New Profiles of Diabetic Ketoacidosis

Type 1 vs Type 2 Diabetes and the Effect of Ethnicity

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Background: Diabetic ketoacidosis (DKA) has been reported to occur in type 2 diabetes, but the frequency and distinguishing features of this syndrome remain to be defined. We determined the "diabetic types," ethnic distributions, and phenotypes of patients with DKA in an urban hospital.

Methods: We reviewed the hospital admissions and followed the clinical course of adults who developed DKA. We classified patients as "type 1," "type 2," or "new onset" based on their treatment history. New-onset patients were reassessed 2 1/2 years or more after the episode of DKA and classified as "type 1" or "type 2" based on insulin requirements. We compared the groups for ethnic distributions and clinical features.

Results: Of 141 patients, 55 (39%) who presented with DKA had type 2 diabetes, while 75 (53%) had type 1 diabetes and 11 (8%) could not be "typed." Hispanics mainly had type 2 and whites predominantly had type 1, while African Americans had a slight preponderance of type 1 diabetes (P = .001). Type 1 patients were mainly lean, while the body mass indexes (BMIs) (calculated as the weight in kilograms divided by the square of height in meters) of type 2 patients were bimodally distributed (33% with BMI < 25 and 51% with BMI > 30; P < .001). Age of onset of diabetes was predominantly younger than 40 years in the type 1 group but was more broadly distributed in the type 2 group (P < .001). Ninety-three percent of the new-onset patients who were reassessed had type 2 diabetes. Half of the type 2 patients had no identifiable stress factor associated with the episode of DKA.

Conclusions: A high proportion of DKA in nonwhite adults occurs in persons with type 2 diabetes, especially in those with previously undiagnosed diabetes. The frequency and clinical heterogeneity of this syndrome in a multiethnic population have significant implications for the diagnosis, classification, and management of adults with diabetes.

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There is a strong perception among physicians that "ketoacidosis is rare in true NIDDM [non-insulin-dependent diabetes mellitus]" and that it occurs in adult patients with type 2 diabetes only in unusual circumstances in association with severe stress. The biochemical basis for this belief is that patients with type 2 diabetes are rarely completely deficient in circulating insulin and are therefore able to avoid exuberant lipolysis and ketogenesis. In recent years, however, diabetic ketoacidosis (DKA) has been reported to occur in patients with type 2 diabetes of different ethnic groups. These reports underscore the phenotypic complexity of type 2 diabetes and invite further debate into the utility of traditional and even more recent clinical classification schemes for diabetes.

We have observed the frequent occurrence of DKA, often without notable precipitating stress, in Hispanics and African Americans with type 2 diabetes admitted to the hospitals of the Harris County Hospital District (HCHD), a multiethnic, public health care system in Houston, Tex. The frequency and distinctive clinical features of this syndrome in different ethnic groups with varying risk for type 2 diabetes need to be analyzed comprehensively. Since we treat a large number of patients with DKA in the HCHD, we assessed the proportions of patients with DKA who had type 1 and type 2 diabetes, and compared the 2 groups for ethnic distribution and clinical phenotype.

RESULTS

The HCHD computer records for 1994 and 1995 revealed a total of 659 admissions with an ICD-9 code for DKA. Of the 272 complete hospital charts available at Ben Taub General Hospital, 181 fulfilled all in-
METHODS AND PATIENTS

SUBJECT IDENTIFICATION

We performed a retrospective analysis together with prospective follow-up of a subset of adult (≥18 years) patients admitted with DKA to Ben Taub General Hospital of the HCHD. Computer records were used to identify admissions with an International Classification of Diseases, Ninth Revision (ICD-9) code\(^{13}\) for DKA (code 250.1) during a 2-year period. Of these, we reviewed all complete charts that were available at the study hospital. Admissions that met the following criteria were entered into the analysis: (1) admission date between January 1, 1994, and December 31, 1995; (2) anion gap of 15 mmol/L or more; (3) blood pH less than 7.30 (however, 5 patients with a pH of 7.30-7.35 were included since they met all other criteria for DKA, and 12 patients without an arterial pH measurement at the time of admission were included because they met all other criteria and had plasma bicarbonate concentrations of ≤17 mmol/L); (4) plasma glucose more than 11.1 mmol/L; (5) documented presence of serum ketone levels of 5.2 mmol/L or more by the Acetest reagent (Bayer Corporation, Pittsburgh, Pa) or urine ketone levels of “moderate” to “large” (>13.9 mmol/L); and (6) absence of concomitant conditions that might result in anion gap acidosis or ketosis, such as pregnancy, renal insufficiency (other than a mild, reversible prerenal state), lactic acidosis, acute alcohol intoxication, or organic poison ingestion.

