Incidence of Type II Diabetes in Mexican Americans Predicted by Fasting Insulin and Glucose Levels, Obesity, and Body-Fat Distribution

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Few data exist on predictors of non-insulin-dependent (type II) diabetes mellitus. We examined body mass index (BMI), ratio of subscapular-to-triceps skin fold (centrality index), and fasting glucose and insulin concentrations as predictors of decompensation to type II diabetes in Mexican Americans, a population at high risk for this disorder. Twenty-eight of 474 initially nondiabetic Mexican Americans developed type II diabetes after 8 yr of follow-up. Converters to diabetes were older and had higher BMIs, centrality indices, and fasting glucose and insulin concentrations than nonconverters. Subjects in the highest quartile of the insulin distribution had 6.6 times the risk of developing type II diabetes as subjects in the remaining three quartiles combined (95% confidence interval [CI] = 3.14–13.7). In multivariate analysis, fasting glucose (odds ratio [OR] = 5.80, 95% CI = 2.57–13.1) and insulin (OR = 3.12, 95% CI = 1.36–7.14) remained significantly related to conversion to diabetes. However, BMI and centrality index, which were significantly related to conversion in the univariate analysis, were no longer significant in the multivariate analysis once glucose and insulin concentrations were taken into consideration, suggesting that the effect of these variables may be mediated by insulin resistance. Nearly half of the incident cases developed in a subset of the population who were simultaneously in the highest quartile of both fasting insulin and glucose concentrations (population-attributable risk 44.2%). Our results support the insulin resistance/pancreatic exhaustion theory of type II diabetes. *Diabetes* 39:283–88, 1990

Although established cases of non-insulin-dependent (type II) diabetes mellitus are characterized by peripheral insulin resistance, β-cell failure, and overproduction of glucose by the liver (1), little is known about the metabolic antecedents of this disorder. Both deficient insulin secretion (2) and insulin resistance (3) have been postulated as precursors of type II diabetes. Prospective evaluation of these hypothesized precursors has been difficult because of the relatively low incidence of diabetes in the general population (e.g., compared with coronary heart disease) and the lack of a definitive marker for the identification of prediabetes. To circumvent these problems, it is attractive to carry out prospective studies in populations at high risk for diabetes, such as Pima Indians (4) and Mexican Americans (5). Both of these populations are characterized by obesity, hyperinsulinemia, and insulin resistance (4–10). In addition, Mexican Americans also have an unfavorable distribution of body fat (8). Prospective studies have shown that both increased overall adiposity (4,11–13) and upper-body adiposity (13) are risk factors for type II diabetes. Likewise, elevated glucose concentration is also associated with an increased risk of this disorder (11,14,15).

Because overall adiposity and unfavorable body-fat distribution are associated with insulin resistance (16–19), it is possible that the deleterious effect of these factors on diabetes risk is mediated by insulin resistance. In support of this hypothesis are prospective studies in Pima Indians (14,20) and Micronesians from the South Pacific island of Nauru (15) showing that hyperinsulinemia, an indirect indicator of insulin resistance, is a risk factor for type II diabetes. Direct evidence for insulin resistance per se as a risk factor for type II diabetes has been reported only in Pima Indians (20,21). A preliminary report has also suggested that insulin resistance predicts conversion to diabetes in offspring of two diabetic parents (22).

Pima Indians and Nauruans are relatively small, genetically isolated populations with unusually high prevalences of diabetes (≥40%; 4,15). In contrast, Mexican Americans

Glucose 1 mM = 18 mg/dl	Insulin 1 pM = 0.167 μU/ml

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have only a moderate, threefold increase in diabetes prevalence compared with non-Hispanic Whites and are a large, free-living population in the United States (8.7 million; 23). Moreover, genetic admixture studies indicate that this population has >50% Caucasian ancestry (24). We hypothesized that increased adiposity, unfavorable body-fat distribution, and hyperinsulinemia would also predict the development of type II diabetes in this population. We further hypothesized that the adverse effects of adiposity and unfavorable body-fat distribution are mediated by insulin resistance assessed indirectly by hyperinsulinemia.

