OBSERVATIONS

Glimepiride Treatment and IGF-I in Adolescents With Type 1 Diabetes

A prospective, randomized, double-blind, placebo-controlled study

Serum IGF-I is reduced in adolescents with type 1 diabetes, and injections of IGF-I improve glycemic control (1). The fact that sulfonylureas can increase IGF-I directly and independent of insulin has not been included in standard literature (2). The first observation of a stimulatory effect on serum IGF-I was made in hypophysectomized rats (3). In in vitro experiments, glibenclamide stimulated growth of human chondrocytes via IGF-I and independent of insulin (4). Glibenclamide and glimepiride had dose-dependent stimulatory effects on IGF-I transcription and production in human liver cells (HuH7) (5).

We recruited 40 pubertal patients with type 1 diabetes of a duration of >1 year (negative for C-peptide) at Ulm (n = 20) and Bern (n = 20). They were randomly allocated at the start of treatment and each participant underwent a 6-week course of either glimepiride (one daily dose of 8.2 μmol = 4 mg; n = 20) or placebo (n = 20) in addition to the multiple injection intensive insulin therapy (Table 1). One patient receiving glimepiride was withdrawn because of viral encephalitis. The primary end point in our study had been defined as the increment of IGF-I between start of treatment and 6–8 weeks thereafter. Assuming a SD of 200 ng/ml, we estimated that in a two-sided statistical test with an α level of 0.05 and a power of 80%, sample sizes of 17 patients per group would be sufficient to attain a significant result, if a true rise in IGF-I from 300 ng/ml (5th percentile) to 500 ng/ml (50th percentile) occurred. The study protocol was approved by the local ethics committees at both centers.

At the time of allocation, both groups were not relevantly different regarding age, sex, weight, height, blood pressure, insulin dose, fasting serum glucose, hypoglycemic events, IGF-I, IGF binding protein-3 (IGFBP-3), HbA$_{1c}$, or serum lipids. No remarkable changes (Mann-Whitney U test) in IGF-I or IGFBP-3 could be observed during glimepiride treatment (Table 1). When compared with the placebo group, no differences could be found. Glimepiride did not influence weight, blood pressure, insulin dosage, fasting serum glucose, rate of hypoglycemias, HbA$_{1c}$, or serum lipids.

In adolescents with type 1 diabetes, the peripheral mode of application of insulin is likely to lead to IGF-I insufficiency, consecutively to growth hormone hypersecretion and an insulin-resistant state. In case oral sulfonylureas could effectively increase IGF-I, they could present a suitable therapeutic option because they are inexpensive, easy to administer, and do not endanger patients by hypoglycemias. An increase of IGF-I to the upper normal range would be desirable and would not likely be associated with severe side effects (6).

For safety reasons, glimepiride, which exhibited a higher stimulatory effect on IGF-I than glibenclamide (5), was given at a usual dose. We anticipated that a treatment duration of 6 weeks should be sufficient to induce a change in IGF-I. The reason why IGF-I did not increase significantly probably lies in the low serum concentrations of glimepiride (median 0.16 μmol/l) achieved with our protocol. Glimepiride levels were up to four times higher in the cell culture experiments (5). The authors consider it appropriate to suggest further studies using higher concentrations of sulfonylureas.

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Table 1—*Serum concentrations of IGF-I and IGFBP-3 in pubertal patients with type 1 diabetes receiving a 6-week course of either glimepiride (G) or placebo (P)*

	Treatment	n	Age	−7	0	+1	+7
IGF-I [ng/ml]	G	19	14.0 (11.9–16.3)	383 (85–675)	388 (117–600)	402 (110–677)	434 (124–572)
	P	20	14.3 (12.0–17.3)	377 (227–567)	385 (224–750)	379 (226–584)	380 (209–597)
IGFBP-3 [mg/l]	G	19	14.0 (11.9–16.3)	4.3 (2.2–5.9)	4.6 (2.7–5.9)	4.5 (2.6–5.3)	4.5 (2.8–6.3)
	P	20	14.3 (12.0–17.3)	4.5 (3.0–5.7)	4.7 (2.9–5.7)	4.9 (3.1–5.6)	4.6 (3.0–5.8)

Where applicable, medians and ranges are given. The patients were studied 6–8 weeks before treatment ("−7"), at the start of treatment ("0"), 1 week after ("+1"), and 6–8 weeks after start of treatment ("+7").

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Prognosis for Coronary Stenoses in Patients With Diabetes and Silent Myocardial Ischemia

Silent myocardial ischemia (SMI) is common in patients with diabetes (1–4). The prognostic value of SMI, evidenced by exercise electrocardiogram (ECG) stress test (5) and thallium 201 myocardial scintigraphy (6), as well as their association (7) in asymptomatic diabetic patients, has recently been demonstrated. About 50% of the patients with SMI exhibit angiographically normal coronary arteries (1,2). In these patients, endothelial dysfunction and abnormalities of coronary microcirculation may be involved (8). So far, the respective roles played by these functional disorders, by the demonstrated silent coronary stenoses, or by both in the poor prognosis of SMI are still unknown.

The aim of this study was to determine the prognostic value of silent coronary stenoses in patients with diabetes. We prospectively recruited 362 asymptomatic patients with diabetes, without prior myocardial infarction, with at least one additional risk factor, and with a normal resting ECG. All of them underwent a myocardial scintigraphy after an exercise or a pharmacological (dipyridamole infusion) stress test to detect SMI. The patients with SMI subsequently underwent a coronary angiography to detect coro-
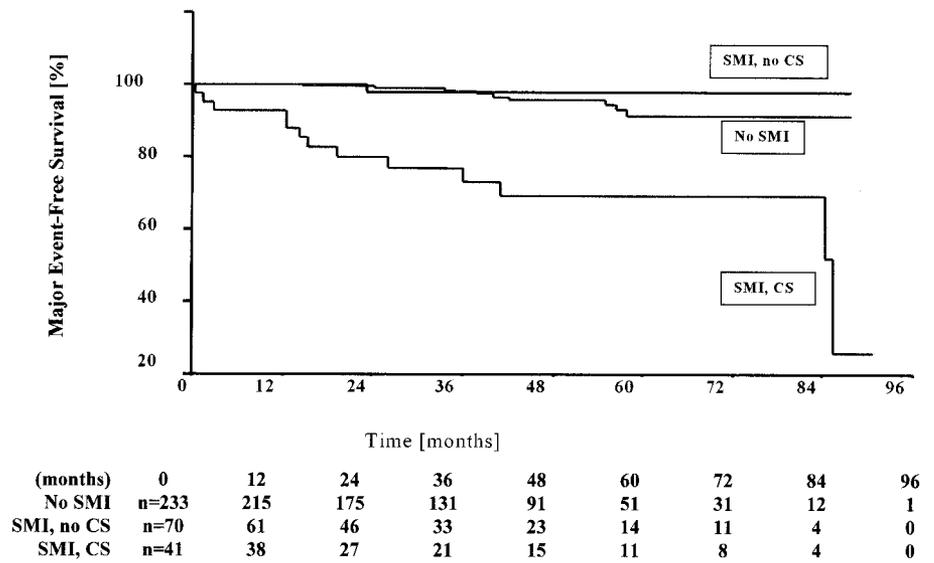
nary stenosis, as previously reported (2). A total of 345 (95.3%) patients were followed-up for 41 ± 24 months (mean ± SD) with regard to the occurrence of major cardiac events (death of cardiac origin, myocardial infarction, unstable angina, heart failure, and secondary need for coronary revascularization).

