Ketosis-Prone Type 2 Diabetes in Patients of Sub-Saharan African Origin

Clinical Pathophysiology and Natural History of β-Cell Dysfunction and Insulin Resistance

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Nonautoimmune ketosis-prone diabetic syndromes are increasingly frequent in nonwhite populations. We have characterized a cohort of patients of sub-Saharan African origin who had ketosis-prone type 2 diabetes (n = 111), type 1 diabetes (n = 21), and type 2 diabetes (n = 88) and were admitted to a hospital for management of uncontrolled diabetes. We compared epidemiological, clinical, and metabolic features at diabetes onset and measured insulin secretion (glucagon-stimulated C-peptide) and insulin action (short intravenous insulin tolerance test) during a 10-year follow-up. Ketosis-prone type 2 diabetes shows a strong male predominance, stronger family history, higher age and BMI, and more severe metabolic decompensation than type 1 diabetes. In ketosis-prone type 2 diabetes, discontinuation of insulin therapy with development of remission of insulin dependence is achieved in 76% of patients (non–insulin dependent), whereas only 24% of patients remain insulin dependent. During evolution, ketosis-prone type 2 diabetes exhibit specific β-cell dysfunction features that distinguish it from type 1 and type 2 diabetes. The clinical course of non–insulin-dependent ketosis-prone type 2 diabetes is characterized by ketotic relapses followed or not by a new remission. Progressive hyperglycemia precedes and is a strong risk factor for ketotic relapses (hazard ratio 38). The probability for non–insulin-dependent ketosis-prone type 2 diabetes to relapse is 90% within 10 years, of whom ~50% will become definitively insulin dependent. Insulin sensitivity is decreased in equal proportion in both ketosis-prone type 2 diabetes and type 2 diabetes, but improves significantly in non–insulin-dependent ketosis-prone type 2 diabetes, only after correction of hyperglycemia. In conclusion, ketosis-prone type 2 diabetes can be distinguished from type 1 diabetes and classical type 2 diabetes by specific features of clinical pathophysiology and also by the natural history of β-cell dysfunction and insulin resistance reflecting a propensity to glucose toxicity. *Diabetes* 53:645–653, 2004

The pathogenesis of diabetes distinguishes type 2 diabetes, resulting from the interaction between insulin resistance and β-cell dysfunction (1), from type 1 diabetes, in which the autoimmune destruction of pancreatic β-cells leads to absolute insulin deficiency (2). Over the past 15 years, a ketosis-prone form of diabetes, which was initially observed in young African Americans (3), has emerged as a new clinical entity. This syndrome of episodic diabetic ketoacidosis without immunologic markers of type 1 diabetes is characterized by insulin dependence at the time of presentation, as in the case of type 1 diabetes, but followed by absence of insulin requirements for years as observed in type 2 diabetes (3,4). This third type of diabetes, which is mostly observed in obese adult African-American (5–8), sub-Saharan African (9), and other adult nonwhite diabetic populations (10–14), is also emerging as a serious clinical entity among African- and Hispanic-American children in the United States (3,15–17). The absence of defined pathophysiological mechanisms has led experts in the American Diabetes Association and the World Health Organization to classify this entity as idiopathic type 1 or type 1B diabetes (18,19). However, most investigators who study this form of diabetes still continue to attribute different names, such as atypical diabetes, Flatbush diabetes, phasic insulin-dependent diabetes, and more recently ketosis-prone diabetes (5,8–10,13,20), thus reflecting the inadequacy of the current classification. Most clinical studies that have focused on ketosis-prone type 2 diabetes suggest disease-specific metabolic defects (5,6), and the classification of these syndromes in the type 1 diabetes group is today a subject of increasing controversy (7,20). However, so far, prospective follow-up of insulin secretion and action is lacking to propose a new classification based on pathogenesis.

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Received for publication 8 June 2003 and accepted in revised form 1 December 2003.

DKA, diabetic ketoacidosis; ICA, islet cell autoantibody; ITT, insulin tolerance test; K_{ITT}, rate of plasma glucose disappearance; OHA, oral hypoglycemic agent.

In this report, we characterize a large cohort of patients of sub-Saharan African descent with ketosis-prone type 2 diabetes, autoimmune type 1 diabetes, and type 2 diabetes, from diabetes onset and for a period of 10 years. We show that ketosis-prone type 2 diabetes can be differentiated from type 1 diabetes and classical type 2 diabetes by specific epidemiologic, clinical, and metabolic features of diabetes onset and by the natural history of impairment in insulin secretion and action.

RESEARCH DESIGN AND METHODS

Patients. We included in a cohort study 233 consecutive unrelated patients of sub-Saharan African descent who were admitted to the Saint-Louis/Lariboisiere University Medical Center, Paris, and the Sud-Francilien Hospital, Corbeil, France, between 1990 and 2000 for medical management of uncontrolled diabetes.

Patients had an initial calculation of BMI. Family history of diabetes was defined by a reported diagnosis in a parent or a sibling. Detailed assessment of medical history, symptoms of hyperglycemia/insulin deficiency (thirst, polyuria, polydipsia, and weight loss), and precipitating cause of diabetic ketoacidosis (DKA) was performed. Diabetes was confirmed on venous plasma glucose, and the diagnosis of DKA was established in the emergency room by a blood glucose level >15 mmol/l, a pH level <7.30, a serum bicarbonate <20 mEq/l, and urine ketones >80 mg/dl (Keto-Diastix; Bayer).

