Colorado IDDM Registry: Lower Incidence of IDDM in Hispanics

Comparison of Disease Characteristics and Care Patterns in Biethnic Population

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The Colorado IDDM Registry identifies newly diagnosed cases of insulin-dependent diabetes mellitus (IDDM) throughout the state. Hispanics in Colorado are a racial mixture of American Indian and White populations. Because American Indians have a low risk of IDDM, and differing frequencies of HLA antigens and haplotypes are reported for Hispanics and non-Hispanics, we compared incidence rates and disease characteristics. Eligible participants were <18 yr of age and Colorado residents at time of diagnosis, diagnosed between 1 January 1978 and 31 December 1983, and on insulin within 2 wk of diagnosis. Subjects were reported by their physicians, and statewide validation of reporting was conducted through review of hospital discharge indexes. Incidence rates for Hispanics (n = 76) were significantly lower than those for non-Hispanics (n = 628), although 95% confidence intervals overlapped for children aged 10–17 yr. Age-adjusted rates were significantly lower in Hispanic than non-Hispanic males, whereas age-adjusted rates for females did not differ. The cumulative risk of IDDM was less for Hispanic males aged 0–17 yr than for non-Hispanic males ($P < .001$); cumulative risk among females was not different ($P = .10$). Clinical onset characteristics and medical care at diagnosis were similar. After diagnosis, hospitalizations per 100 person-yr appeared higher in Hispanics, but ketoacidosis and insulin reactions per 100 person-yr were similar. Difference in rate of hospitalizations may have been due to lower response rates among older non-Hispanics. From the data, it appeared that Hispanics and non-Hispanics had similar disease characteristics and therefore probably the same disease. Further genetic and environmental studies are needed to understand the patterns of Hispanic age-specific incidence rates. ***Diabetes Care*** **12:701–708, 1989**

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Studies of the incidence of insulin-dependent diabetes mellitus (IDDM) in contrasting populations indicate substantial variation in disease risk. A 17-fold difference in risk of developing IDDM is reported between populations with the highest risk (e.g., Finland, 29.5/100,000 per year) and populations with the lowest risk (e.g., Hokkaido, Japan, 1.7/100,000 per year) (1). LaPorte et al. (2) found significantly lower incidence rates in Blacks (9.6/100,000 per year) than in Whites (15.4/100,000 per year) in Allegheny County, Pennsylvania, and researchers in Montreal found both ethnic and socioeconomic differences in incidence (3,4). IDDM appears to be a disease with the highest incidence in northern Europeans and is virtually nonexistent in full-blooded Pima Indians (5).

In Hispanic populations, IDDM has received little attention, despite considerable study of non-insulin-dependent diabetes mellitus. Different DR frequencies and haplotype patterns of the HLA system have been reported in Hispanic compared with non-Hispanic populations (6; C.M. Vadheim, A. Zeidler, J.I. Rotter, M. Langbaum, I.A. Shulman, M.R. Spencer, G. Costin, W.J. Riley, and N.K. Maclaren, unpublished observations). Furthermore, Colorado Hispanics are a stable population who have considerable admixture with the American Indian population (7). These factors suggest the possibility that Colorado Hispanics have a different susceptibility to IDDM compared with the non-Hispanic population.

We present descriptive data from the Colorado IDDM

Registry comparing IDDM in Colorado Hispanics and non-Hispanics. In addition to reporting incidence rates, we assess disease presentation, medical care patterns, and acute complication rates as indicators of disease similarity between the two ethnic groups.

RESEARCH DESIGN AND METHODS

Subjects included in this study were diagnosed with IDDM between 1 January 1978 and 31 December 1983 and eligible for inclusion in the Colorado IDDM Registry. This 6-yr cohort study includes all years for which the first statewide validation of reporting is complete. Eligible subjects were <18 yr of age at time of diagnosis, were residents of Colorado when diagnosed, were placed on insulin within 2 wk of diagnosis, and did not have diabetes secondary to other causes. Subjects were reported to the registry by their physicians with statewide validation of reporting through review of hospital discharge indexes in 95% of the hospitals. Data obtained through physicians' reports or hospital reviews included residence at onset, sex, date of diagnosis, date of birth, race, diagnosing physician, and insulin status after treatment at diagnosis. We estimate that we ascertained 93.3% of all people in the state diagnosed with IDDM during the study period. Estimates of ascertainment did not differ by ethnic group (93.1% for Hispanics and 94.1% for non-Hispanics).

