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DIABETIC KETOACIDOSIS: A COMMON DEBUT OF DIABETES AMONG AFRICAN AMERICANS WITH TYPE 2 DIABETES

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Abstract

Objective—More than half of African Americans (AA) with a new diagnosis of diabetic ketoacidosis have clinical and metabolic features of type 2 diabetes during follow-up. This particular presentation of diabetes has been termed as ketosis-prone type 2 diabetes (KPDM) or atypical diabetes.

Methods—We review the epidemiology, diagnosis, pathophysiology, and acute and long-term management of AA with KPDM and compare these similarities to patients with type 2 diabetes.

Results—In contrast to the long-term insulin requirement of auto-immune type 1 diabetes, patients with KPDM are able to discontinue insulin after a few months of therapy and maintain acceptable glycemic control for many years on either diet or oral agents. Patients with KPDM have significant impairment of both insulin secretion and insulin action at presentation; however, at the time of near-normoglycemia remission, insulin secretion and action improve to levels similar to hyperglycemic patients with ketosis-resistant type 2 diabetes. In the long term, however, patients with KPDM have a decline in β -cell function similar to patients with type 2 diabetes. Recent studies indicate that treatment with metformin and dipeptidyl peptidase-4 inhibitors can prolong the period of near-normoglycemia remission for several years compared to placebo therapy.

Conclusion—KPDM is a unique but common presentation of newly diagnosed African Americans with type 2 diabetes.

Keywords

Ketosis-prone diabetes; diabetic ketoacidosis; African Americans

INTRODUCTION

According to the Centers for Disease Control, the incidence of diabetic ketoacidosis (DKA) is increasing in the United States. Since 1980, the number of hospital discharges for DKA increased from 80,000 in 1988 to ~140,000 in 2009 (1). The majority (66%) of primary

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DISCLOSURE

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DKA episodes occur in patients diagnosed with type 1 diabetes, and the rest (34%) are in patients with type 2 diabetes. DKA, which was previously thought to be a key clinical feature of type 1 diabetes, has been shown to occur in children and adult patients with newly diagnosed type 2 diabetes (2–4). Patients with type 2 diabetes and poor metabolic control can also develop DKA under stressful conditions such as trauma, surgery, or infection (2,4). In addition, DKA can be the clinical presentation of many newly diagnosed children, adolescents, and adult patients with type 2 diabetes without a precipitating cause (5–10). Their clinical presentation is acute with severe hyperglycemia and ketosis similar to classic type 1 diabetes, but after a few months of insulin therapy, patients are able to stop insulin therapy and remain in near-normoglycemia remission with diet and/or oral antidiabetic agents (8–12).

During the past 2 decades, many investigators considered such patients as having a unique subtype of diabetes referred to in the literature as idiopathic type 1 diabetes, atypical diabetes, Flatbush diabetes, diabetes type 1.5 (somewhere between types 1 and 2), and more recently as ketosis-prone type 2 diabetes mellitus (KPDM). Despite their acute presentation, several cross-sectional and longitudinal studies by our group and others have indicated that DKA is a unique but common clinical presentation in newly diagnosed patients with type 2 diabetes rather than a unique subtype of “atypical” diabetes.

While there is considerable heterogeneity in patients who present with DKA, in this review, we will discuss the clinical, immunogenic, and metabolic features and management of patients with newly diagnosed diabetes presenting with KPDM and highlight similarities to patients with ketosis-resistant type 2 diabetes.

HISTORIC BACKGROUND OF KETOSIS-PRONE DIABETES

Since the 1960s, several reports from Africa of “temporary diabetes” (13,) described patients presenting with DKA who not follow the typical course of patients with type 1 diabetes. These patients were able to discontinue insulin after a short course of insulin therapy and be managed with oral antidiabetic agents. Subsequently, Winter et al (6) published a report on 12 obese African American (AA) youth who presented with DKA, but followed an atypical course similar to patients with non-insulin dependent diabetes. These patients despite presenting with DKA, had low prevalence of islet-cell auto-antibodies. After initial treatment with insulin, they were able to discontinue and stay off insulin without DKA recurrence. After discontinuation of insulin, these patients had a C-peptide response to a mixed-meal that was similar to patients without diabetes (6). In the 1990s, studies by our group and Banerji et al. further characterized Black patients of Caribbean and African origin who presented with DKA and low pancreatic auto-antibodies, a majority of whom were able to discontinue insulin after intensive insulin therapy (12,15,16). Our group and others showed that obese AA patients, unlike patients with type 1 diabetes, were able to achieve and maintain adequate glycemic control without insulin therapy (near-normoglycemia remission) due to recovery of pancreatic β -cell function and improvement in insulin sensitivity (11,12). This presentation and clinical course of diabetes has been called diabetes type 1b, atypical diabetes or type 1.5 diabetes, or KPDM to distinguish it from the typical

presentation of type 2 diabetes and from the insulin-dependent form of diabetes or type 1 diabetes (17,18) (Table 1).

