

# Narrative Review: Ketosis-Prone Type 2 Diabetes Mellitus

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Several investigators have reported that more than half of African-American persons with new diagnoses of diabetic ketoacidosis have clinical, metabolic, and immunologic features of type 2 diabetes during follow-up. These patients are usually obese, have a strong family history of diabetes, have a low prevalence of autoimmune markers, and lack a genetic association with HLA. Their initial presentation is acute, with a few days to weeks of polyuria, polydipsia, and weight loss and lack of a precipitating cause of metabolic decompensation. At presentation, they have markedly impaired insulin secretion and insulin action, but intensified diabetic management results in significant improvement in  $\beta$ -cell function and insulin sensitivity sufficient to allow discontinuation of insulin therapy within a few months of follow-up. On discontinuation of insulin therapy, the period of near-normoglycemic remission may

last for a few months to several years. The absence of autoimmune markers and the presence of measurable insulin secretion have proven useful in predicting near-normoglycemic remission and long-term insulin dependence in adult patients with a history of diabetic ketoacidosis. This clinical presentation is commonly reported in African and African-American persons but is also observed in Hispanic persons and those from other minority ethnic groups. The underlying mechanisms for  $\beta$ -cell dysfunction in ketosis-prone type 2 diabetes are not known; however, preliminary evidence suggests an increased susceptibility to glucose desensitization.

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In 1987, Winter and colleagues (1) reported a small cohort of young African-American patients who, despite presenting with severe hyperglycemia or diabetic ketoacidosis, subsequently had clinical and metabolic features of type 2 diabetes. Obesity was present in 46% of these patients, and their insulin secretion in response to mixed-meal stimulation was intermediate between that seen in nondiabetic controls and in patients with type 1 diabetes. They called this form of diabetes *atypical diabetes*. During the past decade, this clinical presentation of diabetes has been increasingly recognized and is believed to account for 25% to 50% of African-American and Hispanic persons with new diagnoses of diabetic ketoacidosis (2–8). Although most cases are reported in African persons and in African-American individuals in the United States, atypical diabetes has also been reported in Native-American (9), Japanese (10, 11), Chinese (12–14), Hispanic (15, 16), and white (15, 17) populations. 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, idiopathic type 1 diabetes, atypical diabetes, Flatbush diabetes, type 1.5 diabetes, and more recently, ketosis-prone type 2 diabetes (1, 3, 4, 6, 15, 18–20). The aims of this review are to review current information regarding the clinical presentation, metabolic and immunologic features, and pathogenesis of ketosis-prone type 2 diabetes and to share our experience in the management of adult patients with this “atypical” form of the disease. We did a computerized search of biomedical journal literature from MEDLINE, PubMed, and Ovid from 1966 to October 2005. We reviewed English-language original and review articles found under the subject headings *ketosis-prone type 2 diabetes* and *atypical diabetes*.

## HISTORICAL BACKGROUND

During the past 5 decades, case studies from Nigeria, Congo, Tanzania, and other sub-Saharan countries have reported small series of patients with atypical presentation

of diabetes (6, 18, 19, 21–24). In the 1960s, Adadevoh (23) and Dodu (21) reported that some adult patients with diabetic ketoacidosis were able to discontinue insulin therapy after a relative short time and remain in near-normoglycemic remission for several months to years. This unique, transient insulin-requiring profile was recognized mainly in patients with newly diagnosed diabetes and was reported as “temporary diabetes in adult Nigerians.” Subsequent reports from other African groups noted the difficulty in classifying such patients as having type 1 and type 2 diabetes during their initial presentation (22, 24).

