OBSERVATIONS

# Physical Activity and Competitive Sports in Children and Adolescents With Type 1 Diabetes

Nowadays, all levels of exercise, including leisure activities, recreational sports, and competitive performance, can be managed by people with type 1 diabetes (1). Because of the benefit of exercise to improve known risk factors for macrovascular disease, in particular, dyslipoproteinemia, hypertension, obesity, and reduced cardiovascular fitness, any kind of physical activity is to be recommended to individuals with diabetes (2–5). In addition to these physical aspects, regular or more intensive sporting activity improves quality of life, self-esteem, and sense of well-being in adolescents and adults with type 1 diabetes (6,7). Furthermore, as a link between physical and behavioral factors, sporting activity correlates to characteristics that are positively attached to general health and disease prevention, including reduced smoking and alcohol consumption as well as improved stress management (8). To optimize the preventive aspect of physical activity, behavioral traits that favor physical activity must be initiated and supported as early as possible in life, that is, during childhood and adolescence.

Therefore, to collect actual data on physical activity and competitive sports in children and adolescents with and without type 1 diabetes, we interviewed 142 children and adolescents with type 1 diabetes of school age (6–18 years) and 97 healthy siblings of similar age and BMI in respect to their time spent for physical activity and sports in school, in competitive sports, and in spare time using a structured questionnaire. In addition, we asked about favorite sports in spare time and about competitive sports. In the diabetes group, duration of diabetes, mean $HbA_{1c}$ over the preceding year, number of insulin injections and insulin dose as well as clinical data were documented. In the control group, age, sex, weight, height, and BMI were recorded.

Sporting habits of children and adolescents with and without diabetes did not differ in terms of time spent for sports in school or in competitive sports. Interestingly, the diabetes group reported significantly more physical activity in spare time than the control subjects (mean hours/week diabetic subjects 6.8, control subjects 4.6; $P = 0.001$). This was true for both girls and boys. As a result of this, also the total time spent with sporting activity per week was significantly higher in the diabetes group than in the control group ($P = 0.001$).

Within the diabetes group, an intensive sporting activity had little effect on diabetes control. Those diabetic subjects who regularly took part in competitive sports ($n = 44$) were physically more active in the rest of their spare time ($P = 0.006$) than those who did not compete ($n = 98$). Mean $HbA_{1c}$ and daily insulin requirements appeared to be lower in the competitive sporting group, but this effect was not significant.

However, physical activity had no adverse effect on diabetes control. When multiple linear regression analysis of variables influencing mean $HbA_{1c}$ levels was carried out, a significant correlation between BMI and $HbA_{1c}$ ($P = 0.007$, $R = 0.277$) was found. In contrast, increased sporting activity only correlated to a reduced daily insulin dose ($P = 0.0014$, $R = -0.193$) but was not related to increased or decreased $HbA_{1c}$ levels.

The selection of sporting disciplines in spare time did not differ between diabetic versus control boys (both ranking biking, soccer, and inline skating as first, second, and third, respectively) or girls (both ranking biking, inline skating, and swimming as first, second, and third, respectively). The competitive sporting disciplines in boys were clearly dominated by ball sports with >50% (soccer, basketball, handball) and followed by racket sports (tennis, table tennis). Competitive sporting disciplines in girls were distributed more widely, but flexibility sports (dancing, gymnastics), racket sports (tennis, table tennis), and ball sports (soccer, handball) were reported in diabetic and control girls without obvious difference.

In conclusion, children and adolescents with diabetes appear to spend even more time with sporting activity than their healthy siblings, especially in spare time. Diabetes does not seem to restrict children and adolescents with diabetes in their selection of specific sporting disciplines in spare time or in competition. Within the diabetes group, attending competitive sports was not associated with better or worse metabolic control, but with a generally higher level of sporting activity in spare time. Finally, this higher sporting activity in diabetic children and adolescents might be caused by either diabetes education, which motivates to a physically active lifestyle, or by a compensating social behavior, in which sports might stand as an important factor for the assimilation within the peer group (2,8).

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**Acknowledgments** — The authors gratefully acknowledge the patience and support of the families who participated in the study.

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# Diabetic Retinopathy and Risk of Blindness in Mexico

## Are we doing enough?

The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) has set present knowledge and practice for diabetic retinopathy prevention and control (1–3). The extent of diabetic retinopathy is unknown in most Latin American countries, where no studies are available. This is in spite of an increase in type 2 diabetes prevalence in countries such as Mexico (4,5) and the fact that diabetic retinopathy can be prevented in 50–80% of cases (6,7). Glycemic control is paramount to reducing the incidence and progression of diabetic retinopathy (8) and requires patient education, doctor awareness, and ample facilities to achieve excellent control.

Since 1992, we have been following a cohort of type 2 diabetic subjects ($n$ = 244) in the city of León, Guanajuato, Mexico (>1 million inhabitants). They were randomly selected at their homes in different quarters of the city. An initial 42% prevalence of diabetic retinopathy was demonstrated with 81% of cases undetected, and two subjects were already blind (9). We have reviewed the first 100 patients (62 women), regarding the incidence and 3-year progression of diabetic retinopathy (graded by the Airlie House scale modified by the Early Treatment Diabetic Retinopathy Study Group). The survey showed that 10 patients had died and 4 had changed their address; they were excluded from analyses. Mean age of the group was 54.4 ± 9.2 (1 SD) years, and mean BMI was 27 kg/m$^2$. Average duration of diabetes was 9 ± 6 years. Mean fasting blood glucose (FBG) and mean GHb were 11.2 ± 4.3 mmol/l (186 ± 72 mg/dl) and 9.04 ± 4.8%, respectively. Glycemic control was poor in 90% of cases whom had values of FBG >9.0 mmol/l (150 mg/dl). GHb was normal in only 15% of the cohort.

In 12 of 52 patients who initially did not have diabetic retinopathy, some degree of retinopathy was demonstrated or there was an incidence of 23%. Further, in 18 of 32 cases, there was progression in diabetic retinopathy (ratio: 56%). Progression was more rapid in patients who had at the outset some diabetic retinopathy (difference −0.332; 95% CI −0.543 to −0.0121; $Z$ = 2.853, $P$ = 0.004). The probability to progress to greater degrees of severity, such as proliferative forms, was also significantly higher in this group (difference −0.212; 95% CI −0.354 to −0.070; $Z$ = 2.569, $P$ = 0.010). We found a significant association between duration of type 2 diabetes and severity of diabetic retinopathy (discriminant analysis, $F$ = 13.99, $P < 0.0001$).

Our 3-year results demonstrate a progression rate 2.24 times higher than the 4-year WESDR index. The difference in incidence between our study and the WESDR might be explained in the duration of follow up. We would expect a similar incidence in diabetic retinopathy after 4 years of follow up. Further, some patients developed the most severe forms of proliferative diabetic retinopathy, which was seven times greater than in the WESDR. That we were able to measure progression to proliferative diabetic retinopathy was simply because laser photocoagulation is expensive and not widely available. Only 17 patients had this form of treatment; while in the WESDR, most patients received it (3).

In our study, diabetic patients had high FBG levels, abnormal GHb, and BMI above the recommended values. All these clinical indicators are relevant to assess the quality of care of the health system in Mexico. In spite of nationwide diabetic programs (10) to control and reduce by preventing some of the most incapacitating or life-threatening complications, these seem not to be efficient. Thus, we are not doing enough for our diabetic patients. There is sufficient evidence for preventing diabetic complications (7,11). If nothing is done, we will soon be facing a large health care problem that will have a huge impact on the quality of life and well-being of people. It is also important to other countries with problems such as ours to study and review their diabetic patients, in particular, looking for diabetic retinopathy. This might reduce future visual handicap in their populations.

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# Spontaneous Recovery of Severe Weight Loss in Diabetic Amyotrophy

Diabetic amyotrophy with severe weight loss is a spectacular syndrome. Usually, many expensive and finally futile tests are done during its long dramatic period of deterioration. No less clinically remarkable is spontaneous recovery. Dynamics of neurological changes in this syndrome have been well described, but the spectacular weight changes associated with diabetic amyotrophy are frequently not even mentioned in the relevant publications.

We have followed two women and one man who were diagnosed with diabetes at the age of 48–53 years and treated with glyburide. Their mean fasting glycemia was 7.9–11.2 mmol/l and glycohemoglobin was 5.8–8.6%. After 7–8 years of the disease, one of them suffered from background retinopathy and two had proteinuria 385–3,000 mg/24 h without elevation of serum creatinine. BMI was 26.8–31.6 kg/m$^2$.

Weight loss started without any obvious reason, lasted 24–34 months, and reached 23–28 kg. During weight loss, one of the patients was treated for several weeks with 20 U NPH insulin without any difference in diabetes control; otherwise, there were no changes in therapy. Weight loss was not accompanied by poor appetite, dyspepsia, or diarrhea. Abdominal sonograms and computed tomography scans were normal. Innumerable hematological, biochemical, and immunological tests remained normal and unchanged throughout the whole clinical course. Control of diabetes remained stable, good-to-fair.