With the permission of the diagnosing physician, subjects' parents were sent a questionnaire requesting demographic and tracking information, family history, medical care and severity at diagnosis, insulin use, and acute complications since diagnosis. Included with the questionnaire was a request for permission to review relevant medical records. Nonresponders were sent a second questionnaire. Continuing nonresponders were telephoned and reminded to return the questionnaire.

Incidence rates were calculated for Hispanic and non-Hispanic populations. Because of the difficulty in identifying people of Spanish heritage (8), Hispanic and non-Hispanic subjects were characterized by two different criteria, and incidence rates were compared. The first criterion was Spanish surname: the 1980 U.S. Census List of Spanish Surnames was used to classify surnames of participants (9). Surnames can be designated as Spanish or non-Spanish for all subjects. However, a surname does not always indicate a child's origin, because Hispanics with non-Spanish surnames are excluded. The second criterion was Spanish origin: questions from the 1980 U.S. Census were used to ask subjects whether they were of Spanish or Hispanic origin or descent (10). Nonresponders designated as Hispanic by their physicians (n = 29) were also considered to be of Spanish origin. Spanish origin could not be determined for 34 of 738 subjects in this cohort (4.6%) because they did not return a questionnaire, and ethnic origin was not available from their physicians.

Age-, sex- and Spanish origin- or Spanish surname-specific denominators for the Hispanic population were generated by the Colorado Division of Local Affairs with the cohort component model (11). Ninety-five percent confidence intervals (CIs) on incidence rates were calculated with the Haenzel, Loveland, and Sirkin (12) Poisson distribution described by Lilienfeld and Lilienfeld (13). When incidence rates for Spanish origin- and Spanish surname-classified Hispanics were compared, the patterns by age and sex and the magnitude of differences in incidence were similar. Therefore, we report the Spanish origin identifier here because it is a more accurate measure of an individual's ethnic identification than Spanish surname.

Most subjects identified as non-Hispanic were White. Of 661 subjects who were not of Spanish origin, or for whom Spanish origin was unknown, only 30 (4.7%) were reported Black or other. These subjects were included in the non-Hispanic numerator when it was known that they were not of Spanish origin. This is consistent with the classification of non-Hispanics in the denominator.

Because the Colorado population is disproportionately young compared with other areas of the U.S., age adjustment (direct method) was calculated from the 1980 U.S. Census population aged 0–17 yr (14,15). CIs on relative risks were determined with the method described by Kahn (14). Estimates of cumulative risk were calculated with the technique by Schlesselman (16). χ^2-Tests of the independence of categorical variables utilized the SPSS statistical package (17). Significance tests comparing mean values were conducted with two-sample t test (18).

For this study, medical records from diagnosis were used to determine severity and blood glucose level and to confirm the date of diagnosis. All other participant data were from self-reports. Onset medical records from physicians' offices and records from hospital admissions were reviewed (n = 478). There was no difference by ethnicity in percentage of participants signing the authorization for release of medical records (91.5% of Hispanics and 86.7% of non-Hispanics returning a questionnaire; P = .35). Laboratory values used in this study are the most severe recorded from any laboratory during the 24-h diagnosis period. Subjects with insufficient data or for whom records were unavailable were excluded from relevant analyses.

The following priority order was established to evaluate disease severity at diagnosis. The blood pH value was used if available. If no pH value was recorded, the serum bicarbonate level was used. If neither pH nor bicarbonate was noted, urine ketone level was used. The following values classified severity at diagnosis for each test (19): pH: normal 7.35+, mild 7.34–7.26, moderate 7.25–7.11, severe <7.10; HCO_3 (meq/L): normal 18.0+, mild 17.9–15.0, moderate 14.9–10.1, severe <10.0.

Urine ketones were considered normal if <1+, otherwise they were not used. Information on hospitaliza-

tion at diagnosis, medical care patterns, insurance, and acute complications was determined by subject report.