In the United States, an “atypical” form of diabetes was first reported in 12 African-American youths (1). Ten of these patients were admitted to the hospital with diabetic ketoacidosis, and 2 were admitted with severe hyperglycemia. The diabetes in these patients was characterized by an acute presentation, an autosomal dominant pattern of inheritance, negative islet-cell antibodies, and an insulin response to mixed meals that was intermediate between that seen in nondiabetic controls and in patients with type 1 diabetes. In contrast to the long-term insulin requirement of type 1 diabetes, these patients discontinued insulin therapy and maintained acceptable glycemic control for many years either by diet or by taking oral agents. In 1994, Banerji and colleagues (4) reported 21 patients with diabetic ketoacidosis who had similar characteristics except for older age at onset and a lower prevalence of obesity. All of these patients were black, were mostly of Caribbean origin, and were labeled as having Flatbush diabetes in recognition

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**Table 1. Clinical Characteristics of Patients with Ketosis-Prone Type 2 Diabetes**

Variable	Study Location (Reference)						
	New York (4, 8)	Atlanta (2, 3)	Taiwan (14)	Dallas (16)	Africa (7)	Paris (6)	Houston (15)
Patients, <i>n</i>	100	112	40	54	21	111	62
Ethnicity, %							
Black	100	100	0	65	100	100	29
White	0	0	0	0	0	0	15
Hispanic	0	0	0	30	0	0	55
Asian	0	0	100	0	0	0	0
Age at presentation, <i>y</i>	45	40	38	35	42	38	39
Men, %	63	66	70	76	70	76	58
Newly diagnosed diabetes mellitus, %	80	79	100	100	86	100	52
Family history of diabetes mellitus, %	78	82	–	–	75	75	88
Body mass index, <i>kg/m</i> <sup>2</sup>	28.8	37.3	22.2	31.6	26	26	30.3
Hemoglobin A <sub>1c</sub> level at presentation, %	–	13.5	12.1	13.5	–	13.4	13.6
Sustained remission (not taking insulin), %	56	71	62	39	48	84	50
Hemoglobin A <sub>1c</sub> level at discontinuation of insulin, %	5.8	6.8	6.3	9.5	6.7	6.3	7.5
Positive anti- $\beta$ -cell autoantibodies, %	2	16	4	0	10	0	18

of the region in New York where most of them resided. The researchers also recognized the presence of measurable pancreatic insulin reserve, absence of autoimmune indicators of  $\beta$ -cell destruction, and increased frequency of HLA-DR3 and HLA-DR4. Subsequently, our group reported on the clinical, metabolic, and immunogenetic features of 2 large cohorts of black patients presenting with unprovoked diabetic ketoacidosis (2, 3, 25). We showed that patients with ketosis-prone type 2 diabetes have a severe but transient defect in insulin secretion and insulin action, which partially resolves after a few weeks of insulin therapy and is followed by near-normoglycemic remission that may last for several months to years.

## PREVALENCE

The prevalence of ketosis-prone type 2 diabetes is not known, but observational studies suggest that this type of diabetes accounts for a substantial number of patients with diabetic ketoacidosis. In the United States, the prevalence has been estimated to be between 20% and 50% in African-American and Hispanic patients with new diagnoses of diabetic ketoacidosis (3, 16, 25–27). In addition to ethnicity, clinical features predictive of future near-normoglycemic remission are obesity and a family history of type 2 diabetes. Among 154 consecutive African-American patients admitted to the hospital with diabetic ketoacidosis, we observed that obesity was present in 29% and that the prevalence of obesity was higher among those with newly diagnosed diabetes (56%) (25). More than 80% of patients have a family history of type 2 diabetes. The mean body mass index at presentation in African-American patients with ketosis-prone type 2 diabetes has ranged between 28  $\text{kg/m}^2$  to 37  $\text{kg/m}^2$  (2, 5, 6, 25). A high rate of obesity is also reported in Hispanic (16, 20) and Chinese (13) persons and in sub-Saharan black African immigrants to Europe (6, 18, 19). Obesity in persons with diabetic ketoaci-

dosis from minority ethnic groups is more common than in white persons, in whom the rate of obesity is less than 20% (28, 29).

