Multitissue Insulin Resistance Despite Near-Normoglycemic Remission in Africans With Ketosis-Prone Diabetes

SIMEON-PIERRE CHOUKEM, MD[1,2]
EUGENE SOBNGWI, MD, PHD[1,2,3]
LILA-SABRINA FETITA, MD[1]
PHILIPPE BOUDOU, PHD[4,5]
ERIC DE KERVILER, MD[6]
YVES BOIRIE, MD, PHD[7]
ISABELLE HAINAULT, PHD[5]
PATRICK VEXIAU, MD[1]
FRANCK MAUVAIS-JARVIS, MD, PHD[8]
FABIEN CALVO, MD, PHD[2]
JEAN-FRANÇOIS GAUTIER, MD, PHD[1,2,5]

OBJECTIVE — To characterize insulin action in Africans with ketosis-prone diabetes (KPD) during remission.

RESEARCH DESIGN AND METHODS — At Saint-Louis Hospital, Paris, France, 15 African patients with KPD with an average 10.5-month insulin-free near-normoglycemic remission period (mean A1C 6.2%) were compared with 17 control subjects matched for age, sex, BMI, and geographical origin. Insulin stimulation of glucose disposal, and insulin suppression of endogenous glucose production (EGP) and nonesterified fatty acids (NEFAs), was studied using a 200-min two-step (10 mU · m^{-2} body surface · min^{-1} and 80 mU · m^{-2} · min^{-1} insulin infusion rates) euglycemic clamp with [6,6-$^2H_2$]glucose as the tracer. Early-phase insulin secretion was determined during an oral glucose tolerance test.

RESULTS — The total glucose disposal was reduced in patients compared with control subjects (7.5 ± 0.8 [mean ± SE] vs. 10.5 ± 0.9 mg · kg^{-1} · min^{-1}; $P = 0.018$). EGP rate was higher in patients than control subjects at baseline (4.0 ± 0.3 vs. 3.0 ± 0.1 mg · kg^{-1} · min^{-1}; $P = 0.001$) and after 200-min insulin infusion (10 mU · m^{-2} · min^{-1}: 1.6 ± 0.2 vs. 0.6 ± 0.1, $P = 0.004$; 80 mU · m^{-2} · min^{-1}: 0.3 ± 0.1 vs. 0 mg · kg^{-1} · min^{-1}, $P = 0.007$). Basal plasma NEFA concentrations were also higher in patients (1,936.7 ± 161.4 vs. 1,230.0 ± 174.1 μmol/l; $P = 0.002$) and remained higher after 100-min 10 mU · m^{-2} · min^{-1} insulin infusion (706.6 ± 96.5 vs. 381.6 ± 55.9 μmol/l; $P = 0.015$).

CONCLUSIONS — The triad hepatic, adipose tissue, and skeletal muscle insulin resistance is observed in patients with KPD during near-normoglycemic remission, suggesting that KPD is a form of type 2 diabetes.

Diabetes Care **31:2332–2337, 2008**

Impairment of insulin sensitivity is considered the background defect that interplays with the add-on progressive β-cell dysfunction to underlie the development of type 2 diabetes (1,2). An atypical form of diabetes, ketosis-prone diabetes (KPD), has been described over the past 2 decades and may represent a significant proportion of diabetes cases in people of sub-Saharan African origin (3,4). Patients with KPD present at onset with acute hyperglycemia, usually >30 mmol/l, and ketosis or ketoacidosis as type 1 diabetes but do not have autoimmune markers against the islet β-cell (3,5–7). The correction of those insulin-requiring acute-phase disorders is followed in >50% of cases by an insulin-free near-normoglycemic remission weeks to months later (8–10), thus resembling the course of type 2 diabetes. The pathogenesis and, consequently, the classification of KPD are still debated. It was classified under idiopathic type 1 diabetes or type 1B diabetes (11). However, growing evidence based on clinical and metabolic studies suggests its high phenotypical likeness to type 2 diabetes, and "ketosis-prone type 2 diabetes" has been proposed as a provisional name and is being used elsewhere (4,8,12). Metabolic studies have evidenced insulin secretion deficiency as the major determinant of the ketotic onset (8–10). This deficit is marked by a loss of acute-phase insulin secretion in response to intravenous glucose (10) or a decrease in C-peptide response to glucagon (9,10). The subsequent remission process is due to a restoration, at least partial, of the β-cell insulin secretory capacity after achievement of good metabolic control (8,10). Insulin action was assessed in three reports, but only toward glucose metabolism, and was found to be normal or decreased while patients were in good metabolic control (6,8,10). Moreover, most studies on KPD have been reported in African-Americans who are more overweight than native Africans and may be metabolically different from them, as suggested earlier (13).

