Islet Immunity and Beta Cell Reserve of Indigenous Black South Africans with Ketoacidosis at Initial Diagnosis of Diabetes

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Objective: Islet immunity and beta cell reserve status were utilized to classify persons with ketoacidosis as the initial manifestation of diabetes. The clinical features of the various diabetes classes were also characterized.

Design: Prospective cross sectional study.

Setting: Nelson Mandela Academic Hospital, Mthatha, Eastern Cape Province, South Africa.

Patients: Indigenous Black South Africans with ketoacidosis as the initial manifestation of diabetes.

Interventions: Islet immunity and beta cell reserve were respectively assessed using serum anti-glutamic acid decarboxylase 65 (GAD) antibody and serum C-peptide after 1 mg of intravenous glucagon.

Outcome measures: Serum anti-GAD 65 antibody ≥ 5 units/L and < 5 units/L, respectively defined anti-GAD 65 positive (A+) and negative (A-). Replete (β+) and deplete (β-) beta cell reserve were serum C-peptide after glucagon injection of ≥ 0.5 ng/mL and < 0.5 ng/mL, respectively. The proportions of patients with A+β-, A+β+, A-β- and A-β+ and their clinical characteristics were determined.

Results: Of the 38 males and 33 females who participated in the study, patients were categorized in various classes: A-β+, 46.5% (n=33/71); A-β-, 26.8% (n=19/71); A+β-, 22.5% (n=16/71); and A+β+, 4.2% (n=3/71). The ages of the various classes were: 41.8 ± 13.8 years for A-β+ (n=33); 36.5 ± 14.6 years for A-β- (n=19); and 20.6 ± 7.1 years for the combination of A+β- with A+β+ (n=19) (P<.0001, P<.0001 for the combination of A+β- and A+β+ vs A-β+, P=.001 for the combination of A+β- and A+β+ vs A-β-and P=.2 for A-β- vs A-β+. The clinical features of type 2 diabetes were most prevalent in A-β+ class while the A+β- and A+β+ groups had the clinical profile of type 1A diabetes.

Conclusions: Most of the indigenous Black South African patients with ketoacidosis as the initial manifestation of diabetes had islet immunity, beta cell reserve status and clinical profiles of type 2 diabetes. (*Ethn Dis*. 2013;23[2]:196-201)

Key Words: Diabetes, Ketoacidosis, Islet Immunity, Beta Cell Reserve, Black South African

Introduction

Diabetic ketoacidosis (DKA) as the first manifestation of diabetes mellitus (DM) is thought to reflect marked insulin depletion and to occur only with type 1 DM as it is characterized by absolute deficiency in insulin secretion.[1,2] Type 2 DM is expected to manifest as a hyperglycemic, hyperosmolar non-ketotic state should a patient present with hyperglycemic crisis as the initial manifestation of DM because of relative insulin deficiency, which though insufficient to prevent hyperglycemia is enough to suppress ketogenesis.[3] There are however, increasing reports of DKA as the first manifestation of DM in patients without the characteristic clinical phenotype of type 1 DM.[4–12] While some researchers have classified these patients with DKA as the first manifestation of DM to be mainly type 2 DM,[4] the terms flatbush DM,[5] obese DKA,[6,7] atypical DM,[10] ketosis prone type 2 DM,[11,12] have been variously utilized to qualify these patients. These atypical presentations of DKA have mainly been in populations of Black African ancestry, with the studies either conducted in African Americans,[5–7,9] or West African immigrants to France and Afro-Carribeans.[10,11]

A recent review classified patients with DKA as the initial manifestation of DM based on islet cell immunity (anti-Glutamic acid decarboxylase antibody) and beta cell reserve into four categories: (A+β-) antibody positive and beta cell reserve deplete, (A-β-) antibody negative and beta cell reserve deplete, (A-β+) antibody negative and beta cell reserve replete, (A+β+) antibody positive and beta cell reserve replete.[13] This review[13] further reports the prevalence of the various combinations of islet immunity and beta cell reserve status and also describes their phenotypic characteristics with their diagnostic and therapeutic implications.

