

Sulfonylurea Treatment Prevents Recurrence of Hyperglycemia in Obese African-American Patients With a History of Hyperglycemic Crises

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OBJECTIVE — Many newly diagnosed obese African-American patients with history of severe hyperglycemia or diabetic ketoacidosis (DKA) are able to discontinue pharmacological treatment with continued good metabolic control. However, many of these individuals relapse into hyperglycemia within 1 year. In such patients, we compared the effect of low-dose sulfonylurea and dietary therapy in the prevention of recurrence of hyperglycemia.

RESEARCH DESIGN AND METHODS — We conducted an intention-to-treat study in 35 obese newly diagnosed diabetic patients (17 with DKA and 18 with severe hyperglycemia). After discontinuation of insulin, seven of 17 patients with DKA and seven of 18 patients with hyperglycemia were managed with diet and glyburide (1.25–2.5 mg/day), whereas other patients were followed with diet alone. In all patients, pancreatic insulin reserve was documented 1 day after resolution of hyperglycemic crises and within 1 week of discontinuation of insulin. Recurrence of hyperglycemia was defined as fasting blood glucose >7.8 mmol/l (140 mg/dl) or random blood glucose >10 mmol/l (180 mg/dl) on two or more consecutive determinations, or $HbA_{1c} >7.5\%$.

RESULTS — Both treatment groups were comparable in age, sex, duration of diabetes, months of insulin therapy, BMI, glucose, and HbA_{1c} . At presentation, the acute C-peptide response to glucagon in obese DKA patients was lower than in patients with hyperglycemia ($P < 0.01$), but responses were comparable after discontinuation of insulin. Sulfonylurea treatment significantly reduced recurrence of hyperglycemia in both obese DKA and obese hyperglycemic patients ($P = 0.03$). With a median follow-up of 16 months, hyperglycemia recurred in six of 10 DKA patients and in five of 11 hyperglycemia patients treated with diet alone, compared with one of seven DKA and one of seven hyperglycemia patients treated with glyburide. Readmission with metabolic decompensation occurred in four patients treated with diet but in none of the patients treated with diet and glyburide.

CONCLUSIONS — Low-dose sulfonylurea therapy prevents recurrence of hyperglycemia in newly diagnosed obese African-American patients with a history of hyperglycemic crises.

Clinical trials in adults with NIDDM have demonstrated that control of hyperglycemia with hypocaloric diet (1,2), oral hypoglycemic agents (3,4), or insulin therapy (5) can induce remission of insulin dependency, particularly shortly after the onset of the illness (1,6). The dura-

tion of near-normoglycemic remission is variable, usually lasting several months (6,7), although long-lasting remissions of many years' duration have been reported (7,8). Remissions are more likely to occur in male individuals with shorter duration of diabetes and who are of normal body

weight or moderately obese (BMI < 30 kg/m²) (9–10). Remissions also appear to be more common in African-American than in white patients (8,10).

Obesity is common in African-American patients with diabetes; it is present in more than half of these patients with newly diagnosed diabetes and hyperglycemic crises (11). The rate of near-normoglycemic remission in these patients is not known, but clearly is of importance in the choice of long-term management. We recently reported (12) that aggressive management of decompensated diabetes results in significant improvement of β -cell function and insulin action, which allowed discontinuation of insulin therapy in 72% of obese African-American patients admitted with diabetic ketoacidosis (DKA) or severe hyperglycemia. Unfortunately, despite this initial response most obese patients relapse into hyperglycemia within 1 year of follow-up.

Several epidemiological, animal, and biochemical studies suggest that the major risk factor for the development of diabetic complications is hyperglycemia (13–15). The recent results of the Diabetes Control and Complications Trial (16) have provided confirmatory evidence that near normalization of glycemia reduces the development and progression of end-organ complications of diabetes. Thus, prevention of recurrence of hyperglycemia in diabetic patients who have successfully achieved near-normoglycemia is likely to decrease long-term diabetic complications. In this study, we determined the effect of low-dose sulfonylurea treatment in preventing recurrence of hyperglycemia after discontinuation of insulin in obese African-American patients with a history of hyperglycemic crises.

RESEARCH DESIGN AND METHODS

The study population of African-Americans included a total of 35 obese patients admitted with hyperglycemic crises, 17 patients with DKA, and 18 patients with severe hyperglycemia (Table 1). Obesity was defined as BMI ≥ 28 kg/m². The diagnosis of DKA was estab-

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DKA, diabetic ketoacidosis.

