Accuracy and Predictive Value of Classification Schemes for Ketosis-Prone Diabetes

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OBJECTIVE — Ketosis-prone diabetes (KPD) is an emerging, heterogeneous syndrome. A sound classification scheme for KPD is essential to guide clinical practice and pathophysiologic studies. Four schemes have been used and are based on immunologic criteria, immunologic criteria and insulin requirement, BMI, and immunologic criteria and β-cell function (Aβ classification). The aim of the present study is to compare the four schemes for accuracy and predictive value in determining whether KPD patients have absent or preserved β-cell function, which is a strong determinant of long-term insulin dependence and clinical phenotype.

RESEARCH DESIGN AND METHODS — Consecutive patients (n = 294) presenting with diabetic ketoacidosis and followed for 12–60 months were classified according to all four schemes. They were evaluated longitudinally for β-cell autoimmunity, clinical and biochemical features, β-cell function, and insulin dependence. β-Cell function was defined by peak plasma C-peptide response to glucagon ≥1.5 ng/ml. The accuracy of each scheme to predict absent or preserved β-cell function after 12 months of follow-up was tested using multiple statistical analyses.

RESULTS — The "Aβ" classification scheme was the most accurate overall, with a sensitivity and specificity of 99.4 and 95.9%, respectively, positive and negative likelihood ratios of 24.55 and 0.01, respectively, and an area under the receiver operator characteristic curve of 0.972.

CONCLUSIONS — The Aβ scheme has the highest accuracy and predictive value in classifying KPD patients with regard to clinical outcomes and pathophysiologic subtypes.

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Diabetes that is not easily classified as either type 1 or type 2 is increasing worldwide, especially in non-Caucasian populations. These forms of diabetes include a heterogeneous syndrome comprising patients who are prone to develop ketosis, although they lack evidence of autoimmune destruction of β-cells. The American Diabetes Association (ADA) has accommodated such patients in its classification scheme of diabetes as a subset of type 1 diabetes, within a category entitled "idiopathic type 1" or "type 1B" diabetes. The most recent position statement of the ADA (1) defines patients with idiopathic type 1 diabetes as those who have insulinopenia of unknown etiology and are prone to develop diabetic ketoacidosis (DKA).

The approach of including all patients who are ketosis prone but lack evidence of β-cell autoimmunity in one "idiopathic" category has the advantage of simplicity but ignores emerging evidence for clinical, phenotypic, and etiological heterogeneity of these patients. Furthermore, the current definition of idiopathic type 1 diabetes offers little aid to clinicians as to the long-term outcomes of these patients, which can be extremely variable, with some requiring life-long insulin therapy due to a permanent, severe β-cell defect and others requiring only temporary insulin treatment due to partially preserved β-cell function or reversible β-cell defects. As patients who would fit the category of "type 1b diabetes" continue to expand worldwide, it is clear that strenuous attempts must be made to reclassify this group into etiologically useful and clinically relevant subtypes.

We and others (2–4) have tracked the clinical presentation, long-term outcomes, β-cell function, and insulin requirements of cohorts of type 1b diabetic patients of different ethnicities. A useful heuristic approach adopted by several investigators in the field (2–5) has been to identify these patients by their presentation with ketosis or DKA. Because the development of DKA can be unequivocally defined in clinical terms and clearly reflects a severe defect in β-cell function at the time of the event, this approach defines a starting point for longitudinal analysis of such patients, which in turn permits the development of disease criteria and case definitions. Unfortunately, separate investigations have led to a proliferation of terms to identify the condition (e.g., Flatbush diabetes [6], atypical diabetes [7], idiopathic type 1 diabetes [8], and ketosis-prone diabetes [KPD] [3,4]), as well as confusion in regard to subtypes of the condition. In this study, we have attempted to test, in an evidence-based manner, the accuracy and predictive value of all published classification schemes that have been used to define and categorize patients prone to develop ketosis. The intent is to formulate optimal classification and nomenclature of KPD in a manner that could facilitate long-term management of these patients, as well as studies aimed at determining the molecular etiologies of the subtypes.