The diabetic patients (190 men and 172 women, 10 type 1 and 352 type 2 diabetes) were 58.5 ± 9.1 years of age. The prevalence of peripheral or carotid occlusive arterial disease was 6%. There was evidence of SMI in 121 (33.4%) patients. A coronary angiography was performed in 92 subjects (44 had significant coronary stenoses [>70%]). A major cardiac event occurred in 23 patients (3 cardiac deaths, 11 myocardial infarctions, 5 unstable angina, 3 congestive heart failures, and 1 noninitial revascularisation procedure). The rate of silent coronary stenoses was significantly higher in the patients with major cardiac events than in those without (13/23 [57%] vs. 29/322 [9%]), with an odds ratio of 13.1 (95% CI 5.3–32.6, $P < 0.001$). SMI (3.6 [1.5–8.5], $P = 0.003$) and peripheral or carotid occlusive arterial disease (3.8 [1.1–12.3], $P = 0.049$) were less strong predictors of major cardiac events. The traditional cardiovascular risk factors, even combined, were not predictive of major cardiac events. According to the Kaplan-Meier analysis, a major cardiac event occurred in 30.9% of the patients with SMI and coronary stenoses, 1.4% of the patients

with SMI but without coronary stenosis, and 4.0% of the patients without SMI (log rank 42.5, $P < 0.0001$) (Fig. 1).

This study shows for the first time that *1*) the presence of silent coronary stenoses with SMI is the main predictive factor for subsequent major cardiac events in diabetic patients and *2*) patients with a normal myocardial scintigraphy and those with an abnormal scintigraphy but without coronary stenosis have a close prognosis.

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Figure 1—*Kaplan-Meier survival curves for the occurrence of major cardiac events according to the absence or presence of SMI or silent coronary stenoses (CS). Log rank 42.5, $P < 0.0001$.*

(months)	0	12	24	36	48	60	72	84	96
No SMI	n=233	215	175	131	91	51	31	12	1
SMI, no CS	n=70	61	46	33	23	14	11	4	0
SMI, CS	n=41	38	27	21	15	11	8	4	0

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Long-Term Discontinuation of Insulin Treatment in a Type 1 Diabetic Patient

A case for late autoimmune diabetes of the adult?

Type 1 diabetes is a well-defined condition requiring life-saving insulin replacement therapy immediately after diagnosis (1). It is also a well-known fact from the natural course of the disease that soon after the insulin therapy has been initiated, insulin requirements decrease, sometimes rapidly, and patients who stopped taking insulin shortly after diabetes diagnosis have been reported (2). However, this so-called "honeymoon period" usually starts several weeks after the diagnosis and rarely exceeds several months' duration. It is believed, however, and has been unfortunately shown in the past, e.g., during wartime, that insulin discontinuation in a long-standing type 1 diabetic patient poses a serious threat to health and life (3,4). We describe a case of a patient with a definite diagnosis of autoimmune diabetes who, 2 years after having been diagnosed with diabetes, stopped insulin treatment for a period of 17 months and did not develop ketoacidosis.

In April 2000, a 19-year-old woman was admitted to the Metabolic Diseases Department due to profound weakness, dizziness, and increased thirst, as well as a 10-kg weight loss in 6 months. The symptoms occurred several months earlier but became more severe within the previous 8 weeks.

The patient was diagnosed with type 1 diabetes in November 1998. Her symptoms at the time gradually developed for 4 months and included increased thirst, polyuria, weight loss, and mild ketoacidosis. At the time of diagnosis, her blood glucose was 17.8 mmol/l. She was positive for islet cell autoantibodies (ICAs), with a titer of 90 JDF units, as well as positive for antibodies against GAD (anti-GAD, 80 units/ml). The treatment on discharge consisted of an intensive insulin regimen: short-acting insulin before meals and long-acting insulin twice daily; the daily requirement of insulin was 46 units.

The patient continued with her treatment for the next 2 years. She was compliant with physician recommendations, adhered to a prescribed diet, and performed self-monitoring of blood glucose four to six times daily. Her mean daily blood glucose ranged from 5.6 to 11.1 mmol/l. However, in November 2000, the patient stopped taking insulin and went on a free diet. The immediate cause of the sudden change of her behavior was a deep conflict with her parents, which eventually led to her leaving home for 13 months. During this time, she, using her words, "was well and completely forgot about her diabetes." In December 2001, she returned to her parents, although she refused to restart insulin therapy or to have a therapeutic session with a psychologist.

When she was admitted to our department in April 2002, her blood glucose was 29.8 mmol/l. It was established that she had not been taking insulin for the previous 17 months, nor had she been measuring her glucose or following any diet. Her body mass was 53 kg, height 165 cm, BMI 19.5 kg/m^2, and blood pressure 120/80 mmHg. No abnormalities in physical examination were found. Her acid-base balance was pH 7.44, serum bicarbonate 20 mmol/l, and base excess −2.8 mmol/l; she also had a trace of ketones in her urine. Her HbA$_{1c}$ was 10.6% and C-peptide 0.21 nmol/l (reference range 0.17–1.2). As at diabetes diagnosis, she was positive for ICAs and anti-GAD, although the titers of these autoantibodies were distinctly lower: 10 JDF units and 5.8 units/ml, respectively. In the beginning, she was treated with intravenous insulin infusion with a mean daily insulin requirement of ~90 units and, after 3 days, transferred to a basal-bolus insulin regimen. At discharge, she was taking 70 units of insulin daily; she was well and accepted reinitiated insulin therapy.

We present a case of a patient diagnosed with type 1 diabetes in whom long-term insulin discontinuation did not result in acute hyperglycemic crises. The diagnosis of type 1 diabetes seems to be valid, because the immunologic tests confirmed that autoimmunologic processes developed in the patient (1). However, lack of severe (or, for that matter, any clinically significant) ketoacidosis during discontinuation of insulin is somewhat surprising. The clinical course of the diabetes was typical of type 2 rather than type 1 diabetes (5). Seventeen months free of insulin therapy suggested that the patient still had residual insulin secretion sufficient to maintain effective glucose metabolism. It is particularly worth noting that autoantibody assays failed to identify that she required insulin to maintain her life. The period of not taking insulin cannot be, however, labeled a "honeymoon period" since the patient was treated with stable doses of insulin for the previous 2 years. The clinical course of the disease is probably most typical of late autoimmune diabetes of the adult

(LADA), which probably should have been diagnosed in the patient (6). LADA has recently gained considerable interest among both researchers and clinicians, probably due to increasing availability of immunological assays (7,8). However, its clinical identification is still unclear, as even the issue of insulin requirement at diagnosis is still a matter of dispute (9,10). The results of several studies indicate that LADA patients might constitute up to one-third of the alleged type 2 diabetic population (6,7,9), and the aberrant course of diabetes should always make one consider LADA as a possible diagnostic option, particularly in younger subjects (7–9).

Discontinuation of insulin treatment is not an uncommon event in diabetes therapy (11,12). HsinYu et al. (11) recently identified three predictors of ceasing insulin therapy: age >40 years at diabetes diagnosis, severe diabetic ketoacidosis as a first symptom, and excessive body weight. We have raised the issue of infection at the moment of diabetes diagnosis as another possible predictor of nonrequirement for insulin in further therapy (12). However, none of the above factors were present in our patient.

In our opinion, two conclusions can be drawn from the case. First, despite years of intensive research, pathophysiology of diabetes is still far from being clear, as even type 1 diabetes seems to be a heterogenous disease. Our patient was developing diabetic symptoms relatively slowly, and had it not been for her age and slim build, she could well have been regarded as a type 2 diabetic subject. Second, the presence of autoantibodies typical of autoimmune diabetes may not definitely lead to the diagnosis of type 1 diabetes because many patients with type 2 diabetes may also present with some features of autoimmunity. Therefore, finding clear, unequivocal criteria for differentiation between type 1 and type 2 diabetes seems to be the urgent issue of utmost importance.