Type 1 diabetes (n = 21) was selected as new onset and was confirmed by the presence of autoantibodies to islet cells (ICAs) and to GAD 65. Type 2 diabetes (n = 88) was defined as previously diagnosed diabetes, already treated by diet or oral hypoglycemic agents (OHAs), without ketosis and in the absence of ICAs and GAD 65 autoantibodies. Ketosis-prone type 2 diabetes (n = 111) was defined as new-onset diabetes without precipitating illness (infection, stress), with the presence of strong ketosis (urine ketones >80 mg/dl) or DKA, and in the absence of ICAs and GAD 65 autoantibodies. Thirteen diabetic patients who were admitted with ketosis, without autoantibodies but with acute precipitating illness, were excluded to avoid misclassification between ketosis-prone type 2 diabetes and type 2 diabetes.

Patients were hospitalized for ~7 days and were treated by intravenous fluids, electrolytes, and insulin therapy. After discharge, patients were similarly cared for at the outpatient diabetes clinic of the previously cited hospitals, where blood glucose, HbA_{1c}, lipids, and anthropometric parameters were determined every 3–6 months. Because prevention of ketotic relapse was an end point for patients in remission of insulin dependence, prompt intensification of pharmacologic therapy was uniformly instituted when blood glucose rose above target values (HbA_{1c} >6.3%). Retrospectively, it must be emphasized that the rate of ketotic relapses could have been decreased if management had been more aggressive and compliance to treatment had been better enforced.

The study protocol was approved by the Institutional Human Subjects Review Board of Saint-Louis Hospital, and all participants gave their informed consent.

Insulin secretion. Pancreatic insulin reserve was assessed during the initial DKA and at least 48 h after resolution of ketosis and normalization of blood glucose by measuring the C-peptide level before and 8 min after the intravenous injection of 1 mg of glucagon as previously described (9). Patients were studied 12 h after an overnight fast and before taking the morning OHA or doing the insulin injection. For longitudinal evaluation of β-cell secretory capacity, C-peptide values were determined regularly in a constant subset of patients who agreed to participate and whose baseline characteristics were representative of the rest of the group. The control population consisted of eight normal volunteers whose mean ± SD age was 39.4 ± 6.5 years and mean ± SD BMI was 26.6 ± 6.2 kg/m.

Insulin sensitivity. Insulin sensitivity was measured at admission and after 6-month follow-up, after an overnight fast. Patients were chosen and studied as described for insulin secretion. We performed a short insulin tolerance test (ITT) with an intravenous bolus injection of regular insulin (0.1 unit/kg body wt), followed by blood glucose determination at 0, 3, 6, 9, 12, and 15 min after insulin injection, and calculation of the rate of plasma glucose disappearance (K_{ITT}) as previously described (9,21). The control population was similar to that of the insulin secretion study.

Immunologic studies. All patients underwent measurement of ICAs and GAD 65 autoantibodies at the time of admission. A new determination was performed for the patients with insulin-dependent ketosis-prone type 2 diabetes during follow-up. GAD 65 autoantibodies were measured by radioimmunoassay method (CIS Bio International, Gif/Yvette, France). ICA titers were determined by comparison of consecutive dilutions of the tested serum to the Juvenile Diabetes Foundation standards serum curve on frozen human pancreatic section from blood 0 group donors, as previously described (22).

Statistical analysis. Results are expressed as mean ± SD unless otherwise stated. For multiple two-by-two group comparisons of β-cell function, a step-down multiple-stage test procedure was used with Wilcoxon's rank-sum tests or Kruskal-Wallis. As the plot of ΔC-peptide in each group showed no evolution between 1 and 3 years, we considered a plateau during this period and we estimated the mean ΔC-peptide for each patient. Longitudinal data recorded during follow-up were analyzed as changes from baseline values. Association between quantitative variables were assessed using Spearman's rank correlation coefficients and partial correlation coefficients when adjusting for other covariates. The prognostic value of an increase in body weight and increase in HbA_{1c} on the hazard of hyperglycemia or relapse, respectively, were tested in a Cox model with time-dependent covariate. The validity of the proportional hazards assumption was checked using Grambsch and Therneau goodness-of-fit test. All tests were performed at a 5% level. Analyses were performed using S-Plus 2000 software (MathSoft, Seattle, WA).

RESULTS

General characteristics of patients at presentation. Table 1 shows the characteristics of patients at admission. There was a predominance of sub-Saharan African patients compared with Afro-Caribbean patients, but both populations shared similar clinical and biological features (data not shown). A family history of diabetes was strongly associated with ketosis-prone type 2 diabetes and with type 2 diabetes compared with type 1 diabetes. The mean age of patients with ketosis-prone type 2 diabetes at admission was not different from that of patients with type 2 diabetes but was 14.6 years higher than that of patients with type 1 diabetes. Whereas both the type 1 diabetes and type 2 diabetes groups showed equal sex distribution, the ketosis-prone type 2 diabetes group showed a strong male predominance (3:1). BMI before symptoms was not different in ketosis-prone type 2 diabetes and type 2 diabetes but was 5.4% higher in ketosis-prone type 2 diabetes compared with type 1 diabetes. Finally, symptoms of metabolic decompensation (hyperglycemia, HbA_{1c}, weight loss, and DKA) were more severe in ketosis-prone type 2 diabetes than in type 1 diabetes or in type 2 diabetes (Table 1).

