Plasma Homocysteine Levels in Hyperinsulinemic Subjects

A n inverse relationship between plasma insulin levels and homocysteine (Hcy) concentrations in type 2 diabetic patients has been previously reported (1) and discussed (2,3). An association between hyperinsulinemia and elevated Hcy levels has been found (4), and others (5) have observed that acute hyperinsulinemia reduces plasma Hcy levels in healthy men. In addition, it has been documented that plasma Hcy could be affected by both metabolic control and duration of disease in type 2 diabetic patients (6). By using the clamp technique, others have found that acute hyperinsulinemia did not influence plasma Hcy levels in patients with type 2 diabetes (7). Although hyperhomocysteinemia has been widely accepted as a risk factor for premature atherosclerosis (8), the complex relationship among insulin levels, insulin resistance, and plasma Hcy has yet to be entirely elucidated.

As part of a screening procedure for detecting subjects with clinical characteristics of the metabolic syndrome in Hungary, we measured total plasma Hcy levels (Abbott IMx) in hyperinsulinemic subjects with different stages of glucose intolerance. In a cohort of middle-aged (40–60 years) hyperinsulinemic subjects (38 men and 53 women, [means ± SD] age 47.6 ± 4.3 years, BMI 34.6 ± 4.9 kg/m², waist-to-hip ratio 0.92 ± 0.07, fasting plasma insulin level >15 µU/ml and/or postprandial [120 min after oral glucose tolerance test with 75 g glucose] plasma insulin level >45 µU/ml, actual blood pressure 146 ± 16/87 ± 9 mmHg, serum LDL cholesterol level 3.73 ± 1.09 mmol/l, HDL cholesterol level 1.12 ± 0.30 mmol/l, triglycerides level 2.97 ± 2.38 mmol/l, and uric acid level 279 ± 79 µmol/l), the plasma Hcy, vitamin B12, and folic acid levels were simultaneously determined. Subjects were classified as having normal glucose tolerance (NGT), impaired glucose tolerance (IGT) or diabetes; subgroups were matched for age, sex, BMI, and actual blood pressure. No antidiabetic or lipid-lowering drugs were used by the patients screened. Normal values of plasma Hcy, folic acid, and vitamin B12 levels in a nondiabetic and nonhyperinsulinemic control group (19 men and 28 women aged 45.0 ± 7.8 years) were also measured.

Although fasting plasma insulin levels were comparable, postprandial values were significantly higher in subjects with IGT or diabetes than in those with NGT. Plasma Hcy levels were not elevated and did not increase significantly with different stages of glucose intolerance in hyperinsulinemic subjects. Folic acid and vitamin B12 levels were also comparable in the investigated subgroups (Table 1). In addition, no significant difference (P > 0.05) was observed between hyperinsulinemic subjects (n = 91) and control subjects (n = 47) when plasma Hcy (9.28 ± 3.81 vs. 9.63 ± 2.70 µmol/l, respectively), folic acid (8.5 ± 5.9 vs. 7.5 ± 2.1 ng/ml), and vitamin B12 levels (423 ± 141 vs. 356 ± 121 pg/ml) were compared. Plasma Hcy levels were significantly (P < 0.001) higher in hyperinsulinemic men (11.34 ± 4.72 µmol/l, n = 38, age 48.1 ± 4.1 years) than in hyperinsulinemic women (7.86 ± 2.13 µmol/l, n = 53, age 47.2 ± 4.5 years). Similarly, serum creatinine values were significantly (P < 0.001) higher in hyperinsulinemic men (104 ± 17 µmol/l) than in hyperinsulinemic women (85 ± 8 µmol/l). Nearly the same prevalence of abnormal plasma Hcy values (i.e., values exceeding the upper limit [12.45 µmol/l] of normal range) was found in the different groups investigated (control subjects 4 of 47 [8.3%], hyperinsulinemic subjects with NGT 6 of 47 [12.8%], IGT 2 of 24 [8.3%], and diabetes 2 of 20 [10.0%]). A weak but statistically significant correlation was found between Hcy levels and age (r = 0.222; P < 0.05), and a stronger correlation was documented between Hcy levels and serum creatinine values (r = 0.658; P < 0.001) in hyperinsulinemic subjects (n = 91).

Our results indicate that hyperhomocysteinemia is not a characteristic feature of the early stages of glucose intolerance in hyperinsulinemic subjects, suggesting that factors other than the plasma Hcy level could have a stronger impact on atherosclerosis at the early stages of the metabolic syndrome. Accordingly, no correlation was found between the degree of insulin resistance and plasma Hcy levels in a recent investigation of normotensive and hypertensive Chinese subjects (9). Obviously, the relationship between insulin and Hcy levels at different stages of glucose intolerance seems to be complex and needs to be further studied, especially in prospective clinical investigations.

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The Chatline as a Communication and Educational Tool in Adolescents With Insulin-Dependent Diabetes

**Preliminary observations**

Self-management of type 1 diabetes treatment is crucial to obtaining metabolic control that will prevent the microvascular complications of the disease. Self-management requires continuing training and education of the patient. This task is particularly complex when dealing with young patients because children’s psychological approach to the disease tends to change as they get older.

We evaluated whether the addition of online communication to the teaching tools generally used in the education of young people with type 1 diabetes increased compliance. In adults, online communication is only superimposed on other means of communication, whereas for young people it represents one of the principal means of social interaction.

In January 2000, we established a chatline for adolescents affected by diabetes and moderated by a diabetologist. Initially, we recruited patients who were familiar with the Internet. As of June 2000, 43 patients (25 young men) affected by type 1 diabetes were enrolled in the study (age range 10.6–24.7 years and disease duration 0.1–15 years). All of the patients were being treated in our Pediatric Diabetological Unit. During chatline sessions, patients use a nickname (only the moderator knows the patients’ real names), which also identifies their gender. Meetings take place weekly and last 90 min. The topic of each meeting is voted on at the beginning of the session. Topics concern management of the disease as well as anxiety as to what the future holds and interpersonal and social relationships. Online messages are keyed and transmitted with the ICQ program. Discussions are recorded by the moderator and subsequently evaluated by a psychologist.

The increase from 8 to 43 patients within 6 months is encouraging, particularly because recruitment was mainly by word-of-mouth. Two young women (aged 24 and 20 years) dropped out after 1.5 and 3 months of discussion, respectively. They were among the oldest of the 43 patients, and metabolic control was scarce in both cases. To evaluate the capacity for self-management, each participant was asked on enrollment and 3 months later, how many times they had decided to change their treatment in the previous 3 months. The percent of positive answers increased from 32.5 to 83.7%, which indicates an improved capacity for self-management. During the study, the mean HbA1c concentration decreased from 8.9 to 7.8% (*P < 0.0001*).

This study indicates that online communication is a useful educational tool for young people with type 1 diabetes. In fact, it improved the main parameters that are generally used to evaluate educative processes. It is difficult to establish the psychological mechanisms underlying this improvement. Anonymity undoubtedly favors a greater freedom of expression of individual problems compared with traditional meetings among young people. This is particularly true regarding one’s private life and sexual matters.

In conclusion, the self-help community that was created in this study improved treatment compliance. We plan to continue this project to determine the long-term effects of this form of communication on young diabetic patients.