Similar reports of DKA as the first manifestation of DM have been found among Black African populations residing within sub Saharan Africa.[14–17] We have, however, a paucity of data with regard to this populations' islet immunity and beta cell reserve status. Our patient population is almost entirely indigenous Black African and we observed that 34% of our admissions for DKA in the period 2008 and 2009 were persons with the index DKA as the first presentation of DM.[18] Knowledge of the islet cell immunity and beta cell reserve profiles of our newly diagnosed DM patients with DKA will allow us to distinguish patients with intact beta cell reserve who are likely to be insulin independent following treatment for DKA from insulin- dependent, beta cell reserve depleted patients. Our findings will also contribute to the literature in regard to the appropriate classification of Black Africans residing in Sub

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Saharan Africa with DKA as the initial manifestation of DM.

METHODS

This prospective cross sectional study of 71 Black African patients who presented to the Nelson Mandela Academic Hospital (NMAH), Mthatha, Eastern Cape of South Africa with DKA as the initial manifestation of DM took place during the period from 2010 to 2012. The NMAH serves as the teaching facility of Walter Sisulu University. The diagnosis of DKA was based on the American Diabetes Association criteria, ie, blood glucose >13.9 mmol/L, serum bicarbonate <18 mmol/L and ketonuria.[19] Ethical clearance was obtained from the ethical committee, Faculty of Health Sciences, Walter Sisulu University. Patients were recruited into the study following written informed consent obtained after resolution of ketoacidosis and conversion of patients from insulin infusion to subcutaneous insulin injections.

Blood Collection for C-peptide and Anti-GAD Antibody

Patients newly diagnosed with DM presenting with DKA to NMAH, like other DKA cases, are admitted to the adult high care unit (AHCU) for stabilization with fluids and insulin infusion and then transferred to the general medical wards once subcutaneous insulin therapy is commenced. Beta cell reserve was assessed by taking a blood sample for c-peptide at 6 minutes after 1 mg of glucagon was given intravenously, which was before scheduled pre-breakfast subcutaneous insulin injection. Anti-GAD antibody was measured in the same blood sample collected for c-peptide assay. In 62 patients, beta cell reserve was assessed 72 hours after the initiation of subcutaneous insulin while the patient was still in hospital. Testing was done after discharge from hospital on an outpatient basis in 9 patients. These 9 patients who were previously admitted with DKA as the first manifestation of diabetes were only recruited into the study at a follow up visit to the DM clinic, as they were not tested during the index admission.

Patient Data

We collected patient data including age, sex, history of DM in first degree relatives (parents and siblings), previous diagnosis of hypertension, weight, height, waist circumference, body mass index (BMI), presence of acanthosis nigricans, blood pressure, c-peptide level and anti-GAD antibody status.

Assay of C-peptide and Anti-GAD

These assays were performed by the National Health Laboratory Service (NHLS). Serum C-peptide is measured by the NHLS using electrochemiluminescence immunoassay ''ECLIA'' on the COBAS E immunoassay analyzer (Roche Diagnostics GmbH Mannheim, Germany). The sensitivity of the assay is .003 nmol/L (.01 ng/mL) with a coefficient of variation (CV) of 1.9% to 2.3%. Anti-GAD antibody is measured using ELISA technique on an automated microplate system (Roche Applied Science, GmbH, Penzberg Germany). The sensitivity of the assay is .06 units/mL and a CV of 5.2% to 5.7%.

Operational Definitions

Body mass index (BMI) was calculated using the Quetelet's formula (weight in kilograms/square of height in meters). Underweight was BMI < 18.5 kg/m^2, overweight, ≥ 25 kg/m^2 to 29.9 kg/m^2 and obesity, ≥ 30 kg/m^2. Height and weight were respectively measured using a Stadiometer and a calibrated weighing scale. Waist circumference was measured midway between the lower border of the ribs and the upper border of the iliac crests. Increased waist circumference was waist circumference >80 cm in females and >94 cm in males as defined by the International Diabetes Federation.[20]

The diagnosis of hypertension was on the basis of any one of the following: history of hypertension, admission systolic blood pressure ≥140 mmHg and or diastolic blood pressure ≥90 mmHg. Hyperosmolality was defined as calculated effective serum osmolality ≥ 320 mmosmols/Kg.[19] Positive (A+) and negative (A-) anti-GAD antibody status were serum anti-GAD 65 antibody ≥5 units/L and <5 units/L, respectively using the cut off levels of the NHLS. Replete (β+) and deplete (β-) beta cell reserve were serum c-peptide following intravenous injection of 1 mg glucagon ≥0.5 ng/mL and <0.5 ng/mL, respectively.