Table 1—Clinical characteristics of subjects on admission

| | Obese DKA | Obese hyperglycemia |
|--------------------------|--------------|------------------------|
| Number of patients | 17 | 18 |
| Age (years) | 41 ± 3 | 52 ± 3 † |
| BMI (kg/m ²) | 38 ± 2 | 39 ± 2 |
| New-onset diabetes | 15 (88) | 16 (89) |
| Glucose (mmol/l) | 36 ± 2 | 35 ± 2 |
| Bicarbonate (meq/l) | 13 ± 1 | 21 ± 1† |
| Venous pH | 7.2 ± 0.02 | 7.4 ± 0.01* |
| HbA _{1c} (%) | 13.4 ± 0.7 | 12.4 ± 0.6 |

Data are means ± SE or n (%). **P* < 0.01; †*P* < 0.05.

lished in the emergency room by a blood pH <7.30, a plasma glucose >13 mmol/l, a bicarbonate level <15 mEq/l, and a positive serum ketone assay at a dilution equal or greater than 1:4 dilutions. Hyperglycemic patients were defined as those with a blood glucose on admission >25 mmol/l, venous pH >7.30, bicarbonate >18 mEq/l, and negative serum ketones by the nitroprusside reaction.

Initial treatment of acute metabolic decompensation and assessment of pancreatic insulin reserve were performed in the metabolic unit at Grady Memorial Hospital, with a protocol approved by the Human Subjects Review Committee of Emory University School of Medicine. Informed written consent was obtained from all subjects. After resolution of hyperglycemia and/or ketoacidosis, all patients were treated with subcutaneous insulin (Humulin 70/30) twice daily. Patients were instructed in a weight-reducing American Diabetes Association diet, home glucose monitoring techniques, and self-adjustment of insulin dosage. Patient education, as well as dietary instruction, was the same for both groups. Dietary instruction was provided by the hospital staff dietitians, and reinforcement of instruction was given at each clinic visit. The insulin dose was adjusted to achieve fasting and premeal blood glucose levels ≤7.8 mmol/l. After discharge, patients were followed in the diabetes clinic at Grady Memorial Hospital every 2 weeks for the first 2 months, and then every month with a median follow-up of 16 months. β-cell function was determined by the acute C-peptide response to glucagon both 1 day after resolution of ketoacidosis and/or hyperglycemia and within 1 week of discontinuation of insulin

therapy. With the exception of diabetes and obesity, none had evidence of other diseases or were taking drugs known to affect carbohydrate metabolism. All patients with history of alcohol abuse or with obvious precipitating causes for the development of hyperglycemia (i.e., stress, infection, trauma) were excluded.

Obese patients who successfully discontinued insulin and remained in good metabolic control (fasting and premeal blood glucose <7.8 mmol/l) with diet alone for 1 week underwent a second glucagon-stimulated C-peptide test and were invited to participate in the study to determine whether treatment with low-dose sulfonylurea (glyburide 1.25–2.5 mg/day) would prevent the recurrence of hyperglycemia during follow-up. Patient randomization was based on the last digit of the hospital number to either ADA diet (odd numbers) or ADA diet plus glyburide (even numbers). Recurrence of hyperglycemia was defined as fasting serum glucose >7.8 mmol/l or random serum glucose >10 mmol/l, or HbA_{1c} >7.5%.

Assessment of β-cell function

Evaluation of pancreatic insulin reserve was performed 1 day after resolution of ketoacidosis and/or hyperglycemia and within 1 week of discontinuation of insulin therapy by measuring the changes in C-peptide levels after glucagon injection. Patients received 1 mg i.v. glucagon, and serum was obtained for glucose and C-peptide levels at 0, 3, and 6 min. All studies were begun at 8:00 A.M. after an overnight fast.

Analytic methods

Blood samples were collected in prechilled tubes and immediately centrifuged at 1,200 rpm to obtain a cell-free specimen. Serum was stored at –20°C until determination of glucose and C-peptide levels. Serum glucose was measured by the glucose hexokinase method with a Boehringer Mannheim/Hitachi 747-200 analyzer (Indianapolis, IN). Serum C-peptide was determined by the hospital laboratory using a double antibody radioimmunoassay method (Incstar RIA kit, Stillwater, MN).

Statistical analyses

Clinical and laboratory data of the patients was abstracted into an analytic database. Quality control procedures, database management, and all statistical analyses were performed using SAS software (SAS Institute, Version 5 ed., Cary, NC). Standard

descriptive statistics, including means, SD, medians, and ranges, were used to characterize the sample. Among both obese DKA and obese hyperglycemia patients, those randomized to diet alone and those on diet and glyburide were compared in terms of clinical characteristics as well as measures of pancreatic insulin reserve. For features that were continuous measures, the comparison was made with Student's *t* test or Wilcoxon's rank-sum tests (17) for variables that did not appear normally distributed, such as weight change. For features that were dichotomous, the comparison was made with Fisher exact test. Data are expressed as means ± SE. Statistical significance was defined as *P* < 0.05.

Time to recurrence of hyperglycemia was the primary endpoint for the comparison between the diet and the diet plus glyburide groups. Additional stratified and Cox's proportional hazards models were used to assess potential confounders of the treatment effect as well as to evaluate the predictive value of these independent variables. Such multivariate assessment will be limited in power, given the overall sample size of 35.

RESULTS

The clinical characteristics and metabolic parameters on admission are shown in Table 1. The obese DKA group (12 males and 5 females) included 15 patients with newly diagnosed diabetes and two with a known duration of diabetes of less than 2 years and had a mean BMI of 36 kg/m². The obese patients with hyperglycemia (8 males and 10 females) included 16 patients with newly diagnosed diabetes and had a mean BMI of 38 kg/m². A family history of diabetes was elicited in 80 and 72% of obese patients with DKA and hyperglycemia, respectively. Obese patients with DKA had a mean plasma glucose level of 37 mmol/l (652 mg/dl), serum bicarbonate of 13 mEq/l, venous pH of 7.25, and a positive acetoacetate ≥1:4. Obese hyperglycemic patients had a similar plasma glucose level on admission (36 mmol/l) but lacked features of metabolic acidosis. Admission levels of glycosylated hemoglobin were markedly elevated in both groups, with a mean HbA_{1c} ≥12%.

After resolution of hyperglycemia and/or ketoacidosis all patients were treated with subcutaneous insulin at a starting dose of 0.6 U/kg of body weight, and dosage was adjusted to achieve fasting and premeal blood glucose less than 7.8 mmol/l (140 mg/dl). During follow-up, insulin was tapered after blood glucose was at targeted

Table 2—Clinical characteristics of subjects at randomization

| | Obese DKA | | Obese hyperglycemia | |
|------------------------------------|-----------|-----------|---------------------|-----------|
| | Diet | Glyburide | Diet | Glyburide |
| Number of patients | 10 | 7 | 11 | 7 |
| Age (years) | 41 ± 4 | 41 ± 4 | 50 ± 4 | 55 ± 5 |
| BMI (kg/m ²) | 36 ± 3 | 42 ± 3 | 40 ± 3 | 37 ± 2 |
| New-onset diabetes | 10 | 5 | 10 | 6 |
| Glucose (mmol/l) | 5.5 ± 1 | 5.2 ± 1 | 5.8 ± 1 | 4.7 ± 1 |
| HbA _{1c} (%) | 6.8 ± 0.1 | 7.0 ± 0.1 | 6.8 ± 0.2 | 6.5 ± 0.1 |
| Weight change since admission (kg) | 5 ± 2 | 2 ± 2 | 1 ± 2 | 3 ± 1 |

Data are n or means ± SE.

levels for 2 weeks or sooner if a patient experienced hypoglycemic reactions. The mean time of insulin therapy until discontinuation of insulin was 9 ± 1 weeks in obese patients with ketoacidosis and 8 ± 1 weeks in obese hyperglycemic subjects. The clinical characteristics at randomization are shown in Table 2. Seven of 17 patients with DKA and seven of 18 patients with hyperglycemia received glyburide (1.25–2.5 mg/day) within 2 weeks of discontinuation of insulin, whereas the other patients were followed with diet alone. Both treatment groups were comparable in age, sex, duration of diabetes, BMI, glucose, and HbA_{1c} at randomization.

Pancreatic β -cell function

Pancreatic insulin reserve was determined by changes in serum C-peptide levels after glucagon administration, both 1 day after resolution of hyperglycemia and/or ketoacidosis and within 1 week of discontinuation of insulin. At presentation, with glucose averaging ~11 mmol/dl, basal and stimulated C-peptide levels in the obese DKA patients (1.6 ± 0.1 and 2.6 ± 0.2 ng/ml) were lower than in obese patients with hyperglycemia (1.9 ± 0.1 and 3.9 ± 0.2 ng/ml; both $P < 0.01$). The incremental C-peptide response to glucagon (incremental change in C-peptide over baseline levels) was 1.3 ± 0.2 ng/ml in obese patients with DKA, lower than the C-peptide response of 2.0 ± 0.3 ng/ml in obese hyperglycemic subjects ($P < 0.01$). During follow-up, obese patients with ketoacidosis exhibited a significant improvement in basal and stimulated C-peptide levels, with incremental C-peptide response to glucagon similar to obese patients with hyperglycemia (both, 1.6 ng/dl).

Clinical course

With a mean follow-up of 16 months, recurrence of hyperglycemia after discontinuation

of insulin was higher when patients were treated with diet alone compared with patients treated with diet and sulfonylurea. Hyperglycemia recurred in six of 10 patients with DKA and in five of 11 patients with hyperglycemia treated with diet alone compared with one of seven patients with DKA and one of seven patients treated with glyburide. A generalized Wilcoxon's survival curve analysis (Fig. 1) revealed that sulfonylurea treatment significantly reduced recurrence of hyperglycemia in both obese DKA and obese hyperglycemic patients ($P = 0.03$). Readmission with severe metabolic decompensation occurred in four patients treated with diet alone but in none of the patients treated with diet and glyburide. Readmissions were more common in patients with a previous history of DKA (three patients) compared with obese hyperglycemia (one patient). Despite an initial good response to diet therapy, two obese patients with a previous history of DKA developed a second episode of ketoacidosis 6 and 9 months after discontinuation of insulin without apparent precipitating cause. Dietary indiscretion was determined to be the precipitating cause for hyperglycemia in the other two patients who required readmission.

Analysis of clinical characteristics, weight change, and pancreatic insulin reserve failed to recognize factors that might predict patients at high risk of recurrence of hyperglycemia. The weight change during insulin treatment before randomization was comparable in both groups. The average weight loss from the time of withdrawal of insulin to relapse or completion of the study was 4 ± 3 kg in patients who responded to diet therapy, 6 ± 1 kg in patients who failed on diet alone, and 3 ± 1 kg in patients treated with diet and gly-

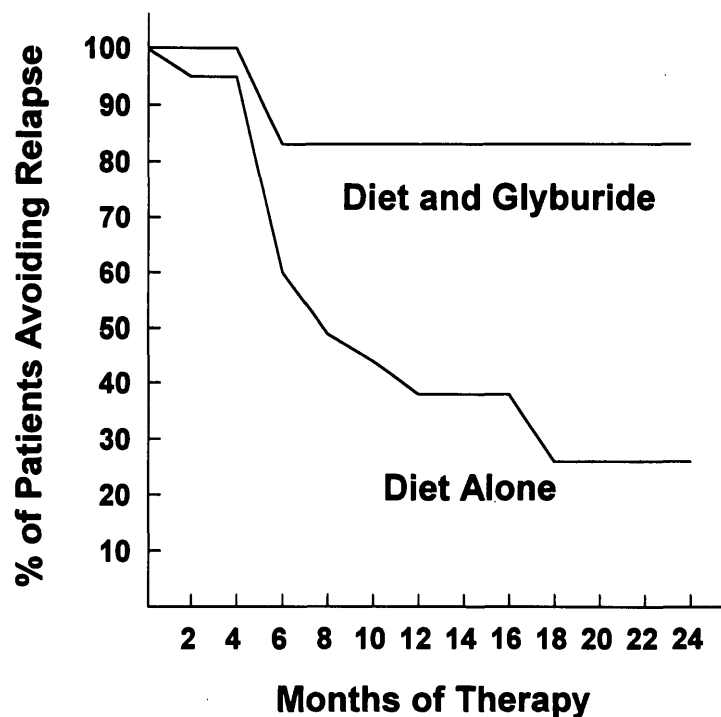


Figure 1—Percent of patients avoiding recurrence of hyperglycemia in obese African-American patients with a history of hyperglycemic crises. Low-dose sulfonylurea treatment significantly reduced recurrence of hyperglycemia ($P = 0.03$). A generalized Wilcoxon's test was used to contrast the Kaplan-Meier curves between the two groups.

buride. Thus, weight change was not an adequate reason for differences in recurrence of hyperglycemia among treatment groups. Similarly, although initial baseline and stimulated C-peptide tests were lower in obese patients with ketoacidosis compared with obese patients with hyperglycemia, at randomization the C-peptide response to glucagon was not different in patients with or without recurrence of hyperglycemia during follow-up. Proportional hazards modeling including age, sex, body weight, glucose, and HbA_{1c} failed to find confounders of the treatment effect or independent predictors of recurrence of hyperglycemia.

Treatment with sulfonylurea was well tolerated, and no serious hypoglycemic events occurred. Two patients taking 2.5 mg of glyburide had a blood glucose level of 3.3 mmol/l (60 mg/dl) or less at some time during therapy. None of these episodes were symptomatic, but the dose of glyburide in these patients was reduced by half without further episodes of hypoglycemia. Hypoglycemia was not a problem in obese diabetic patients treated with diet alone.