As is typical for the syndrome, the patients developed severe weakness (mostly of the pelvic girdle) and at the nadir were wheelchair bound; the leg pains were only moderate. Symptoms of peripheral neuropathy (absent ankle and diminished knee reflexes, absent vibration sense over the toes, diminished light touch over the feet) were present and unchanged throughout the clinical course.

Spontaneous recovery from the syndrome was slow but complete. The patients first resumed walking with a cane, and later were able to move freely, even in the hills.

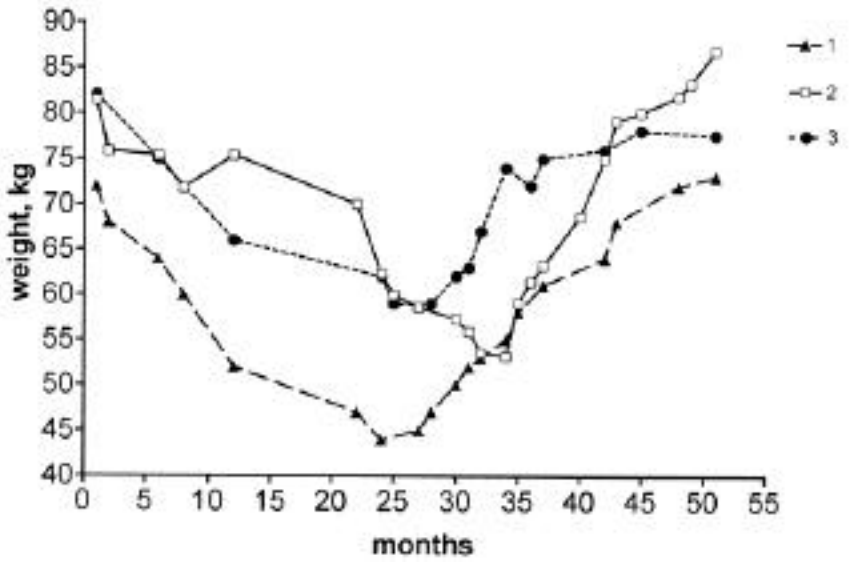


**Figure 1—***Weight changes in three patients with diabetic amyotrophy graphed from the beginning of weight loss.*

All the lost weight was slowly regained (Fig. 1). There was no recurrence of the syndrome in the following 2–16 years.

At the height of the syndrome, motor neurography (femoralis, tibialis, peroneal) showed normal distal latencies, mildly reduced or normal amplitudes, mildly decreased velocities, and mildly prolonged F-latencies with normal chronodyspersion and F-frequencies. A sensory neurography (sural nerves) showed normal or mildly prolonged distal latencies, normal or mildly reduced velocities, and reduced amplitudes. No response was elicited from either superficial peroneal nerve. These findings indicated mild sensorimotor axonal polyneuropathy and were the same at the height of the syndrome and after the regain of weight. Electromyography, however, was quite different. Marked pathologic changes seen in proximal muscles innervated by different nerves showed no correspondence with radicular or nerve distribution. At the height of the syndrome, an electromyogram of the proximal lower limb muscles (vastus medialis and lateralis, tensor fasciae latae, adductor magnus, gluteus medius) showed denervation consisting of diffuse fibrillations and positive sharp waves. A muscle units morphology consisted of normal or mildly increased amplitude and prolonged polyphasic and unstable units with reduced recruitment (which reflects early reinnervation changes). Distal muscles (tibialis anterior, gastrocnemius, peroneus longus) showed only mild denervation with moderate reinnervation changes. A test done a year later demonstrated lesser denervation potentials with much larger units, which were mostly unstable and polyphasic with reduced recruitment (progressing reinnervation). The last study, done after complete regain of weight, showed no denervation potentials and enlarged muscle units potentials, most of which were stable; recruitment was reduced, and firing rate was normal. Fibrillations virtually disappeared. These changes reflected late reinnervation and carried a good prognosis.

In this syndrome, weight loss is usually moderate (1–4), but Pascoe et al. (5) recorded in 31 of 44 patients a mean weight loss of 18 kg (though it is not clear how many of them had type 2 diabetes). However, no patients become cachectic. Trying to explain weight recovery, D'Costa et al. (6) studied four patients who had lost 10–21 kg. Three patients completely recovered and one improved while treated with pancreatic supplements and a high calorie diet. Obviously, this was not a controlled study. Krendel et al. (4) noted dramatic improvement in their patients treated with prednisone, immunoglobulin, or cyclophosphamide. However, our observations show that patients also recover spontaneously, which demonstrates the unpredictability paradox. In short, this rare syndrome gives us a chance to optimistically predict recovery from this frustrating condition. It also stresses the utmost

importance of performing controlled studies before any clinical recommendations of effective treatment are made.

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# Obesity, Microalbuminuria, Hyperinsulinemia, and Increased Plasminogen Activator Inhibitor 1 Activity Associated With Parasympathetic Neuropathy in Type 2 Diabetes

An abnormally low degree of heart-rate variation (the electrocardiographic R-R interval variation recorded during 1 min of six maximal expirations and inspirations) during deep breathing is a feature of parasympathetic neuropathy (1) that may be found in subjects with impaired glucose tolerance (2) and in type 2 diabetic patients at the time of diagnosis of diabetes (3). Recently, Töyry et al. (4) reported that the frequency of parasympathetic neuropathy increases with the duration of type 2 diabetes. This prompted us to evaluate the prevalence of parasympathetic neuropathy, including its relation to cardiovascular risk factors, in 79 type 2 diabetic patients (age 53 ± 7 years [range 40–64]) from a previous study (5) 4–5 years after the diagnosis of diabetes. The expiration-to-inspiration (E/I) ratio (age-corrected values [abnormal *Z* score] less than −1.64 SD) was used as a test of the R-R interval variation (1). Plasminogen activator inhibitor 1 (PAI-1) activity (reference values 0–16 U/ml) was measured with the Spectrolyse (Biopool, Umeå, Sweden).

Parasympathetic neuropathy, i.e., an abnormal E/I ratio, was found in 9 of 79 (12%) patients. Table 1 shows that the frequency of microalbuminuria was significantly increased in patients with parasympathetic neuropathy. Table 1 also shows that mean BMI, mean fasting plasma C-peptide, and mean PAI-1 activity were significantly higher in patients with parasympathetic neuropathy than in those without.

In our current study, the frequency of parasympathetic neuropathy was low (12%) 4–5 years after the diagnosis of type 2 diabetes; indeed, a slightly lower frequency than that (20%) reported by Töyry et al. (4). In that study, however, absolute and not age-corrected E/I ratios were used, which may explain the slight discrepancy in the frequency of parasympathetic neuropathy. We have previously shown that the E/I ratio deteriorates with time in type 2 diabetes (6). Hence, in agreement with Töyry et al. (4) and, most recently, Cohen et al. (7), parasympathetic neuropathy appears to be a progressive complication in type 2 diabetes.

There is an association between obesity and parasympathetic neuropathy in type 2 diabetes (8), as confirmed in the current study. The correlation between parasympathetic neuropathy and obesity in type 2 diabetic patients appears, therefore, to be a consistent finding.

We recently reported findings from a previous study of type 2 diabetic patients different from those reported here indicating that parasympathetic neuropathy was associated with elevated fasting C-peptide values signifying hyperinsulinemia (9). A similar association was found in the current study. In our previous study, we showed that, independent from obesity, hyperinsulinemia was related to parasympathetic neuropathy (9). Although obesity contributes to hyperinsulinemia, regression analysis in the current study also indicated that the E/I ratio, and not only BMI, was associated with hyperinsulinemia. In agreement, parasympathetic neuropathy has been associated with severe insulin resistance in type 2 diabetic patients (10).

In this study, microalbuminuria was associated with parasympathetic neuropathy. This study therefore confirms a recently found correlation between albuminuria and parasympathetic neuropathy (7). This correlation may be due to vascular endothelial dysfunction. Increased PAI-1 activity, a well-established cardiovascular risk factor, was demonstrated in our patients with parasympathetic neuropathy. Increased PAI-1 activity predicts myocardial infarction and sudden coronary death (11). Accordingly, elevated PAI-1 levels sec-

**Table 1—*Clinical and biochemical features in type 2 diabetic patients with and without parasympathetic neuropathy***

| | Patients with parasympathetic neuropathy | Patients without parasympathetic neuropathy |
|---|---|---|
| *n* | 9 | 70 |
| Microalbuminuria (<20 µg/min) | 5 (56)* | 15 (21) |
| BMI (kg/m$^2$) | 34.8 ± 6.6† | 29.1 ± 5.3 |
| Blood pressure (mmHg) | | |
| Systolic | 148 ± 14 | 142 ± 18 |
| Diastolic | 89 ± 6 | 90 ± 10 |
| $HbA_{1c}$ (%) | 7.9 ± 1.5 | 7.6 ± 1.8 |
| Fasting blood glucose (mmol/l) | 10.7 ± 2.0 | 10.9 ± 4.0 |
| Fasting plasma C-peptide (nmol/l) | 1.5 ± 0.5‡ | 1.0 ± 0.4 |
| PAI-1 (U/ml) | 36.1 ± 11.3§ | 24.3 ± 16.0 |

Data are *n* (%) or means ± SD. A difference in frequency was tested with the Fisher's test and differences between groups with the Mann-Whitney *U* test. *$P$ = 0.04, †$P$ = 0.02, ‡$P$ = 0.005, §$P$ = 0.01.

ondary to hyperinsulinemia may contribute to the bad prognosis in diabetic autonomic neuropathy.

