OBSERVATIONS

Increase in Serum Uric Acid Is Selectively Associated With Stroke in Type 2 Diabetes

Hyperuricemia has previously been described as a strong predictor of well-defined cerebrovascular complications (stroke) in a Finnish cohort of patients with type 2 diabetes (1). To evaluate whether serum uric concentration would be selectively associated with presence of stroke as compared with transient ischemic attack (TIA) in a group of hospitalized diabetic patients, we studied 835 patients (220 affected with type 2 diabetes and 615 nondiabetic subjects), who were consecutively admitted to and subsequently discharged from our hospital for TIA ($n = 386$) or stroke ($n = 449$) during the period 1 January 1998 to 31 December 1999. Stroke was classified by means of computerized tomography as ischemic (thromboembolic) in 363 cases (81%) and hemorrhagic in 86 (19%). TIA was defined as an acute loss of focal cerebral function lasting <24 h presumed to be due to ischemic vascular disease and without clinical or biochemical evidence of hypoglycemia. Those who were determined to be affected with TIA were chosen as control subjects because patients with stroke and with TIA appeared homogeneously exposed to previous chronic drug therapy or to hospitalization and, moreover, because they were characterized by co-presence of about the same risk factors for cardiovascular disease.

Regardless of whether they were affected with diabetes, there was no difference in serum creatinine among the groups of patients, and the percentage of those chronically taking drugs (at home) potentially able to modify serum uric acid was similar. The serum uric acid values (means ± SD) were similar in groups with and without diabetes (340.8 ± 99.9 vs. 343.8 ± 96.9 μmol/l, P = NS). In the diabetic group, serum urate was significantly higher in patients with stroke (n = 138, 354.5 ± 118.4 μmol/l) than in those with TIA (n = 82, 318.8 ± 88 μmol/l, $P = 0.001$), whereas no difference was observed in the group of nondiabetic patients (343.8 ± 100.5 μmol/l in 304 patients with TIA vs. 343.8 ± 104.1 μmol/l in 311 subjects with stroke, P = NS). These findings were confirmed after also excluding patients with hemorrhagic stroke, and the relative risk for stroke was linearly related to serum urate concentration in the diabetic group, since the odds ratio (adjusted for sex, age, blood pressure, serum creatinine, plasma glucose, and lipids for the presence of coronary heart disease and of atrial fibrillation) in the fourth urate quartile was significantly higher than in the first quartile (1 vs. 1.32 [95% CI 1.07–1.41], $P < 0.05$).

From these findings, it is impossible to recognize whether an increase in serum urate is a predisposing risk factor or can instead be considered the effect of stroke itself, or both. Serum uric acid is a soluble antioxidant scavenger (2), and oxidative stress is a hallmark of tissues' hyperglycemic milieu (3). In addition, the increase in serum uric acid is a feature of the metabolic syndrome (4). Furthermore, serum uric acid may be considered as a marker of acute endothelial dysfunction, since hyperuricemia has been observed to be associated with raised endothelin levels (5), and there is evidence of uric acid involvement, via purine metabolism, in the process of thrombus formation (6). In conclusion, our data suggest a selective relationship between serum uric acid and stroke in type 2 diabetes. Whether treatment aimed at reducing serum uric acid can be useful to prevent acute cerebrovascular events in these patients remains to be ascertained.

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Use of Insulin Glargine During Pregnancy in a Type 1 Diabetic Woman

The patient was a 37-year-old registered nurse recently followed during her second pregnancy complicated by diabetes. Type 1 diabetes was diagnosed at age 9 years. She was initially referred to us for management of her first diabetic pregnancy in June 1998 at 10 weeks' gestation with twins. She was on a multiple daily insulin injection (MDI) regimen with human regular insulin (three times daily before meals) and NPH insulin at bedtime. Her initial HbA_{1c} at the time of referral was 7.6%. She was free of any clinical signs of diabetic retinopathy or peripheral neuropathy, and her urine microalbumin tests were negative. She had a prior history of hypoglycemia unawareness with recurrent episodes of severe hypoglycemia.

She was converted to lispro (Humalog) insulin before the evening meal, and her glycemic control was progressively

improved throughout the remainder of her pregnancy, with sequential HbA_{1c} results of 7.2, 6.1, and 5.8%. She was found on ultrasound to have lost one of her twins at 13 weeks' gestation, but she then went on to deliver a healthy baby girl by spontaneous vaginal delivery at 36 weeks' gestation. Other than transient neonatal hypoglycemia (nadir 25 mg/dl), and transient neonatal jaundice, the patient and infant did well postpartum. She was seen once during the postpartum period and was subsequently followed by her primary care physician.

She was referred back to us for management of her second pregnancy in May 2001, in the 9th week of gestation. She was taking regular insulin before breakfast, lispro insulin before her noon and evening meals, and NPH insulin at bedtime. Her HbA_{1c} was 5.5% and remained below 6.6% throughout the remainder of her pregnancy. Her pregnancy was complicated by nausea and dizziness during the daytime, and she was having frequent hypoglycemic reactions during the night. Her husband repeatedly found her unresponsive and diaphoretic between 1 A.M. and 3 A.M., despite reductions in her bedtime NPH insulin dose, and despite having an adequate bedtime snack. She required intramuscular glucagon injections on repeated occasions (as many as three times in 1 week) when her husband was unable to arouse her from sleep. She had normal blood pressure (132/70 mmHg) and heart rate (72 bpm), and her electrolytes were normal (K^+ 4.4 mEq/l). Although a random serum cortisol was low (4.6 g/dl) in the late afternoon, she was reluctant to undergo an ACTH stimulation test during her pregnancy.

