Effects of Intravenous Glucose Load on Insulin Secretion in Patients With Ketosis-Prone Diabetes During Near-Normoglycemia Remission

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OBJECTIVE — Most patients with ketosis-prone type 2 diabetes (KPD) discontinue insulin therapy and remain in near-normoglycemic remission. The aim of this study was to determine the effect of glucotoxicity on β-cell function during remission in obese patients with KPD.

RESEARCH DESIGN AND METHODS — Age- and BMI-matched obese African Americans with a history of KPD ($n = 8$), severe hyperglycemia but without ketosis (ketosis-resistant type 2 diabetes, $n = 7$), and obese control subjects ($n = 13$) underwent intravenous infusion of 10% dextrose at a rate of 200 mg per m^2/min for 20 h. β-Cell function was assessed by changes in insulin and C-peptide concentrations during dextrose infusion and by changes in acute insulin response (AIR) and first-phase insulin release (FPIR) to arginine stimulation before and after dextrose infusion.

RESULTS — The mean ± SD time to discontinue insulin therapy was 7.1 ± 1.7 weeks in KPD and 9.6 ± 2.3 weeks in ketosis-resistant type 2 diabetes (NS). During a 20-h dextrose infusion, changes in insulin, C-peptide, and the C-peptide–to–glucose ratio were similar among diabetic and control groups. During dextrose infusion, subjects with ketosis-resistant type 2 diabetes had greater areas under the curve for blood glucose than subjects with KPD and control subjects ($P < 0.05$). The AIR and FPIR to arginine stimulation as well as glucose potentiation to arginine assessed before and after dextrose infusion were not different among the study groups.

CONCLUSIONS — Near-normoglycemia remission in obese African American patients with KPD and ketosis-resistant type 2 diabetes is associated with a remarkable recovery in basal and stimulated insulin secretion. At near-normoglycemia remission, patients with KPD displayed a pattern of insulin secretion similar to that of patients with ketosis-resistant type 2 diabetes and obese nondiabetic subjects.

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The majority of obese African American patients with newly diagnosed diabetes presenting with unprovoked diabetic ketoacidosis (DKA) display clinical and metabolic features of type 2 diabetes during follow-up and are able to maintain near-normoglycemic remission from several months to years without insulin or oral agents (1–7). This variant of type 2 diabetes has been referred to in the literature as atypical diabetes, type 1B diabetes, and ketosis-prone type 2 diabetes (KPD) (1,6). We and others have reported that for more than half of the patients with KPD, aggressive insulin therapy for ~10 weeks results in significant recovery of β-cell function and in improvement in insulin sensitivity to allow discontinuation of insulin therapy (2,3,5,8–10).

The underlying mechanism for the transient insulin deficiency leading to severe hyperglycemia ketoacidosis in African Americans with KPD is unknown. It is possible that sustained hyperglycemia per se before the development of DKA downregulates the β-cell insulin production capacity. The concept of "glucotoxicity" has been put forward to explain the contribution of toxic effects of hyperglycemia on β-cell function (11). The ability of patients with KPD to be withdrawn from insulin therapy and remain in near-normoglycemic remission suggests hyperglycemia-induced transient β-cell dysfunction. However, it is not known exactly how the β-cells respond to hyperglycemia and whether patients with KPD during the near-normoglycemia remission phase will display deterioration of insulin secretion after a sustained glucose challenge. In this study, we hypothesized that, compared with obese type 2 diabetic patients with hyperglycemia and obese nondiabetic control subjects, obese African Americans with KPD during near-normoglycemia remission will experience a diminished insulin response to sustained elevations in blood glucose or β-cell glucotoxicity. All subjects underwent a 20-h infusion of dextrose solution with serial measurements of insulin, C-peptide, and blood glucose and a sequential arginine stimulation test before and after dextrose infusion.

RESEARCH DESIGN AND METHODS — A group of 8 obese (BMI >30 kg/m^2) African American patients with newly diagnosed diabetes and a history of unprovoked DKA, 7 patients with ketosis-resistant type 2 diabetes, and 13 obese nondiabetic control subjects participated in this study. The diagnosis of DKA was established by standard American Diabetes Association criteria (12). The ketosis-resistant type 2 diabetes group included patients with recently diagnosed diabetes with blood glucose >400 mg/dl but without metabolic acidosis or ketosis. The control nondiabetic group included obese subjects, matched

for age and BMI, with a fasting glucose <100 mg/dl and a 2-h glucose <140 mg/dl during a (75-g) oral glucose tolerance test. This study was conducted at the Clinical Research Center at Grady Memorial Hospital (Atlanta, GA) and was approved by the Emory University institutional review board.

