

## OBSERVATIONS

## Improvement of Asthma After Administration of Pioglitazone

We describe the case of a 71-year-old man who was being followed as an outpatient for type 2 diabetes, hyperlipidemia, hypertension, and asthma. He was a past smoker with a BMI of 25.6 kg/m<sup>2</sup>. Because he had only mild wheezing at night, he was not under medical treatment for asthma. As his level of HbA<sub>1c</sub> remained between 6.6 and 6.8% under treatment with 2.5 mg glibenclamide, 30 mg pioglitazone (an insulin-sensitizing drug) was added to his treatment. Several days later, he noticed that his wheezing had disappeared. The pulmonary function tests showed improvement of forced vital capacity from 2.33 to 3.02 l and forced expiratory volume in one second from 1.46 to 2.03 l, one month after the start of treatment with pioglitazone. No significant change was observed in the serum level of total IgE (76 vs. 66 IU/ml, reference interval <250 IU/ml). The level of HbA<sub>1c</sub> (reference interval 4.3–5.8%) also decreased from 6.7 to 5.9% 3 months later. In this patient, pioglitazone seemed to be effective for both diabetes and asthma.

Before treating this patient, we had treated another man with diabetes and asthma with pioglitazone. He had been on fenoterol hydrobromide by mouth and beclomethasone dipropionate by inhalation. Several days after he was started on 15 mg pioglitazone, he stopped wheezing and coughing. Pioglitazone was discontinued 6 months later because his level of HbA<sub>1c</sub> had not decreased significantly, but his respiratory symptoms recurred. As this patient did not undergo pulmonary function tests, we had no objective evidence of the improvement of his asthma.

Based on the findings obtained from these two patients with diabetes and asthma, we suppose that pioglitazone may ameliorate symptoms of asthma. Pioglitazone is one of the thiazolidinedione compounds that have been used as anti-diabetic drugs (1). Recent studies have re-

vealed that thiazolidinedione compounds also have various nonhypoglycemic effects, such as anti-inflammatory, anti-atherosclerotic, and anti-cancer effects, in cultured cells and experimental animal models (1,2). Although some of their effects are mediated through activation of the peroxisome proliferator-activated receptor- $\gamma$ , an alternative mechanism has also been suggested (3). Thiazolidinedione compounds suppress the activation of macrophages and reduce nitric oxide and inflammatory cytokines, such as tumor necrosis factor- $\alpha$ , interleukin-1 $\beta$ , and interleukin-6 (4,5). In asthma, many mediators secreted from macrophages, mast cells, neutrophils, lymphocytes, and eosinophils are known to contribute to its pathogenesis. Pioglitazone may suppress the production of some of those mediators of asthma. The effect of thiazolidinedione compounds on glycemia takes weeks to occur, and their maximal hypoglycemic effect is not observed until several months of treatment have passed. The fact that the effect of pioglitazone on asthma was observed within several days after the start of treatment implies that a mechanism different from that for glycemia is probably operative in the case of asthma. Elucidation of the mechanism may enable the design of a novel class of drugs for asthma.

In this report, we presented two case subjects whose symptoms related to asthma had remitted during treatment with pioglitazone. However, objective data to show improvement of asthma were not sufficient. More clinical cases will be needed to draw a definite conclusion.

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## Gastroesophageal Reflux Disease and Progressive Nephropathy After Improving Glycemic Control in an Adolescent With Diabetic Dwarfism

Since the description of Mauriac's syndrome, or diabetic dwarfism, in 1930s, this syndrome, consisting of growth retardation, delayed puberty, and hepatomegaly, has rarely been encountered in type 1 diabetic children, especially since the advent of better diabetic management by insulin administration. The cause of growth failure has remained obscure, although it is presumably related to poor metabolic control of diabetes and depressed IGF-1 values (1). Improving diabetic control can result in the resolution of Mauriac's syndrome. However, the clinical response may not be complete and may even result in progressive deterioration of microvascular complications, such as retinopathy or nephropathy (2,3).

We report here a 19-year-old adolescent with 10 years' duration of type 1 diabetes and typical features of Mauriac's syndrome who developed gastroesophageal reflux disease (GERD) and progressive nephropathy after improving glycemic control. Since the onset of his overt disease, he received suboptimal insulin therapy (4–10 units/day). He was referred 3 years ago with the problems of short stature and delayed puberty. Hormonal evaluation showed normal thyroid

function and increased growth hormone (GH) value (24.3 ng/ml), but his glycemic control was very poor, as shown by an HbA<sub>1c</sub> value of 13.2%. Also, there was no evidence of nephropathy (serum creatinine 0.6 mg/dl) or microalbuminuria. Because better diabetic control may normalize growth and delay or prevent microvascular complications, the insulin dose was increased step by step. Unfortunately, GERD occurred 3 months later, and symptomatic treatment was prescribed. During the following 2 years, he achieved a growth rate of 3–4 cm/year after improved diabetic control (HbA<sub>1c</sub> values from 13.2 to 9.0 to 5.74%), but progressive nephropathy (serum creatinine 2.0 mg/dl, proteinuria, and hypertension) and deteriorated GERD (from grade 2 to grade 4) was encountered. Delayed puberty (Tanner stage III) and short stature (145 cm, 42 kg) with attenuated bone age (14.5 years old) were still noted. Endocrinological studies were performed again and showed normal values of thyroid hormones, GH, cortisol, leutinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone (4.50 ng/ml, lower limit of normal range 3–10 ng/ml). However, an LH-releasing hormone stimulation test revealed blunted FSH response (3.25, 4.14, 4.1, and 4.68  $\mu$ IU/ml at 0, 15, 30, and 60 min, respectively) but normal LH response (4.26, 13.18, 16.25, and 16.91  $\mu$ IU/ml at 0, 15, 30, and 60 min, respectively). Because there was no strong evidence of endocrinopathy for his short stature, he received intensive glycemic control, keeping HbA<sub>1c</sub> values around 7%, in addition to hypertensive management during the following year. However, GERD and progressive deteriorated renal function persisted and finally resulted in end-stage organ failure and hemodialysis.

