Lack of Lipotoxicity Effect on β-Cell Dysfunction in Ketosis-Prone Type 2 Diabetes

Guillermo E. Umpierrez, md[1]
Dawn Smiley, md[1]
Gonzalo Robalino, md[1]

Limin Peng, phd[2]
Aidar R. Gosmanov, md, phd[1]
Abbas E. Kitabchi, phd, md[3]

OBJECTIVE — Over half of newly diagnosed obese African Americans with diabetic ketoacidosis (DKA) discontinue insulin therapy and go through a period of near-normoglycemia remission. This subtype of diabetes is known as ketosis-prone type 2 diabetes (KPDM).

RESEARCH DESIGN AND METHODS — To investigate the role of lipotoxicity on β-cell function, eight obese African Americans with KPDM, eight obese subjects with type 2 diabetes with severe hyperglycemia without ketosis (ketosis-resistant type 2 diabetes), and nine nondiabetic obese control subjects underwent intravenous infusion of 20% intralipid at 40 ml/h for 48 h. β-Cell function was assessed by changes in insulin and C-peptide concentration during infusions and by changes in acute insulin response to arginine stimulation (AIR_{arg}) before and after lipid infusion.

RESULTS — The mean time to discontinue insulin therapy was 11.0 ± 8.0 weeks in KPDM and 9.6 ± 2.2 weeks in ketosis-resistant type 2 diabetes ($P = $ NS). At remission, KPDM and ketosis-resistant type 2 diabetes had similar glucose (94 ± 14 vs. 109 ± 20 mg/dl), A1C (5.7 ± 0.4 vs. $6.3 \pm 1.1\%$), and baseline AIR_{arg} response (34.8 ± 30 vs. 64 ± 69 μU/ml). $P = $ NS despite a fourfold increase in free fatty acid (FFA) levels (0.4 ± 0.3 to 1.8 ± 1.1 mmol/l, $P < 0.01$) during the 48-h intralipid infusion; the response to AIR_{arg} stimulation, as well as changes in insulin and C-peptide levels, were similar among obese patients with KPDM, patients with ketosis-resistant type 2 diabetes, and nondiabetic control subjects.

CONCLUSIONS — Near-normoglycemia remission in obese African American patients with KPDM and ketosis-resistant type 2 diabetes is associated with a remarkable recovery in basal and stimulated insulin secretion. A high FFA level by intralipid infusion for 48 h was not associated with β-cell decompensation (lipotoxicity) in KPDM patients.

Diabetes Care 33:626–631, 2010

More than half of newly diagnosed African American patients presenting with unprovoked diabetic ketoacidosis (DKA) are obese (1,2). In contrast to the chronic insulin dependence of type 1 diabetic patients with ketoacidosis, most obese African American patients with DKA display clinical and metabolic features of type 2 diabetes during follow-up (2–5). We and others have reported that at presentation, obese African American patients with DKA have greater insulin secretion than lean type 1 diabetic patients with DKA but significantly lower than in obese type 2 diabetic patients with hyperglycemia (no ketoacidosis) (1,4,6). In such patients, aggressive diabetic management results in significant improvement in β-cell function sufficient to allow discontinuation of insulin therapy and go through a period of near-normoglycemia remission, which may last for a few months to several years (4,6–8). A recent longitudinal study (6) reported that after 10 years after diabetes onset, 40% of patients with KPDM are still insulin independent. This clinical presentation is commonly reported in Africans and in black individuals in the U.S., but is also observed in Native American, Japanese, Chinese, Hispanic, and Caucasian populations (2,3). Because of the mixed features of type 1 and type 2 diabetes, this variant of type 2 diabetes has been referred to in the literature as diabetes type 1B, atypical diabetes, diabetes type 1 ½, Flatbush diabetes, and, more recently, as ketosis-prone type 2 diabetes (KPDM).

The underlying mechanism for the transient insulin deficiency leading to severe hyperglycemia ketoacidosis in African Americans with KPDM is not known. We hypothesized that obese African Americans with KPDM, as compared with those with hyperglycemia (without ketosis) and obese control subjects, will prove particularly susceptible to desensitization of β-cells due to sustained elevations in free fatty acid (FFA) levels or β-cell lipotoxicity. To test this hypothesis, a group of obese African Americans with KPDM and obese subjects with severe hyperglycemia (ketosis-resistant type 2 diabetes) underwent a 48-h infusion of 20% intralipid at 40 ml/h in order to increase FFA levels approximately fourfold from baseline at near-normoglycemia remission (>1 week of discontinuation of insulin therapy).