In this study, we aimed at characterizing all aspects of insulin action in Africans with KPD when in the near-normoglycemic state without insulin treatment compared with control subjects of the same geographic origin.

RESEARCH DESIGN AND METHODS

— This study was undertaken at the Clinical Investigation Center

From the [1]Department of Diabetes and Endocrinology, Saint-Louis Hospital, Assistance Publique–Hôpitaux de Paris, University Paris-Diderot Paris 7, Paris, France; [2]INSERM, Clinical Investigation Center CIC9504, Saint-Louis Hospital, Assistance Publique–Hôpitaux de Paris, University Paris-Diderot Paris 7, Paris, France; the [3]Institute of Health and Society, University of Newcastle, Newcastle upon Tyne, U.K.; the [4]Unit of Transfer in Molecular Oncology and Hormonology, Saint-Louis Hospital, Assistance Publique–Hôpitaux de Paris, University Paris-Diderot Paris 7, Paris, France; [5]INSERM UMRS 872, Cordeliers Research Center, Paris, France; the [6]Department of Radiology and Medical Imaging, Saint-Louis Hospital, Assistance Publique–Hôpitaux de Paris, University Paris-Diderot Paris 7, Paris, France; [7]UMR1019, University of Clermont 1, CRNH-Auvergne, Clermont-Ferrand, France; and the [8]Department of Medicine, Division of Endocrinology, Metabolism and Molecular Medicine, Northwestern University School of Medicine, Chicago, Illinois.

Corresponding author: Jean-François Gautier, jean-francois.gautier@sls.aphp.fr.

Received 17 May 2008 and accepted 14 September 2008.

Published ahead of print at http://care.diabetesjournals.org on 22 September 2008. DOI: 10.2337/dc08-0914.

of Saint-Louis University Hospital, Paris, France. We studied 15 subjects of sub-Saharan African origin with KPD who were in insulin-free remission, along with 17 healthy control subjects of the same geographic origin, with normal glucose tolerance. All participants were from West and Central Africa; they were born in Africa with no other racial antecedent in their ancestry and had migrated to France at adult age. KPD was defined as previously described (8). All patients had been diagnosed, had received insulin treatment at diagnosis, and were followed in the Department of Diabetes and Endocrinology of our hospital. Insulin-free remission was defined as maintenance of an A1C level ≤7.0% for at least 3 months after the withdrawal of insulin treatment, which was initiated at onset or relapse. Healthy control subjects were recruited by advertisement; they were matched to patients for age, sex, and BMI and were free of any family history of type 2 diabetes among their first-degree relatives. The age at inclusion averaged 44 years in each group. Diabetes was of short duration (6–72 months, mean 25.2), and patients had been in insulin-free remission for 3–45 months (mean 10.5). As antidiabetic treatment, most patients were on metformin alone ($n = 8$) or combined to a sulfonylurea ($n = 2$). Two patients were on diet alone, one on a sulfonylurea alone, one on a glinide, and one on acarbose. Four patients had presented with diabetes ketoacidosis (at least 2+ ketonuria and plasma bicarbonate <15 mmol/l and/or arterial pH <7.30), whereas the others had ketosis (at least 2+ ketonuria).

Participants underwent a screening, and those included had normal liver, cardiovascular, pulmonary, and kidney function assessed by medical history, physical examination, electrocardiography, and routine biochemical and hematological tests, as well as negative hepatitis B and C and human immunodeficiency viruses' serological tests. The A1C level was also confirmed in patients during that visit. Patients on oral antidiabetic drugs were asked to stop them at least 5 days before the procedures, and no healthy control subject was taking a drug known to affect glucose or lipid homeostasis. Fasting blood glucose of all patients remained below 8.2 mmol/l. The study was approved by the ethics committee of Paris Saint-Louis, and each participant gave a written informed consent to participate.