Balasubramanian and colleagues (27) reviewed the clinical profiles of 141 adults admitted to the hospital with diabetic ketoacidosis. At presentation, 39% of patients were considered to have type 1 diabetes, 53% were considered to have type 2 diabetes, and 8% were not classified. Twenty-eight percent of patients had newly diagnosed diabetes, 93% of whom were reassessed at least 2 years after their initial episode of diabetic ketoacidosis and were considered to have type 2 diabetes (27). More recently, Piñero-Piloña and Raskin (20) reported that the incidence of this type of diabetes among persons with new-onset diabetes with diabetic ketoacidosis was approximately 60%. In agreement with the U.S. experience, African studies have reported that 42% to 64% of patients with diabetic ketoacidosis initially treated with insulin therapy do not have classic type 1 diabetes and may experience prolonged remission (7, 22, 23, 30). The prevalence of ketosis-prone type 2 diabetes seems to be lower in Asian and white persons and may represent fewer than 10% of cases of diabetic ketoacidosis (13, 15, 31).

## CLINICAL PRESENTATION

Most adults with ketosis-prone type 2 diabetes are obese, middle-aged persons with newly diagnosed diabetes who present with unprovoked diabetic ketoacidosis (Table 1). The initial presentation is usually acute. These patients have a history of polyuria, polydipsia, and weight loss for less than 4 to 6 weeks (2, 6, 17, 25). The mean age at diagnosis is 40 years (SD, 2) (range, 33 to 53 years). More than three fourths of patients with ketosis-prone type 2 diabetes present as having new-onset diabetes. Several series of patients with ketosis-prone type 2 diabetes show a 2- or 3-fold higher prevalence in men (2, 6, 17, 20, 25). This

**Table 2. Features Predictive of Future Near-Normoglycemic Remission in Adults with Diabetic Ketoacidosis**

African-American, Hispanic, and other minority groups
Newly diagnosed diabetes
Obesity
Family history of type 2 diabetes
Negative autoantibodies (islet cells or glutamic acid decarboxylase)
Fasting C-peptide levels >0.33 nmol/L within 1 week after resolution of diabetic ketoacidosis or >0.5 nmol/L during follow-up*
Glucagon-stimulated C-peptide level >0.5 nmol/L at presentation and >0.75 nmol/L during follow-up

\* The fasting and glucagon-stimulated C-peptide tests are measured within 1 week of diabetic ketoacidosis and after 6 to 8 weeks of follow-up. The glucagon-stimulated C-peptide test was administered as follows. After a 10-hour overnight fast, blood samples were drawn at baseline and at 3 or 6 minutes after injection of glucagon (1 mg) to measure levels of glucose and C-peptide (2, 3).

is in contrast to series of white patients with type 1 diabetes, which report that women are more likely than men to develop diabetic ketoacidosis (29, 32). The male predominance in ketosis-prone type 2 diabetes seems to be independent of the degree of obesity and age at presentation. The reason for the sex difference is unknown; however, it has been attributed to hormonal factors, body fat distribution, and changes in insulin sensitivity (20).

Physical examination reveals signs of dehydration, dry mucous membranes, and tachycardia. Substantial hypotension or changes in mental status are seldom seen at admission. Glucose level and acid-base parameters at presentation are similar to those reported in lean patients with diabetic ketoacidosis. In our series (2, 3, 25, 33), the mean level of glucose at admission has ranged between 38 to 40 mmol/L (684 to 720 mg/dL), with a mean serum bicarbonate level of 12 to 14 mmol/L, pH level of 7.22 to 7.25, and hemoglobin A<sub>1c</sub> level between 12% and 14% (2, 3, 25, 33).

## CLINICAL COURSE

Few studies have analyzed the clinical course and predictors of near-normoglycemic remission in adults with diabetic ketoacidosis (Table 2). McFarlane and colleagues (5) described the clinical course of African-American persons from Brooklyn admitted to the hospital with newly diagnosed ketoacidosis who were followed for at least 1 year. Remission was defined as a hemoglobin A<sub>1c</sub> level of 6.3% or less and a fasting plasma glucose level of less than 6.6 mmol/L (<120 mg/dL) 3 months after therapy with all pharmacologic agents was discontinued. Forty-two percent of patients achieved remission after a mean of 83 days and remained in remission during 20 months of follow-up. There were no differences in age, sex, plasma glucose level at presentation, changes in body mass index, magnitude of weight change, or pharmacologic agents used between patients who achieved remission and those who did not. We also observed that near-normoglycemic remission was achieved in 70% of obese African-American patients after 9

weeks of follow-up (2, 6, 33). More recently, Mauvais-Jarvis and colleagues (6) reported that discontinuation of insulin therapy with subsequent remission was achieved in 76% of sub-Saharan African patients with diabetic ketoacidosis after a mean of 14.3 weeks (range, 1 to 150 weeks) of insulin therapy. Ten years after their first presentation, 40% of patients did not require insulin injections (6).

