Clinical Characteristics of IDDM in Hispanics and Non-Hispanic Whites

Little evidence of heterogeneity by ethnicity

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OBJECTIVE — To compare the clinical characteristics of IDDM in HD and NHWD subjects in order to evaluate potential heterogeneity of IDDM by ethnicity.

RESEARCH DESIGN AND METHODS — HD subjects (n = 73) and NHWD subjects (n = 97) were recruited from the Colorado IDDM Registry. The registry included individuals who were Colorado residents, <18 yr old at diagnosis, placed on insulin within 2 wk of diagnosis, and had diabetes not secondary to other conditions. Residual β-cell function was measured as the 1-h C-peptide response to a Sustacal challenge.

RESULTS — HD subjects were similar to NHWD subjects in insulin dose, HbA_1, HLA-DR antigens, ICAs, and family history of IDDM. HD subjects were more likely to have a family history of NIDDM than NHWD subjects (11 vs. 3%, P = 0.03). HD girls had higher C-peptide levels (0.27 vs. 0.11 nm/L [0.83 vs. 0.33 ng/ml], P = 0.01), BMI (22.7 vs. 20.9 kg/m^2 P = 0.04), subscapular skinfold thickness (18.9 vs. 15.0 mm, P = 0.04), and WHR (0.81 vs. 0.77, P = 0.03) than NHWD females. After controlling for diabetes duration, BMI, sex, and family history of NIDDM, residual β-cell function was associated significantly with Hispanic ethnicity, although the term accounted for just 3% of the overall variability in C-peptide levels.

CONCLUSIONS — Little evidence of heterogeneity by ethnicity of IDDM patients in the Colorado IDDM Registry was found. Ethnic differences in C-peptide levels may be related to differences in body fat distribution in females rather than heterogeneity of the disease.

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IDDM, INSULIN-DEPENDENT DIABETES MELLITUS; HD SUBJECT, HISPANIC DIABETIC SUBJECT; NHWD SUBJECT, NON-HISPANIC WHITE DIABETIC SUBJECT; HLA, HUMAN LEUKOCYTE ANTIGEN; ICA, ISLET CELL ANTIBODY; NIDDM, NON-INSULIN-DEPENDENT DIABETES MELLITUS; BMI, BODY MASS INDEX; WHR, WAIST-TO-HIP RATIO; JDF U, JUVENILE DIABETES FOUNDATION UNIT; SAS, STATISTICAL ANALYSIS SOFTWARE; MODY, MATURITY-ONSET DIABETES IN THE YOUNG.

Clinical and metabolic studies of IDDM in the US black population have detected heterogeneity in the expression of diabetes, which has been attributed to the misclassification of early-onset NIDDM as IDDM in some cases (1). The increased prevalence of NIDDM in US blacks compared with US whites (2) may contribute to classification errors. Hispanic Americans also have an increased incidence (3) and prevalence (4) of NIDDM compared with non-Hispanic whites. However, because no studies characterizing IDDM in the Hispanic population have been conducted, it is unknown whether diabetes heterogeneity, similar to that seen in blacks, occurs in Hispanic Americans. Our initial report on ethnic differences in IDDM incidence in Colorado demonstrated that Hispanics had a lower incidence compared with non-Hispanics (5). Although this relationship was true for Hispanic and non-Hispanic boys of all ages (0–17 yr), Hispanic girls had an IDDM incidence nearly identical to that in non-Hispanic females in the older age range (10–17 yr). This suggested that a possible misclassification of early-onset NIDDM as IDDM in Hispanic girls may have been elevating incidence rates artificially in this age-group. Markers of clinical care, such as severity and age at diagnosis, hospitalization, ketoacidosis, and insulin reaction incidence, also were examined in that report, and no significant differences between HD and NHWD individuals were found. However, these characteristics were insufficient to determine if diabetes heterogeneity existed at the metabolic or the genetic level.