CLASSIFICATION

Subjects were classified as “type 1” if they had been treated with insulin exclusively since the first diagnosis of diabetes, as “type 2” if they had a prior history of prolonged treatment with diet alone or oral hypoglycemics, or as “new onset” if the episode of DKA was the first manifestation of diabetes. Attempts were made to contact all new-onset patients at least 2½ years after the defining episode of DKA to determine current status. New-onset patients were then reclassified as “type 1” if they had been treated with insulin uninterruptedly since the episode of DKA, “type 2” if they had managed to discontinue insulin altogether or for significant periods without recurrence of DKA, or “unknown” if treatment status could not be determined reliably.

CLINICAL FEATURES AND PHENOTYPES

The data were analyzed for ethnic distributions of type 1 and type 2 diabetes, biochemical indexes, age, sex, age of onset of diabetes, BMI (calculated as weight in kilograms divided by the square of height in meters), number of episodes of DKA, and associated stressful events. Ethnicity was determined by patient self-identification. A stressful event was defined by clinical or biochemical evidence of any infectious, inflammatory, painful, or physically traumatic process, or the use of any drugs likely to elevate plasma catecholamine or cortisol levels. In patients with a diagnosis of diabetes prior to the presenting episode of DKA, noncompliance with insulin or oral hypoglycemic therapy was noted if the admission history made specific mention of it.

DATA ANALYSIS

Demographic and clinical characteristics of type 1, type 2, and unknown patients were compared using $\chi^2$ tests for categorical variables and analysis of variance for continuous variables. Comparisons of patient characteristics were made using data from the patient’s initial admission during the study period.

African Americans showed a slight preponderance of type 1 (53%), with a large number of type 2 patients (44%) and 3% unknown. The group differences in distribution of diabetic types were significant ($P<.001$) by the Pearson $\chi^2$ test.

Table 1 compares type 1 and type 2 patients for biochemical parameters relevant to DKA. There were no differences between the 2 groups in serum electrolyte concentrations, renal functions, plasma glucose concentration, arterial pH, anion gap, serum osmolality, or degree of ketosis. A large number of patients with DKA of both types were significantly hyperosmolar (serum osmolality was $>320$ mOsm/L in 26% of type 1 patients and in 25% of type 2 patients), as has been noted previously in an urban US population.7

Several significant clinical characteristics are compared in Table 2. Type 2 patients were significantly older than type 1 patients. Men outnumbered women to the same degree in both groups. Type 1 patients had more recurrences of DKA. Only 2 type 2 patients had a repeat episode of DKA during the study period, and both managed to discontinue continuous insulin treatment some time after the second episode. No new-onset patient had a repeat episode of DKA. Mean BMI was significantly greater in type 2 patients. A subgroup analysis of BMI

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revealed interesting differences (Figure 4). Type 1 patients were predominantly lean, with a sharp decline in prevalence with increasing BMI. However, the BMIs of type 2 patients showed a bimodal distribution, with a cluster of lean patients (33% with BMI <25) and another of obese patients (51% with BMI >30). The group differences in distribution of BMI were significant by the Pearson \( \chi^2 \) test at \( P < .001 \).

Ages of onset were different between the 2 groups and heterogeneous in the type 2 group (Figure 5). Most type 1 patients developed diabetes before age 40 years, whereas the type 2 patients showed a broader distribution (39% < 40 years and 54% \( \geq 40 \) years). The group differences in distribution of ages of onset were significant by the Pearson \( \chi^2 \) test at \( P < .001 \). There was no correspondence between any stratum of BMI or ethnicity and either stratum of age of onset in the type 2 group.

Table 3 shows that the majority of the previously diagnosed type 2 patients (55%) and almost half of the new-onset type 2 patients (46%) had no identifiable physical stress factor associated with the episode of DKA. Diabetic ketoacidosis in previously diagnosed type 1 patients was most often linked to omission of insulin treatment and, in previously diagnosed type 2 patients, to (usually prolonged) omission of oral hypoglycemic drug therapy.