Classification of Patients

Patients were categorized using anti-GAD antibody status and beta cell reserve (serum c-peptide level after 1 mg of intravenous glucagon) into one of four groups: A+β-, A-β-, A-β+ and A+β+.

Data Analysis

Data were entered into an Excel spread sheet. The proportions of patients with the various classes of DKA (A+β-, A-β-, A-β+ and A+β+) were determined. These classes were compared for differences in age, sex,

family history of DM, hypertension, presence of acanthosis nigricans, waist circumference and BMI to ascertain if any clinical characteristics distinguished these groups. Continuous variables are expressed as mean ± standard deviation (SD) and number of observations (*n*) for the variable of interest while categorical variables are presented as percentages (%) and number of observations (*n*) for the variable of interest. Means of continuous variables were assessed across groups using student's t test with Bonferroni correction for multiple comparisons while categorical variables were compared using the Chi square test. Statistical significance was $P \leq .05$. Statistical analyses were performed with statistical package for social sciences (SPSS) version 18.0 (SPSS Inc, IL, Chicago, USA).

RESULTS

We analyzed data from 71 patients, 33 females and 38 males, who were admitted with DKA as the first manifestation of DM. The mean age of all patients ($n=71$) was 34.7 ± 15.3 years with an age range of 13–73 years. Underweight (BMI of <18.5 kg/m^2) was found in 8.5% ($n=6/71$) while obesity (BMI ≥ 30 kg/m^2) was found among 35.2% ($n=25/71$) patients. The range of anti-GAD in the 71 patients was 0.4 units/L to >100 units/L. Positive anti-GAD antibody (A+) defined as serum anti-GAD antibody ≥5 units/L was found in 26.8% ($n=19/71$) patients. Six patients had anti-GAD antibody titres >100 units/L. Serum c-peptide levels ranged from <.1 ng/mL to 14.6 ng/mL. Replete beta cell reserve (β+) defined as stimulated c-peptide ≥.5 ng/mL as documented in 50.7% ($n=36/71$) patients.

Table 1 shows that the A-β+ group was most associated with DKA and was found in about half of all presentations. The least prevalent group were patients who were A+β+, comprising only 4.2% ($n=3/71$) of all DKA presentations.

Table 1. Demographic and clinical characteristics of all patients

Female	46.5% ($n=33/71$)
Age <30 years	42.3% ($n=30/71$)
Diabetes in 1st degree relative	40.8% ($n=29/71$)
Acanthosis nigricans	36.6% ($n=26/71$)
Increased waist circumference	54.9% ($n=39/71$)
Hypertension	31.0% ($n=22/71$)
Hyperosmolar DKA	32.4% ($n=23/71$)
Non-hyperosmolar DKA	67.6% ($n=48/71$)
A+β- (anti-GAD antibody positive and beta cell reserve deplete)	22.5% ($n=16/71$)
A-β- (anti-GAD antibody negative and beta cell reserve deplete)	26.8% ($n=19/71$)
A-β+ (anti-GAD antibody negative and beta cell reserve replete)	46.5% ($n=33/71$)
A+β+ (anti-GAD antibody positive and beta cell reserve replete)	4.2% ($n=3/71$)

DKA, diabetic ketoacidosis; GAD, glutamic acid decarboxylase.

The majority of patients were older than aged 30 years and had increased waist circumference. The presence of acanthosis nigricans and hypertension were each found in about a third of all patients. History of DM in a first degree relative (parents and siblings) was found in a minority of patients. Non-hyperosmolar and hyperosmolar DKA was found in 67.6% ($n=48/71$) and 32.4% ($n=23/71$) of all admissions, respectively.

Table 2 shows the demographic, serum anti-GAD and c-peptide levels of the 3 patients who were A+β+. These 3 patients (2 females, 1 male) were all teenagers. None had peripheral features of insulin resistance such as acanthosis nigricans, increased waist circumference or obesity. The serum anti-GAD levels ranged from minimally to markedly elevated. In 2 cases, ketoacidosis was non-hyperosmolar and hyperosomolar in 1 case.