Adequate insulin administration and a high degree of metabolic control are needed to support the growth and maturation of children with type 1 diabetes. Increased GH production with decreased IGF-1 concentration is found in prepubertal and pubertal diabetic patients (4). The enhanced GH response in diabetic children is not related to glycemic control, but is probably caused by a lack of IGF-1 negative feedback (1,5). However, insulin also plays an important role in the GH:IGF-1 axis because it can influence GH action at the receptor level, IGF-1 production by the liver, and IGF-1 bioac-

tivity via its regulation of the IGF-1 binding protein IGFBP-1 (1,6). Thus, underinsulinization in type 1 diabetic children can result in growth delay and growth attenuation; when severe, this can result in Mauriac's syndrome, or diabetic dwarfism. If the underinsulinization was not of prolonged duration, improved insulin delivery will help in restoring normal growth and maturation in diabetic dwarfism. However, rapid deterioration of retinopathy and nephropathy have been reported when insulin treatment is undertaken too aggressively, and the pathophysiology is still obscure (2,3).

Our patient has diabetes of long-term duration with underinsulinization, which could result in his short stature, delayed puberty, and attenuated bone age, as seen in Mauriac's syndrome, although we did not check his IGF-1 values. The appearance and progressive deterioration of GERD has not been reported in diabetic dwarfism after improving diabetic control. Also, the absent or blunted FSH response to the LHRH stimulation test may have some impact on the incomplete resolution of maturation after improving glycemic control in Mauriac's syndrome, because FSH plays an important role in steroidogenesis by inducing maturation of Leydig cells (7) and androgens work in part by enhancing GH secretion and also stimulating IGF-1 production (the testosterone level of our patient is in the lower limit of the normal range). In summary, GERD is a rare, potentially serious complication during efforts to improve glycemic control in Mauriac's syndrome, and the effect of rapidly improving glycemic control on esophageal motility has not been formally evaluated in diabetic patients (8). This issue should be elucidated in the future.

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## Good Long-Term Quality of Life Without Diabetic Complications With 20 Years of Continuous Subcutaneous Insulin Infusion Therapy in a Brittle Diabetic Elderly Patient

More than 20 years have passed since continuous subcutaneous insulin infusion (CSII) was proposed as a means of controlling glycemia

in insulin-dependent diabetes by Pickup et al. (1). Since that time, the American Diabetes Association has approved CSII as an effective means of implementing intensive diabetes management, with the goal of achieving near normal levels of blood glucose and improved lifestyle flexibility (2). Although the effect of long-term control with CSII with regard to complications has been studied (3–5), the duration of these studies does not exceed 20 years. After 20 years of diabetes, nearly all patients with type 1 diabetes and 60% of patients with type 2 diabetes have some degree of retinopathy (6), and most have other diabetic complications, including macrovascular disease (7).

We hereby report a patient with brittle diabetes with good long-term quality of life without any diabetic complications who was treated by CSII for 20 years (8,9). The patient is a 72-year-old woman (height 147 cm, weight 45.5 kg, and BMI 21 kg/m<sup>2</sup>). Her blood pressure was 104/60 mmHg. The subject's type 1 diabetes was initially manifested by a diabetic coma at 49 years of age (in 1979). At 51 years of age, she was treated by CSII with short-acting neutral buffered insulin, using the Nipro (Osaka, Japan) apparatus because her daily activities were disrupted due to frequent severe hypoglycemic and hyperglycemic coma (mean amplitude of glycemic excursion [MAGE] 270 mg/dl) and because of the poor glycemic control (HbA<sub>1c</sub> 11.5%) achieved with multiple-dose insulin injections (8). Although the therapy was effective (MAGE 50 mg/dl and HbA<sub>1c</sub> 7%), at 55 and 59 years of age, hypoglycemic coma frequently occurred. The occurrence of coma was resolved after the patient was treated with thyroid and glucocorticoid hormones because she had hypothyroidism due to chronic thyroiditis and isolated ACTH deficiency. Alternative therapy with short-acting neutral nonbuffered insulin induced severe hyper- and hypoglycemic coma (MAGE 170 mg/dl) (9). Therefore, the therapy was switched to CSII with short-acting acidified insulin, and the patient is now using lispro insulin. The basal insulin infusion rate was 0.3 units/h, and bolus injections at breakfast, lunch, and dinner were 5, 2, and 3 units, respectively. This regimen was effective. MAGE and HbA<sub>1c</sub> were maintained at 30–40 mg/dl and 4.9–7.1%, respectively. In this case, a wide swing of blood glucose concentrations was worsened by

deficiency of counterregulatory hormones and the nonbuffered insulin used in CSII. At 66 years of age, the patient was prescribed an oral ACE inhibitor and Ca<sup>2+</sup> antagonist for hypertension. At 69 years of age, she was treated with antibiotics for bronchial ectasia.

