Immunogenetic Analysis Suggests Different Pathogenesis for Obese and Lean African-Americans With Diabetic Ketoacidosis

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OBJECTIVE — When presenting with diabetic ketoacidosis (DKA), lean and obese patients differ in their subsequent clinical course. Although lean patients tend to remain insulin dependent, most obese patients recover endogenous insulin secretion and discontinue insulin therapy. The aim of this study was to determine whether obese African-American patients with DKA could be determined to have type 1 or type 2 diabetes based on insulin secretion or the presence of immunological and genetic markers.

RESEARCH DESIGN AND METHODS — This was a prospective study that analyzed the clinical characteristics, insulin secretion indices, immunological markers (islet cell, GAD, ICA512, and insulin autoantibodies), and HLA susceptibility genes (DR/DQ) in 131 patients with DKA (77 obese and 54 lean), 51 obese patients with hyperglycemia but no DKA, and 25 nondiabetic subjects. All subjects were African-American. β-cell function was evaluated by the C-peptide response to glucagon (1 mg i.v.) within 48 h of resolution of DKA or hyperglycemia.

RESULTS — The acute C-peptide response was lower in obese DKA patients (1.0 ± 0.1 ng/ml) than in obese patients with hyperglycemia (1.7 ± 0.2 ng/ml, $P < 0.01$), but was higher than that in lean DKA patients (0.2 ± 0.1 ng/ml, both $P < 0.01$). The overall prevalence of autoantibodies in obese subjects with DKA (17%) and obese subjects with hyperglycemia (16%) was lower than that in lean subjects with DKA (65%, $P < 0.01$). Obese patients with hyperglycemia and positive autoantibodies had lower rates of insulin secretion than those without antibodies. Regardless of body weight, all DKA patients with GAD autoantibodies carried the DQB1*0201 allele. However, there were no significant differences in HLA distribution between the three patient groups.

CONCLUSIONS — Our results indicate that most obese African-American patients with DKA have type 2 diabetes characterized by higher insulin secretion, the absence of autoimmune markers, and a lack of HLA genetic association. In contrast, most lean African-American patients with DKA have metabolic and immunological features of type 1 diabetes. At presentation, assessment of β-cell function and determination of autoimmune markers allow for correct classification of diabetes in African-Americans with hyperglycemic crises.

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Abbreviations: ANOVA, analysis of variance; DKA, diabetic ketoacidosis; IAA, insulin autoantibody; ICA, islet cell antibody; ICA152, protein tyrosine phosphate; JDF U, Juvenile Diabetes Foundation units; LADA, latent autoimmune diabetes of the adult.

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

Of African-American patients with newly diagnosed diabetes who present with diabetic ketoacidosis (DKA), 56% are obese (1). In contrast to the chronic insulin dependence of type 1 diabetes with DKA, most obese African-Americans with DKA exhibit the clinical course and metabolic features characteristic of type 2 diabetes (2–7). Basal and stimulated insulin secretion to glucose and nonglucose secretagogues in obese African-American patients with DKA have been reported to be intermediate between lean patients with a history of DKA and nondiabetic control subjects (2,5). We recently reported that improvement in metabolic control results in a marked increase in β-cell function and insulin sensitivity that is sufficient to allow discontinuation of insulin therapy in 72% of patients after a mean follow-up of 9 ± 1 weeks (5,7).

Limited information is available regarding the presence of immunological markers and HLA susceptibility genes for autoimmune pancreatic β-cell destruction in obese African-Americans with a history of DKA. Winter et al. (2) reported 12 young patients with episodic DKA who had negative insulin autoantibodies (IAAs) and islet cell antibodies (ICAs) and had no HLA association. More recently, Banerji et al. (3) reported that 21 patients with similar clinical features had negative autoimmune markers of type 1 diabetes but an increased frequency of HLA-DR3 or HLA-DR4. Because of the small number of patients in these studies and their conflicting results, the recent report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus of the American Diabetes Association classified these patients as having idiopathic type 1 diabetes (8).