Three types of acute complications were defined as: hospitalizations, episodes of diabetes-related illness (self-defined by subject report) requiring hospitalization overnight; ketoacidosis, episodes severe enough to require treatment with intravenous fluids; and insulin reactions, episodes severe enough to cause loss of consciousness (see APPENDIX 1 for the questions used). Because subjects completed questionnaires over a variable time period from 0 to 100 mo after diagnosis, episodes of acute complications that occurred from onset to the time of the questionnaire were reported over varying portions of this interval. The incidence rates of hospitalization, ketoacidosis, and insulin reactions per person-year were calculated to compare the two groups, taking into account the variable duration of follow-up (14).

RESULTS

Incidence. Table 1 shows incidence rates per 100,000/yr by age and ethnic group. Incidence rates were lower for Hispanics than for non-Hispanics. However, 95% CIs overlap for children aged 10–17 yr.

Figure 1 depicts incidence rates per 100,000/yr by ethnic group, sex, and age. Rates for all groups peaked in subjects aged 10–14 yr then declined. Female rates rose more rapidly than those for males, so that rates from ages 5 to 9 yr were almost as high as rates at 10–14 yr, especially in non-Hispanic females. Most striking were the consistently lower rates for Hispanic males compared with non-Hispanic males. In each age group Hispanic male rates were below the lower 95% CI for non-Hispanic males. Hispanic female incidence rates resembled the rates for non-Hispanic females, although rates for Hispanics <10 yr of age were significantly below those for non-Hispanic females.

Table 2 shows incidence rates and relative risks by ethnic group and sex, age adjusted to the 1980 U.S. Census population distribution aged 0–17 yr. Age-adjusted Hispanic male rates were significantly lower than the rates for non-Hispanic males, with a relative risk of 0.42. Age-adjusted rates for Hispanic females were not significantly lower compared with rates for non-Hispanic females.

Figure 2 shows the relative risk of developing IDDM in Hispanics compared with non-Hispanics by sex and age at diagnosis. The relative risk for Hispanic compared with non-Hispanic children, aged 0–4 yr, was <0.5. The relative risk was higher in Hispanic females than males, and by 15–17 yr of age, the relative risk for Hispanic females was >1. The relative risk for males was consistently <1 over the entire age range studied.

Estimates of cumulative risk from 0 to 17 yr of age indicate that 277/100,000 non-Spanish origin children will develop IDDM by age 17 yr compared with 173 cases/100,000 Spanish origin children ($P < .001$). The ethnic difference was predominantly among males because 122/100,000 Hispanic males will develop IDDM compared with 290/100,000 non-Hispanic males ($P < .001$), whereas among females the difference was not significant (225 Hispanic vs. 262 non-Hispanic cases/100,000 females by 18 yr of age; $P = .10$).

Participation. Hispanic subjects were less likely to participate by returning a questionnaire (61.8% of eligible Spanish origin subjects [47 of 76] vs. 79.9% of eligible non-Spanish origin subjects [502 of 628]; $P = .001$). Responders and nonresponders were compared to see whether they differed for the set of variables available in both groups. No significant differences were found by sex, age at diagnosis, region of the state (front range versus outlying areas), or type of reporting physician. Among non-Hispanics, a higher percentage of nonresponders compared with responders were in the older age groups at the time they received the questionnaire ($P < .001$). Hispanic and non-Hispanic responders and nonresponders differed by duration of diabetes with a higher percentage of those with longer duration among the nonresponders (Hispanics $P = .004$; non-Hispanics $P < .001$).

TABLE 1
Incidence rates per 100,000/yr by Spanish origin in Colorado, 1978–1983

	Age (yr)				Total
Spanish origin	0–4	5–9	10–14	15–17	
Cases	8	21	33	14	76†
Population*	38,139	36,103	35,550	23,663	133,455
Rate	3.50	9.69	15.47	9.86	9.49
95% confidence intervals	1.51–6.90	6.00–14.83	10.65–21.75	5.38–16.56	7.52–11.94
Non-Spanish origin					
Cases	94	194	254	86	628†
Population*	179,751	178,438	192,092	133,256	683,537
Rate	8.72	18.12	22.04	10.76	15.31
95% confidence intervals	7.09–10.74	15.70–20.91	19.16–25.34	8.85–13.68	14.14–16.57

*As of 1 July 1980.
†Thirty-four subjects for whom Spanish origin was missing were removed from analyses.