Anthropometric measurements and dual-energy X-ray absorptiometry

In all participants, height (to the nearest 0.5 cm) was measured using a wall-stuck stadiometer, and weight was measured to the nearest 0.1 kg (SECA scale, Hamburg, Germany). The BMI was calculated as the weight (in kilograms) divided by the square of the height (in meters). The waist circumference (to the nearest 1 cm) was measured at the midway between the lower costal margin and the iliac crest, while the person was in the upright position, using a nonstretchable tape. Percent fat, fat mass, and fat-free mass were measured by dual-energy X-ray absorptiometry using an absorptiometer (Hologic QDR-1000/W; Wilmington, MA). The anthropometric characteristics and body mass distribution were comparable between the two groups.

Metabolic assessments

Oral glucose tolerance test. To confirm normal glucose tolerance in control subjects and to estimate the β-cell function in all participants, an oral glucose tolerance test was performed on the screening visit after a 12-h overnight fast. Blood samples were collected before (t0) and 30 (t30) and 120 min (t120) after a 75-g oral glucose load, for determination of plasma glucose and insulin concentrations. The glucose tolerance status was classified according to the current American Diabetes Association criteria (1).

Euglycemic clamp. A two-step euglycemic-hyperinsulinemic clamp was performed within the week after the screening visit, after a 12-h in-hospital overnight fast. It consisted of a first step (low-dose insulin infusion) at 10 mU/m^2 body surface per min for 100 min to measure the effects of insulin on plasma nonesterified fatty acids (NEFAs). This was followed by a primed 100-min step (high-dose insulin infusion) at 80 mU/m^2 per min insulin infusion to evaluate the effects of insulin on glucose disposal. The endogenous glucose production was also measured during the whole procedure. Fasting (basal) blood samples were collected at −70 and −60 min before the starting of the clamp. At −60 min, a priming bolus of 3 mg/kg D-[6,6-$^2H_2$]glucose (deuterated glucose) (96 molar percent excess) (Assistance Publique-Hôpitaux de Paris, Paris, France) was injected, followed by a continuous infusion at 0.05 mg · kg^{-1} · min^{-1} for 260 min. Continuous insulin infusion was then started at t0, and glucose concentration was measured every 5 min during the whole procedure. Blood glucose level was clamped at 5.5 mmol/l using a variable infusion of 20% glucose, based on the negative feedback principle (14). Arterialized blood samples were drawn at baseline for the measurement of basal [6,6-$^2H_2$]glucose enrichment and every 10 min during the last 20 min of each step (80th, 90th, and 100th min and 180th, 190th, and 200th min) for the measurement of plasma insulin, NEFA, and [6,6-$^2H_2$]glucose enrichment.

Analytical techniques

All assays were run in duplicate. Plasma glucose was measured by the hexokinase method (Roche Diagnostics, Mannheim, Germany). The high-performance liquid chromatography method was used to measure A1C.

Plasma insulin was measured using immuno-radiometric assays (BI-INSULIN IRMA; Cis Bio-International, Gif-Sur-Yvette, France) with a detection limit of 0.2 μU/ml and an intra- and interassay coefficient of variation (CV) <9.5%.

Plasma NEFA concentrations were determined using the colorimetric method (Randox Laboratories, Antrim, U.K.).

Plasma [$^2H_2$]glucose enrichment was measured by selected ion monitoring electron impact gas chromatography–mass spectrometry (5971A; Hewlett-Packard, Palo Alto, CA) as previously described (15). All other biochemical tests were done using routine laboratory methods.

Calculations

Basal concentration of each biochemical parameter was calculated as the mean of two values obtained from blood samples collected 10 min apart, and the steady-state concentrations were the average of the three values measured 10 min apart during the last 20 min of each step.

For endogenous glucose production (EGP), after an overnight fast, steady-state conditions for the deuterated glucose prevailed, and the basal EGP (bEGP) equaled the rate of glucose appearance (R_a). It was therefore calculated as the deuterated glucose infusion rate (mg · kg^{-1} · min^{-1}) divided by the plasma enrichment of [6,6-$^2H_2$]glucose. During the two steps of the euglycemic clamp, due to the non–steady-state conditions, the Steele's equation was used to estimate the R_a (16). The residual EGP at the last 20 min of the first (residual EGP$_1$ [rEGP$_1$]) and second (re-

sidual EGP_2 [$rEGP_2$]) steps of the glucose clamp were therefore obtained by subtracting the unlabeled glucose infusion rate from the total R_a at each step of the clamp. Negative values of EGP, observed only at the high-infusion step, were considered as nil EGP. The product EGP × plasma insulin at basal and at the end of each step was used as the hepatic insulin resistance index (17).