To determine if obese African-American patients with DKA could be determined to have type 1 or type 2 diabetes based on insulin secretion or the presence of immunological and genetic markers, we conducted a prospective study in a large number of African-American patients presenting with acute hyperglycemic crises.

RESEARCH DESIGN AND METHODS

Study subjects

The study population included 131 patients with DKA (77 obese and 54 lean), 51 obese patients with severe hyperglycemia, and 25 nondiabetic obese subjects. All subjects were African-Americans, who are defined as black subjects born in the U.S. whose two biological black parents were also born in the U.S. Obesity was defined as BMI ≥28 kg/m^2. The diagnosis of DKA was established in the emergency department by a blood pH level of <7.30, a plasma glucose level of >13 mmol/l (250 mg/dl), a serum bicarbonate level of <15 mEq/l, and a positive serum acetoacetate test at a dilution of >1:4 or a serum β-hydroxybutyrate level of >3 mmol/l. Hyperglycemic patients were defined by a blood glucose level on admission of >25 mmol/l (450 mg/dl), a venous pH level of >7.3, a serum bicarbonate level of >18 mEq/l, and a negative serum acetoacetate test at a 1:2 dilution or a serum β-hydroxybutyrate level of <3 mmol/l.

Lean and obese patients with DKA and/or hyperglycemia were admitted for medical management and were treated with a low-dose insulin infusion protocol (9). Obese control subjects were studied as outpatients. All studies were conducted with informed consent at the Metabolic Unit of Grady Memorial Hospital with protocols approved by the Human Subjects Review Committee of Emory University School of Medicine. No subjects had evidence of acute diseases other than diabetes or obesity, and no subjects were taking drugs known to affect carbohydrate metabolism. All patients with obvious precipitating causes for the development of DKA (e.g., surgery, stress, infection, or trauma) were excluded.

Insulin secretion

Pancreatic insulin reserve was determined in all patients within 48 h after resolution of DKA or hyperglycemia by measuring the changes in C-peptide level after glucagon infusion. Patients received a 1 mg of i.v. glucagon, and serum was obtained for glucose and C-peptide levels at 0, 3, and 6 min. All patients were studied at ~8 h after an overnight fast. Serum was stored at −20°C for determination of glucose by the hexokinase method (Boehringer Mannheim/Hitachi 747-200 analyzer; Indianapolis, IN) and C-peptide by a double-antibody radioimmunoassay method (Incstar RIA Kit; Stillwater, MN).

Immunological studies

All diabetic and control subjects underwent testing for autoantibodies to islet cells (ICAs), insulin (IAAs), GAD, and protein tyrosine phosphate (ICA512) by using EDTA plasma stored at −80°C until analysis.

ICAs were measured by indirect immunofluorescence by using blood group O frozen human pancreas as previously described (10). The same pancreas was used throughout the study. Each assay required ~200 µl of serum. Samples were titrated in dilutions to determine the endpoint titer for conversion to Juvenile Diabetes Foundation units (JDF U) (9). Interassay standard deviation (coefficient of variation) was 16% at 27 JDF U. The lower limit of detection was 4 JDF U. The laboratory participates in ICA proficiency workshops.

Competitive IAAs were measured with a radiobinding assay by using acid-charcoal extraction and cold insulin displacement (11). The laboratory participates in proficiency workshops. The assay cutoff for positive samples was 0.79%, which was defined as the 99th percentile among 92 nondiabetic control subjects. Each test required 160 µl of serum.

Antibodies to radiolabeled recombinant human GAD65 were quantified by fluid-phase immunoprecipitation assay and scintillation counting as described (12). The assay threshold for positive samples was the mean + 3 SDs of 115 control sera. Each test required 4 µl of serum. The assay showed high sensitivity in an international workshop (13).