Clinical dissection of ketosis-prone type 2 diabetes. Patients were cared for as outlined in RESEARCH DESIGN AND METHODS. During follow-up, we divided patients with ketosis-prone type 2 diabetes into two subgroups. The first group (non–insulin-dependent ketosis-prone type 2 diabetes, n = 84) was composed of patients in whom discontinuation of insulin was decided by the attending physician following repeated episodes of hypoglycemia or tight blood glucose control despite continuous decrease in insulin doses. Near normoglycemic remission of insulin dependence (HbA_{1c} <6.3%) was obtained with diet alone or small doses of OHA. The mean duration of insulin therapy to obtain remission was 14.3 weeks (range, 1–150). The second group (insulin-dependent ketosis-prone type 2 diabetes, n = 27) was composed of patients in whom we could not obtain remission of insulin dependence during a mean follow-up of 352.8 ± 92.5 weeks. These patients required insulin doses 2.1 times higher than in non–insulin-dependent ketosis-prone type 2 diabetes at discharge to prevent metabolic decompensation and the development of ketosis (Table 2).

Both ketosis-prone type 2 diabetes groups increased their body weight between immigration to France and the onset of diabetes (P < 0.0001). Those with insulin-depen-

TABLE 1
Clinical parameters at admission

	Without ketosis	With ketosis		
	Type 2 diabetes	Type 1 diabetes	Ketosis-prone type 2 diabetes	*P*
n	88	21	111	
Ketosis	0 (0)	16 (76.2)	111 (100)	0.0001*
DKA	0 (0)	2 (9.5)	66 (59.5)	0.0001*
ICA, GAD 65 autoantibodies	0 (0)	21 (100)	0 (0)	—
New-onset diabetes	16 (18.2)	21 (100)	111 (100)	—
Duration of diabetes (years)	6.8 ± 5.2	0	0	—
Precipitating factors	48 (54.5)	7 (33.3)	0 (0)	—
Ethnic origin				0.020*
Sub-Saharan Africa	59 (67.1)	16 (76.2)	93 (83.8)	—
Caribbean Islands	29 (32.9)	5 (23.8)	18 (16.2)	—
Family history of diabetes	64 (72.7)	1 (4.8)	75 (67.6)	<0.0001†
Men/women (%)	42 (47.7)/46 (52.3)	10 (47.6)/11 (52.4)	84 (75.7)/27 (24.3)	0.0001†
Age at onset (years)	39.6 ± 11.8	25.3 ± 9.9	39.1 ± 9.5	<0.0001‡
BMI before symptoms (kg/m^2)	29.5 ± 5.5	23.1 ± 1.5	28.5 ± 5.1	<0.0001‡
BMI at admission (kg/m^2)	28.4 ± 6.0	20.7 ± 1.6	24.9 ± 4.8	<0.0001§
Obese (BMI >30 kg/m^2)	29 (32.9)	0 (0)	20 (20.6)	—
Overweight (25 < BMI < 30 kg/m^2)	29 (32.9)	3 (14.3)	28 (28.9)	—
Lean (BMI <25 kg/m^2)	30 (34.2)	18 (85.7)	49 (50.5)	0.0033*
Weight loss (kg)	2.9 ± 3.6	6.7 ± 2.2	9.8 ± 6.1	0.029‡
Duration of symptoms (days)	62.5 ± 25.2	27.0 ± 7.2	23.9 ± 19.5	0.7
Glucose (mmol/l)	19.8 ± 6.6	20.9 ± 12.6	30.5 ± 13.1	0.0001‡
HbA_{1c} (%)	10.5 ± 2.6	11.6 ± 3.5	13.4 ± 2.1	<0.0001‡
Bicarbonates (mmol/l)	23.9 ± 2.2	19.4 ± 6.5	15.3 ± 6.3	0.4‡
Arterial pH	7.36 ± 0.4	7.28 ± 0.7	7.19 ± 0.8	0.09‡
Initial treatment				
Insulin	52 (59.1)	21 (100)	111 (100)	—
OHA	17 (19.3)	0%	0%	—

Data are patient number (%) or means ± SD. Normal HbA_{1c} is <6%. *Ketosis-prone type 2 diabetes vs. type 1 diabetes comparing lean vs. overweight and obese (χ^2); †overall three-group comparison (χ^2); ‡ketosis-prone diabetes vs. type 1 diabetes (Wilcoxon rank-sum test); §overall three-group comparison (Kruskal-Wallis test).

dent ketosis-prone type 2 diabetes were leaner than those with non–insulin-dependent ketosis-prone type 2 diabetes, and the male predominance was higher in the ketosis-prone type 2 diabetes insulin dependent group. The two groups were not different with regard to other parameters (Table 2).

Natural history of pancreatic β-cell function. β-Cell function was assessed in the three diabetic groups and compared with control subjects at presentation and during a 10-year follow-up period. We used the C-peptide response to glucagon, which is the best predictor of further remission in ketosis-prone type 2 diabetes (6,9) (Fig. 1).

TABLE 2
Dissection of ketosis-prone type 2 diabetes

	Ketosis-prone type 2 diabetes NID (84 [75.7%])	Ketosis-prone type 2 diabetes ID (27 [24.3%])	*P*
Men (%)	57 (74.0)	25 (92.6)	0.011
Family history of diabetes	59 (70.2)	17 (62.9)	0.65
Age (years)	40.2 ± 9.6	38.8 ± 8.6	0.45
BMI at immigration (kg/m^2)*	25.4 ± 3.5	23.2 ± 3.4	0.01
BMI before symptoms (kg/m^2)	29.2 ± 5.1	26.1 ± 4.4	0.007
BMI at admission (kg/m^2)	25.3 ± 3.6	23.1 ± 3.6	0.018
HbA_{1c} at admission (%)	13.4 ± 1.9	13.4 ± 2.5	0.92
Weight loss (kg)	9.8 ± 6.3	9.7 ± 5.4	1.0
Duration of symptoms (days)	25.2 ± 21.6	16.0 ± 8.6	0.15
Fasting blood glucose at discharge (mmol/l)	6.16 ± 1.7	6.82 ± 2.3	0.39
Insulin requirement at discharge (units · kg^{-1} · day^{-1})	0.36 ± 0.25	0.76 ± 0.27	<0.0001
Normoglycemic remission	84 (100)	0 (0)	
Duration of insulin therapy (weeks)	14.3 ± 25.9	352.8 ± 92.5†	

Data are means ± SD. Normal HbA_{1c} is <6%. *All patients were born in sub-Saharan Africa or the Caribbean islands, and the average length of residency in France was 14.6 ± 11.2 years. †Mean duration of follow-up without remission of insulin dependence and without discontinuation of insulin therapy. ID, insulin dependent; NID, non-ID.