The patient is now 72 years of age, and at the time of this study (2001), her fasting blood glucose was 100 mg/dl (normal <110 mg/dl), her HbA<sub>1c</sub> was 4.8% (normal 4.5–5.8%), and her MAGE was 20 mg/dl. The subject's urinary albumin excretion rate was 7.2 mg/day (normal <25 mg/day) or <4 µg/mg creatinine (normal <30 µg/mg creatinine). Her tendon and Achilles' reflexes were normal, and her nerve conduction velocities in the distal motor and sensory nerves were 48 and 52 m/s, respectively (normal >40 m/s). The minimal latency of F-wave in the ulnar nerve was 21.8 ms (normal <30 ms). The patient's heart rate variation at rest was 3.1% (normal 1.1–3.5%). Seven-field stereo fundus photographs showed no abnormality. The concentrations of total, HDL, and LDL cholesterol and triglycerides were 237, 76, 147, and 58 mg/dl, respectively (normal <200, >40, <130, and <150 mg/dl, respectively). The findings of an exercise tolerance test, using conventional electrocardiogram (treadmill test), were negative, and carotid intima-media thickness was 0.8 mm (normal <1.0 mm) (10). Bone mineral density at the lumbar spine (L2–4) was 8.79 g/cm<sup>2</sup> (normal 8.45–8.70 g/cm<sup>2</sup>). All of these findings indicate that this patient has not experienced complications of chronic diabetes over the 20-year period of treatment (7).

The reason for the underlying absence of chronic diabetic complications is that this patient has maintained good glycemic control, as indicated by HbA<sub>1c</sub> levels that were sustained at <7% for 20 years. In addition, although there is not a precise definition of brittle diabetes, this case may be considered as one of brittle diabetes (11). The outcome of patients with brittle diabetes is miserable (12). However, the experience with this patient indicates that CSII can stabilize wide swings in blood glucose concentrations and maintain good quality of life over a long period of time while attempting to understand the specific etiology of brittle diabetes (12,13). Moreover, this case shows that CSII is useful in elderly pa-

tients, although its safety has not been demonstrated in elderly patients (2).

In conclusion, this case demonstrates that CSII can be tolerated as well as effective in maintaining a good quality of life without diabetic complications over a long period of time (20 years in a type 1 diabetic patient). Our experience suggests that even though the patient has the brittle type of diabetes and is elderly, if HbA<sub>1c</sub> level can be maintained at <7%, as indicated by the study of the Diabetes Control and Complications Trial Research Group (4), chronic diabetic complications can be avoided.

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## Glargine and Lispro

### Two cases of mistaken identity

Insulin glargine (Lantus; Aventis, Parsippany, NJ) is a recently available basal insulin analog that appears to have a more consistent activity profile than comparable long-acting insulin products (1). It is typically administered as a single injection before bedtime. Due to minor modification of the amino acid sequence in both the A- and B-chains of the insulin molecule, glargine is soluble only in an acidic pH (2). When injected, glargine precipitates in the neutral pH of subcutaneous tissues, prolonging its systemic absorption (2). Clinical trials have demonstrated that compared with NPH insulin, glargine improves fasting glucose in patients with type 1 diabetes (3) and results in less nocturnal hypoglycemia in patients with both type 1 (4) and type 2 (5) diabetes. It may be particularly useful in individuals who demonstrate labile blood glucose control with conventional insulin formulations. One immediately obvious difference between glargine and other long- (or intermediate-) acting insulins is that the product is a clear solution, similar to short-acting products, not a semi-opaque suspension. To avoid confusion with such insulins, Lantus is mar-

keted in a vial of unique shape, taller and thinner than all other insulin vials, and the label contains purple print. We herein report, however, our recent experience with two patients who mistakenly administered a rapid-acting insulin analog in lieu of their usual glargine dose.

The first patient is a 25-year-old woman with type 1 diabetes duration of 6 years. She had generally been under good control, with a recent HbA<sub>1c</sub> of 7.0% (normal range 4.3–6.4%). There was no history of diabetes-related complications, including retinopathy or other medical conditions, and her compliance had always been excellent. Her regimen included insulin glargine, 22 units nightly at bedtime plus adjusted-dose insulin lispro (Humalog; Eli Lilly, Indianapolis, IN) before meals, which she had been using for the previous 2 months without difficulty. On 14 October 2001, she accidentally drew her scheduled bedtime dose of 22 units from her lispro vial rather than her glargine vial, realizing her error only after it had been administered. At that time, her blood glucose measured 160 mg/dl on a home glucose meter. The patient was instructed to preemptively consume carbohydrate calories, but her intake was limited because of nausea. By 90 min after the injection, her blood glucose measured 90 mg/dl, and by 2 h, it had dropped to 57 mg/dl. She was, at that point, referred to the emergency ward, where intravenous dextrose was administered to reverse her hypoglycemia. Five hours after the insulin injection, her blood glucose stabilized in the 160 mg/dl range.