Autoantibodies to ICA512/IA2 (14) were measured by fluid-phase immunoprecipitation assay. The 1047-nucleotide cytoplasmic portion of ICA512 mRNA (corrected from the original published sequence [15] to include the full intracellular sequence) was amplified by reverse transcription–polymerase chain reaction from human glioblastoma line HTB-14 American Type Culture Collection (ATCC) integrated into the pcDNAII expression plasmid (Invitrogen, San Diego, CA). The antigen was translated in vitro with [^{35}S]methionine (Promega, Madison, WI). Immunoprecipitation assays used 4 µl of serum incubated in duplicate overnight at 4°C with radiolabeled antigen. After precipitation and washing, protein-A sepharose pellets underwent scintillation counting. The cutoff for positivity was the mean + 3SDs of 79 control sera. The polypeptide product was highly recognized by autoantibodies in 74.1% of 498 newly diagnosed diabetic children aged 0–15 years (12). In 70 additional type 1 diabetic sera, sensitivity was identical to that of the longer ICA512.bdc antigen construct (16). Assay sensitivity was 98.3% among 120 healthy control subjects. The assay was 98% specific and had 57% sensitivity in an international combined antibody workshop (13).

HLA typing

Genomic DNA was isolated from peripheral blood leukocytes by an automated extractor (Model 340A; Applied Biosystems, Foster City, CA). HLA class II typing was performed by a reverse dot-blot sequence-specific oligonucleotide method (17). The second exons of the DR, DQA1, and DQB1 were amplified by the polymerase chain reaction (18) and were labeled by the incorporation of digoxigenin-labeled dUTP (18).

Statistical analysis

Descriptive statistics including means, SEM, and ranges were used to characterize each of the four groups. Comparison of categorical measures (e.g., sex, family history, and presence of antibodies) between groups was carried out by using contingency table analyses. For categorical comparisons, χ^2 statistics or Fisher's exact test were used to assess significance. Comparisons of continuous measures (e.g., BMI, baseline β-cell function, and duration of symptoms) between groups were carried out with a one-way analysis of variance (ANOVA). Tukey's adjustment for pairwise comparisons were used to maintain a type I error of 0.05 for each variable assessed. Repeated measures ANOVA was used to compare changes in C-peptide levels after glucagon administration between groups, and adjustment of the type I error rate was made for pairwise comparisons. Use of all ANOVA techniques included evaluation of model assumptions. *P* values are unadjusted for the number of variables compared, but conclusions regarding associations are based on adjustment for multiplicity.

RESULTS

Study subjects

The clinical characteristics and metabolic parameters on admission are shown in Table 1. The obese DKA group (49 men and 28 women, mean age at diabetes onset

40 ± 2 years) had a mean BMI of 37 ± 1 kg/m^2 and included 64 (83%) newly diagnosed patients and 13 patients with a duration of diabetes of 1 ± 3 years. The obese patients with hyperglycemia (34 men and 17 women, mean age at onset 46 ± 2 years) had a mean BMI of 37 ± 1 kg/m^2 and included 40 (78%) newly diagnosed patients and 11 patients with a duration of diabetes of 6 ± 1 years. The lean DKA group (34 men and 20 women, mean age at onset 36 ± 2 years) had a mean BMI of 22 ± 1 kg/m^2 and included 15 (28%) newly diagnosed patients and 39 patients with a duration of diabetes of 8 ± 1 years. Nondiabetic control subjects (9 men and 16 women) had a mean BMI of 29 ± 2 kg/m^2.

All diabetic patients presented with moderate to severe symptoms of insulin deficiency (e.g., polyuria, polydipsia, and weight loss). The mean reported duration of symptoms in obese subjects with DKA (21 ± 3 days) was intermediate between lean patients with DKA (9 ± 1 days) and obese patients with hyperglycemia (29 ± 5 days). A family history of diabetes was more prevalent in the obese patients with DKA (82%) or hyperglycemia (74%) than in the lean patients with DKA (40%) ($P < 0.01$). Similarly, a family history of obesity was more common in obese subjects with DKA (84%) and obese subjects with hyperglycemia (78%) than in lean subjects with DKA (31%) ($P < 0.01$).