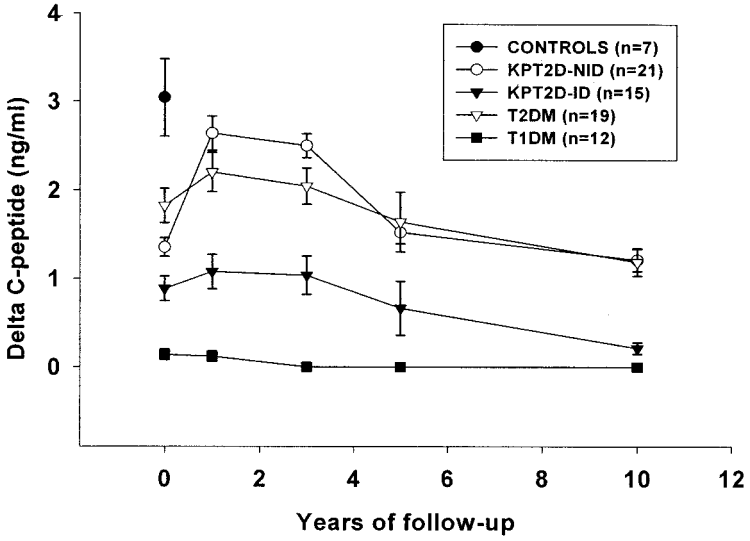

FIG. 1. β-Cell function in ketosis-prone type 2 diabetes. β-Cell insulin secretory reserve was assessed in a cohort of subjects with non–insulin-dependent ketosis-prone type 2 diabetes (n = 21), insulin-dependent ketosis-prone type 2 diabetes (n = 15), type 1 diabetes (n = 12), type 2 diabetes (n = 19), and control subjects (n = 8) by measuring C-peptide response after intravenous glucagon injection after correction of hyperglycemia, at the indicated times, and during 10 years of follow-up. Data represent the mean ± SE ΔC-peptide between 0 and 8 min. ID, insulin dependent; NID, non-ID.

Patients with type 2 diabetes showed a 40% decrease in β-cell function at admission compared with control subjects both during the hyperglycemic crisis (data not shown) and after correction of hyperglycemia ($P < 0.01$); they did not experience significant β-cell recovery during follow-up, and overall they lost 62% of insulin secretory capacity within 10 years compared with control subjects ($P < 0.0001$). Patients with type 1 diabetes showed lower C-peptide at admission than any other diabetic group ($P < 0.001$), and they lost detectable insulin secretion 1 year after diabetes onset.

At admission, during the DKA, both patients with non–insulin-dependent ketosis-prone type 2 diabetes and patients with insulin-dependent ketosis-prone type 2 diabetes had low ΔC-peptide (0.21 ± 0.07 [n = 6]; 0.12 ± 0.06 [n = 4] ng/ml, respectively). After correction of hyperglycemia and ketosis, the ΔC-peptide improved in patients with non–insulin-dependent ketosis-prone type 2 diabetes ($P < 0.05$), but they showed lower ΔC-peptide than patients with type 2 diabetes ($P < 0.05$; Fig. 1). During the first 3-year period, patients with non–insulin-dependent ketosis-prone type 2 diabetes displayed an 80% improvement in ΔC-peptide (P = 0.0002). This β-cell recovery was higher than that of all other groups ($P < 0.05$). Overall, patients with non–insulin-dependent ketosis-prone type 2 diabetes lost 60% of their insulin secretory capacity within 10 years compared with control subjects ($P < 0.0001$). Patients with insulin-dependent ketosis-prone type 2 diabetes had lower initial C-peptide (P = 0.022) than patients with non–insulin-dependent ketosis-prone type 2 diabetes, they showed no significant β-cell recovery, and they displayed a faster loss of residual β-cell function. At 10 years, they maintained higher C-peptide than patients with type 1 diabetes ($P < 0.001$; Fig. 1).

Natural history of insulin sensitivity. Insulin sensitivity was assessed at admission during an intravenous ITT and was equally impaired in the type 2 diabetes, insulin-dependent ketosis-prone type 2 diabetes, and non–