RESEARCH DESIGN AND METHODS

The San Antonio Heart Study is a population-based study of diabetes and cardiovascular disease in Mexican Americans and non-Hispanic Whites. From 1979 to 1982, we randomly sampled households from several San Antonio census tracts: two low-income (barrio) census tracts (96% Mexican American), two middle-income (transitional) census tracts (52% Mexican American and 48% non-Hispanic White), and a cluster of suburban census tracts (10% Mexican American and 90% non-Hispanic White) (25). Stratified random sampling was used in the middle-income and suburban census tracts to ensure the inclusion of approximately equal numbers of each ethnic group in the study sample. All men and nonpregnant women 25–64 yr of age residing in the randomly selected households were eligible for the study. Subjects received a home interview followed by a clinic examination. One thousand two hundred eighty-eight Mexican Americans and 927 non-Hispanic Whites attended the clinic examination. The overall response rate was 63.9%. Mexican Americans were defined as individuals whose ancestry and cultural traditions were of Mexican national origin (26). A detailed description of the 1979–1982 survey has been published (25). The study was approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio, and all subjects gave informed consent.

At baseline examination, blood specimens were obtained after a 12- to 14-h fast for plasma glucose and serum insulin determinations. A 75-g glucose equivalent load (Glucola, Ames, Elkhart, IN) was then administered, and blood specimens were obtained 1 and 2 h later for plasma glucose determinations. Plasma glucose concentrations were measured with an Abbott bichromatic analyzer (South Pasadena, CA). Fasting plasma insulin levels were measured with a commercial radioimmunoassay (Diagnostic Products, Los Angeles, CA; 9).

Anthropometric measurements (height, weight, and subscapular and triceps skin folds) were made after each participant had removed his or her shoes and upper garments and donned an examination gown. The triceps skin fold was measured posteriorly over the right triceps muscle at a level midway between the acromial and olecranon processes, with the subject's arm hanging relaxed at the side. The subscapular skin fold was also measured on the right side just below the inferior angle of the scapula following the natural contour of the skin. Body mass index (BMI) was calculated as weight (kg) divided by height (m^2). The ratio of subscapular-to-triceps skin fold (centrality index) was chosen as a measure of central adiposity.

Beginning in October 1987, an 8-yr follow-up study was begun to ascertain the incidence of type II diabetes and coronary heart disease. This paper reports results of the follow-up of participants from the first three census tracts (1 low income, 1 middle income, and 1 upper income; n = 666 Mexican Americans). Vital status was ascertained on 98% of subjects. The follow-up examination consisted of an initial home or telephone interview followed by a medical examination performed in a mobile clinic located in the participant's neighborhood. Response rates to the home interview and medical examination are given in Table 1. This article is restricted to the 474 Mexican Americans who were free of diabetes at the baseline examination in 1979–1982 (i.e., population at risk) and who attended the medical examination 8 yr later. (The number of initially nondiabetic non-Hispanic Whites who converted to type II diabetes [6 of 301] was too small to allow analysis of risk factors for conversion to diabetes in this ethnic group.)

At the follow-up examination, plasma glucose was measured in the fasting state and 2 h after the administration of a 75-g glucose equivalent load (Koladex or Orangedex, Custom, Baltimore, MD). The methods used for glucose, insulin, and anthropometric measurements were identical to those used in the baseline examination.

Diabetes mellitus was diagnosed according to the criteria of the World Health Organization (WHO; fasting plasma glucose level ≥7.8 mM and/or 2-h plasma glucose level ≥11.1 mM; 27). (In previous reports [5,9,25], we used the National Diabetes Data Group criteria [28], which require an additional, intermediate post–glucose load measurement. However, because in the follow-up examination only fasting and 2-h post–glucose load blood specimens were obtained, we used the simpler WHO criteria in this report. The concordance between the two criteria in the overall San Antonio Heart Study population was 98%.) Diabetic subjects who did not meet the WHO plasma glucose criteria but who were being treated with oral antidiabetic agents or insulin were also considered to have diabetes. Diabetic subjects who were not

TABLE 1
Response rates to 8-yr follow-up of Mexican Americans

	Neighborhood			
	Barrio	Transitional	Suburban	Total
Baseline examination	221	177	268	666
Status at follow-up				
Deceased	12	7	0	19
Unknown	5	3	3	11
Refused	0	2	3	5
Ineligible*	1	0	0	1
Eligible for follow-up	208	170	268	646
Responded to home interview	203 (98)	165 (97)	262 (98)	630 (98)
Attended clinic examination	161 (77)	139 (82)	228 (85)	528 (82)
Diabetes at baseline	27	10	17	54
Free of diabetes at baseline†	134	129	211	474