Although insulin glargine had only recently been approved for use in the U.S., its use during pregnancy has not been studied and it is considered to be in Pregnancy Category C (1). Despite the lack of safety data in pregnancy, we made the decision to substitute evening glargine for her bedtime NPH insulin. It was deemed that the risks of repeated severe hypoglycemia and the potential for repeated glucagon injections, with resultant elevations in serum ketone levels, would likely have deleterious effects on the mother and fetus (2). She was therefore converted to insulin glargine in the evening during her 14th week of pregnancy, and NPH insulin was discontinued. Her subsequent diabetic control remained excellent, with HbA_{1c} levels $<6\%$ and serum fructosamine levels between 234 and 296 mol/l (normal range 0–285). She had no episodes of severe hypoglycemia requiring assistance or glucagon injection throughout the remainder of her pregnancy. Dilated eye exams during and after her pregnancy did not show signs of retinopathy. She was induced and delivered vaginally a healthy baby boy at 36 weeks' gestation. The birth weight was 7 lb 12 oz, and the baby did not appear macrosomic. The postpartum period was uneventful except for transient neonatal hypoglycemia requiring tube feedings for <48 h.

Insulin glargine has several potential advantages in the management of pregnancies complicated by type 1 diabetes. As in this case, nocturnal hypoglycemia may be a significant clinical problem in women attempting to maintain the stringent glycemic targets recommended for diabetic pregnancies (3). Because nocturnal hypoglycemia is less common with bedtime insulin glargine– versus bedtime NPH–based MDI insulin regimens (4), it may offer clear advantages in this clinical setting. Potential concerns of insulin glargine use during pregnancy are a report of increased mitogenicity of glargine versus human insulin in a malignant cell line (osteosarcoma Saos/B10) (5), and the observation of a three-grade progression of retinopathy in some patients with type 2 diabetes treated with insulin glargine for $\leq$1 year (6). Further studies are clearly needed to better define the efficacy and safety of insulin glargine use during pregnancy.

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Effect of C-Peptide on Glucose Metabolism in Patients With Type 1 Diabetes

In recent years, various biological activities of C-peptide have been confirmed, e.g., its ability to improve skin capillary blood flow in the feet, increase microvascular blood flow and oxygen uptake in the exercising forearm, decrease urinary albumin excretion, and improve nerve function in patients with type 1 diabetes (1,2). Furthermore, C-peptide stimulates glucose transport in human muscle strips of nondiabetic and diabetic subjects (3). Using a sequential insulin clamp technique, Li et al. (4) demonstrated that C-peptide in physiological concentrations stimulates body glucose utilization in diabetic rats. In a recent investigation by Grunberger et al. (5), C-peptide was shown to activate insulin receptor tyrosine kinase, insulin receptor substrate-1, tyrosine phosphorylation, phosphatidylinositol 3-kinase, mitogen-activated protein kinase phosphorylation, p90 Rsk (90-kDa ribosomal 56 protein kinase), and glycogen synthase kinase-3 phosphorylation. In addition, C-peptide mimics the effect of insulin, such as gly-

cogen synthesis and amino acid uptake in rat muscle cells. However, in clinical studies involving C-peptide treatment for 1 or 3 months in type 1 diabetic patients, no clear-cut effect on blood glucose concentrations could be observed (2). In summary, it remains to be elucidated whether C-peptide has a clinically relevant metabolic effect in humans.

We studied the glucodynamic effects of intravenous C-peptide infusion during a euglycemic glucose clamp in patients with type 1 diabetes. A total of 10 patients (6 men and 4 women, aged 25–45 years, duration of diabetes 15 ± 10 years) with baseline C-peptide levels <0.1 mmol/l were included in this double-blind, placebo-controlled, two-way crossover study. The patients arrived at the institute on the evening before the study. After admission, the patients were connected to a Biostator (Life Science Instruments, Elkhardt, IN) and remained fasting overnight. The blood glucose was stabilized at a target blood glucose level of 5.5 mmol/l by means of variable low-dose intravenous insulin infusion. Two hours before the start of the experimental procedure (C-peptide or placebo infusion), the insulin infusion was fixed at a constant rate of 0.2 mU · kg^{-1} · min^{-1}. This infusion remained constant until the end of the experiments. The patients received C-peptide (98% purity; Clinalfa AG, Läufelfingen, Switzerland) intravenously in two different concentrations, 2 pmol · kg^{-1} · min^{-1} for 90 min and 8 pmol · kg^{-1} · min^{-1} for another 90 min. For placebo infusion, the patients received D-mannitol (Clinalfa AG) in an equal amount. Areas under the curve for glucose infusion rates were calculated for the infusion time of C-peptide or placebo.

The amount of insulin infused overnight was identical on both study arms. Also, not-significant differences were observed with respect to the time course of the insulin infusion and the insulin levels established. C-peptide infusion resulted in an increase of serum C-peptide levels during the low infusion period from 0 to 0.58 ± 0.20 nmol/l (means ± SD) and to 2.3 ± 0.67 nmol/l during the high infusion period ($P <$ 0.01, respectively). In comparison with the metabolic effect observed during placebo infusion, the glucose infusion necessary to keep blood glucose constant was lower during the low C-peptide infusion period (26 [6–745] vs. 69 [33–132] mg · kg^{-1} · min^{-1}; $P < 0.05$) (median [interquartile range]) and tended to be lower during the high infusion period (29 [10–104] vs. 88 [63–120] mg · kg^{-1} · min^{-1}; $P = 0.07$). Total glucose consumption during the whole infusion period (180 min) was lower during C-peptide infusion compared with placebo infusion (48 [18–162] vs. 151 [51–287] mg · kg^{-1} · min^{-1}; $P < 0.05$). Serum insulin levels were comparable during placebo and C-peptide infusion periods (13 ± 8 vs. 12 ± 8 μU/ml; NS).