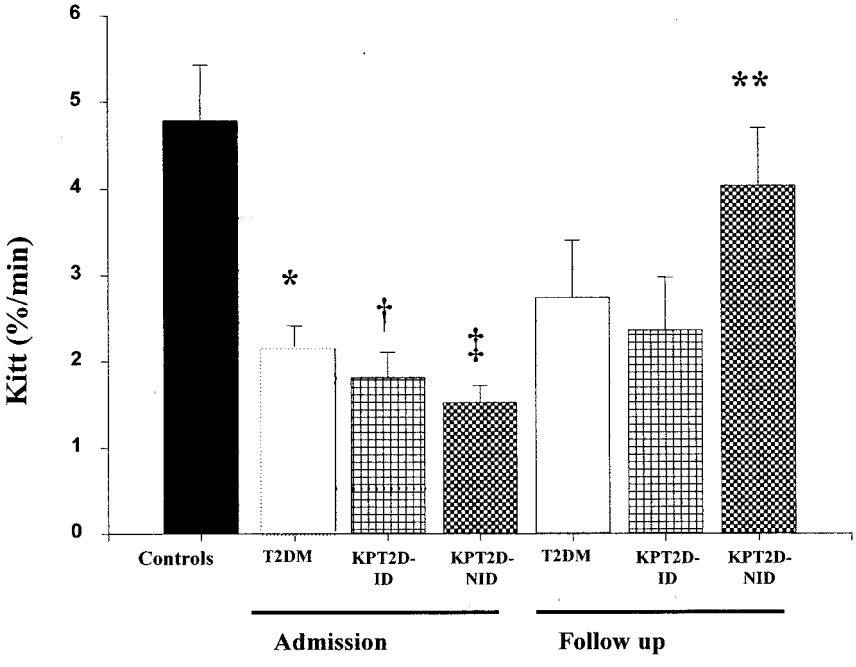

FIG. 2. Insulin resistance in ketosis-prone type 2 diabetes. Insulin sensitivity was assessed at admission and after 6-month follow-up during an intravenous ITT in control subjects (n = 8) and in the type 2 diabetes (n = 19), insulin-dependent ketosis-prone type 2 diabetes (n = 8), and non–insulin-dependent ketosis-prone type 2 diabetes (n = 12) groups, as described in RESEARCH DESIGN AND METHODS. Data represent the mean ± SE K_{ITT}. At admission: *P = 0.0019, †P = 0.0022, ‡P < 0.0001, for type 2 diabetes, insulin-dependent ketosis-prone type 2 diabetes, and non–insulin-dependent ketosis-prone type 2 diabetes vs. control subjects, respectively. At follow up: **P < 0.01: increase in non–insulin-dependent ketosis-prone type 2 diabetes compared with type 2 diabetes and non–insulin-dependent type 1 diabetes. ID, insulin dependent; NID, non-ID.

insulin-dependent ketosis-prone type 2 diabetes groups, compared with control subjects (Fig. 2). Insulin sensitivity was reassessed 6 months after the initial admission. The K_{ITT} did not improve significantly in the type 2 diabetes group ($P = 0.098$) and in the insulin-dependent ketosis-prone type 2 diabetes group ($P = 0.16$). On the contrary, there was a 213% improvement in insulin sensitivity in the ketosis-prone type 2 diabetes non–insulin-dependent group ($P = 0.0039$), which almost reached nondiabetic values (Fig. 2). The rise in insulin sensitivity was more pronounced in the ketosis-prone type 2 diabetes non–insulin-dependent group than in other groups.

Lipids are also an important factor of insulin resistance (23,24). The triglyceride levels were measured 3 months after the initial metabolic decompensation and were not significantly different in the three groups of patients compared with control subjects (control [mmol/l], 0.96 ± 0.3; type 2 diabetes, 1.06 ± 0.7; insulin-dependent ketosis-prone type 2 diabetes, 1.04 ± 0.5; non–insulin-dependent ketosis-prone type 2 diabetes, 1.22 ± 0.8; $P = 0.55$).

Clinical course of remissions and relapses. Insulin-dependent ketosis-prone type 2 diabetes is characterized by the settlement of permanent insulin dependence at the onset of diabetes. On the contrary, patients with non–insulin-dependent ketosis-prone type 2 diabetes develop normoglycemic remissions that can be interrupted by hyperglycemic and ketotic relapses followed or not by another remission of insulin dependence. The mean duration of remission until the first relapse was 40.5 ± 23.2 months (range, 6–120), but 34 (40%) patients were still in remission at the end of follow-up. In our non–insulin-dependent ketosis-prone type 2 diabetes cohort, we observed 33 relapses, among which 24 (73%) subsequently went into a new remission. Figure 3*A* represents the probability of relapse, which ranges from 9% in the first year to 90% after 10 years. Among patients with non–insulin-dependent ketosis-prone type 2 diabetes who relapsed, some remained definitively insulin dependent, and Fig. 3*B* represents the probability for those who relapsed to become definitively insulin dependent. This risk remained low (<40%) within 10 years and peaked to 60% (95% CI, 38–74) after 10 years. Similarly, in type 2 diabetes ($n = 40$), 57.5% of patients were under insulin therapy after 10 years of follow-up. Finally, the patients with insulin-dependent ketosis-prone type 2 diabetes did not seem to exhibit the "brittleness" characteristic of long-standing type 1 diabetes and did not show any significant increase in the incidence of severe hypoglycemia compared with non–insulin-dependent ketosis-prone type 2 diabetes (data not shown).

Role of obesity and hyperglycemia in relapses. The role of obesity in the development acute β-cell failure was studied by retrospectively comparing the evolution of body weight and blood glucose in two groups of patients with non–insulin-dependent ketosis-prone type 2 diabetes: one in which patients remained in remission ($n = 15$) and one in which patients relapsed in ketosis ($n = 22$). There was no change in body weight in the remission group, whereas we observed a mean 3.1% increase ($P = 0.033$) in body weight in the relapse group (compare Fig. 4*A* with 4*C*). In this latter group, the increase in BMI preceded the rise in blood glucose (compare Fig. 4*B* with 4*D*). However,