Values are n. Values in parentheses are percentages.
*Mental deficiency at follow-up.
†Population at risk.

taking insulin were considered to have type II diabetes. Subjects taking insulin whose age at onset was >40 yr and who had a BMI ≥30 kg/m² were also considered to have type II diabetes. Other diabetic subjects were considered to have insulin-dependent diabetes or to be unclassifiable. Because this report is concerned with risk factors for conversion to type II diabetes, subjects who had diabetes at the baseline examination were excluded from these analyses (n = 54). Of the 474 nondiabetic subjects at baseline, 87.1% had normal glucose tolerance (NGT; 2-h glucose <140 mg/dl) and 12.9% had impaired glucose tolerance (IGT; 2-h glucose ≥140 but <200 mg/dl).

Age-adjusted group means for baseline variables were computed for subjects who subsequently converted to diabetes and for those who remained free of disease by analysis of covariance (Table 2). In these analyses, centrality index was also adjusted for sex by analysis of covariance, because there is an important sex difference in this variable. In Tables 3 and 4, the dependent or outcome variable is the occurrence of diabetes. Multiple logistic regression analysis was used to estimate the odds ratio (OR) associated with each risk factor adjusted for all other risk factors (Table 4; 29). In these analyses, centrality index and fasting glucose and insulin concentrations were treated as categorical variables, with the highest quartile compared with the lowest three quartiles. Age was categorized in 10-yr intervals (25–34, 35–44, 45–54, and 55–64 yr). For obesity, subjects were considered to be obese (BMI ≥27 kg/m²) or nonobese (<27 kg/m²). However, the results were similar when all risk factors were analyzed as continuous variables. The Lemeshow and Hosmer (30) criterion was used to evaluate the goodness of fit of the multiple logistic models. All models fit well (P > 0.30). Initially, first-order interactions between risk factors (e.g., sex × insulin or age × BMI) were included in the models, but because these interactions were all nonsignificant (P > 0.20), they were excluded from the final models.

RESULTS

We compared the baseline characteristics of subjects who converted to type II diabetes with those who remained free of diabetes after 8 yr of follow-up (Table 2). Subjects who converted to diabetes were older and had greater overall adiposity, more central adiposity, and higher fasting and 2-h glucose and fasting insulin levels. There was no significant sex difference in the proportion of subjects who developed diabetes.

TABLE 2
Age-adjusted baseline characteristics of Mexican Americans according to diabetes status at 8-yr follow-up

	Converted to diabetes	Remained healthy	P
n	28	446	
Sex (F/M)	14/14	262/184	0.313
Age (yr)	45.2 ± 2.0	41.1 ± 0.5	<0.001
BMI (kg/m²)	29.8 ± 0.9	26.6 ± 0.2	<0.001
Centrality index	1.32 ± 0.90	1.16 ± 0.20	0.036
Fasting insulin (μU/ml)	24.1 ± 3.4	12.5 ± 0.8	<0.001
Fasting glucose (mg/dl)	103.6 ± 1.7	90.6 ± 0.4	<0.001
2-h glucose (mg/dl)	143.0 ± 7.0	110.2 ± 1.6	<0.001

Values are means ± SE where indicated.
BMI, body mass index; centrality index, ratio of subscapular-to-triceps skin fold. The latter was adjusted for sex by analysis of covariance.

TABLE 3
Unadjusted relative risk (RR) of non-insulin-dependent diabetes in highest vs. remaining 3 quartiles of various risk factors

	8-Yr incidence (%)				
	Lowest 3 quartiles	Highest quartile	RR	95% CI	P
Age (yr)	4.4	7.4	1.68	0.80–3.51	0.171
BMI (kg/m²)	3.9	7.7	1.97	1.16–3.34	0.009
Centrality index	4.6	8.4	1.83	1.06–3.15	0.032
Fasting insulin (μU/ml)	2.0	13.2	6.60	3.14–13.7	<0.001
Fasting glucose (mg/dl)	1.2	15.8	13.2	4.93–23.2	<0.001
IGT (yes/no)	3.0	18.5	6.17	3.04–12.5	<0.001