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Abbreviations: ADA, American Diabetes Association; AUC, area under the curve; DKA, diabetic ketoacidosis; GAD, glutamic acid decarboxylase; KPD, ketosis-prone diabetes; KDP-ID, KPD–insulin dependent; KDP-NID, KDP–noninsulin dependent; LR, likelihood ratio; PPV, positive predictive value; NPV, negative predictive value; ROC, receiver operating characteristic.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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See accompanying editorial, p. 2755.

Classification schemes

We have termed the four published schemes to classify patients with KPD as the "ADA" (5), the "modified ADA" (4), the "BMI-based" (2), and the "Aβ " (3) classification schemes.

According to the ADA expert committee, the occurrence of DKA signifies that a person has type 1 diabetes. Type 1 diabetic patients are further classified as having "type 1a" diabetes if they have serologic markers of islet cell autoimmunity (autoantibodies against glutamic acid decarboxylase [GAD]—Mr 65 [GAD65] or Mr 67 [GAD 67]—or islet cell autoantibodies) and as "type 1b" (idiopathic type 1) if they lack such markers (1). The ADA classification scheme has been adopted unchanged by KPD investigators at the University of Texas-Southwestern Medical School, Dallas, Texas, who classify all ketosis-prone diabetic patients as type 1a or type 1b. They define as type 1a those KPD patients with low β-cell function, autoimmune markers, and clinical characteristics of type 1 diabetes and as type 1b those KPD patients with some preservation of β-cell function and clinical characteristics of type 2 diabetes (5,8).

A modified ADA classification scheme has been used by investigators at the University of Paris, Paris, France, who differentiate KPD patients into three groups, as follows. Patients with autoantibodies against islet cell or β-cell antigens are defined as "type 1a," while those who lack autoantibodies are subdivided into two groups: "KPD–insulin dependent" (KPD-ID) and "KPD–noninsulin dependent" (KPD-NID), based on long-term requirement for exogenous insulin. Both type 1a and KPD-ID patients have clinical characteristics of type 1 diabetes with poor β-cell function, while subjects with KPD-NID have clinical characteristics of type 2 diabetes with preserved β-cell function (4).

The BMI-based classification scheme utilizes BMI as a criterion to distinguish KPD subtypes. This approach by investigators at Emory University, Atlanta, Georgia, differentiates KPD patients into "lean" (defined by these investigators as BMI <28 kg/m^2) and "obese" (BMI ≥ 28 kg/m^2) subtypes. "Lean KPD" patients are those with clinical characteristics of type 1 diabetes with low β-cell function, while "obese KPD" patients are those with clinical characteristics of type 2 diabetes with some preservation of β-cell function (2,9).

The Aβ classification has been utilized by investigators at Baylor College of Medicine, Houston, Texas, and the University of Washington, Seattle, Washington. This approach is based on the presence or absence of markers of β-cell autoimmunity (autoantibodies) together with presence or absence of β-cell function. KPD patients are differentiated into four categories: A+β−, those with autoimmunity and absent β-cell function; A+β+, those with autoimmunity but preserved β-cell function; A−β−, those without autoimmunity but absent β-cell function; and A−β+, those without autoimmunity and preserved β-cell function. A+β− and A−β− patients are immunologically and genetically distinct from each other but share clinical characteristics of type 1 diabetes with low β-cell function, while A+β+ and A−β+ patients are immunologically and genetically distinct from each other but share clinical characteristics of type 2 diabetes with preserved β-cell function (3).

RESEARCH DESIGN AND METHODS

— To compare the accuracy of these four classification schemes of KPD, we analyzed clinical, biochemical, and serological data from 294 consecutive patients who presented with DKA to the Ben Taub General Hospital, Houston, Texas, between June 1999 and December 2003 and were followed longitudinally in a dedicated clinic for a mean duration of 31 months (range 12–60 months). This is a multiethnic cohort (44.8% African American, 43.5% Hispanic, 10.8% Caucasian, and <1% Asian). Fifty-four percent of these patients had a probable precipitating cause for DKA (18% acute illness and 36% noncompliance with antidiabetic therapy). For inclusion of a patient in the analysis, all of the following information was required: BMI, β-cell autoantibodies (GAD65, GAD67, and IA-2 antibodies measured by the reference center at the Robert H. Williams Laboratory, University of Washington, Seattle, Washington [3]), β-cell function (as measured by a glucagon stimulation test) within 2 weeks of resolution of the index DKA episode and again 6–12 months later), regular follow-up in the dedicated study clinic (at least two visits per year), and recorded information on dose and frequency of insulin treatment as an outpatient after the index DKA episode.