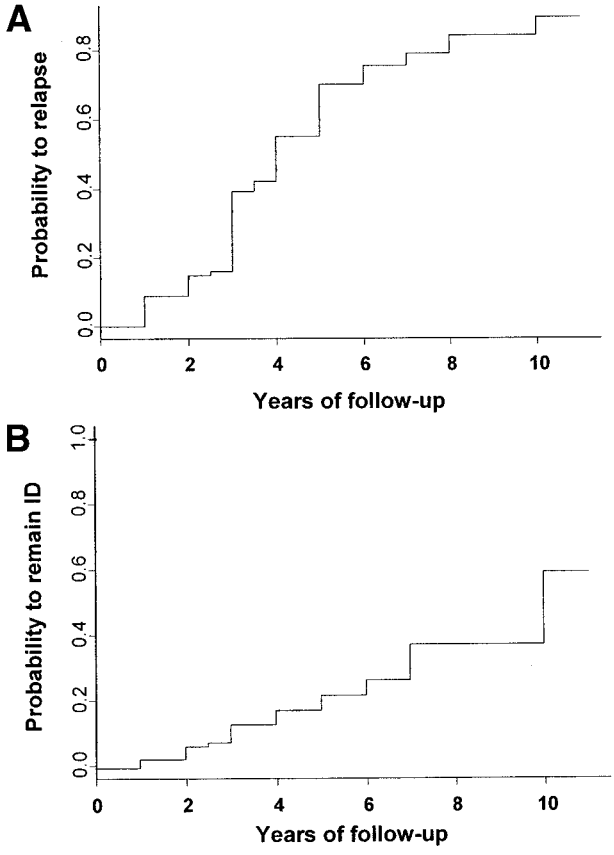

FIG. 3. Clinical course of relapses and onset of insulin dependence in ketosis-prone type 2 diabetes. *A*: Kaplan-Meier estimates of the cumulative incidence of ketotic relapses in non–insulin-dependent ketosis-prone type 2 diabetes. *B*: Kaplan-Meier estimates of the onset of permanent insulin dependence in patients with non–insulin-dependent ketosis-prone type 2 diabetes who relapse.

this increase in body weight concerned 15 (68.2%) of 22 patients. The prognostic value of an increase in body weight >5% of that at the initial ketotic episode, on the risk of relapse, was tested considering a rise in HbA_{1c} >7%. We observed a trend to higher risk, with an estimated hazard ratio (HR) of 2.3 (95% CI, 0.9–5.9; $P = 0.083$).

To investigate the responsibility of previous hyperglycemia (glucose toxicity) in the development of ketotic relapses, we compared the evolution of HbA_{1c} with the onset of ketotic relapse in the same cohort of patients with non–insulin-dependent ketosis-prone type 2 diabetes. This group developed a rapid degradation of blood glucose in the period preceding a relapse (Fig. 4*D*). The median duration between the development of hyperglycemia (HbA_{1c} >6.3%) and the onset of a ketotic relapse was 12 months (95% CI, 6–21, Kaplan-Meier). During this period, the insulin secretory reserve, measured before the onset of hyperglycemia and during readmission for relapse, dramatically deteriorated (ΔC-peptide, 2.88 ± 0.21 vs. 0.19 ± 0.08 ng/ml; $P < 0.05$). There was no precipitating illness other than hyperglycemia. The increase in HbA_{1c} >6.3% was associated with an increased risk of ketotic relapse with an HR of 38 (95% CI, 5–286; $P = 0.0004$). Thus, hyperglycemia preceded and was strongly associated with the subsequent development of an insulin-deficient, ketotic relapse.

Evolution of blood glucose control. In patients with

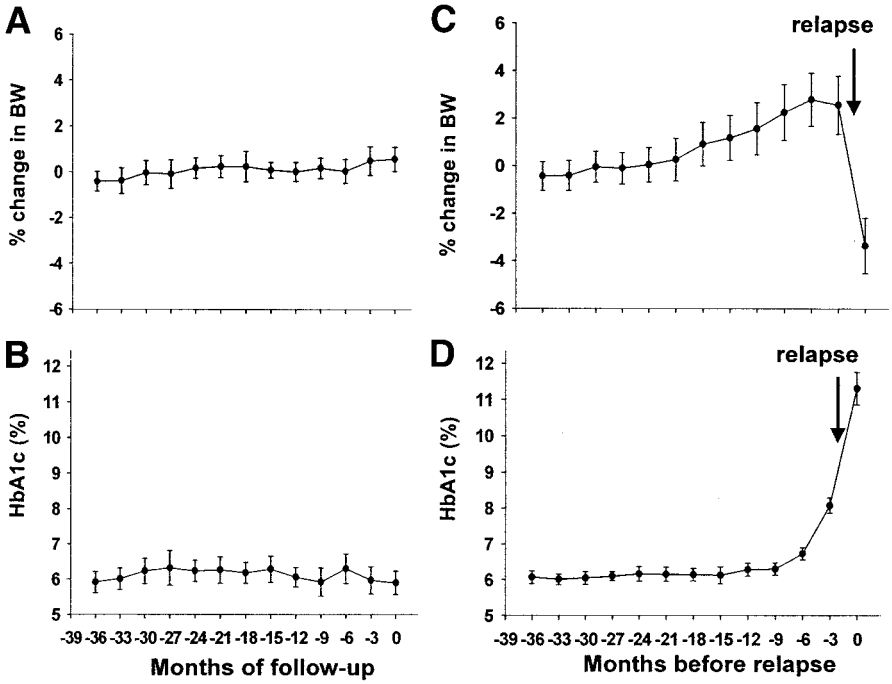

FIG. 4. Effect of obesity and hyperglycemia on relapses in ketosis-prone type 2 diabetes. Patients with non–insulin-dependent ketosis-prone type 2 diabetes were studied during a normoglycemic remission for 36 months. We compared body weight (% increase from the initial ketotic episode) and HbA_{1c} in patients with non–insulin-dependent ketosis-prone type 2 diabetes who remained in remission (*A* and *B*, respectively, $n = 15$) with patients with non–insulin-dependent ketosis-prone type 2 diabetes who developed a ketotic relapse (*C* and *D*, respectively, $n = 22$). The relapse was defined by hyperglycemia, the onset of weight loss, urine glucose >56 mmol/l, and urine ketones >80 mg/dl and is represented by an arrow. Data represent the mean ± SE % increase in body weight (*A* and *C*) and HbA_{1c} (*B* and *D*) during the 33 months preceding the relapse (−3 months).