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**Plasma Levels of Natriuretic Peptides Are Correlated With Renin Activity in Normotensive Type 2 Diabetic Patients**

Decreased renin release has been reported in diabetic patients (1,2). Hypertension, nephropathy, and autonomic dysfunction have been proposed as the potential causative factors of this abnormality (3). However, decreased renin activity has also been described in normotensive diabetic patients without overt nephropathy and autonomic dysfunction (1), which suggests that an unidentified mechanism may also be involved in renin release. Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) regulate the body fluid volume, blood pressure, and vascular tone through the A-type guanylate cyclase-coupled receptor natriuretic peptide receptor-A (NPR-A) (4,5). Elevation of plasma ANP and BNP levels has been reported in diabetic patients (6,7). ANP inhibits renin release in cultured renal juxtaglomerular cells by an NPR-A–mediated mechanism (8). Thus, it is conceivable that natriuretic peptide induces suppression of renin release in diabetic patients. However, the relationship between plasma renin activity and the level of natriuretic peptides has not yet been assessed in diabetic patients. In the present study, we measured plasma levels of ANP and BNP and investigated their relationship with both plasma renin activity and the circulating...
The plasma ANP level was inversely and significantly correlated with the plasma aldosterone level ($r = -0.37$, $P < 0.05$) in diabetic patients. There was a weak negative correlation between the plasma ANP level and renin activity ($r = -0.29$, $P = 0.06$). There was a positive and significant correlation between plasma renin activity and the plasma aldosterone level ($r = 0.56$, $P < 0.0001$). Plasma renin activity and the plasma level of aldosterone were not significantly correlated with HbA1c.

Elevation of natriuretic peptides may occur in the presence of diabetic nephropathy before overt proteinuria (6,7). The results of the present study showed that plasma BNP and ANP levels correlate inversely with the plasma renin activity. Both BNP and ANP are thought to inhibit renin release from renal juxtaglomerular cells through NPR-A (8,11). Different metabolic roles in blood or different affinity to different metalloproteinase in diabetic patients.

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**Scotomata From Panretinal Photocoagulation Are Not Perceived as a Result of Perceptual Filling-in Generated by Plasticity in the Visual Cortex**

Laser panretinal photocoagulation (PRP) is now established as the treatment of choice for patients with proliferative diabetic retinopathy (1), albeit at the expense of a subjectively and objectively identifiable loss of retinal function. One of the functional complications of PRP is a loss of visual field (2,3), and these modifications can be so severe that some patients fail to meet visual field standards for driving (4). However, in our clinical experience, PRP-treated patients do not complain of perceiving focal defects in their visual field, suggesting that they are unaware of these field alterations. Mechanisms resulting in unawareness of defects in the visual field include perceptual filling-in (5). Perceptual filling-in is widely considered to be due to mechanisms related to plasticity in the visual cortex (5). In clinical practice, the major implications of the dissociation between actual and perceived defects in the visual field and its very occurrence have rarely been recognized. However, its clinical significance is far reaching.

The aim of this study was to assess visual field defects in patients who received PRP using argon laser to investigate the perception of such defects and to consider their possible clinical implications.

Five diabetic patients who had had full PRP in both eyes with an argon laser at least 1 year previously (range 1 to 5 years, mean 2.6) for proliferative diabetic retinopathy were included in the study. Informed consent was obtained from all subjects after the procedures involved were fully explained. The eyes were treated with 500 µm laser spots with a pulse duration of 0.1 s. Their best corrected visual acuity was 8/10 or better. Patients’ ages ranged from 46 to 72 years (mean 61 years). All patients were men and had type 2 diabetes treated with insulin.

We asked each patient if they had noticed any visual troubles in every day life (i.e., when reading or watching television) after laser treatment. We also asked the patient to monocularly and binocularly watch a Maddox cross fixed on a wall and to tell us if he noticed anything special, such as if there were parts of the cross that were perceived as missing or spots on the wall. In each patient, visual fields were tested in both eyes using the following three methods: 1) Goldmann kinetic perimetry using a V/4 target to detect absolute scotomata, 2) Octopus 2000 R automated static perimetry (Interzeag) with the program N1, and 3) Scanning laser ophthalmoscope (SLO) microperimetry (Rodenstock) using Goldmann III stimulus sizes.

When asked, patients indicated that they had not noticed any restriction in visual fields in every day life, including when reading or watching television, nor did they report any visual disturbances while watching the Maddox cross. In all patients, absolute scotomas were observed using Goldmann perimetry. Scotomas were consistently located in the midperiphery. Automated computerized static perimetry in the central 30° field of vision showed a diffuse constriction of the visual field. SLO microperimetry displayed scotomas corresponding to the laser scars.

In the current study, we observed that, although conspicuous visual field defects were present, the patients were unaware of scotomas. These observations show that this type of scotoma induces cortical reorganization resulting in a perceptual filling-in process, which does not restore function to the destroyed tissue but helps to compensate for gaps in perception.

Changes in visual perception resulting from filling-in cause dissociation between actual and perceived defects in the visual fields. This dissociation occurs so frequently and produces such marked effects in everyday life that, from a clinical point of view, it may be the most important type of dissociation to occur in the visual system. For instance, filling-in has a very beneficial effect in patients who received PRP by preventing them from seeing as through a strainer. However, filling-in may also be a handicap because it may significantly delay the recognition of visual field defects, and hence treatment, especially when scotomas do not affect the foveal function (i.e., when visual acuity is preserved). 6)

As showed in our study, it also causes underestimation from the ophthalmologists and the patients of visual dysfunction caused by photocoagulation in diabetic retinopathy and that may have some consequences on driving safety.

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**References**


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**Do Polynesians Have Obesity-Driven Fuel-Mediated Teratogenesis?**

Pederson and Freinkel (1) hypothesized that intrauterine exposure of the fetus of diabetic women during pregnancy to an excess supply of fuel (e.g., glucose) causes permanent change to the fetus, leading to a larger birth weight and an increased risk of developing type 2 diabetes later in life. This hypothesis is known as the fuel-mediated teratogenesis theory.
Polynesians are an ethnic group prone to larger babies (2), a high prevalence of obesity and type 2 diabetes, onset of diabetes at an early age (3), and a high proportion (16–18%) of women with type 2 diabetes first diagnosed during pregnancy (4). Therefore, we have investigated the extent to which increasing obesity among pregnant nondiabetic Polynesian women was associated with increasing maternal glycemia and whether this, in turn, was associated with fetal hyperinsulinism.

Data were available from 63 consecutive normal pregnant Polynesian women as previously reported (5,6). All women received a 100-g oral glucose tolerance test between the 28th and 32nd week of pregnancy. Women were excluded if there were any medical or obstetric conditions. At delivery, umbilical cord samples were taken. Gestational age was assessed using Dubowitz criteria and birth weight, and skinfold measurements on the babies were taken. Gestational age was assessed using the Dubowitz criteria and birth weight, and skinfold measurements on the babies were taken as described previously (5,6). Glucose, triglyceride, nonesterified fatty acids (NEFA), insulin, C-peptide, and IGF-1 were assayed using a double-antibody radioimmunoassay (RIA) (intra-assay and interassay coefficients of variation were <5 and <8%, respectively). Statistical analyses were undertaken using SPSS for Windows (SPSS, Chicago). Metabolic and anthropometric data were compared across tertiles of maternal BMI using one-way analysis of variance. Non-normally distributed variables were logarithmically transformed for analysis. Pearson's correlations were used to assess the relationship between maternal BMI and physical characteristics. Because of the relationship between BMI and age, relationships between maternal BMI and maternal metabolic characteristics were assessed using partial correlations adjusted for age. The gestational age was the same across maternal BMI tertiles (40 ± 1 weeks, range 7–42). Birth weight ranged from 2,430 to 4,820 g. Table 1 compares the characteristics of mothers and babies across tertiles of BMI. Increases in maternal BMI was correlated with increased birth weight, maternal antenatal glycemia, and umbilical cord insulin concentrations. Analysis of variance across tertiles confirmed the relationship between BMI and both birth weight and insulin, but not maternal glucose. The umbilical cord geometric mean insulin:C-peptide ratio was significantly different (\(P = 0.007\)) across tertiles of maternal BMI and umbilical cord leptin, IGF-1, and increased dietary fat and total caloric intakes. The fuel-mediated teratogenesis hypothesis is supported by observational data in the offspring of women who had gestational diabetes (8,9). If our observations and our hypothesis are confirmed, they suggest that the current epidemic of obesity may lead to a higher-than-expected prevalence of type 2 diabetes. Antenatal obesity may induce fuel-mediated teratogenesis in the offspring, which may predispose future generations to obesity and type 2 diabetes.