In contrast to the results obtained with isolated human muscle strips and in streptozotocin-induced diabetic rats, our study could not demonstrate an activation of glucose metabolism during short-term C-peptide supplementation in patients with type 1 diabetes. In this context, it is interesting that Grunberger et al. (5) found that the maximal insulinomimetic effects of C-peptide on rat muscle cells could be reached in a low concentration range (0.3–3 nmol/l) and that higher doses of C-peptide blunted the stimulatory responses. The authors speculated that low C-peptide and insulin concentrations might be helpful for fuel storage and that high postprandial C-peptide concentrations could blunt the peripheral insulin effects. Since, in our study, postprandial C-peptide levels had been reached already within the low infusion range, it might be possible that the C-peptide levels reached in our human experiment reflect a postprandial state and that they were in a range in which insulin effects on glucose metabolism are sufficiently inhibited. Further studies are necessary to evaluate whether there are dose-dependent differences in the effect of C-peptide on glucose metabolism in patients with type 1 diabetes in a low concentration range.

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GAD Antibody in Mitochondrial Diabetes Associated With tRNA$^{(UUR)}$ Mutation at Position 3271

A possible association of pancreatic autoimmunity with mitochondrial diabetes, which is associated with pathogenetic mitochondrial DNA (mtDNA) abnormalities (1), has been controversial. The study by Kobayashi et al. (2) and our study (3) previously reported that islet cell antibody (ICA) was detected in, respectively, 42% (13 of 31) and 18% (2 of 11) of patients with mitochondrial diabetes associated with tRNA$^{(UUR)}$ mutation at position 3243 (MD3243). These results support an mtDNA abnormality associated with ICA-related pancreatic autoimmune abnormality. Kobayashi et al. (2) and we (4) also reported that 6.5% (2 of 31) and 0% (0 of 11), respectively, of MD3243 patients had GAD antibody (GADA), suggesting that GADA is not often detected in MD3243. We speculated that immunological background is somewhat different

between autoimmune-associated mitochondrial diabetes and typical type 1 diabetes (4).

In 1996, we reported a family having mitochondrial diabetes associated with mitochondrial $tRNA^{(UUR)}$ mutation at position 3271 (MD3271) (5). The proband was treated with diet alone and had several manifestations that are common in MD3243. The details of his clinical pictures are described in our previous reports (5,6). When we studied him in 1996, at age 40 years, GADA was not detected (<0.3 units/ml). However, in 2001, the titer of GADA was found to be positive (4.4 units/ml; GADA is considered to be positive at >1.5, which is >3 SD above the mean of 100 normal controls), whereas his ICA remained negative (<1.25 Juvenile Diabetes Foundation units).

These findings are important for three reasons. First, this is the first report to provide evidence of pancreatic autoimmune disorder associated with mtDNA abnormality other than 3243 mtDNA mutation. Second, this case suggests that GADA can be detected with passage of time in mitochondrial diabetes. Third, the low titer of GADA and negative ICA suggest that the immunological background of MD3271 may be different from typical type 1 diabetes.

As for the mechanism by which GADA changes from negative to positive over time, several explanations could be possible. It has been hypothesized that mitochondrial dysfunction in pancreatic β-cells could produce hyperexpression of GAD (7). Myers et al. (8) reported that specific inhibition of mitochondrial respiration enhances the expression of GAD in both fetal mouse pancreatic tissue and hamster HIT-T15 cells. Furthermore, it is well known that with aging, mitochondrial function decreases and mtDNA mutations accumulate (9–11). Therefore, in mitochondrial diabetes, GADA could become positive because of the aging-related decline of mitochondrial function, which could be facilitated by the congenital handicap of having pathogenic mitochondrial DNA mutation. It might also be a result of the fluctuating feature of pancreatic autoimmune antibodies. Kobayashi et al. (12) reported that 5 of 49 ICA-positive patients with diabetes showed fluctuations of ICA reactivity during the observation period of ~67 months.

In conclusion, this is the first report to suggest the association of a mtDNA bp 3271 mutation with GADA. This case should be closely followed in the future, especially for pancreatic autoimmunity and insulin secretion capacity.

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Reducing Mistakes in Patient Administration of Glargine and Lispro

Adlersberg et al. (1) described two cases of patients who became severely hypoglycemic after mistaking rapid-acting insulins for long-acting insulin glargine (Lantus; Aventis, Parsippany, NJ). Mistakes by patients in administering different kinds of insulin is not a new phenomena. However, any measures taken to prevent confusion would be helpful, including the authors recommendations of improved patient awareness, alternative packaging, and a tinted solution. Although the insulin glargine vial is 1 cm taller and its circumference is smaller than both the lispro (Humalog; Eli Lilly, Indianapolis, IN) and aspart (Novolog; Novo Nordisk, Princeton, NJ) vials, they can still be confused.

A simple solution to this problem, which has been quite effective in my patients, is the implementation of the insulin pen or cartridge in the admnistration of the short-acting insulins. At present, glargine can only be injected using a syringe, and it may be a good idea to continue this method of delivery in patients using two different types of insulin in the

future, when glargine will be available in a cartridge or pen form.

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Increased Incidence of Type 1 Diabetes in the South of Spain

Recent studies, both within and outside Europe, of the incidence of type 1 diabetes in children have produced dissimilar results, although they generally agree on an important annual increase, especially in children <5 years of age (1). Data from Spain solely concerning the population of Catalonia (~15% of the Spanish population) showed a stable incidence from 1990 to 1994, with 12.3 type 1 diabetic subjects per 100,000 children <15 years of age (2). We present data concerning the change in the incidence of type 1 diabetes in the population of the pronvince of Málaga (Andalusia) over a period of 19 years. These data are in contrast with those reported by EURODIAB for the Spanish population (3). Studies reporting the changes in the incidence of type 1 diabetes in children around the world fail to show data for Spain (4). We therefore believe that in addition to showing interesting results (5), our study provides data worth collecting for inclusion in other reports.