In this report, we present the results of a detailed substudy on ethnic differences in IDDM among subjects in the Colorado IDDM Registry. To evaluate more fully the potential heterogeneity of diabetes by ethnicity, we compared measures of diabetes control, insulin secretion, body fat distribution, genetic markers of IDDM, and family history of diabetes in HD and NHWD subjects.

Table 1—*Characteristics of patients with IDDM by ethnicity and participation status*

	Hispanic			Non-Hispanic white		
	Full participant	Questionnaires only	Nonparticipant	Full participant	Questionnaires only	Nonparticipant
N	62	13	43	82	17	23
Mean age (yr)	17.0	17.6	19.0	16.9	15.8	17.4
Mean age at diagnosis (yr)	9.4	10.4	10.5	9.4	7.0	9.0
Mean duration of IDDM (yr)	7.1	6.8	8.2	7.0	8.4	7.9
Boys/Girls (%)	41.9/58.1	53.8/46.2	30.2/69.8	43.9/46.1	35.3/64.7	52.2/47.8

Comparisons yielded no significant differences.

RESEARCH DESIGN AND METHODS

Study population

The study population was recruited from the Colorado IDDM Registry, which has been described previously (6). Eligibility criteria for inclusion in the registry were: *1*) diagnosis of IDDM between 1978 and 1988, *2*) residence in Colorado at the time of diagnosis, *3*) <18 yr old at diagnosis, *4*) placement on insulin within 2 wk of diagnosis, and *5*) diabetes not secondary to other conditions. All living registry subjects who reported Hispanic origin (n = 118) were eligible for the Ethnic Differences in IDDM Study. A similar size random sample of diabetic subjects who reported being non-Hispanic white (n = 122) also was selected for recruitment from a pool of 784 registry subjects. A total of 99 NHWD and 75 HD subjects were recruited into the study. A comparison of the characteristics of participants and nonparticipants is presented in Table 1. Full participants were those who completed a questionnaire and had either attended a study clinic or provided a blood sample. Partial participants provided questionnaire information only. We found no significant differences in age, duration of IDDM, age at diagnosis of diabetes, or sex by participation status for either ethnic group. Two multiple case families, each of which had two diabetic siblings, participated in the study; however, because of the familial nature of some of the characteristics, only one diabetic subject per family was used in the analyses presented in this study. Also, two subjects who were pregnant at the time of the study were excluded. Therefore, 73 HD and 97 NHWD subjects were included in these analyses.

Data collection

Questionnaire data on diabetes, medical history, and family history of diabetes were collected. First-degree relatives (parents and siblings) were classified as having IDDM if they were insulin-requiring diabetic individuals and <35 yr old at diagnosis. Insulin-taking diabetic relatives who were diagnosed at ≥35 yr were classified as NIDDM, as were diabetic relatives who did not require insulin. Adopted participants (n = 8) were not included in these comparisons.

Participants were seen for the examination at one of several locations, including the University Hospital, The Barbara Davis Center for Childhood Diabetes (Denver, CO), field clinics held at local hospitals and in outlying areas; or some were visited at their homes. Most subjects (n = 124) attended the clinic, at which height, weight, waist and hip circumference, skinfold thickness, HbA_1, HLA, ICAs, and insulin secretion were measured. Another 15 subjects sent in blood samples for HLA and ICA analyses. HbA_1 levels were determined by the column chromatography method (Quik-Step Fast Hemoglobin Test System, Isolab, Akron, OH). HLA-DR serological typing was performed using commercially available trays (One Lambda, Los Angeles, CA), after separating B-cells by nylon wool columns (7). The presence of ICAs was determined by indirect immunofluorescence (8) and defined by ≥10 JDF U. Waist circumference was measured at the midpoint between the highest point of the iliac crest and lowest part of the costal margin in the midaxillary line. Hip circumference was measured at the level of the greater femoral trochanter. The following definitions were used: BMI as weight/height (kg/m^2), and WHR as waist circumference/hip circumference (mm/mm).