CONCLUSIONS — In contrast with the chronic insulin dependence of IDDM, most obese African-American patients with recently diagnosed diabetes admitted with hyperglycemic crises have a subsequent clinical course typical of NIDDM. Winter et al. (18) and Banerji et al. (19) described black patients with atypical diabetes who may present with symptoms of severe insulin deficiency, with or without ketoacidosis, but display features of NIDDM. Characteristically, these patients have negative autoimmune markers and measurable insulin secretion, which is intermediate between secretion in nondiabetic control subjects and that in patients with typical IDDM. Recently, we reported a group of obese African-American patients with DKA or severe hyperglycemia with similar clinical, metabolic, and immunological features (12). In these patients, aggressive management of their decompensated diabetes resulted in significant improvement in β -cell function and insulin sensitivity sufficient to allow discontinuation of insulin therapy.

The present study confirms our previous observation that improvement of metabolic control in obese patients with history of DKA or severe hyperglycemia results in significant improvement in basal and stimulated C-peptide levels, indicating that the initial poor insulin response cannot be

attributed to irreversible damage to β -cells but to a functional and reversible defect, probably a consequence of hyperglycemia. The harmful metabolic effects of chronic hyperglycemia have been referred to as “glucose toxicity” (20,21). Although the pathogenesis of glucotoxicity is not completely understood, it appears that hyperglycemia downregulates the glucose transport system (21), which impairs insulin secretion (22,23) and insulin action (23,24). In addition, chronic exposure to hyperglycemia may decrease insulin gene transcription and/or expression (25). Therefore, every attempt should be made to disrupt this vicious cycle by optimizing glycemic control.

We have observed that despite improvement in β -cell function and near-normoglycemia remission, many obese African-American patients with a history of severe hyperglycemia or ketoacidosis relapse into hyperglycemia within 1 year of follow-up. In an attempt to prevent such decompensation, we compared the effect of low-dose sulfonylurea versus hypocaloric diet after discontinuation of insulin. Our data indicate that low-dose sulfonylurea treatment significantly reduces recurrence of hyperglycemia in obese patients with history of hyperglycemic crises. In addition, our study indicates that although most obese African-American patients with recently diagnosed diabetes are able to discontinue insulin, they remain at high risk for recurrence of hyperglycemia if managed with diet alone. In such patients, the combination of hypocaloric diet and low-dose sulfonylurea is well tolerated and prevents both recurrence of hyperglycemia and readmissions with hyperglycemic crises.

Banerji et al. (26) were the first to report that prolongation of near-normoglycemia remission in black NIDDM subjects is significantly increased with glipizide treatment. These authors compared the effect of low-dose glipizide with placebo or no therapy in 30 black NIDDM subjects with history of severe hyperglycemia who remained in near-normoglycemic remission at least 3 months after discontinuation of all pharmacological antidiabetic therapy. During the course of therapy or follow-up, they observed recurrence of hyperglycemia in six of 10 subjects in the no-therapy and placebo groups and in two of 10 in the glipizide treatment group. In addition, to confirm this previous report, our results indicate that low-dose sulfonylurea can be started soon after discontinuation of insulin

therapy and that it prevents recurrence of hyperglycemia not only in obese patients with history of hyperglycemia but also in obese patients with history of ketoacidosis.

Interventions proposed for primary prevention or maintenance of remission in patients with NIDDM include weight reduction (2,7), exercise (2), and administration of drugs currently used in the treatment of NIDDM (3–6,8). Hypocaloric diets and weight loss improve glycemic control and allow some patients to keep their diabetes in remission for months to several years (2,6,7). Sulfonylurea drugs decrease hyperglycemia by increasing insulin secretion and insulin action (27). Patients who have achieved euglycemia on sulfonylurea therapy can be taken off of sulfonylurea, and ~50% will remain in remission for periods up to 6–12 months (7). Most of these patients, however, will relapse with hyperglycemia at some future time (6,28). Biguanide drugs, which inhibit hepatic glucose production (29,30) and increase the sensitivity of peripheral tissues to insulin (31), have also been shown to delay recurrence of hyperglycemia after cessation of therapy (32). Two additional drugs that may prove to be of benefit in prevention of NIDDM include thiazolidinediones, which improve insulin action (33), and glucosidase inhibitors, which decrease glucose levels by delaying intestinal glucose absorption (34). Long-term and randomized clinical trials combining dietary intervention with these agents are needed to determine the most efficacious therapeutic scheme to prevent the progression from near-normoglycemic remission to overt hyperglycemia.

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