At presentation, obese patients with DKA had a mean plasma glucose level of 36 mmol/l (644 mg/dl), a mean serum bicarbonate level of 14 mEq/l, a mean venous pH level of 7.24, and a mean anion gap of 27 mEq/l. Obese hyperglycemic patients had similar plasma glucose levels (37 mmol/l) but lacked features of metabolic acidosis. Lean patients with DKA had a plasma glucose level of 37 mmol/l (662 mg/dl) but were more acidotic than the obese subjects with DKA, with a mean serum bicarbonate level of 12 mEq/l, a mean venous pH level of 7.18, and a mean anion gap of 26 mEq/l. Mean HbA_{1c} was >12% in all diabetic groups on admission. Nondiabetic control subjects had a mean plasma glucose level of 5.3 mmol/l and a mean HbA_{1c} level of 5.4 ± 0.1%.

Table 1—*Clinical characteristics of subjects on admission*

	Lean DKA	Obese DKA	Obese hyperglycemia	Control
n	54	77	51	25
Age (years)	36 ± 2	40 ± 2	46 ± 2	38 ± 2
Sex (M/F)	34/20	49/28	34/17	9/16
New-onset diabetes	15 (28)	64 (83)	40 (78)	—
BMI (kg/m^2)	22 ± 1	37 ± 1	37 ± 1	30 ± 2
Glucose (mmol/l)	36 ± 2	36 ± 2	37 ± 2	5 ± 1
Venous pH	7.18 ± 0.02	7.24 ± 0.01	7.4 ± 0.01	—
Bicarbonate (mEq/l)	12 ± 1	14 ± 1	22 ± 1	24 ± 2
HbA_{1c} (%)	13.0 ± 0.4	13.5 ± 0.4	12.4 ± 0.4	5.4 ± 0.1

Data are means ± SEM or *n* (%).

β-Cell function

As shown in Table 2, with a mean blood glucose level averaging ~11 mmol/l, basal and stimulated C-peptide levels in obese patients with DKA (1.5 and 2.5 ng/ml) were significantly greater than in lean patients with DKA (0.5 and 0.6 ng/ml, both $P < 0.01$) but were lower than in obese patients with hyperglycemia (1.8 and 3.5 ng/ml, both $P < 0.01$). Differences in the acute C-peptide response to glucagon (incremental changes in C-peptide over baseline levels) in the three diabetic groups were maintained when results were compared between patients with newly and previously diagnosed diabetes. In lean patients with DKA, the acute C-peptide response was 0.3 ± 0.1 ng/ml in newly diagnosed patients and 0.2 ± 0.03 ng/ml in previously diagnosed diabetic patients. In obese diabetic subjects, the acute C-peptide response in obese DKA was 1.1 ± 0.1 and 1.0 ± 0.1 ng/ml and in obese hyperglycemia, the acute C-peptide was 1.8 ± 0.2 and 1.7 ± 0.2 ng/ml in patients with newly and previously diagnosed diabetes, respectively. The acute C-peptide response to glucagon in nondiabetic control subjects (2.3 ng/ml) was higher than in all diabetic groups.

Frequency of autoantibodies

The prevalence of autoantibodies in obese and lean patients with DKA, obese hyperglycemic patients, and nondiabetic control subjects is compared in Fig. 1. Among 77 obese subjects with DKA, 10 (13%) were positive for ICA, 2 (3%) for GAD, 1 (1%) for ICA512, and 2 (3%) for IAA. Thirteen (17%) obese patients with DKA had one or more positive antibody tests. In obese patients with newly diagnosed diabetes, the prevalence of autoantibodies was similar to that of patients with previously diagnosed diabetes. Among newly diagnosed obese subjects, tests for ICA were positive in 12%, GAD in 3%, ICA512 in 4%, and IAA in 5%. The prevalence of autoantibodies in obese patients with hyperglycemia was similar to that in obese patients with DKA, with 16% of patients having one or more positive antibodies. The prevalence of positive antibodies in lean subjects with DKA was significantly higher than in obese patients with hyperglycemia or DKA. Among 54 lean subjects with DKA, 26 (48%) tested positive for ICA, 28 (52%) for GAD, 6 (11%) for ICA512, and 3 (20%) for IAA. The IAA data exclude 39 patients treated with insulin before admission because these are not interpretable as autoantibodies. Among lean patients with newly diagnosed diabetes, the prevalence of positive autoantibodies was similar to that for patients with previously diagnosed diabetes. ICA was detected in 48% of patients, GAD in 35%, ICA512 in 27%, and IAA in 27%. One obese nondiabetic control subject was positive for ICA but was negative for GAD, ICA512, and IAA. This subject had a normal fasting blood glucose level, an HbA_{1c} level of 5.4%, and a normal oral glucose tolerance test.