**Table 1—Maternal and infant characteristics across tertiles of BMI**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Tertiles (kg/m²)</th>
<th>P across tertiles</th>
<th>r*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal BMI (kg/m²)</td>
<td>&lt;25.0</td>
<td>25.0–31.7</td>
<td>&gt;31.8</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>22</td>
<td>21</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3,400 ± 640</td>
<td>3,500 ± 340</td>
<td>3,780 ± 380</td>
<td>0.030</td>
</tr>
<tr>
<td>Maternal 36-week fasting glucose (mmol/l)</td>
<td>5.1 ± 0.6</td>
<td>5.0 ± 0.5</td>
<td>5.3 ± 0.5</td>
<td>0.030</td>
</tr>
<tr>
<td>Insulin (µmol/l)</td>
<td>10.0</td>
<td>14.0</td>
<td>14.9</td>
<td></td>
</tr>
<tr>
<td>Insulin:C-peptide</td>
<td>45.2</td>
<td>59.5</td>
<td>54.2</td>
<td></td>
</tr>
<tr>
<td>Leptin (ng/ml)</td>
<td>15.0</td>
<td>14.0</td>
<td>15.6</td>
<td></td>
</tr>
<tr>
<td>IGF-1 (ng/ml)</td>
<td>35.4</td>
<td>28.1</td>
<td>37.2</td>
<td></td>
</tr>
</tbody>
</table>

Data are means ± SD, unless otherwise indicated. Partial correlations for maternal metabolic characteristics are adjusted for age. *Pearson's correlation vs. BMI for physical characteristics.

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A 12-h Intravenous Insulin Infusion Restores the β-Cell Response Torpidity to Sulfonylureas in Patients Affected by Type 2 Diabetes

The efficacy of oral hypoglycemic agents (OHAs) in the treatment of type 2 diabetes is of limited duration in many patients. If these drugs are no longer effective, insulin should be admin-

istered; this clinical phenomenon is called secondary failure (SF) to OHA (1). Hyperglycemia has a direct toxic effect on both insulin secretion and action, so the antecedent hyperglycemic state might also play a role in the impairment of OHA sensitivity (2). In nonobese type 2 diabetic subjects preferentially treated with sulfonylureas, a defect in insulin secretion appears to be more important than the peripheral insulin resistance, which is prevalent in obese subjects (3). Recently, some authors have tried to restore sulfonylurea sensitivity by using intermittent insulin therapy, hoping that the reduction of hyperglycemia may improve insulin secretion and action (4,5).

We evaluated whether short-term glycemic control by intravenous insulin infusion could restore sulfonylurea sensitivity in a group of SF nonobese type 2 diabetic patients identified by strict clinical and metabolic criteria. We studied 15 nonobese type 2 diabetic patients (age at diagnosis of diabetes >35 years, duration of known disease >3 years, and duration of previous positive response to sulfonylureas >2 years) who were receiving a maximal dose of glibenclamide at 15 mg/day, had known compliance to both diet and pharmacological control (fasting glucose levels >10 mmol/l for ≥3 months), and were islet cell antibody– and GAD antibody–negative. These patients were submitted to a 12-h intravenous insulin infusion to achieve adequate glycemic control, using the algorithm proposed by Mokan and Gerich (6), which was adjusted on the basis of the blood glucose levels (measured at 60-min intervals). The goal was to induce and maintain near-normal blood glucose concentrations (5–7 mmol/l) in the subsequent hours.

In each subject, the glycemic profile and pancreatic β-cell secretion (serum C-peptide) levels were evaluated before and both 2 and 7 days after insulin infusion, and only the glibenclamide treatment was maintained. The patients in which adequate metabolic control was achieved were further evaluated 2, 4, and 6 months later for β-cell–secretory activity and glycated hemoglobin.

The responders (n = 6) showed a significant amelioration of metabolic control and β-cell secretion from the second day after the insulin infusion treatment. This condition was maintained for ≥6 months (Table 1). On the contrary, the nonresponders (n = 9), were not satisfactorily controlled by glibenclamide alone at 7 days after insulin infusion and were successively treated with insulin therapy. Before insulin infusion, this group had significantly higher levels (mean ± SD) of serum glucose (15.22 ± 1.8 vs. 12.88 ± 2.0 mmol/l) and glycated hemoglobin (10.3 ± 1.7% vs. 8.3 ± 1.25%) and a longer duration of metabolic derangement (28.8 ± 18.8 vs. 7.8 ± 3.1 months) than the responders.

In conclusion, in almost the half of the diabetic patients studied, a short-term (12-h) insulin infusion provided long-term restoration of normal blood glucose levels. This was probably caused by β-cell resensitization to sulfonylurea action, and may constitute an effective treatment of SF in nonobese subjects with relatively recent metabolic derangement.

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Table 1—Metabolic parameters at admission and after insulin infusion in the responders

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Basal</th>
<th>2 days</th>
<th>7 days</th>
<th>2 months</th>
<th>4 months</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose (mmol/l)</td>
<td>11.28 ± 0.7</td>
<td>8.05 ± 1.4↑</td>
<td>7.50 ± 1.7↑</td>
<td>8.22 ± 2.0*</td>
<td>7.66 ± 1.8*</td>
<td>8.27 ± 1.4*</td>
</tr>
<tr>
<td>Mean glucose (mmol/l)</td>
<td>12.88 ± 1.9</td>
<td>9.55 ± 1.5↑</td>
<td>8.44 ± 1.9↑</td>
<td>7.27 ± 1.3*</td>
<td>7.22 ± 0.9*</td>
<td>7.11 ± 0.6*</td>
</tr>
<tr>
<td>Fasting C-peptide (ng/ml)</td>
<td>0.56 ± 0.3</td>
<td>0.83 ± 0.53 —</td>
<td>—</td>
<td>0.60 ± 0.4</td>
<td>0.73 ± 0.36</td>
<td>0.46 ± 0.23</td>
</tr>
<tr>
<td>C-Peptide postmeal (ng/ml)</td>
<td>1.0 ± 0.66</td>
<td>1.46 ± 0.93↑ —</td>
<td>—</td>
<td>0.86 ± 0.5</td>
<td>0.96 ± 0.46</td>
<td>0.96 ± 0.43</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.3 ± 1.2</td>
<td>—</td>
<td>—</td>
<td>6.4 ± 0.6†</td>
<td>6.5 ± 0.6‡</td>
<td>6.7 ± 0.5‡</td>
</tr>
</tbody>
</table>

Data are means ± SD. *P < 0.01, †P < 0.01, ‡P < 0.05 vs. basal.
A Retrospective Study on 435 Women With Gestational Diabetes

Fasting plasma glucose is not sensitive enough for screening but predicts a need for insulin treatment.

Gestational diabetes mellitus (GDM) is a state of impaired glucose tolerance during pregnancy. It occurs in 2–5% of pregnancies depending on the population described and the criteria used for diagnosis (1). Because gestational adaptations include many hormonal changes that promote insulin resistance, pregnancy may be considered diabetogenic (1). GDM increases pregnancy morbidity and the subsequent likelihood of future diabetes in the mother (2,3).