Patients with diabetic ketoacidosis who achieve remission frequently have recurrence of hyperglycemia or ketosis if treated with diet alone after discontinuation of insulin therapy (2, 8, 33). Two studies reported that 60% and 67% of patients with ketosis-prone type 2 diabetes relapsed into hyperglycemia within 2 years if treated with diet alone (2, 33). In such patients, treatment with sulfonylurea or metformin has proven effective in prolonging the duration of normoglycemic remission and in preventing readmission for ketoacidosis (2, 6, 33). Other investigators, however, have observed a limited and unpredictable response to oral hypoglycemic agents and have recommended long-term insulin treatment in patients with ketosis-prone type 2 diabetes (15–17).

Weight loss before the initial admission is common in obese patients with diabetic ketoacidosis, but additional weight loss does not seem to predict the ability of these patients to achieve near-normoglycemic remission. Mean weight loss before admission ranges between 4 and 12 kg (2, 6, 26). In our series, among patients who achieved remission, one third continued to lose weight, one third maintained their weight, and the remainder regained the initial weight lost (2, 3).

## IMMUNOGENETIC STUDIES

Several groups have reported on the prevalence of autoantibodies to islet cells, insulin, glutamic acid decarboxylase, and protein tyrosine phosphatase in patients with ketosis-prone type 2 diabetes (Table 1). The rate of positive autoimmune markers has ranged between 0% and 18%. The prevalence of autoantibodies in obese African-American patients with diabetic ketoacidosis (17%) is similar to that in obese patients with nonketotic hyperglycemia (16%) but is substantially lower than in lean patients with type 1 diabetes who have diabetic ketoacidosis (66%) (2, 6, 33). The rate of positive autoantibodies seems to be similar to that reported in patients with type 2 diabetes (34–37). This subset of patients with positive autoantibodies is recognized as having latent autoimmune adult diabetes (34, 38–40) or slowly progressing type 1 diabetes (36, 41). During follow-up, most patients with latent autoimmune diabetes have features of insulin dependence, including a propensity toward developing ketosis and complete  $\beta$ -cell failure (38, 42). Of interest, patients with ketosis-prone type 2 diabetes and positive autoantibodies have considerably reduced basal and stimulated insulin secretion compared with those with negative autoantibodies (43, 44) and

are more likely to relapse into hyperglycemia and to become insulin dependent (6).

## GENETIC STUDIES

Analyses of relative frequencies of HLA alleles in ketosis-prone type 2 diabetes have produced conflicting results. Most investigators have failed to find an association with HLA susceptibility alleles (1–3, 6, 7). In contrast, others have found an increased frequency of HLA-DR3 and HLA-DR4 compared with nondiabetic populations (4, 7, 15). Maldonado and colleagues (15) reported on the association of HLA class II genotype and the presence of positive autoantibodies in a cohort of patients with diabetic ketoacidosis. They found that patients with positive autoantibodies have a higher frequency of DQA\*03 and DQB1\*02, 2 alleles strongly associated with susceptibility to autoimmune type 1 diabetes; however, the frequency of these HLA alleles was low in patients with negative autoantibodies. Because most patients have negative autoimmune markers, HLA association may not be a prominent feature of ketosis-prone type 2 diabetes.