Stimulated C-peptide measurements were done on subjects who had fasted ≥9.5 h before the clinic visit (n = 88). Residual β-cell function was measured as the C-peptide peak response to a challenge with 7 kcal/kg Sustacal (14 g/dl carbohydrate, 24 g/dl fat, and 6.1 g/dl protein, 1 kcal/ml; Mead Johnson, Belleville, Ontario, Canada). Serum C-peptide was measured by competitive radioimmunoassay (9). The subjects whose blood was drawn either before or after the recommended 60 ± 5-min postchallenge measurement (n = 12), had reported an illness within the past 8 wk (n = 28), had smoked or consumed alcohol less than 24 h beforehand (n = 7), used medication

(n = 19), or had liver, kidney, or thyroid disease (n = 4) were included in the C-peptide analysis after it was determined that they did not bias the sample. This was done by running the univariate analyses with and without the aforementioned individuals and observing that the results did not differ. In addition, a term that distinguished between those with and those without the aforementioned problems was added to the regression model of C-peptide; and it was not significant (data not shown).

Table 2—*Descriptive characteristics of study population by ethnicity*

	Hispanic		Non-Hispanic white	
	N	Value	N	Value
Current age (yr)	73	16.2 ± 5.2	97	16.0 ± 5.7
IDDM duration (yr)	73	6.3 ± 3.3	97	6.5 ± 2.9
Age at diagnosis (yr)	73	10.0 ± 4.1	97	9.5 ± 4.2
Sex of subject (B/G)(%)	73	44/56	97	42/58
Maternal education (%)*†	71	30	94	4§
Paternal education (%)*†	65	32	91	5§
Family income (%)†§	64	56	87	23§

Values are means ± SD or %.
* <12 yr of school.
† It was not mandatory that subjects provide this information—thus, the difference in number of subjects for these characteristics.
‡ <$20,000/yr.
§ $P < 0.0001$.

Statistical analyses

Full and partial participants were used in the analyses. Participants with missing questionnaires or clinical data were excluded only from the comparisons for which they were missing data. The effective sample sizes (n) for each comparison are listed in the tables. Continuous variables were analyzed with the SAS System procedure GLM in order to adjust for attained age (BMI, WHR, and subscapular skinfold) or diabetes duration (insulin dose, HbA_1, and C-peptide). Categorical variables were analyzed with the χ^2 statistic and the SAS procedure LOGISTIC to control for IDDM duration (ICA), or family size and current maternal age (family history of diabetes). Multiple linear regression analysis was used to examine the relationship between selected characteristics and C-peptide levels. In the regression analysis, diabetes duration was $\log_{10}$ transformed to achieve linearity.

RESULTS — Current age, diabetes duration, and age at diagnosis of diabetes were similar by ethnicity overall (Table 2) and after stratification by sex (data not shown). Both HD and NHWD subject groups had more girls than boys. A larger proportion of the parents of HD subjects did not finish high school compared with parents of NHWD subjects. HD families also were more likely to have an annual income <$20,000. The current age of the subject's mother, which was used as a marker for the age of the family, did not differ in HD and NHWD subjects (41.1 vs. 42.0 yr, respectively).

Duration-adjusted insulin dose and HbA_1 did not differ by ethnic group in boys and girls (Table 3). Mean stimulated C-peptide level was higher in HD girls compared with NHWD girls, after adjusting for duration of diabetes (0.27 vs. 0.11 nM/L [0.83 vs. 0.33 ng/ml], $P = 0.01$). Stimulated C-peptide levels in boys did not differ by ethnic group. HD girls also had a greater age-adjusted BMI (22.7 vs. 20.9 kg/m^2, $P = 0.04$), subscapular skinfold thickness (18.9 vs. 15.0 mm, $P = 0.04$), and WHR (0.81 vs. 0.77 mm/mm, $P = 0.03$) than NHWD girls. BMI, subscapular skinfold thickness, and WHR did not differ by ethnicity in boys.