The second patient is a 52-year-old female college professor with type 1 diabetes duration of almost 40 years. Her control was fair, with a recent HbA<sub>1c</sub> of 7.4%, on a regimen of 17 units glargine (started 3 months previously), administered in the morning, plus adjusted-dose lispro before meals, which she took by separate injection. There was no history of diabetes-related complications or any other significant medical disorders. Her compliance had been excellent. On the morning of 16 October 2001, she inadvertently injected 17 units lispro instead of glargine. At the time of administration, her blood glucose was 315 mg/dl, at which point she would have normally taken 5 units lispro. Despite eating nearly continuously for the subsequent 3 h, her blood glucose dropped to as low as 67

mg/dl and finally stabilized in the 85 mg/dl range. No further intervention was required.

These cases serve to underscore a significant new risk that may be associated when insulin glargine is used in combination with short-acting insulins (regular, lispro, and aspart). Before the availability of glargine, the distinction between long- (or intermediate-) acting insulins and short-acting insulins was obvious, with the former being cloudy in appearance, whereas the latter was clear. We propose that these patient errors occurred because of the similarity in appearance between glargine and short-acting insulins, despite glargine's unique vial shape and label. It should be noted that the two patients in whom these episodes occurred had normal cognitive function, no visual impairment, and had previously demonstrated impeccable compliance. In addition, they had been counseled about the likeness in appearance between their two insulin products at the initiation of glargine therapy. Despite this, both admitted that it was indeed the similarity between their insulins, glargine and lispro, that led to the confusion.

We recommend that patients should be made aware of the potential danger of confusing glargine with their short-acting insulins and educated in strategies to help avoid such accidents. We also recommend that the manufacturer of glargine insulin, Aventis Pharmaceuticals, in cooperation with the Food and Drug Administration, consider further alternative packaging or perhaps even solution tinting to more easily distinguish it from the widely used short-acting preparations.

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## Angioneurotic Edema as a Side Effect of Pioglitazone

**T**hiazolidinediones are agents used to improve insulin sensitivity in type 2 diabetes. We are currently conducting an institutional review board–approved research study to examine the effects of pioglitazone on metabolic parameters in upper body–obese volunteers. One of the volunteers developed a sore throat 7 days after starting the pioglitazone (30 mg, once daily), followed by dyspnea and swelling of the lips and tongue. On physical examination, swollen lips and tenderness of the pharynx were noted and slight wheezing was heard. No rash was seen. Laboratory values, including leukocytes and eosinophils, were normal. This condition was diagnosed as an angioneurotic edema, and the symptoms rapidly diminished af-

ter administration of intravenous steroids.

The volunteer had been using Orthotricycline for several years, which was continued after this event without problems. She had not eaten allergenic foods (such as strawberries or shrimp) or anything out of the ordinary. She had multiple allergies, including to radiographic contrast dye, codeine, Ultram, and Midrin. She had not previously experienced angioneurotic edema.

After discontinuation of pioglitazone, the symptoms did not recur. We concluded that the angioneurotic edema was caused by pioglitazone, even though, to our knowledge, this has not been reported as a side effect before.

This finding, however, is of particular importance, considering the frequent use of thiazolidinediones as comedication with ACE inhibitors and other drugs known to cause angioneurotic edema. In case this condition occurs, thiazolidinediones, pioglitazone in particular, should also be considered as the possible trigger.

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S.S. and M.D.J. have received research support from Takeda to investigate the effects of pioglitazone on intramuscular triglyceride metabolism.

## Effect of Private Health Insurance on Health Care Access and Health Status of Diabetic Patients Covered by Medicare

**A** previous study showed that 93% of adults with diabetes in the U.S. population have some form of health insurance, and 52% have multiple sources of insurance (1). An important but unanswered question is whether the source and nature of health insurance influences access to care, quality of care, and health status and outcomes for patients with diabetes. To investigate this is-

sue, we analyzed data from the third National Health and Nutrition Examination Survey, which included a representative national sample of 721 adults aged  $\geq 65$  years with diagnosed diabetes who had Medicare health insurance coverage. Structured questionnaires and clinical and laboratory assessments were used to determine whether they had private health insurance and the frequencies of physician visits, screening for diabetes complications, and treatment and control of hyperglycemia, obesity, proteinuria, hypertension, and dyslipidemia.

Of all patients, 26% were not covered by private health insurance. These individuals were more likely to be of minority race and ethnicity, to have less education and lower income, and to be covered by Medicaid. They were similar to those with private insurance regarding health care access and utilization, including having a primary source of ambulatory medical care (97 vs. 98%), having a primary physician at this source (92 vs. 95%), attending four or more physician visits in the past year (81 vs. 73%), using diabetes therapy (78 vs. 74% using insulin or oral agents), taking at least three prescription medications (66 vs. 65%), and receiving blood pressure screening in the previous 6 months (91 vs. 94%). However, lower proportions took two or more insulin injections per day (31 vs. 56%), self-monitored their blood glucose (23 vs. 42% for insulin users), had an eye examination in the past year (63 vs. 75%), had their cholesterol checked (65 vs. 80%), or were treated for their hypertension (72 vs. 87%) or dyslipidemia (25 vs. 50%).