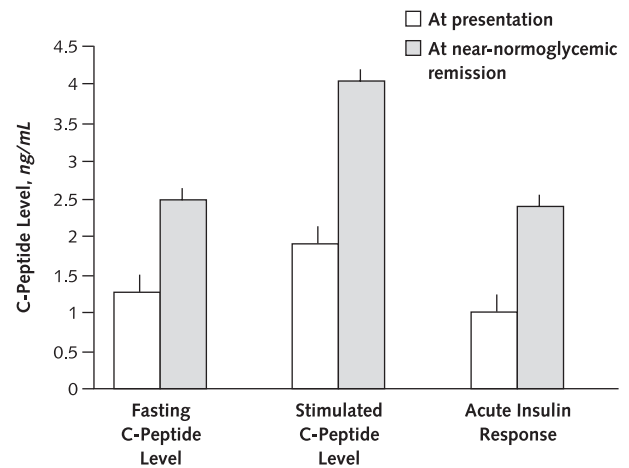
Although genetic susceptibility to ketosis-prone type 2 diabetes is likely, it is not known whether the model is polygenic or has a major gene influence. A point mutation Gly574Ser in the HNF1- $\alpha$  gene was proposed as a marker of ketosis-prone type 2 diabetes in African-American children and adolescents (45), but a recent report in adults excluded this association (46). Recently, a missense mutation (Arg121Trp) of PAX4 has been implicated in early and insulin-deficient type 2 diabetes in Japanese patients (47). PAX4 is a transcription factor that is essential in the differentiation of embryonic pancreatic progenitors into insulin-producing  $\beta$  cells in the mammalian pancreas (48). Japanese persons who carry the Arg121Trp variant are characterized as having either transient insulin dependence at diabetes onset or a rapid evolution toward insulin deficiency, suggesting that mutations of PAX4 lead to severe  $\beta$ -cell dysfunction in humans. Recently, an R133W mutation in PAX4 was identified (homozygous in 4% and heterozygous in 27%) in a West African population with ketosis-prone type 2 diabetes (49). Because R133W heterozygosity has also been found in 15% of West African persons with type 2 diabetes, in 22% of West African nondiabetic controls, and in 14% of African-American controls, but was not in white persons (0%), this abnormality in the PAX4 gene may be more population-specific than causal.

## METABOLIC STUDIES

### Function of the $\beta$ Cell

The insulin response to oral and intravenous glucose load, test meals, and nonglucose secretagogues has been reported after resolution of ketoacidosis (2, 3, 6, 7), at normoglycemic remission (2–5, 12, 15, 50), and during follow-up (1, 4, 7, 8, 51) in patients with ketosis-prone

**Figure.** Levels of plasma C-peptide before and after glucagon stimulation (1 mg intravenously) in patients with ketosis-prone type 2 diabetes.



Insulin secretion was assessed 1 day after resolution of diabetic ketoacidosis (at presentation) and after 10 weeks of follow-up (2, 3). Data are expressed as means and SDs. Acute insulin response to glucagon is the incremental change in C-peptide level over the baseline level. To convert values to nmol/L, multiply by 0.333.

type 2 diabetes. We measured  $\beta$ -cell function shortly after resolution of ketoacidosis or hyperglycemia and at normoglycemic remission in a large group of obese African-American patients with diabetic ketoacidosis with similar hyperglycemia levels but without ketosis. Their mean glucose level at admission was greater than 33 mmol/L (>600 mg/dL) (2, 6, 33). Intravenous glucose infusion 1 day after resolution of ketoacidosis did not evoke any insulin response; however, improvement of metabolic control resulted in insulin levels that were 3-fold higher than those obtained during the initial test. Pancreatic insulin reserve determined by changes in C-peptide levels after glucagon stimulation, both 1 day after resolution of diabetic ketoacidosis and after 12 weeks of follow-up, is shown in the **Figure**. After resolution of hyperglycemia, basal and stimulated C-peptide levels in obese patients with diabetic ketoacidosis were statistically significantly greater than those in lean patients with diabetic ketoacidosis but were lower than those in obese patients with type 2 diabetes and similar levels of hyperglycemia levels but without ketosis. During follow-up, obese patients with diabetic ketoacidosis had substantial improvement in basal and stimulated C-peptide levels, but the acute insulin response remained lower than in obese nondiabetic controls. Recent studies have reported similar insulin responses in patients with ketosis-prone type 2 diabetes (6, 51, 52) and estimated that patients who achieved normoglycemic remission had an 80% improvement in fasting and stimulated C-peptide levels, whereas those who did not achieve remission lost 60% of their insulin-secreting capacity (6). These findings indi-