At presentation, diabetic patients with DKA and hyperglycemia were treated with a low-dose intravenous insulin infusion protocol (12). After resolution of ketoacidosis and/or hyperglycemia, patients were treated with NPH and regular insulin twice daily at a starting dose of 0.8 units/kg body weight and weaned per our previously described protocol (13).

Near-normoglycemia remission was defined as the ability to discontinue insulin therapy for >1 week and remaining in good glycemic control (fasting blood glucose <130 mg/dl, random blood glucose <180 mg/dl, and A1C <7%). Diabetic subjects were admitted to the Grady Memorial Hospital Research Center ≥1 week after discontinuation of insulin therapy. After an overnight fast, an intravenous catheter was placed in each forearm, one for infusion and one for blood sampling.

Twenty-hour dextrose infusion protocol

An infusion of 10% dextrose with 5 mEq/l of KCl was administered for 20 h at 200 mg per m²/min. The administration of dextrose at this rate has been shown to result in mild-to-moderate elevation in blood glucose levels in controlled studies (14). During dextrose infusion, blood samples were also drawn every 60 min for the determination of insulin and C-peptide and every 4 h for measurement of free fatty acids (FFAs). The glucose infusion started at 12:00 noon and continued until 8:00 A.M. on the next morning. Subjects consumed a 2,000 calories/day isocaloric diet (20% of calories derived from protein, 30% from fat, and 50% from carbohydrate) served before the dextrose infusion and at 6:00 P.M. during the glucose infusion.

Arginine stimulation test

An arginine stimulation test enables estimations of the β-cell function and the glucose potentiation of insulin secretion (15). Two sequential arginine stimulation tests were performed, the first set before and the second after completion of the 20-h dextrose infusion. Each arginine stimulation test set was performed at baseline and after a 45-min infusion of 10% dextrose at 200 mg per m²/min. A maximally stimulatory dose of 10% arginine (5 g) was injected as a bolus over a period of 30 s, and blood samples were drawn at −30, 0, 2, 3, 4, 5, 7, 15, and 30 min for measurement of glucose and insulin levels.

Calculations

Acute insulin response (AIR) to arginine was defined as the difference between basal (−30 and 0 min) and the mean insulin values at 2, 3, 4, and 5 min after each arginine pulse at fasting glucose (AIR_1) as well as after 45 min of dextrose infusion at 200 mg per m²/min (AIR_2). First-phase insulin release (FPIR) was calculated as the sum of the insulin levels at 2, 3, 5, and 7 min after arginine infusion. Insulin resistance was estimated by homeostasis model assessment of insulin resistance (HOMA-IR) derived from fasting plasma glucose and insulin (HOMA-IR = fasting insulin [milliunits per liter] × fasting glucose [millimoles per liter]/22.5). We also estimated insulin sensitivity for the level of insulin secretion (HOMA-IR/FPIR), which is predictive of progression to β-cell failure and to type 1 diabetes (16).

Laboratory methods

Plasma glucose was measured using the glucose oxidase method. Levels of insulin, C-peptide, and FFAs were measured in plasma using solid-phase, two-site sequential chemiluminescent immunometric assays on the DPC Immulite analyzer (Diagnostic Products, Los Angeles, CA). The instrument calibrations for the assays were performed as recommended by the manufacturer and were within the specifications.

Statistical analysis

All data in the text and tables are expressed as means ± SD, and the data in figures are expressed as means ± SEM. Comparisons among the nondiabetic control group, KPD group, and obese diabetic group with hyperglycemia were conducted using a nonparametric Kruskal-Wallis test for continuous variables and a Fisher exact test for categorical variables. Further analysis for statistical differences between groups was performed by ANOVA. With glucose infusion data, repeated-measures analyses were performed to assess the group difference simultaneously with the change over time in blood glucose, insulin, and C-peptide–to–glucose ratio, adopting an AIR_1 within-subjects correlation structure. Statistical significance was defined as $P < 0.05$. Statistical analysis was performed using SAS (version 9.2; SAS Institute, Cary, NC).