Despite these differences in indicators of health care access and use, there were few differences between those without and with private insurance in clinical indicators of health status, including blood glucose and blood pressure control, obesity, proteinuria, and lipid levels. These indicators of health status included HbA<sub>1c</sub> >7.0 (56 vs. 54%), microalbuminuria or clinical proteinuria (43 vs. 38%), BMI >30 kg/m<sup>2</sup> (men 20 vs. 18%, women 34 vs. 40%), undiagnosed hypertension ( $\geq 140/90$  mmHg, 16 vs. 8%), diagnosed but uncontrolled hypertension (43 vs. 45%), total cholesterol  $\geq 240$  mg/dl (35 vs. 33%), LDL cholesterol  $\geq 130$  mg/dl (56 vs. 46%), HDL cholesterol >45 mg/dl (47 vs. 58%), and triglycerides  $\geq 200$  mg/dl (36 vs. 41%). Adjustment for socio-demographic differences (age, sex, race,

education, and income) and for Medicaid coverage status did not alter these findings.

In conclusion, there are some differences in sociodemographic characteristics and in health care access and use between diabetic patients who have and do not have private health insurance to supplement their Medicare coverage. However, there are few differences in clinical health status between these two groups, and the health status of patients with diabetes who are covered by Medicare does not appear to be improved by having private health insurance.

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## Does Microalbuminuria Predict Diabetic Nephropathy?

Tabaei et al. (1) conclude that "Microalbuminuria may not be as sensitive and specific a predictor of diabetic nephropathy as previously suggested. Other markers of risk for diabetic nephropathy are needed for optimal clinical management."

This conclusion is based on a 7-year follow-up study of nine (eight women) normotensive type 1 diabetic patients with microalbuminuria and seven middle-aged normotensive type 2 diabetic patients (mainly women) with microalbuminuria. Their conclusions and proposals should be interpreted with great caution because numerous flaws are at hand: 1) a subset of only 32% of the original cohort was investigated, giving rise to many different kinds of biases as demonstrated, e.g., in relation to the included patient population; 2) the generally accepted criteria for microalbuminuria was not fulfilled,

**Table 1—Progression of microalbuminuria to nephropathy in diabetic patients**

Author (reference)	n	Observation period (years)	Patients developing nephropathy (%/years)
<b>Type 1*</b>			
Viberti et al. (3)	46	2	13
Laffel et al. (4)	70	2	9.3
Crepaldi et al. (5)	34	3	6.9
Euclid Study Group (6)	34	2	10.2
Mathiesen et al. (7)	23	4	7.5
Prima Study Group (8)	18	2	0
Atlantis Study Group (9)	46	2	5.5
<b>Type 2</b>			
Mogensen et al. (10)	59	9	2.4
Nelson et al. (11)	50	4	9.3
Ravid et al. (12)	49	5	8.4
Gaede et al. (12)	80	4	5.8
Ahmad et al. (14)	51	5	4.8
Estacio et al. (15)	150	5	4.0
HOPE Study Group (16)	1140	4.5	4.5
Parving et al. (17)	201	2	7.5
Parving et al. (18)	86	5	7.0

\*Data based on the placebo arm in randomized double-blind studies lasting ≥2 years.

neither at baseline nor at the end of the study; 3) values for urinary albumin excretion rate or albumin/creatinine ratio were not presented; 4) the results dealing with progression are presented without any confidence interval, and because the number of patients was extremely small, the confidence interval would be extremely wide; 5) six of seven type 2 diabetic patients and two of nine type 1 diabetic patients received ACE inhibitors at the end of the follow-up; 6) no information of relevant treatment during the follow-up was presented; and 7) the authors have selected references that suit their purpose, including a review article (2) that disregarded all studies in microalbuminuric type 1 and type 2 diabetic patients lasting <5 years.

To compensate for this lack of a balanced view, we have included Table 1, which deals with the outcome of microalbuminuria in type 1 and type 2 diabetic patients. It is quite apparent from the table that the study by Tabaei et al. (1) is the smallest ever reported in the literature.

In conclusion, microalbuminuria is the best documented predictor of high risk for development of diabetic nephropathy in both type 1 and type 2 diabetes, and numerous trials in type 1 (3-9) and type 2 (12-17) diabetes have documented and demonstrated the usefulness

of microalbuminuria in intervention studies.

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## Lipoma and Sensory Neuropathy in Mitochondrial Diabetes Associated With tRNA Mutation at Position 3271

We previously reported the first identified case of mitochondrial diabetes caused by a T-to-C transition at position 3271 (1). At age 32 years, the patient had lower limb paresthesia. Since beginning diet therapy at age 33 years, his glycemic control has generally been good (HbA<sub>1c</sub> 6-7%) and the paresthesia has disappeared.

During 12 years of follow-up, we observed two important clinical features: 1) lower limb paresthesia manifesting even with mild hyperglycemia (e.g., HbA<sub>1c</sub> ~7.5%) and 2) lipoma (round, 10-mm diameter) manifesting at age 44 years over the left breast.

Low et al. (2) hypothesized that lipid peroxidation under hyperglycemic conditions causes mitochondrial DNA (mtDNA) mutations that increase oxygen radicals, causing further damage to the mitochondrial respiratory chain, ultimately resulting in sensory neuropathy. Regarding the lower limb paresthesia of this patient, we speculate that lack of an effective mechanism for maintaining mitochondrial function renders sensory nerves susceptible to hyperglycemic toxicity, thereby producing symptoms.

As for the lipoma, several such cases have been described in the literature. Berkovic et al. (3) reported on four patients, two with multiple symmetric lipomatosis and two with lipoma and

multisystem disorder, all with mitochondrial dysfunction. Holme et al. (4) suggested that mtDNA mutations may be either a direct or an indirect cause of perturbation of the maturation process of adipocytes. In benign symmetric lipomatosis (Madelung's disease), functional sympathetic denervation of adipose tissue is thought to cause an abnormal free fatty acid response to epinephrine. Therefore, lipoma may be a manifestation of peripheral nerve system denervation caused by mitochondrial dysfunction.