Classification

All subjects were classified according to the criteria of each of the four KPD classification schemes. β-Cell function 12 months after the index DKA was defined as "preserved" if the fasting serum C-peptide level was ≥1 ng/ml or the maximum glucagon-stimulated serum C-peptide level was ≥1.5 ng/ml or "absent" if the fasting serum C-peptide level was <1 ng/ml or the maximum glucagon-stimulated serum C-peptide level was <1.5 ng/ml. These cutoff levels and the correlations between the fasting C-peptide cutoff and the peak glucagon-stimulated C-peptide cutoff have been validated by previously published receiver operator characteristic (ROC) analyses (3,10,11).

We tested the ability of each classification scheme to predict preserved or absent β-cell function 12 months after the index DKA because of the importance of sustained preservation of β-cell function to the clinical outcomes of patients with KPD (3,7,12,13). We tested these differences using sensitivity, specificity, positive predictive values (PPVs) and negative predictive values (NPVs), positive (+) and negative (−) likelihood ratios (LRs), and ROC analyses. For the ADA classification system, patients classified as "type 1b" were considered as having a positive test result for predicting preserved β-cell function 12 months after the index DKA, whereas those classified as "type 1a" were considered to have a negative test result for predicting preserved β-cell function 12 months after the index DKA. For the modified-ADA classification scheme, patients classified as KPD-NID were considered to have a positive test result for predicting preserved β-cell function 12 months after the index DKA, whereas patients classified as either type 1a or KPD-ID were considered to have a negative test result for predicting preserved β-cell function 12 months after the index DKA. For the BMI-based classification, patients classified as "obese" were considered to have a positive test result for predicting preserved β-cell function 12 months after the index DKA and those classified as "lean" were considered to have a negative test result for predicting preserved β-cell function 12 months after the index DKA. For the Aβ classification scheme, patients classified as A+β+ or A−β+ were considered to have a positive test result for predicting preserved β-cell function 12 months after the index DKA, whereas those classified A+β− or A−β − were considered to have a negative test result for predicting preserved β-cell function 12 months after the index DKA.

Table 1—*Clinical characteristics of the 294 patients*

Age at presentation	38 ± 11
Age at diagnosis of diabetes	33 ± 14
Years with diabetes (range)	4.1 ± 7.3 (0–45)
Male	175 (60)
Ethnicity	
African American	132 (45)
Hispanic	128 (44)
Caucasian	32 (11)
Asian	2 (<1)
Precipitating factor	
Acute illness	54 (18)
Noncompliance	105 (36)
New-onset diabetes (unprovoked DKA)	135 (46)
BMI (kg/m^2)	29.4 ± 8.7 (16.9–63.9)
Distribution of BMI	
Lean (BMI < 25 kg/m^2)	112 (39)
Overweight (BMI 25–29.9 kg/m^2)	69 (24)
Obese (BMI ≥30 kg/m^2)	109 (37)
Baseline A1C	13.4 ± 2.5

Data are means ± SD, means ± SD (range), and *n* (%).

Statistical methods

Sensitivity of each classification scheme was calculated by dividing the number of subjects with a positive test result by the number of subjects with preserved β-cell function 12 months after the index DKA. Specificity was calculated by dividing the number of subjects with a negative test result by the number of subjects with absent β-cell function 12 months after the index DKA (14,15). PPV was calculating by dividing the number of subjects with preserved β-cell function 12 months after the index DKA by the number of subjects with a positive test result. NPV was calculated by dividing the number of subjects with absent β-cell function 12 months after the index DKA by the number of subjects with a negative test result (14,15).

The LRs indicate how much a test result raises or lowers the pretest probability of the target disease. The formulas used for determining LR were:

+LR = sensitivity/(1 − specificity)

−LR = (1 − sensitivity)/specificity.