RESULTS

Patient characteristics

The clinical characteristics of patients with KPD, patients with ketosis-resistant diabetes, and nondiabetic control subjects are shown in Table 1. Age and BMI were similar among study groups. Most patients with KPD and ketosis-resistant type 2 diabetes had a strong family history of diabetes, had newly diagnosed diabetes at presentation, and were predominantly men. On admission, the patients with KPD had a mean blood glucose level of 712 ± 342 mg/dl and had metabolic acidosis. The ketosis-resistant diabetic patients with hyperglycemia had an admission blood glucose of 492 ± 163 mg/dl but lacked the features of metabolic acidosis (Table 1). The mean time to achieve remission and insulin discontinuation was similar in obese patients with KPD and ketosis-resistant diabetes (Table 1). At remission, both groups of patients with diabetes had similar glucose and A1C levels.

Metabolic studies and AIR to arginine stimulation

The results of fasting glucose and plasma insulin levels and arginine stimulation tests are shown in Table 2. At near-normoglycemic remission, plasma concentrations of fasting blood glucose, insulin, C-peptide, and HOMA-IR values were not significantly different between patients with KPD and obese nondiabetic control subjects (NS). However, patients with ketosis-resistant diabetes had higher fasting glucose and HOMA-IR compared with control subjects ($P < 0.05$). Fasting FFA levels were not significantly different between diabetic patients at remission and control subjects (Table 2).

AIR and FPIR to arginine stimulation was not significantly different in patients with KPD and ketosis-resistant type 2 diabetes compared with those in control subjects both before and after a 20-h dextrose infusion (Table 2, Fig. 1). Similarly, the FPIR adjusted for insulin sensitivity (HOMA IR–to–FPIR ratio) was similar between groups before and after a glucose load (Table 2).

Table 1—Clinical features of control subjects and subjects with KPD and ketosis-resistant type 2 diabetes presenting with hyperglycemia

	Control	KPD	Ketosis-resistant diabetes
n	13	8	7
Age (years)	40.0 ± 9.3	42.8 ± 10.6	49.7 ± 8.1
Sex (male/female)	1/12	6/2	5/2
Newly diagnosed diabetes (%)	—	100	100
Family history of diabetes (%)	77	88	100
BMI (kg/m²)	35.5 ± 5.0	38.6 ± 4.9	37.2 ± 5.6
Weight (kg)	96.3 ± 13.9	120.3 ± 23.3	110.2 ± 19.7
Body surface area (m²)	2.1 ± 0.2	2.4 ± 0.3	2.3 ± 0.3
Blood glucose at presentation (mg/dl)	90 ± 9	712 ± 342*	492 ± 163*
A1C at presentation (%)	—	12.1 ± 3.6	13.0 ± 2.3
Bicarbonate (mmol/l)	—	14 ± 4†	24 ± 3
pH	—	7.20 ± 0.22	7.37 ± 0.04
Anion gap (mmol/l)	—	24.8 ± 7.2†	12.8 ± 5.4
β-Hydroxybutyrate (mmol/l)	—	6.3 ± 3.0†	1.02 ± 0.4
Time to remission (weeks)	—	7.1 ± 1.7	9.6 ± 2.3
A1C at remission (%)	—	5.9 ± 0.3	6.4 ± 1.1
Blood glucose at remission (mg/dl)	—	95 ± 9	104 ± 18

Data are means ± SD or %. *$P < 0.01$ vs. control. †$P < 0.05$ vs. ketosis-resistant diabetes.

Glucose, insulin, C-peptide–to–glucose ratio, and FFAs during 20-h dextrose infusion

Dextrose infusion at a rate of 200 mg per m²/min (~25 g glucose/h or 250 ml/h of 10% dextrose solution for a 100-kg person) resulted in mild elevation of blood glucose from baseline in both diabetic and control subjects (Fig. 2*A*). Repeated-measures analyses showed that, during the infusion, blood glucose concentration significantly increased over time from baseline in all groups ($P < 0.05$). However, the patients with KPD had only mild blood glucose elevation during a 20-h dextrose infusion, which was similar to that in the control group; in contrast, the patients with ketosis-resistant diabetes had greater blood glucose elevation during dextrose infusion compared with that in the two other groups ($P = 0.006$). The area under the curve for glucose levels was similar between the control and KPD groups but was significantly greater in obese subjects with ketosis-resistant type 2 diabetes at 2,469 ± 254, 2,804 ± 344, and 3,607 ± 254 mg/dl per 20 h, respectively ($P = 0.002$).