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# Use of a Paired Value of Fasting Plasma Glucose and Glycated Hemoglobin in Predicting the Likelihood of Diabetes in a Community

We have previously reported that in Hong Kong Chinese with various risk factors for glucose intolerance, the use of paired values of fasting plasma glucose (FPG) of 6.1 mmol/l (the cutoff for impaired fasting glucose) and $HbA_{1c}$ of 6.1% (the optimal value corresponding to 2-h plasma glucose [PG] ≥11.1 mmol/l using receiver operative characteristic curve analysis) helped to identify potential diabetic subjects (1,2). For paired values above these cutoffs, the likelihood ratio (LR) that this would occur in diabetic subjects was 17.22 based on 1997 American Diabetes Association criteria using FPG alone (3), and 12.75 based on 1985 World Health Organization criteria with oral glucose tolerance test (OGTT). Subjects with FPG ≥6.1 mmol/l but <7.0 mmol/l and $HbA_{1c}$ ≥6.1% would still require OGTT to confirm diabetes, but overall savings of 82.6% of OGTT performed would nevertheless be achieved (2). These findings have been criticized in light of the fact that the study population consisted of individuals at high risk for diabetes (4). We have therefore extended the analysis, using FPG and $HbA_{1c}$ to predict diabetes, to a population-based database from a previously reported study of prevalence of diabetes in Hong Kong (5).

Among the 1,513 subjects, 27 had a known history of diabetes and were excluded from the analysis (5). Of the 1,486 subjects with no history of diabetes, 894 were men and 592 were women. Their mean age (± SD) was 37.3 ± 9.1 years (median 37.0, range 18–66). Table 1 shows the analysis of LR of glucose intolerance based on FPG and $HbA_{1c}$. Paired values of FPG ≥6.1 mmol/l and $HbA_{1c}$ ≥6.1% had 75 times increased likelihood to occur in diabetic subjects than in nondiabetic subjects. For those who had paired values of FPG <6.1 mmol/l and $HbA_{1c}$ <6.1%, the LR of having either diabetes or abnormal glucose tolerance was 0.4 and 0.7, respectively. Thus, the reliability of the use of these paired values of FPG and $HbA_{1c}$ in predicting diabetes appears to be as good in population-based samples as in those taken from high-risk subjects.

We and other researchers have emphasized the importance of 2-h PG in diagnosing diabetes in certain populations, such as Hong Kong Chinese. The omission of 2-h PG would lead to fewer subjects being diagnosed and to a sub-

**Table 1—*Analysis of LR of glucose intolerance based on FPG and $HbA_{1c}$***

| FPG (mmol/l) | $HbA_{1c}$ (%) | *n* | ADA criteria (*n*) | | | LR | |
|---|---|---|---|---|---|---|---|
| | | | Normal | IGT | Diabetes | Abnormal | Diabetes |
| ≥6.1 | ≥6.1 | 18 | 1 | 4 | 13 | 141.9 | 74.7 |
| ≥6.1 | <6.1 | 41 | 13 | 12 | 16 | 18.0 | 18.4 |
| <6.1 | ≥6.1 | 38 | 32 | 2 | 4 | 1.6 | 3.4 |
| <6.1 | <6.1 | 1,389 | 1,281 | 91 | 17 | 0.7 | 0.4 |
| | | 1,486 | 1,327 | 109 | 50 | | |

Abnormal glucose tolerance includes patients with IGT or diabetes. ADA, American Diabetes Association; IGT, impaired glucose tolerance.

stantially lower overall prevalence rate (reduced by half in our locality) (6). We believe that the idea of using paired values of FPG and $HbA_{1c}$ is very useful in identifying potential diabetic subjects. Those with high FPG and $HbA_{1c}$ values may be selected for OGTT, thus reducing the risk of missing the diagnosis in those subjects with FPG <7.0 mmol/l while minimizing the number of patients requiring a full OGTT. We believe that this diagnostic approach deserves further evaluation.

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# Painful Peripheral Diabetic Neuropathy Treated With Venlafaxine HCl Extended Release Capsules

The painful peripheral neuropathy syndrome associated with diabetes remains a perplexing problem for the patient and clinician. Despite the great number of studies on the elucidation of the pathophysiology involved (1,2) and the various recommendations for treatment (3–8), none have proved to be consistently effective. Recently, a type 2 diabetic patient with this syndrome was seen and treated with venlafaxine HCl extended release capsules (Effexor XR; Wyeth-Ayerst, CITY, STATE). His prompt relief led to the treatment of an additional 10 patients who also responded positively.

A 41-year-old man with a family history of type 2 diabetes developed mild nocturia in December of 1997. He was found to have elevated blood sugars of ~11 mmol/l and was treated with diet and glipizide (glucotrol XL; Pfizer, CITY, STATE) 10 mg/day with a good clinical response, and his $HbA_{1c}$ dropped down to 6.8%. After 7 months, he developed severe burning paresthesia from the mid-tibial region distal. The pain was so severe that he could not wear shoes. He had no relief with acetaminophen, codeine, or amitriptyline.

Venlafaxine 75 mg/day was started, and within 5 days he had a 95% relief of pain, was able to wear shoes, and asked to go back to work. After 1 week, the medicine was stopped, and within 3 days, the pain began to recur. He restarted the medication and within 3 days was pain-free. He continues to take the medication.

Because of the dramatic response cited in the above patient, venlafaxine was tried in 10 additional patients with type 2 diabetes and painful peripheral neuropathy. The patients varied from 35 to 71 years of age and had a known diabetes duration of 2–25 years. They had been treated with an oral agent or a combination of oral agents and various types of insulin. Four were male, six were female. All had been treated unsuccessfully with other medications known to alleviate the pain of diabetic peripheral neuropathy.

When venlafaxine, at a dose of 37.5–75 mg/day, was added, all patients had a 75–100% reduction in pain within 3–14 days. No side effects were seen. One patient stopped the medication after being pain-free and after 2 days had a recurrence of the pain. Venlafaxine was restarted, and the discomfort was promptly relieved.

Studies from The Diabetes Control and Complications Trial (9) and the U.K. Prospective Diabetes Study Group (10) have shown that normalization of blood glucose in diabetic patients can prevent or delay the onset of diabetic neuropathy in both type 1 and type 2 patients. Nevertheless, because control is difficult to achieve, this condition remains very common and difficult to treat.

Aldose reductase inhibitors (3), mexiletine (4), capsaicin (5), and gabapentin (6), along with tricyclic antidepressants (7) and Tegretal (8), have been recommended for treatment with varying degrees of success. The rather dramatic response of this condition to venlafaxine is reported.

Venlafaxine is an antidepressant that not only inhibits the reuptake of the neurotransmitters serotonin and norepinephrine and, weakly, dopamine, but also does not block the mucsarinic, histaminergic, and adrenergic receptors (11). These later three actions are associated with the side effects often seen with tricyclic antidepressants and can cause symptoms unacceptable to patients.

Because fluoxetine hydrochloride, a relatively pure serotonin uptake inhibitor, does not help in this pain state (7), it would seem that venlafaxine exerts its effect either through the norepinephrine or dopamine pathways. It is unlikely that the pain relief seen in these patients was due to spontaneous remissions because it recurred when medication was stopped in two patients. It is also unlikely that the relief was due to mood alterations because the relief occurred so rapidly.

This observation would suggest that venlafaxine HCl may be useful in the painful peripheral neuropathy seen in some diabetic patients.

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# Diet Therapy Improved Ketosis Without Insulin Therapy in a Case of Anti-GAD65$^+$ Diabetes

Ketosis is generally considered to be a sign of insulin deficiency, and insulin therapy is usually required for survival. It is one of the features of type 1 diabetes, although it sometimes occurs in type 2 diabetes in association with infection, debilitating illness, or starvation. Here we report a case of anti-GAD65$^+$ diabetes with ketosis, generally considered as type 1 diabetes, without apparent precipitating factors. To our surprise, diet therapy improved ketosis without insulin therapy in this case.