The insulin-stimulated glucose disposal rate (*M*) was calculated from the glucose infusion rate during the last 20 min of the second step of the glucose clamp after accounting for interindividual differences in glucose space (14) and was expressed in milligram per kilogram of body fat-free mass per minute. Total glucose disposal (TGD) rate was obtained by adding $rEGP_2$ to *M*.

The insulinogenic index ($\Delta insulin_{0\text{-}30}/\Delta glucose_{0\text{-}30}$) was used to estimate the early insulin secretion during the oral glucose tolerance test and the product of the TGD and the insulinogenic index as a measure of β-cell function.

The homeostasis model assessment–insulin resistance (HOMA-IR) index was calculated as fasting glucose (mmol/l) × fasting insulin (μU/ml)/22.5.

At baseline and at the end of each clamp step, we used the product mean NEFA concentration × mean plasma insulin as a surrogate of the adipose insulin resistance (that is, the resistance to NEFA suppression by insulin).

Statistical analysis

Results are represented as means ± SE and percentage, unless stated otherwise. Statistical analysis was performed using SPSS software version 12.0 (SPSS, Chicago, IL). We used the Fisher's exact test to compare categorical variables and the nonparametric Mann-Whitney *U* test for quantitative variables. The level of significance was set at $P < 0.05$.

RESULTS

Characteristics of the participants and biochemical and metabolic parameters

The age at inclusion and BMI were comparable between the two groups (Table 1). Fasting plasma glucose level was <7.0 mmol/l in 87% ($n = 13$) of patients. During the oral glucose tolerance test, two patients had the profile of impaired glucose tolerance and others fulfilled the criteria of diabetes. As shown in Table 1, there was no significant difference between patients with KPD and controls with respect to plasma lipid parameters. Patients had a significantly higher fasting plasma glucose concentration; fasting plasma insulin levels were also higher in patients, although the difference was not significant (Table 2). The insulinogenic index was significantly higher in the control group (Table 2). The insulinogenic index of patients who presented initially with ketoacidosis was not different from that of individuals who presented with ketosis alone (4.5 ± 1.6 vs. 4.7 ± 1.1; $P = 0.95$). During insulin infusion, steady-state plasma insulin concentrations at the last 20 min of step one ($SSPI_1$) and step two ($SSPI_2$) were comparable between the two groups (Table 2).

Table 1—*General, anthropometric, and biochemical characteristics of participants*

	KPD	Control subjects	*P*
n	15	17	—
Age (years)	43.9 ± 3.0	44.0 ± 2.1	0.9
Sex (F/M)	2/13	2/15	0.65
Age at migration to France (years)	30.3 ± 2.0	32.2 ± 2.1	0.54
Systolic blood pressure (mmHg)	136.9 ± 3.9	131.6 ± 4.8	0.23
Diastolic blood pressure (mmHg)	75.3 ± 3.3	75.1 ± 2.5	0.88
BMI (kg/m^2)	26.6 ± 0.8	25.0 ± 0.7	0.19
Waist circumference (cm)	92.4 ± 5.8	88.1 ± 4.3	0.74
Body fat (%)	21.1 ± 1.2	18.5 ± 1.9	0.1
Whole-body lean mass (kg)	58.5 ± 2.7	58.1 ± 2.5	0.9
Whole-body fat mass (kg)	17.2 ± 1.7	14.0 ± 1.6	0.18
Trunk fat mass (kg)	6.5 ± 0.7	5.0 ± 0.7	0.11
Total cholesterol (mmol/l)	4.9 ± 0.3	5.5 ± 0.3	0.12
HDL cholesterol (mmol/l)	1.4 ± 0.1	1.6 ± 0.1	0.13
LDL cholesterol (mmol/l)	3.0 ± 0.2	3.5 ± 0.3	0.18
Triglycerides (mmol/l)	1.2 ± 0.2	1.1 ± 0.1	0.5

Data are means ± SE.