All subjects experienced statistically significant increases in insulin concentration and insulin secretion as assessed by the C-peptide–to–glucose ratio during the 20-h glucose infusion (Fig. 2*B* and *C*). However, neither subjects with KPD nor those with ketosis-resistant diabetes had significant changes in insulin and the C-peptide–to–glucose ratio compared with the control group assessed at most time points (Fig. 2*B* and *C*) or by the area under the curve (NS).

In nondiabetic control patients, dextrose infusion was associated with a significant decrease in FFA levels. Preinfusion FFA levels (113 ± 21 μmol/l) markedly declined during dextrose infusion to 63 ± 8, 70 ± 7, 56 ± 2, and 42 ± 8 μmol/l at 8, 12, 16, and 20 h, respectively ($P < 0.05$). In contrast, in the groups with KPD and ketosis-resistant diabetes, levels of FFAs did not substantially change from the baseline value throughout the 20-h dextrose infusion (NS).

CONCLUSIONS — The two major findings in our study are the remarkable recovery of basal and stimulated insulin secretion during the near-normoglycemic remission in patients with newly diagnosed KPD, and the lack of β-cell failure (glucotoxicity) after a short-term intravenous dextrose infusion. Patients with KPD at near-normoglycemia remission showed a magnitude of insulin secretion in response to a 20-h dextrose infusion and AIR to arginine stimulation similar to the response observed in nondiabetic control and ketosis-resistant type 2 diabetic subjects.

A large body of evidence indicates that the majority of patients with KPD display clinical, metabolic, and immunological features of type 2 diabetes, are able to discontinue insulin therapy in 2–3 months, and remain in normoglycemic remission for months to several years (1–3,5,6). Previous work demonstrated that at presentation patients with KPD have no insulin response to glucose; however, during remission such patients are able to produce insulin in response to intravenous glucose similar to nondiabetic subjects (5,7). In addition, the resolution of hyperglycemia after 10–12 weeks of in-

Table 2—Metabolic characteristics of nondiabetic control subjects, subjects with KPD, and subjects with ketosis-resistant type 2 diabetes at near-normoglycemia remission