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Mitochondrial tRNA$^{Leu(UUR)}$ Mutation at Position 3243 and Symptomatic Polyneuropathy in Type 2 Diabetes

In 1994, we documented a high frequency of complicated posttreatment neuropathy in patients with mitochondrial diabetes associated with tRNA$^{Leu(UUR)}$ mutation at position 3243′ (MDM3243) (1). Thereafter, experimental studies accumulated evidence that mitochondria are a major culprit in the initiation and development of complications of diabetes through oxidative stress or altered redox changes (2–4). We recently confirmed our previous observation on the association of mitochondrial DNA (mtDNA) mutation with clinical symptoms of diabetic distal polyneuropathy by conducting a large-scale study. A total of 271 Japanese patients with type 2 diabetes at Saiseikai Central Hospital were subjected and divided into two groups. Patients who had leg symptoms not only at the time of this study, but also in their history were regarded as positive and were classified into group 1. Symptomatic neuropathy was assessed by the presence of one, two, or all of the following symptoms over a previous 5-year period: numbness in the feet, pricking sensation in the feet, and deep or burning pain in the legs. Subjects without these subjective symptoms were classified into group 2. The definition of neuropathy was based on criteria for the diagnosis of diabetic polyneuropathy, proposed by the committee for discussing diabetic neuropathy in Japan (5). Detection of the 3243 mtDNA mutation was performed by integrating two methods (PCR/restriction fragment–length polymorphism [RFLP] and allele-specific PCR amplification), which improve the sensitivity of detecting the mutation in leukocytes (6). The detective threshold of finding heteroplasmy degree is as small as 0.2%. The details of this integrated methodology have been described previously (7).

In result, of 271 subjects 11 were found to have the 3243 mtDNA mutation, a frequency of 4.1%. All showed clinical differences from the syndromes of

MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes), CPEO (chronic progressive external ophthalmoplegia), and MERRF (myoclonic epilepsy associated with ragged red fibers). Among all subjects, 91 were assigned to group 1 and 180 to group 2. In group 2, two were found to have the 3243 mutation, and the frequency of finding the mutation was 1.1%. In group 1, nine were found to have the 3243 mutation, and the frequency of finding the mutation was 9.8%, which was significantly higher than that of group 2 ($P < 0.001$ by χ^2 analysis). Thus, the 3243 mtDNA mutation is frequently found among diabetic patients with symptomatic polyneuropathy (group 1). Additionally, patients of group 1 had earlier onset of diabetes and a higher frequency of retinopathy, nephropathy, and insulin therapy (data not shown here).

Oxidative stress may be the leading proposed mechanism for understanding the relation fully, because reactive oxygen species is associated with a number of pathological conditions of diabetes. Low et al. (2) hypothesized that lipid peroxidation under hyperglycemic conditions causes mtDNA mutations that increase oxygen radicals, causing further damage to mitochondrial respiratory chain, ultimately resulting in sensory neuropathy. Interestingly, the 3243 mtDNA mutation itself increases intracellular reactive oxygen species production (8), which may in turn cause secondary somatic mutations in diabetes, making a vicious cycle (9). Therefore, we speculate that in diabetic patients with high oxidative stress, when the effective mechanism for maintaining mitochondrial function is lacking, the vicious cycle of oxidative stress with increase of the 3243 mtDNA mutation may be facilitated. Furthermore, when patients have a certain amount of innate 3243 mtDNA mutation inherited from the mother, the disadvantage renders the patients all the more susceptible to oxidative stress under hyperglycemia, thereby precipitating the vicious cycle and producing symptomatic neuropathy.

The frequency of finding the 3243 mtDNA mutation in this study was 4.1% in total. This frequency is higher than the reported data of other researchers in Japanese subjects (6,10). One reason for this is because Saiseikai Central Hospital is the Diabetes Centers where patients with complications are likely to be referred to from local clinics, thus the hospital bias may have increased the frequency of finding the 3243 mtDNA mutation. The second plausible reason is that in this study, the detective threshold of finding heteroplasmy degree for the 3243 mtDNA mutation is more sensitive than that of other researchers, where the detected threshold is ~1% (6,10). This highly sensitive methodology (7) decreases the number of overlooked patients carrying a very small degree of heteroplasmy, which in turn leads to the increased frequency of finding the mutation.

In conclusion, sensory neuropathy in diabetes is associated with the 3243 mtDNA mutation. This result of human study supports the recent evidence of experimental studies (2,3). However, further studies are needed to reveal the association of sensory neuropathy with more varieties of mitochondrial DNA abnormalities than the 3243 mutation.

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Glucose Response to Intense Aerobic Exercise in Type 1 Diabetes

Maintenance of near euglycemia despite a drastic decrease in insulin dose

In patients with type 1 diabetes, hypoglycemia or degradation in blood glucose control may occur during and after physical exercise (1–3). This may be avoided in patients with good glycemic

control by decreasing insulin doses and/or ingesting carbohydrate. Although most sport activities involve intense muscle exercise, current recommendations are based on studies on moderate exercise (4). We therefore investigated the effect of a drastic reduction in insulin dose before a 60-min high-intensity cycle exercise in 12 subjects with uncomplicated type 1 diabetes (age 32 ± 7 years, BMI 23 ± 7 kg/m^2, HbA$_{1c}$ $7.2 \pm 3.8\%$, and $V_{O_{2max}}$ 40 ± 27 ml $\cdot$ min^{-1} $\cdot$ kg^{-1} [mean $\pm$ SD]). Six patients were treated with three daily injections (regular insulin in the morning and at noon and mixed regular NPH insulin before dinner). The six remaining patients were treated with two daily injections (30% regular/70% NPH insulin). After determination of $V_{O_{2max}}$, patients reported to the laboratory on two separate occasions, 1 week apart, in randomized order 90 min after breakfast (60 g carbohydrates, 10 g lipids, and 8 g proteins) to perform a 60-min exercise session on an ergocycle at 70% $V_{O_{2max}}$. On one occasion, exercise was performed with the usual morning insulin dose. On the other, morning insulin dose was reduced by 90% for patients treated with three daily injections and by 50% for patients treated with two injections per day. Power output was monitored and strictly maintained during the tests to correspond to ~70% $V_{O_{2max}}$.

Changes in plasma glucose (PG) levels were analyzed by a mixed-model AN-COVA, with a random subject effect and random coefficients for time within each subject, using the SAS version 6.12 software package (SAS Institute, Cary, NC).

At the beginning of exercise and over the test period, PG levels were higher in the experimental condition with insulin dose reduction ($P < 0.0001$) (Fig. 1). Changes in PG levels were similar in both conditions during exercise and recovery

($P = 0.99$). No difference was observed when considering insulin regimen. During exercise, the mean decrease in PG concentrations was -0.085 ± 0.012 mmol $\cdot$ l^{-1} $\cdot$ min^{-1} (mean $\pm$ SE) ($P < 0.0001$), whereas no significant variation was observed during the recovery period. When exercise was performed without reducing insulin doses, eight patients (66%) had hypoglycemia and were given oral sucrose (22 ± 3 g). Changes in plasma lactate, growth hormone, cortisol, glucagon, and norepinephrine were not statistically different. The peak of plasma epinephrine concentration was higher in the test without insulin reduction: 2.3 ± 1.5 vs. 1.1 ± 0.7 nmol/l ($P < 0.04$, Student's t test).