RESEARCH DESIGN AND METHODS — A group of eight newly diagnosed obese (BMI >30 kg/m^2) African American patients with a history of unprovoked DKA, eight patients with type 2 diabetes with severe hyperglycemia but without ketoacidosis, and nine obese nondiabetic control subjects participated in this study. The diagnosis of DKA was established by a plasma glucose level >250 mg/dl (13.8 mmol/l), a serum bicarbonate <18 mmol/l, a blood pH <7.3, and a serum β-hydroxybutyrate level >3 mmol/l (9). The obese type 2 diabetic hyperglycemic group included patients with recently diagnosed diabetes who presented with glucose >400 mg/dl but without ketosis. The control nondiabetic group included obese subjects, matched for age and BMI, with a fasting glucose
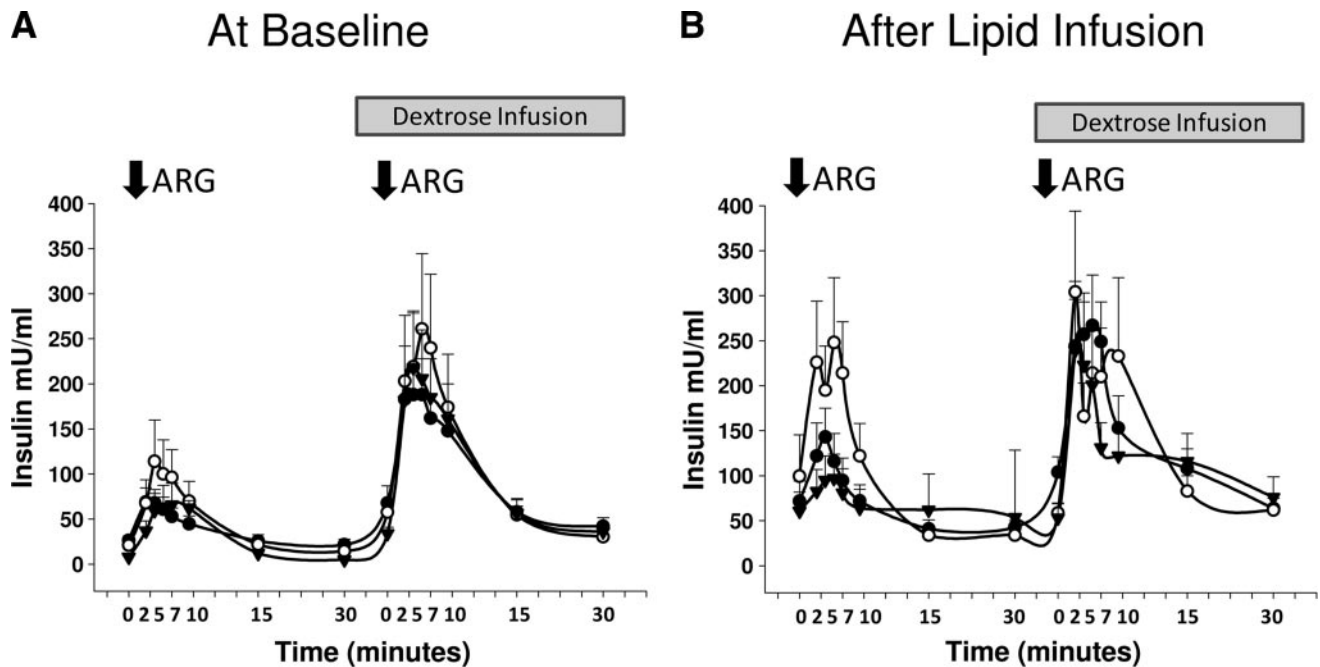
Figure 1—*Arginine stimulation tests performed prior to and following a 48-h intralipid infusion in obese subjects with KPDM, obese type 2 diabetic subjects with hyperglycemia (ketosis resistant), and obese nondiabetic control subjects. A maximally stimulatory dose of 10% arginine (5 g) was injected at baseline plasma glucose and following an infusion of 10% dextrose with 5 mEq/l of KCl at 200 mg/m² per minute for 45 min. Values are means ± SE. ●, KPDM; ○, hyperglycemia; ▼, control.*

<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 unit at Grady Memorial Hospital, Atlanta, Georgia, 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 (1,2). 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 wt. The insulin dose was adjusted to achieve a fasting and premeal glucose level <130 mg/dl. At discharge, patients were followed at the outpatient Grady diabetes clinic every 2–4 weeks for the first 2 months, then every 2 months. Total insulin dose was tapered after blood glucose remained within targeted levels for 2–4 weeks or sooner if a patient experienced hypoglycemia (<70 mg/dl).