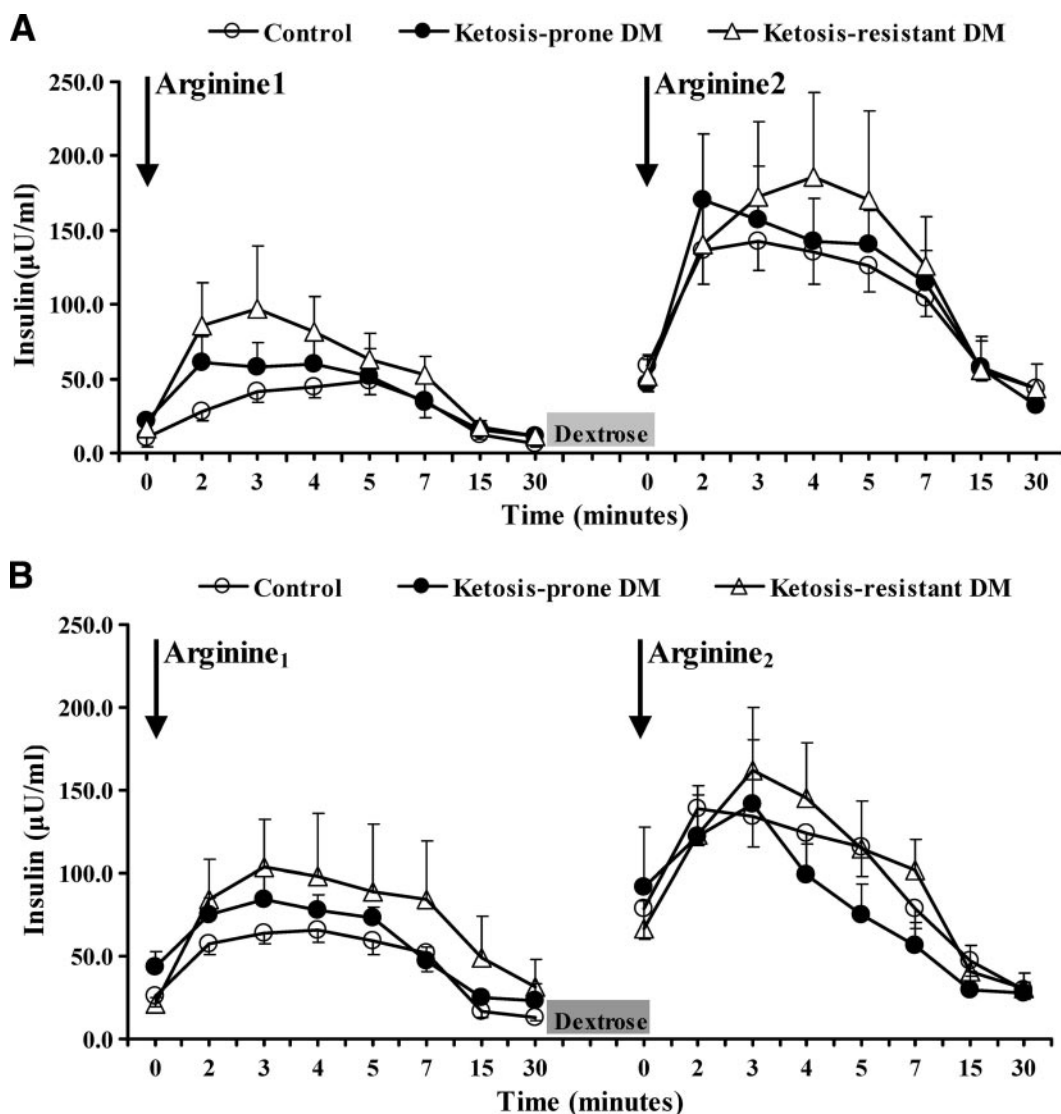|	Control	KPD	Ketosis-resistant diabetes
n	13	8	7
Fasting glucose (mg/dl)	88 ± 2	95 ± 3	104 ± 8*
Fasting insulin (μU/ml)	10.7 ± 1.7	16.0 ± 4.5	15.8 ± 3.0
Fasting C-peptide (ng/ml)	2.3 ± 0.6	2.7 ± 0.6	2.7 ± 0.6
HOMA-IR	2.3 ± 0.4	3.6 ± 1.0	4.0 ± 0.8*
FFAs (μmol/l)	113 ± 21	120 ± 35	117 ± 29
AIR and FPIR to arginine stimulation and HOMA-IR–to–FPIR ratio before and after glucose infusion (200 mg per m²/min) for 20 h			
Before 20-h glucose infusion			
Preinfusion AIR$_1$ (μU/ml)	31 ± 6	39 ± 14	52 ± 23
FPIR (μU/ml)	197 ± 33	264 ± 80	339 ± 221
HOMA-IR–to–FPIR ratio	0.014 ± 0.003	0.015 ± 0.003	0.013 ± 0.002
After 20-h glucose infusion			
Postinfusion AIR$_1$ (μU/ml)	40 ± 5	34 ± 13	62 ± 27
FPIR (μU/ml)	299 ± 30	359 ± 42	381 ± 147
HOMA-IR–to–FPIR ratio	0.010 ± 0.002	0.012 ± 0.005	0.013 ± 0.005

Data are means ± SE. *$P < 0.05$ vs. control.

Figure 1—*Arginine stimulation tests performed before (A) and after (B) a 20-h dextrose infusion in control subjects, subjects with KPD, and subjects with ketosis-resistant diabetes (DM). A maximally stimulatory dose of 10% arginine (5 g) was injected at baseline plasma glucose and after an infusion of 10% dextrose at 200 mg per m²/min for 45 min. Data are means ± SE. BG, blood glucose in milligrams per deciliter.*

sulin therapy results in improvement of peripheral insulin sensitivity. Hence, these studies suggested that patients with KPD who achieved near-normoglycemic remission may not have irreversible β-cell damage; rather, these patients who present with a hyperglycemic crisis have only transient functional abnormalities of insulin secretion or β-cell "desensitization."