Thus, our present case raises the possibility of an association between lipoma and sensory polyneuropathy, both of which appear to be manifestations of mitochondrial diabetes caused by the 3271 mtDNA mutation. This case supports the previous observation of Klopstock et al. (5), indicating a high frequency of peripheral neuropathy in multiple symmetric lipomatosis patients with mitochondrial dysfunction.

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## Thickness of the Supraspinatus and Biceps Tendons in Diabetic Patients

The effect of diabetes on tendons is not well known. There are some studies that analyze the impact of diabetes on tendon structures. It has been shown that chronic hyperglycemia causes some structural changes in tendon collagen (1,2). To the best of our knowledge, there is no published study on biceps and supraspinatus tendons. To observe the effect of diabetes on tendons, we studied the biceps and supraspinatus tendons because they can be easily measured by the ultrasonography (USG) technique. We measured both of these tendons using high resolution USG in 150 diabetic patients (50 type 1 and 100 type 2 diabetic patients, 75 men and 75 women, mean age  $50.17 \pm 15$  years [ $\pm$ SD]) and 94 control outpatients (47 men and 47 women, mean age  $47.53 \pm 14$  years) recruited from our clinic population.

All studies were performed and interpreted by a single radiologist using and Aloka SSD 620 ultrasound machine (Tokyo) with 7.5 MHz linear probe. The shoulder was examined by standard techniques (3). Maximal supraspinatus tendon thickness was measured on a longitudinal view, just in front of the lateral part of the humeral head (4). The long head of the biceps tendon was viewed in the bicipital groove, and its transverse thickness was measured (5).

Specifically, in diabetic patients, the thickness of the right biceps (RB) tendon was equal to  $4 \pm 1.05$  mm, whereas it was  $2.95 \pm 0.38$  mm in the control group ( $P < 0.0001$ ). For the left biceps (LB) ten-

don, the thickness was  $4.04 \pm 1.02$  mm in diabetic patients and  $2.97 \pm 0.26$  mm in the control group ( $P < 0.0001$ ). Similarly, the tendon thickness of the right supraspinatus (RS) and left supraspinatus (LS) was  $6.60 \pm 1.25$  and  $6.58 \pm 1.18$  mm in diabetic patients and  $4.91 \pm 0.41$  and  $4.96 \pm 0.39$  mm in the control group, respectively ( $P < 0.0001$ ). The results of a logistic regression analysis indicated that the relative risk of a tendon increase in diabetic patients, as compared with the control group, was equal to 16.14 for the RB tendon, 60.66 for the LB tendon, 22.75 for the RS tendon, and 24.28 for the LS tendon.

Our results clearly indicated that there was a positive correlation between age and all four of the shoulder tendon thicknesses, i.e.,  $P < 0.05$  for RB and RS and  $P < 0.001$  for LB and LS. On the other hand, we did not observe such a statistical relationship in the control group. Furthermore, there was only a positive correlation between the duration of diabetes and the thickness of both RB and LS, i.e.,  $P < 0.05$ .

There are some similar studies on patients with amyloidosis (4). They found thickening of the rotator cuff due to the deposition of a  $\beta_2$ -microglobulin amyloidosis of the patients on chronic hemodialysis. In our study, none of the patients had a terminal kidney disease or had undergone hemodialysis treatment.

In summary, we observed an increase in biceps and supraspinatus tendon thickness in diabetic patients that was aggravated with aging in diabetic patients, although such a relationship did not exist for the control group. Our study is an important step in the direction of explaining this newly recognized complication of diabetes by using a noninvasive and relatively inexpensive USG technique, even though we need further studies to support our claim.

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## Impaired Cerebrovascular Reactivity in Type 1 Diabetic Children

The risk of vascular disease is not distributed equally among type 1 diabetic patients. Subgroups exist with a relatively low risk versus a high risk of vascular disease (1). Screening for diabetic retinopathy and nephropathy is the most widely used parameter to obtain additional information on the vascular state in patients with diabetes. However, in children, both vascular screening parameters have shown certain limitations (2). The Doppler method has been demonstrated to detect diabetic vasculopathy at a very early stage of endothelial dysfunction. We investigated the neurovascular coupling mechanism that adapts cerebral blood flow to cortical activity and performed a functional transcranial Doppler test using a visual stimulus.

The aim of our present investigation was to describe endothelial function in healthy children and patients suffering from type 1 diabetes for less and greater than 5 years without any apparent diabetic complications, such as microalbuminuria or retinopathy. All children had a normal 24-h ambulatory arterial blood pressure recording and a normal lipid status. We evaluated evoked blood flow ve-