cate that the impaired  $\beta$ -cell function in patients with ketosis-prone type 2 diabetes cannot be attributed to irreversible  $\beta$ -cell damage but can be attributed to transient functional abnormalities of the  $\beta$  cells. Although the underlying mechanisms are not known, investigators have hypothesized an increased susceptibility to  $\beta$ -cell desensitization due to elevations of plasma glucose (glucose toxicity) (2, 6, 10) or sustained elevation of free fatty acid levels (lipotoxicity) (16, 19).

To investigate the pathogenesis of acute  $\beta$ -cell failure, we have studied susceptibility to glucose toxicity and lipotoxicity in obese African-American patients with ketosis-prone type 2 diabetes (53). The function of the  $\beta$  cells was assessed by changes in levels of insulin and C-peptide during a 20-hour glucose infusion (200 mg/m<sup>2</sup> per min), and a 48-hour infusion of Intralipid (Pfizer Inc, New York, New York, 20% solution at 40 mL/h) plus heparin infusion (250 U/h) to increase levels of free fatty acid in obese patients. Dextrose infusion rapidly increased levels of C-peptide by 4- to 5-fold during the first 10 hours; thereafter, insulin secretion progressively decreased. After 20 hours of glucose infusion, levels of insulin and C-peptide were lower than preinfusion baseline levels. However, increasing free fatty acid levels by 3-fold during the 48-hour Intralipid and heparin infusion was not associated with a deleterious effect on insulin secretion (53). Chronic hyperglycemia has been associated with impaired insulin secretion in animal models in which  $\beta$ -cell mass has been surgically reduced (54) or glucose levels were increased by continuous infusion (55). Studies done on humans have also shown that  $\beta$ -cell function improves after hyperglycemia is relieved by successful diabetes therapy (32, 55, 56). Although the pathogenesis of glucose toxicity is not completely understood, it seems that chronic hyperglycemia induces a generalized downregulation of the glucose-processing system that leads to impaired  $\beta$ -cell function and insulinopenia (56–59). Recent evidence indicates that the impaired  $\beta$ -cell response involves a reduction in the insulin and *PDX-1* gene expression (60–62). Pancreatic duodenal homeobox factor-1 (*PDX-1*) is a key transcriptional factor that regulates gene transcription in response to glucose (63).

### Insulin Action

Assessment of insulin sensitivity by using the euglycemic hyperinsulinemic clamp (4) and the minimal model approach (2, 6, 51) have indicated that shortly after admission to the hospital, glucose disposal is markedly depressed in patients with ketosis-prone type 2 diabetes compared with weight-matched controls. During follow-up, improvement of metabolic control resulted in a 200% improvement in insulin action and insulin sensitivity increased to levels not significantly different from those in obese healthy patients. More recently, studies in Chinese persons (12) and sub-Saharan black African persons (6) confirmed the severe but transient impairment of insulin action.

Chronic hyperglycemia has been shown to impair insulin action and glucose uptake in peripheral tissues (56, 57, 64). The mechanism by which chronic hyperglycemia causes impaired insulin sensitivity is not completely understood but probably relates to an alteration in insulin signaling at the postreceptor level (58, 65, 66). Using muscle biopsy specimens obtained within 2 days of resolution of ketoacidosis and during near-normoglycemic remission from patients with ketosis-prone type 2 diabetes, we studied the pattern of Akt-1 and Akt-2 expression and insulin-stimulated phosphorylation (67). We observed that hyperglycemia selectively decreases Akt-2 expression and insulin-stimulated phosphorylation on the serine residue without affecting threonine phosphorylation. Improved metabolic control resulted in 70% greater Akt expression in muscle during near-normoglycemic remission than during the hyperglycemic period. Insulin signaling upstream of Akt-2 did not seem to be involved as insulin-receptor phosphorylation, and expression of insulin receptor, insulin-receptor substrates 1 and 2, and phosphatidylinositol-3-kinase were unchanged. Altered expression of Akt-2 at presentation was accompanied by reduced expression of many other signal transduction proteins, increased expression of enzymes counterregulatory to insulin action, and a pro-apoptotic pattern of protein expression. These results provide evidence that diminished Akt-2 activation is a critical mechanism for hyperglycemia-induced insulin resistance in skeletal muscle.