Experimental procedures

Participants were admitted to the Grady Hospital General Clinical Research Center, in random order, on two occasions for a 48-h infusion of intralipid and saline 1 week after discontinuation of insulin therapy. After an overnight fast, an intra-venous catheter was placed in each forearm, one for infusion and one for blood sampling. Subjects received a 48-h infusion of intralipid (20%) at 40 ml/h. The 20% intralipid long-chain triglyceride emulsion is composed of linoleic acid (50% oleic acid; 26% palmitic acid; 10% stearic acid; 9% egg yolk; 3.5% phospholipids).

Sequential arginine stimulation tests

To assess the baseline insulin secretion and glucose-potentiating effect, sequential arginine stimulation tests (10) were performed at baseline plasma glucose and following an infusion of 10% dextrose with 5 mEq/l of KCl at 200 mg/m² per min for 45 min using a peristaltic pump. A maximally stimulatory dose of 10% arginine (5 g) was injected at each time as a bolus over a period of 30 s, and blood samples were drawn at −30, 0, and 2, 3, 4, 5, 7, 15, and 30 min for measurement of glucose, insulin, and C-peptide levels. Acute insulin response to arginine (AIR$_{arg}$) was defined as the difference between basal and the mean insulin values at 2, 4, and 5 min following each arginine pulse. Sequential arginine stimulation was performed at baseline prior to and at the end of the 48-h intralipid and saline infusion.

Forty-eight–hour intralipid infusion protocol

Following the initial arginine stimulation test, subjects received a 48-h infusion of intralipid (20%) at 40 ml/h. Blood samples were drawn on admission for glucose, insulin, C-peptide, and FFAs. During the infusion, glucose was measured every 2 h at the bedside using a glucose meter, and blood samples were drawn every 4 h for laboratory assays including glucose, insulin, C-peptide, and FFAs. During the study period, subjects consumed a 2,000-calorie diet/day consisting of 20% of calories derived from protein, 30% from fat, and 50% from carbohydrate. Lipid and saline infusion was started at ~12 noon (Fig. 1) and continued for 48 h.

Laboratory methods

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

Table 1—*Clinical features of subjects with KPDM, ketosis-resistant type 2 diabetes with hyperglycemia (ketosis resistant), and nondiabetic control subjects*

	KPDM	Ketosis resistant	Nondiabetic control subjects
n	8	8	9
Age (years)	39 ± 10	48 ± 9	40 ± 7
Sex (male/female) (n)	6/2	6/2	2/7
Race (African Americans) (%)	8 (100)	8 (100)	9 (100)
Newly diagnosed diabetes (%)	8 (100)	8 (100)	—
Family history of diabetes (%)	7 (88)	8 (100)	8 (89)
BMI (kg/m²)	38 ± 4	38 ± 5	37 ± 9
Positive GAD antibodies (%)	0 (0)	0 (0)	—
A1C at presentation (%)	12.1 ± 3	12.8 ± 2	—
Blood glucose at presentation (mg/dl)	891 ± 282	537 ± 140	88 ± 9
Bicarbonate (mEq/l)	14 ± 4	23 ± 3	—
pH	7.19 ± 0.24	7.36 ± 0.04	—
Anion gap (mEq/l)	23 ± 7	14 ± 7	—
Time to insulin discontinuation (remission) (weeks)	11.0 ± 8.0	9.6 ± 2.2	—
A1C at remission (%)	5.7 ± 0.4	6.3 ± 1.1	—
Blood glucose at remission (mg/dl)	94 ± 14	109 ± 20	—

Data are means ± SD, unless otherwise indicated.

Statistical analysis

All data in the text and Table 1 are expressed as means ± SD, and the data in the figures are expressed as means ± SE. Comparisons among the nondiabetic control group, KPDM group, and obese diabetic group with hyperglycemia were conducted using nonparametric Kruskal-Wallis for continuous variables and using the Fisher's exact test for categorical variables. With infusion data, repeated-measures analyses were carried out to assess the group difference simultaneously with the change over time in FFAs, blood glucose, insulin, C-peptide, and the C-peptide–to–glucose ratio (1). Statistical significance was defined as $P < 0.05$. Statistical analysis was performed using the SAS version 9.2.

RESULTS

Patient characteristics

The clinical characteristics of patients with KPDM, hyperglycemia without ketosis, and nondiabetic control subjects are shown in Table 1. All patients were African American, obese, had recently diagnosed diabetes, and were mostly male with a strong family history of diabetes. On admission, KPDM patients had a mean blood glucose level of 891 ± 282 mg/dl, a serum bicarbonate of 14 ± 4 mEq/l, a venous pH of 7.19 ± 0.24, an anion gap of 23 ± 7 mEq/l, and a β-hydroxybutyrate level >3.0 mmol/l. Keto-

sis-resistant type 2 diabetic patients with hyperglycemia had a blood glucose on admission of 537 ± 140 mg/dl, a serum bicarbonate of 23 ± 3 mEq/l, venous pH 7.36 ± 0.04, anion gap 14 ± 7 mEq/l, and β-hydroxybutyrate <3.0 mmol/l. Obese nondiabetic control subjects had a mean fasting blood glucose of 88 ± 9 mg/dl. Admission levels of A1C were 12.1% in KPDM and 13% in obese hyperglycemic subjects.