There is no universal consensus regarding screening for and diagnosing GDM (4). In addition to glucose, obesity, a previous macrosomic infant, and the use of fasting glucose measurement have been recommended in screening (5). In Europe, GDM is mostly diagnosed using a 2-h 75-g oral glucose tolerance test (OGTT), whereas in the U.S., a 50-g oral glucose load is generally used for screening and 100-g 3-h OGTT for diagnosing GDM (4,6).

To investigate whether our present diagnostic method for GDM (2-h 75-g OGTT) is still useful, if it could be simplified without losing sensitivity, and whether a need for insulin treatment can be predicted at the time of diagnosis of GDM, 435 Finnish women with GDM and a singleton pregnancy, who gave birth at Oulu University Hospital during the period 1984 to 1994 were studied. The women included in the study were diagnosed as having GDM for the first time in the index pregnancy. The control group was pair-matched for age (± 2 years), parity (nulliparous, 1–3, and >3 deliveries), and date of delivery. The 2-h 75-g OGTT was carried out using the following indications: glucosuria, BMI ≥25 kg/m² or previous delivery of a macrosomic infant, and expected macrosomic infant (≥4500 g), or expected macrosomic infant in the current pregnancy. GDM was diagnosed if at least one of the glucose values was abnormal. The limits of abnormal capillary blood glucose values were as follows: fasting ≥4.8, 1-h ≥10, and 2-h ≥8.7 mmol/l, which are the 97.5 percentile values of the levels recommended by the Fourth International Workshop-Conference on GDM (7).

After diagnosing GDM, all women were treated by diet (1,600–1,800 kcal/day). Fasting and postprandial (1.5–2 h after meal) capillary blood glucose values were assessed in the maternity welfare clinics. Guar gum, a galactomannan-rich seed extract of the leguminous plant Cyamopsis tetragonoloba, was added if the fasting or postprandial value was repeatedly over 4.8 or 6.7 mmol/l, respectively. If normoglycemia was not achieved, women were hospitalized for a 24-h glucose profile, and insulin treatment was started and patients who needed insulin therapy followed their blood glucose values by self-monitoring.

The mean age of the GDM women was 31.6 years (range 18–46) and that of the control subjects was 31.4 years (range 19–46). Women with GDM had a higher BMI (26.4 kg/m² [17–47] vs. 22.9 [16–38], P < 0.0005) and their weight gain during the pregnancy was significantly less than that of the control women. Of the women in our study, 57.7% of the women with GDM and 40.0% of the control subjects had a family history of diabetes. Of the patients with GDM, 134 of 435 (36.6%) were treated by diet only. Because of high fasting or postprandial glucose levels in 156 of 435 (35.9%) of the patients, insulin was given and in 120 of 435 (27.6%) guar gum was started.

One third of all the subjects had either one, two, or three abnormal values in the OGTT, and 57.1% of those requiring insulin treatment had three abnormal values. In the insulin group, 14.3% had one abnormal value, and this was a significantly lower incidence than in the diet (31.3%) and guar gum group (37.6%). Women who were treated by diet or with guar gum mostly had one or two abnormal values in the OGTT. The insulin group showed a significantly higher incidence of abnormal postprandial glucose levels (75.0%) than the other groups (diet 30.3 and guar gum group 37.6%).

There were no significant differences in maternal age, parity, or gravidity between the groups.

The OGTT was performed as described (7) and the OGTT value of ≥6.7 mmol/l yielded sensitivity of 50.8% in the diagnosis of GDM. Table 1 shows abnormal glucose values at different time points in the OGTT.

| Table 1—Abnormal OGTT values in patients with GDM in different treatment groups |
|-----------------|--------|--------|--------|--------|
| n               | All    | Diet   | Guar gum | Insulin |
| Fasting level ≥ 4.8 mmol/l | 252 (69.6) | 93 (62.0) | 93 (57.0) | 106 (89.1) |
| 95% CI           | 0.649–0.744 | 0.542–0.698 | 0.463–0.672 | 0.835–0.947† |
| 1-h level ≥ 10.0 mmol/l | 257 (71.0) | 104 (69.3) | 60 (64.5) | 93 (78.2) |
| 95% CI           | 0.663–0.757 | 0.620–0.767 | 0.539–0.742 | 0.707–0.856† |
| 2-h level ≥ 8.7 mmol/l | 243 (67.1) | 94 (62.7) | 59 (63.4) | 90 (75.6) |
| 95% CI           | 0.623–0.720 | 0.549–0.704 | 0.528–0.732 | 0.679–0.833* |

Data are n or n (%) unless otherwise indicated. *P < 0.05 compared with diet, †P < 0.05 compared with guar gum.
OGTT. 89.1% of the subjects in the insulin group and 60.0% in the diet/guar gum groups had an abnormal fasting glucose level ($\geq 4.8$ mmol/l). There was a trend toward higher incidence of abnormal glucose levels at each time point of the OGTT in the insulin group.

In this comparative pair-matched study, a pathological fasting glucose level ($\geq 4.8$ mmol/l) was found in 69.6% of women with GDM. A postprandial glucose level of $\geq 6.7$ mmol/l was a weaker indicator of GDM, revealing only 50.7% of the patients. In a prospective study, Reichelt et al. (5) found that a fasting plasma glucose value of 4.7 mmol/l is a good threshold in screening for GDM yielding a sensitivity of 94%. In another study, a threshold value of 4.8 mmol/l was found to yield a sensitivity of 81% and a specificity of 76% (8). It has to be noted that both of these studies were conducted in populations with an ethnic background different from our own, and unlike our study, women with previous GDM were also included. The Fourth International Workshop-Conference on GDM (7) recommended the use of 5.3 mmol/l as a threshold value for fasting glucose. However, the present results show that using this value only 39.2% of all patients would have had an abnormal fasting glucose value. This was observed earlier in clinical practice, and therefore, as in several other centers, we used the lower threshold value of the 97.5 percentile point.

Systematic screening procedures and diagnostic criteria for GDM vary in different countries. We have used a 2-h 75-g OGTT, and if one or more of the values was abnormal, GDM was diagnosed. If the diagnosis had been based on two abnormal values instead of one, 27.3% of the subjects with GDM would not have been diagnosed. Langer et al. (9) have also shown that one abnormal value in the OGTT should be regarded as a pathological finding. In their study, the diagnosis of GDM was based on abnormal glucose values in the OGTT, and those having only one abnormal value were not treated as cases of GDM. They had significantly poorer neonatal outcome, perhaps as a result of poor glycemic control. Similarly, our results also emphasize the importance of treatment of subjects with one abnormal value because 14.3% in this group needed insulin treatment.

We found that a pathological fasting glucose level of $\geq 4.8$ mmol/l effectively predicts a need for insulin during the pregnancy. It had the best sensitivity (89.1%) when compared with the 1-h or 2-h OGTT values. In a recent study, it has also been shown that fasting glucose is the best predictor of the need for insulin, although even higher values (5.1–5.3 mmol/l) were used (10).

The present results suggest that neither fasting nor postprandial glucose levels are sensitive enough in screening for GDM, although both are good indicators of a need for insulin treatment during pregnancy. The 2-h 75-g OGTT is useful for diagnosing GDM, and one abnormal value should be used as a criterion of diagnosis. If a fasting glucose level of $\geq 4.8$ mmol/l is used for screening or if two abnormal values in the OGTT are required for diagnosis, ~30% of GDM cases would remain undiagnosed.

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HbA1c Does Not Reflect Prandial Plasma Glucose Excursions in Type 2 Diabetes

In recent years, an increasing number of epidemiological studies in the U.S. and Europe have demonstrated that postprandial plasma glucose is a strong predictor for cardiovascular mortality (1,2). There is much evidence suggesting that excessive postprandial glucose excursions lead to endothelial dysfunction (3), perturbed coagulation (4), and the generation of free radicals (5), all of which may contribute to cardiovascular disease. Although it hasn’t been proven in prospective studies, it may be assumed that reduction of prandial glucose excursions improves the cardiovascular outcome in individuals with diabetes and impaired glucose tolerance (IGT).