Table 2—*Metabolic parameters and indexes of insulin action*

	KPD	Control subjects	*P*
Fasting plasma glucose (mmol/l)	6.3 ± 0.2	4.9 ± 0.1	<0.001
Fasting plasma insulin (μU/ml)	9.4 ± 1.9	6.7 ± 1.0	0.33
Insulinogenic index (mU/mmol)	4.6 ± 0.9	21.3 ± 5.4	0.001
HOMA-IR	3.1 ± 0.6	1.1 ± 0.2	0.005
$SSPI_1$ (μU/ml)	20.9 ± 3.3	17.4 ± 1.2	0.82
$SSPI_2$ (μU/ml)	189.6 ± 20.5	181.5 ± 14.8	0.89
TGD ($mg \cdot kg^{-1} \cdot min^{-1}$)	7.5 ± 0.8	10.5 ± 0.9	0.018
TGD × insulinogenic index	28.1 ± 4.0	193.3 ± 46.1	<0.001
bEGP ($mg \cdot kg^{-1} \cdot min^{-1}$)	4.0 ± 0.3	3.0 ± 0.1	0.001
$rEGP_1$ ($mg \cdot kg^{-1} \cdot min^{-1}$)	1.6 ± 0.2	0.6 ± 0.1	0.004
bEGP × FPI ($mg \cdot kg^{-1} \cdot min^{-1} \cdot mU \cdot l^{-1}$)	35.9 ± 7.2	20.7 ± 3.6	0.04
$rEGP_1 \times SSPI_1$ ($mg \cdot kg^{-1} \cdot min^{-1} \cdot mU \cdot l^{-1}$)	33.2 ± 7.2	10.9 ± 2.8	0.006
$rEGP_2 \times SSPI_2$ ($mg \cdot kg^{-1} \cdot min^{-1} \cdot mU \cdot l^{-1}$)	50.3 ± 22.1	0	0.007
Fasting NEFA (μmol/l)	1,936.7 ± 161.4	1,230.0 ± 174.1	0.002
$SSNEFA_1$ (μmol/l)	706.6 ± 96.5	381.6 ± 55.9	0.015
$SSNEFA_2$ (μmol/l)	187.8 ± 27.7	116.1 ± 11.2	0.05
Fasting IR_{NEFA} ($10^3 \cdot \mu mol \cdot mU \cdot l^{-2}$)	17.7 ± 3.2	8.0 ± 1.7	0.009
IR_{NEFA1} ($10^3 \cdot \mu mol \cdot mU \cdot l^{-2}$)	17.4 ± 4.6	6.9 ± 1.4	0.05
IR_{NEFA2} ($10^3 \cdot \mu mol \cdot mU \cdot l^{-2}$)	40.2 ± 9.2	21.2 ± 2.6	0.06

Data are means ± SE. SSNEFA, steady-state nonesterified fatty acid; IR_{NEFA}, insulin resistance index to NEFA disappearance ($_1$ and $_2$ denote the last 20 min of the first and second steps of the glucose clamp, respectively).

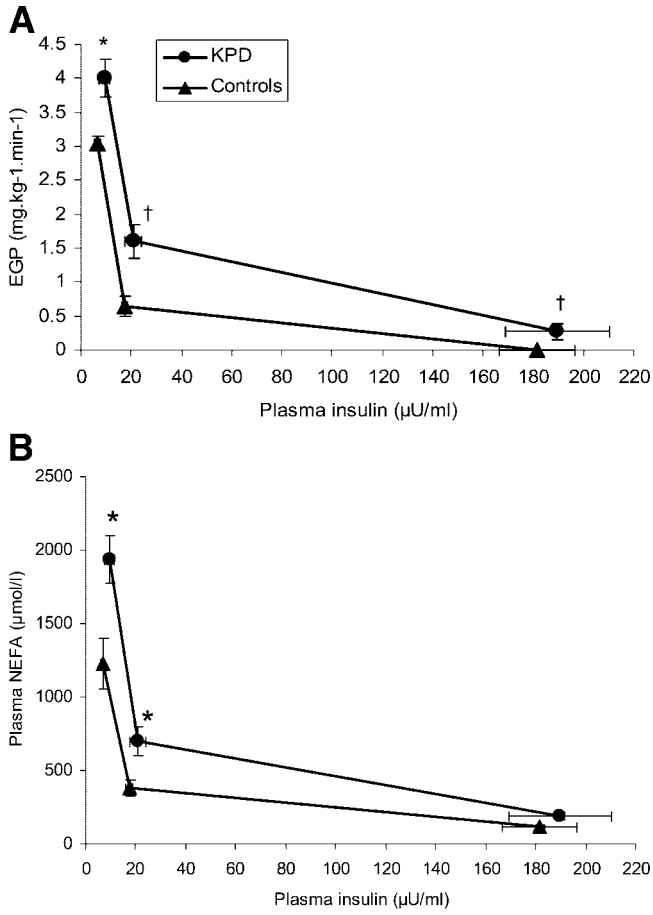

Figure 1—*Endogenous glucose production rate* (A) *and plasma NEFA concentrations* (B) *at baseline and during insulin infusion in KPD patients* (●) *and control subjects* (▲). *Values represent means ± SE.* *P < *0.05,* †P < *0.01 vs. control subjects.*