Table 2—*Pancreatic insulin reserve determined by glucagon-stimulated C-peptide*

	Lean DKA	Obese DKA	Obese hyperglycemia	Control
Basal C-peptide (ng/ml)	0.5 ± 0.1*	1.5 ± 0.1	1.8 ± 0.1	1.9 ± 0.1
Stimulated C-peptide	0.6 ± 0.1*	2.5 ± 0.1	3.5 ± 0.3*	4.2 ± 0.3*
Acute C-peptide response	0.2 ± 0.03*	1.0 ± 0.1	1.7 ± 0.2*	2.3 ± 0.2*

Data are means ± SEM. *$P < 0.01$ vs. obese DKA.

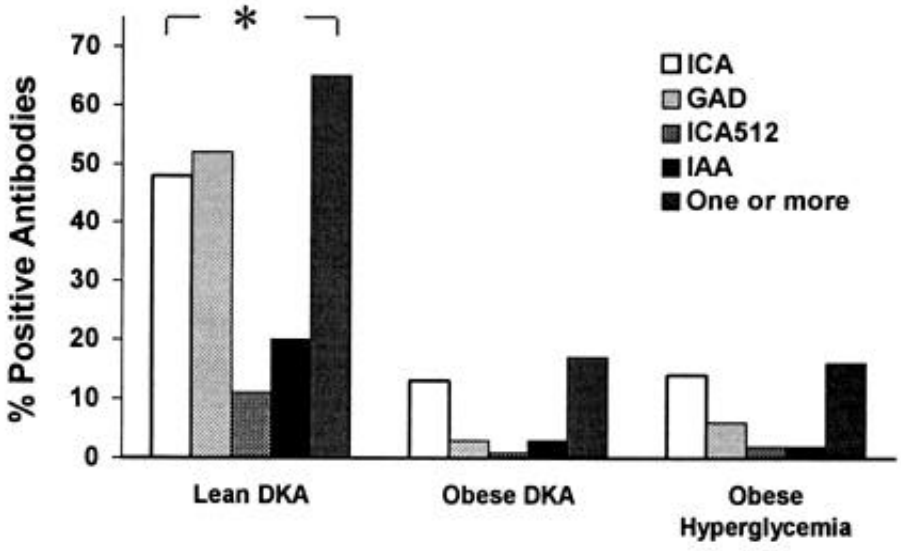

Figure 1—*Comparison of the prevalence of positive autoantibodies in 54 lean patients with DKA (lean DKA), 77 obese patients with DKA (obese DKA), and 51 obese patients with hyperglycemia (obese hyperglycemia). *P < 0.01 vs. obese DKA and obese hyperglycemia.*

Relationship of insulin secretion to autoantibody status

Correlation of the C-peptide response to glucagon and presence of autoantibodies (ICA, GAD, ICA512, and IAA) is shown in Fig. 2. Obese patients with DKA with or without autoantibodies have significantly higher insulin secretion than lean patients with DKA (both $P < 0.01$). However, in either DKA group, the mean C-peptide response was not significantly different between patients with or without antibodies. Thus, in patients with DKA, the presence of autoantibodies showed a minimal effect in predicting overall insulin secretion. In contrast, obese subjects with hyperglycemia and positive antibodies had only half of the insulin secretion of patients without antibodies. Although results did not reach statistical significance ($P = 0.06$), the acute C-peptide response to glucagon in obese hyperglycemic patients with positive antibodies (1.2 ± 0.2 ng/ml) was lower than in patients with negative autoantibodies (2.0 ± 0.2 ng/ml). Differences in C-peptide response in all diabetic groups were maintained, regardless of their antibody status, when results were compared between patients with newly and previously diagnosed diabetes.