The mean time to achieve remission and insulin discontinuation in obese KPDM subjects was 11 ± 8 and 9.6 ± 2.2 weeks in obese patients with hyperglycemia ($P = $ NS). At remission, KPDM and type 2 diabetes had similar glucose (94 ± 14 vs. 109 ± 20 mg/dl) and hemoglobin A1C (5.7 ± 0.4 vs. 6.3 ± 1.1%) levels, respectively.

Sequential arginine stimulation tests

Changes in insulin concentration during sequential arginine stimulation tests at baseline and after dextrose infusion prior to and after the 48-h intralipid infusion are shown in Fig. 1*A* and *B*, respectively. From these values, the AIR$_{arg}$ (difference between basal and the mean insulin values at 2, 3, 4, and 5 min) was calculated before and after the 48-h intralipid infusion. At baseline, starting at a mean glucose concentration of 113 ± 20 mg/dl in obese hyperglycemia and 96 ± 13 mg/dl in KPDM, the baseline AIR$_{arg}$ response in obese type 2 diabetic subjects with hyperglycemia (64 ± 69 μU/ml) was higher

but not significantly different from that in obese KPDM subjects (34.8 ± 30.3 μU/ml). Nondiabetic control subjects had a baseline blood glucose of 91 ± 12 mg/dl and an AIR$_{arg}$ of 44 ± 51 μU/ml. The P value for blood glucose difference among these three groups is 0.004, and the P value for AIR$_{arg}$ difference is 0.857. Following the basal arginine test, subjects received the administration of dextrose infusion (200 mg · kg^{-1} · min^{-1}) for 45 min followed by a second pulse of arginine. Dextrose infusion resulted in a further increase in insulin secretion (glucose potentiating effect) in diabetic and control subjects. With a mean basal blood glucose of 163 ± 32 mg/dl in KPDM, 172 ± 55 mg/dl in obese hyperglycemia, and 172 ± 23 in obese control subjects, we also observed a higher AIR$_{arg}$ in obese hyperglycemic subjects (178 ± 204 μU/ml), but results were not significantly different from those observed in obese KPDM (98 ± 107 μU/ml) or nondiabetic control subjects (163 ± 138 μU/ml).

To assess the impact of intralipid infusion on insulin secretion, a repeated arginine stimulation test was performed within 1 h of completing the 48-h intralipid infusion. Of interest, we observed no significant differences in AIR$_{arg}$ between the two diabetic groups and in nondiabetic subjects, and all groups maintained the glucose-potentiating effect during arginine stimulations (Fig. 1*B*). KPDM patients had a baseline mean blood glucose concentration of 116 ± 31 mg/dl and an AIR$_{arg}$ of 33 ± 55 μU/ml compared with patients with hyperglycemia who had a baseline mean blood glucose of 132 ± 29 mg/dl and an AIR$_{arg}$ of 115 ± 120 μU/ml after lipid infusion ($P = 0.159$). Nondiabetic control subjects had a baseline mean blood glucose of 99 ± 15 mg/dl and an AIR$_{arg}$ of 21 ± 71 μU/ml. Dextrose infusion for 45 min resulted in a further increase in arginine-stimulated insulin secretion, with an AIR$_{arg}$ of 150 ± 168 μU/ml in KPDM, 183 ± 168 μU/ml in hyperglycemic subjects, and 113 ± 90 μU/ml in nondiabetic control subjects. There were no significant differences in change of insulin area under the curve (AUC) or glucose AUC in response to sequential arginine stimulation from baseline among three groups.

Plasma FFAs, glucose, C-peptide, and C-peptide–to–glucose ratio during intralipid infusion