Málaga is situated in southern Spain and has a population of 1,260,560 inhabitants (3.2% of all Spain), with 237,000 children (18.8%) <14 years of age. This study of diabetes tendency was carried out with incidence data in this population from 1982 to 2000. All type 1 diabetic children <14 years of age diagnosed between 1 January 1982 and 31 December 2000 were included. We used the capture-recapture method to estimate the degree of ascertainment of the primary source, which was through hospital records. The secondary source was the data from the Málaga Diabetes Association. The incidence was calculated with 95% CI, assuming a Poisson distribution. Two models were used to evaluate the tendency over time. The first was a nonparametric linear correlation model, where the coefficient of regression was the mean relative increase of the yearly incidence. The second was a logistic regression model, calculating the odds ratio of the global model.

During the 19-year period, a total of 739 diabetic children <14 years of age were registered prospectively. The degree of ascertainment was 98.8%, and there was no significant variation during the period. The linear tendency for the change in the incidence is expressed by regression equation: incidence = $0.60 \times$ year + 10.2 ($R^2 = 0.62$, $P = 0.01$).

The mean incidence during the whole period was 16.3 (15.1–17.4) per 100,000 (range 8.45–26.6); for 1990–1994 (the period published by EURODIAB), it was 16.7 per 100,000 (significantly greater than that for Catalonia), and for the last 5 years, it was 20.8 per 100,000. This latest figure reflects an area with a very high incidence of childhood type 1 diabetes. In a previous retrospective transverse study (6) from 1998 to 2000 in the provinces of Seville, Granada, and Málaga (3,850,000 inhabitants, 10% of the Spanish population), the mean incidence was 20.7 cases per 100,000, confirming the high incidence levels seen in the Málaga study. The latest data from the Catalonian register (1996–1998) show no significant change in incidence of type 1 diabetes (from 12.4 to 13.7 per 100,000).

Linear regression analysis of the tendency showed an annual increase of 3.15% (1.9–4.4), and logistic regression analysis showed an annual increase of 3.8% (2.4–5.2). This increase in type 1 diabetes in Málaga is similar to the mean reported for European countries (3.4%), but both the increase and the incidence are greater than that given for Spain in the EURODIAB study (3).

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Anticonvulsant Hypersensitivity Syndrome With Marked Eosinophilia in Treatment of Diabetic Neuropathy

Anticonvulsant hypersensitivity syndrome (AHS) caused by phenytoin, carbamazepine, or phenobarbital sodium is a rare, but sometimes life-threatening, drug reaction (1,2). These

drugs have been widely used not only for convulsive disease but also for neuralgia in diabetic neuropathy (3). Here, we report a very rare case of AHS with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) with marked eosinophilia in a patient with diabetic neuropathy.

CASE REPORT

A 50-year-old man with type 2 diabetes was prescribed carbamazepine for painful diabetic neuropathy. At 5 weeks after exposure, he suffered from malaise, appetite loss, rash, and intermittent fever. Carbamazepine was immediately stopped and he was admitted. He appeared drowsy and had intermittent fever (temperatures to 39.0°C), lymphadenopathy at the left axillary without tenderness, and purpuric skin rash on his face, trunk, and extremities. Laboratory studies revealed an alanine aminotransferase level of 754 IU/l, aspartate aminotransferase of 359 IU/l, alkaline phosphatase of 1,685 IU/l, γ-glutamyl transpeptidase of 1,483 IU/l, total bilirubin of 0.6 mg/dl, and peripheral white blood cell (WBC) count of 9,200/mm^3 with eosinophilia (23.1%, 2,125/mm^3).

Although liver dysfunction had improved immediately after cessation of the drug, his lymphoadenopathy had worsened, and his body temperature fluctuated between 37.5 and 39.0°C for another 2 weeks. The counts of both WBC and eosinophils increased considerably, reaching peaks of 23,100/mm^3 and 8,400/mm^3, respectively. He developed bilateral pleural effusion without any sign of congestion, although his cardiac function, including echocardiography, and renal function were normal. He also had marked hyponatremia of 124 mEq/l, with a urinary sodium level of 60 mEq/l, an arginine vasopressin of 1.2 pg/ml, and plasma osmolality of 268 mOsm/l. SIADH was diagnosed due to the absence of other diseases known to cause hyponatremia.

His eosinophilia and fever gradually improved, with the disappearance of pleural effusion 2 weeks after the cessation of carbamazepine. Concomitantly, his hyponatremia became normalized, with marked diuresis.

DISCUSSION

The diagnostic criteria for AHS are the triad of fever, rash, and internal organ involvement (1). The onset usually occurs 1–8 weeks after exposure (1). The fever may persist for several weeks, even after cessation of the drug (2). In AHS, hepatitis is the most common cause of death (2). Liver dysfunction may be worsened even after the discontinuation of the drug.

Hematological abnormalities such as leukocytosis with atypical lymphocytes, eosinophilia, or leukopenia are frequently observed (2). An absolute eosinophil count of >1,500/mm^3 can lead to multiple organ failure (4). In our case, the appearance of pleural effusion was notable, and its clinical course suggested that eosinophilia was involved in its pathogenesis, probably by causing pleuritis. Hyponatremia due to SIADH was also observed in our case, and carbamazepine has been reported as a cause (5,6). SIADH caused by carbamazepine is generally normalized by its discontinuation in a short period (6). But hyponatremia worsened even after cessation of the drug in our case. It was likely that AHS with eosinophilia and/or its organ involvement, such as pleural lesion, was involved in SIADH.

Phenytoin, carbamazepine, and phenobarbital are metabolized to hydroxylated aromatic compounds, and the insufficient detoxification of these metabolites by epoxide hydrolase might be involved in the development of AHS (7). This might be one of the reasons for the potential cross-reactivity with other aromatic anticonvulsants in AHS. The rechallenge was reported to induce the immediate toxic reaction, which might be fatal in some cases (2).

In vitro testing using lymphocyte toxicity assay has shown a familial occurrence of AHS, with an autosomal pattern of inheritance (7). This suggests the risk of patients' siblings' for a reaction to aromatic anticonvulsants. Because it is common that patients have a strong familial predilection for type 2 diabetes, the accurate diagnosis of AHS will also be important for siblings, especially in families with a strong history of diabetes.