A 46-year-old Japanese man, who had undergone a health check every year and had been careful not to overeat or overdrink, showed a fasting plasma glucose (FPG) level in 1997 of 5.9 mmol/l. He had noticed polyuria and body weight loss (from 61 to 52 kg within 6 months) since January 1998 and thirst and general fatigue since June 1998; therefore, he presented to our hospital in July 1998. He had not had a poor condition such as infection, debilitating illness, starvation, or overdrinking. On presentation to our hospital, BMI was 18.5 kg/m$^2$, postprandial plasma glucose level was 14.3 mmol/l, $HbA_{1c}$ level was 10.7% (normal range 4.2–5.5), and urine ketone bodies were strongly positive (3+: acetoacetic acid level >80 mg/dl; repeatedly detected). Even though we recommended immediate admission to the hospital and commencement of insulin therapy because of hyperglycemia with ketosis, he refused our recommendation. Thus, we told him to return to our hospital if his symptoms worsened, and made him promise to keep to a strict diet (1,600 kcal/day). Two weeks later, ketonuria had disappeared and FPG level had decreased to 7.2 mmol/l. A month later, FPG level had further decreased to 5.9 mmol/l, although GAD65 antibody was found to be positive with a high titer (46.3 U/ml [cutoff <1.5]; 100% sensitivity and 100% specificity of the assay in GAD antibody proficiency test [Immunology of Diabetes Workshop]; Lab ID number 305) and the patient was found to have HLA DR4 and DR9, major HLA types in Japanese type 1 diabetes. No other autoantibodies, including IA-2 antibody, were detected, and no other autoimmune diseases, such as autoimmune thyroid disease, was observed. Fasting and postprandial serum C-peptide levels were 0.26 and 1.26 nmol/l, respectively, urine C-peptide level was 15.6 mmol/day, and glucagon-stimulated serum C-peptide level was 0.53 nmol/l (6 min after intravenous injection of 1 mg glucagon), indicating that ability of intrinsic insulin secretion was preserved. Six months later, he was still in a good metabolic condition (FPG 5.9 mmol/l, $HbA_{1c}$ 5.8%, fasting serum C-peptide 0.36 nmol/l), although GAD65 antibody was persistently positive (36.3 U/ml).

We would generally consider that this case should be classified as type 1 diabetes, characterized by pancreatic β-cell destruction and autoimmune reaction (1), because GAD65 antibody was persistently positive with a high titer, and he had typical symptoms such as thirst, polyuria, general fatigue, weight loss, and ketosis with hyperglycemia. Although one might argue that the positivity of GAD65 antibody in this case might be a "nonspecific" phenomenon rather than a "specific" phenomenon related to β-cell destruction, most cases with a high titer (>10 U/ml) of GAD65 antibody require insulin therapy within 5 years (2), and a case of T-cell insulitis in a patient with anti-GAD65$^+$ diabetes without ketosis has been reported (3). We therefore think that this case should be classified as type 1 diabetes in spite of the patient's nonketotic state at present. However, β-cell destruction could not be considered rapidly (or aggressively) progressive, because intrinsic insulin secretion in this case seemed to be preserved, and IA-2 antibody, which is more strongly related to β-cell destruction (4), was negative. Considering the "transient" ketotic state in this case, we speculate that β-cell dysfunction due to some cause must have existed if β-cell destruction had not occurred or progressed gradually (or transiently). In this case, ketosis occurred without apparent precipitating factors such as overdrinking, and thus β-cell dysfunction might have developed due to only a slight increase in calorie intake, and strict diet therapy might have reversed the β-cell dysfunction. We have previously proposed that β-cell mass may be better preserved than previously imagined at the onset of type 1 diabetes in mice (5) and in humans (3). The evidence that a ketotic state can be reversed without insulin therapy in type 1 diabetes with residual β-cell function supports this hypothesis.

Unlike the three cases of anti-GAD65$^+$ patients resulting in a non-insulin-dependent state that we reported previously (6), GAD65 antibodies were persistently detected in this case, and thus, we must follow this case closely because of the possibility of progression to an insulin-requiring state in the future. Even though

we have experienced this extremely rare case of anti-GAD65$^+$ diabetes with ketosis improved by only diet therapy, we are not sure whether insulin therapy is the treatment of choice for such cases. A prospective randomized study is in progress to examine whether insulin treatment really suppresses the progression to an insulin-requiring state in anti-GAD65$^+$ diabetes with residual β-cell function. Recognition of cases like this is important for the proper classification of diabetes and for understanding the pathophysiology of type 1 diabetes.

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# Homeostasis Model Assessment as a Clinical Index of Insulin Resistance

## Comparison with the minimal model analysis

Insulin resistance plays an important role in the development of type 2 diabetes and atherosclerosis. Various methods have been proposed to evaluate insulin sensitivity in vivo. The euglycemic clamp study and minimal model analysis (MINMOD) are standard tools for estimating insulin sensitivity, but the procedures are rather complex and expensive (1–3). HOMA IR (insulin resistance index assessed by homeostasis model assessment, defined as the product of fasting plasma insulin and glucose divided by 22.5) is a tool to estimate insulin sensitivity from a single sample (4). Matthews et al. (4) demonstrated that HOMA IR is closely correlated with insulin resistance index assessed by euglycemic clamp (clamp IR) in type 2 diabetic patients. But the validity of HOMA as an estimate of insulin sensitivity is to be examined in other methods and other populations. Very recently, Emoto et al. (5) demonstrated that HOMA IR highly correlated with clamp IR in diabetic subjects. They revealed log-transformed HOMA IR correlated more strongly with clamp IR than HOMA IR per se. In this study, we first applied MINMOD during a frequently sampled intravenous glucose tolerance test (FSIGT) to evaluate the validity of log-transformed HOMA IR.

We examined 70 Japanese subjects (42 subjects with normal glucose tolerance, age 20–25 years, BMI 15–38.3 kg/m$^2$; 19 with impaired glucose tolerance, age 20–47 years, BMI 17–39.3 kg/m$^2$; 9 with untreated type 2 diabetes, age 17–58 years, BMI 18.6–24.5 kg/m$^2$) to assess insulin sensitivity. They had an FSIGT performed, and the blood samples were analyzed to obtain the insulin sensitivity index ($S_I$) derived from MINMOD as previously described (6–8). The statistical analysis was performed with the StatView 5 system (Berkeley, CA).

We observed a significant correlation between HOMA IR and $S_I$ of MINMOD ($r = 0.603$, $P < 0.0001$). Because the visual inspection suggested a hyperbolic relationship between HOMA IR and MINMOD $S_I$, we analyzed the correlation of log-transformed HOMA IR with MINMOD $S_I$. Log-transformed HOMA IR correlated more strongly with MINMOD $S_I$ ($r = 0.667$, $P < 0.0001$) than HOMA IR per se. These results are in agreement with the results of clamp studies (4,5).

In conclusion, the log-transformed HOMA IR is considered as an adequate surrogate for insulin sensitivity. In large population studies, log-transformed HOMA IR can be used as an index of insulin sensitivity, comparable with $S_I$ of MINMOD.

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# Cutting the Gordian Knot

## Addition of metformin to insulin therapy in a patient with uncontrolled diabetes and schizophrenia

The task of achieving good glycemic control in patients with type 2 diabetes is often frustrating, especially when poor compliance and insulin resistance complicate treatment. We describe here a difficult patient with insulin-requiring type 2 diabetes and schizophrenia in whom the addition of metformin to her insulin therapy resulted in a remarkable improvement in glycemic control.

The patient is a 53-year-old African-American woman with a 30-year history of type 2 diabetes who had been on insulin for the past 9 years. In October of 1991, she was referred to the diabetes clinic at the University Hospital (now Boston Medical Center) from an inpatient psychiatric facility, where she was undergoing long-term treatment for schizophrenia. According to the referral note, her major metabolic problem was poor glycemic control. She was compliant with an insulin regimen of ultralente 45 U and regular 10 U every morning, but was noncompliant with her prescribed diet. Her $HbA_{1c}$ level was 7.4%, and she weighed 193 lb. She was taking clozapine, which had controlled the psychotic features of her schizophrenia for several years and was not thought to be a contributing factor to her poor glycemic control (3). At the time of her initial evaluation, it was evident that the patient was a poor historian and had little capacity to understand her disease despite repeated efforts to educate her.

With the assistance of visiting nurses and the staff at the group home in which she resided, the patient religiously monitored her blood glucose levels on a daily basis. Despite this, the period from her initial evaluation in 1991 to May of 1998 was characterized by repeated changes in her insulin dose, as well as swings in body weight and $HbA_{1c}$ levels. For instance, in 1992, her $HbA_{1c}$ increased from 5.1 to 10.1% over a 6-month period and then returned to 6.1% within 9 months, when her insulin dose was incrementally increased from 48 to 78 U. Between January 1995 and May 1998, her $HbA_{1c}$ varied between 6.5 and 11.7%, and her insulin dose (70/30 NPH/regular) between 20 and 126 U/day. Her weight increased whenever the dose of insulin was raised, and she gained a total of 33 lb during this period. An especially frustrating problem for the visiting nurses and clinic physicians during this time were intermittent episodes of hypoglycemia, which necessitated lowering her insulin dose, and long periods of persistent hyperglycemia (fasting plasma glucose >200 mg/dl) that necessitated raising it. Efforts made to adjust her diet met with little permanent success. Likewise, combination therapy with a sulfonylurea and insulin did not result in a lasting improvement in glycemic control. Because of mildly abnormal liver function tests, metformin was not added to her therapeutic regimen during this time.

In June of 1998, the patient's record showed morning finger-stick blood glucose values ranging between 214 and 354 mg/dl and predinner values between 203 and 353 mg/dl. Her weight had peaked at 238 lb. When repeated liver function tests were found to be normal in early July, metformin 500 mg t.i.d. was added to the insulin dose of 90 U/day that she had been on since April. After 3 months of metformin therapy, the patient's $HbA_{1c}$ had decreased from 8.9 to 5.7%, and her fasting blood glucose levels ranged between 70 and 148 mg/dl. Her insulin requirement had decreased by 30%, and she had lost 4 lb. At her clinic visit in October, she reported feeling a decreased desire for food and denied symptoms of hypoglycemia.