Intralipid infusion resulted in rapid and sustained elevations of FFA levels from
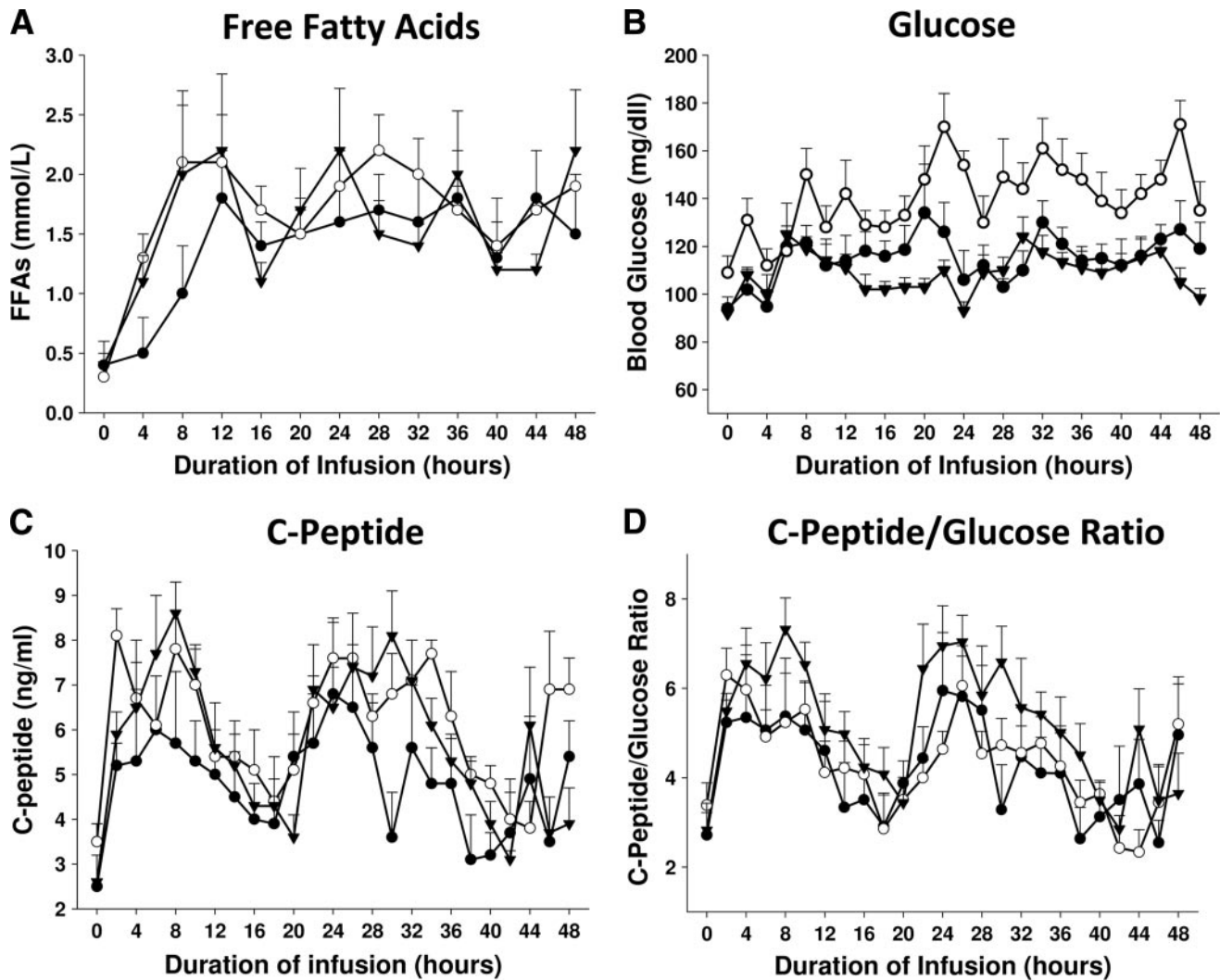
Figure 2—*Changes in plasma free fatty acids* (A), *plasma glucose* (B), *and C-peptide* (C) *and C-peptide–to–glucose ratio* (D) *during 48-h intralipid infusion in obese subjects with KPDM, type 2 diabetic subjects with hyperglycemia, and obese nondiabetic control subjects. Values are means ± SE.* ●, *KPDM;* ○, *hyperglycemia;* ▼, *control.*

baseline in both diabetic and control groups (Fig. 2*A*). From a fasting FFA of 0.4 ± 0.3 mmol/l in diabetic subjects and 0.4 ± 0.3 mmol/l in control subjects, FFA levels increased to 1.5 ± 1.1 mmol/l in KPDM, 1.9 ± 0.4 mmol/l in obese type 2 diabetes with hyperglycemia, and 1.8 ± 1.1 mmol/l in nondiabetic control subjects at the end of intralipid infusion, respectively (P = NS difference between groups at baseline or during intralipid infusion).

Compared with baseline levels, changes in blood glucose values during intralipid infusion (Fig. 2*B*) increased from baseline glucose levels of 94 ± 14 to 120 ± 33 mg/dl in KPDM (P = 0.012) at the end of the intralipid infusion, from 109 ± 20 to 136 ± 35 mg/dl in obese subjects with hyperglycemia (P = 0.103), and from 92 ± 12 to 98 ± 12 mg/dl (P =

0.266) in nondiabetic control subjects. Mean blood glucose at the end of infusion was not significantly different between the two diabetic groups. During intralipid infusion, the AUC for glucose levels (assuming linear interpolation) were $5,204 \pm 1,222$ in KPDM, $6,420 \pm 1,332$ in type 2 diabetes with hyperglycemia, and $5,230 \pm 436$ in nondiabetic control group. Analysis based on repeated-measures ANOVA showed that blood glucose increased significantly from baseline at the end of infusion (P = 0.002) and was significantly different among groups (P = 0.019).