Evidence has shown that the continuous exposure of β-cells to an elevated glucose concentration impairs insulin production and, if high glucose persists long enough, leads to irreversible damage of β-cells, a concept called "glucotoxicity" (11). Although most evidence supporting the phenomenon of β-cell damage is born from in vitro and in vivo studies (17), the

concept of pancreatic glucotoxicity is thought to underlie loss of insulin production in the progression of type 2 diabetes (18,19). Intensive insulin treatment has been shown to provide long-term β-cell benefits not only in KPD but also in the setting of initial therapy for type 2 diabetes. Weng et al. (20) recently reported that 1 week of intensive insulin administration in patients with newly diagnosed type 2 diabetes resulted in remission of diabetes in half of the patients after 1 year of follow-up. In our study, we tested whether prolonged glucose exposure in patients with KPD at remission would result in β-cell dysfunction. We found that the patients with KPD experience increases in insulin and C-peptide levels and in the C-peptide–to–glucose ratio

similar to those in control subjects during the 20-h dextrose infusion (Fig. 2). In addition, control subjects and patients with KPD had a comparable area under curve for glucose, suggesting that insulin-mediated glucose disposal in patients with KPD at remission is similar to that observed in nondiabetic obese subjects.

In an attempt to understand the in vivo phenomenon of pancreatic glucotoxicity, β-cell responsiveness to prolonged dextrose infusion was studied previously in healthy subjects. In lean or overweight nondiabetic humans, the infusion of dextrose ranging up to 68 h and resulting in sustained hyperglycemia at levels between 108 and 170 mg/dl did not cause suppression of insulin secretion (14, 21,22). Also, ex vivo incubation of human
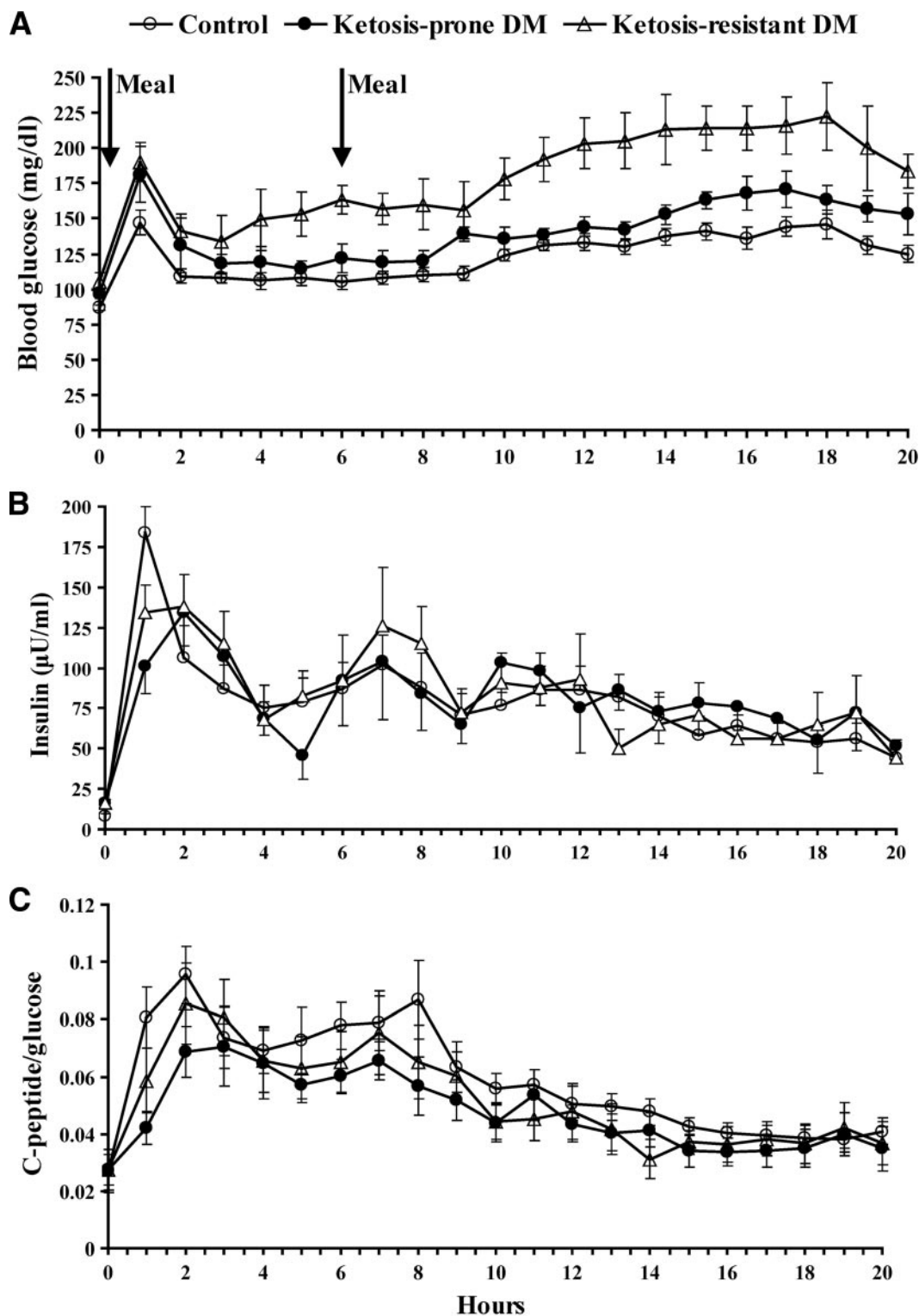
Figure 2—*Changes in blood glucose (A), insulin (B), and the C-peptide–to–glucose ratio (C) during a 20-h glucose infusion as 10% dextrose at 200 mg per m²/min in control subjects, subjects with KPD, and subjects with ketosis-resistant diabetes (DM) 1 week after achieving near-normoglycemic remission. Data are means ± SE.*