At 1 month after her October clinic visit, the patient was admitted to the Medical Intensive Care Unit at Boston Medical Center because of severe sepsis secondary to a urinary tract infection. After a 3-month hospital stay including rehabilitation, she returned to the clinic. At this time, her weight was 191 lb, the lowest it had been since 1991, and her $HbA_{1c}$ was 5.9%. A random blood glucose was 130 mg/dl. She no longer required insulin and was maintained on metformin 500 mg t.i.d. Serum creatinine levels and liver function tests were normal. She reported feeling quite well.

The addition of metformin has proven useful in patients with type 2 diabetes who require large doses of insulin to achieve good glycemic control. In the largest randomized control trial to date, Giugliano et al. (1), showed that obese poorly controlled insulin-requiring patients with type 2 diabetes could achieve excellent glycemic control and reduce their daily dose of insulin by 25% by adding metformin to their therapy. Similar results have been reported by others (2–6). The present report adds to this literature by demonstrating the utility of metformin in an extremely difficult patient in whom lack of compliance with diet and the presence of significant mental illness were complicating factors. The case was especially frustrating because the patient "wanted to do better," but could not despite a considerable effort (e.g., she monitored her blood glucose twice daily). What impressed us was that, after years of clearly documented inconsistent improvements and failures, this frustration was overcome by adding metformin to her therapy. In effect, metformin was the sword that cut the complex Gordian knot (see APPENDIX) of her care.

Mechanistic studies suggest that metformin lowers blood glucose levels by diminishing insulin resistance in the liver and, to a lesser extent, in peripheral tissues (7–9). In addition, metformin appears independently to diminish food intake (4,10). The latter effect, as well as a decreased insulin requirement, almost certainly accounts for the lesser weight gain when metformin is added to insulin in many diabetic patients. Based on these observations and the patient's statement that she "did not feel as hungry as before," we believe diminished food intake was a major factor contributing to her improvement.

In conclusion, this case illustrates that metformin can induce a dramatic improve-

ment in glycemic control in certain noncompliant patients with type 2 diabetes. In agreement with previous studies, it suggests that this can occur even without major weight loss. The patient's response to a serious illness underscores the fact that major weight loss can allow some individuals who once required large insulin doses to maintain acceptable glycemic control on oral therapy alone. Whether this improvement is sustained with continuation of metformin therapy in the absence of insulin remains to be determined.

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## APPENDIX

### The Gordian knot

In Greek legend, an intricate knot tied by Gordius, King of Phrygia (in Asia Minor), symbolized a seemingly insoluble problem (11). According to legend, Gordius was a peasant whom the Phrygians named king in response to a prophecy that their troubles would cease if they chose for this office the first man to approach the Temple of Zeus in a wagon. Gordius dedicated his wagon to the god, fastening it to a pole with a knot so artful that it defied untying.

Legends arose that the man who undid the Gordian knot would be ruler of all Asia. Alexander the Great, on his invasion of Asia, was shown the knot and found the key to untying it. According to another account, he cut the knot with his sword. "Cutting the Gordian knot" has thus come to stand for a bold solution to a complicated problem.

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# The Relationship Between Leptin and the Insulin Resistance Syndrome Is Disturbed in Type 2 Diabetic Subjects With Parasympathetic Neuropathy

Leptin, released from adipocytes (1), regulates food intake by activating receptors in the central nervous system leading to reduced food intake (2) and increased energy expenditure (3). Human obesity is associated with increased leptin, which correlates with features of the insulin resistance syndrome (4). Since leptin increases sympathetic nerve activity (5) and norepinephrine turnover (6), it is possible that the relationship between leptin and parameters of the insulin resistance syndrome is mediated by autonomic nerves. This relationship may, therefore, be compromised by concomitant autonomic neuropathy (7), which in type 2 diabetes is associated with obesity (8), hyperinsulinemia, and hypertriglyceridemia (9).

To clarify whether parasympathetic neuropathy affects the relationships between leptin and the insulin resistance syndrome, we related serum leptin measured by radioimmunoassay (Linco, St. Charles, MO) to parasympathetic nervous function and metabolic variables in 82 type 2 diabetic patients (9) (51 men) 5 years after diagnosis of diabetes. Parasympathetic nervous function was assessed by R-R interval variation, expressed as the expiration-to-inspiration (E/I) ratio during deep breathing (10). The study was approved by the Ethical Committee at the University of Lund, Sweden. Informed consent was obtained from all subjects. Differences between groups were evaluated with Mann-Whitney *U* tests. Spearman rank-sum testing was used for correlations. $P < 0.05$ was considered significant. Results are presented as means ± SD.

Serum leptin was higher in the 31 women than in the 51 men with type 2 diabetes (18.2 ± 9.1 vs. 8.6 ± 5.6 ng/ml; $P < 0001$). In women, serum leptin correlated with BMI ($r = 0.75$; $P < 0.0001$) and fasting C-peptide ($r = 0.64$; $P < 0.001$), and inversely with E/I SD ($r = -0.36$; $P < 0.05$). The relationships between serum leptin and BMI ($P < 0.0001$) and fasting C-peptide ($P < 0.001$) persisted in multiple regression analysis with serum leptin as the dependent variable, and BMI, fasting C-peptide, and E/I SD as independent variables.

Serum leptin was higher in women with ($n = 9$) than in women without ($n = 22$) parasympathetic neuropathy (24.8 ± 8.6 vs. 15.4 ± 7.9 ng/ml; $P < 0.05$). In women without parasympathetic neuropathy, serum leptin correlated with BMI ($r = 0.75$; $P < 0.001$) and fasting C-peptide ($r = 0.58$; $P < 0.01$), whereas no such correlations occurred in women with parasympathetic neuropathy.

In men, serum leptin correlated with BMI ($r = 0.63$; $P < 0.0001$), systolic ($r = 0.36$; $P < 0.05$) and diastolic ($r = 0.33$; $P < 0.05$) blood pressures, triglycerides ($r = 0.31$; $P < 0.05$), and fasting C-peptide ($r = 0.63$; $P < 0.001$), and inversely with Cr-EDTA clearance ($r = -0.56$; $P < 0.0001$). The relationships between serum leptin and BMI ($P < 0.0001$), systolic ($P < 0.01$) and diastolic ($P < 0.05$) blood pressures, fasting C-peptide ($P < 0.0001$), and Cr-EDTA clearance ($P < 0.001$) persisted in multiple regression analysis with serum leptin as the dependent variable and BMI, systolic and diastolic blood pressures, triglycerides, fasting C-peptide, and Cr-EDTA clearance as independent variables.

There were no differences in serum leptin levels between men with ($n = 15$) and without ($n = 36$) parasympathetic neuropathy. In men without parasympathetic neuropathy, serum leptin correlated directly with BMI ($r = 0.62$; $P < 0.001$), fasting C-peptide ($r = 0.69$; $P < 0.001$), and triglycerides ($r = 0.37$; $P < 0.05$), and inversely with Cr-EDTA clearance ($r = -0.54$; $P < 0.01$). Similar correlations were found in men with parasympathetic neuropathy (serum leptin vs. BMI [$r = 0.54$; $P < 0.05$], fasting C-peptide [$r = 0.56$; $P < 0.05$], and Cr-EDTA clearance [$r = -0.63$; $P < 0.05$]).

A major finding in this study is that serum leptin levels are higher in women with neuropathy than in those without neuropathy and that leptin levels correlate with the degree of neuropathy as measured by E/I SD in subjects with diabetes. Women with neuropathy also exhibited higher BMI, as well as higher glucose and C-peptide levels, than women without neuropathy. The higher leptin levels in women with parasympathetic neuropathy may reflect that the insulin resistance syndrome was more pronounced; the variables of this syndrome correlate with leptin levels (4). This conclusion is supported by the multiple regression analysis, which revealed that the correlation between leptin and the parasympathetic E/I ratio was lost after adjusting for the influence of other parameters.

Another major finding of our study is that the association between leptin and the parameters of the insulin resistance syndrome (BMI, C-peptide) was lost in type 2 diabetic women with parasympathetic neuropathy. This suggests that parasympathetic neuropathy disrupts the relationship between serum leptin and the metabolic syndrome in diabetic women. Therefore, parasympathetic neuropathy seems to be associated not only with a more marked expression of the insulin resistance syndrome (9), but also with an alteration in the relationship between this syndrome and leptin. Two possibilities might explain this finding. First, the presence of neuropathy in the parasympathetic nervous system may disrupt an action of leptin, which, through a feedback mechanism, would further increase leptin levels. Second, nerves might influence leptin release from adipocytes, and such an effect might be altered in neuropathy. Further studies are required to elucidate this.

In conclusion, our study suggests that the relationship between leptin levels and the insulin resistance syndrome in women with type 2 diabetes requires intact parasympathetic nerve function.