Insulin-mediated glucose disposal

Mean TGD rate was reduced by 30% in KPD patients ($P = 0.018$) (Table 2). This difference remained significant after adjustment for BMI ($P = 0.034$). The HOMA-IR was accordingly higher in KPD patients. The product of TGD and insulinogenic index was also markedly reduced in KPD patients compared with control subjects (Table 2).

Endogenous glucose production

The EGP was significantly higher in patients at baseline (bEGP) and at the end of the first step ($rEGP_1$) of the glucose clamp (Table 2). During the last step of the clamp, $rEGP_2$ was 0 in control subjects, whereas it was still positive in four patients, and the difference between the two groups was significant ($P = 0.007$). The EGP as a function of the plasma insulin level (dose-response curve) is displayed in Fig. 1*A*. The hepatic insulin resistance index was 33% higher in patients at basal (bEGP × fasting plasma insulin). During both low-dose ($rEGP_1 \times SSPI_1$) and high-dose ($rEGP_2 \times SSPI_2$) insulin infusions, this index remained higher in patients (Table 2).

NEFA suppression

Basal NEFA concentration was 57% higher in patients compared with control subjects (Table 2), even after adjustment for BMI ($P = 0.024$). It remained significantly elevated at the end of the low-dose insulin infusion step ($SSNEFA_1$) and at the borderline significance level at the end of the high-dose insulin infusion step ($SSNEFA_2$) of the euglycemic clamp (Table 2). By contrast, the relative decline from baseline was similar between the two groups, whatever the step (in patients and control subjects, respectively: first step 61.5 ± 5.5 vs. 64.9 ± 4.2%, $P = 0.7$; second step 89.5 ± 1.8 vs. 88.2 ± 1.6%, $P = 0.5$). Figure 1*B* presents the plasma NEFA concentration as a function of plasma insulin levels. Insulin resistance index to NEFA disappearance (IR_{NEFA}) was doubled in patients compared with controls at basal (fasting IR_{NEFA}) and during the clamp (IR_{NEFA1} and IR_{NEFA2}), with the difference being statistically significant at basal but at borderline significance at the first and second steps (Table 2).

CONCLUSIONS — Because ketosis is the hallmark of KPD, the role of insulin secretion has been widely studied at onset and in the long-term course of the disease (6,8–10). In two among these studies, insulin sensitivity toward glucose metabolism was evaluated using either the euglycemic clamp (6) or the minimal model (10). Compared with control subjects' values, it was reported to be similar (10) or reduced (6) in patients with or without insulin treatment after they recovered from the acute ketotic episode. We also previously used the intravenous insulin tolerance test to evaluate insulin sensitivity in a larger cohort of KPD patients (8). We showed that, although markedly impaired during the ketotic phase, insulin sensitivity improved significantly after 6 months of follow-up and almost reached nondiabetic values in patients who became insulin independent but not in patients who still required insulin for metabolic control.

In the present study, to assess various aspects of insulin action in patients with KPD in near-normoglycemic remission, we used a two-step euglycemic-hyperinsulinemic clamp to compare them with matched control subjects with normal glucose tolerance. This allowed us to provide a direct and complete characterization of insulin sensitivity in a phenotype of diabetes that still requires thorough insight for appropriate classification and treatment. The first finding of our study is that despite insulin-free near-normoglycemic remission in sub-Saharan African adults with KPD, insulin-mediated glucose disposal is markedly reduced. This was previously suggested by Banerji et al. (6) in patients with KPD in good metabolic control, either insulin treated or not.

Another important finding is that despite insulin-free near-normoglycemic remission, in the postabsorptive state, patients with KPD display a higher endogenous glucose production rate, which mostly corresponds to hepatic glucose production (18). This is related to an increased hepatic insulin resistance as evidenced by the higher basal hepatic insulin resistance index (bEGP × fasting plasma insulin). During both low- and high-dose insulin infusions, this index remained higher in patients, indicating that for a

given insulin concentration, the suppression of EGP was less marked in them compared with control subjects.