type 2 diabetes, hyperglycemia was sustained during the 10-year follow-up period, without development of acute insulin deficiency and ketosis. Thus, in type 2 diabetes, the rise in HbA_{1c} >6.3% was not a risk factor for ketotic relapse as in the case of non–insulin-dependent ketosis-prone type 2 diabetes. In the type 1 diabetes and the ketosis-prone type 2 diabetes insulin-dependent groups, blood glucose control was severely altered during this period. On the contrary, patients with non–insulin-dependent ketosis-prone type 2 diabetes maintained good metabolic control (Table 3).

DISCUSSION

In this study, we have characterized a large cohort of urban ketosis-prone type 2 diabetic patients of sub-Saharan African descent from diabetes onset and for a period of 10 years, and we show that this disorder exhibits specific defects in insulin secretion and action. We divided ketosis-prone type 2 diabetes into two groups on the basis of the presence or absence of subsequent insulin dependence. Patients with ketosis-prone type 2 diabetes and permanent insulin dependence represent only 23% of our patients and display a strong and irreversible β-cell failure as in the case of type 1 diabetes. However, these patients maintain higher insulin synthesis/production than patients with type 1 diabetes during the course of their disease. Five years after diabetes onset, patients with insulin-dependent ketosis-prone type 2 diabetes retain 22% of their insulin secretory capacity in contrast to total loss of β-cell function after 1 year in type 1 diabetes. Thus, in these patients, the non–autoimmune-mediated impairment of β-cell function is slower than in type 1 diabetes. Insulin-dependent ketosis-prone type 2 diabetes should not be confused with late autoimmune diabetes because autoantibodies were negative in all patients at admission and during follow-up (data not shown). However, some rare type 1 diabetes with low antibody reactivity may have been classified in this ketosis-prone type 2 diabetes insulin-dependent group. Patients with ketosis-prone type 2 diabetes with phasic insulin dependence and normoglycemic remissions (non–insulin-dependent ketosis-prone type 2 diabetes) represent the majority of our patients (77%) and display a reversible β-cell dysfunction. Indeed, after the initial episode of acute insulin deficiency, these patients restore their insulin secretion for a long period of time, helping them to develop normoglycemic remissions

TABLE 3
Evolution of blood glucose control

	Years after discharge						
	1	2	3	4	5	7	10
Type 2 diabetes	6.8 (0.2)	7.2 (0.2)	7.8 (0.2)	8.4 (0.2)	8.6 (0.3)	8.9 (0.5)	9.0 (0.4)
n	88	88	79	79	67	23	23
Type 1 diabetes	7.8 (0.4)	8.4 (0.6)	9.1 (0.4)	9.6 (0.5)	10.9 (0.9)	10.1 (0.5)	10.5 (0.8)
n	12	12	12	12	12	12	12
Ketosis-prone type 2 diabetes ID	6.9 (0.3)	7.8 (0.2)	8.2 (0.3)	9.7 (0.4)	10.1 (0.6)	10.1 (0.7)	10.6 (0.7)
n	27	27	27	21	17	15	15
Ketosis-prone type 2 diabetes NID	5.6 (0.1)	5.7 (0.1)	6.1 (0.2)	6.4 (0.3)	6.7 (0.3)	7 (0.5)	7.4 (0.5)
n	84	80	75	67	60	39	21

Data are mean HbA_{1c} (SE) for each subgroup. Normal HbA_{1c} is <6%. ID, insulin dependent NID, non-ID.

lasting for up to 10 years. This pattern of acute and reversible insulin deficiency has already been described by other investigators (6,25). We show that the evolution of β-cell dysfunction in non–insulin-dependent ketosis-prone type 2 diabetes is slowly progressive and more similar to that of type 2 diabetes than to that of type 1 diabetes: 10 years after diabetes onset, patients with non–insulin-dependent ketosis-prone type 2 diabetes have lost only 60% of their insulin secretory capacity relative to nonobese control subjects (compared with 61% in type 2 diabetes), and 40% of these patients are still non–insulin dependent (compared with 32.5% in type 2 diabetes). This observation strongly argues against the classification of ketosis-prone type 2 diabetes as a subtype of type 1 diabetes with total destruction of β-cells.

The role of glucose toxicity in the pathogenesis of acute and phasic β-cell failure of patients with ketosis-prone type 2 diabetes has been hypothesized (6,9,20). We show that ketotic relapses are preceded by a 12-month progressive rise in blood glucose, which in turn increases the risk of relapse by 38. In addition, the β-cell function dramatically deteriorates between the onset of hyperglycemia and the readmission for relapse. Thus, patients with non–insulin-dependent ketosis-prone type 2 diabetes cannot sustain chronic hyperglycemia without developing severe β-cell failure. In addition, in non–insulin-dependent ketosis-prone type 2 diabetes, restoration of normoglycemia after insulin therapy is accompanied by a dramatic and prolonged improvement in β-cell insulin secretory reserve that is more complete than that observed in other forms of diabetes. These data demonstrate that, in non–insulin-dependent ketosis-prone type 2 diabetes, hyperglycemia leads to insulin deficiency and ketosis, whereas prompt return to normoglycemia restores insulin secretion. Therefore, patients with ketosis-prone type 2 diabetes display a β-cell propensity to glucose toxicity. On the contrary, our patients with type 2 diabetes are resistant to ketosis despite a decade of hyperglycemia. In addition, it is known that patients with type 2 diabetes in severe decompensation such as hyperglycemic, hyperosmolar, nonketotic state can maintain some level of β-cell function for a long time, allowing enough insulin secretion to prevent ketosis (26,27).