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# Insulin Resistance

## Does it play a role in peripheral neuropathy?

At the time of diagnosis, up to 25% of diabetic patients show evidence of peripheral neuropathy by electrodiagnostic testing (1). While neuropathy in newly diagnosed diabetic patients has been previously postulated to be secondary to the long duration of unrecognized hyperglycemia, there is clinical evidence that suggests otherwise. Studies aimed at tighter glycemic control have not shown clear and consistent benefit toward preventing the progression of diabetic neuropathy (2). Furthermore, a subset of patients who undergo pancreatic transplantation show continued progression of neuropathy despite significant improvement in their glucose utilization (3). Notably, in a study of those who underwent simultaneous kidney and pancreas transplants, obesity and fasting hyperinsulinemia were associated with impaired initial recovery of nerve conduction scores and long-term improvement in nerve amplitudes (4).

In the obese but nondiabetic state, tissue sensitivity toward insulin is greatly diminished. However, glucose homeostasis is maintained within a relatively normal range by a compensatory increase in insulin secretion. Hyperinsulinemia has been reported to cause neuropathologic changes in diabetic animals treated with excess exogenous insulin (5). Moreover, patients with insulin-secreting tumors develop generalized paresthesia and symmetrical distal weakness much like that found in diabetic patients (6). In a corresponding animal model, Dyer and Messing (7) demonstrated

neuropathologic changes in transgenic mice that developed functional insulin-secreting tumors of the pancreas that temporally coincided with the onset of hyperinsulinemia. These changes consisted of large-diameter axonal degeneration involving both motor and sensory axons.

We studied patients seen in consultation from 1996–1998 who presented initially with primary neuropathologic complaints. Those who appeared clinically to have propensity for type 2 diabetes were further investigated for elevated serum insulin levels. Among this subset of patients, eight individuals who had a fasting plasma glucose of ≤135 mg/dl and fasting insulin levels of >14 μU/ml were selected for review. Peripheral neuropathy was documented by clinical examination, nerve conduction studies, and electromyography. Moreover, quantitative sensory testing was performed using the Pressure-Specified Sensory Device (PSSD) (Sensory Management Services, Lutherville, MD). The PSSD measures the cutaneous pressure threshold for static and moving touch, as well as one- and two-point discrimination. It is a noninvasive test that can be performed in the office without pain or discomfort to the patient.

All eight patients were women. Mean age was 48.0 ± 8.9 years, ranging from 35 to 66 years of age. Mean weight and height were 97.5 ± 15.6 kg and 160 ± 8.8 cm, respectively. Mean BMI was 38.0 ± 3.8 kg/m$^2$. All eight patients had been previously diagnosed with hypertension and were on antihypertensive medication at the time of evaluation. Fasting plasma glucose and fasting plasma insulin averaged 100.5 ± 17.3 mg/dl and 39.2 ± 17.0 μU/dl, respectively. Four patients had family history of diabetes. Six patients were hypercholesterolemic, with a mean cholesterol of 233.7 ± 53.9 mg/dl. PSSD results for all eight patients demonstrated markedly abnormal cutaneous pressure threshold for one- and two-point static and moving touch in peroneal, posterior tibial, and sural nerve sensory distribution. Corresponding nerve conduction studies and electromyography confirmed these findings.

Peripheral neuropathy in our series of patients was consistent with bilaterally symmetric distal axonal loss, the pattern of neuropathy observed among diabetic patients. All patients in our series also shared a cluster of diagnoses associated with type 2 diabetes, including obesity, hypertension, family history of diabetes, and hypercholesterolemia. However, the fasting plasma glucose levels were within the normal range, whereas the fasting plasma insulin levels were markedly elevated. Thus, we suggest an association between insulin resistance, compensatory hyperinsulinemia, and peripheral neuropathy.

It must be noted that markedly elevated serum insulin levels in these individuals does not imply a causative role. In this matter, further study is warranted. However, if insulin resistance does lead to compensatory hyperinsulinism and subsequent development of peripheral neuropathy, then targeting insulin resistance in the setting of physiologic euglycemia may have a future role in retarding, or perhaps even reversing, the neuropathologic changes seen in these individuals. Based on what is already known about the recently released troglitazone and others in the class of thiazolidinediones, it would be of great interest to study whether treating insulin resistance would improve peripheral neuropathy in the hyperinsulinemic nondiabetic state.

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# Smoking Increases Serum Levels of Transforming Growth Factor-β in Diabetic Patients

Cigarette smoking is not only a cardiovascular risk factor but also increases the prevalence and progression of microvascular disorders in patients with diabetes. Several cross-sectional and clinical prospective studies have demonstrated that tobacco consumption is an independent risk factor for developing nephropathy, increasing albuminuria, and accelerating renal injury in both type 1 and type 2 diabetes (1).

Transforming growth factor-β (TGF-β) is a profibrogenic cytokine that promotes cell growth and regulates extracellular matrix production. Plasma levels of TGF-β have been reported to be elevated in patients with type 2 diabetes and diabetes complications (2). High-content glucose medium increases TGF-β mRNA and protein levels in cultured proximal tubular cells and glomerular epithelial and mesangial cells. Moreover, overexpression of TGF-β in the glomeruli and tubulointerstitium in experimental and human diabetes has been reported (3). In addition, neutralizing anti–TGF-β antibodies reduce glomerular hypertrophy and attenuate the increase of extracellular matrix mRNA levels in streptozotocin-induced diabetic mice (4). These data strongly support the hypothesis that TGF-β is an important mediator of diabetic renal hypertrophy and extracellular matrix expansion in experimental and human diabetic nephropathy.

In a recent study (5), nicotine was reported to promote TGF-β and basic fibroblastic growth factor release by bovine aortic endothelial cells. In another study (6), cigarette smoke condensate induced an increase in cell adhesion molecules in human endothelial cells through protein kinase C activation, which is a common pathway for TGF-β synthesis.

Until now, no information existed regarding the effect of smoking on TGF-β

**Table 1—*Patient characteristics and TGF-β levels***

| | Diabetic patients | | Control subjects | |
|---|---|---|---|---|
| | Smokers | Nonsmokers | Smokers | Nonsmokers |
| *n* | 8 | 8 | 9 | 10 |
| Age (years) | 34 ± 4 | 30 ± 3 | 36 ± 4 | 36 ± 7 |
| Sex (% male) | 50 | 40 | 70 | 65 |
| Diabetes duration (years) | 10 ± 5 | 12 ± 7 | — | — |
| BMI (kg/m$^2$) | 23.1 ± 1.5 | 22.3 ± 1.8 | 24.1 ± 1.7 | 24.2 ± 1.9 |
| $HbA_{1c}$ (%) | 7.0 ± 1.1 | 7.1 ± 0.9 | — | — |
| Urinary cotinine (ng/ml) | 1,427 ± 893 | 17 ± 45 | 1,218 ± 683 | 3 ± 6 |
| Urinary albumin excretion (μg/min) | 5.1 ± 3.5 | 4.1 ± 2.6 | — | — |
| TGF-β (ng/ml) | 17.9 ± 6.2* | 8.6 ± 5.1 | 3.1 ± 2.4 | 3.6 ± 1.7 |

Data are means ± SD. *$P < 0.05$ (diabetic smokers vs. other groups) by analysis of variance.

levels in diabetes. We therefore studied the serum levels of TGF-β in a group of 16 type 1 diabetic patients with normal renal function and blood pressure (8 nonsmokers and 8 smokers who smoked >15 cigarettes/day) matched for age, diabetes duration, and $HbA_{1c}$ levels. The control group consisted of 19 nondiabetic subjects (10 nonsmokers and 9 smokers). Activated TGF-β was measured via enzyme immunoassay.

In this pilot study, diabetic smokers had plasma TGF-β levels that were twice that of a comparable group of nonsmoking diabetic patients. When considering all diabetic patients, we confirmed that serum levels of TGF-β are elevated in type 1 diabetes (means ± SD 13.3 ± 7.3 vs. 3.4 ± 2.0 ng/ml, $P < 0.001$) similar to levels previously described for type 2 diabetes. No differences were found between smokers and nonsmokers in the control group, nor was any relationship observed between TGF-β plasma levels and the other variables evaluated (Table 1).

To our knowledge, this is the first study to show that smoking may be associated with a higher production of TGF-β in patients with diabetes. This effect has not been reported in nondiabetic smokers, which suggests that tobacco consumption may amplify the effect of hyperglycemia on the production of TGF-β and thus may explain the greater prevalence of microvascular complications observed in diabetic smokers.