Our last important finding is that at fasting and during the low-dose insulin infusion, plasma NEFA concentrations were higher in patients than in control subjects. This was substantiated by the higher basal adipose insulin resistance index, demonstrating that KPD patients in near-normoglycemic remission display adipose insulin resistance. Of note, increased circulating NEFAs may in turn worsen insulin resistance and the insulin secretion defect. The lack of difference in NEFA response to insulin infusion may be related to the good metabolic control of patients or to the small number of subjects studied. Absolute basal NEFA concentrations seem quite high in our subjects. This may be because we did not use a lipolysis inhibitor during blood sample collection, although higher NEFA levels have been previously reported in black populations (19).

Reduced muscle glucose uptake and decreased liver and adipose insulin sensitivity have also been reported in Caucasians with type 2 diabetes by Groop et al. (20) and are usually considered as characteristic features of type 2 diabetes (21,22). However, in these reports, diabetic patients were hyperglycemic, with mean fasting plasma glucose at 10.5 mmol/l (22) or A1C level averaging 9.6% (20). In our study, patients were in near-normoglycemia with mean A1C level at 6.2%. Although all antidiabetic medications, if any, were discontinued many days before the investigation, fasting plasma glucose averaged 6.3 mmol/l and was below the diabetic-defining cutoff of 7 mmol/l in 87% of patients. Thus, this is the first investigation of diabetic patients in a metabolic state close to normoglycemia without insulin treatment. The multiorgan insulin resistance observed in near-normoglycemia suggests that these defects are primary rather than secondary to the diabetic state. We also show that the impairment of insulin sensitivity is associated with a decreased early-phase insulin secretion resulting in a drastically reduced index of β-cell function (TGD × insulinogenic index). Indeed, it is now recognized that type 2 diabetes develops when insulin secretion is unable to compensate for insulin resistance (23,24).

The fact that patients with KPD display metabolic abnormalities that characterize type 2 diabetes does not explain the ketotic onset or relapses that define KPD. A genetic defect or an environmental factor making the β-cells more susceptible to gluco- and/or lipotoxicity may be a potential factor. To date, no prominent genetic factor has been identified. We recently proposed that an endemic asymptomatic viral infection may be the ketotic precipitating factor in such patients from sub-Saharan Africa. Among possible candidates, we focused on *human herpesvirus-8* (HHV-8). We found a high association between KPD and HHV-8 infection and evidenced that this virus was able to infect human β-cells in vitro (25).

We acknowledge that the small number of subjects may have minimized the role of BMI and/or percent body fat on the insulin sensitivity defects. Indeed, these anthropometric parameters were slightly higher in patients, although not significantly. However, adjustment for BMI or percent body fat did not change the significance of our results. Also, it should be noted that despite the near-normoglycemic state, the higher fasting plasma glucose in patients might have by itself worsened the insulinogenic index (26).

In conclusion, in the context of near-normoglycemic remission, we observe insulin resistance at the level of muscle, adipose tissue, and liver. As suggested in reports on the recovery of β-cell function after the acute phase of KPD (8,10), these findings strongly indicate that KPD is a subtype of type 2 diabetes in which an uncommon factor triggers the ketotic onset or relapses.

Acknowledgments— This work was supported by an institutional grant (PHRC) from Assistance Publique–Hôpitaux de Paris, the French Diabetes Association (AFD), a nonprofit organization, and the French-speaking Association for the Study of Diabetes and Metabolic Diseases (ALFEDIAM).

Part of these results was presented at the 43rd European Association for the Study of Diabetes (EASD) annual meeting [S. Choukem et al. *Diabetologia* 50 (Suppl. 1):S277, 2007].

The authors are grateful to the participants, the nurse staff of the Clinical Investigation Center, and the technical staff of the Hormones Laboratory at Saint-Louis Hospital for their dedication.