Table 3 shows a comparison of the demographic and clinical parameters of the following group (A+β-), (A-β-) and (A-β+). Group A+β- patients were younger than those in Group A-β- (20.6 ± 7.1 vs 36.5 ± 14.6 years, $P=.0001$). Group A+β- was also younger than Group A-β+(20.6 ± 7.1 vs 41.8 ± 13.8 years, $P<.0001$). Groups A-β- and A-β+ had comparable ages (36.5 ± 14.6 vs 41.8 ± 13.8 years, $P=.1994$). The presence of hypertension, acanthosis nigricans, elevated waist circumference and obesity, which are all markers and correlates of insulin resistance, were all most prevalent with Group A-β+, followed by Group A-β- and least prevalent with Group A+β- patients.

Figure 1 shows that a small proportion of patients in all 3 groups had a BMI <18.5 kg/m^2. The majority of patients in group A+β- had a normal BMI while the majority of patients in the A-β- and A-β+ groups had a BMI ≥ 25 kg/m^2. The A-β+ group had the highest proportion of obese patients while the A+β- group had the least percentage of obese patients.

A paternal history of DM was recorded in 21.1% ($n=15/71$) of all patients while a maternal history of DM was documented in 19.7% ($n=14/71$) patients. Both parents had a history of DM in 4.2% ($n=3/71$) patients. Table 4 shows that groups A+β- and A-β+ patients had their fathers as the first degree relative most frequently diagnosed with DM while group A-β- patients had their mothers as the first degree relative most commonly diagnosed with diabetes.

Table 5 shows similar proportions of groups A+β-, A-β- and A-β+ regardless of presentation for hyperosmolar or non-hyperosmolar DKA. Group A-β+ was, however, the commonest group in both the hyperosmolar and non-hyperosmolar groups. The hyperosmolar DKA group had more females than the non-hyperosmolar DKA group. The

Table 2. Demographic, serum antibody and c-peptide profiles of A+β+ patients

	Sex	Age (years)	AN	WC (cm)	BMI (kg/m^2)	Serum Osmolality (mosmols/kg)	AGAD Units/L	CPEPT ng/mL
1	F	18	absent	74	20.6	290.2	8.2	.5
2	F	18	absent	78	17.9	339.9	>100	.8
3	M	15	absent	65	17.1	282.6	26.5	.6

A+β+, anti-GAD antibody positive and beta cell reserve positive; AN, Acanthosis nigricans; WC, waist circumference; BMI, body mass index; AGAD: anti-glutamic acid decarboxylase antibody; CPEPT, connecting-peptide; F, female; M, male.

proportion of patients with hypertension, acanthosis nigricans, increased waist circumference and obesity were similar in the hyperosmolar and non-hyperosmolar groups.

DISCUSSION

In this study, we reviewed the profiles of 71 patients with DKA as the initial manifestation of DM. Similar to other studies,[11,12] we found that patients with A-β+, which is consistent with type 2 DM, comprised the majority of presentations (almost a half of all admissions). These A-β+ patients with ketoacidosis as the first manifestation of diabetes have been classified as ketosis prone type 2 DM,[11,12] and also had higher frequency of the clinical correlates of insulin resistance and the metabolic syndrome such as acanthosis nigricans, increased waist circumference and hypertension as expected with type 2 DM. The greater representation of patients with type 2 DM among patients with DKA as the first presentation of DM is likely a reflection of the increasing prevalence of DM and, in particular, type 2 DM in our community. Indeed, the estimated global prevalence of DM is 285 million persons for 2010 and is projected to be 439 million cases by 2030.[21] If the projected global increase in DM, the bulk of which will occur in developing countries such as ours, is not curtailed, we expect more cases of DKA occurring in hitherto undiagnosed type 2 DM persons. This underscores the need to screen persons at risk for type 2 DM so that a diagnosis may be made while patients are still asymptomatic.

Patients who were A+β-, the classic laboratory parameters of type 1A DM, comprised about a quarter of our patients. The clinical profile of our A+β- patients is similar to that described in another population of non-Black African ancestry with type 1A DM.[22] These A+β- patients were relatively young with a mean age younger than aged 25 years and had very low prevalence of acanthosis nigricans (n=1/15), hypertension (n=1/15), obesity (n=1/15) and increased waist circumference (n=2/15). Those in the A+β+ patient group who were anti-GAD positive but with a preserved c-peptide response to glucagon were also type 1A DM because of anti-GAD positivity. Furthermore, these patients were young and with a low waist circumference as are typical with type 1 DM.