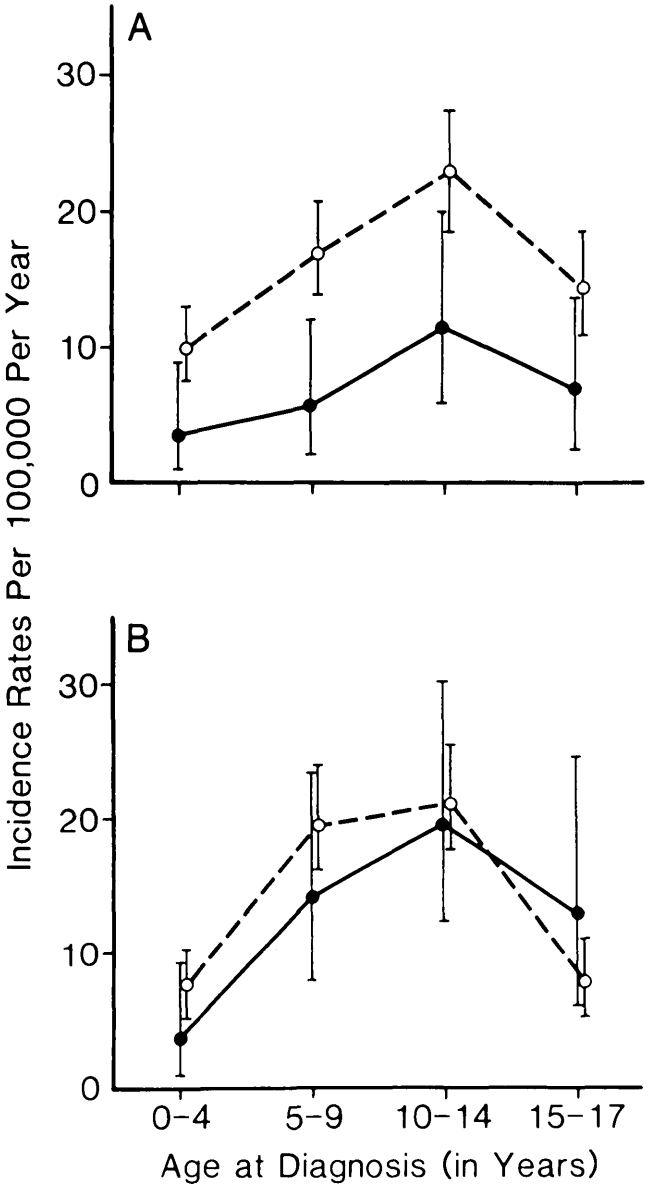

FIG. 1. Incidence rates per 100,000/yr by age at diagnosis in males (*A*), and females (*B*) in Colorado, 1978–1983. ○, Non-Spanish origin; ●, Spanish origin.

