Original Articles

GAD Antibody Negative NIDDM in Adult Black Subjects With Diabetic Ketoacidosis and Increased Frequency of Human Leukocyte Antigen DR3 and DR4

Flatbush Diabetes

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The objective of this study is to understand the metabolic and immunologic basis of diabetes in adult blacks with diabetic ketoacidosis (DKA). Twenty-one black adults presenting with DKA ([mean ± SD] blood pH = 7.18 ± 0.09, plasma glucose = 693 ± 208 mg/dl, and positive serum ketones) had a subsequent clinical course of non-insulin-dependent diabetes mellitus (NIDDM). Human leukocyte antigens (HLAs) DR and DQ and antibodies to glutamic acid decarboxylase (GAD) and islet cell cytoplasmic proteins (ICP) were measured to assess autoimmunity. Insulin action was evaluated by the euglycemic insulin clamp, and insulin secretion was measured by C-peptide responses to oral glucose. Ketoacidosis was treated with insulin. Two subjects had a precipitating illness; four had a history of NIDDM. At the time of study, subjects' glycemic control was good (HbA_{1c} = 5.7 ± 1.6%). Nine subjects were treated with insulin, and 12 were on either sulfonylurea treatment or diet alone. Men (n = 12) were younger than women (n = 9) (40.8 ± 9.8 and 51.1 ± 6.3 years of age, respectively, $P < 0.05$) but similar in body mass index (27.8 ± 2.7 and 29.98 ± 4.1 kg/m^2, respectively). Antibodies to GAD and ICP were absent. All but one subject was insulin resistant compared with normal subjects (glucose disposal 3.56 ± 0.04 vs. 6.86 ± 0.02 mg·kg^{-1}·min^{-1}), and insulin secretion was lower. HLA DR3 and DR4 frequency was higher than in nondiabetic black control subjects (65 vs. 30%, $P < 0.012$). We conclude that black adults presenting with DKA have a subsequent clinical course and metabolic features (insulin resistance in the presence of good glycemic control and continued C-peptide response) characteristic of NIDDM. The absence of GAD or ICP antibodies makes β-cell autoimmune destruction unlikely. The increased frequency of HLA DR3 and DR4 suggests genetic components of insulin-dependent diabetes mellitus (IDDM) and NIDDM. *Diabetes* 43:741–745, 1994

The classification of diabetes into non-insulin-dependent diabetes mellitus (NIDDM) and insulin-dependent diabetes mellitus (IDDM), although usually useful, is clearly an oversimplification (1,2). Winter et al. (3) described atypical diabetes in black youths who presented with acute symptoms of insulin deficiency. Fajans (4) characterized maturity-onset diabetes of the young. Groop et al. (5) and Tuomi et al. (6) defined latent autoimmune diabetes in adults presenting with mild hyperglycemia and initially not requiring insulin treatment. The genetics of NIDDM are complex and may consist of many abnormalities (7,8).

We noted that many adult black patients presenting with severe diabetic ketoacidosis (DKA) have a subsequent clinical course typical of NIDDM. This study characterizes the pathophysiology involved and indicates that these subjects represent a further unique subset of NIDDM. Whether these subjects have the genetic components of both NIDDM and IDDM will require further study.

RESEARCH DESIGN AND METHODS

The study population consisted of a random selection of 21 black individuals who had presented with severe DKA that required hospitalization and treatment with insulin, intravenous fluids, and electrolytes. The diagnosis of DKA was defined as a blood pH ≤7.30 within the first 24 h with positive serum ketones (acetoacetate test). None had lactic acidosis or renal failure. The clinical characteristics and presentation are in Tables 1 and 2. Patients were studied between 4 and 120 months after the acute episode of DKA while in good glycemic control. Nine patients were on insulin, four were on sulfonylurea, and seven were on dietary treatment. Their weight had been stable for at least 2 months before the study. No patient had significant renal, hepatic, or cardiac disease, and none was using agents known to affect glucose metabolism.

The control population for insulin secretion consisted of 16 normal volunteers (13 black and 3 white) whose mean age ± SD was 43.75 ± 8.8 years. The control group for glucose disposal consisted of eight normal volunteers (five black, three white) whose mean age was 45 years (range 31 to 59 years) and whose body mass index (BMI) was 25.2 ± 3.0 kg/m^2. All subjects had consumed at least 150 g of carbohydrate for 3 days before any study.