CLINICAL PRESENTATION

DKA can present in both patients with newly diagnosed diabetes, as well as patients with pre-existing diabetes. Most patients with KPDM are overweight or obese with newly diagnosed diabetes and usually present with an acute and short history of hyperglycemic symptoms (12). Even though there are no studies describing the duration and severity of the period of antecedent hyperglycemia prior to DKA, most patients report a short duration (<4 weeks) of polyuria, polydipsia, and weight loss. Patients usually present with markedly elevated glucose of >500 mg/dL, a mean glycated hemoglobin A1c (HbA1c) >10% and a blood pH <7.30 accompanied by ketoacidosis, such as that seen with presentation of DKA in type 1 diabetes (10,12,19,20). Unlike patients with type 1 diabetes, most patients with KPDM have physical signs consistent with type 2 diabetes such as acanthosis nigricans, obesity, and abdominal adiposity (12). Further, almost 80% of patients with KPDM have a strong family history of type 2, and there is a higher prevalence in males compared to females (17,21). KPDM has been well described in Blacks (11,12,15,22) but has also been shown to affect other populations at high risk for type 2 diabetes such as Chinese, Japanese, Hispanic, and South Asian populations (7,22–24).

Clinical Course

The time to resolution of DKA and response to insulin infusion is similar to that reported in patients with type 1 diabetes. After acute treatment, patients with KPDM are insulin resistant, frequently requiring an initial subcutaneous starting insulin dose of 0.8 to 1.2 units/kg/day (12). Unlike the insulin dependence seen in type 1 diabetes after a few weeks (usually 2 to 12 weeks), insulin requirements decrease, and approximately 70% of patients who present with obese DKA achieve near-normoglycemia remission (21) and are able to remain off insulin therapy (Table 2). The definition of near-normoglycemia remission varies, but near-normoglycemia remission is defined by our group as glycated hemoglobin A1c (HbA1c) < 7% and the ability to maintain fasting blood glucose <130 mg/dL off subcutaneous insulin therapy for at least 1 week (12). McFarlane et al (11) defined near-normoglycemia remission as being off all antihyperglycemic therapy for at least 3 months with an HbA1c <6.3% and fasting plasma glucose <124 mg/dL. After presentation of KPDM, with their definition of remission, 42% of patients were able to achieve near-normoglycemia remission and were able to sustain near-normoglycemia remission for at least 20 months. Similar to the results by our group, Mauvais-Jarvis et al (8) described a cohort of 111 obese African patients of sub-Saharan origin who presented with DKA; of them, >70% of patients were able to achieve near-normoglycemia remission from insulin lasting for several years.

Several factors affect the long-term clinical course of patients who present with KPDM, such as the presence of auto-immune and human leukocyte antigen (HLA) antibodies and lack/ presence of a precipitating cause of DKA. Balasubramanyam et al (25) and Maldonado et al (7) proposed a classification system for patients who present with new-onset DKA based on

presence of pancreatic auto-antibodies (A+/-) and β -cell reserve (β +/-). β -cell reserve was defined as fasting C-peptide >1 ng/mL or stimulated C-peptide level 1.5 ng/mL at 1 year after the initial DKA episode. This classification system showed that patients who presented with DKA with A- β + status follow a clinical course to that of patients described by our group (12,26) and Banerji et al (27,28). Unlike A+ β - patients with type 1 diabetes, patients who are A- β + show β -cell recovery with intensive insulin treatment and are able to maintain near-normoglycemia remission from insulin for many years. Further studies by the group also examined the role of masked or overt antibodies to the DPD epitope of the 65-kDa glutamate decarboxylase (GAD-65). In patients who presented with masked auto-antibodies to DPD epitope of GAD-65, there was increased β -cell reserve even in the presence of pancreatic auto-antibodies and lack of these masked antibodies to the DPD epitope were associated with type 1 diabetes susceptibility HLA alleles (29).