In both sexes, the distribution of HLA-DR antigens was similar in HD and NHWD subjects. Although more NHWD subjects were ICA$^+$ compared with HD subjects after adjusting for duration, this was not significant. The low prevalence of ICA is likely attributable to the length of time since IDDM diagnosis in this population. In the 30 subjects with <3 yr duration, 15% of HD and 23% of NHWD subjects were ICA$^+$ ($P = 0.7$). The prevalence of IDDM in first-degree relatives did not differ by ethnicity. In both boys and girls, HD subjects were three times more likely to have a first-degree relative with NIDDM than NHWD subjects, although this was not statistically significant. When boys and girls were combined, HD subjects were significantly more likely to have an NIDDM relative than NHWD subjects (11 vs. 3%, $P = 0.03$), after adjusting for family size and current maternal age.

Figure 1 shows a strong, nonlinear relationship between peak C-peptide response after Sustacal challenge and duration of diabetes in both HD and NHWD subjects. A multiple linear regression model was used to investigate characteristics that contribute to loss of β-cell function after diagnosis of IDDM. As expected, IDDM duration ($\log_{10}$ transformed) was a significant determinant of C-peptide levels, and explained 38% of the variability (Table 4). Higher C-peptide levels also were associated independently with Hispanic ethnicity ($r^2 = 0.03$, $P = 0.03$), higher BMI ($r^2 = 0.08$, $P = 0.0005$), and family history of NIDDM ($r^2 = 0.03$, $P = 0.03$). Gender was not statistically significant but was kept in the model because of the observed ethnic differences in C-peptide levels in girls. Forty-nine percent of the total variation in C-peptide levels was

Table 3—*Diabetes characteristics of study population by sex and ethnicity*

	Boys				Girls			
	Hispanic		Non-Hispanic white		Hispanic		Non-Hispanic white	
	N	Values	*N*	Values	*N*	Values	*N*	Values
Insulin dose (U/kg)*	18	0.80 ± 0.05	24	0.86 ± 0.04	26	0.92 ± 0.06	41	0.96 ± 0.05
HbA_1 (%)*	22	11.7 ± 0.5	25	11.1 ± 0.5	30	11.7 ± 0.4	41	11.2 ± 0.3
C-peptide (nM)*	17	0.15 ± 0.03	21	0.08 ± 0.03	22	0.27 ± 0.05	28	0.11 ± 0.04†
BMI (kg/m^2)‡	23	21.2 ± 0.6	27	21.8 ± 0.6	31	22.7 ± 0.7	43	20.9 ± 0.6†
Subscapular skinfold thickness (mm)‡	23	11.2 ± 0.8	26	11.1 ± 0.7	30	18.9 ± 1.4	41	15.0 ± 1.2†
WHR (mm/mm)‡	23	0.84 ± 0.03	26	0.87 ± 0.03	30	0.81 ± 0.01	41	0.77 ± 0.01†
HLA status								
DR3/4	24	13	32	28	31	32	42	24
DR3/x		21		28		19		24
DR4/x		54		34		22		36
DRx/x		12		9		25		17
ICAs*	24	4	34	15	35	11	43	16
IDDM family history§	30	10	37	10	40	8	55	4
NIDDM family history§	30	7	37	0	40	15	55	5

Values are means ± SE or %. *n*, number of subjects. See METHODS section, statistical analyses discussion, for explanation.
* Adjusted for diabetes duration.
† $P < 0.05$.
‡ Adjusted for attained age.
§ Adjusted for family size and current age of mother.

explained by the five variables. Subscapular skinfold thickness and WHR also were added individually to the model. However, because these measures did not contribute to the model of C-peptide as strongly as BMI, they were removed, and BMI was left in the model as the sole marker of obesity in these analyses. HLA-DR status, ICA^+, and age at diagnosis did not contribute significantly to the model; neither was an interaction term of ethnicity and gender significant (data not shown).

Two outlying stimulated C-peptide values were recorded in this population (Fig. 1*A* and 1*B*). Subject A was an 11-yr-old HD girl with a diagnosis of diabetes at 3 yr of age. She is currently not taking insulin, has a BMI of 15.7, a serotype of HLA-DR3/X, and a negative family history of diabetes mellitus. Subject B was a 25-yr-old HD boy who has been on insulin continuously since diagnosis at age 15 yr, is currently on an insulin dose of 0.41 U/kg, has a BMI of 28.2, a serotype of HLA-DR4/9, and a strong family history of IDDM and NIDDM. The removal of these individuals from the regression model resulted in findings similar to those presented in Table 4, except that the family history of NIDDM variable was no longer significant (data not shown).