Intralipid infusion for 48 h resulted in a sustained increase in C-peptide levels in KPDM and hyperglycemic patients from a baseline of 2.5 ± 1.2 and 3.5 ± 1.1 ng/ml to a mean level of 5.4 ± 2.3 and 6.5 ± 2.1 ng/ml at the end of the infusion, respec-

tively (both P = 0.102 from baseline and P = 0.247 between the two diabetic groups) (Fig. 2*C*). In nondiabetic control subjects, C-peptide levels increased from a baseline of 2.6 ± 1.7 ng/ml to a mean of 3.9 ± 2.4 ng/ml at the end of the infusion (P = 0.229). Insulin secretion estimated by the C-peptide–to–glucose ratio (C-peptide [ng/ml]/glucose [mg/dl] × 100) and by differences in AUC during intralipid infusion (11). There were no significant differences in the C-peptide–to–glucose ratio (Fig. 2*D*) or in the AUC for C-peptide, insulin, and C-peptide–to–glucose ratio during the 48-h intralipid infusion. Repeated-measures analyses revealed no differences in FFAs, C-peptide, or C-peptide–to–glucose ratio among KPDM, obese subjects with hyperglycemia, and nondiabetic control subjects although there were significant increases

from baseline. These results indicate that increased FFAs during intralipid infusion for 48 h were not associated with impaired insulin secretion or β-cell lipotoxicity in obese subjects with KPDM or with a history of hyperglycemia without ketoacidosis.

CONCLUSIONS — Over half of adult subjects with recently diagnosed diabetes presenting with DKA display clinical, metabolic, and immunological features of type 2 diabetes, including a high rate of obesity, a strong family history of diabetes, a low prevalence of autoimmune markers, and lack of HLA genetic association (2,3). Many of such patients discontinue insulin therapy within a few months of treatment and remain in good glycemic control with diet and/or oral antidiabetic therapy for several years (1,2,4,6). Metabolic studies have evidenced insulin secretion deficiency as the major determinant of metabolic decompensation in KPDM patients. We previously reported that intravenous glucose infusion shortly after resolution of DKA did not evoke any insulin response; however, improvement of metabolic control resulted in threefold higher insulin levels at near-normoglycemia remission (1,5). Changes in C-peptide response after a mixed meal or glucagon stimulation have been shown to be intermediate between lean type 1 diabetic patients with DKA and obese hyperglycemic patients with type 2 diabetes (1,5–7). The subsequent remission is due to a restoration, at least partial, of the β-cell insulin secretory capacity after achievement of good metabolic control (6,8). KPDM patients who achieved remission experienced an 80% improvement in fasting and stimulated C-peptide levels, whereas those who did not achieve remission lost 60% of their insulin secretory capacity (6). These findings indicate that the impaired β-cell function in KPDM patients cannot be attributed to an irreversible β-cell damage but to transient functional abnormalities of the β-cells.

Clinical and experimental data indicate that increased FFAs may contribute to the development of peripheral insulin resistance and type 2 diabetes (12). In addition to inhibiting insulin action, recent evidence indicates that FFAs have an important role in the regulation of β-cell function (13). In vitro and animal studies have shown that prolonged exposure of rat (14) and human (15) islets to fatty acids decreases glucose-stimulated insulin secretion. In addition, FFAs inhibit insulin gene expression (15,16), in part via negative regulation of the transcription factor pancreatic duodenum homeobox-1 (17). FFAs may also reduce efficiency of proinsulin to insulin conversion within the β-cells (14) and may impair potassium ATP channel–dependent and potassium ATP channel–independent pathways of insulin secretion (14). In humans, sustained (24–48 h) elevation of FFAs may decrease glucose-stimulated insulin secretion in nondiabetic individuals (12,18,19). Accordingly, we hypothesized that β-cell lipotoxicity may explain the metabolic decompensation in obese African Americans with KPDM and that such patients will be more susceptible to FFA-induced β-cell dysfunction than obese patients with ketosis-resistant type 2 diabetes and obese nondiabetic control subjects.