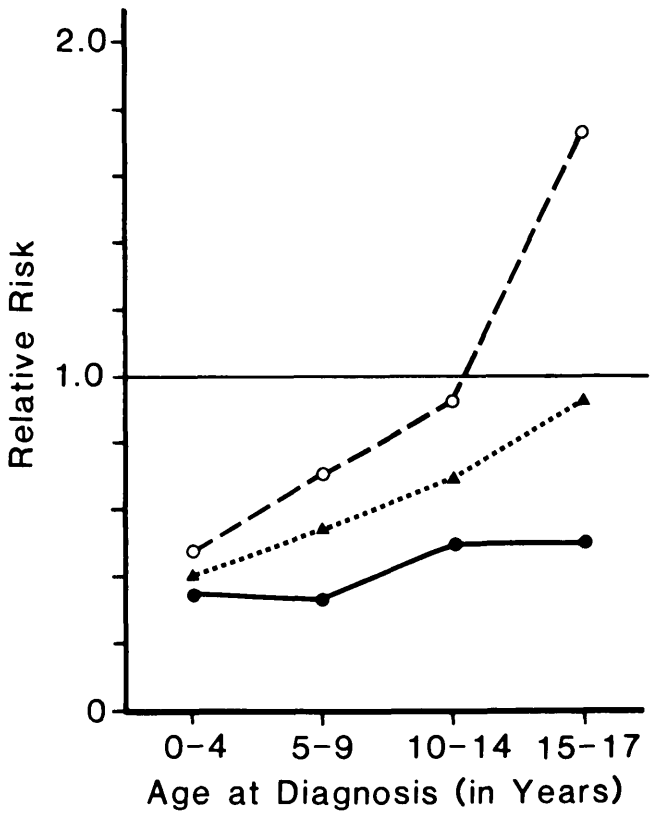

FIG. 2. Relative risk (Hispanic versus non-Hispanic) by age at diagnosis in Colorado, 1978–1983. ●, Male; ○, female; ▲, total.

Characteristics at diagnosis. Because incidence rates differed, we wanted to ascertain whether other characteristics were similar for Hispanics and non-Hispanics. Comparison of selected demographic characteristics (Table 3) indicated median income was lower among Hispanics than non-Hispanics. Hispanics reported lower average maternal and paternal education than non-Hispanics.

Among Hispanics, 55.3% reported a family history of diabetes compared with 40.4% of non-Hispanics (P = .07). Hispanics reported a first-degree relative with diabetes more frequently than non-Hispanics (25.5 vs. 13.4%; P = .02). The mean number of first-degree relatives was not different between the two groups (4.2 for Hispanics and 3.7 for non-Hispanics; P = .08). Categorization of type of diabetes (IDDM subject designated as on insulin and diagnosed at <30 yr of age) indicated a tendency for Hispanics to report more first-degree relatives with non-insulin-dependent diabetes mellitus, whereas non-Hispanics appeared to report more first-degree relatives with IDDM (data not shown).

TABLE 2
Age-adjusted incidence rates per 100,000/yr by Spanish origin in Colorado, 1978–1983

	Spanish origin		Non-Spanish origin		
	n	Rate	*n*	Rate	Relative risk
Males	27	6.90 (4.51–10.00)	339	16.32 (14.48–17.97)	0.42 (0.24–0.66)
Females	49	12.73 (9.58–16.85)	289	14.55 (12.95–16.35)	0.87 (0.63–1.16)

95% confidence intervals in parentheses.

TABLE 3
Comparison of selected demographic characteristics by Spanish origin in Colorado, 1978–1983

	Spanish origin	*n**	Non-Spanish origin	*n**	*P*
Median income group†	$15,000–19,999	43/47	$25,000–34,999	469/502	<.001
Maternal education (yr, mean ± SE)	11.6 ± 0.4	45/47	13.8 ± 0.1	495/502	<.0005
Paternal education (yr, mean ± SE)	11.7 ± 0.5	40/47	14.4 ± 0.1	460/502	<.0005
Age at diagnosis (yr, mean ± SE)‡	10.1 ± 0.5	76/76	9.7 ± 0.2	628/628	<.0005
Diabetes in first-degree relative§	25.5%	12/47	13.4%	67/502	.02
Health insurance	72.3%	34/47	87.8%	441/502	.01

*Number reporting/number who returned questionnaire. Number of subjects varied due to incomplete data on some subjects.
†Total family income before taxes.
‡Age at diagnosis was available on all subjects.
§Biologic parents, full siblings, or biologic children of subject.

Review of clinical presentation of IDDM for Hispanic and non-Hispanic children was based on data from medical records. On average, Hispanics were slightly older at diagnosis than non-Hispanics. Differences in blood glucose levels at diagnosis indicated that non-Hispanics had higher levels than Hispanics. However, when the groups were stratified by age this difference was significant only among 15- to 17-yr-olds ($P < .01$). Both groups showed considerable variability and substantial hyperglycemia.

Data on severity of ketoacidosis at diagnosis indicated that among non-Hispanics ~33% of subjects were moderate to severe, ~33% were normal, and ~33% were unclassifiable. Hispanics did not differ significantly from non-Hispanics by severity. The number of Hispanics was too small to allow adjustment of severity for age (43 of 47 Hispanics and 435 of 502 non-Hispanics signed the authorization for release of medical records; $P = .35$).