The clinical course also differs for patients with a lack/presence of a precipitating cause for the DKA. Nalini et al (30) characterized the differences in long-term outcomes in a subset of patients who are A-/ β + and presenting with new-onset provoked compared to unprovoked DKA. The patients with precipitating cause for the DKA were mostly Hispanic, presented with a lower glucose and HbA1c level at presentation along with lower measures of pancreatic β -cell function over the long-term compared to patients with unprovoked new-onset diabetes. Patients who did not have a precipitating cause of DKA were mostly AA, male, and had higher HbA1c at presentation. However, over the long term, patients with unprovoked DKA had higher β -cell function and were characterized by recovery of insulin secretion after a few weeks of insulin treatment (30). Further studies by the group showed that in A- β + patients who present with unprovoked DKA, there is an increased frequency of the protective HLA class II DQB1*0602 allele (30) and a lack of islet-specific T-cell response (31).

The long-term clinical course of patients who present with new-onset unprovoked DKA with negative pancreatic auto-antibodies is similar to that of patients with type 2 diabetes. Despite the ability to achieve remission from insulin and antidiabetic agents, many patients with KPDM exhibit insulin resistance of the muscle, adipose tissue, and liver, similar to patients with type 2 diabetes (32). Mauvais-Jarvis et al (8) followed a cohort of 111 obese African patients of Sub-Saharan origin who presented with unprovoked DKA for 10 years; of them, >70% of patients were able to achieve near-normoglycemia remission from insulin lasting for several years. In a subset of these patients, they also measured longitudinal measures of β -cell function using glucagon-stimulated C-peptide levels and compared them to patients with type 2 diabetes that presented without DKA and patients with type 1 diabetes. In the patients who attained β -cell recovery, long-term decline in β -cell function was similar to patients with type 2 diabetes. Even though 40% of patients remained in remission for up to 10 years, most needed oral antidiabetic agents, and almost 50% needed to be on insulin due to declining endogenous insulin secretion. Despite a few patients having ketotic relapses, the clinical course of patients who achieve remission is similar to that seen in patients with a more typical presentation of type 2 diabetes, where declining β -cell function frequently necessitated therapy escalation (33).

Our group and others have also studied obese AA patients who presented with hyperglycemia without ketosis with similar glucose levels as obese patients who present with DKA. These patients who are ketosis resistant have a similar clinical course as patients who present with DKA. At presentation, these patients who present with severe hyperglycemia also require similar amounts of insulin as patients who present with DKA (21). With intensive insulin treatment, ketosis-resistant patients also achieve near-normoglycemia remission from insulin (11,12,27). Our group along with McFarlane et al showed that similar remission from insulin occurs in obese AA patients who present with severe hyperglycemia (glucose levels >400 mg/dL) without the presence of ketoacidosis (11,12,21,26).

KPDM PATHOPHYSIOLOGY

Pancreatic β -cell function in KPDM

The unique aspect of KPDM is the initial episode of ketoacidosis despite the physical features of type 2 diabetes. While several studies show the initial decompensation of β -cell function and subsequent recovery, the etiology of the initial β -cell decompensation and subsequent recovery is not known and the reason for propensity for ketosis is poorly understood. The study by Patel et al. (30) used the novel approach of dynamic testing with tracers and metabolomics to show that patients with KPDM have reduced β -hydroxybutyrate oxidation along with increased branched chain amino acid catabolism leading toward ketogenesis. While the development of DKA is unique, the long-term β -cell decline seen in ketosis-prone diabetes is similar to patients with ketosis-resistant type 2 diabetes.

Since ketotic relapses are preceded by a period of hyperglycemia (8), our group determined if exposure to sustained elevated glucose and free fatty acid (FFA) levels induce β cell decompensation by causing gluco- and lipotoxicity (31). Obese patients who presented with DKA and severe hyperglycemia received 10% dextrose infusion at 200 mg/m²/min for 20-hours during near-normoglycemia remission. β -cell function was assessed by arginine stimulation before and after glucose load. We reported a remarkable improvement in β -cell function in both ketosis prone and ketosis resistant, with comparable response to sequential arginine stimulation comparable to the response observed in obese nondiabetic controls (31). We also investigated if patients with KPDM were susceptible to acute lipotoxicity by infusing high levels of FFAs (32) in patients who already achieved near-normoglycemia remission. Despite increasing FFAs levels fourfold from baseline during a 48-hour intralipid infusion, we found that increased FFAs were not associated with impaired insulin secretion or β -cell lipotoxicity. The results of these studies found that at near-normoglycemia remission, even with exposure to large amounts of glucose and FFAs, the β -cells responded appropriately to arginine stimulation as ketosis-resistant patients with type 2 diabetes and obese nondiabetic controls.