The A-β- group constituted about a quarter of our patients and is the expected finding in type 1B DM, which is non-auto-immune type 1 diabetes. In one study,[12] A-β- patients were comparably young with relatively low rates of obesity, as A+β- patients and could be considered to have idiopathic type 1 DM (Type 1B DM). Our A-β- group was however, older than the A+β- group. The A-β- patients in this study had clinical features that were similar to the A-β+ group (type 2 DM) with respect to age and the high proportions of participants with acanthosis nigricans and elevated waist circumference. The A-β-

Table 3. Demographic and clinical parameters of various Aβ groups

	A+β-	A-β-	A-β+	
	n=19	*n*=19	*n*=33	*P*
Female, %	47.4 (n=19)	26.3 (n=19)	57.6 (n=33)	.09
Age (years)	20.6±7.1 (n=19)	36.5±14.6 (n=19)	41.8±13.8 (n=33)	<.0001
Age <30 years (%)	89.5 (n=17/19)	31.6 (n=6/19)	21.2 (n=7/33)	<.0001
Diabetes in 1st degree relative (%)	31.6 (n=6/19)	52.6 (n=10/19)	39.4 (n=13/33)	.47
Acanthosis nigricans (%)	5.3 (n=1/19)	42.1 (n=8/19)	51.5 (n=17/33)	.003
Hypertension (%)	5.3 (n=1/19)	10.5 (n=2/19)	57.6 (n=19/33)	<.0001
Increased waist circumference (%)	10.5 (n=2/19)	63.2 (n=12/19)	75.8 (n=25/33)	<.0001
Obesity (%)	5.3 (n=1/19)	36.8 (n=7/19)	51.5 (n=17/33)	.004
Hyperosmolarity (%)	31.6 (n=6/19)	31.6 (n=6/19)	33.3 (n=11/33)	.99
Blood glucose (mmol/L)	29.2±13.3 (n=19)	37.1±19.0 (n=19)	36.1±20.9 (n=33)	.37

A+β- (anti-GAD antibody positive and beta cell reserve deplete); A-β- (anti-GAD antibody negative and beta cell reserve deplete); A-β+ (anti-GAD antibody negative and beta cell reserve replete).

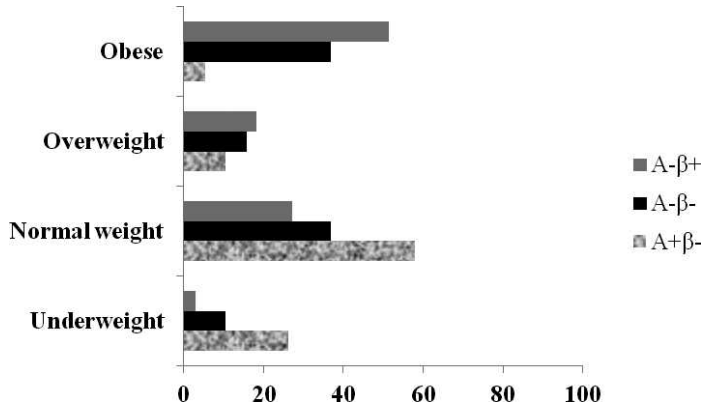

Fig 1. Percentages of patients in the Aβ groups with underweight, normal weight, overweight and obesity

Table 4. Proportions of first degree relatives with diabetes in the various groups

	A+β-	A-β-	A-β+	
	n=19	*n*=19	*n*=33	*P*
Father (%)	21.1 (*n*=4/19)	15.8 (*n*=3/19)	24.2 (*n*=8/33)	.78
Mother (%)	15.8 (*n*=3/19)	36.8 (*n*=7/19)	12.1 (*n*=4/33)	.09
Both parents (%)	5.3 (*n*=1/19)	0 (*n*=0/19)	6.1 (*n*=2/33)	.56
Siblings (%)	0 (*n*=0/19)	21.1 (*n*=4/19)	12.1 (*n*=4/33)	.12
No family history of diabetes (%)	68.4 (*n*=13/19)	47.4 (*n*=9/19)	60.6 (*n*=20/33)	.41