Table 1—Descriptive and Doppler data

	Control subjects	Diabetes duration <5 years	Diabetes duration >5 years	P
Descriptive data				
Volunteers (n)	29	29	53	
Girl/boy ratio (n)	14/13	15/14	25/28	
Age (years)	13.3 ± 2.7	13 ± 2	14.8 ± 2.5	NS*
BMI (kg/m <sup>2</sup> )	19.5 ± 2.4	19.4 ± 2.8	22.4 ± 3.7	NS*
Diabetes duration (years)	—	2.9 ± 1.5	8.4 ± 2.3	<0.001†
Fasting glucose level (mmol/l)	—	9.8 ± 1.2	10.4 ± 1.5	NS†
Last HbA <sub>1c</sub> (%)	—	8 ± 2	8.4 ± 1.7	NS†
Long-term (>2 years) HbA <sub>1c</sub> (%)	—	7.9 ± 1.1	7.5 ± 1	NS†
Albumin/creatinin ratio	—	11 ± 11	8.6 ± 6.6	NS‡
24-h RR recording above reference (%)	—	13 ± 17	14 ± 20	NS‡
Cholesterol (mmol/l)	4.14 ± .6	4.7 ± 0.9	4.3 ± 0.7	NS*
Triglyceride (mmol/l)	1.1 ± 0.3	1.1 ± 0.3	1.2 ± 0.3	NS*
HDL cholesterol (mmol/l)	—	1.8 ± 0.4	1.7 ± 0.3	NS†
LDL cholesterol (mmol/l)	—	2.4 ± 0.5	2.2 ± 0.7	NS†
LDL/HDL ratio	—	1.3	1.3	—
Insulin dose (IE/kg)	—	1 ± 0.25	1 ± 0.2	NS†
Doppler data				
Resting blood flow velocity (cm/s)	60 ± 10	65 ± 14	58 ± 12	NS*
Time delay (s)	1.7 ± 1	1.8 ± 1	1.5 ± 1.1	NS*
Rate time (s)	3 ± 1.8	3.2 ± 1.6	3 ± 1.8	NS*
Gain, difference to baseline (%)	15.2 ± 4	18.3 ± 7.5	17.5 ± 5.5	NS*
Attenuation	0.38 ± 0.13	0.47 ± 0.14	0.48 ± 0.16	<0.025*
Natural frequency (1/s)	0.22 ± 0.06	0.21 ± 0.05	0.21 ± 0.05	NS*

Data are means ± SD unless otherwise indicated. Statistical methods: \*ANOVA, †t test, ‡Wilcoxon's rank sum test.

locity changes in the posterior cerebral artery according to a control system approach, specifying a five-parameter model (3). The parameters specifying the entire time course of the blood flow regulation were time delay, rate time, attenuation, gain, and natural frequency. The time delay is the time span between change in test conditions (signalized by a tone) and the evoked flow response. The rate time specifies the initial up-stroke in flow velocity, whereas the attenuation parameter describes the damping of the system before the stable new blood flow level is reached, as indicated by the gain parameter. The natural frequency describes the oscillation of the system as if it were undamped. The results of descriptive as well as Doppler data are shown in Table 1 together with statistical results.

It is still an open discussion as to what extent a diabetic state results in vascular alterations in children. The increase in the parameter attenuation in both diabetic groups is indicative of a lack of dilative agents under regulative conditions, thus

increasing the vessel wall rigidity. Because the parameter gain remained unchanged, the initial functional impairment was completely compensated when stable blood flow conditions were reached. This constellation is in agreement with the understanding of endothelial dysfunction (1,2). A total of 10% of the patients with a diabetes duration <5 years and 15% of those with a duration of >5 years showed attenuation values above the upper tolerance limit of  $2\sigma_{\text{control}}$  of the healthy subjects. None of the data sets fell beyond the lower limit. Because the HbA<sub>1c</sub> values of the outliers were not statistically different compared with their group values, correlation of both is weak, and the evaluation of HbA<sub>1c</sub> status together with endothelial function might assess the individual vascular risk more appropriately. Besides the limitation that the cerebrovasculature differs from the peripheral vasculature in many aspects, we presented a painless and easy-to-perform method that may indeed be feasible for investigating and

monitoring endothelial function in children.

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## COMMENTS AND RESPONSES

### Subcutaneous Glucose Monitoring

#### Microdialysis vs. intracorporeal

This letter is in response to the study by Jungheim et al. (1) in the September issue of *Diabetes Care*. They studied a subcutaneous glucose monitoring system in 23 subjects with diabetes over a 3-day period. They report a satisfactory mean absolute difference (MAD) between sensor values and capillary blood glucose of 14.8%.

I agree with the authors that their sensor, which uses microdialysis, appears to function in a stable fashion. It is impressive that they found it necessary to calibrate the device only once during this period, at a mean time of 4.7 h after insertion. As the authors point out, this stability (if verified) probably constitutes an advantage over intracorporeally placed sensors, which tend to undergo a decline in sensitivity over time and therefore require periodic recalibration.

However, I believe that another part of this report is misleading. Their first sentence states that devices for continuous glucose monitoring should display the data in real time rather than retrospectively. I think all workers in this field and all potential users of these devices would agree. It is for precisely this reason that I think that it is invalid for the authors to subtract 31 min from the time value for each sensed glucose value. I understand their rationale: the microdialysis system creates an intrinsic lag (time for fluid transportation through the dialysis system). Nonetheless, when a patient with diabetes uses this system in real time, this lag cannot be conveniently removed by subtraction. In fact, this could be a problem in the clinical situation of rapidly de-

clining glycemia when the patient needs to know the glucose level immediately. I believe that in the displayed figure, the time values for the sensor readings were retrospectively corrected for this 31-min delay; thus, it would appear much different without such a correction. It would be more clinically relevant to show the actual time values. Furthermore, it appears that the MAD of 14.8% was also based on time-corrected values, and I suspect that the MAD would be substantially greater without this correction. Studies performed by my colleagues and I using intracorporeal sensors have not used corrections for sensor delay (2–6).