The study was approved by the institutional review board of the State

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NIDDM, non-insulin-dependent diabetes mellitus; IDDM, insulin-dependent diabetes mellitus; DKA, diabetic ketoacidosis; BMI, body mass index; HLA, human leukocyte antigen; HGP, hepatic glucose production; ICP, islet cell cytoplasmic protein; ICA, islet cell cytoplasmic antibody; GAD, glutamic acid decarboxylase.

TABLE 1
Clinical characteristics of DKA-NIDDM subjects at time of study

	Men	Women
n	12	9
Positive family history	9	5
BMI (kg/m^2)	27.8 ± 2.75	29.98 ± 4.1
(range)	(24.2–31.9)	(20.2–33.8)
Age at presentation (years)	40.8 ± 9.76	51.11 ± 6.27*
Prior history of diabetes	2	2
HbA_{1c} (%)	5.6 ± 1.4	5.8 ± 1.7

Data are means ± SD. Normal HbA_{1c} is <4.9%. *$P < 0.05$.

University of New York, Health Science Center at Brooklyn. All patients signed an informed consent. Patients were studied at the Clinical Research Center.

Insulin secretion. A 75-g oral glucose tolerence test was done with blood samples obtained at 0, 30, 60, 90, and 120 min for plasma glucose and C-peptide determinations (double antibody radioimmunoassay with a lower limit detection of 0.7 ng/ml).

Insulin sensitivity. Insulin sensitivity was measured using the euglycemic hyperinsulinemic clamp and a D-[3-^{3}H]glucose infusion (9) as described previously by us (10,11). Glucose was clamped at 100 mg/dl, and, therefore, urinary glucose loss was not present. Patients were studied in the basal state and at insulin infusion rates of 1.0 mU · kg^{-1} · min^{-1} for 120 min. The latter dose measured overall glucose disposal and defined in vivo insulin sensitivity primarily at the level of muscle. The rates of glucose appearance and overall glucose disappearance were measured during the basal and insulin-infused states by infusing D-[3-^{3}H]glucose in a primed continuous manner. Steele's equations for non-steady-state kinetics were used to determine rates of appearance and disappearance (12).

The glucose disposal is the sum of exogenously administered glucose and hepatic glucose production (HGP). The isotopic determination of glucose kinetics sometimes resulted in an underestimation of the R_D during hyperglycemia, as evidenced by negative values for HGP (13). When this occurred, HGP was considered to be completely suppressed and the glucose disposal rate was assumed to be the steady-state glucose infusion rate.

Immunologic studies. Islet cell cytoplasmic antibodies (ICA) were measured by G. Eisenbarth and R. Jackson with Wistar-Furth rat pancreas as a substrate, an anti-islet monoclonal antibody (A2 B5) to identify islets, and fluorescein-conjugated protein A to identify patient autoantibodies (14).

Glutamic acid decarboxylase (GAD) antibodies were determined using a radioimmunoprecipitation assay as described previously (6,15). Affinity purified porcine brain GAD that was enzymatically active, containing both the 67,000 and 65,000 M_r isoforms, was iodinated with ^{125}I. After preabsorption with pooled normal sera, 100,000 counts/min of ^{125}I-labeled GAD was incubated overnight with test sera that was diluted 1:2 in Tris-triton buffer (0.02 M Tris, 0.15 M NaCl, 5% wt/vol Triton X-100, ph 7.4). Protein A-Sepharose was used to precipitate the ^{125}I-GAD-antibody complex. The results were expressed as units = counts of radioactivity precipitated by the test sera divided by that of the reference serum (which was defined as having 100 U). Positivity was defined as the mean ± 3 SD for blood donor sera that were tested concurrently.

HLA typing. HLA phenotyping for class II antigens was performed on B-cells using standard serological methods with an eosin dye exclusion microcytotoxicity assay and commercial typing trays (16,17), as described previously by us (18).