Relative risk was calculated by dividing the incidence in the highest quartile by the incidence in the lowest 3 quartiles. Cutpoints for the highest quartile for each variable: centrality index, ≥1.62 for men and ≥1.14 for women; insulin ≥14.55 μU/ml; and glucose, ≥95.5 mg/dl. Age was dichotomized at 45 yr, and body mass index (BMI) was dichotomized at 27 kg/m². Impaired glucose tolerance (IGT) was defined as 2-h glucose value between 140 and 200 mg/dl (27). CI, confidence interval. Centrality index, ratio of subscapular-to-triceps skin fold.

We performed univariate analyses to show the risk of type II diabetes for the highest quartile of a risk factor versus the lowest three quartiles of that risk factor (Table 3). BMI, centrality index, and fasting insulin and glucose concentrations were all significant univariate predictors of the incidence of diabetes. Subjects with IGT at baseline had a 6.17 times greater risk of developing diabetes than subjects with NGT at baseline (95% confidence interval [CI] = 3.04–12.5, P < 0.001). Subjects in the highest quartile of the insulin distribution had 6.60 times the risk of conversion to diabetes as subjects in the lowest three quartiles (95% CI = 3.14–13.7, P < 0.001). We also evaluated the effect of insulin concentrations on incidence of diabetes separately for individuals with baseline NGT versus baseline IGT. In the former, the incidence of diabetes was 1.7% among subjects in the lowest three insulin quartiles versus 7.0% among subjects in the highest insulin quartile, whereas in subjects with baseline IGT, the incidence of diabetes was 11.4% in the lowest insulin group and 26.9% in the highest insulin group. Thus, in both baseline glucose-tolerance categories, higher fasting insulin concentrations were associated with conversion to type II diabetes. The effect of insulin appeared to be greater in subjects with baseline NGT than with baseline IGT (relative risk [RR] associated with being in the highest insulin quartile was 4.12 for the former and 2.36 for the latter). This difference was not statistically significant, however (χ^2-value for homogeneity = 0.34, P = 0.56), perhaps because of the low number of subjects with baseline IGT (n = 61).

In the above analyses, the RRs associated with each predictor variable were not adjusted for the other predictor variables. Therefore, we carried out a multiple logistic analysis to assess the effects of each risk factor on conversion to

TABLE 4
Multiple logistic regression analysis of 8-yr incidence of non-insulin-dependent diabetes

	OR	95% CI	*P*
Sex (M/F)	1.15	0.72–1.88	0.576
Age	1.12	0.75–1.68	0.581
BMI	1.21	0.75–1.96	0.440
Centrality index	1.14	0.58–1.91	0.620
Fasting insulin	3.12	1.36–7.14	0.006
Fasting glucose	5.80	2.57–13.1	<0.001

Odds ratios (ORs) compare odds for subjects in the highest quartile vs. lowest 3 quartiles for fasting insulin and glucose and centrality index. OR for body mass index (BMI) compares subjects with BMI ≥27 kg/m² to those with BMI <27 kg/m²; for age, OR compares individuals of a given age with those 10 yr younger. CI, confidence interval; centrality index, ratio of subscapular-to-triceps skin fold.

type II diabetes while simultaneously adjusting for all other risk factors (Table 4). Fasting glucose and insulin concentrations remained significantly associated with incidence of type II diabetes, even after adjustment for other covariates. The adjusted odds of developing diabetes among subjects in the highest insulin quartile was >3 times higher than among those in the lowest three quartiles (OR = 3.12, 95% CI = 1.36–7.14). However, age, BMI, and centrality index were no longer significantly associated with diabetes incidence, suggesting that the effect of these variables may be mediated by increasing insulin resistance as reflected by higher glucose and insulin levels. We also examined BMI, centrality index, and fasting insulin and glucose as continuous rather than dichotomous variables. The results were very similar to those presented in Table 4, with fasting glucose and insulin significantly associated with diabetes incidence ($P < 0.01$) but age, BMI, and centrality index not associated (data not shown).

We also considered the effect of fasting insulin after adjustment for age, BMI, centrality index, and glucose level in two additional multiple logistic models, one for subjects with baseline NGT and the other for subjects with baseline IGT. