duration with insulin aspart is not known, the response is consistent over the lifetime of the infusion site, and has not been accompanied by an increased frequency of hypoglycemia. The improved predictability of insulin aspart has encouraged P.L. and his family to more confidently adjust the insulin pump settings to maintain tighter glycemic control without increasing the risk of hypoglycemia.

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A Case Showing Complete Insulin Independence After Severe Diabetic Ketoacidosis Associated With Tacrolimus Treatment

Post-transplant diabetes mellitus (PTDM) is a major metabolic complication after kidney transplantation (1). Diabetogenic potential of tacrolimus is known to be much higher than that of cyclosporine in the early post-transplantation period (2). Tacrolimus may cause PTDM by transcriptional inhibition of the insulin gene in the β-cell, which is known to be potentially reversible (3). We report a renal allograft recipient showing complete insulin independence after severe diabetic ketoacidosis associated with tacrolimus treatment.

A 35-year-old woman was admitted to the hospital via emergency room because of altered mentality. Six months before admission, she had undergone kidney transplantation for end-stage renal failure, the underlying cause of which was unknown. Immunosuppressive treatment consisted of tacrolimus, prednisolone, and mycophenolate mofetil. Before kidney transplantation she had never been diagnosed with diabetes, and her fasting plasma glucose (FPG) was 5.3 mmol/l. Her BMI was 21.8 kg/m^2. None of her family members had been clinically diagnosed with diabetes. After successful kidney transplantation, she maintained an excellent renal function and her clinical course was otherwise unremarkable. Four months after transplantation, she began suffering from thirst and lost 5 kg of weight. A few days before admission, anorexia and severe fatigue developed. When she reported to the emergency room with altered mentality, her blood pressure was 94/44 mmHg, pulse rate was 106/min, respiration rate was 16/min, and temperature was 36.1°C. On examination, her tongue was dehydrated and her skin turgor was decreased. Her initial laboratory tests revealed plasma glucose 39.6 mmol/l, HbA_{1c} 14.7%, pH 6.80, pCO_2 9 mmHg, pO_2 156 mmHg, HCO_3^- 1.4 mmol/l, serum sodium 130 mmol/l, potassium 5.3 mmol/l, chloride 107 mmol/l, and total CO_2 3 mmol/l. The initial anion gap was 20 mmol/l. The result of a urine ketone test was strongly positive and serum creatinine was 970 μmol/l. Her plasma C-peptide was under the detection limit, and the anti-GAD antibody was negative. The plasma tacrolimus level was 11.1 ng/ml. After studying the physical examination, laboratory findings, and radiological study, we could not find any evidence of infection.

Initial treatment consisted of large volumes of intravenous saline, intravenous insulin, and sodium bicarbonate. After 36 h her arterial pH and serum anion gap were normalized, and her urine ketone also disappeared. Thereafter, she was gradually switched to subcutaneous insulin. From hospital day 8, cyclosporine was substituted for tacrolimus, while continuing other immunosuppressants. Her initial insulin requirement was 50 IU/day and gradually decreased as her general condition improved. At hospital day 20, she no longer needed insulin therapy and was eventually discharged.

After 3 months, she showed normal glucose tolerance on a 75-g oral glucose tolerance test. Her fasting plasma insulin level was 58.2 pmol/l, fasting plasma C-peptide was 0.66 nmol/l, and HbA_{1c} was 6.2%. There was no evidence of deteriorated renal function.

As suggested by in vitro and in vivo studies (3), the PTDM associated with tacrolimus can be completely reversible, even in the case of severe diabetic ketoacidosis. In addition, this report implies, although anecdotal, that cyclosporine can be an effective alternative for tacrolimus to overcome severe β-cell toxicity while providing adequate immunosuppression.

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Mortality in Concurrent Type 1 Diabetes and Anorexia Nervosa

We would like to add our experience of the clinical course and prognosis in patients with type 1 diabetes and eating disorders to that reported by Nielsen et al. (1) who reported a standardized mortality ratio of 14.5 in female patients with a diagnosis of type 1 diabetes and anorexia nervosa.

We performed a 12-year follow-up of a cohort of 14 women with type 1 diabetes and eating disorders (12 with anorexia nervosa) originally studied in 1987 (2). Of the 14 subjects, 5 had died (36%), 2 were blind, and 3 were receiving renal replacement therapy; most notably, 11 of the 14 subjects suffered from severe autonomic neuropathic symptoms. Data from 1999, or at the time of death, revealed that the median (range) age of the cohort was 37 years (25–46), with a duration of diabetes of 26 years (14–33). The age of death of the five patients was 30 years (25–42) with a duration of diabetes at death of 19 years (14–26).

Two patients were found dead at home and, as both had hypoglycemic unawareness, there was strong circumstantial evidence that the deaths were related to hypoglycemia. One patient died as a result of ketoacidosis after deliberate in-

sulin omission. Another patient died following a sudden respiratory arrest 48 h after bone graft surgery for a nonuniting fracture. The final patient died from emaciation due to severe autonomic neuropathy affecting her bowel, resulting in intractable diarrhea and vomiting.

All 14 women had some degree of retinopathy and only 3 of the 14 women had normoalbuminuria. All but three women had complained of painful neuropathic symptoms. Interestingly, half of the cohort had at least one pregnancy, with one woman having three children.

Of the 14 women, 10 had recovered from their eating disorder in that they no longer fulfilled the criteria for diagnosis. Data from 1999, or at the time of death, revealed that the median (range) BMI of the cohort was 23.5 kg/m^2 (16–30).

In summary, our results accord with those of Neilsen et al. We have found a 36% mortality over 12 years, and in keeping with other series, we report a high rate of microvascular morbidity (3,4).

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Elevated Serum Concentration of Adipose-Derived Factor, Adiponectin, in Patients With Type 1 Diabetes

Adiponectin, also referred to as Acrp30, AdipoQ, and GBP28, is a plasma protein exclusively produced by adipose tissue and a possible insulin-sensitizing agent (1–6). Serum adiponectin levels are negatively correlated to BMI in healthy individuals and decreased in type 2 diabetic patients (1–6). However, serum adiponectin levels in type 1 diabetes have not been elucidated.

We examined the serum adiponectin concentrations in 46 type 1 diabetic patients (21 males and 25 females) and compared them with those of BMI-matched healthy control subjects (17 males and 19 females). Mean age was 33 ± 3 and 33 ± 4 years, BMI was 19.8 ± 0.5 and 19.9 ± 0.6 kg/m^2, HbA_{1c} level was 9.7± 0.7 and 10.4 ± 0.6%, duration of diabetes was 3.2 ± 0.9 and 3.4 ± 1.3 years, and urinary C-peptide excretion was 18.4 ± 4.3 and 18.0 ± 2.4 μg/day in male and female patients, respectively. High prevalence of GAD antibody or islet cell antibodies (91.3%) indicated autoimmune-associated β-cell destruction in those patients. Two patients suffered from simple diabetic retinopathy, and two other patients had microalbuminuria, but no patient suffered from macroalbuminuria, continuous proteinuria, or elevated serum creatinin. All patients revealed normal electrocardiogram at rest. In the control group, mean age was 34 ± 1 and 33 ± 2 years and BMI was 20.8 ± 0.4 and 20.2 ± 0.5 in males and females, respectively. There were no significant differences in age and BMI between type 1 diabetic patients and control subjects, in either males or females. Informed consent was obtained from all patients and healthy control subjects. Serum adiponectin levels were determined by enzyme-linked immunosorbent assay (2). Intra- and interassay variation in our laboratory was 3.3 and 7.4%, respectively. Unexpectedly, serum adiponectin levels were markedly higher in type 1 diabetic patients (13.6 ± 1.8 μg/ml in males, and 16.1 ± 1.6 μg/ml in females) than in healthy control subjects (6.9 ± 0.7 μg/ml in males and 10.0 ± 0.8 μg/ml in females, respectively; $P < 0.01$).

Serum adiponectin levels also were determined before and during the insulin replacement therapy in seven patients. Exogenous insulin (0.49 ± 0.10 units · kg^{-1} · day^{-1}) had been injected for 1.9 ± 0.7 years after the onset of overt diabetes. HbA_{1c} levels before and during insulin therapy were 10.7 ± 1.3 and 8.2 ± 1.1%, and BMI was 18.3 ± 0.5 and 20.0 ± 0.6 kg/m^2, respectively. There was no significant difference in serum adiponectin levels before (11.5 ± 1.3 μg/ml) and during insulin therapy (14.3 ± 3.7 μg/ml) .

Our results have demonstrated that serum adiponectin levels, which have been reported to decrease in type 2 diabetes (3,4), surprisingly increased in type 1 diabetes. Plasma glucose or insulin concentration is a possible regulator of circulating adiponectin level. Among them, hyperglycemia is a common feature of type 1 and type 2 diabetes. Therefore, hyperglycemia itself is not a critical determinant for circulating adiponectin level in vivo.

Chronic exposure of insulin decreased the gene expression of adiponectin in the cultured 3T3-L1 adipocytes (7), suggesting that absolute insulin deficiency may contribute to elevated level of serum adiponectin in type 1 diabetes. However, our longitudinal study showed insulin therapy did not change serum adiponectin levels in type 1 diabetic patients. Berg et al. (6) demonstrated that circulating levels of adiponectin did not change before or after the onset of overt diabetes in NOD mice, although serum insulin levels dramatically decreased after the onset of diabetes. Therefore, factors other than plasma glucose and insulin levels must play a significant role in controlling the serum adiponectin concentration in type 1 diabetes.

Recently, it has been reported that leptin, another adipocyte-derived protein, modulates T-cell immune response (8) and accelerates the development of autoimmune diabetes in NOD mice (9). We have previously reported that adiponectin modulates the expression of endothelial adhesion molecules in vitro (10), which were dysregulated in the pancreas of type 1 diabetic patients (11). Our present results have indicated that serum adiponectin levels increased in type 1 diabetes, suggesting that adiponectin, an adipocyte-derived protein, might influ-

ence immune responses as leptin does in autoimmune diabetes.

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Not All Long-Acting Insulins Are The Same

Glargine (Lantus) is an insulin analog recently available in the U.S. It is a long-acting insulin but differs from other long-acting insulins (such as NPH, Lente, and ultralente) because it is clear as opposed to cloudy. It also has an acidic pH and should not be mixed with other insulins. Because it is new and patients and physicians do not have a long history of using it, mistakes can occur. A number of our patients have mixed glargine and rapid-acting insulin, in spite of being instructed not to. Additionally, it is no longer possible to distinguish between short- and long-acting insulins by clear or cloudy, respectively.

F.R. is a 55-year-old police officer with slowly progressive type 1 diabetes, diagnosed at age 53 years with positive anti-GAD antibodies. As oral agents lost their efficacy, an injection of evening NPH was added to his treatment. Due to his schedule, which involved working 3–4 nights a week, it was impossible to lower his fasting blood glucose levels on a bedtime NPH/daytime oral agents regimen. He was switched to twice-daily NPH and rapid-acting insulin. His HbA_{1c} level remained elevated at 8.8%. When glargine became available he was switched from twice-daily NPH to evening glargine, plus premeal rapid-acting insulin. He was taught carbohydrate counting and was followed closely. His glargine did not seem to control his daytime blood glucose levels, so he was switched to twice-daily injections of glargine. In spite of the new treatment and close follow-up, F.R. seemed to have more erratic blood glucose levels and more unexplained lows and highs than would have been expected on glargine. Therefore, he was put on a continuous glucose sensor to better document his blood glucose levels.

His sensor was picked up from his home on a Saturday by one of our diabetes educators (L.S.). When interviewing the patient, he said he was taking Lente ("L") insulin. He produced his vial of insulin, which was in fact Lente. On review, his original prescription was clearly written for Lantus and the pharmacy had erroneously given the patient Lente. Since the patient had never had a sample of Lantus, and assumed that the pharmacy filled the correct prescription, he did not question the insulin type. On his blood glucose–monitoring records he had written "L" and when speaking about his long-acting insulin, had described it only as "L," not as Lente.

Use of new medications can improve outcomes, but can also lead to confusion. After being started on a new insulin regi-

men, patients should be queried about their use of the insulin (e.g. "Do you mix insulins?", "What do your insulins look like?"), and also should be encouraged to bring their insulin vials into the clinic. Although patients often carry their rapid- or short-acting insulins with them, a basal insulin given at night might not be included in their insulin carrying kit. Finally, perhaps prescriptions for Lantus insulin should be written as the generic glargine, to avoid confusion with Lente.

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COMMENTS AND RESPONSES

Response to Montori et al.

Montori et al. (1) have performed an extensive and impressive review of the literature addressing the incidence of post-transplantation diabetes (PTD), risk factors for its development, prognostic implications, and optimal management of the disease. We would like to comment on some aspects of their article.

First, prospective cohort studies are generally accepted to have the most appropriate design to assess the incidence of a disease (2). In the present review, seven randomized clinical trials of immunosuppressive drugs, four case-control studies, and only four cohort studies were included to assess the incidence of PTD. Moreover, only one RCT and one CC study met the review's methodological quality criterion on PTD surveillance. In this perspective, the incidence figures may have been underestimated and should be interpreted with caution.

Second, the authors call for further research to establish criteria for diagnosing PTD on the basis of its prognostic complications. We feel that until such documentation is available, physicians and scientists should rely on the evidence from the general population and implement the diagnostic criteria for diabetes given by the American Diabetes Association (3) and the Expert Committee (4). There is no reason to believe that solid organ transplant recipients are better protected against the harmful effects of chronic hyperglycemia than otherwise healthy individuals.

Moreover, in our opinion, the review underestimates the impact of glucocorticoids on the development of PTD. We addressed this question specifically in a single-center prospective cohort study (5) a few years ago. A total of 173 consecutive previously nondiabetic renal-transplant recipients were observed during a period of 3 months from the day of transplantation (5). All patients received prednisolone, 97% received cyclosporine A (CsA), and 87% received azathioprine. Ten weeks after transplantation, the majority (n = 167) underwent a 75-g oral glucose tolerance test (OGTT). Several potential risk factors for PTD were assessed, including the daily doses of prednisolone and CsA, the total doses of steroids, intravenous methyl prednisolone and oral prednisolone, and the CsA whole blood through levels. The actual daily prednisolone dose was strongly and independently associated with the development of PTD. Ten months later, 91 of the first 103 patients were recruited to a follow-up study including a repeated OGTT (6). The results showed that tapering off prednisolone, but not CsA, significantly improved glucose tolerance during the follow-up period.

In addition, the importance of a family history of diabetes was questioned. Hathaway et al. (7) reported that a family history of diabetes was an independent risk factor for PTD (odds ratio 5.00) in a prospective cohort study including 86 patients followed for at least 18 months post-transplantation. We confirmed this finding in our study (odds ratio 3.93) (5).

Finally, we agree that trials evaluating the safety and efficacy of oral glucose-lowering agents are needed. We have previously documented that glipizide does not interfere with CsA pharmacokinetics (8), and this oral hypoglycemic agent probably is less likely to cause hypoglycemia than other sulfonylureas (9).

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Response to Hjelmesæth et al.

We appreciate the comments of Hjelmesæth et al. (1) in this issue of *Diabetes Care*, who have made important contributions to the field

of post-transplantation diabetes (PTD) and thank them for their interest in our work. We echo their remarks about the uncertainty surrounding the true incidence of PTD and agree that prospective studies conducted using sound methods are the best source of reliable estimates of the incidence of PTD. Their work on the impact of glucocorticoids on PTD concurs with the results of our metaregression (2) suggesting that the incidence of PTD varies with the choice of immunosuppression.

The lack of a uniform definition for PTD furthers the uncertainty about the estimates of true incidence of PTD. The American Diabetes Association (ADA) Expert Committee criteria for diagnosis of diabetes take advantage of the glycemic threshold above which the risk for microvascular complications, namely retinopathy, increases rapidly (3). In the post-transplantation period, researchers have failed to identify a similar glycemic threshold (if one exists) for macrovascular complications and infections, the main adverse outcomes of PTD. Furthermore, the relentless deterioration of β-cell function of type 2 diabetes may not occur in PTD (4). Thus, the ADA diagnostic criteria fail to appropriately characterize the prognosis and natural history of PTD. Alternatively, randomized trials of antihyperglycemic strategies after transplantation could identify a glycemic threshold above which it becomes optimally safe and cost-effective to intervene.

Family history of diabetes is an important risk factor in other forms of diabetes and may well be an important risk factor for PTD, as Hjelmesæth et al. argue. However, family history of diabetes is a very difficult variable to measure. Sackett (5) notes that family information bias—when "the flow of family information about exposure and illness is stimulated by, and directed to, a new case in its midst" leading to different family histories of illness obtained from affected and unaffected siblings—may overestimate its impact. Until researchers systematically collect family history data using the same protocol in all participants before transplantation (and report doing so like Hjelmesæth et al. [4]), we will remain uncertain as to the true importance of this risk factor.

Also, we concur with Hjelmesæth and colleagues that the issues of efficacy (e.g., prevention of adverse outcomes of PTD and improved quality of life), safety (e.g., hypoglycemia and interaction with immunosuppressive agents), and cost-effectiveness will be determining factors in the design of antihyperglycemic regimens for transplant recipients.

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