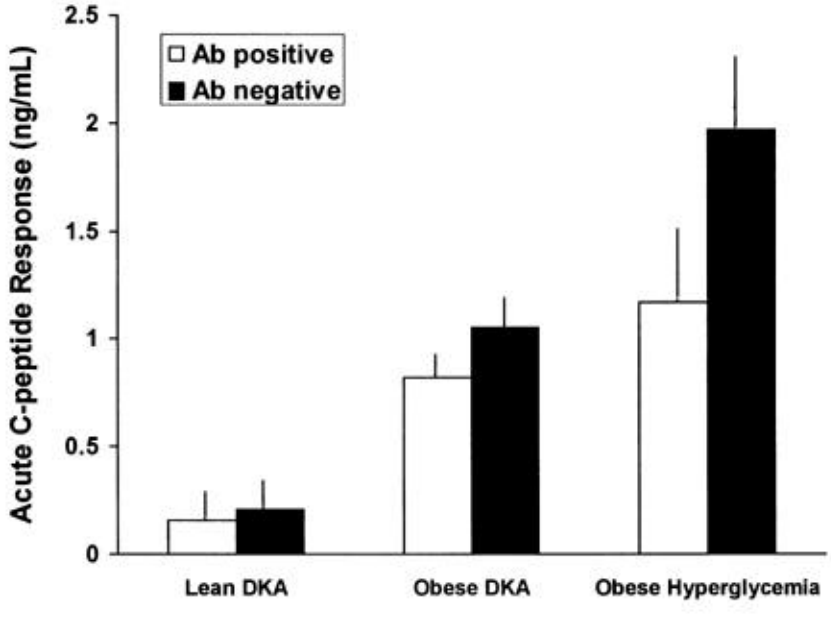

Figure 2—*Relationship of acute C-peptide response to glucagon and autoantibody status. Acute C-peptide response indicates incremental C-peptide changes in C-peptide over baseline levels. Studies were performed within 48 h after resolution of DKA and/or hyperglycemia. Values are means ± SEM. Ab, antibody.*

HLA-DR and HLA-DQ genotypes

Patients with DKA and/or hyperglycemia ($n = 65$) were genotyped at the HLA locus for DRB1, DQA1, and DQB1 alleles (Table 3). Results were compared with 42 African-American nondiabetic subjects. Of the lean patients with DKA, 39% were positive for the HLA-DRB1*03 or -*04 alleles commonly associated with type 1 diabetes of childhood onset (19). Interestingly, all lean patients with DKA with anti-GAD antibody responses carried the DQB1*0201 allele linked either to a DRB1*03, -*09, or -*07 allele at the DR locus. One patient in the obese DKA group with positive GAD antibodies also carried the DQB1*0201 allele. The DQB1*0602 allele, which has been described as protective of type 1 diabetes in Caucasians (20), was present in 20% of the lean and 25% of obese patients with DKA, although none of the patients with GAD antibodies carried this allele. There were no statistically significant differences in HLA distribution between the obese DKA, obese hyperglycemic, and lean DKA groups.

CONCLUSIONS — Of African-American patients admitted with DKA, 29% are obese, and the prevalence of obesity is even higher (56%) among those with newly diagnosed diabetes (1). Characteristically, these patients have diminished but measurable insulin secretion that is intermediate between secretion in nondiabetic control subjects and that in lean DKA patients (3,5). Despite presenting with DKA, several reports have indicated that, after a few months of insulin treatment, many obese African-American patients with a history of DKA achieve near-normoglycemic remission and remain in good metabolic control with diet and/or oral hypoglycemic agents (5–8). In clinical practice, correct classification of diabetes type at the time of diagnosis is often difficult but is clearly important in decisions regarding long-term management. In such populations, recognition of metabolic and immunological markers of type 1 diabetes will allow patients to remain on

insulin therapy because diet and oral pharmacological therapy are likely to fail (12). Furthermore, these markers will identify patients who may benefit from treatment with secretory and/or immune intervention (21) or low-dose insulin (22) that may preserve remaining β-cell function. In addition, many immunomodulatory therapies may be considered at this late stage of diabetes that may slow the progression of autoimmunity in adults (23,24) or improve the regenerative capacity of β-cells (25,26).