Auto-immune Etiology

Given the presentation of DKA, several studies have examined the role of HLA subtypes in KPDM. An extensive discussion on the role of HLA markers and pancreatic auto-antibodies in the clinical course of KPDM was discussed previously. Some but not all studies showed

that patients with KPDM lack the auto-immune antibodies against GAD-65, islet cells, and insulin (6,15). However, in the study by Banerji et al, there was an increased prevalence of HLADR3 and DR4 alleles in Black patients who presented with DKA, which are known to confer risk of type 1 diabetes (15). Our study in patients presenting with KPDM and severe hyperglycemia showed that patients with KPDM have similar pancreatic auto-antibody and HLA type 1 risk allele prevalence to patients who presented with type 2 diabetes and hyperglycemia (16).

Viral Etiology

Due the association between type 1 diabetes and DKA and studies with viral infections causing acute insulin resistance (33–36), a reversible viral etiology by the herpes virus was investigated as the etiology of KPDM. A cross-sectional study found increased prevalence of antibodies to human herpes virus 8 (HHV8) in KPDM compared to type 2 diabetes that did not present DKA (37). However, a follow-up study showed that HHV8 status does not correlate with insulin sensitivity, nonesterified fatty acid release, or endogenous glucose production during a euglycemic-hyperinsulinemic clamp study (38).

Genetic Etiology

A study of Maldonado et al proposed that DKA patients with A- β + included a heterogeneous type of diabetes with glucose toxicity playing a role in β -cell dysfunction (7). Further, they also showed that KPDM is not a monogenic form of diabetes (44), and genetic studies showed that KPDM does not have a unique genetic etiology. While no specific genetic mutations were found, several studies investigated the role of candidate genes in KPDM. A missense mutation Gly574Ser in the maturity-onset diabetes of the young candidate gene *HNF-1 α* was found to be significantly associated with KPDM in children (45). However, the same mutation occurred at a similar frequency in adult patients with KPDM, type 1 diabetes, and type 2 diabetes (46). The same group showed that patients with KPDM have an increased prevalence of a mutation in *PAX-4* (47) and *NGN3* (48), both genes involved in β -cell development. Given the high prevalence of KPDM in males, they also examined the role of an X-linked disorder in glucose-6-phosphate dehydrogenase (G6PD) deficiency in KPDM pathogenesis. Even though they found an increased G6PD deficiency in patients who presented with KPDM, they did not find an increased prevalence of gene mutations (49) and were not able to find any association between hyperglycemia and G6PD activity (50).

MAINTAINING NEAR-NORMOGLYCEMIA REMISSION

The period of near-normoglycemia remission is variable after the initial treatment of KPDM. The period of near-normoglycemia has varied from 6 to 120 months (8). Despite the initial remission from insulin, many patients continue to have insulin resistance and develop hyperglycemia. Similar to patients with type 2 diabetes, glycemic control can be maintained with oral agents. We and others have shown that treatment with sulfonylureas can prolong the period of near-normoglycemia remission (25,41). More recently, we also showed that treatment with metformin or sitagliptin is equally efficacious in prolonging near-normoglycemia remission (21). We studied 48 AA patients who presented with severe

hyperglycemia and DKA and randomized the patients who achieved remission from insulin to metformin, sitagliptin, or placebo. Serial oral glucose tolerance tests were performed to assess measures of insulin sensitivity and β -cell function. We found that patients who received metformin or sitagliptin sustained near-normoglycemia remission significantly longer than patients randomized to placebo (Fig. 1) (21). The prolongation of near-normoglycemia remission was due to higher β -cell function in patients who sustained near-normoglycemia remission compared to those who had hyperglycemic relapse.

This maintenance of remission in KPDM is similar to that reported in patients with type 2 diabetes where early intensive insulin therapy yields improvement in β -cell function (27). In a study of 382 patients in China, short-term treatment with insulin in patients with type 2 diabetes restored β -cell function compared to oral hypoglycemia agents with patients achieving remission from treatment in approximately 5 to 6 days (26). After 1 year of follow-up, the patients that continued to remain in remission had higher insulin secretion compared to patients who did not achieve or maintain remission. A pilot study investigated the effect of sitagliptin in prolonging remission off antidiabetic therapy after short-term intensive insulin therapy in patients with early type 2 diabetes (51). This study showed that β -cell function declined similarly in patients with randomized to placebo or sitagliptin. A possible reason for the lack of difference could be that both groups received metformin in addition to the study drug. Similar to our trial, it is possible that metformin was enough to sustain near-normoglycemia remission. However, the same group conducted a subsequent study showing that remission can be prolonged by treatment with a glucagon-like peptide 1 receptor agonist due to increased β -cell function (27).