The higher the +LR ratio, the greater the increase in pretest probability of having the target outcome (preserved β-cell function). The lower the −LR ratio, the greater the decrease in pretest probability of having the target outcome. A test with 100% sensitivity and 100% specificity would have a +LR of infinity and a −LR of 0 (14,15).

ROC analysis is a statistical representation of the relationship between false-positive and true-positive rates. A standard technique to evaluate this relationship is by comparing areas under the ROC curves. If a test predicted the outcome perfectly (in this case, preserved β-cell function), it would have a value above which the entire abnormal population would fall and below which all normal values would fall. It would be perfectly sensitive and pass through the point (0,1) on a grid. The closer the ROC curve for experimental data approaches this ideal point (area under the curve [AUC] = 1.0), the better the discriminating ability of the test. A test with no predictive ability would produce a curve that followed the diagonal of the grid with an AUC of 0.5 (16). ROC curve analyses were performed using the JMP 5.0 statistical package (SAS Institute, 2002).

RESULTS — The demographic and clinical characteristics of the 294 subjects (Table 1) were mean age 38 ± 11 years, mean age at diagnosis of diabetes 33 ± 14 years, 60% male, mean BMI 29.4 ± 8.7 kg/m^2 (range 16.9–63.9), mean HbA_{1c} (A1C) at index DKA 13.4 ± 2.5%, mean A1C 12 months after the index DKA 7.01 ± 1.86%, mean peak stimulated C-peptide at baseline 2.9 ± 1.6 ng/ml, and mean stimulated C-peptide level 12 months after the index DKA 4.3 ± 2.2 ng/ml. The distribution of KPD subtypes by the classification schemes is presented in Table 2.

For the ADA classification scheme (Table 3), sensitivity was 48.8%, specificity 94.2%, PPV 71.9%, NPV 28.1%, +LR 8.34, and −LR 0.54. The ROC AUC was 0.707.

For the modified ADA classification, sensitivity was 31.6%, specificity 99.2%, PPV 98.2%, NPV 51.1%, +LR 38.99, and −LR 0.69. The ROC AUC was 0.703.

For the BMI-based classification, sensitivity was 67.3%, specificity 85.8%, PPV 78.6%, NPV 77.2%, +LR 4.75 and −LR 0.38. The ROC AUC was 0.766.

For the Aβ classification, sensitivity was 99.4%, specificity was 95.9%, PPV was 97.1%, NPV was 99.2%, +LR was 24.55, and −LR was 0.01. The ROC AUC was 0.972.

The results of the accuracy tests were very similar when the 138 subjects with new-onset KPD were analyzed separately (Table 3).

CONCLUSIONS — KPD is a heterogeneous syndrome in which the pathophysiologic basis and clinical, biochemical, and genetic features have spread beyond the current definitions of "types" of diabetes (2–4,6,8,9,17–22). As may be expected with any heterogeneous condition described in different ethnic groups, numerous classification schemes have been utilized by different investigators to characterize this syndrome. We have compared the four current KPD classification schemes that are based on prospective analysis of well-defined cohorts of adult patients presenting with ketosis in a large, multiethnic cohort followed longitudinally and tested repeatedly for 12–60 months. The results demonstrate that the Aβ classification scheme is the most accurate scheme in terms of sensitivity, NPV, −LR, and ROC AUC and provides a high degree of specificity, a +LR, and a PPV. The modified ADA classification is most accurate in terms of specificity, +LR, and PPV but has low sensitivity, a NPV, and an inconclusive −LR. The BMI-based and traditional ADA classification schemes are less accurate overall than the other two.

The ADA classification scheme lacks flexibility to accommodate the heterogeneity of KPD because it applies only to patients with type 1 diabetes, defined as those with complete β-cell failure who require insulin for survival (23). A striking aspect of KPD is that a substantial proportion of patients, especially (but not exclusively) of non-Caucasian ethnicity, do not have complete β-cell failure and do not require insulin for long-term survival. Indeed, 31% of our cohort who presented with DKA (without a notable precipitating factor or stress) have been successfully withdrawn from insulin therapy and have remained in excellent glycemic control without ketosis for 12 months or longer.