In this study, our aim was to determine if obese African-American patients with DKA could be determined to have type 1 or autoimmune diabetes versus type 2 or nonautoimmune diabetes on the basis of pancreatic insulin reserve and/or the presence of immunological and genetic markers. Our results indicate that most obese African-American patients with DKA have type 2 diabetes and that they differ from lean patients with DKA in that they have significantly higher pancreatic insulin reserves and a lower prevalence of autoantibodies. In addition, this study indicates that presentation with DKA is not a reliable marker to classify African-Americans by diabetes type.

The evaluation of β-cell function in patients with diabetes is difficult and is complicated by the effect of hyperglycemia on insulin secretion. Characteristically, patients with type 2 diabetes have blunted insulin release to oral or intravenous glucose tolerance tests in the presence of hyperglycemia (27–29), but the β-cells continue to respond to nonglucose secretagogues (e.g., glucagon, arginine, and β-adrenergic agonists) (28–30). Among nonglucose secretagogues, glucagon stimulation is most commonly used because this test is easy to use and provides a rapid and accurate determination of β-cell function in patients with recent episodes of hyperglycemia. We found that basal and stimulated C-peptide levels in obese patients with DKA were significantly greater than in lean patients with DKA but were lower than in obese patients with hyperglycemia. The lower C-peptide response to glucagon in obese patients with DKA versus obese patients with hyperglycemia suggests that lower insulin secretion in obese DKA leads to the development of ketoacidosis.

Type 1 diabetes is an autoimmune disease that was first described to be associated with ICAs and IAAs (31,32). More recently, antibodies to GAD and ICA512/IA2 have been detected in most patients before and at the onset of type 1 diabetes (16,33,34). ICA is found in 65–85%, GAD is found in 60–75%, and IAA is found in up to 50% of newly diagnosed children with type 1 diabetes (33–35). Immunological studies in children have found that ICA gradually disappears after the diagnosis of diabetes (19). In patients with adult-onset diabetes, GAD autoantibodies (GADab) are more prevalent than ICA512 (36), and in general, GADab remain positive for many years. Because several antigens contribute to ICA reactivity including GAD (37) and ICA512 (38), it is possible that, because of GAD reactivity, patients with onset of type 1 diabetes at an older age may not have the rapidly disappearing ICA observed in younger patients (19). In our study, we found a higher prevalence of autoimmune markers in lean patients with DKA (65%) than in obese patients with DKA (17%) and obese patients with hyperglycemia (16%) (both $P < 0.01$). These results indicate that most lean patients with DKA have type 1 or the autoimmune form of diabetes and that most obese patients with DKA and/or hyperglycemia have type 2 or the nonautoimmune form of diabetes.

The rate of β-cell destruction is quite variable in patients with type 1 diabetes. Although most young patients present with severe symptoms of insulin deficiency and DKA, some adults may retain residual β-cell function sufficient to prevent DKA for many years (39–41). Among obese patients with hyperglycemia, we found that those who were positive for ICA and/or GAD antibodies had lower insulin secretion than those without antibodies. These findings are consistent with previous reports (6,39,41). Niskanen et al. (39) and Tuomi et al. (42) reported that patients with apparent type 2 diabetes and antibodies to GAD and/or ICA had lower pancreatic insulin reserves determined by low C-peptide responses to glucagon. When these patients were divided based on their C-peptide response to glucagon, antibodies to ICA or GAD were detected in more than half of the insulin-deficient group but were present in only 12% of the non-insulin-dependent group. Although many of these patients with positive autoantibodies can be managed with oral antidiabetic agents, a 10-year prospective study (41) found that most patients will eventually develop features of insulin dependence as manifested by ketosis proneness and progressive β-cell failure. This form of type 1 diabetes has been