Statistical analysis. Glucose and C-peptide response to oral glucose was calculated as the area under the curve by trapezoidal estimation. Data are expressed as means ± SE unless otherwise stated. Differences in HLA allele frequencies between normal control subjects and the diabetic group were analyzed using the χ^2 test or Fisher's exact test. Where the HLA antigens to be tested were identified a priori (HLA DR2, DR3, and DR4), a Yates correction was not used and $P < 0.05$ was considered statistically significant.

RESULTS

Clinical characteristics and course. The 21 patients studied consisted of 12 men and 9 women (Table 1). The men developed DKA at a significantly younger age than did the women (40.8 ± 9.76 and 51.1 ± 6.27, $P < 0.05$) and tended to be less obese than the women, although neither group was markedly obese. Three-quarters of the men and more than half of the women had a positive family history of diabetes.

TABLE 2
Clinical presentation of diabetic ketoacidosis

Patient number	Age (years)	Sex	Blood pH	Plasma glucose (mg/dl)	Ketones serum
1	40	M	7.23	660	Large
2	36	M	7.16	612	Large
3	45	M	7.28	830	Large
4	34	M	7.28	612	Small
5	42	F	7.11	814	1:16
6	57	F	7.22	558	Large
7	32	M	6.94	1,126	Large
8	51	F	7.30	826	1:16
9	38	M	7.18	388	1:32
10	45	F	7.03	608	1:8
11	35	M	7.22	330	Large
12	51	F	7.10	899	Large
13	40	M	7.28	756	Mod
14	59	F	7.12	900	Large
15	54	F	7.09	464	Large
16	49	F	7.24	400	—
17	56	M	7.19	719	Large
18	42	M	7.20	911	Large
19	58	F	7.24	925	Mod
20	27	M	7.25	711	Large
21	59	M	7.21	506	Large
X ± SD	45.2 ± 9		7.18 ± 0.9	693 ± 208	

On admission, the patients were severely acidotic (Table 2), with a mean blood pH ± SD of 7.18 ± 0.09 (range 6.94–7.3). Serum ketones were positive for acetoacetate in all patients and ranged from small to large. The mean serum glucose ± SD was 693 ± 208 mg/dl and ranged from 333 to 1,126 mg/dl. A prior history of NIDDM was present in 4 of 21 patients. (Patients 5, 7, 10, and 17 had diabetes for 11, 5, 0.09, and 0.33 years, respectively, and had been treated with

TABLE 3
Clinical course

Patient number	Treatment at time of study	Interval from DKA to study (months)	Duration of initial insulin treatment (months)
1	Insulin	5	5
2	Insulin	4	4
5	Insulin	50	50*
6	Insulin	46	46
7	Insulin	48	48*
16	Insulin	120	120
17	Insulin	3	3*
18	Insulin	5	5
20	Insulin	8	8
3	Sulfonylureas	34	2
4	Sulfonylureas	12	1
13	Sulfonylureas	7	6
15	Sulfonylureas	84	1
19	Sulfonylureas	14	6
21	Sulfonylureas	4	1
8	Diet	7	5
9	Diet	48	14
10	Diet	24	14*
11	Diet	18	15
12	Diet	8	4
14	Diet	17	4

*Patients with a prior history of diabetes.

sulfonylureas alone, sulfonylureas for 4 years and insulin for 1 year, insulin alone, and no treatment, respectively.) Sepsis was the only identifiable precipitating illness and occurred in two subjects (patients 5 and 10). The onset of DKA appeared to be spontaneous in the remaining 19 patients. Table 3 shows the clinical course of these patients after their presentation with DKA. Initial treatment of all patients included insulin, with subsequent insulin treatment varying from 4 weeks to 120 months. However, at the time of study, less than half (9 of 21 patients) were on insulin, and 6 of 21 were on oral sulfonylurea hypoglycemic agents. Six patients were on diet treatment alone with near-normal fasting plasma glucose and glycosylated hemoglobin. No relationship was noted between the duration of diabetes and type of treatment. The interval from the time of DKA to the time of metabolic studies varied from 3 to 120 months.

Insulin secretion. Mean ± SD fasting plasma glucose at the time of study was 124 ± 30 mg/dl. For the subset on diet alone, the fasting plasma glucose was 113 ± 5 mg/dl. The mean ± SD of the glucose area in response to oral glucose, shown on Table 4, was significantly higher in the DKA-NIDDM subjects than in the nondiabetic normal control subjects (24,778 ± 6,382 and 15,002 ± 2,295 mg · dl^{-1} · min^{-1}, $P < 0.001$). The C-peptide area in response to oral glucose was significantly lower in the DKA-NIDDM subjects than in control subjects (393 ± 268 and 513 ± 120 ng · ml^{-1} · min^{-1}, $P < 0.025$). The maximal C-peptide response in this group was also lower compared with the normal control subjects (4.6 ± 3.4 and 6.1 ± 1.4 ng/ml, $P < 0.014$). The fasting plasma C-peptide levels were similar in the two groups (1.7 ± 1.04 and 1.5 ± 0.52 ng/ml). Individuals with C-peptide responses below 2 SD of the mean of normal control subjects (i.e., <273 ng · ml^{-1} · min^{-1}) were markedly insulin deficient, and all eight were on insulin therapy; only one of the remaining subjects with a C-peptide response in the normal range was on insulin treatment.

Insulin action. Glucose disposal in response to a 1 mU · kg^{-1} · min^{-1} insulin infusion was studied while patients were under good glycemic control, as shown by a mean HbA_{1c} ± SD of 5.7 ± 1.6% (normal ≤4.9%, by high-performance liquid chromatography). Table 5 shows that the DKA-NIDDM subjects had significantly lower insulin-mediated glucose disposal compared with nondiabetic control subjects (mean glucose disposal ± SE = 3.56 ± 0.04 and 6.88 ± 0.02 mg · kg^{-1} · min^{-1}, $P < 0.001$). The BMI of the DKA-NIDDM subjects ranged from 20.2 to 33.3 kg/m^2. All but one subject were insulin-resistant (glucose disposal <5.5 mg · kg^{-1} · min^{-1}). This subject had a BMI of 20.2 kg/m^2 and a glucose disposal of 5.8 mg · kg^{-1} · min^{-1}.

GAD and IC antibodies. No patients were positive for ICA and all were negative for GAD antibodies except one (no. 16), who was borderline positive.

HLA studies. HLA DR and DQ typing showed that the DKA-NIDDM subjects had a significantly greater frequency of HLA DR4 compared with nondiabetic black control (n = 89) subjects (25 vs. 5.6%, $P < 0.0067$). No subject was homozygous for HLA DR3 or DR4, and none had both DR3 and DR4. The frequency of subjects with either HLA DR3 or DR4 was significantly greater than for nondiabetic black control subjects (65.0 vs. 30.3%, $P < 0.012$); no other differences were noted in HLA DR antigen frequencies, including HLA DR2 (10 vs. 15.7%, respectively). Because of the small numbers of patients, there were no meaningful HLA DR-DQ associations. HLA DQw1 antigen frequency was significantly lower in these subjects than in control subjects (0 vs. 35.96%, $P < 0.001$ without and $P < 0.02$ with a Yates correction). A similar low HLA DQw1 antigen frequency was noted in our ordinary NIDDM subjects who present without DKA (18). No other significant differences in antigen frequency in HLA DQw2, DQw3, DQw4, DQw6, and DQw7 were seen between patients and control subjects (30 vs. 34.8%, 5 vs. 16.85%, 0 vs. 4.5%, 60 vs. 39.3%, and 45 vs. 31.46%, respectively). Because HLA DQw7, 8, and 9 are splits of DQw3, a positive DQw3 (negative for DQw7) represents either DQw8 or DQw9. The HLA DR and DQ antigen frequencies and their associations with our normal nondiabetic black control population have been previously reported and are not different from those reported in the literature (18).

DISCUSSION

This study describes adult black subjects who presented with severe symptoms of insulin deficiency and ketoacidosis that initially suggested the diagnosis of IDDM. Their subsequent clinical course and metabolic features (insulin resistance and presence of insulin secretion) were typical of NIDDM, as was the absence of GAD antibodies and ICAs. An increased frequency of HLA DR3 and DR4, typical of IDDM, suggested that these subjects may possess the genotypic features of both NIDDM and IDDM.