CONCLUSIONS— Although several studies have investigated heterogeneity of IDDM in whites (10–22), only a few studies have compared characteristics of IDDM by race (23–25) or ethnicity (5,26,27), partly because of the difficulty of assembling a sufficiently large diabetic cohort of an ethnic or racial group at low risk for IDDM. The Colorado IDDM Registry contains the largest population-based cohort of Hispanics with IDDM in the United States (5), and provided an excellent resource with which to examine IDDM heterogeneity by ethnicity. After controlling for duration, BMI, sex, and family history of NIDDM, ethnicity itself accounted for only a small portion (3%) of the variability in C-peptide levels in this cohort.

C-peptide, a measure of endogenous insulin secretion, is used to evaluate residual β-cell function in diabetic subjects. Moreover, C-peptide levels distinguish IDDM from other types of diabetes. For example, blacks with MODY had C-peptide levels that were intermediate between those of nondiabetic control subjects and IDDM patients (1). Also, a comparison of fasting C-peptide in diabetic whites and Pima Indians, who were taking insulin and diagnosed with diabetes <21 yr of age, showed increased insulin secretion in the Pima Indians, suggesting that this group had an early-onset NIDDM, and that the whites had a more typical IDDM (28). Predictors of C-peptide levels in IDDM patients include diabetes duration, age at diagno-

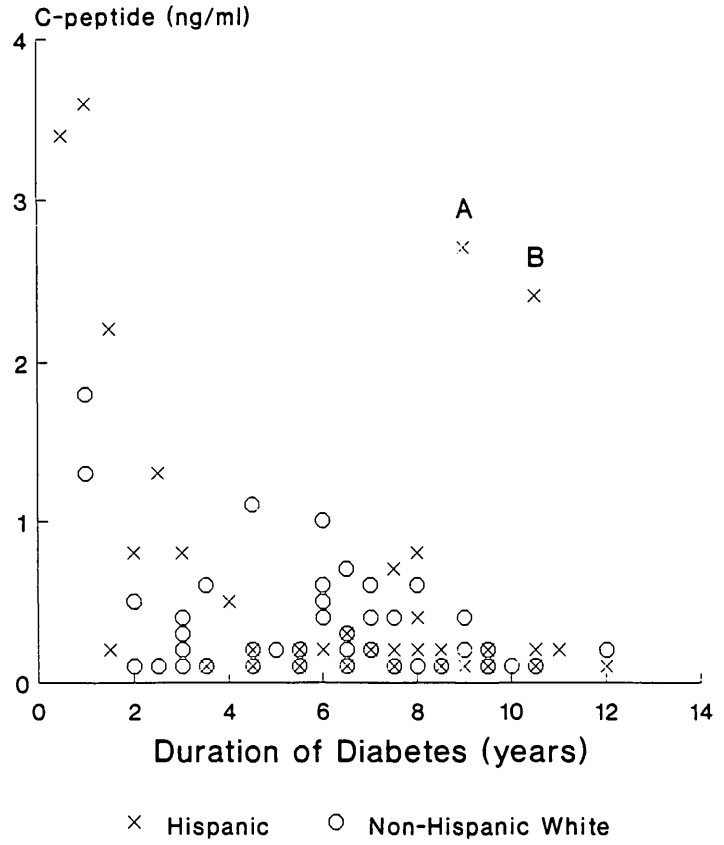

Figure 1—*Cross-sectional stimulated serum C-peptide peak (1 h) concentrations (ng/ml) by duration of diabetes (yr) in HD (X) and NHWD (O) subjects.*

sis, sex, ICA at diagnosis, and HLA serotype (10,11,13,17,29).

Few data in the literature examine whether ethnicity or race influences the rate of β-cell decline in IDDM patients. In our population, HD girls had higher stimulated C-peptide levels compared with NHWD girls. A previous study in nondiabetic adults demonstrated that Hispanics had elevated insulin and C-peptide levels compared with non-Hispanic whites (30), therefore, our results may reflect a relative hyperinsulinemia in the Hispanic ethnic group. The C-peptide analyses in our study and in the aforementioned studies (1,24) are limited because they are cross-sectional. True decline in β-cell function cannot be measured adequately without following individual IDDM patients over time. However, cross-sectional measures of C-peptide do enable the researcher to estimate levels of β-cell function on a group basis.

The ethnic difference in BMI was seen only in the girls in our diabetic cohort. This is consistent with findings in nondiabetic adults in Colorado, where Hispanic women were heavier than non-Hispanic white women, whereas men showed no ethnic differences in BMI (30). This suggests that the increased insulin secretion in Hispanic women may be related to the propensity of Hispanic women for obesity, rather than the existence of a different type of diabetes. Previous studies have not measured BMI in Hispanics with IDDM. A study of race differences in IDDM showed that black and white diabetic patients did not differ in BMI in either sex; however, these patients were obtained from a diabetes specialty clinic and may not have been a representative group of IDDM patients (24).

Individuals with NIDDM have a stronger family history of diabetes than individuals with IDDM (1,31). The higher prevalence of NIDDM in the families of our HD subjects compared with NHWD subjects may reflect the higher prevalence of NIDDM in the general Hispanic population (4). Moreover, the independent association between positive family history of NIDDM and residual β-cell function represents potential heterogeneity that is unrelated to either ethnicity or obesity.

Subjects in our study had to pass relatively stringent criteria to be eligible

Table 4—*Multiple linear regression analyses: C-peptide levels by subject characteristics*

	Parameter estimate	Standard error	*P*	Partial R^2
IDDM duration*	−1.46	0.19	0.0001	0.38
Ethnicity†	0.24	0.11	0.03	0.03
Sex‡	0.17	0.11	0.12	0.01
BMI	0.05	0.01	0.005	0.08
Family history of NIDDM§	0.59	0.27	0.03	0.03
Constant	−0.83	0.42	0.05	—

n = 88, R^2 = 0.49, and the model F-value = 15.9.
* Log_{10} transformation.
† NHWD = referent group.
‡ Boys = referent group.
§ Negative family history = referent group.

for the Colorado IDDM Registry, as described in METHODS. To verify the accuracy of IDDM diagnosis, each new case in the registry was reviewed for eligibility criteria on receipt of the baseline questionnaire and medical records of the diagnosis period (if available). At any point where questionable information was received, the cases were reviewed in detail by a diabetologist (G.J.K.) to determine whether they fulfilled the criteria for IDDM or other types of diabetes. Because the onset of IDDM and MODY may be similarly acute, and the eligibility criteria for the registry focus on the diagnosis period, individuals with MODY or early-onset NIDDM could be included in our registry. These individuals may be detected by examining the natural histories of their diabetes, which are likely to differ in insulin use and dosage, residual β-cell function, and body fat distribution. Examination of the characteristics of the two individuals with outlying C-peptide values suggests that these individuals may not have typical IDDM. The diagnosis of diabetes and subsequent insulin treatment of subject A may have been the result of a transient hyperglycemia with concurrent illness rather than the onset of IDDM; whereas characteristics of subject B suggest a potential combination of IDDM and NIDDM. Individuals with atypical IDDM, such as these, probably exist in all large IDDM study cohorts because of the difficulty of accurately classifying IDDM in some cases. There is no indication, however, that the atypical IDDM characteristics of these individuals are related to their ethnicity.

This cross-sectional investigation of a biethnic population from the Colorado IDDM Registry did not demonstrate heterogeneity of IDDM in Hispanics and non-Hispanic whites. The observed variability in some of the clinical and metabolic characteristics likely represents a spectrum of disease states within IDDM rather than ethnic differences in type of diabetes.

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