### MANAGEMENT

Successful therapy for diabetic ketoacidosis requires aggressive fluid and electrolyte replacement and administration of insulin, followed by careful scrutiny for precipitating factors for metabolic decompensation (68). Our protocol for inpatient management of obese patients with diabetic ketoacidosis is shown in **Table 3**. The use of this protocol resulted in resolution of hyperglycemia by a mean of 6 hours and resolution of ketoacidosis by 12 to 14 hours (25). After resolution of diabetic ketoacidosis, subcutaneous multidose insulin treatment is started at a dose of 0.8 U/kg of body weight. The insulin dose is adjusted to achieve fasting and premeal blood glucose levels less than 6.6 mmol/L (<120 mg/dL). Because of the initial  $\beta$ -cell dysfunction and insulin resistance, insulin requirements are higher during the first 2 to 4 weeks, with a mean insulin dose of 1 to 1.2 U/kg. Thereafter, insulin requirements progressively decrease. We recommend tapering insulin doses once levels of fasting blood glucose remain less than 6.6 mmol/L (<120 mg/dL) for 2 weeks or if hypoglycemia occurs. When this protocol is followed, approximately 70% of obese patients with new diagnoses of diabetic ketoacidosis are able to discontinue insulin therapy after a mean follow-up of 9 weeks (2, 25).

After discontinuation of insulin therapy, if patients are treated with diet alone, hyperglycemia frequently occurs

within 2 years of follow-up (2, 8, 33). Low-dose sulfonylurea and metformin treatment prolong the duration of remission for 24 to 40 months (2, 6, 33). Some investigators, however, have raised concerns about the use of sulfonylurea in patients with ketosis-prone type 2 diabetes, especially in those with positive autoantibodies (6). A 10-year prospective study compared the effect of small doses of subcutaneous insulin versus low-dose sulfonylurea treatment in the progression of  $\beta$ -cell dysfunction in Japanese patients with ketosis-prone type 2 diabetes who had islet cell antibodies. Seroconversion of autoantibody status from positive to negative occurred in 80% of patients shortly after initiation of insulin therapy, but islet-cell autoantibodies remained positive in all patients treated with sulfonylurea. In addition, the response of C-peptide to glucagon improved statistically significantly after 6 and 12 months in the insulin-treated group but decreased progressively in the sulfonylurea-treated group (44).

Assessment of insulin secretion has been helpful in predicting near-normoglycemic remission in obese patients with a history of diabetic ketoacidosis (6, 17). Most investigators recommend intravenous glucagon stimulation to assess pancreatic insulin reserve (6, 7, 12, 15, 17). For this test, C-peptide levels are measured before and at 3 or 6 minutes after the administration of glucagon (1 mg) (2, 3, 33). Basal and stimulated C-peptide levels greater than 0.33 nmol/L and greater than 0.5 nmol/L shortly after presentation, and greater than 0.5 nmol/L and greater than 0.75 nmol/L during follow-up, predict remission in patients with a history of diabetic ketoacidosis (2, 3, 5–7, 15, 33, 69).