A cardinal issue is how to assess prandial glycemia in diabetes. Glycated hemoglobin, which reflects a persons integrated measure of overall plasma glucose during the previous few months, has been found to be elevated by ~1.5% in people with IGT (6), indicating a significant impact of prandial glucose levels on this variable in this group. Analogously, Avignon et al. (7) recently demonstrated that postprandial (2:00 P.M. and 5:00 P.M.) plasma glucose
concentrations correlated independently and significantly with HbA1c in type 2 diabetic individuals, whereas fasting plasma glucose levels did not. This could leave one with the impression that HbA1c is a significant marker of postprandial glycemia in type 2 diabetic individuals.

To test this hypothesis, we explored the relationship between HbA1c and both fasting and 24-h plasma glucose levels by carefully monitoring prandial glucose concentration levels in 19 drug-naive type 2 diabetic patients. The average age was 58 years (range 46–70), BMI was 31.7 kg/m² (24.2–44.6), fasting plasma glucose was 10.0 mmol/l (6.4–14.7), and HbA1c was 7.2% (5.8–12.0). The patients were either treated solely with diet or had oral hypoglycemic agents withdrawn for at least 8 weeks. Glycemic control was assessed by 24-h plasma glucose profiles based on 44 samples, of which 40 were drawn between 8:00 A.M. and 10:00 P.M. HbA1c was determined by high-pressure liquid chromatography (normal range 4.1–6.0%). Standard meals were served as breakfast (8:00 A.M.), lunch (12:00 P.M.), and dinner (6:00 P.M.). Seventeen younger healthy volunteers acted as a control group.

We found modest ratios between the incremental prandial area under the curve (AUC) and total 24-h AUC of plasma glucose in the diabetic individuals, accounting for only 8.8 ± 0.8% (mean ± SD); however, this was significantly higher than in control subjects (5.4 ± 0.6%, P < 0.01). The incremental prandial periods were defined as the periods from 8:00 A.M. to 4:00 P.M. (i.e., breakfast and lunch), and from 6:00 P.M. to 10:00 P.M. (i.e., dinner). When the diabetic patients were divided into two groups based on whether their fasting plasma glucose was above or below 10 mmol/l, the prandial glycemcic component of the latter group displaying acceptable glycemcic control (i.e., an average fasting plasma glucose of 8.2 mmol/l and an HbA1c of 6.7%, n = 11) raised but still constituted <10% of the total 24-h plasma glucose.

Fasting and the average of the three 1-h and 2-h postprandial plasma glucose concentrations were significantly correlated with HbA1c (r = 0.69, P < 0.01; r = 0.61, P < 0.01; and r = 0.55, P < 0.05, respectively), as assessed by parametric bivariate correlations, whereas the incremental prandial AUC of plasma glucose did not significantly correlate (r = –0.03, P = 0.9).

Only fasting plasma glucose correlated independently with HbA1c (r = 0.69, P = 0.002 applying backwards elimination technique) in a multiple linear regression analyses model that included the variables of fasting plasma glucose and one of the following: 1-h plasma glucose, 2-h plasma glucose, the prandial incremental area under the curve for glucose, or all of the above. Similar observations were made in the subgroup with acceptable glycemic control (data not provided).

It is obvious that prandial glucose excursions per se contribute very little to the HbA1c level, given the biochemical kinetics of glycated hemoglobin and the fact that the prandial glycemic component, even in well-controlled type 2 diabetic patients, is moderate compared with the average circadian plasma glucose level. The situation may be different in diabetic patients with fasting plasma glucose levels within the normal range and in some insulin-treated type 2 diabetic patients with very limited B-cell function, although similar results were found in subjects with mild and more severe diabetes in our study. Patient population and design may account for the discrepancy between the literature and both the current observations and those of a previous study (7). However, it should be noted that the present study allows us to dissect the prandial glucose excursions meticulously.

In conclusion, in our attempt to minimize prandial plasma glucose excursions in type 2 diabetes either pharmacologically or nonpharmacologically, HbA1c should be disregarded as a relevant marker per se of the postprandial plasma glucose level in the vast majority of patients. Other surrogate measures need to be evaluated. So far, reliable assessment of circulating prandial glucose concentrations can only be made by blood glucose measurements, and an appropriate number should be included in self-monitoring of blood glucose programs.

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8. Diabetic nephropathy has become the most common cause of end-stage renal disease in Europe and North America, particularly because of the increasing number of nephrotic type 2 diabetic patients (1). The survival rate of diabetic patients with renal insufficiency is lower than that of nondiabetic patients, but survival has improved during the last 5 years.
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patients aged <40 and ≥40 years who were started on renal replacement therapy from 1991 to 1997 at our dialysis center. ◆, type 1 diabetic patients; □, type 2 diabetic patients; ▲, nondiabetic patients aged <40 years; ×, nondiabetic subjects ≥40 years.

decade, especially in uremic type 1 diabetic patients and, to a lower extent, in type 2 diabetic patients (2,3). The survival of uremic patients is partly dependent on the type of renal replacement therapy used. The decision to use continuous ambulatory peritoneal dialysis versus hemodialysis must be made on an individual basis (4).

In our study, we determined changes in the percentage of new type 1 and type 2 diabetic patients requiring renal replacement therapy at our dialysis center from 1991 to 1997, and we evaluated the 1- and 5-year overall survival rates in type 1 and type 2 diabetic patients in comparison with age-matched nondiabetic patients, regardless of the applied method of renal replacement therapy (hemodialysis, continuous ambulatory or cycling peritoneal dialysis, renal transplantation alone, or simultaneous pancreas-kidney transplantation). In addition, we compared the prevalence of macroangiopathic diseases in each patient group at the start of dialysis treatment.

A total of 209 uremic patients who were started on dialysis therapy at our dialysis center from 1991 to 1997 were included in the study. The diabetic patients were divided into type 1 and type 2 diabetic categories, and the nondiabetic subjects were grouped according to those aged <40 or ≥40 years at the start of dialysis therapy. Sixteen (8%) patients had type 1 diabetes, and 67 (32%) had type 2 diabetes; their mean age was 34 ± 3 vs. 64 ± 5 years, respectively. During the same period, dialysis therapy was initiated in 34 (16%) nondiabetic patients aged <40 years and 92 (44%) nondiabetic subjects aged ≥40 years; the mean age in the two patient groups was 31 ± 3 vs. 60 ± 9 years, respectively.

All of our type 1 diabetic patients without severe atherosclerotic vascular disease (13 of 16 patients) were registered for simultaneous kidney-pancreas transplantation. All type 2 diabetic patients aged <65 years with no severe macroangiopathic complications (12 of 67 patients) were registered for kidney transplantation alone. Kidney transplantations were performed at the First Department of Surgery in the General Hospital Linz by Dr. P. Brücke; the pancreas-kidney transplantations were performed at the University in Innsbruck by Prof. Dr. M. Margreiter. During the period of observation, 94% of type 1 diabetic patients were transplanted, 75% underwent simultaneous pancreas-kidney transplantation, and 19% received kidney grafts alone. During the same period, 65% of nondiabetic patients aged <40 years received a kidney graft. In contrast, renal transplantation was performed only in 6% of the type 2 diabetic patients and in 11% of the nondiabetic subjects with age ≥40 years. The 1- and 5-year survival rates were approximately the same in type 1 diabetic (100 and 82%, respectively) and age-matched nondiabetic patients (97 and 88%). In contrast, the survival rates of the type 2 diabetic patients (80 and 29%) were lower than those for nondiabetic patients aged ≥40 years (79 and 39%), but the difference was not significant. The poor survival of our type 2 diabetic patients can partly be explained by the high mean age of these patients (64 ± 5 years). The survival rates of the two diabetic patient groups and the nondiabetic patients are shown in Fig. 1.