I think readers may have taken away a misleading message from this report, i.e., that dialysis-based sensors are likely to be more stable over time than intracorporeal systems. I think a more balanced set of conclusions would be that dialysis-based sensors are likely to be more stable over time than intracorporeal systems; on the other hand, dialysis-based sensors are more likely than intracorporeal sensors to exhibit error caused by delays intrinsic to the device, and judgments of superiority of one system over the other await prospective studies where sensor accuracy is assessed in real time.

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### Response to Ward

We read with interest the comments of Ward (1) on our microdialysis-based continuous glucose monitoring system. We especially appreciate that he shares our delight on the stability (i.e., lack of time-dependent signal decline) of this system, which has been verified by standardized regression analysis.

Furthermore, Ward raises the important general question of the optimal way to evaluate a continuous glucose monitoring device—an open question so far. Our suggestion is to perform an evaluation of a continuous glucose monitoring device in a stepwise approach consisting of a technical evaluation followed by a clinical evaluation.

First, there is certainly a need for an accuracy and precision analysis (2) to evaluate the technical performance of a device. Obviously, for this evaluation, glucose values generated by test and reference method are matched according to the moment at which the samples are taken and not according to the moment at which they are measured. Consequently, for the technical evaluation presented, it was not only justified but also mandatory to correct the data for the time lag between sample collection and analysis.

We agree with Ward that there is also a need for a clinical evaluation to predict the clinical efficiency of continuous glucose monitoring devices. But how should an appropriate clinical evaluation of real-time continuous glucose monitoring devices be done? Ward proposed an evaluation by performing a simple accuracy and precision analysis of the data without correcting for the time lag between sample collection and measurement display. This approach totally

ignores the additional information on the trend of glucose change, which is a major advantage of real-time continuous glucose monitoring. Therefore, we reckon that it is not appropriate to only use the proposed method for clinical evaluation of a real-time continuous glucose monitoring device. After finalization of the development of algorithms 1) providing trend information and 2) integrating hypo- and hyperglycemia alarms, a more sophisticated clinical evaluation of our device should follow.

There is no doubt that minimizing the system's characteristic time lag between sample collection within the body and the subsequent display of the measurement result will increase the system's effectiveness. Decreasing the inner volume and the length of the tubing as well as increasing the perfusion velocity of our microdialysis-based system are realizable tasks for future developments.

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## Response to Ernst

Ernst (1) makes several valid and important points regarding complementary and alternative medicine (CAM) use. The benefit/risk ratio of CAM therapies should be evaluated in the same way that conventional therapies are. Patients often lack appropriate education to make these choices. Advice from untrained retail staff is often unreliable. The popular media often provides unsatisfactory coverage of health care issues.

However, through the use of anecdote, selective use of data, and oversimplification, Ernst reaches some unfounded conclusions. Consider that it would be easy to construct a similarly misleading portrayal of conventional medicine by focusing on the alarming rate of adverse drug reactions (the fourth leading cause of death in the U.S.) (2) and ignoring conventional medicine's great benefits.

Significantly, Ernst dismisses the potential benefits of CAM therapies in diabetic care. Implicitly, CAM therapies have not enjoyed the scientific attention that conventional treatments have received. Increasingly, however, CAM therapies suggested for diabetes have been the subject of encouraging preliminary research into their efficacy, mechanisms of action, and safety (3–10). Each therapy should be rigorously evaluated using all available evidence, not dismissed collectively.

Ernst's commentary bears a discouragingly hostile tone. The great majority of health care providers, whether alternative or conventional, are committed to serving their patients. Patients navigate a complex and shifting health care system to the best of their ability. Let all medical professionals strive to cultivate a cooperative relationship with their peers, respect their patients, and maintain an objective approach to medical science.

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## Response to Letter by Gibson

I am obliged to Nathaniel Gibson (1) for his letter in this issue of *Diabetes Care* because his comments enable me to

clarify several points. He is correct in calling part of the evidence I quoted "anecdotal." This pertains particularly to the cases where providers of complementary and alternative medicine (CAM) have hindered access to essential conventional treatments. Sadly, at the current time, such information can only be considered anecdotal because there is, to the best of my knowledge, no systematic research into this area. At my department, we are all in favor of being systematic; we have published >50 systematic reviews of CAM (a full list is available from me free of charge). But in this case, I fear that the onus is on the providers of CAM to systematically demonstrate that the anecdotal reports that have been published are in fact rarities.

Mr. Gibson also argues that I neglect the evidence about the benefit of CAM, and he cites a number of recent studies. Several (systematic) reviews of this area

exist (2–5), but none of them conclude that CAM has an established place in the treatment of diabetes. Even Gibson categorizes the evidence he quotes as "preliminary." To me, this indicates that reliable risk-benefit assessments are not currently possible.

In my view, Mr. Gibson's most interesting point is that he accuses me of being "hostile." A commentary on the hidden risks of CAM obviously has the purpose of critically discussing certain issues. Perhaps Mr. Gibson, like many proponents of CAM, confuses hostility with criticism. I believe that in any area of medicine, productive (internal) criticism is an essential element that generates progress and credibility. Thus, I intend to continue conducting critical analyses of CAM in the conviction and hope that they are a credit (not a discredit) and a step forwards (not backwards) for CAM.

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