Clinical and genetic studies indicate that ketosis-prone type 2 diabetes is not a subtype of maturity-onset diabetes of the young or tropical fibrocalculous diabetes. Maturity-onset diabetes of the young is an autosomal dominant form of diabetes, which usually develops during childhood, adolescence, or young adulthood (70, 71). It most commonly occurs in white and South Asian persons (71, 72) and is rare in African-American persons (1, 72). The predominant physiologic feature is a defect in insulin secretion (71, 73) caused by mutations in the glucokinase gene or mutations of transcription factors that regulate expression of the insulin gene and insulin production (54, 74). Most patients with maturity-onset diabetes of the young do not require insulin and can be treated with oral hypoglycemic agents, such as sulfonylureas (70). Tropical fibrocalculous diabetes is a type of diabetes reported in the tropical areas of Asia, Africa, and South America (75, 76). The clinical syndrome consists of a triad of chronic painful pancreatitis, malabsorption, and steatorrhea due to pancreatic exocrine insufficiency, along with diabetes mellitus. Patients' histories frequently include chronic caloric and protein malnutrition. Pancreatic calculi can be detected in more than 90% of patients. Tropical diabetes is usually severe and often must be controlled with insulin; however, patients rarely become ketotic after insulin is withdrawn.

**Table 3. Management of Obese Patients with Ketosis-Prone Diabetes Mellitus\***

**Initial insulin orders**

An initial intravenous bolus at 0.1 U/kg of body weight, followed by continuous insulin infusion at 0.1 U/kg per h.  
When blood glucose levels are <13.8 mmol/L (<250 mg/dL), change intravenous fluids to 5% dextrose and 0.45% saline and reduce the insulin infusion rate to 0.05 U/kg per h to keep glucose levels at approximately 11.1 mmol/L (approximately 200 mg/dL) until resolution of ketoacidosis.

**After the resolution of diabetic ketoacidosis**

Start multidose insulin at a dose of 0.8 U/kg of body weight. Adjust insulin dose to achieve target fasting and premeal glucose levels <6.6 mmol/L (<120 mg/dL).  
Monitor patients every 2 weeks for the first 2 months to adjust insulin therapy, then every 2 or 3 months depending on glycemic control. The mean insulin requirement to achieve the target blood glucose level is usually 1 to 1.2 U/kg of body weight.  
Start tapering insulin once fasting blood glucose levels are <6.6 mmol/L (<120 mg/dL) for 2 weeks or if the patient experiences hypoglycemia. Decrease total insulin dose by 25% at each visit.  
Measure GAD antibodies and  $\beta$ -cell function (fasting C-peptide or glucagon-stimulated C-peptide test).

**After discontinuation of insulin therapy**

For patients with negative GAD and with fasting or stimulated C-peptide levels >0.5 nmol/L and >0.75 nmol/L, respectively, start therapy with low-dose sulfonylurea (glyburide, 1.25–2.5 mg/d) or metformin (500 mg twice per day).  
Patients with positive GAD or with inadequate insulin secretion are more likely to relapse. Insulin therapy may be continued, and patients should be carefully monitored for recurrence of hyperglycemia or ketosis.

\* GAD = glutamic acid decarboxylase.

**SUMMARY**

Recent evidence indicates that what was once described as “atypical diabetes” is a common clinical presentation, affecting 20% to 50% of African-American and Hispanic patients with new diagnoses of diabetic ketoacidosis. Most patients with ketosis-prone type 2 diabetes are obese, middle-aged men with a strong family history of type 2 diabetes. Severe impairment of both insulin secretion and insulin action are found at presentation, and aggressive diabetic management results in marked improvement in  $\beta$ -cell function and insulin sensitivity sufficient to allow discontinuation of insulin therapy within a few months of treatment. The remission phase is usually less than 2 years when patients are treated with diet alone; however, low-dose sulfonylurea and metformin therapy may delay the recurrence of hyperglycemia. The pathophysiologic mechanisms involved in its cause are unknown, but preliminary evidence suggests that patients with ketosis-prone type 2 diabetes have a unique propensity to glucose desensitization. Determination of autoimmune markers (islet-cell and glutamic acid decarboxylase antibodies) is useful in excluding patients with slow-onset type 1 diabetes or latent autoimmune diabetes. The presence of positive autoantibodies and measurement of basal or glucagon-stimulated C-peptide levels may be useful in predicting near-normoglycemic remission and long-term insulin de-

pendence in obese patients with a history of diabetic ketoacidosis.

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