The prevalence of cardiovascular disease (49 vs. 17%, P < 0.005) and peripheral vascular disease (24 vs. 10%, P < 0.05) was significantly higher in the type 2 diabetic patients compared with their age-matched nondiabetic subjects. In the type 1 diabetic patients, the prevalence of macroangiopathic diseases was only tentatively higher than that in the nondiabetic individuals. Cardiovascular events were the most common cause of death in each group.

Our study demonstrated that the percentage of uremic type 2 diabetic patients who started on dialysis therapy was also increasing during the years 1991–1997, but the increase was not significant. The mean percentage was 32% for the entire period. In contrast, the number of patients with type 1 diabetes requiring renal replacement therapy remained unchanged during the last decade (5). The mean number of uremic type 1 diabetic patients as a percent of the number of total patients was 8% from 1991 to 1997.

Furthermore, in our type 2 diabetic patients, the 5-year survival rate was poor (29 vs. 39% in the nondiabetic patients aged ≥40 years). This poor prognosis can partly be explained by a high mean age of the patients (64 ± 5 years). In addition, the prevalence of macrovascular diseases was significantly higher in the type 2 diabetic patients in comparison with their age-matched nondiabetic subjects. Only 6% of the uremic patients with type 2 diabetes were transplanted; the majority of the patients remained on hemodialysis. During the same period of observation, 11% of the age-matched nondiabetic patients with
end-stage renal disease received a kidney transplant.

In our type 1 diabetic patients, the 1- and 5-year survival rates (100 and 82%, respectively) were much better than those reported in the 1980s, and they are approximately as high as those in our age-matched nondiabetic patient group (97 and 88%, respectively). The improvement in prognosis in our type 1 diabetic patients can mainly be explained by the high rate of pancreas-kidney transplantations in this group. The majority (75%) of our patients with type 1 diabetes simultaneously received a pancreas-kidney transplant; 19% received a kidney transplant alone. In contrast, only 65% of all nondiabetic patients aged <40 years received a kidney graft during the same period. Moreover, patients with simultaneous pancreas-kidney transplantation have the advantage of a shorter waiting time in comparison with patients with kidney transplantation alone. In our study, the mean waiting time for pancreas-kidney grafts was 7 months (range 0–18) and 29 months (11–52) in the group that received a kidney graft alone.

We conclude that the number of new diabetic patients who started on dialysis therapy at our dialysis center during the years 1991–1997 was persistently high with a tendentially increasing percentage of type 2 diabetic patients. The overall 5-year survival rate for type 1 diabetic and nondiabetic patients aged <40 years was approximately the same. The significant improvement in the prognosis of the uremic patients with type 1 diabetes could mainly be explained by the high rate of simultaneous pancreas-kidney transplantations in this group. In contrast, the 5-year survival rate of the type 2 diabetic patients was tendentially lower than that in the nondiabetic patients aged ≥40 years; renal transplantation was performed in only a minority of these patients because of a high prevalence of macrovascular diseases.

**Comments and Responses**

**Inverse Relationship Between Blood Glucose and Autonomic Function in Healthy Subjects**

Recent observations show that cardiovascular autonomic function inversely relates to blood glucose (BG) levels in nondiabetic patients (1–4). Baroreflex sensitivity (BRS), which is a sensitive measure of cardiovascular autonomic function, was negatively associated with HbA1c levels in a cohort of 288 subjects with a normal glucose tolerance in the Hoorn study (1). The corrected QT (QTc) duration, which is another measure of cardiac autonomic function, was related to high fasting blood glucose (BG) levels (>5.1 and <7.8 mmol/l) in a population-based study of 6,543 healthy subjects in the Netherlands (2). In an acute study, an increase in QTc duration in response to hyperglycemia was shown in healthy subjects (3). In a recent paper by Watkins et al. (4), an inverse relationship between BRS and BG levels was present in healthy subjects. This observation is in accordance with findings we have recently made.

We studied the association between BRS and BG levels in 40 healthy subjects (21 men, 19 women). Their age was 55 ± 10 years (mean ± SD) and their BMI was 27 ± 4 kg/m². Four subjects were smokers (two men, two women), none used any medication, and all had a blood pressure below 160/90 mmHg and a fasting BG level <7.0 mmol/l. All measurements were carried out after 30 min supine rest in the morning in a quiet room kept at constant temperature (24°C), with the subjects fasting and refraining from both drinking caffeine-bearing drinks and smoking. BRS was measured by the transfer function technique using the CARSPAN program, as recently outlined (5). A discrete Fourier transformation was performed on 300 s of noninvasive blood pressure and heart rate recordings using a Finapres 2300 (Ohmeda, Englewood, CO). BRS was defined as the mean modulus between systolic blood pressure and heart rate spectral transformation was performed on 300 s of noninvasive blood pressure and heart rate frequency band with at least 0.5 coherence. Parameters that had a skewed distribution were logarithmically transformed. Univariate correlations were sought with Pearson's correlation coefficient, and linear regression analyses (backward method) were used to identify the determinants of BRS. BRS was 9.5 ± 5.0 ms/mmHg (mean ± SD), the BG level was 4.9 ± 0.6 mmol/l, blood pressure was 130/84 ± 16/9 mmHg, and the fasting insulin level was 9.5 ± 6 µU/l. Univariately, BRS was related to BG (r = −0.50, P = 0.002) (Fig. 1), to systolic blood pressure (r = −0.60, P < 0.001), to diastolic blood pressure (r = −0.38, P = 0.02), to age (r = −0.43, P = 0.006), and to LDL cholesterol (r = −0.36, P = 0.03), and not to BMI, fasting insulin level, glucose-to-insulin ratio, triglycerides, and HDL cholesterol. In a linear regression model, only BG and systolic blood pressure independently contributed 23% (P = 0.002) and 12% (P = 0.03) to the variance of BRS (multiple r = 0.64, P < 0.001).

These findings confirm the presence of a negative relationship between BRS and BG in healthy subjects. This relationship was independent from other risk factors, in contrast to the study by Watkins et al. (4), in which the relationship was explained by the association with age, blood pressure,
Baroreflex sensitivity is depressed in microalbuminuric type 1 diabetic patients at rest and during sympathetic manoeuvres. Diabetologia 42:1343–1349, 1999

Glycemic Control and Impaired Autonomic Function

Is glucose the sole culprit?

Preconceptions in the field of diabetes research have recently been challenged on several fronts, leading to progress in the recognition of new categories of impaired glucose tolerance and insulin resistance, as well as new criteria for the fasting plasma glucose levels used in defining diabetes-related risk (1). Advances have also been made in understanding the interaction between glycemic control and autonomic function, with new noninvasive tests of heart rate variability and baroreflex sensitivity (BRS) providing more sensitive and less invasive ways of detecting small changes in autonomic control (2). One consequence of this progress is the recognition that the relationship between glycemic control and reduced autonomic function exists even over the range of fasting glucose (FG) levels considered nondiabetic.