To test the lipotoxicity hypothesis, we assessed β-cell function by changes in AIR_{arg} both at baseline and during glucose infusion before and after the 48-h intralipid infusion and by changes in insulin and C-peptide concentration during lipid infusion. The concentrations of FFAs achieved during intralipid infusion (Fig. 2*A*) were similar to the levels of FFAs previously reported in ketosis-prone diabetic patients at presentation with DKA (20). Among the single amino acids known to stimulate insulin secretion in humans, arginine is the most potent (21). Arginine plus glucose, given intravenously, have been shown to act synergistically on insulin secretion resulting in a greater rise of serum insulin than the sum of the response to separate infusions of glucose and arginine (10,21). The hyperglycemic potentiating effect of insulin response to arginine is a sensitive indicator of pancreatic insulin secretory capacity (21,22). Despite a recent history of severe hyperglycemia and ketoacidosis, KPDM patients exhibit an appropriate glucose-potentiating effect indicating a remarkable recovery of insulin secretion during remission. Serum concentration of C-peptide and insulin were similar between groups during the 48-h intralipid infusion, and the glucose-potentiating effect of arginine in KPDM patients was similar to that observed in type 2 diabetic patients and to nondiabetic control subjects. These results allow us to conclude that short-term high FFA levels are not a primary pathophysiologic factor in the development of β-cell decompensation in KPDM patients.

We acknowledge the following limitations in this study. The duration of intralipid infusion in our study was limited to 48 h. Kashyap et al. (12) reported that a 4-day lipid infusion in subjects at high-risk of developing type 2 diabetes impairs insulin secretion in response to mixed meals and to intravenous glucose. The lack of short-term lipotoxicity could also be explained by the fact that we studied patients after remission under the near-normoglycemia state. Previous studies have shown that high fat administration impairs insulin secretion only in the context of chronic hyperglycemia (23). Briaud et al. (24) reported that antecedent hyperglycemia, not plasma lipid levels, lead to high islet triacylglycerol content and decreased insulin gene expression and that both hyperlipidemia and hyperglycemia must be present simultaneously for FFAs to affect β-cell function (24). In addition, we did not measure C-peptide levels during sequential arginine stimulation tests in order to estimate changes in insulin clearance. Finally, intralipid emulsion is a soybean oil–based lipid emulsion rich in omega-6 polyunsaturated fatty acids (25) that are different from human dietary intake. It is not known if comparable increases in FFAs by repeated oral fat load can impair insulin secretion in obese subjects with KPDM and type 2 diabetes.

In summary, our studies indicate that KPDM represents a subset of type 2 diabetes and that the near-normoglycemia remission phase is associated with a remarkable recovery in insulin secretion. Despite a recent history of severe hyperglycemia and ketoacidosis, at remission, KPDM patients have similar basal and stimulated insulin secretion than subjects with nonketotic hyperglycemia and obese nondiabetic control subjects. In addition, our study indicates that despite a fourfold increase in FFA levels, basal and stimulated insulin secretion was preserved, suggesting that short-term high FFA levels are not a primary pathophysiologic factor in the development of β-cell decompensation in KPDM patients.

References

1. Umpierrez GE, Casals MM, Gebhart SP, Mixon PS, Clark WS, Phillips LS. Diabetic ketoacidosis in obese African-Americans. Diabetes 1995;44:790–795

2. Umpierrez GE, Smiley D, Kitabchi AE. Narrative review: ketosis-prone type 2 diabetes mellitus. Ann Intern Med 2006;144:350–357

3. Balasubramanyam A, Nalini R, Hampe CS, Maldonado M. Syndromes of ketosis-prone diabetes mellitus. Endocr Rev 2008;29:292–302

4. Banerji MA, Chaiken RL, Huey H, Tuomi T, Norin AJ, Mackay IR, Rowley MJ, Zimmet PZ, Lebovitz HE. GAD antibody negative NIDDM in adult black subjects with diabetic ketoacidosis and increased frequency of human leukocyte antigen DR3 and DR4: flatbush diabetes. Diabetes 1994;43:741–745

5. Umpierrez GE, Woo W, Hagopian WA, Isaacs SD, Palmer JP, Gaur LK, Nepom GT, Clark WS, Mixon PS, Kitabchi AE. Immunogenetic analysis suggests different pathogenesis for obese and lean African-Americans with diabetic ketoacidosis. Diabetes Care 1999;22:1517–1523

6. Mauvais-Jarvis F, Sobngwi E, Porcher R, Riveline JP, Kevorkian JP, Vaisse C, Charpentier G, Guillausseau PJ, Vexiau P, Gautier JF. Ketosis-prone type 2 diabetes in patients of sub-Saharan African origin: clinical pathophysiology and natural history of β-cell dysfunction and insulin resistance. Diabetes 2004;53:645–653

7. Maldonado M, Hampe CS, Gaur LK, D'Amico S, Iyer D, Hammerle LP, Bolgiano D, Rodriguez L, Rajan A, Lernmark A, Balasubramanyam A. Ketosis-prone diabetes: dissection of a heterogeneous syndrome using an immunogenetic and beta-cell functional classification, prospective analysis, and clinical outcomes. J Clin Endocrinol Metab 2003;88:5090–5098