References

1. American Diabetes Association: Standards of medical care in diabetes: 2007. *Diabetes Care* 30 (Suppl. 1):S4–S41, 2007
2. Kasuga M: Insulin resistance and pancreatic beta cell failure. *J Clin Invest* 116:1756–1760, 2006
3. Sobngwi E, Mauvais-Jarvis F, Vexiau P, Mbanya JC, Gautier JF: Diabetes in Africans. Part 2: Ketosis-prone atypical diabetes mellitus. *Diabete Metab* 28:5–12, 2002
4. Umpierrez GE, Smiley D, Kitabchi AE: Narrative review: ketosis-prone type 2 diabetes mellitus. *Ann Intern Med* 144:350–357, 2006
5. Winter WE, Maclaren NK, Riley WJ, Clarke DW, Kappy MS, Spillar RP: Maturity-onset diabetes of youth in black Americans. *N Engl J Med* 316:285–291, 1987
6. 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* 43: 741–745, 1994
7. Balasubramanyam A, Zern JW, Hyman DJ, Pavlik V: New profiles of diabetic ketoacidosis: type 1 vs type 2 diabetes and the effect of ethnicity. *Arch Intern Med* 159:2317–2322, 1999
8. 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 beta-cell dysfunction and insulin resistance. *Diabetes* 53:645–653, 2004
9. Sobngwi E, Vexiau P, Levy V, Lepage V, Mauvais-Jarvis F, Leblanc H, Mbanya JC, Gautier JF: Metabolic and immunogenetic prediction of long-term insulin remission in African patients with atypical diabetes. *Diabet Med* 19:832–835, 2002
10. Umpierrez GE, Casals MM, Gebhart SP, Mixon PS, Clark WS, Phillips LS: Diabetic ketoacidosis in obese African-Americans. *Diabetes* 44:790–795, 1995
11. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183–1197, 1997
12. Sobngwi E, Gautier JF: Adult-onset idiopathic type I or ketosis-prone type II diabetes: evidence to revisit diabetes classification. *Diabetologia* 45:283–285, 2002
13. Osei K, Cottrell DA, Adenuwon CA, Ezenwaka EC, Akanji AO, O'Dorisio TM: Serum insulin and glucose concentrations in people at risk for type II diabetes: a comparative study of African Americans and Nigerians. *Diabetes Care* 16:1367–1375, 1993
14. DeFronzo RA, Tobin JD, Andres R: Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol* 237:E214–E223, 1979

15. Boirie Y, Gachon P, Beaufrere B: Splanchnic and whole-body leucine kinetics in young and elderly men. *Am J Clin Nutr* 65:489–495, 1997
16. Steele R: Influences of glucose loading and of injected insulin on hepatic glucose output. *Ann N Y Acad Sci* 82:420–430, 1959
17. Abdul-Ghani MA, Jenkinson CP, Richardson DK, Tripathy D, DeFronzo RA: Insulin secretion and action in subjects with impaired fasting glucose and impaired glucose tolerance: results from the Veterans Administration Genetic Epidemiology Study. *Diabetes* 55:1430–1435, 2006
18. Consoli A: Role of liver in pathophysiology of NIDDM. *Diabetes Care* 15:430–441, 1992
19. Buthelezi EP, van der Merwe MT, Lönnroth PN, Gray IP, Crowther NJ: Ethnic differences in responsiveness of adipocyte lipolytic activity to insulin. *Obes Res* 8:171–178, 2000
20. Groop LC, Bonadonna RC, DelPrato S, Ratheiser K, Zyck K, Ferrannini E, DeFronzo RA: Glucose and free fatty acid metabolism in non-insulin-dependent diabetes mellitus: evidence for multiple sites of insulin resistance. *J Clin Invest* 84: 205–213, 1989
21. DeFronzo RA, Bonadonna RC, Ferrannini E: Pathogenesis of NIDDM: a balanced overview. *Diabetes Care* 15:318–368, 1992
22. Mitrakou A, Kelley D, Veneman T, Jenssen T, Pangburn T, Reilly J, Gerich J: Contribution of abnormal muscle and liver glucose metabolism to postprandial hyperglycemia in NIDDM. *Diabetes* 39: 1381–1390, 1990
23. Weyer C, Bogardus C, Mott DM, Pratley RE: The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *J Clin Invest* 104:787–794, 1999
24. Kahn SE: The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of type 2 diabetes. *Diabetologia* 46:3–19, 2003
25. Sobngwi E, Choukem SP, Agbalika F, Blondeau B, Fetita LS, Lebbe C, Thiam D, Cattan P, Larghero J, Foufelle F, Ferre P, Vexiau P, Calvo F, Gautier JF: Ketosis-prone type 2 diabetes mellitus and human herpesvirus 8 infection in sub-Saharan Africans. *JAMA* 299:2770–2776, 2008
26. Brunzell JD, Robertson RP, Lerner RL, Hazzard WR, Ensinck JW, Bierman EL, Porte DJ: Relationships between fasting plasma glucose levels and insulin secretion during intravenous glucose tolerance tests. *J Clin Endocrinol Metab* 42:222–229, 1976