The timely recognition of AHS and discontinuation of the drug are critical for avoiding fatal multiple organ failure. Attention must also be paid to the cross-reactivity of other aromatic anticonvulsants for the treatment of diabetic neuropathy in patients with AHS as well as the risk to siblings of patients.

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Is HbA_{1c} Influenced More Strongly by Preprandial or Postprandial Glycemia in Type 1 Diabetes?

The relative contribution of preprandial and postprandial glycemia to HbA_{1c} has been the subject of increased interest in recent years; however, according to the American Diabetes Association, there are insufficient data to determine this accurately (1).

The objective of our study was to evaluate the accuracy of preprandial and

postprandial glycemia in predicting overall glycemic control as estimated by HbA_{1c} in type 1 diabetes.

We analyzed 112 consecutive home blood glucose records from type 1 diabetic patients who were on an intensive diabetes therapy program and who had had diabetes for >5 years. Each home blood glucose record included the blood glucose values performed before and 2 h after breakfast, lunch, and dinner during a period of 6 weeks (mean number of glucose measures performed: 237). HbA_{1c} was measured at the end of each record period by high performance liquid chromatography. Home blood glucose monitoring was performed with the same glucose meters in all patients (One Touch Profile; Lifescan, Milipitas, CA).

Mean daily glycemia, mean preprandial glycemia, and mean postprandial glycemia values were obtained from each record. Records were classified in two groups, according to HbA_{1c} results: good glycemic control (HbA_{1c} <7%) and poor glycemic control (HbA_{1c} ≥7%). Regression lines for HbA_{1c} and each glycemic value were obtained. We calculated the expected values of glycemia (mean daily glucose, mean preprandial glucose, and mean postprandial glucose) for HbA_{1c} levels of 7% according to the corresponding regression line. We then used these values to make additional classifications of the records within the good and poor glycemic control groups. Sensitivity, specificity, and positive predictive value of mean daily glycemia, mean preprandial glycemia, and mean postprandial glycemia were calculated.

The study results showed that good glycemic control records (HbA_{1c} <7%) had significantly lower glycemic values than poor glycemic control records (HbA_{1c} ≥7%): mean daily glycemia 143.1 ± 14.8 mg/dl vs. 157.5 ± 15.4 mg/dl ($P = 0.000$), mean preprandial glycemia 136.2 ± 17.4 mg/dl vs. 152.8 ± 16.6 mg/dl ($P = 0.000$), and mean postprandial glycemia 151.9 ± 18.7 mg/dl vs. 162.8 ± 23.8 mg/dl ($P = 0.008$), respectively. Significant linear correlations were found between HbA_{1c} and mean daily glycemia ($r = 0.635$, $P = 0.000$), mean preprandial glycemia ($r = 0.631$, $P = 0.000$), and mean postprandial glycemia ($r = 0.415$, $P = 0.000$). Mean daily glycemia showed the best sensitivity (77%), specificity (71%), and positive predictive value (76%) in predicting good glycemic control. Mean preprandial glycemia had better sensitivity (74%), specificity (67%), and positive predictive value (73%) than mean postprandial glycemia (67, 61, and 67%, respectively).

The results of this study suggest that preprandial glycemia is a better predictor of overall glycemic control, as estimated by HbA_{1c}, than postprandial glycemia in type 1 diabetes.

Our data are in agreement with those recently reported in this journal by Bonora et al. (2) in type 2 diabetes and with a recent review of the available data on postprandial glucose by the American Diabetes Association (1). A higher contribution of preprandrial than postprandial glycemia to mean daily glycemia, due to the fact that more hours are spent in the interprandial period than in the postprandial one, could probably explain these findings. In fact, it was the mean daily glycemia that correlated the most strongly with HbA_{1c} in both the study by Bonora et al. and our study as well as in most of the available studies analyzed by the American Diabetes Association (1,2).

If postprandial glycemia is confirmed as an independent contributing factor in cardiovascular disease (3), the fact that preprandial glycemia is a better predictor of HbA_{1c} than postprandial glycemia could suggest that HbA_{1c} may not exactly reflect the harmful effects of hyperglycemia in diabetes macrovascular complications. This could explain why the Diabetes Control and Complications Trial (DCCT) and the U.K. Prospective Diabetes Study (UKPDS) showed a significant improvement in glycemic control (as estimated by HbA_{1c}) in the intensive therapy groups but did not definitely demonstrate a risk reduction in macrovascular complications.

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Risk Factors for Microalbuminuria and Macroalbuminuria in Type 2 Diabetic Patients

A 9-year follow-up study

Several risk factors have been related to the development of diabetic nephropathy (DN) in type 2 diabetic patients, such as hyperglycemia, arterial hypertension, dyslipidemia, and smoking (1–5). Higher urinary albumin excretion rate (UAER) levels, even within the normal range, have been suggested to predict the development of DN in type 2 diabetic patients (1,2). Glomerular hyperfiltration has been investigated as a putative risk factor with conflicting results (6,7).

The aim of this study was to analyze risk factors for micro- and macroalbuminuria in a cohort of 52 normoalbuminuric type 2 diabetic patients (UAER <20 μg/min, 30 men, aged 53 ± 6 years, diabetes duration 6 years). Baseline clinical and renal evaluation (glomerular filtration rate [GFR] and UAER measurements) was performed from January 1988 through December 1989 (8). Patients were reevaluated between January 1998 and March 2000; they were followed-up for a median of 9.3 years (range 2.4–11.6). All patients gave written informed consent before participating.

Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg. UAER was measured by radioimmunoassay

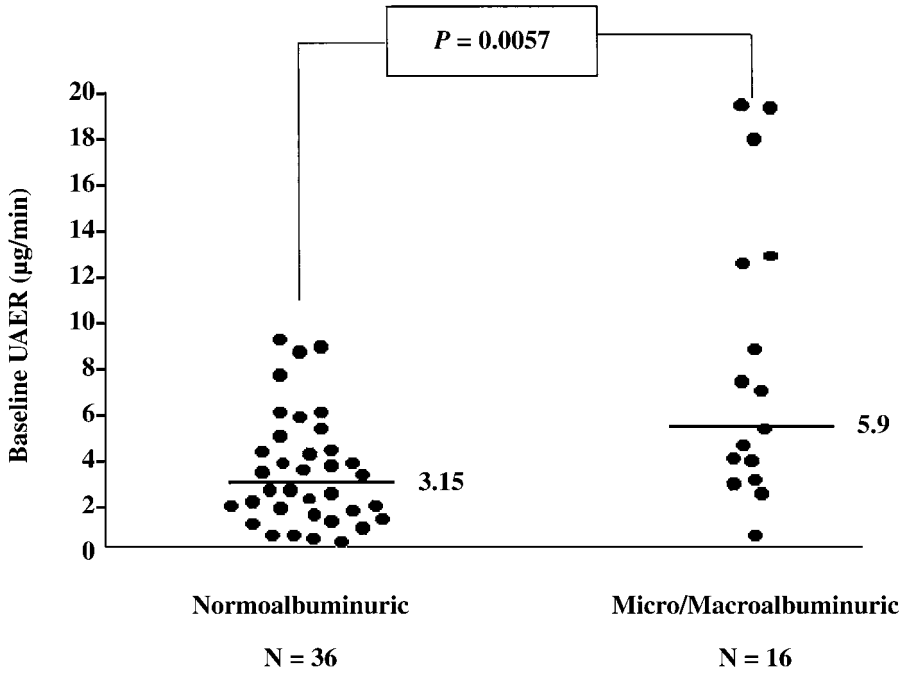

Figure 1—*Baseline UAER values of normo- and microalbuminuric patients at follow-up.*

(DPC, Los Angeles) at baseline and by immunoturbidimetry at follow-up (R = 0.98 for both methods) in random urine samples and was confirmed by 24-h collections of sterile urine over a 6-month period (interassay coefficient of variation [CV] 6.9% and intra-assay CV 3.8%). Micro- and macroalbuminuria were defined as UAER values of 20–200 and >200 μg/min, respectively, and were confirmed twice (9).

A total of 14 (27%) patients developed microalbuminuria, and 2 (4%) developed macroalbuminuria. These patients had higher baseline fasting plasma glucose (FPG) (12.10 ± 3.94 vs. 9.05 ± 3.33 mmol/l, P = 0.006) and UAER (median 5.9 vs. 3.2 μg/min, P = 0.0057) (Fig. 1) and a higher proportion of nonproliferative retinopathy (44 vs. 8%, P = 0.0057) than persistently normoalbuminuric patients. In a Cox regression analysis (backward stepwise), only UAER (hazard ratio [HR] 1.24, 95% CI 1.11–1.39, P = 0.0002) and retinopathy at baseline (9.3, 2.5–34.8, P = 0.001) remained significantly related to micro- and macroalbuminuria; blood pressure, GFR, and plasma glucose were excluded from the model. Of 16 micro- and macroalbuminuric patients, 5 presented baseline UAER >10 μg/min (χ^2 test, P = 0.0016). On the other hand, none of the persistently normoalbuminuric patients presented initial UAER above that level. Therefore, a Cox regression analysis was also performed with baseline UAER as an independent categorical variable (values above or below 10 μg/min). The HR for UAER >10 μg/min was 29.4 (95% CI 6.26–138.7, P = 0.0001), and the HR for retinopathy was 11.9 (3.0–47.2, P = 0.0004). FPG, mean arterial blood pressure, and GFR were excluded from the model.

There were no differences between the groups regarding the use of β-blockers (two users in each group) and ACE inhibitors (two patients in the persistently normoalbuminuric group and none in the other). GFR values (118 ± 22 vs. 125 ± 20 ml · min^{-1} · 1.73 m^{-2}) and the number of hyperfiltering patients (22 vs. 31%), respectively, were not different between the groups at baseline.

The observed cumulative incidence of 31% observed in our study is similar to that reported in other studies after a similar follow-up period: 34% in Finland (2) and 51% in Israel (5).

Gall et al. (1) described a significantly higher baseline albuminuria in patients who progressed compared with those who remained normoalbuminuric (14 vs. 7 mg/24 h), and UAER was significantly related to the development of DN in Cox regression. These data also suggest that levels of UAER below the critical value of 20 μg/min recommended by the American Diabetes Association (9) could be already signaling the presence of renal damage.

Diabetic retinopathy was also a strong risk factor and is probably a marker of the presence of microvascular disease rather than a risk factor per se, because nephropathy and retinopathy seem to share the same environmental predisposing factors, such as hyperglycemia and arterial hypertension.

In conclusion, higher normal UAER and nonproliferative retinopathy are predictors of micro- and macroalbuminuria. These data suggest that the currently recommended cutoff value of UAER used to predict development of micro- and macroalbuminuria should be lowered.

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Finger Sepsis in Two Poorly Controlled Diabetic Patients With Reuse of Lancets

Finger sepsis has been occasionally reported as a complication of home blood glucose self-monitoring (1,2). The use of automatic lancets with disposable needles should theoretically reduce the risk of infection. However, we observed two cases of finger sepsis in patients who used automatic lancets.

M.D., a 61-year-old women with BMI of 33.3 kg/m^2 and type 2 diabetes duration of 21 years, was treated with insulin (82 units/day in four administrations) and 2,550 mg/day metformin. HbA_{1c} was 14.0% (upper limit of normal 6.2%). The patient showed microalbuminuria with normal creatinine levels, chronic neuropathy with increased vibratory perception threshold bilaterally, and a neuropathic ulcer in the paramalleolar region of the left foot, whereas there was no evidence of retinopathy or macrovascular complications. The patient was also affected by hypertension, treated with enalapril and furosemide, and untreated hypertriglicerydemia and hypercholesterolemia. She was suffering from major depression, treated with amitriptiline and clomipramine. An abscess of the tip of the third finger of the right hand was observed; body temperature, measured at 2:00 P.M., was 37.8°C. *S. aureus*, *S. agalactiae*, and *E. faecalis* were isolated from the abscess. Despite general antibiotic treatment with teicoplanine, netilmicin, clindamicin, and ciprofloxacin as well as local antisepsis and drainage of the abscess, no significant improvement of the lesion was observed. The necrosis enlarged, and the results of a X-ray examination of the finger were compatible with the diagnosis of osteomyelitis. After 2 weeks, the third phalanx of the finger was amputated.

E.P, a 57-year-old woman, was affected by type 2 diabetes with a duration of 1 year, and her BMI was 27.6 kg/m^2. The patient was treated with insulin (20 units/day in four administrations), 7.5 mg/day glibenclamide, and 1,200 mg/day metformin. HbA_{1c} was 11.7%. She showed signs of neuropathy, with increased vibratory perception thresholds without any evidence of micro- or macrovascular complications. The patient also reported uncontrolled and untreated hypertension. Her mood was remarkably depressed. She showed an abscess of the tip of the third finger of the right hand, with extensive necrosis. *Staphylococcus* α-hemolytic, *Candida* nonalbicans, and unidentified anaerobial bacteria were isolated. Despite general treatment with teicoplanin, imipenem, and fluconazole, the lesion did not heal. The distal phalanx was amputated 3 weeks later.

Both patients were self-monitoring their blood glucose six times a week on average, using an automatic lancet. Although they had been advised to change disposable needles of the lancet each time, they both reported to have used the same needle for several weeks. Repeated use of a disposable needle could have contributed to infection. Poor metabolic control could have inhibited healing, contributing to the negative outcome. These two cases suggest that all patients, and particularly those with poor metabolic control, should be clearly instructed to change disposable needles of automatic lancets and to observe careful hygiene when self-monitoring blood glucose levels.

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Insulin Confusion: An Observation

This letter is in response to the letter of Adlersberg et al. (1). They reported two cases in which patients mistakenly administered a rapid-acting insulin instead of glargine insulin at bedtime, despite the distinct vial shape and purple markings used to differentiate glargine.

In our practice, we have had four similar incidences despite warning patients of the potential for confusion resulting from the similarities in appearance of these clear insulins. Each case we have experienced in our clinic has occurred with patients using a vial and syringe to administer the rapid-acting insulin.

Therefore, we have made it standard practice for patients starting on insulin glargine to use an insulin pen delivery system for bolus doses of short-acting insulin, if possible. This offers the dual benefit of the convenience of using the insulin pen for multiple daily injections as well as almost completely eliminating the possibility of confusing the long- and rapid-acting insulins.

When glargine is eventually marketed in pens, we hope that Aventis will clearly differentiate these pens by color, shape, and markings to prevent future mishaps from occurring.

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H.L. has received honoraria for speaking engagements from Eli Lilly, Takeda, Merck, Novo Nordisk, Aventis, and Knoll and holds stock in Pfizer.

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COMMENTS AND RESPONSES

Third Trimester Maternal Glucose Levels From Diurnal Profiles in Nondiabetic Pregnancies: Correlation With Sonographic Parameters of Fetal Growth

A response to Parretti et al. and Jovanovic

Parretti et al. (1) report an important study in which diurnal profiles performed on home blood-glucose monitoring were related to sonographic parameters of fetal growth. They imply in their introduction that the number of published studies concerning normoglycemia in nondiabetic pregnancies are few, a point that is also made by Jovanovic (2) in the accompanying editorial entitled "What is so bad about a big baby?"

Table 1 shows the diurnal plasma glucose profiles at 29 and 35 weeks gestation on identical diets from the subjects of our randomized controlled trial of low and relatively high dietary fiber diets given to women selected as being of normal weight and known to be nondiabetic (3). This study was published in 1983. In the original publication, two arms of the trial containing 12 and 13 subjects, respectively, were published separately for comparative purposes but have been combined for the purpose of this letter. Meals were taken as follows: breakfast before admission, midmorning snack at 1030 h, mid-day meal at 1200 h, mid-afternoon snack at 1515 h, evening meal at 1730 h, and supper at 2130 h. In these healthy women there was no deterioration in glucose homeostasis between 29 and 35 weeks gestation when studied on identical test meals (3).

In an earlier review (4) of factors possibly causative of macrosomia in the fetus of diabetic women, despite apparently good diabetic control, I raised three hypotheses that might explain how glucose could cause such an effect. The first hypothesis quoted Jovanovic et al. (5), stating that the postprandial glycemic peaks may be particularly high in diabetic pregnancy. However, these peaks may not be recorded on routine testing, a suggestion that has received further support in a recent publication from the North of England (6). The second hypothesis suggested that during overnight fasting, minor variations of fasting glycemia might have a disproportionate effect on fetal insulinization and growth. We provided some evidence to support this hypothesis in our own publication, again from nondiabetic women selected for body weight and studied in relation to fetal insulinization and neonatal anthropometry (7). This revealed a positive correlation between maternal fasting glucose in the third trimester and birth weight. The third hypothesis to explain macrosomia, despite good control in the diabetic mother, was that idiosyncracy might be operating in terms of transplacental glucose kinetics in individual maternal fetal pairs with different rates of glucose transfer, despite similar maternal glycemic levels. This latter hypothesis remains under investigation in our laboratory.

Table 1—*Diurnal plasma glucose profiles (mg/dl) at different gestational ages*

Hours	29 weeks	35 weeks
1000	86.7 ± 16.3	85.8 ± 14.3
1100	94.0 ± 20.5	91.1 ± 21.2
1200	90.4 ± 3.3	88.2 ± 18.3
1300	103.9 ± 21.0	102.1 ± 20.2
1400	90.9 ± 17.1	85.5 ± 14.6
1500	89.7 ± 15.3	84.7 ± 16.7
1600	91.5 ± 12.8	85.8 ± 13.2
1700	81.6 ± 12.3	79.6 ± 16.7
1800	99.0 ± 16.2	98.4 ± 22.9
1900	97.5 ± 23.3	102.7 ± 18.8
2000	87.7 ± 20.9	90.5 ± 14.1
2200	99.2 ± 15.9	91.7 ± 19.5
2400	86.3 ± 13.3	83.5 ± 15.4
0200	77.2 ± 13.7	74.5 ± 12.5
0400	73.5 ± 10.1	74.1 ± 12.9
0600	76.4 ± 10.2	73.8 ± 13.9
0700	74.0 ± 9.3	74.2 ± 11.5

Data are means ± SD.

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Response to Fraser

The letter by Dr. Robert Fraser (1) adds to the article by Paretti et al. (2) and to my editorial entitled, "What is so bad about a big baby?" (3). Fraser underscores the fact that the peak postprandial glucose response in normal

healthy pregnant women is at the 1-h postprandial time point. I appreciate that he combined his two studies into one table for reference. He showed that the highest blood glucose levels in normal pregnant women are <105 mg/dl, similar to the findings in the paper by Parretti et al., and in his table the peak appears 1 h after eating (lunch at 12 noon and peak response at 1:00 P.M.). The American Diabetes Association's treatment guidelines for pregnant diabetic women suggest that glucose levels can be as high as 140 mg/dl at the 1-h and 120 mg/dl at the 2-h postprandial time point, clearly recommending action only when the glucose is in hyperglycemic ranges, in comparison with the Parretti et al. study, our Diabetes in Early Pregnancy Trial (4), and the table presented in Dr. Fraser's letter. Perhaps maintaining such high thresholds for action in the treatment of diabetic pregnant women may have contributed to our sustained increased prevalence of macrosomia in infants of diabetic mothers, despite "good glucose control." It is time to reconsider our guidelines.

In addition, Dr. Fraser reminds us of his three theories as causative factors for macrosomia seen in pregnancies complicated by diabetes. Although his theories are all plausible, I would like to emphasize my belief that postprandial glucose may play the most important role by suggesting an additional theory that explains the significance of a transient postprandial elevation of maternal glucose. The renal threshold for glucose in the fetus is probably <110 mg/dl. We know this fact from the studies (5) of the renal threshold for glucose in premature neonates (<30 weeks gestation). When the maternal glucose level is >110 mg/dl, the intravenous glucose load for the fetus causes fetal glycosyria. Therefore, maternal diabetes out of control is associated with polyhydramios from fetal polyuria. After 20 weeks gestation, the fetus begins to swallow the amniotic fluid. Minor, transient elevations of blood glucose on the maternal side not only result in elevations of blood glucose on the fetal side, but also result in glucose-enriched amniotic fluid ingested by the fetus for hours. The gut stimulus for insulin production in the fetus may be more potent than the transient intravenous hyperglycemia. Thus, hyperglycemia for less than an hour once a day in the mother may produce a fetal insulin stimulus, through the oral route, for hours. Elevations of maternal glucose levels more frequently (after every meal, for example) may produce a more prolonged oral glucose load for the fetus. The "over-nutrition" of extra glucose provided to the fetus by both the intravenous route and the oral route produces an overfed, fat fetus.

I repeat: it is time to revise our guidelines for care of pregnant diabetic women to allow us to provide optimal nutrition for the fetus by taking action when the peak postprandial glucose level is elevated above the normal range. The normal range is now defined as a 1-h postprandial glucose level <105 mg/dl.

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Response to Fraser

In relation to our recent paper (1) on third trimester glucose levels in nondiabetic pregnant women, Dr. Fraser (2) reports some data on glucose profiles from nondiabetic nonobese pregnant women in the third trimester. We believe that these data are interesting first because there are few contributions on this topic and second because Dr. Fraser's study relies on glucose profiles consisting of 17 determinations per day. However, there are some important differences in the two studies. Our study involved 51 pregnant women undergoing home glucose self-monitoring throughout the third trimester, whereas Dr. Fraser's study relates to a smaller group of women who were hospitalized and investigated only at 29 and 35 weeks, therefore showing the same limiting factors (which were quoted in our manuscript) of all previous investigations on this subject.

In our study, we found a slight but progressive increase of glycemia throughout the third trimester, as assessed by comparing overall glucose values from glucose profiles between 28 and 38 weeks, whereas Dr. Fraser could not find any deterioration of glycemia during the third trimester. In this respect, it is noteworthy that, despite this trend of deterioration, the difference between overall glucose values at 28 and 38 weeks was not statistically significant in our study. Perhaps the failure to demonstrate deterioration in Dr. Fraser's investigation arises from the shorter time period considered (6 weeks). In addition, if we look at overall glucose values found in our study group between 28 and 34 weeks or between 30 and 36 weeks, this tendency of deterioration is much less evident. A comparison between our results and Dr. Fraser's findings is not possible because they used plasma glucose determinations, whereas we used blood glucose fingersticks. However, it seems that Dr. Fraser's results somewhat support our findings by confirming that glycemia at the 1-h postprandial time point in the third trimester of pregnancy is well below the currently accepted thresholds for a tight metabolic control in diabetic pregnancy and does not exceed 105 mg/dl.

Regarding the issue of factors possibly causative of macrosomia in diabetic pregnancy despite good metabolic control, we believe, in agreement with Jovanovic (3), that "macrosomia despite normoglycemia" is often "macrosomia because of undetected hyperglycemia." Actually, postprandial glycemic peaks can be very high in diabetic

women and may not be identified on routine glucose monitoring, but our study, providing a true definition of normoglycemia in nondiabetic pregnancy, suggests an additional possibility, "macrosomia because of undertreated hyperglycemia."

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