A+β- (anti-GAD antibody positive and beta cell reserve deplete), A-β- (anti-GAD antibody negative and beta cell reserve deplete), A-β+ (anti-GAD antibody negative and beta cell reserve replete).

group however, had similarly low frequencies of hypertension as the A+β- (type 1A) group. It is possible that our A-β- group was a heterogeneous group that included patients with type 1B DM and type 2 DM. Hyperglycemia and lipotoxicity has been shown to suppress the pancreatic beta cell.[23,24] As our patients were mostly evaluated 72 hours after transfer to the general wards, it is possible that the A-β- with type 2 DM, as suggested by the presence of acanthosis nigricans and increased waist circumference, mounted a blunted c-peptide response to glucagon injection because of the suppressive effects of hyperglycemia and lipotoxicity on the beta cell.

Table 5. Demographic and clinical indices of hyperosmolar and non-hyperosmolar DKA

	Hyperosmolar	Non-hyperosmolar	*P*
Female, %	60.9% (*n*=14/23)	39.6% (*n*=19/45)	.05
Age (years)	33.8±17.4 (*n*=23)	35.1±14.3 (*n*=48)	.75
Diabetes in 1st degree relative (%)	39.1 (*n*=9/23)	41.7 (*n*=20/48)	.42
Acanthosis Nigricans (%)	47.8 (*n*=11/23)	31.3 (*n*=15/48)	.10
Hypertension (%)	34.8 (*n*=8/23)	29.2 (*n*=14/48)	.32
Increased waist circumference (%)	52.2 (*n*=12/23)	56.3 (*n*=25/45)	.38
Obese (%)	39.1% (*n*=9/23)	33.3% (*n*=16/48)	.32
Anti-GAD antibody positive (%)	26.1 (*n*=6/23)	27.1 (*n*=13/48)	.47
Replete beta cell reserve (%)	47.8 (*n*=11/23)	50.0 (*n*=24/48)	.53
Aβ Groups (%)			.02
A+β-	26.1 (*n*=6/23)	27.1 (13/48)	
A-β-	26.1 (*n*=6/23)	27.1 (13/48)	
A-β+	47.8 (*n*=4/22)	45.8 (22/48)	

DKA, diabetic ketoacidosis; A+β- (anti-GAD antibody positive and beta cell reserve deplete); A-β- (anti-GAD antibody negative and beta cell reserve deplete); A-β+ (anti-GAD antibody negative and beta cell reserve replete).

We had previously reported a strong association between hyperosmolar DKA and a new diagnosis of diabetes.[18] In this study, groups A+β-, A-β- and A-β+ were similarly represented in both hyperosmolar and non-hyperosmolar groups with the A-β+ group constituting the majority of both groups.

The antibody (A) and beta cell reserve (β) status of the patient has therapeutic implications. While a depleted beta cell reserve (β-) will be an indication for insulin therapy, the presence of anti-GAD antibodies (A+) is predictive of subsequent insulin therapy.[25] Patients in the A+β- group (type 1A DM) are likely to be dependent on insulin injections to achieve glycemic control and prevent a repeat hyperglycemic crisis. Patients in A-β+ group (type 2 DM) may be controlled following resolution of hyperglycemic crisis with the combination of diet and oral hypoglycemic agents. Patients in A+β+ group may, following resolution of the index crisis, be initially managed on diet and oral hypoglycemic agents but are likely to soon become insulin dependent considering their anti-GAD positivity. The A-β- patients will need to be further re-evaluated to distinguish those with persistently low or undetectable c-peptide (type 1B DM) requiring insulin therapy from those who recover beta cell function (type 2 DM) following a period of euglycemia that may be prescribed oral hypoglycemic agents.

The limitations of the study include non-performance of tyrosine phosphatase (IA2) and insulin antibodies. We also did not perform HLA studies in our patients. We intend to follow our

We found that patients with A-β+, which is consistent with type 2 DM, comprised the majority of presentations (almost a half of all admissions).

patients over a period of time to assess for associations of Aβ status with glycemic control in relation to various glucose lowering agents.

CONCLUSION

Patients with the biochemical and clinical profiles of type 2 DM constitute the majority of those with DKA as the first manifestation of diabetes, regardless of hyperosmolality. Greater efforts are needed to reduce the pandemic of type 2 diabetes and to stem the tide of presentations for DKA in persons not previously diagnosed with diabetes.

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