Obesity also seems to predispose to β-cell failure in ketosis-prone type 2 diabetes. First, ketosis-prone type 2 diabetes occurs in overweight individuals in the United States and Asia (5,6,8,13,15), and we show that this is also the case in sub-Saharan African immigrants to Europe. Second, patients with ketosis-prone type 2 diabetes develop progressive increase in body weight both before the onset of the initial DKA revealing diabetes and before the onset of ketotic relapses. The role of obesity in acute β-cell failure is also emphasized by the alarming epidemic of type 2 diabetes in African- and Hispanic-American children in the United States in whom type 2 diabetes represents up to 50% of new-onset diabetes, of which 25–40% present with DKA (15–17,28). This epidemic is not described in European and African children (29,30) but is on the rise in Asian children (31) and suggests that we are facing a new form of nutritionally induced diabetes of minorities and immigrant populations occurring in obese urban individuals.

Insulin resistance is detected in all of our patients with ketosis-prone type 2 diabetes, as in those with type 2 diabetes at admission. In patients with type 2 diabetes, in whom insulin resistance is multifactorial and strict normoglycemia was not achieved, resolution of hyperglycemia improves insulin sensitivity only partially. In non–insulin-dependent ketosis-prone type 2 diabetes, despite the presence of obesity, insulin resistance is entirely reversed by correction of hyperglycemia, whereas in patients with insulin-dependent ketosis-prone type 2 diabetes, in whom normoglycemic remission is not achieved, insulin resistance is not reversible. This suggests that in non–insulin-dependent and insulin-dependent ketosis-prone type 2 diabetes, insulin action is dramatically influenced by glucose toxicity that is still present in insulin-dependent ketosis-prone type 2 diabetes because of poor metabolic control. Similarly, Umpierrez et al. (6) described a complete restoration of insulin action in obese African Americans with ketosis-prone type 2 diabetes after normalization of blood glucose. In addition, Banerji et al. (5) described a different distribution of insulin resistance in nonobese African-American diabetic patients with half of the type 2 diabetes being normally insulin sensitive, whereas all patients with ketosis-prone type 2 diabetes were insulin resistant. Thus, in patients with ketosis-prone type 2 diabetes and of sub-Saharan African descent, insulin resistance does not share the classical features observed in type 2 diabetes, and our study, along with those of others, suggests that glucose toxicity could play a major role in its development.

The underlying molecular abnormalities responsible for ketosis-prone type 2 diabetes and distinguishing insulin-dependent from non–insulin-dependent ketosis-prone type 2 diabetes are unknown. Umpierrez et al. (6) also showed two populations of African-American patients with ketosis-prone type 2 diabetes, with either permanent or phasic insulin dependence, and suggested different pathogeneses according to their immunogenetic status (32). In our cohort, no significant difference with classical HLA haplotypes is observed (9). Reports of a point mutation Gly574Ser in the HNF1-α gene have been proposed to be a marker of ketosis-prone type 2 diabetes in African-American adolescents (33), but we excluded this association in our ketosis-prone type 2 diabetes cohort (34). There is current debate on the respective roles of glucose toxicity or lipotoxicity in the β-cell failure observed in type 2 diabetes (24,27,35,36). In ketosis-prone type 2 diabetes, triglyceride levels are not significantly increased, but free fatty acid levels have not been assessed. However, at the level of hyperglycemia observed in ketosis-prone type 2 diabetes (30 mmol/l), which is not common in diabetes, glucose metabolism in β-cells would stimulate lipogenesis, leading to lipid accumulation and thus to glucolipotoxicity even in the presence of near-normal circulating lipid level (36). Thus, one may hypothesize that in ketosis-prone type 2 diabetes, a genetic propensity to glucotoxicity- or glucolipotoxicity-induced oxidative stress could be the mechanism responsible for both acute β-cell failure and insulin resistance (37). Indeed, preliminary studies from our group indicate that ketosis-prone type 2 diabetes is associated with low glucose-6-phosphate dehydrogenase activity, an intracellular enzyme essential to defense mechanisms against oxidative stress (38).

In summary, evidence presented in this study shows that the ketosis-prone type 2 diabetes syndrome includes one major subgroup with preserved insulin secretion and prolonged remissions and a rarer subtype with permanent insulin dependence. Ketosis-prone type 2 diabetes is different from type 1 diabetes with genetic inheritance 12 times stronger, age of onset 14 years higher, BMI 4% higher, and a more severe insulinopenic onset. During a decade of follow-up, pancreatic β-cells from patients with ketosis-prone type 2 diabetes and type 1 diabetes behave differently, and 10 years after diabetes onset, 40% of patients with non–insulin-dependent ketosis-prone type 2 diabetes are still non–insulin dependent. Patients with ketosis-prone type 2 diabetes display a unique propensity to glucose toxicity and a specific pattern of phasic impairment in insulin secretion and action. Most importantly, unlike in the cases of typical type 2 diabetes and type 1 diabetes, which have been characterized in American and European white individuals and display a similar sex distribution, ketosis-prone type 2 diabetes is observed mostly in nonwhite populations and represents the only human form of diabetes to display a strong male predominance (6,8,13,14).

ACKNOWLEDGMENTS

This work was supported by the Assistance Publique, Hôpitaux de Paris, and a grant from the French Diabetes Association (ALFEDIAM/2000) to F.M.J.

We are grateful to André Warnet, MD, for access to patients' medical records at Lariboisiere Hospital.

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