Table 3—*HLA class II alleles*

HLA II genotypes	Control	Lean DKA	Obese DKA	Obese hyperglycemia	χ^2	*P* value
n	42	21	19	15	—	—
DRB1 locus						
DRB1*15	38	33	21	27	0.577	0.902
DRB1*03	48	29	21	13	0.044	0.998
DRB1*0301	19	24	16	13	0.593	0.898
DRB1*04	10	29	21	7	0.155	0.984
DRB1*07	21	14	11	20	0.729	0.866
DRB1*other	52	71	74	80	0.143	0.986
DQA1 locus						
DQA1*01	76	76	84	100	0.198	0.978
DQA1*01	76	76	84	100	0.198	0.978
DQA1*0102	55	38	47	53	0.641	0.887
DQA1*02	24	10	16	20	0.569	0.904
DQA1*other	74	81	79	67	0.766	0.858
DQB1 locus						
DQB1*02	45	43	37	27	0.629	0.890
DQB1*03	38	62	58	53	0.251	0.969
DQB1*0301	31	29	37	40	0.867	0.833
DQB1*0302	7	10	16	0	0.409	0.938
DQB1*06	57	43	53	53	0.765	0.858
DQB1*0602	38	24	26	20	0.469	0.926
DQB1*other	41	43	37	47	0.947	0.814

Data are %. These selected genotypes are frequently reported to be associated with type 1 diabetes in Caucasian and African-American populations.

described in the literature as latent autoimmune diabetes of the adult (LADA) (37,42) or slowly progressive type 1 diabetes (40,41). Although this slow autoimmune form of type 1 diabetes has been reported in Europe (37,39,42,43), Japan (40,41), China (43), the U.S. (44), Saudi Arabia (45), and Thailand and Korea (46), it has not been previously reported in African-Americans. Thus, obese African-Americans with hyperglycemia and positive autoantibodies, many of whom will experience near-normoglycemic remission (5), may represent the African-American version of the slowly progressive form of type 1 diabetes described in other ethnic groups.

Limited and conflicting information is available regarding the prevalence of HLA susceptibility genes in African-Americans with hyperglycemic crises. Winter et al. (2) reported that the frequency of HLA-DR3 and HLA-DR4 antigens was not increased in 12 African-American youths with diabetes. In contrast, Banerji et al. (3) reported an increased frequency of HLA-DR3 or HLA-DR4 (65%) versus control subjects (30%) in 21 African-American patients with DKA. In this larger survey, no statistically significant HLA differences were found in the overall genotype distribution between the obese DKA, the obese hyperglycemia, and the lean DKA groups. Nevertheless, a strong association was found between anti-GAD antibodies and the HLA DQB1*0201 allele linked either to a DRB1*03, -*09, or -*07 allele at the DR locus, which suggests that the HLA genotype, particularly DQB1*0201, provides a fertile background for the penetration of the autoantibody phenotype, particularly in the lean DKA group. It was also of interest that the DQB1*0602 allele, described as protective for type 1 diabetes in childhood-onset Caucasian studies, was present at normal frequency in each of our DKA patient groups and was negatively associated with GAD antibodies. The lack of HLA genetic association could be related to the age at onset of diabetes in our patients because population studies (20) have suggested that the strong positive and negative HLA association with type 1 diabetes is evident in childhood onset and does not significantly correlate with late-onset disease.

We have determined that ~80% of obese African-American patients with DKA have type 2 diabetes characterized by higher insulin secretion, the absence of autoimmune markers, and a lack of HLA genetic association. In contrast, most lean African-American patients with DKA have clinical, metabolic, and immunological features of type 1 diabetes. At presentation, assessment of β-cell function and determination of autoimmune markers allow correct classification of diabetes type in obese African-Americans with hyperglycemic crises.

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