Table 2—*Distribution of KPD subtypes by the four classification schemes*

	All 294 KPD patients followed for >12 months	Subset of 138 patients with new-onset diabetes
Aβ		
A+β+	5%	7%
A−β+	55%	74%
A+β−	19%	6%
A−β−	21%	13%
Modified ADA		
KPD-NID	19%	23%
KPD-ID	57%	64%
Type 1a	24%	13%
BMI based		
Lean	63%	36%
Obese	37$	64%
ADA		
Type 1a	24%	13%
Type 1b	76%	87%

Table 3—*Accuracy of the four classification schemes in defining KPD*

	Sensitivity	Specificity	PPV	NPV	+LR	−LR	ROC AUC
All 294 subjects presenting with DKA							
Aβ	99.4	95.9	97.1	99.2	24.55	0.01	0.972
Modified ADA	31.6	99.2	98.2	51.1	38.99	0.69	0.703
BMI based	67.3	85.8	78.6	77.2	4.75	0.38	0.766
ADA	48.8	94.2	71.9	28.1	8.34	0.54	0.707
138 subjects presenting with DKA and new-onset diabetes							
Aβ	99.1	95.5	99.1	95.5	21.79	0.01	0.969
Modified ADA	34.5	100	100	22.5	∞	0.66	0.672
BMI based	72.2	76.2	94.3	33.3	3.03	0.37	0.742
ADA	89.7	22.7	85.9	29.4	1.16	0.45	0.562

Furthermore, KPD patients demonstrate that the presence or absence of islet cell autoantibodies or HLA susceptibility alleles are not necessarily the key determinant of β-cell function. Some patients with islet cell autoantibodies have clinical and biochemical characteristics of type 2 diabetes (overweight, with strong family history of type 2 diabetes, and preserved β-cell function), while some patients who lack all evidence of islet cell autoantibodies or HLA susceptibility have strong clinical and biochemical characteristics of type 1 diabetes (lean, with completely absent β-cell function) (3,24–26).

The BMI-based classification has the advantage of being the simplest to use, since it does not require specific laboratory testing. Its disadvantage is that BMI lacks both sensitivity and specificity as a distinguishing marker of β-cell function. While a majority of obese patients with KPD have preserved β-cell function, so do many lean patients, and there are certainly obese patients with completely absent β-cell function (3,4,7,21,22,27). With the rapidly growing epidemic of obesity affecting patients with all phenotypes of diabetes, the BMI-based KPD classification scheme has limited accuracy in predicting preserved β-cell function and long-term insulin dependence.

The modified ADA classification has the advantage of being a clinically oriented, simple scheme. It has the highest specificity, PPV, and +LR, since almost all of the subjects with absent β-cell function at 12 months were classified as either type 1a or KPD-ID. However, its disadvantages are low sensitivity, NPV, and −LR, since a sizable proportion of subjects with preserved β-cell function at 12 months were still receiving exogenous insulin and were thus classified as KPD-ID. Of note, a similar drawback arising from the classification of diabetes based on the requirement for exogenous insulin treatment was a key reason that the ADA adopted a change in nomenclature from "insulin-dependent diabetes" (type 1 diabetes) and "non–insulin-dependent diabetes" (type 2 diabetes) to "type 1" and "type 2" diabetes (23). Furthermore, this is a classification that acquires its high specificity only retroactively, after following the clinical course of the patients for an indefinite period of time. When patients are first identified as having KPD, i.e., at the time of the index episode of DKA, they can only be classified based on their autoantibody status, since all are initially treated with exogenous insulin as outpatients. According to the modified ADA scheme, patients with β-cell autoantibodies are classified immediately as type 1A; the remainder are classified only subsequently, depending on their long-term requirement for exogenous insulin treatment, as KPD-ID or KPD-NID.