In previous studies, decreasing insulin dose before moderate exercise (~55% $V_{O_{2max}}$) was not associated with degradation in blood glucose control during and after exercise (1,4,5). However, most sport activities, whether individual (running, biking, hiking, and swimming) or team (basketball, football, and handball) involve intense muscle exercise. We show here that a 90% reduction of morning regular insulin before intense exercise allows the maintenance of near normal blood glucose levels without occurrence of hypoglycemia. When insulin was not reduced, two-thirds of patients experienced hypoglycemia.

This study emphasizes the importance of insulin-independent contraction-induced glucose uptake by muscle, previously demonstrated in healthy men (6) and mice lacking muscle insulin receptor (rev. in 7).

In conclusion, we demonstrate that type 1 diabetic patients can perform intense muscle exercise after a 50–90% reduction in insulin dose, depending on their insulin regimen. This decrease pre-

vents hypoglycemia without worsening metabolic control. Such advice could be given to young type 1 diabetic patients engaged in sports activities.

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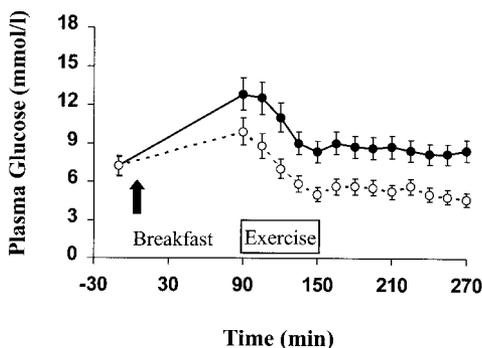**Figure 1**—*Changes in PG levels during exercise and recovery performed with (■) and without (□) insulin reduction. Of 12 patients, 8 received oral glucose during the condition without insulin reduction. Data are expressed as mean ± SE (n = 12).*

Multiple Cranial Mononeuropathies With Acetylcholine Receptor Antibody in Mitochondrial Diabetes

In 1997, we reported the first identified case of mitochondrial diabetes caused by a T-to-C transition at position 3264 (1). The patient had type 2 diabetes, lipoma, facial palsy, ophthalmoplegia, and hearing loss. His unique profile suggests the heterogeneity of mitochondrial (mt)DNA-related diabetes. Among the characteristics, bilateral facial palsy and ophthalmoplegia (right eye) were noteworthy because they have not been reported in mitochondrial diabetes associated with other pathogenetic mutations. At age 59 years, facial palsy appeared first on the right side and 6 months later on the left side. It occurred without pain and became persistent. At age 64 years, ophthalmoplegia occurred with transient ocular pain with ptosis and pupillary sparing. Interestingly, during the follow-up we observed that serum acetylcholine receptor antibody was positive at age 65 years (0.6 nmol/l; the titer is considered to be positive at >0.2 nmol/l, which is 2 SD above the mean of 170 normal control subjects). Edrophonium chloride (Tensilon) test was negative. Repetitive nerve stimulation was negative, and GAD antibody was negative.

Disordered autoimmunity such as islet cell antibody (ICA) and GAD antibody has been described in several case reports of mitochondrial diabetes or MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes) (2–4). As for acetylcholine receptor antibody, it has been reported in two elderly women with external ophthalmoplegia; one of the two women had diabetes (5). Because ragged-red fibers and elevated lactic acid were observed in the patients, Mitsikostas et al. pointed out that ophthalmoplegia and acetylcholine receptor antibody are correlated with mitochondrial myopathies. Therefore, in this case, the association of cranial nerve palsies and positive acetylcholine receptor antibody may not be a fortuitous coincidence. It was speculated that mitochondrial DNA abnormality causes not only diabetes but also the immune destruction associated with acetylcholine receptor antibody, which develops bilateral facial nerve palsy and ophthalmoplegia.

However, as for ophthalmoplegia, this patient's condition was complicated with ocular pain at onset and did not respond to the tensilon test. Because pain is not a manifestation of myasthenia gravis, vascular factors may be involved, overlapping on the pathogenesis of autoimmune factor. Since the report of Asbury et al. (6) in 1970, the etiology to understand ophthalmoplegia in diabetes has been hypothesized to result from diabetic microvascular injury involving small vessels that supply nerves. This patient had strongly succinate dehydrogenase reactive vessels that contained proliferation of abnormal mitochondria in the smooth muscle cells (1). Therefore, the ophthalmoplegia might be triggered by vascular events associated with a proliferation of abnormal mitochondria in vascular smooth muscle cells. Thus, this case suggests that cranial mononeuropathies in diabetes could possibly be caused by the synergistic effects of mitochondrial genetic abnormality, disordered autoimmunity, and/or microvascular abnormality.

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Photography or Ophthalmoscopy for Detection of Diabetic Retinopathy?

The U.K. National Screening Committee recommended digital fundus photography as the screening method of choice for diabetic retinopathy (DR). However, concerns have been expressed about replacing ophthalmoscopy with slit-lamp biomicroscopy by digital photography. These concerns included the possibility of missing peripheral and stereoscopic visible retinal lesions; increased chance of a technical failure compared with ophthalmoscopy, resulting in more reexaminations; and higher cost (1). New data from our study of 453 patients with diabetes, aged 31–86 years, highlight the need for a careful consideration of the retinal area photographed and the minimal resolution of images to detect DR.

We compared nonstereoscopic two-field 45° digital fundus photography after pharmacological mydriasis with indirect ophthalmoscopy and slit-lamp biomicroscopy performed by an ophthalmologically trained physician for the

detection of any DR. The photographs were made with a Canon CR5 nonmydriatic camera, interfaced to a 3-CCD color video camera (resolution 785 × 576 pixels). They were digitized, compressed (10:1 JPEG), and independently analyzed by the ophthalmologically trained physician and an ophthalmologist with a 17-inch monitor using Adobe Photoshop. In cases of disagreement, the judgement of another ophthalmologist was decisive. DR was detected by ophthalmoscopy in 16% of 442 right eyes that had both ophthalmoscopy and any gradable photography, as well as by photography in 8%. The agreement was moderate (κ statistic 0.54 ± 0.06) due to a sensitivity for detection of DR by photography of 44% compared with ophthalmoscopy. One reason for this low sensitivity could be that the resolution of the digital photographs was too low to detect small retinal lesions; 68% of the eyes with retinopathy missed by digital photography had only microaneurysms, small dot hemorrhages, or hard exudates in the area of both photographic fields. This is expected to become less of a problem because digital resolution improves rapidly in new cameras. However, the other reason for the low sensitivity of fundus photography was that retinal lesions were located outside the two photographic fields in 17% of the eyes with DR discovered by ophthalmoscopy.

This study focused on comparison of detecting any DR, since, except for two eyes treated with photocoagulation, only eyes with minimal and moderate nonproliferative retinopathy were detected. The U.K. Prospective Diabetes Study showed that microaneurysms alone are predictive for worsening retinopathy after 3–12 years (2). Therefore, it may be important to also detect small lesions, since these may be the first signs that blood glucose or blood pressure control needs to be reevaluated or possibly intensified. Furthermore, detection of any retinopathy instead of no retinopathy might indicate other reexamination intervals, while less sensitive detection methods could give patients false reassurance that their microvascular status is in good condition.

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Health-Related Quality of Life in Patients With Newly Diagnosed Type 1 Diabetes

Having type 1 diabetes will permanently change a patient's life. From the moment of diagnosis, patients will have to consider their diet, insulin therapy, exercise, and self-monitoring of blood glucose every day. This will influence a patient's health-related quality of life (1).