**COMMENT**

Our results indicate that a large percentage of patients from a multiethnic, urban US population who present with DKA have type 2 diabetes. The proportion of patients with DKA with type 2 diabetes is greatest among Hispanics, while whites have the highest proportion of type 1 patients and a low proportion of type 2 patients with DKA. The great majority of previously undiagnosed adult patients who present with DKA have type 2 diabetes. Strikingly, these patients often lapse into ketoacidosis after many weeks of symptomatic hyperglycemia without an additional, identifiable “stressful” event.

Patients with type 2 diabetes who experience ketoacidosis are phenotypically heterogeneous. While the majority are obese, a significant proportion are lean, whereas the type 1 patients are predominantly lean. Similarly, while the majority of type 1 patients with DKA develop diabetes at an early age, patients with type 2 diabetes and DKA are distributed fairly evenly between early and late onset.

The lean subgroup of African American type 2 patients with DKA likely includes some persons of the “Flatbush diabetes” type, who are positive for human leukocyte antigens DR3 and DR4 but negative for the islet cell–specific antibodies typical of type 1 diabetes. This syndrome itself may be a subtype of the “phasic IDDM [insulin-dependent diabetes mellitus]” described in the Caribbean, Asia, and Africa. The subgroup of those who are both lean and have early-onset diabetes could include some patients with the “atypical diabetes mellitus” of African Americans. Similarly, some obese type 2 subjects are similar to patients described by
Umpierrez et al., who were obese African Americans without circulating islet-cell antibody and a severely blunted but reversible β-cell response to glucose. Others who are both obese and have early-onset diabetes could belong to the expanding category of “NIDDM of youth.” The proliferation of terms used to describe these forms of diabetes reflects the inadequacy of current classification schemes, especially in regard to minority and immigrant populations. These forms themselves could subsume multiple genotypic or phenotypic subtypes, which could be complicated further by variable expression in different ethnic groups. Until a more flexible classification scheme is conceived, it might be reasonable to define a person’s diabetes with terms to specify both pathogenesis (“type 1” or “type 2”), and proneness to ketoacidosis (“ketoacidosis prone” or “ketoacidosis resistant”). Alternatively, a system that includes an assessment of insulin secretory reserve in the definition of diabetes might be useful.

Five percent to 10% of Swedish patients who develop diabetes in later life have late-onset type 1 diabetes when screened for islet cell–specific antibodies and clinical manifestations. While such rigorous studies are lacking in Hispanics and African Americans, it is unlikely that our nonwhite type 2 patients with DKA in fact have late-onset type 1 diabetes. The incidence of type 1 diabetes (as defined by insulin dependence) is low in adult Mexican Americans, who constitute the majority of Hispanic patients in the HCHD. Many Mexican American, Native American, and African American children who were initially classified as “insulin dependent” because they presented with DKA have had to be reclassified subsequently as “non–insulin-dependent.” Subsets of type 2 African Americans with DKA have been negative for islet cell–specific antibodies. Still, it is possible that some of our lean type 2 subjects could have islet-cell autoantibodies, predisposing them to insulin dependence in later years.

We adopted clinically accepted criteria for the classification of diabetes, based on the definition that type 2 patients do not require uninterrupted insulin therapy to avoid DKA. Our estimate of the proportion of DKA with type 2 diabetes could have been diminished by the

| Table 1. Biochemical Profiles of Admissions by Diabetic Classification* |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Biochemical Parameters** | **Type 1** (n = 98) | **Type 2** (n = 58) | **Unknown** (n = 11) | **P** |
| Sodium, mmol/L | 134 ± 6 | 132 ± 8 | 132 ± 4 | 29 |
| Chloride, mmol/L | 94 ± 14 | 94 ± 15 | 90 ± 23 | 70 |
| Potassium, mmol/L | 5.2 ± 1.2 | 4.9 ± 1.2 | 4.7 ± 1.1 | 25 |
| Bicarbonate, mmol/L | 13 ± 13 | 12 ± 4 | 12 ± 7 | 92 |
| Serum urea nitrogen, mmol/L | 10.4 ± 6.8 | 11.8 ± 8.6 | 7.5 ± 5.4 | 21 |
| Creatinine, µmol/L | 159 ± 115 | 159 ± 97 | 115 ± 62 | 48 |
| Glucose, mmol/L | 34.9 ± 17.6 | 40.6 ± 23.8 | 34.5 ± 24.7 | 22 |
| Anion gap, mmol/L | 27 ± 8 | 25 ± 7 | 24 ± 5 | 10 |
| Osmolality, mOsm/L † | 314 ± 23 | 318 ± 33 | 306 ± 30 | 40 |
| Arterial pH ‡ | 7.14 ± 0.12 | 7.17 ± 0.12 | 7.19 ± 0.14 | .59 |
| Total | 91 | 54 | 11 | |
| Serum ketones, mmol/L § | 37 | 18 | 3 | .53 |
| Small | 26 | 19 | 0 | .53 |
| Moderate | 15 | 9 | 1 | |
| Total | 78 | 42 | 4 | |