8. McFarlane SI, Chaiken RL, Hirsch S, Harrington P, Lebovitz HE, Banerji MA. Near-normoglycaemic remission in African-Americans with type 2 diabetes mellitus is associated with recovery of beta cell function. Diabet Med 2001;18:10–16

9. Kitabchi AE, Umpierrez GE, Murphy MB, Kreisberg RA. Hyperglycemic crises in adult patients with diabetes: a consensus statement from the American Diabetes Association. Diabetes Care 2006;29:2739–2748

10. van Haeften TW, Voetberg GA, Gerich JE, van der Veen EA. Dose-response characteristics for arginine-stimulated insulin secretion in man and influence of hyperglycemia. J Clin Endocrinol Metab 1989;69:1059–1064

11. Umpierrez GE, Smiley D, Robalino G, Peng L, Kitabchi AE, Khan B, Le A, Quyyumi A, Brown V, Phillips LS. Intravenous intralipid-induced blood pressure elevation and endothelial dysfunction in obese African-Americans with type 2 diabetes. J Clin Endocrinol Metab 2009;94:609–614

12. Kashyap S, Belfort R, Gastaldelli A, Pratipanawatr T, Berria R, Pratipanawatr W, Bajaj M, Mandarino L, DeFronzo R, Cusi K. A sustained increase in plasma free fatty acids impairs insulin secretion in nondiabetic subjects genetically predisposed to develop type 2 diabetes. Diabetes 2003;52:2461–2474

13. Unger RH, Zhou YT. Lipotoxicity of β-cells in obesity and in other causes of fatty acid spillover. Diabetes 2001;50(Suppl. 1):S118–S121

14. Zhou YP, Grill VE. Long-term exposure of rat pancreatic islets to fatty acids inhibits glucose-induced insulin secretion and biosynthesis through a glucose fatty acid cycle. J Clin Invest 1994;93:870–876

15. Yoshikawa H, Tajiri Y, Sako Y, Hashimoto T, Umeda F, Nawata H. Effects of free fatty acids on beta-cell functions: a possible involvement of peroxisome proliferator-activated receptors alpha or pancreatic/duodenal homeobox. Metabolism 2001;50:613–618

16. Jacqueminet S, Briaud I, Rouault C, Reach G, Poitout V. Inhibition of insulin gene expression by long-term exposure of pancreatic beta cells to palmitate is dependent on the presence of a stimulatory glucose concentration. Metabolism 2000;49:532–536

17. Gremlich S, Bonny C, Waeber G, Thorens B. Fatty acids decrease IDX-1 expression in rat pancreatic islets and reduce GLUT2, glucokinase, insulin, and somatostatin levels. J Biol Chem 1997;272:30261–30269

18. Carpentier A, Mittelman SD, Bergman RN, Giacca A, Lewis GF. Prolonged elevation of plasma free fatty acids impairs pancreatic β-cell function in obese nondiabetic humans but not in individuals with type 2 diabetes. Diabetes 2000;49:399–408

19. Carpentier A, Mittelman SD, Lamarche B, Bergman RN, Giacca A, Lewis GF. Acute enhancement of insulin secretion by FFA in humans is lost with prolonged FFA elevation. Am J Physiol 1999;276:E1055–E1066

20. Stentz FB, Umpierrez GE, Cuervo R, Kitabchi AE. Proinflammatory cytokines, markers of cardiovascular risks, oxidative stress, and lipid peroxidation in patients with hyperglycemic crises. Diabetes 2004;53:2079–2086

21. Kahn SE. Clinical review 135: The importance of beta-cell failure in the development and progression of type 2 diabetes. J Clin Endocrinol Metab 2001;86:4047–4058

22. Halter JB, Graf RJ, Porte D Jr. Potentiation of insulin secretory responses by plasma glucose levels in man: evidence that hyperglycemia in diabetes compensates for imparied glucose potentiation. J Clin Endocrinol Metab 1979;48:946–954

23. Poitout V, Briaud I, Kelpe C, Hagman D. Gluco-lipotoxicity of the pancreatic beta cell. Ann Endocrinol (Paris) 2004;65:37–41

24. Briaud I, Kelpe CL, Johnson LM, Tran PO, Poitout V. Differential effects of hyperlipidemia on insulin secretion in islets of Langerhans from hyperglycemic versus normoglycemic rats. Diabetes 2002;51:662–668

25. Waitzberg DL, Torrinhas RS, Jacintho TM. New parenteral lipid emulsions for clinical use. J Parenter Enteral Nutr 2006;30:351–367