The aim of this study was to investigate the health-related quality of life of patients with newly diagnosed type 1 diabetes in the first year after diagnosis and to compare their health-related quality of life, 1 year after diagnosis, with people of comparable age from the general population.

Health-related quality of life was assessed using the RAND-36 (2). The RAND-36 is an instrument containing eight different life domains, from which a physical component summary (PCS) and a mental component summary (MCS) can be calculated. Wilcoxon's signed-rank tests were used to compare scores at baseline with scores at 1 year and to compare scores between populations.

We studied 15 patients (5 men and 10 women) with newly diagnosed type 1 diabetes aged 29.2 ± 12.0 years (range 14–54; mean ± SD). HbA$_{1c}$ levels declined significantly after 1 year (14.3 vs. 6.9%, $P = 0.001$).

The PCS showed a statistically significant improvement in the first year after diagnosis from 48.8 ± 7.3 to 54.4 ± 3.4 ($P = 0.004$). The MCS increased but did not show a statistically significant increase 1 year after diagnosis (47.1 ± 12.5 to 50.8 ± 11.5, $P = 0.173$).

After 1 year, health-related quality of life was comparable with that of subjects in the general population (PCS 52.8 ± 1.8, $P = 0.053$; MCS 50.7 ± 1.5, $P = 0.570$).

Although health-related quality of life is initially decreased when the diagnosis of type 1 diabetes is made, the impact of all the cumbersome aspects of the disease appears to be minimal 1 year after diagnosis. Therapy and self-management are apparently accepted and incorporated fairly quickly into daily life, at least in the first year after diagnosis. Although the number of patients included in this study is not large, we nevertheless found statistically significant changes in health-related quality of life over time.

We can conclude that health-related quality of life, physical health-related quality of life in particular, improves in patients with newly diagnosed type 1 diabetes within the first year after diagnosis. One year after diagnosis, health-related quality of life is comparable with that of subjects from the general population.

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Performance of Serum Cystatin-C Versus Serum Creatinine in Subjects With Type 1 Diabetes

Glomerular filtration rate (GFR) is considered the best marker of renal function, and its estimation using inulin or ^{51}Cr-EDTA is considered the "gold standard." Such determination is inconvenient and often replaced by an estimate of creatinine clearance (CrCl) derived from the formula of Cockroft and Gault (CG). Serum cystatin-C was recently proposed as a reliable alternative routine marker of GFR in pediatric, adult, and elderly subjects (1–4). Although Dharnidharka et al. (5) thouroughly review the issue of comparing cystatin-C and creatinine in relation to reference GFR measurements, few reports deal with the comparison of serum creatinine and cystatin-C in diabetic patients (5–9). Odozze et al. (6) suggested that serum cystatin was not superior to creatinine for estimating GFR in type 1 and type 2 diabetic patients with early renal impairment, while others clearly hint toward cystatin-C measurement being a more sensitive and specific GFR marker in type 2 diabetic subjects with normal or slightly reduced GFRs (5–8). Mussap et al. (9) found that cystatin-C was more accurate than creatinine in discriminating diabetic subjects according to ^{51}Cr-EDTA GFR.

In the November 2002 issue of *Diabetes Care*, Tan et al. (10) reported the clinical usefulness of cystatin-C for GFR estimation in subjects with type 1 diabetes using iohexol clearance as the "gold standard" GFR measurement and discriminant ratio (DR) methodology (10,

11). Using the same DR approach (11), we assessed, from intra- and intersubject variability, the performance of cystatin-C (particle-enhanced immunonephelometric method, N Latex Cystatin-C; Dade Behring) in 46 subjects with type 1 diabetes spanning a wide range of kidney function, as compared with that of serum creatinine (8). Age and diabetes duration were 45 ± 16 and 18 ± 12 years, respectively, BMI 24 ± 3 kg/m^2, and HbA$_{1c}$ 8.7 ± 1.5%. Median CrCl estimated by the CG formula was 92 ml/min (range: 15–149; 25–75th percentile: 81–110), adjusted to a body surface area of 1.73 m^2, with normo- (CG 70–120 ml/min), hyper- (CG >120), and hypofiltration (CG <70) present in 63, 20, and 17%, respectively. Serum creatinine levels were 1.01 ± 0.73 and 1.02 ± 1.00 mg/dl and cystatin-C 1.00 ± 0.67 and 0.98 ± 0.73 mg/l on days 1 and 2, respectively. A close linear relationship was observed between means of duplicates for creatinine and cystatin-C (Pearson product-moment correlation 0.97). The DR (ratio of the underlying between-subject to within-subject SD) was 3.92 for creatinine and 9.09 for cystatin-C ($P < 0.0001$), implying superior discriminating ability for cystatin-C. Once adjusted for attenuation, measured Pearson product-moment correlation increased to 1.00. The unbiased linear regression equation between methods had a slope of 0.83 and an intercept at 0.16. We conclude that serum cystatin-C better discriminates among a population of type 1 diabetic patients with regard to their estimated GFR, as compared with conventional serum creatinine measurement, and recommend its routine use for estimating kidney function in this population.

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Both Continuous Subcutaneous Insulin Infusion and a Multiple Daily Insulin Injection Regimen With Glargine as Basal Insulin Are Equally Better Than Traditional Multiple Daily Insulin Injection Treatment

Diabetes Control and Complications Trial results showed that strict metabolic control may substantially reduce the risk of long-term microvascular complications (1). Over the study period, which averaged 7 years, the mean HbA_{1c} level in the intensive group treatment was 7.2%. Current guidelines of treatment for type 1 diabetes propose a goal of HbA_{1c} <7% (2). Nevertheless, in usual clinical practice, an acceptable metabolic control is achieved in a too low proportion of patients, even under multiple daily insulin injections (MDIs) (3). A recent meta-analysis of randomized trials concluded that continuous subcutaneous insulin infusion (CSII) permits a small improvement in blood glucose control with respect to MDIs (4). Glargine insulin is a human insulin analog that might mimic the effects of CSII at single basal infusion rate. Preliminary studies indicate that glargine may reduce the incidence of hypoglycemia and fasting blood glucose compared with NPH (5).

Whether an MDI treatment with glargine as long-acting insulin may offer similar results to those obtained with CSII is still unknown (6). For this purpose, we evaluated, in an open parallel group trial of 1-year duration involving 32 type 1 diabetic patients that had been treated with MDIs (regular or lispro insulin before each meal plus NPH as basal insulin) for at least 1 year, the efficacy of two regimens of intensive insulin treatment: CSII versus MDIs with lispro at each meal plus glargine as basal insulin. These patients were selected because of poor metabolic control (HbA_{1c} >8% in the previous year) despite MDI treatment. Two patients in both groups had a history of severe hypoglycemic episodes. Data are expressed as mean ± SD.

Sixteen type 1 diabetic patients (age 37.7 ± 11.2 years, 8 men, 8 women, duration of diabetes 19.6 ± 9.2 years) were treated with CSII, receiving lispro at multiple basal infusion rates plus boluses at meals, for a 1-year period (CSII group).

Sixteen type 1 diabetic patients (age 42.9 ± 15.6 years, 7 men, 9 women, duration of diabetes 14.7 ± 11.1 year) were treated with MDIs with lispro at each meal combined with glargine injected at dinner or at bedtime, for a 1-year period (glargine group).

In all patients, HbA_{1c}, fasting blood glucose, total cholesterol, HDL cholesterol, triglycerides, uric acid, insulin requirement, and severe hypoglycemic episodes (i.e., hypoglycemic event requiring assistance from another person or resulting in a seizure or coma) were evaluated every 3 months during the year before the study and during active treatment. We compared the mean ± SD of these parameters for the year preceding the study with those of active treatment (CSII or glargine) using the Student's *t* test for paired data.