β-cells with medium containing 180 mg/dl revealed no signs of glucotoxicity (23). Boden et al. (21), however, demonstrated that, in overweight subjects, insulin secretion did not fall until 68 h of dextrose infusion that was associated with a blood glucose level of 227 mg/dl. We do not know whether exposure to higher glucose concentrations would result in β-cell failure in patients with KPD.

The hyperglycemic potentiating effect of the insulin response to arginine is a sensitive indicator of β-cell secretory capacity (18,24). The patients with KPD demonstrated an appropriate glucose-

potentiating effect in response to arginine injection (Table 2). We did not observe increases in insulin secretion in all groups studied in response to the second arginine infusion after a 20-h dextrose infusion (Table 2, Fig. 1); however, we were not able to achieve a similar degree of hyperglycemia during the second arginine infusion. The ability of patients with KPD to appropriately increase insulin secretion to prolonged glucose infusion and during repeated arginine stimulation indicated a remarkable recovery of insulin secretion during near-normoglycemia remission. These results suggest that the patients with KPD during remission have significant β-cell reserve to counteract the deleterious effect of short-term mild hyperglycemia.

Our study also indicates that patients with ketosis-resistant type 2 diabetes are more insulin resistant than the patients with KPD. The surrogate marker of insulin resistance, HOMA-IR, was higher in the patients with ketosis-resistant diabetes (Table 2), and blood glucose levels were also higher during a 20-h dextrose infusion, suggesting lower glucose utilization than that in control subjects and patients with KPD (Fig. 2). These findings are in accord with previous work by Garvey et al. (25). These authors demonstrated that in patients with poorly controlled type 2 diabetes, intensive insulin therapy for 3 weeks results in improvement in β-cell function; however, despite improved glycemic control, patients will remain insulin-resistant. Increased peripheral insulin resistance in patients with KPD and ketosis-resistant diabetes compared with healthy control subjects is also suggested by the lack of suppression of FFA during a 20-h dextrose infusion.

We acknowledge the following limitations in this study. We anticipated that the infusion of dextrose at 200 mg per m^2/min for 20 h (10% dextrose at 250–300 ml/h) would result in significant hyperglycemia in patients with a recent history of DKA and/or severe hyperglycemia. However, we observed only mild hyperglycemia that may not have been sufficient to impair β-cell responses. A higher dextrose infusion rate resulting in a higher glucose concentration may be needed to achieve significant glucotoxicity (21). It is also feasible that the development of glucotoxicity requires the presence of elevated FFAs. In addition to inhibiting insulin action, recent evidence indicates that FFAs have an important role in regulation of β-cell function (11).

Finally, our study included only African Americans, so the effect of prolonged dextrose infusion in patients with KPD from different ethnic populations needs to be determined in future studies.

In summary, our studies demonstrate that, in patients with KPD, near-normoglycemia remission is associated with a remarkable recovery in insulin secretion. Despite a recent history of severe hyperglycemia and ketoacidosis, patients with KPD in remission had basal and stimulated insulin secretion similar to those in obese healthy control subjects sufficient to prevent hyperglycemia during dextrose infusion.

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