We also compared Hispanics and non-Hispanics on selected aspects of medical care at diagnosis. The frequency of hospitalization at diagnosis was similar for the two groups (83% of Hispanics vs. 88.6% of non-Hispanics; $P = .25$). Among those who were hospitalized at diagnosis, the duration was ~1 wk, although Hispanics stayed 1 day longer on average than non-Hispanics ($P = .15$). Hispanics were less frequently referred after diagnosis (59.6 vs. 67.9%), although this difference was not significant. More than 50% of both groups saw endocrinologists; another 15–20% saw pediatricians. Non-Hispanics more frequently reported having health insurance (87.8 vs. 72.3%; $P = .01$).

Incidence of acute complication. We compared rates of subject-reported acute complications from diagnosis to the time the questionnaire was completed. Of 47 Hispanic and 502 non-Hispanic subjects who returned questionnaires, the average length of time from diagnosis to completion of the questionnaire was 36 vs. 29.6 mo, respectively ($P = .05$). The percentage of subjects who had any hospitalizations subsequent to the diagnosis period was similar. However, the rate of hospitalizations per 100 person-yr was higher in Hispanics (26.1 vs. 18.3). Both groups stayed in the hospital an average of 4 days/hospitalization. Comparison of Hispanics to non-Hispanics for rates of ketoacidosis and insulin reactions showed no differences between the two groups.

DISCUSSION

In Colorado, IDDM incidence rates were lower for Hispanics than non-Hispanics. This difference was consistent with the San Diego data of Lorenzi et al. (20), who studied Mexican-American and White IDDM subjects through retrospective review of hospital records and found fewer than expected cases of IDDM among Mexican Americans. Incidence rates calculated from Table 2 were lower in Mexican Americans (4.1/100,000 per year) than Whites (9.54/100,000 per year). Completeness of ascertainment is not stated, and it appears that no outpatient contacts were made. Thus, the San Diego incidence rates may be underestimates.

The incidence of IDDM in Terrassa, Spain (21) was reported to be 10.6 and 6.8/100,000 per year (in two consecutive years), similar to that of Colorado Hispanics. This suggests that lower incidence among descendants of Spanish settlers might be expected. Alternatively, Pima Indians have virtually no IDDM, and it may be that American Indian admixture with Colorado Hispanics contributed to lowered susceptibility to IDDM among Hispanics (5,7).

Differences in HLA antigen or haplotype frequencies associated with IDDM have been reported in Hispanics compared with non-Hispanics (6,22,23; C.M. Vadheim, A. Zeidler, J.I. Rotter, M. Langbaum, I.A. Shulman, M.R. Spencer, G. Costin, W.J. Riley, and N.K. Maclaren, unpublished observations), although some of the differences may be artifacts of small sample size. Antigen and haplotype data were not available in our population-based study; however, reports from other studies suggest that differences in incidence might be expected in the two ethnic groups.

The different pattern of incidence rates by sex found among Hispanics was intriguing. Reported associations of sex with HLA-DR antigens in people with IDDM suggest that susceptibility patterns or environmental pres-

sures could operate differently between the sexes (24,25). Alternatively, the increasing relative risk in older Hispanic females may reflect misclassification of early-onset NIDDM, which occurs at a higher prevalence in Colorado Hispanic females than males (26). Because height and weight at diagnosis were unavailable, we could not determine body mass index or insulin dose per kilogram to evaluate the possibility of misclassification.

Questionnaire response rates were lower among Hispanics than non-Hispanics. Lack of participation may be due to such factors as lower average education or an outlook that does not place value on research efforts. Language problems are unlikely to play a part in the low response rate for Hispanics. Ninety-three percent of Colorado Hispanics were born in the U.S. (27). U.S. Census figures indicate that only 0.01% of all Colorado individuals >5 yr of age do not speak English well.

Significant differences between responders and nonresponders were found in two areas. First, among non-Hispanics, nonresponders were more frequently in the older age groups. A similar trend existed among Hispanics, but it was not significant. Second, in both ethnic groups a higher percentage of nonresponders were those who had IDDM of longer duration at the time they received the questionnaire. A higher response rate closer to diagnosis may occur because motivation to respond to medical and research efforts is greatest while families are still adjusting to the condition. Analyses adjusting for both age and duration of disease at receipt of the questionnaire were not conducted because of small numbers of Hispanics.