We have been unable to find a report that describes the relative frequency of IDDM versus NIDDM in the subsequent clinical and metabolic course of adults presenting with DKA. DKA is considered to be a cardinal feature of IDDM or type I diabetes and implies an absolute insulin deficiency with an immunopathological etiology. Little is known about the prevalence of IDDM among black compared with white adults, although IDDM frequency in black children is one-half to one-fourth that of white children (19). IDDM is less prevalent among African blacks than American blacks, which is attributed to American blacks' genetic admixture with whites (20,21). IDDM is characterized by a variety of immune markers directed against the β-cell, including ICA and GAD antibody (22). These markers may be identified years before and after the development of clinical disease

TABLE 4
C-peptide response to 75 g of oral glucose in DKA and control subjects

	n	Fasting C-peptide (ng/ml)	Maximum C-peptide (ng/ml)	C-peptide area 0–120 min (ng · ml^{-1} · min^{-1})	Glucose area 0–120 min (mg · dl^{-1} · min^{-1})	Fasting plasma glucose (mg/dl)
DKA-NIDDM patients	21	1.7 ± 1.04	4.6 ± 3.4*	393.2 ± 268.2†	24,778 ± 6,382‡	124 ± 30‡
Control subjects	16	1.5 ± 0.5	6.11 ± 1.44	513.0 ± 120.0	15,002 ± 2,295	94 ± 30

Data are means ± SD. For DKA-NIDDM patients vs. control subjects: *$P = 0.0136$; †$P = 0.0248$; ‡$P < 0.001$ by Wilcoxon's two-sample test.

TABLE 5
Glucose disposal in response to 1 mU · kg^{-1} · min^{-1} insulin infusion in DKA-NIDDM and control subjects

	n	Glucose disposal (mg · kg^{-1} · min^{-1})	BMI (kg/m^2)	Basal plasma glucose (mg/dl)
DKA-NIDDM patients	20	3.53 ± 0.4*	28.5 ± 0.8	107 ± 5.0
Control subjects	9	7.59 ± 0.3	25.2 ± 1.0	101 ± 3.0

Data are means ± SE. *P < 0.001 DKA-NIDDM patients vs. control subjects.

and can be used to identify immunologically mediated diabetes (IDDM versus NIDDM), regardless of their clinical presentation and age of presentation (6). The black adults presenting with DKA did not have ICA or GAD antibodies, which suggests that, despite the severely insulin-deficient state in which they presented, they are unlikely to have the latent immune form of diabetes described in Finnish adults (6). The absence of GAD antibody is unlikely to be because of the absence of residual pancreatic antigen or to a long duration after the onset of disease, because measurements of GAD antibodies were made within a year of presentation in half the patients (10 of 21) and most had adequate functioning pancreatic β-cells, based on their C-peptide response. In classic childhood IDDM, there is a lower prevalence of ICA in blacks than in whites (23). Alternatively, these subjects could have antibodies to other, unmeasured islet antigens.

Among black adults, the predominant form of diabetes is NIDDM, and our DKA subjects appear to be a subset of NIDDM. Among black youths, a similar atypical, severely insulin-deficient presentation of NIDDM has been described by Winter et al (3). It is characterized by acute onset, (some with ketosis) but with subsequent residual insulin secretion, lack of dependence on exogenous insulin, and absence of ICAs or HLA markers of IDDM. Indirect studies of insulin binding suggested insulin resistance. Our subjects appear to have similar features in presentation, clinical course, residual insulin secretion, insulin resistance, and absence of ICA and GAD antibody, but they differed in several ways: all had ketoacidosis, many were older, and there was an increased frequency of HLA DR3 and DR4. A tendency toward ketosis has also been described among obese adult NIDDM subjects with marked insulin deficiency who developed ketonuria or ketoacidosis on withdrawal of insulin treatment; unfortunately, the race of the subjects was not specified (24).