In the CSII group, compared with traditional MDI treatment, there was a significant decrease of HbA_{1c} (9.2 ± 1.6% during traditional MDI vs. 8.2 ± 1.2% during CSII, *P* < 0.001), fasting plasma glucose (11.9 ± 3.5 vs. 8.1 ± 2.8 mmol/l, *P* < 0.001), triglycerides (100.9 ± 41.6 vs. 85.5 ± 41.4 mg/dl, *P* < 0.05), severe hypoglycemic episodes (0.37 vs. 0.12 per patient/year, *P* < 0.05), and insulin requirement (50.4 ± 18 vs. 40.1 ± 13.1 units/day, *P* < 0.001). In the glargine group, compared with traditional MDI treatment, there was a significant decrease of HbA_{1c} (8.5 ± 1.3 vs. 7.9 ± 1.2%, *P* < 0.001), fasting plasma glucose (12.3 ± 3.9 vs. 10.5 ± 3.1 mmol/l, *P* < 0.001), triglycerides (90.6 ± 50.8 vs. 77.0 ± 39.3 mg/dl, *P* < 0.05), and severe hypoglycemic episodes (0.43 vs. 0.18 episodes per patient/year, *P* < 0.05). Insulin dose was unmodified (44.0 ± 11.1 vs. 43.1 ± 11.1 units/day, NS). There was no significant change in BMI in either the CSII (24.7 ± 4.2 vs. 24.6 ± 4 kg/m^2) or glargine group (22.8 ± 2.9 vs. 22.9 ± 3 kg/m^2).

We compared the responses to CSII and MDI with glargine by analyzing (using a nonpaired *t* test) the differences between measured variables before and after the two treatments. No significant difference between the two groups was present in the degree of improvement of HbA_{1c}, fasting plasma glucose, triglycerides, or severe hypoglycemic episodes. Only insulin requirement reduction was significantly greater in the CSII than in the glargine group (−10.3 ± 3.3 vs. −0.9 ± 0.3 units/day, respectively, *P* < 0.001).

The number of severe hypoglycemic episodes decreased both during pump treatment and during lispro plus glargine treatment, confirming the results of previous controlled trials (4). These findings are probably related to the lower variability in subcutaneous insulin absorption during CSII and to the unique profile of glargine biological action (5).

In our study, CSII was not associated with an increase in body weight. The presence of a dietitian specifically dedicated to this patient group may have helped to avoid this adverse effect of CSII (7).

In conclusion, we demonstrated that both CSII and MDIs with lispro plus glargine equally improve metabolic control and reduce severe hypoglycemia in type 1 diabetic patients that are unsatisfactorily controlled on MDIs using NPH as basal insulin.

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A Comparison of Basal Insulin Delivery

Continuous subcutaneous insulin infusion versus glargine

Continuous subcutaneous insulin infusion (CSII) is believed to more closely mimic pancreatic function and therefore to create more stability in blood glucose than multiple daily insulin injections (MDIs). One of the unique features of CSII is the ability to preprogram changes in basal insulin delivery. This feature is especially useful during the night when insulin pharmacokinetics and the dawn phenomenon may change basal insulin requirements (1). Glargine is an insulin analog designed to mimic endogenous insulin secretion patterns and has been proposed as a longer-acting, peakless insulin that can be administered once a day, usually at bedtime (2). In the present study, glargine was compared, during nighttime hours, with preprogrammed rates of lispro delivery in patients using CSII.

A sample of 19 patients, already scheduled for continuous glucose monitoring system (CGMS; Medtronic Mini-Med, Northridge, CA) evaluation, were included in the study. CGMS data were compared between 11 subjects on CSII (lispro) and 8 subjects on MDIs (lipro and glargine) and were evaluated during the overnight period. Age (46.4 ± 10.5 vs. 40.4 ± 10.0 years), duration of diabetes (9.6 ± 5.3 vs. 15.5 ± 8.7 years), and HbA$_{1c}$ (7.3 ± 0.6 vs. 7.1 ± 1.0%) were similar between the groups.

Significant differences in nighttime glucose control were identified as a function of type of therapy. Subjects treated with glargine spent significantly more time outside target sensor glucose ranges (70–200 mg/dl) than subjects treated with CSII (50.7 vs. 20.9%, $P = 0.04$). Specifically, subjects treated with glargine experienced a threefold increase in time exposed to glucose values <70 mg/dl when compared with subjects treated with CSII (34.7 vs. 12.8%, $P = 0.03$). Subjects treated with glargine spent twice the amount of time exposed to glucose values >200 mg/dl (16.0 vs. 8.1%, $P =$ NS). The average hourly basal insulin rate was significantly greater in subjects treated with glargine than subjects treated with CSII (0.8 ± 0.4 vs. 0.5 ± 0.3 units · kg^{-1} · h^{-1}, $P = 0.002$). The mean number of nocturnal basal rate settings used by the CSII group was 2.4 ± 0.7; changes in basal rate are not possible with glargine.

These results highlight the challenges in developing a basal insulin that works as effectively as CSII therapy. Statistically equivalent baseline HbA$_{1c}$ between the two groups reflected a balance between the time spent with glucose values >200 mg/dl and <70 mg/dl in the glargine group and time spent within target sensor glucose values in the CSII group. Lepore et al. (3) report that "an ideal basal insulin candidate is a peakless, long-lasting preparation that mimics the flat interprandial insulin secretion of nondiabetic subjects, with reproducible subcutaneous absorption." According to the ideal basal insulin requirements suggested by Lepore et al., glargine appears to be superior to other intermittent, or long-acting, insulins such as NPH, lente, and ultralente. However, our results suggest that while glargine may most closely meet the criteria set by Lepore et al., the ideal basal insulin must also be delivered at a variable rate to satisfy changing daily insulin requirements. CSII is the only current means of achieving this variable rate.

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Thalidomide-Associated Hyperglycemia and Diabetes

Case report and review of literature

A 70-year-old patient with refractory multiple myeloma, renal failure, and colon cancer was admitted with severe hyperglycemia (612 mg/dl). During the previous 3 weeks he had developed polyuria, polydipsia, fatigue, and a 2-kg weight loss. He had no personal or family history of diabetes. He had developed stress-related hyperglycemia during hospitalization for colon cancer surgery 4 years earlier. He was treated with insulin in the hospital and discharged on medical nutrition therapy. He was diagnosed with multiple myeloma 3 months later and was treated with chemotherapy and steroids for 12 months. His plasma glucose levels ranged from 98 to 114 mg/dl during this period. He was not treated with glucocorticoids or antidiabetic agents for the next 3 years, and during this period plasma glucose values were <125 mg/dl. Four weeks prior to this hospitalization, thalidomide 400 mg/day was started for treatment of refractory multiple myeloma. Physical examination revealed an afebrile thin patient (BMI 21 kg/m^2), and no precipitating factors for diabetic ketoacidosis

were identified. Laboratory investigations showed no acidosis, ketonuria, or leukocytosis. A1C was elevated at 9.9%. He received 10 units of regular insulin subcutaneously on admission. His subsequent capillary blood glucose values (with corresponding insulin doses in parentheses) were 512 (10 units), 247 (2 units), 282 (4 units), 126 (0 units), and 94 mg/dl (0 units). He received a total of 26 units of regular insulin over a period of 36 h. He refused insulin therapy on a long-term basis and was treated with glipizide GITS 5 mg/day. Three weeks later his symptoms were resolved. His fasting plasma glucose values 4, 8, 12, and 16 weeks after admission were 83, 151, 141, and 80 mg/dl, respectively. A1C after 20 weeks of glipizide GITS therapy was 5.4%. Thalidomide therapy was continued for treatment of his myeloma.