Lefrandt et al. (3) propose that the relationship between poor glycemic control and impaired autonomic function is attributable to the impact of high FG levels, with elevations in insulin playing a nonsignificant role. To support this, they describe several studies that find a relationship between FG and impaired autonomic function (4–6). We concur that there is substantial evidence linking poor glycemic control to poor autonomic function (7,8). However, there is some evidence supporting a stronger role for relationships between other metabolic markers (i.e., HbA1c and insulin) and impairment of autonomic function. For example, although HbA1c was

Figure 1—Relationship between baroreflex sensitivity and fasting blood glucose in 40 healthy subjects.
negatively correlated with BRS in the cohort of volunteers with normal glucose tolerance \((n = 288)\) tested in the Hoorn study, FG was not related to BRS independently of age; furthermore, fasting insulin (FI) was related to autonomic dysfunction in the newly diagnosed diabetic volunteers \((n = 95)\) (4). Similarly, although the Atherosclerosis Risk in Communities (ARIC) study \((n = 1,779)\) found that FG and FI were each inversely related to vagal control in univariate models, only FI was significantly related in a multivariate model adjusted for age, race, and sex (6). Additional studies have reported a significant correlation between corrected QT interval (QTc) dispersion and FI—but not FG—in nondiabetic volunteers (9,10). Studies in diabetic samples also have failed consistently to find a significant correlation between autonomic function and FG (11,12), but have reported a relationship between FI and subsequent development of parasympathetic neuropathy in type 2 diabetics (12,13). It has also been noted that the majority of type 1 diabetics show neither any change or worsening autonomic function under insulin treatment, even though the insulin has increased the hyperglycemia (14). Our own recent study is consistent with these observations. We found that FG and FI were each related to BRS in univariate models, but only FI was significantly related in a multivariate model adjusted for significant covariates in 162 young nondiabetic volunteers (15).

Clearly, there is a relationship between glycemic control and autonomic function, but the specific roles played by either glucose or insulin remain unclear. Elevations in insulin are present with elevated glucose in many cases of abnormal glycemic control (type 2 diabetes, impaired glucose tolerance, hyperinsulinemia, and treated type 1 diabetes), making insulin a possible contributor to autonomic dysfunction. However, we are only at the frontier of identifying how markers of metabolic control influence autonomic function, and although emerging evidence suggests a role for insulin in autonomic neuropathy, future studies are needed to examine the mechanism underlying the autonomic effects of insulin and glucose.

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Response to Decochez et al.

Autoantibody levels during the early course of type 1 diabetes

We have read with interest the article by Decochez et al. (1) concerning autoantibody levels at diagnosis and during the first years of follow-up in subjects with type 1 diabetes. In their paper, they reported that 14 of 194 subjects (~8%) clinically diagnosed with type 1 diabetes were antibody-negative (negative for islet cell antibodies [ICA], GAD65, insulin autoantibodies [IAAs], and IAA2 protein antibodies [IAA2As]) at clinical onset. However, because of seroconversion of some of those subjects who were initially negative, only 6% remained consistently negative for ICA, GADA, and IAA2 during the follow-up. They concluded that determination of autoantibodies at clinical onset could underestimate the number of subjects with autoimmune-induced type 1 diabetes. We aimed to investigate the autoantibody course from the onset of type 1 diabetes, paying particular attention to those subjects without any evidence of autoimmunity against β-cell.

Sixty-four consecutive newly diagnosed type 1 diabetic patients (23.9 ± 5.1 years old, 42 men and 22 women) were included in our study. Type 1 diabetes was diagnosed according to the National Diabetes Data Group criteria (2). The study protocol was approved by the Hospital.
Clinic i Universitari ethics committee. GADA, I2A2, and IAA were measured as previously reported (3). ICAs were determined by indirect immunofluorescence according to international workshops, with both the sensitivity and specificity being 80%. Titers were expressed as Juvenile Diabetes Foundation units (JDF U). The cut-off value for positivity was determined as the 99th percentile of antibody level obtained in 500 healthy control subjects (≥10 JDF U). In our group of newly diagnosed type 1 diabetic subjects, 12 (19%) were negative for all autoantibodies at onset (antibody−). At this time, the only difference between antibody+ and antibody− subjects, in terms of clinical data, concerned GHB, which was higher in the antibody+ group (11.7 ± 2.1 vs. 9.9 ± 2.1%, P < 0.05). After 6 and 12 months of follow-up, all of them remained consistently antibody−.

We are in complete agreement with Decochez et al. (1) in considering that to avoid underestimation of autoimmune-induced type 1 diabetes, it is necessary to perform serial antibody determinations during the follow-up of the disease. This is of increased importance for those subjects who have been diagnosed after adolescence.

It is remarkable that the proportion of antibody− subjects at onset is higher in our group of patients than in the study by Decochez et al. This may be due, at least in part, to geographical origin, as well as, antibody measurement methodology and differences in age at diagnosis (no children in our study). Most interestingly, and in contrast to their results, none of our antibody− subjects became antibody+ for any of the antibodies tested after 6 and 12 months of follow-up. It should be pointed out that our follow-up lasted only 12 months, and thus, it is still possible that some seroconversions (mainly before 24 months of follow-up in Decochez et al’s study) could occur in the future.

Among those subjects remaining consistently negative for autoimmunity, it should be considered that the presence of other unknown and noncurrently measured antibodies cannot be ruled out (4,5). On the other hand, autoantibodies may have disappeared during the prediabetic stages or may appear later on in the course of the disease. However, there would still be a proportion of patients who could be allocated in the subcategory named type 1b or idiopathic diabetes (6). Up to now, it seems that this category encompasses only a minor proportion of subjects with type 1 diabetes, mostly those with neoneuproid ancestry. Fluctuating insulinopenia, as well as an abrupt onset with additional exocrine pancreatic tissue damage, has been previously described (6–8). In light of the scarce data concerning this presumably heterogeneous and still largely unknown disorder (physiopathology, clinical course, and prognosis), the identification of subjects truly affected by type 1b diabetes represents a great clinical challenge.

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**Response to Aguilera et al.**

Autoantibody levels during the early course of type 1 diabetes

We thank Aguilera et al. (1) for their interest in our work and their comments. We agree with them that differences in age at diagnosis, geographical origin, and antibody assays may help explain the tendency toward a higher frequency of multiple antibody-negativity in their series of adult patients as compared with our study (2) (12/64 in the Spanish study vs. 14/194 in our study; P < 0.02 by Yates corrected χ2 test). In addition, one of the Belgian inclusion criteria stipulated that patients had to remain on insulin 2 years after diagnosis. This may have led to the exclusion of certain antibody-negative patients initially classified as having type 1 diabetes on clinical grounds but no longer requiring insulin.

Our observation that seroconversion to antibody-positivity or significant increase in antibody levels are by no means exceptional events after diagnosis of diabetes is in agreement with observations by other groups (3,4). However, seroconversion to antibody-positivity in subjects initially negative for all four autoantibody types tested is a relatively rare event that may not be noted in smaller patient studies. Because relatively low peak antibody levels are usually reached during late seroconversion, the antibody assays used need to achieve high diagnostic sensitivity at the cutoff point for 99% specificity, as well as state-of-the-art long-term reproducibility, to be able to pick up this phenomenon. Aguilera et al. (1) do not report the diagnostic performance of
Letters

Progressive Hypoglycemia’s Impact on Driving Simulation Performance

Occurrence, awareness, and correction

There are four aspects of Cox et al.’s (1) study on progressive hypoglycemia’s impact on driving simulation performance that concerns us. First, arterialized blood glucose values are difficult to relate to capillary values taken by patients who are about to drive. We suspect that under such circumstances, patients’ values could well be substantially lower than arterialized blood glucose values; whether the values were measured from plasma or whole blood would make a considerable difference, and we are puzzled as to which sample was used.

Our second concern regards the statistical analysis and expression of the results. It appears that no allowance has been made for repeated measures or multiple testing, and because there are >50 P values listed in the article, we suggest that those considered significant with P < 0.05 or <0.1 are less than convincing.

Third, we also find it unhelpful that the results are expressed as z scores in the absence of information about the distribution of the raw data or detail about the statistical tests applied. In the case of the driving parameters, can we be reassured that ceiling effects have not produced skewed distributions in any of the measures? For example, if in the initial drive there were few high-speed violations, then the estimated standard deviation for this measure would be small and unstable, resulting in z scores for the hypoglycemic stage that are hard to interpret and may systematically overstate true effects. The composite driving score used to classify subjects as severely impaired could be particularly vulnerable to the cumulative effect of such bias.

Finally, the article listed no information on a period effect, and we believe that a driver’s concentration, particularly on a simulator, is likely to be impaired at ~2 h after the start of the experiment compared with during the first hour, especially as the study’s subjects were required to rate eight symptoms on a seven-point scale every 5 min. Perhaps the most troublesome aspect of the study’s results is the failure of some impaired subjects to take corrective action. However, given the level of demands placed on the subjects by the data collection process, as well as scant information on how they were briefed, it is impossible to generalize this finding. Because patients are blinded to the results when using this technique, for future studies, we recommend that some should not be made hypoglycemic to act as a control group. Given the absence of a control group and the statistical problems that we have outlined, we believe that this study does not merit the concerns of patient providers or licensing authorities.

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References

Hypoglycemia Driving Research

The letter by Burden and Spiers (1) in this issue raises a concern about using arterialized plasma for blood glucose levels, because arterialized samples may not reflect capillary readings. Arterialized blood samples compared with venous blood samples, however, better reflect the ambient glucose concentration delivered to the tissue (2). Insulin infusion studies routinely (3) use arterialized blood instead of venous blood samples, because arterialized blood samples more accurately reflect capillary blood glucose readings.

In response to the concern about multiple contrasts, Table 4 in our previously published article (4) presents only a maximum of nine contrasts for any one set of related variables (e.g., EEG, steering, braking, and self-treatment variables). In the RESULTS section of our article (4), we present significant differences only with P < 0.01 because of multiple comparisons. To indicate possible trends, Table 4 includes all P levels <0.1, but it does not state that the tests with P levels >0.01 are considered significant. In other words, all comparisons with P > 0.1 are deemed not significant, but that does not necessarily mean that all other comparisons are significant. They indicate trends, which are evidenced by the corresponding significance level.

As previously mentioned (4), we used deviation z scores so that performance scores on the different driving measures, with different means and variances, would be comparable. Additionally, because the risk value is a result of a complex calculation, it would make no sense to the reader to report, for example, a mean risk midline score of 2.7 during hypoglycemia (or even a difference of 1.1 between hypoglycemia
and euglycemia). However, a risk midline deviation z score of 0.5 clearly means that during hypoglycemia the group scored 0.5 SDs above the euglycemic average.

Furthermore, Burden and Spiers ask if we can be reassured that ceiling effects have not resulted in a skewed distribution. “For example,” they clarify, “if, in the initial drive, there were few high-speed violations, then the estimated SD for this measure would be small and unstable” (1). However, the example accompanying this statement is inappropriate and thereby leads to the inaccurate speculations and conclusion made by the authors. A look at Table 4 will reveal that most variables (with the exception of “off-road”) are actually continuous, not “a few high-speed violations.” Off-road is a wide-range (0 to ~40) integer that represents the number of driving course segments in which the driver drove off-road, which, when normalized through a z score, approximates a continuous variable. Moreover, a deviation z score of a continuous variable from its baseline condition would generally have a symmetric distribution (in fact, taking a deviation z score is a standard way to normalize a variable). Lastly, it is a fundamental mistake to believe that a summary score of random variables could be “particularly vulnerable” to a bias in one variable. In fact, exactly the opposite is true: the standardized distribution of a sum of independent random variables tends to be normal according to the central limit theorem. In addition, there do not need to be many variables—computer generators of pseudorandom Gaussian numbers use only six additives to produce approximately normal distribution. In short, the technique that we used (deviation z scores initially and then a cumulative score) tends to eliminate any skewness that might have been present in the raw variables and to normalize the measures, thus ensuring that the normality assumptions of the statistical tests are met.

As our article (4) reports, drivers drove for 30 min twice, with a 30-min rest in between, not 2 hours rest as was suggested by Burden and Spiers. The effects of fatigue were investigated during the study but were not presented in the article because no fatigue effects were observed. To investigate fatigue effects, we examined the 30-min drive during euglycemia. All continuous driving variables were averaged in 5-min increments and then compared by 1 × 6 repeated measures of analysis of variance. No significant results and, most importantly, no trends were observed for any of the driving variables (all P values >0.1). We thank these authors for the opportunity to demonstrate there was no fatigue effect.

Burden and Spiers raise a concern that verbally giving a single-digit rating for symptoms seven times during each drive was too demanding. This may be equivalent to saying that it would be too demanding for diabetic drivers to carry on a conversation while driving or to self-treat while driving and talking.

Given that the 33% rate of self-treatment in this study parallels the 40% who reported they would self-treat when their actual blood glucose level was <3.3 mmol in two independent multicenter studies (5), these results seem very realistic, as we discussed in the original article. However, we do agree with Burden and Spiers’ claim that only 33% of the subjects engaged in self-treatment is quite distressing. In another study we demonstrated that self-treatment was 89% determined by experienced neurogenic and neuroglycopenic symptoms and progression of neuroglycopenia, as reflected in EEG changes, and was not a reflection of some methodological artifact (unpublished observations, D.J.C., L.A.G.-F., B.P.K., W.L.C.).

As we mentioned in our original article (4), “the direct relevance of these findings to actual driving risk is unclear,” and “these findings cannot be implied to have direct relevance to driving privileges.” However, we feel these findings do have significant generalizability, because the same driving simulator procedure has differentiated high- and low-risk groups (e.g., Alzheimer patients versus care takers, middle-aged versus senior drivers, and young drivers with versus young drivers without attention deficit/hyperactivity disorder) and experimental manipulations (e.g., placebo versus ritalin and placebo versus ethanol). Performance on the simulator also predicts future accidents among senior drivers, and, finally, reanalysis of the hypoglycemia data demonstrates that subjects with driving mishaps (crashes or tickets) during the previous 2 years performed significantly worse on the simulator while driving during hypoglycemia (unpublished observations, D.J.C., L.A.G.-F., B.P.K., W.L.C.).

As for a control group, within-subject repeated measure designs are generally more powerful than between-group comparisons because they control for intersubject variance. Instead of a control group, we used a control condition of the most conservative fashion. We always had the control condition occur first, allowing any practice effect to enhance hypoglycemic driving. This design allowed us to use deviation z scores that, as explained above, are most appropriate for this case.

Based on our experience, we would encourage future researchers to use a repeated measure design and to measure arterialized rather than venous blood, but to also use a second comparison group—a hypoglycemic no-drive condition. Such a control condition would allow the determination of whether the process and/or demand of driving interferes with awareness of hypoglycemia and its self-treatment.

To say that this research “does not merit any concern” is analogous to saying “don’t consider any research you have a difference in opinion with.” Clinical science will only progress with such dialogues when differences of opinion are actively presented, considered, and discussed. We thank Burden and Spiers for the opportunity to discuss and address these issues.

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BORIS KOVATCHEV, PHD
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Acknowledgments — This research was supported by National Institutes of Health Grants DK28288 and RR00847.

References
5. Clarke WL, Cox DJ, Gonder-Frederick LA, Kovatchev B: Hypoglycemia and the decision to drive a motor vehicle by persons with diabetes. JAMA 282:750–752, 1999
Erratum


In Table 4 of the above article, an incorrect formula was used to determine the positive predictive value (PPV) prevalence. The corrected table appears here.

<table>
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<th>Test</th>
<th>Metabolic state</th>
<th>Cutoff point</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
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*Cutoff point expressed as qualitative dipstick determination, †cutoff point expressed as millimoles per liter, ‡cutoff point expressed as percent HbA1c.