CONCLUSION

KPDM has been described as a unique subtype of diabetes or atypical diabetes. However, the current data shows that the clinical course, prevalence of auto-immune markers, and improvement of insulin secretion and insulin action of KPDM patients is similar to patients with type 2 diabetes over the long term. Their initial presentation is characterized by significant impairment in β -cell function and insulin resistance, which can improve with intensive short-term insulin therapy in obese patients to levels similar to patients with ketosis-resistant type 2 diabetes. These data suggest that KPDM is not a unique subtype of diabetes; rather, it is a common presentation in newly diagnosed obese AA with ketoacidosis. Even though most of the studies were performed in AA, KPDM also presents in other minority populations. Future studies are needed to characterize the underlying mechanisms of ketoacidosis and outline clinical course variability in different minority populations.

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Abbreviations

A(+/-)	auto-antibody positive/negative
AA	African Americans
DKA	diabetic ketoacidosis
FFA	free fatty acids
G6PD	glucose-6-phosphate dehydrogenase
GAD-65	65-kDA glutamic acid decarboxylase
HBA1c	glycated hemoglobin A1c
HHV8	human herpes virus 8
HLA	human leukocyte antigen
KPDM	ketosis-prone type 2 diabetes

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Fig. 1.

Cox proportional hazards of failure-free survival between metformin, sitagliptin, and placebo in obese African American patients presenting with diabetic ketoacidosis and severe hyperglycemia. There was a significant difference was found between the placebo, metformin, and sitagliptin groups ($P=0.015$) but not between the sitagliptin and metformin groups ($P=0.75$) (copyright, American Diabetes Association, *Diabetes Care*).

Table 1

Differences and Similarities between Type 1, Type 2, and KPDM

	Type 1 diabetes	Type 2 diabetes	KPDM
Age of presentation	Childhood, adolescence	Adolescence, adulthood	Adolescence, adulthood
BMI	Lean	Overweight-Obese	Overweight-Obese
Ethnicity	Predominantly Caucasian	Multi-ethnic	Predominantly Blacks and other minorities
Family history of type 2 diabetes	No	Frequent	Frequent
Male:female ratio	1:1	1:1	3:1
Acanthosis	No	Yes	Yes
Presentation			
Ketosis	Yes	No	Yes
Insulin secretion	None	Yes	None
Insulin sensitivity	Higher than nondiabetics	Similar to obese nondiabetics	Lower than obese nondiabetics
Treatment	Insulin	Oral hypoglycemic agents/Insulin	Insulin
Remission from insulin	No	Yes	Yes
Clinical Course			
Ketosis	Yes	No	Ketotic relapses preceded by hyperglycemia
Insulin secretion	Absent	Present but decreases over time	Markedly reduced at presentation; β -cell recovery with intensive therapy; decreases over time
Insulin sensitivity	Higher than nondiabetics	Reduced; similar to obese nondiabetics	Reduced; similar to obese nondiabetics
Long-term treatment	Insulin	Treat with oral agents, may progress to insulin	Transient insulin requirement at presentation; oral agents may prolong insulin remission phase

Abbreviations: BMI = body mass index; KPDM = ketosis-prone type 2 diabetes mellitus.

Table 2

Clinical Course of Patients Presenting with Ketosis-Prone Diabetes Mellitus

	At presentation	Near-normoglycemia remission	Long-term follow-up
Symptoms	Polyuria, polydipsia, weight loss	None	None
Plasma glucose, mg/dL	>400	<126	Variable, risk of recurrence
HbA1c, %	>10	<7%	Variable
pH	<7.30	Normal	Normal
Bicarbonate, mmol	<18	Normal	Normal
β -hydroxybutyrate, mmol/L	Positive, >3	Normal	Normal
β -cell auto-antibodies	Negative	Negative	Negative
Fasting and stimulated insulin secretion	Markedly reduced	Improved, similar to patients with T2D	Variable, progressive decline as in T2D
Insulin sensitivity	Markedly reduced	Improved, similar to patients with T2D	Variable, progressive decline as in T2D
Need for insulin treatment	Yes	None	May be needed with long-term follow-up
Response to oral antidiabetic agents	No	Yes	Yes

Abbreviations: HbA1c = glycated hemoglobin A1c; T2D = type 2 diabetes.