Thalidomide, withdrawn for teratogenicity, was reintroduced in 1997 as an immunomodulator to treat erythema nodosum leprosum. Its mechanism of action is thought to involve the inhibition of tumor necrosis factor (TNF)-α–mediated angiogenesis of the lesion. To our knowledge, thalidomide treatment has not previously been reported to cause or to worsen diabetes. We believe this to be the first report of extreme hyperglycemia occurring after initiation of thalidomide therapy. Iqbal et al. (1) investigated the role of thalidomide as a TNF-α antagonist on six patients with diabetes. They administered placebo or 150 mg of thalidomide for 3 weeks in a crossover design and performed isoglycemic-hyperinsulinemic clamps before and after therapy. They reported that thalidomide decreased insulin-stimulated peripheral glucose uptake by 31% (increased insulin resistance) and decreased glycogen synthesis by 48%. Wilson et al. (2) studied insulin antagonism by using a bioassay (rat diaphragm assay) in mothers giving birth to children with congenital malformations in 1966. They observed that antagonism to insulin was present in 5 of 6 (83%) mothers exposed to thalidomide in their first trimester compared with 14 of 50 (28%) mothers in the control group.

In a prostate cancer study, Figg et al. (3) observed that decreasing the dose of thalidomide improved hyperglycemia, suggesting that thalidomide may have contributed to the hyperglycemia. Our patient developed diabetes shortly after initiation of thalidomide. We believe this

to be the first report of extreme hyperglycemia associated with thalidomide therapy.

This case should prompt additional studies to evaluate hyperglycemia in patients treated with thalidomide. Until then, we recommend screening for diabetes before thalidomide treatment and regular follow-up of plasma glucose levels.

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Myocardial Dysfunction in Maternally Inherited Diabetes and Deafness

The pattern and degree of myocardial involvement in maternally inherited diabetes and deafness (MIDD) is unclear (1–3). A recent French multicenter study that examined 54 patients with MIDD described left ventricular hypertrophy (LVH) in 8 and congestive heart failure (CHF) in 2 patients (2). Here, we reported a patient with mtDNA 3243 mutation who developed the full clinical, echocardiographic, and radiologic picture of CHF.

A 54-year-old man with diabetes since age 23 years was diagnosed as having MIDD based on the findings of deaf-

ness, familial history of diabetes, and short stature involving his younger brother and mother. His older brother also presented diabetes but not short stature or deafness. Insulin was started when the patient was age 38 years, and he never presented ketosis. On physical examination, blood pressure was normal. Right hemiparesy was present as sequelae of a previous cerebrovascular accident. Autonomic and peripheral neuropathy were detected. Fundoscopy disclosed nonproliferative diabetic retinopathy. Laboratorial evaluation included a glucagon test that displayed decreased pancreatic insulin secretion (baseline and 6-min C-peptide values of 1.2 and 1.3 ng/ml, respectively). Urinary albumin excretion was 1,112 mg/24 h, and serum creatinine was 1.6 mg/dl. The younger brother and mother, but not the older brother, also presented macroalbuminuria. The analysis of mitochondrial DNA obtained from peripheral leukocytes revealed an A→G mutation at position 3243 in the patient and in his mother. The older and younger brother were not affected. Cerebral MRI revealed multiple hyperintense areas in cortex, globus pallidus, and cortical atrophy. Blood lactate concentration was 1.45 mmol/l at baseline ($n = 0.3$–1.3 mmol/l) and increased to 2.26 mmol/l after a carbohydrate-rich meal. Thyroid hormone concentrations were T4 = 2.6 μg/dl (normal range 4.5–12.5 μg/dl), thyroid-stimulating hormone = 16.4 μUI/ml (upper limit 4.5 μUI/ml). Anti-thyroperoxidase was normal, and oral thyroxine was started. An echocardiogram was performed and revealed a diffuse pattern of birefringence, which is suggestive of myocardial infiltration with an ejection fraction of 54% and LVH. The blood cell count found 20,000 leukocytes, with 34% of eosinophils. The patient's records confirmed eosinophilia (exceeding 1,500/μl) in the previous 6 months, which persisted after antiparasitic treatment. The presumptive diagnosis of eosinophilic myocardial dysfunction was assumed and prednisone therapy (60 mg/day) was started.

The patient visited the emergency unit 4 months later presenting resting dyspnea and pronounced bilateral lower-limb edema. A chest X-ray revealed the presence of pulmonary effusion. The electrocardiogram showed possible lateral ischemia and atrial enlargement. The echocardiogram disclosed a small peri-

cardial effusion, a diffuse birefringence pattern, and an ejection fraction of 41%, suggesting myocardiopathy. Cardiac catheterization was performed and revealed a 50% segmental lesion on the anterior descendent artery. A myocardial biopsy was indicated and demonstrated muscle fiber hypertrophy and degenerative changes, features consistent with the presence of dilated cardiomyopathy, eliminating the diagnosis of eosinophilic myocardiopathy.

Previous cases of cardiac dysfunction in mitochondrial diabetes have been described (2–4). A Japanese group showed the fast progressive nature of cardiac involvement in a diabetic patient who developed mitochondrial cardiomyopathy, with diffuse left ventricle hypokinesis. The endomyocardial biopsy described mild hypertrophy and myofibrils disarrangement with vacuolar degeneration, a pattern similar to our findings. Accordingly, our patient also presented a fast progression to heart failure, with deterioration of cardiac function over a period of 4 months. Momiyama et al. (5) studied 12 diabetic patients with mtDNA 3243 mutation and pointed out that they have a significantly higher proportion of LVH as compared with ordinary diabetic patients (33 vs. 7%). We believe that the present report contributes to characterize the myocardial involvement in the mitochondrial syndrome, providing clues to understanding the related disease mechanisms.

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Effect of Cigarette Smoking on Urinary Podocyte Excretion in Early Diabetic Nephropathy

S moking has been pinpointed as a factor causing progression of chronic nephropathies. It is worth noting that smoking increases urinary albumin concentration, even at albumin concentrations below that of microalbuminuria (1). There is growing evidence that smoking not only increases the risk of albuminuria but also the risk of renal functional deterioration (1). The frequency of nephropathy is progressively higher with increasing cigarette consumption. The available literature documents that smoking increases the risk of developing microalbuminuria, accelerates the rate of progression from microalbumunuria to manifest proteinuria, and accelerates the progression of renal failure (1). Chase et al. (2) reported that in a group of 359 young patients with type 1 diabetes, the prevalence of borderline and frankly elevated urinary albumin excretion rates was 2.8-fold higher in smokers than in nonsmokers. Concerning the risk of microalbumunuria progressing to overt proteinuria, a 4-year prospective study on 794 patients with type 2 diabetes reported a 2- to 2.5-fold higher relative risk in heavy smokers than in nonsmokers (3). Cigarette smoking in patients with kidney disease, including diabetic nephropathy, is associated with myointimal hyperplasia of intrarenal arteries, and there is a trend toward arteriolar hyalinosis in smokers. The renal vessels are the main targets of cigarette smoke in the kidney (4). In addition, smoke damages endothelial cells, and nicotine induces smooth muscle cell proliferation (5). However, the effects of smoking on podocyte injuries in patients with diabetic nephropathy are still unclear.