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# Lispro in the Treatment of Insulin Allergy

A 41-year-old woman was referred to us for management of uncontrolled diabetes. The patient's blood glucose was 27.7–33.3 mmol/l at the time of consultation. Past medical history was significant for type 2 diabetes, which was diagnosed ~18 years ago and controlled on diet alone for the first 2 years. She became pregnant and required insulin, which was continued throughout the pregnancy. She had some symptoms, including hives and mild wheezing, but they were not recognized as allergic manifestations to insulin. Insulin was discontinued after delivery, which resulted in elevated blood glucose, and therefore insulin was restarted. The patient developed severe allergic reactions to insulin at that time, including both local and systemic manifestations. These allergic reactions occurred with all forms of insulin, including beef, pork, and human. In fact, she had the worst symptoms with human insulin. She was started on chlorpropamide (Diabinese; Pfizer Labs, New York), which she discontinued secondary to gastrointestinal symptoms. The patient was lost to follow-up for the next 2 years, and she stayed off all medications. When she presented again, chlorpropamide was restarted, and she was given advice to lose weight. The patient was under the care of an endocrinologist at that time. It was planned to perform an insulin desensitization procedure because of the difficulty in controlling the patient's blood glucose with oral hypoglycemics. The patient successfully underwent insulin desensitization with regular insulin, and treatment was initiated with Lente and regular insulin. She tolerated insulin for about 2 years, but later developed an allergic reaction to insulin, making her quit treatment with insulin. After that, she was tried on different sulfonylureas, metformin, repaglinide, and troglitazone without any success. When the patient was seen by us, she had developed several complications of diabetes including nephropathy, retinopathy, peripheral neuropathy, gastroparesis, and coronary artery disease. She was on hemodialysis and she was legally blind. Other medical problems included congestive heart failure, primary

hypothyroidism, and dyslipidemia. The patient's medications included glyburide (Glynase; Pharmacia and Upjohn, Kalamazoo, MI) 6 mg b.i.d., repaglinide (Prandin; Novo Nordisk, Princeton, NJ) 2 mg before each meal, troglitazone (Rezulin; Parke-Davis, Morris Plains, NJ) 600 mg, nitroglycerin patch 0.2 mg, thyroxine (Synthroid; Knoll Pharmaceuticals, Mount Olive, NJ) 100 µg, and calcium carbonate (Tums; SmithKline Beecham, Pittsburgh, PA). Physical examination revealed a blood pressure of 130/80 mmHg, a pulse at 84/min, and weight at 223 lb. The rest of the examination showed blindness, peripheral neuropathy, and bilateral pitting edema.

The relevant laboratory data for the patient is as follows: sodium 136 mmol/l, potassium 4.1 mmol/l, glucose 18.98 mmol/l, BUN 21.7 mmol/l, creatinine 406.6 pmol/l, glycosylated hemoglobin 16.6%, and serum insulin 28.8 pmol/l. Insulin antibodies to beef, pork, and human insulin were negative.

The patient was admitted to the hospital, and treatment with lispro (Humalog) was initiated. She tolerated subcutaneous lispro without any evidence of allergic reactions, and subsequently, she was started on lispro injections with each meal. Sulfonylurea and repaglinide were discontinued and patient remained on troglitazone. The patient's glycemic profile improved significantly and repeat glycosylated hemoglobin was 7.2%. The patient completed 6 months of treatment with lispro without any allergic reactions, and her sense of well-being improved dramatically.

**Discussion**

Allergic reaction to insulin has been a known complication of insulin therapy ever since exogenous insulin treatment was begun. With the introduction of recombinant human insulin, allergic reactions to insulin preparations have become rare (1). But it has been reported that diabetic patients who had allergic reactions to animal-species insulin continued to experience allergic reactions when treated with human insulin (2). This was similar in our patient, making the management of diabetes a challenge to the physician.

The insulin analog, lispro, has been developed by cross-switching two amino acids at positions B-28 and B-29. This chemical modification involves the dimerization site of the insulin molecule. Self-association and dimerization are markedly reduced, and dimers dissociate readily to their monomeric forms (3). The presence of insulin in monomer form instead of aggregated form is likely to be less antigenic and could have a beneficial effect in immunogenic complications (4,5). Therefore, it was suggested that lispro might be an option in treating patients with insulin allergy. Several case reports confirmed that the insulin analog, lispro, can be used to treat patients who have allergic reactions to any species of insulin and immunogenic insulin resistance (6–8).

Consistent with these observations, our patient also tolerated lispro without any allergic reactions. Our report adds to the existing reports that the insulin analog, lispro, is a useful option to treat patients with allergic reactions to insulin.

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R.K. has received support from Eli Lilly as part of the Lilly Lecture Bureau.

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# Fasting Serum Insulin Concentrations Are Associated With QTc Duration Independent of Serum Leptin, Percent Body Fat, and BMI

A prolonged heart rate–adjusted QT interval (corrected QT interval [QTc]) is a risk factor for sudden death in patients with myocardial infarction (1). Also, within the normal range of QTc in the general population, men with long QTc are at higher risk for coronary heart disease (2). This elevated risk has been attributed to the predominance of left sympathetic nerve activity (3) or myocardial membrane defects (4), leading to electrical instability in situations of high sympathetic activity. It is well known that both leptin (5) and insulin (6) stimulate sympathetic activity. In the present study, we measured serum leptin and insulin levels in relation to QTc in young Japanese men.

QT intervals were measured by a software program by means of an automated electrocardiogram (FCP-4266, Fukuda Denshi, Tokyo) and a differential threshold technique (7), and then QTc was calculated according to the Bazett formula (8). Insulin and leptin were assayed using commercially available kits (Pharmacia, Tokyo, and Linco Res., St. Charles, MO, respectively).

In Pearson's simple regression analysis, QTc showed positive correlations with fasting insulin ($r = 0.15$, $P = 0.02$) and leptin ($r = 0.16$, $P = 0.02$). QTc also showed positive correlations with systolic blood pressure (sBP) ($r = 0.18$, $P = 0.009$) and diastolic blood pressure (dBP) ($r = 0.21$, $P = 0.002$). Associations of QTc with BMI and fat mass ($r = 0.13$,

**Table 1—*QTc, blood pressure, and characteristics of 198 young Japanese men stratified by tertiles of fasting insulin***

| | Tertile of fasting insulin | | |
|---|---|---|---|
| | Low | Median | High |
| *n* | 59 | 63 | 76 |
| QTc (ms) | 378 ± 22 | 386 ± 27 | 390 ± 19* |
| BMI (kg/m$^2$) | 20.1 ± 1.6 | 21.3 ± 2.9 | 23.0 ± 4.7*† |
| Body fat (%) | 15.7 ± 2.9 | 18.5 ± 5.2* | 20.2 ± 7.3* |
| Fat mass (kg) | 9.4 ± 2.5 | 11.9 ± 5.0 | 14.7 ± 9.2*† |
| sBP (mmHg) | 117 ± 13 | 119 ± 11 | 125 ± 12*† |
| dBP (mmHg) | 70 ± 9 | 70 ± 8 | 73 ± 8 |
| Glucose (mmol/l) | 4.8 ± 0.4 | 4.9 ± 0.4* | 5.1 ± 0.3*† |
| Insulin (pmol/l) | 32 ± 5 | 44 ± 3* | 67 ± 23*† |
| Leptin (ng/ml) | 1.2 ± 0.5 | 1.9 ± 1.3 | 3.1 ± 4.0*† |

Data are means ± SD. *Significantly different ($P < 0.05$) vs. low tertile; †significantly different ($P < 0.05$) vs. median tertile.

$P = 0.06$ each) did not reach statistical significance.

Young Japanese men were divided into three groups according to tertiles of fasting serum insulin (Table 1). As compared with men in the low insulin tertile, men in the top tertile of fasting serum insulin concentration had longer QTc. In addition, they had higher BMI, percent body fat, and fat mass compared with those of men in a low tertile. Furthermore, they had higher sBP; they also had higher fasting plasma glucose and leptin. The results for the men in the middle insulin tertile were intermediate between the two groups. The results pertaining to the leptin tertile were similar in nature to those regarding the insulin tertiles (data not shown).

In stepwise multiple regression analysis for QTc, which included all variables shown in Table 1, dBP ($F = 9.3$, $P = 0.002$) and log(insulin) ($F = 3.7$, $P = 0.05$) emerged as predictors of QTc. The two variables explained only 6% of QTc variability. In the model excluding sBP and dBP, only log(insulin) emerged as a determinant of QTc ($F = 6.3$, $P = 0.01$).

An independent association of QTc with fasting insulin in young healthy men found in the present study may be compatible with the hypothesis that insulin-induced sympathetic activity is one of the factors contributing to QTc prolongation, because it is well known that insulin stimulates sympathetic activity (6).

QT interval prolongation has been reported to be common in obesity (9). Recently, leptin, an adipose tissue–secreted protein, has been reported to have a variety of functions, including activation of the sympathetic nervous system in addition to energy balance regulation (5). Therefore, QT prolongation in overweight people (9) may be a consequence of high serum leptin concentrations. In the present study, however, serum insulin, but not leptin, was a predictor of QTc independent of BMI and body fat.

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## COMMENTS AND RESPONSES

# Considering Psychosocial Variables in Evaluating Assessments of Glycemic Control

In a recent study examining the correspondence between $HbA_{1c}$ and fasting plasma glucose (FPG), it was concluded that biologic variations may account for the discrepancy between measures (1). We have taken a different approach to this relationship and have shown that the discrepancy between these measures may be the result of preparatory behaviors in which individuals may engage before the office visit (2). A characteristic of those patients whose FPG is lower than expected based on $HbA_{1c}$ measures is high

cognitive abilities. On the other hand, those patients, who present with elevated FPG values relative to their $HbA_{1c}$ levels, score highest on a test of depression.

Apparently, for some patients with diabetes, the office visit may provide a surmountable challenge to their ability to appear adherent. Conversely, those with elevated depression who present with elevated FPG, may be calling out for help or may be additionally distressed by the upcoming office visit. Psychosocial variables need to be considered in evaluating assessments of glycemic control acutely and over the longer term.

