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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 (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 m²/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.

The underlying mechanism for the transient insulin deficiency leading to severe hyperglycemia ketoadosis in African Americans with KPD is unknown. It is possible that sustained hyperglycemia may be responsible. The concept of “glucotoxicity” has been put forward to explain the contribution of toxic effects of hyperglycemia on β-cell function. 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/m²) African American patients with newly diagnosed diabetes and a history of uncomplicated 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 toler-
ance test. This study was conducted at the Clinical Research Center at Grady Mem-
orial Hospital (Atlanta, GA) and was approved by the Emory University institu-
tional 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 hyper-
glycemia, 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 insu-
lin therapy for >1 week and remaining in 
good glycemic control (fasting blood glu-
cose <130 mg/dl, random blood glucose 
<180 mg/dl, and A1C <7%). Diabetic 
subjects were admitted to the Grady Me-
crosis potentiation of insulin secretion 
(HOMA-IR) derived from fasting plasma 
glucose and insulin (HOMA-IR = fasting 
insulin [milliunits per liter] \times fasting glu-
cose [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 se-
quential chemiluminescent immuno-
metric assays on the DPC Immulite analyzer 
(Diagnostic Products, Los Angeles, CA).

Statistical analysis
All data in the text and tables are ex-
pressed as means ± SD, and the data in 
figures are expressed as means ± SEM. 
Comparisons among the nondiabetic 
control group, KPD group, and obese di-
abetic group with hyperglycemia were 
conducted using a nonparametric 
Kruskal-Wallis test for continuous vari-
able and a Fisher exact test for categori-
cal variables. Further analysis for statistical 
differences between groups was per-
formed by ANOVA. With glucose infu-
dion data, repeated-measures analyses 
were performed to assess the group differ-
ence simultaneously with the change over 
time in blood glucose, insulin, and C-
peptide-to–glucose ratio, adopting an 
AIRF within-subjects correlation struc-
ture. Statistical significance was defined as 
P < 0.05. Statistical analysis was per-
formed using SAS (version 9.2; SAS Insti-
tute, Cary, NC).

RESULTS

Patient characteristics
The clinical characteristics of patients 
with KPD, patients with ketosis-resistant 
diabetes, and nondiabetic control sub-
jects 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 ac-
dosis. The ketosis-resistant diabetic pa-
tients 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 discontin-
uation 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 con-
centrations 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 di-
abetes compared with those in control 
subjects both before and after a 20-h dex-
trose infusion (Table 2, Fig. 1). Similarly, 
the FPIR adjusted for insulin sensitivity 
(HOMA IR–to–FPIR ratio) was similar be-
tween 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

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

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

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

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>KPD</th>
<th>Ketosis-resistant diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>13</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>88 ± 2</td>
<td>95 ± 3</td>
<td>104 ± 8*</td>
</tr>
<tr>
<td>Fasting insulin (μU/ml)</td>
<td>10.7 ± 1.7</td>
<td>16.0 ± 4.5</td>
<td>15.8 ± 3.0</td>
</tr>
<tr>
<td>Fasting C-peptide (ng/ml)</td>
<td>2.3 ± 0.6</td>
<td>2.7 ± 0.6</td>
<td>2.7 ± 0.6</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.3 ± 0.4</td>
<td>3.6 ± 1.0</td>
<td>4.0 ± 0.8*</td>
</tr>
<tr>
<td>FFAs (μmol/l)</td>
<td>113 ± 21</td>
<td>120 ± 35</td>
<td>117 ± 29</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>KPD</th>
<th>Ketosis-resistant diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preinfusion AIR₁ (μU/ml)</td>
<td>31 ± 6</td>
<td>39 ± 14</td>
<td>52 ± 23</td>
</tr>
<tr>
<td>FPIR (μU/ml)</td>
<td>197 ± 33</td>
<td>264 ± 80</td>
<td>339 ± 221</td>
</tr>
<tr>
<td>HOMA-IR-to–FPIR ratio</td>
<td>0.014 ± 0.003</td>
<td>0.015 ± 0.003</td>
<td>0.013 ± 0.002</td>
</tr>
</tbody>
</table>

After 20-h glucose infusion

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>KPD</th>
<th>Ketosis-resistant diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postinfusion AIR₁ (μU/ml)</td>
<td>40 ± 5</td>
<td>34 ± 13</td>
<td>62 ± 27</td>
</tr>
<tr>
<td>FPIR (μU/ml)</td>
<td>299 ± 30</td>
<td>359 ± 42</td>
<td>381 ± 147</td>
</tr>
<tr>
<td>HOMA-IR-to–FPIR ratio</td>
<td>0.010 ± 0.002</td>
<td>0.012 ± 0.005</td>
<td>0.013 ± 0.005</td>
</tr>
</tbody>
</table>

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

β-Cell function in KPD

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. 2A). 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 μg/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. 2B 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. 2B 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 (3, 7). In addition, the resolution of hyperglycemia after 10–12 weeks of in-
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
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-

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.
These results suggest that the 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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