Onset characteristics and acute complications were compared to see whether, among subjects with IDDM, Hispanics have the same characteristics as non-Hispanics. Blood glucose levels, measures of severity, hospitalization, duration of hospital stay, referral, and type of physician providing care were similar for the two groups. These characteristics suggested that Hispanics and non-Hispanics have the same disease. Given that nonrespondents tended to be older (especially among the non-Hispanics) and had IDDM of longer duration, it may be that differences between the two groups at older ages or at longer duration were obscured.

Significantly lower income and maternal and paternal

APPENDIX 1
The following questions were used to collect information about acute complications after diagnosis

- Since diagnosis, has your child ever been hospitalized?
  1 _____ Yes 2 _____ No 3 _____ don't know
- If yes, please tell us the following information for each hospitalization.

Date of Admission	Number of nights	Hospital name	City	Was this diabetes-related? Yes	No	Don't know
__ __/__ __/__ __						
__ __/__ __/__ __						
__ __/__ __/__ __						
mo day year						

- Has your child ever had to receive intravenous (IV) therapy (a needle in the hand or arm attached to a tube which leads to a bottle containing fluid) for ketoacidosis or coma since the diagnosis period?
  1 _____ Yes 2 _____ No
- If yes, please tell us the following information for each time this happened.

Date IV was received	Where IV was received (hospital, doctor's office, etc.) Name	City	Was the child hospitalized overnight for this? Yes	No
__ __/__ __/__ __				
__ __/__ __/__ __				
__ __/__ __/__ __				
mo day year				

- Has your child ever had an insulin reaction (low blood sugar) bad enough to pass out (lose consciousness) since diagnosis?
  1 _____ Yes 2 _____ No
- If yes, please tell us the following information for each time this happened.

Date of passing out	Did this take place in: 1 Home	2 School	3 Other	Did this result in a hospitalization? 1 Yes	2 No
__ __/__ __/__ __					
__ __/__ __/__ __					
__ __/__ __/__ __					
mo day year					

education levels among Hispanics were not unexpected. These reflect characteristics of the total Colorado Hispanic population (27). Siemiatycki et al. (4) found an increased risk for IDDM among wealthier as opposed to poorer classes in Montreal. It is possible that lower incidence among Hispanics is due to a social class effect in our data, but statewide denominator data by social class and ethnic group were not available to examine this issue.

Comparison of self-reported complications subsequent to diagnosis must be viewed with caution because independent validation of the subject report was not available. Hispanics had higher rates of hospitalization per 100 person-yr subsequent to diagnosis. This difference was not tested statistically because repeated episodes may occur in the same subject. Because 45.5% of Hispanics compared with 49.2% of non-Hispanics ($P = .75$) were diagnosed by or referred to diabetes specialty clinics, it is unlikely that different health-care providers explained the observed difference in hospitalization patterns. In addition, if incidence of subsequent ketoacidosis is used as an index to quality of care, it would appear that Hispanics and non-Hispanics received similar care. Hispanics had medical insurance less frequently. It may be that for economic reasons they did not seek medical care routinely, and consequently suffered more episodes of hospitalization.

From the data, the incidence of IDDM in Colorado Hispanics is lower than in non-Hispanics. The course of disease also appears similar, supporting the hypothesis that IDDM in the two ethnic groups is the same. However, clinical and immunological differences may exist and long-term prognosis may differ.

The population observations are consistent with both ethnic differences in genetic risk and possible environmental differences. We are conducting a clinical and epidemiological study of Colorado Hispanics with IDDM, including HLA typing and islet cell antibody levels, which should help determine whether lower Hispanic incidence is associated with different patterns of immunogenetic markers, and whether misclassification with NIDDM plays a role in observed incidence patterns by sex. This new study should improve our understanding of Hispanic and non-Hispanic differences in IDDM.

ACKNOWLEDGMENTS

We acknowledge the core staff of the Colorado IDDM Registry Mary Wilfawn, Lisa O'Keefe, and Dave Garneau. Dr. Richard H. Jones provided statistical advice. Reed Reynolds of the Colorado Division of Local Affairs provided expertise in determining denominators. Susan Gale contributed computer programming skill. Tica McCollom provided secretarial assistance.

This research was funded by National Institutes of Health Grant DK-32493.

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