*All values are mean (SD), unless otherwise indicated.
† “Effective” serum osmolality was calculated as Z × Na + Glucose/18.
‡ Arterial pH measurements at the time of admission were available for 156 admissions. In the remainder, serum bicarbonate concentration was 17 mmol/L or less, and all other criteria for diabetic ketoacidosis were fulfilled.
§ Serum ketone levels were measured by the “Acetest” reagent (Bayer Corporation, Pittsburgh, Pa), which is sensitive only to acetoacetic acid and acetone. According to details supplied by the manufacturer, “small” is about 5.2 mmol/L, “moderate” is about 10.4 mmol/L, and “large” is about 20.8 mmol/L. Serum ketone measurements at the time of admission were available for 124 admissions. In the remainder, urine ketone levels were moderate (6.9-13.9 mmol/L) or large (>13.9 mmol/L).

| Table 2. Patient Characteristics by Diabetic Classification* |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Characteristic** | **Type 1** (n = 75) | **Type 2** (n = 55) | **Unknown** (n = 11) | **P** (by ANOVA) |
| Age, y | 35.5 ± 10.1 | 47.3 ± 13.7 | 40.2 ± 12.8 | <.001 |
| Sex, M:F | 43:32 | 34:23 | 8:3 | .62 |
| No. of DKA admissions (average No. per patient) | 99 (1.14) | 57 (1.04) | 10 (1.00) | <.01 |
| BMI, kg/m² † | 24.2 ± 7.8 | 30.5 ± 7.5 | 24.3 ± 6.8 | <.001 |
| Total | 51 | 44 | 8 | |

*ANOVA indicates analysis of variance; DKA, diabetic ketoacidosis; and BMI, body mass index.
† BMI could not be obtained on all patients.

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common practice of placing all patients who have had DKA on lifelong, continuous insulin treatment. Indeed, we were able to observe the “natural” evolution of the type 2 syndrome in our new-onset patients after the episode of DKA precisely because a large number discontinued using their prescribed insulin treatment without consulting their physicians or keeping follow-up clinic appointments.

There is a common perception that significant physical stress (other than the effects of persistent hyperglycemia per se) is a prerequisite for patients with type 2 diabetes to develop DKA.\(^1\)\(^,\)\(^2\)\(^,\)\(^24\) However, we found that about half of our type 2 patients had no identifiable antecedent or concurrent stressful condition. In subtypes of African Americans,\(^3\)\(^,\)\(^4\) DKA appears to be precipitated by transient insulinopenia. An adequate insulin secretory response is restored in these patients by aggressive management of diabetes. Similar abnormalities of insulin secretion in the face of mounting insulin resistance may play a role in the development of DKA in Hispanic patients with type 2 diabetes.

Omission of insulin therapy for a variety of reasons has been shown to be the leading precipitating cause of DKA in urban, African American patients with known diabetes.\(^25\) The role of noncompliance in precipitating DKA specifically in type 2 patients is likely to be complex. Many of our “previously diagnosed” type 2 patients had no obvious precipitating cause other than prolonged omission of oral hypoglycemic therapy, as noted in the admission histories. However, since we did not collect compliance data systematically, we cannot comment on other behaviors that might have influenced progression to DKA, such as diet and physical activity. Overall, noncompliance could have been underreported or overreported in the charts we analyzed. Future prospective studies should examine comprehensively the impact of treatment compliance in precipitating DKA in patients with type 2 diabetes.

In conclusion, we have found that the syndrome of DKA with type 2 diabetes presents commonly in a multiethnic, urban population with a high prevalence of diabetes. In adults of certain nonwhite ethnic groups, the majority of cases of DKA occur in type 2 patients, especially if they do not carry a prior diagnosis of diabetes. Physicians should be aware of these features for optimal long-term management of their patients with DKA.

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