The Aβ classification scheme for KPD, which is based on both the presence or absence of β-cell autoantibodies and the presence or absence of β-cell function measured shortly after the correction of the acidosis and stabilization of hyperglycemia from the index DKA episode, has consistently higher accuracy measures than the other schemes. It has the disadvantage of requiring at least two different tests to classify patients. However, long-term follow-up and repeat testing of β-cell function in a very large number of KPD patients have demonstrated a very high correlation between results obtained at baseline (within 1–2 weeks of the index episode of DKA) and those obtained upon retesting 6 or 12 months later (3). β-Cell functional testing can also be simplified, as the fasting serum C-peptide concentration has been shown to correlate very well with the value of C-peptide response following glucagon stimulation in these patients (3). Hence, it is possible to use a simple, quantitative measure of β-cell function shortly after the correction of the acidosis of the index DKA episode as a key predictive factor, and the majority of KPD subjects will be accurately classified with regard to the probability of having preserved or absent β-cell function after 12 months of follow-up. As a result of this, the Aβ scheme has the highest AUC for ROC analysis. It also has the highest sensitivity, NPV, and −LR, as well as high specificity, a +LR, and PPV. Besides predicting long-term clinical and biochemical behavior of subjects with KPD, it permits accurate discrimination between four distinct phenotypes of KPD at the time of diagnosis. This is useful for prospective analysis of patients with each of these subtypes, including studies to determine the etiologies underlying each (28).

Almost all patients classified as A+β− or A−β− tend to have the clinical and biochemical characteristics of type 1 diabetes, i.e., they require exogenous insulin to preserve life (3). Less than 1% of the subjects classified initially as A−β− showed improvement in β-cell function with long-term follow-up and retesting. In addition to the distinguishing characteristic of β-cell autoantibody status, there are other important genetic distinctions between these two β− groups. These are the focus of current investigations (3,28), which may reveal further criteria to discriminate between them and limit misclassification.

Subjects classified as A+β+ have two possible clinical outcomes. Despite their older age of onset, tendency to overweight/obesity, and strong family history, approximately half have a clinical course that resembles type 1 diabetes, with progressive deterioration of β-cell function and inability to discontinue insulin treatment. The remainder have a clinical course that resembles type 2 diabetes, with long-term preservation of β-cell function and the ability to discontinue insulin treatment (3). Hence, the Aβ classification scheme is less accurate in predicting long-term outcomes in this subset. However, A+β+ patients comprise the smallest subgroup of KPD patients (5%), and ongoing genetic investigations suggest that co-inheritance of certain HLA allelotypes (specifically, one or more alleles associated with β-cell autoimmunity, such as DQB1*02 [3]) may distinguish those who can discontinue insulin treatment. For the present, patients classified as A+β+ should be followed closely with repeated testing of β-cell function to determine their clinical course (28).

Subjects classified as A−β+ have

clinical and biochemical characteristics of type 2 diabetes. In these patients, β-cell function is substantial when measured within 1–2 weeks of the index DKA and improves further when measured 6–12 months afterward. Insulin can be safely discontinued in the majority of these patients (3).

In conclusion, the Aβ classification accurately classifies patients with KPD and strongly predicts their long-term clinical and biochemical behavior. It also distinguishes subgroups of KPD, which can be used to design and implement investigations into their pathogenic mechanisms (28). However, acceptance of any new nomenclature may encounter resistance, especially as the terms "type 1" and "type 2" diabetes are so widely utilized by both medical professionals and lay persons. Hence, it might be useful to subsume the classification of KPD into the terminology of "type 1" and "type 2" diabetes. To align the Aβ classification scheme with this widely accepted terminology, we suggest the following nomenclature to classify KPD:

KPD type 1A. These are A+β− patients. They have permanent and complete β-cell failure with serologic markers of islet cell autoimmunity. They require lifelong exogenous insulin therapy.

KPD type 1B. These are A−β− patients. They have permanent and complete β-cell failure but lack serologic markers of islet cell autoimmunity. They require lifelong exogenous insulin therapy.

KPD type 2A. These are A+β+ patients. They have preserved β-cell function at the time of diagnosis but also have serologic markers of islet cell autoimmunity. Some have a reversible form of β-cell dysfunction, characterized by prolonged preservation of β-cell function and ability to discontinue exogenous insulin therapy, while others have progressive β-cell failure and require lifelong exogenous insulin therapy.

KPD type 2B. These are A−β+ patients. They have preserved β-cell function and lack serologic markers of islet cell autoimmunity. The majority (especially if new onset) can discontinue exogenous insulin therapy.

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