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# Diabetes Prevalence in Offspring of Elderly Men With Known and Newly Diagnosed Diabetes

Most studies concerning diabetes prevalence in families asked subjects about parental history of diabetes by using offspring as index individuals. Compared with nondiabetic subjects, those subjects with diabetes more often reported a history of diabetes in their parents (1,2). However, this approach is subject to various types of biases. Diabetic subjects may be more aware of the presence of diabetes in their parents, resulting in an overestimation of the risk associated with parental history. On the other hand, selective mortality of the parents may lead to an underestimation of the effect because parents in prestadia of diabetes or with undiagnosed diabetes are likely to die at a younger age. Another issue is that it has been suggested that having a father with diabetes does not substantially increase the risk of diabetes (3). We therefore used fathers as index people and assessed the prevalence of diabetes in the offspring of men who participated in the Zutphen Elderly Study (4).

In 1990, an oral glucose tolerance test was conducted, and men were classified according to the World Health Organization (WHO) criteria (4). By questionnaire, we assessed diabetes in the offspring of all men with impaired glucose tolerance ($n$ = 24), newly diagnosed type 2 diabetes ($n$ = 20), and treated type 2 diabetes ($n$ = 20) and of a random sample of men with normal glucose tolerance ($n$ = 51). Of the 325 children, questionnaires and informed consent were completed by 273 (88% of those alive). The fathers were aged 73–92 years. Mean age of the adult children was 46.4 years. The average number and the BMI of the adult children were not appreciably different according to the diabetes status of the father.

For gestational and nongestational diabetes combined, the prevalence was highest in offspring of fathers with treated type 2 diabetes (10%), followed by the offspring of men with newly diagnosed diabetes (6.4%), and diabetes prevalence was low in the offspring of men with impaired glucose tolerance (1.6%) and of men with normal glucose tolerance (1.7%). After adjustment for age and sex, the odds ratio of diabetes (gestational diabetes included) was 5.2 (95% CI 1.3–20) for those having a father with diabetes (treated or newly diagnosed). Nongestational diabetes was only reported by children of fathers with treated diabetes ($n$ = 5; including one child with type 1 diabetes), and by one child (type 1 diabetes) with a father with normal glucose tolerance.

These results indicate an excess of diabetes prevalence in the offspring of men with type 2 diabetes and support the findings that a paternal history of diabetes increases diabetes risk.

Remarkably, in the offspring of men with newly diagnosed diabetes, only the cases of gestational diabetes (a herald of type 2 diabetes [5]) were reported. This may be explained by diagnosis bias. Having a parent with diagnosed diabetes may increase the likelihood of the diagnosis of nongestational diabetes, whereas the likelihood of detection of gestational diabetes may be high, regardless of awareness of parental diabetes. This confirms that studies of clinically diagnosed diabetes should take into account the possibility that awareness of diabetes presence in family members affects the likelihood of a diagnosis.

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# Impaired Fasting Glucose and Cardiovascular Disease

In a recent issue of *Diabetes Care*, Tominaga et al. (1) addressed an important question: to what extent is impaired fasting glucose, as defined on the basis of

the American Diabetes Association Expert Committee criteria, a risk factor for cardiovascular disease? Unfortunately, their conclusions are not supported by the data. In essence, Tominaga et al. (1) report a nonsignificant odds ratio of 1.3 for death from cardiovascular disease among patients with impaired fasting glucose, relative to those patients with normal fasting glucose. However, this odds ratio is based on an extremely small sample size: 155 subjects with 832 person-years of follow-up and 3 cardiovascular disease events. Predictably, the CIs around this odds ratio are extremely wide, ranging from 0.01 to 141. Thus, their study lacked power to address this question, and both the title and conclusions are misleading. The study also lacked power to address the related issue of the risk for all-cause mortality associated with fasting glucose, relative to those with normal glucose tolerance.

As discussed by Perry and Barron in their editorial (2), impaired fasting glucose is an inherently unstable and far from homogenous entity, containing individuals with normal glucose tolerance, impaired glucose tolerance based on WHO criteria, and a significant minority with diabetes. Thus, it is likely that cardiovascular disease risk in individuals with impaired fasting glucose is higher than in individuals with normal fasting glucose and lower than in individuals with diabetes. Indeed, the limited data from the work by Tominaga et al. (1), as summarized in their Fig. 2, suggest that this is in fact the case.

In regard to the wider issue raised by this study, it is important to avoid an endless and ultimately sterile debate on the relative merits of different systems for classification and diagnosis of diabetes. Systems based on the oral glucose tolerance test and fasting glucose levels each have their attractions and limitations. However, the challenge we face is to ensure that people with abnormal glucose tolerance in the community are detected. In this context, a screening test, based on measurements of fasting glucose, combined with oral glucose tolerance test in individuals with abnormal fasting glucose concentrations may well be the best compromise between the ideal and the pragmatic.

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## Is Gastroparesis in Diabetes Cured by Gastrectomy?

We read with interest the recent letter from Bell et al. (1) reporting gastroparesis cured by gastrectomy. The authors describe a 56-year-old woman with vitiligo, hypothyroidism, and type 1 diabetes. Diabetes was diagnosed at age 41; at age 48, she developed such symptoms as early satiety, anorexia, nausea, and occasional vomiting, which were thought to be caused by diabetic gastroparesis. Because of gastric bleeding, a total gastrectomy with Roux-en-Y esophagojejunostomy was performed. In the histologic evaluation of the resected specimen, a carcinoid tumor with diffuse infiltration of the gastric mucosa and without evidence of local or distant spread was diagnosed (1).

Carcinoid tumors are thought to arise from neuroendocrine cells, which in gastric carcinoid tumors are predominantly the mucosal enterochromaffin-like cells (2). The symptoms of gastric carcinoids include anorexia, nausea, vomiting, epigastric discomfort, and diarrhea (3), very much resembling the symptoms of diabetic patients with autonomic neuropathy and gastroparesis (4). The diagnosis of gastroparesis in the patient described was based on clinical symptoms (1), but postprandial upper gastrointestinal sensations and diabetic gastroparesis are poorly correlated (5).

Risk factors for the development of autonomic neuropathy with gastroparesis in a diabetic patient are long duration of diabetes (~20 years) and poor glycemic control. The authors stated that the patient had no retinopathy (1), although gastroparesis is associated with a high frequency of other diabetic complications (6). Data on diabetic nephropathy and current $HbA_{1c}$ values in this patient would allow an estimation of diabetic complications.

Multiple small gastric carcinoids are frequently induced by reactive hypergastrinemia as a consequence of chronic atrophic autoimmune gastritis (with or without pernicious anemia), which per se may induce delayed gastric emptying (7). Vitiligo, thyroid disease, and type 1 diabetes may represent a polyglandular autoimmune syndrome (8). Finally, it is reported that hypothyroidism causes a delay in gastric emptying (9). Therefore, results of the hormone (3,8,9) and antibody (7,8) status and additional data on the histological evaluation of the stomach (2,3) in the patient described would be helpful in evaluating all the possible causes for presumed gastroparesis and in establishing a diagnosis.

Delayed gastric emptying needs to be demonstrated with radioscintigraphic emptying studies using solid or semisolid meals. Only these studies can show whether a patient has normal, delayed, or even accelerated gastric emptying (10). By indicating that gastroparesis was cured by gastrectomy, the title is misleading. Total gastrectomy alleviated the symptoms, but the cause of those symptoms remains unclear.

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## Response to Schnedl et al.

Dr. Schnedl and his colleagues make two points (1). The first is that the symptoms of gastroparesis could be mimicked by the presence of carcinoid tumor. We feel that this is an unlikely explanation because the total mass of carcinoid would be insufficient to cause these symptoms. However, because no urine 5-OH indole acetic acid levels or serum scrotonin levels were obtained at that time, we can only speculate on this point.

The second point is that this patient's diabetes was of such short duration that the diagnosis of gastroparesis is unlikely, especially because she did not have retinopathy. Unfortunately, those of us who treat patients with diabetes know this not to be the case. Severe distal symmetrical polyneuropathy accompanied by equally severe autonomic neuropathy may occur, especially in type 1 diabetes at a very early stage. Because of the short duration of diabetes, this is not accompanied by retinopathy and is most likely due to autoimmune demyelinization of the peripheral and autonomic nerves. This explanation is most likely shown in this patient, who also had hypothyroidism and vitiligo.

It is highly unlikely that her symptoms occurred from something other than gastroparesis. She had clinical evidence of neuropathy with loss of ankle jerks and vibration and pain sensation to knee level. In addition, she had loss of pain sensation to her wrists bilaterally. She had other manifestations of autonomic neuropathy, with diabetic diarrhea and orthostatic hypotension. Therefore, we are totally convinced that her symptoms of early satiety, anorexia, nausea, and vomiting of old food were due to diabetic gastroparesis: if it sounds, looks, and feels like a horse, it is unlikely to be a zebra.

Since we submitted this case report (2), another report describing favorable outcomes of gastrectomy in four patients with diabetic gastroparesis has been published (3).

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