NIDDM among blacks in the United States and in South Africa may be characterized by insulin deficiency with or without insulin resistance (10,25–28). In the nonobese BMI range of 24.5–28.5 kg/m^2 (Table 6), ordinary diabetic subjects have a bimodal distribution of insulin action, with half the patients being normally insulin-sensitive and the other half insulin-resistant. This distribution is significantly different in the DKA subjects, all of whom were insulin-resistant. At a BMI >28.5 kg/m^2, insulin resistance was present equally in both groups. One could speculate that ketosis developed in these subjects because the marked insulin resistance created a relatively greater degree of insulin deficiency. These data in blacks are in contrast to those in whites, where NIDDM has been reported to be primarily of the insulin-resistant type, and IDDM has been reported as having variable insulin-mediated glucose disposal (29–32).

TABLE 6
Insulin resistance and BMI in black individuals with DKA-NIDDM and ordinary non-DKA NIDDM subjects

BMI (kg/m^2)	DKA-NIDDM patients (number with insulin resistance/total)	Ordinary non-DKA NIDDM subjects (number with insulin resistance/total)
<24.5	0/1	1/8
24.5–28.5	8/8*	10/22
>28.5	11/11	8/9

*P < 0.01 DKA vs. ordinary non-DKA NIDDM subjects.

Yki-Jarvinen and Koivisto (29) showed that insulin-mediated glucose disposal was normal in two-thirds of the IDDM subjects studied between 3 months and 11 years after onset and in one-half the subjects studied between 11–20 years. Subjects who were in remission with near-normal glycemic control had normal insulin sensitivity. Thus, in true IDDM, without chronic hyperglycemia, insulin-mediated glucose disposal is not a fundamental defect (32). This characteristic contrasts with our DKA patients, in whom insulin action is clearly abnormal and distinguishes them from IDDM.

Insulin secretion in our DKA-NIDDM subjects was lower than the normal control group and black insulin-resistant non-DKA NIDDM subjects (28). This suggests that the marked but temporary insulin deficiency in conjunction with the insulin resistance may be the cause of ketoacidosis.

IDDM has been associated with an increased frequency of HLA DR3 and DR4, a decreased frequency of DR2, an association with HLA DQw8, and an aspartate substitution on the β-chain (33). Our patients have an increased frequency of HLA DR3 and DR4 without a decrease in HLA DR2 frequency compared with a nondiabetic black control population. HLA DQw8 has been reported to be associated with IDDM in Caribbean blacks (34); however, it is unlikely that HLA DQw8 would be increased in our patients considering we did not find any increase in frequency of HLA DQw3. Thus, our DKA-NIDDM subjects have an HLA profile that is similar but not identical to that of typical IDDM. Because the DKA-NIDDM subjects have features of both NIDDM and IDDM, it could be speculated that they may have the gene(s) for both disorders.

In our urban hospital, there are ~150 cases/year of adult DKA, largely among black subjects. This phenomenon is well known to the house staff, who refer to this etiological hybrid as "Flat-bush Diabetes" after the neighborhood surrounding the hospital. The annual incidence is not known. We studied a subset who was willing to undergo investigations; thus, this is not a population-based study. The majority of our subjects (80%) were newly diagnosed when they presented with DKA and did not have identifiable precipitating factors. Twenty percent (n = 4) were previously known to have diabetes and in half of those patients (2 of 4), a precipitating factor was identified (sepsis). This finding contrasts a white population-based study of DKA by Faich et al. (35), in which 80% were previously diagnosed diabetic subjects in whom two-thirds to three-fourths had an identifiable precipitating event (noncompliance and infection). The annual incidence was 46 of 10,000.

Similar data were reported in a non-population–based study of whites from England (36). Although 46% of the DKA subjects were adults (>44 years of age), Faich et al. (35) did not speculate on which type of diabetes this might represent.

We have described a unique form of diabetes among black adults whose new onset of diabetes presents with severe DKA and whose subsequent clinical course is that of NIDDM. The patients are resistant to insulin-mediated glucose disposal, have significant residual C-peptide secretory capacity, and do not have GAD antibodies or ICA. Many are obese and have positive family histories of diabetes. Interestingly, there is an increased frequency of HLA DR3 and DR4 antigens, which is typical of IDDM.

In conclusion, when DKA presents in adult black patients, the subsequent clinical course is likely to be that of NIDDM, and the pathogenesis is likely to be that of insulin-resistant NIDDM. Despite an HLA antigen profile compatible with IDDM, the associated autoimmune phenomena appear to be absent.

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