The podocyte is a highly differentiated cell that is strategically located on the outside of the glomerular capillary wall. Podocytes play an important role in glomerular filtration. Injuries to the podocytes are accompanied by marked morphological changes. The most severe podocyte lesion occurs as podocytes detach from the glomerular basement membrane, and these cells subsequently appear in the urine (6). By measuring urinary podocytes, we previously reported that podocyte injury may occur in patients with early diabetic nephropathy (7). Meyer et al. (8) reported that among the glomerular morphological characteristics used to diagnose nephropathy, urinary podocyte number was the best predictor in diabetic patients. The aim of the present study was to determine whether smoking affects podocyte injuries in patients with type 2 diabetes with microalbuminuria.

Eighty type 2 diabetic patients with microalbuminuria (50 men and 30 women, mean age 50.8 years, 50 smokers and 30 nonsmokers) and 30 healthy subjects (18 men and 12 women, mean age 49.5 years) were included in the present study. No patients had serum creatinine levels in excess of 2.0 mg/dl. Urinary podocytes were examined by immunofluorescence microscopy as previously reported (6,7). Urinary podocytes were detected in 35 diabetic patients with microalbuminuria (27 smokers and 8 nonsmokers, 1.4 ± 0.7 cells/ml) but were not detected in the remaining 45 patients (23 smokers and 22 nonsmokers) or the 30 healthy subjects. More podocytes are excreted in the urine in smokers (27 of 50 patients) with microalbuminuria than in

nonsmokers (8 of 30 patients) with microalbuminuria ($P = 0.017$, χ^2 test). The 27 diabetic patients (smokers) who had urinary podocytes were divided into two groups: 13 patients who stopped smoking and 14 patients who continued smoking. Urinary podocytes disappeared after 3 years in 10 of the 13 patients who had stopped smoking, whereas urinary podocytes increased in all patients who continued to smoke (from 1.1 ± 0.8 to 1.7 ± 0.4 cells/ml, $P < 0.01$). These data suggest that smoking may be associated with podocyte injuries in patients with early diabetic nephropathy.

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Exemplary Report and Missed Opportunities

The influence of worldview and the difficulty of overcoming our training

‖n reading the recent report by Kirkman et al. (1), I was simultaneously impressed and troubled. I was impressed by the attempt of this important work to improve the quality of care among seven rural primary care practices. Their detailed reporting of both initial and long-term results, and of both quality of care and physiological outcomes, was impressive. Especially noteworthy was their inclusion of longer-term, 2-year data, which are seldom reported. Their candor in discussing the failure to maintain the initial performance improvements, as well as their insightful discussion of potential reasons for these findings and the characteristics of systems that successfully improve quality, are refreshing and informative.

I was troubled, however, by the findings concerning the smoking cessation counseling index. I was struck by the validity of the observations of Kuhn (2) and Anderson (3), especially pertaining to diabetes management, that one's worldview determines how problems are identified and addressed. The authors report that they dropped any further consideration of improvement on the smoking cessation measure due to the very low baseline level of documentation of smoking status. I wonder, if this had been the case with low levels of documentation of A1C status, would the authors have made a similar decision? Instead, they would likely have used this as a rationale for redoubling their efforts to regularly collect and intervene on this measure. The dropping of smoking documentation and counseling was especially disappointing given the unquestioned clinical importance of smoking status and the availability of very cost-effective primary care–based interventions to improve smoking assessment and counseling (4).

I cannot help but speculate whether the prevailing biomedical perspective in which many of us have been trained (and which still largely dominates diabetes care [3]) did not influence this decision. Another finding reported in the Kirkman et al. (1) article further heightened this impression: the patient education program did not impact many of the intended patients in these practices. It would seem to be a well-integrated clinical activity to have a patient education program that was tied to the quality issues that the providers were focusing on. However, there are two major concerns: *1*) the decision to offer group-based educational sessions on a predetermined topic, rather than problem-based learning and self-management sessions on topics of interest and concern to patients (5,6), and *2*) most diabetes educators have been trained to offer such group sessions and continue to do so, despite strong evidence that even under the best conditions, only a minority of patients will attend such sessions, and this modality often fails to reach those who are most in need of such assistance. If instead an approach had been used that focused on the ultimate panel or population-based impact (7) (e.g., www.re-aim.org), and on problem-based learning that was focused on issues of concern to patients, it is likely that alternative approaches, such as nurse-based self-management training or proactive phone counseling, would have been selected.

My purpose is not to criticize these investigators, who are leaders in their field and have provided an important report that focuses on many of the complex issues involved in translating research into practice. Rather, the point is that we all need to "think differently" and to ask hard questions of ourselves when faced with such translation challenges. The models and methods in which most of us have been trained have been partial causes of our current dilemma. As Einstein is reported to have said, "The significant problems we face cannot be resolved by thinking at the same level that created the problems."

It is hoped that evidence-based guidelines that place equal emphasis on important patient self-management behaviors as on laboratory assays and checklists and flow diagrams, such as those being developed by the Evidence-Based

Behavioral Medicine Committee of the Society of Behavioral Medicine (8), will help us to think differently, to ask the hard translation questions, and to experiment with the innovations necessary to close the quality chasm.

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COMMENTS AND RESPONSES

Response to Glasgow

We appreciate Dr. Glasgow's (1) interest in our article (2) and the opportunity to respond to his comments. He seems to impute a biased worldview to our decision to drop smoking cessation counseling from chart audits subsequent to the baseline audit. First, we can assure him that we were not disinterested in the issue of smoking, as evidenced by the fact that this was one of the areas identified up front as important by the primary care physicians who invited us into their community. Data collection limitations alone drove the decision to drop this measure from subsequent analyses. Our sole source of data for the study was the charts kept by a group of independent solo practitioners, each of whom had a different system for keeping patient information. The auditors had to extract a wealth of information about both physician and patient behavior from these charts in a highly labor-intensive process. For each measure of adherence to guidelines, we had to ascertain both a numerator (the number of patients whose charts showed that they received the recommended care) and a denominator (the number of eligible patients). In all guideline areas except smoking cessation counseling, including the example Glasgow gives, the denominator was relatively easy to ascertain (e.g., all diabetic patients, all diabetic patients <75 years of age, all diabetic patients using insulin). However, since only smokers would be eligible for smoking cessation counseling, we needed a good estimate of the denominator (the number of smokers), which was not available in our dataset. As can be seen in Table 1 of our article (2), documentation of current smoking was only present for 23 patients in the baseline audit. This 8% rate is far below estimates of smoking in the state of Indiana, and was felt to be too unstable a denominator to allow meaningful follow-up of interventions targeted at the numerator.

Second, Dr. Glasgow feels that group-based educational sessions on predetermined topics were doomed to fail. Our sessions for the lay public were highly interactive, well attended, and linked temporally to the physician sessions. Not all studies have shown that group education performs less well than individualized instruction (3), but we agree that there are more potent patient education interventions than those we used in our study. However, interventions such as nurse-based self-management training or proactive phone counseling are costly to initiate and sustain. In closed systems such as Kaiser Permanente or the Veterans Affairs, in which the payor theoretically will recoup the savings that ensue from improved patient self-management, there is an incentive to fund such programs (although, interestingly, they are still rare). Unfortunately, in the amorphous health care system we studied, which is not atypical for much of the U.S., no organized force exists to develop and fund such interventions. We sought to make our interventions less costly and translatable to current systems that do not have funds for nurse case managers or one-on-one education with each high-risk subject.

We agree that there is a need to ask hard translational questions and to search for innovative solutions to the "quality chasm." Solutions will vary depending upon the resources available in the local environment. It is evident that these are not simple problems or they would have been solved by now.

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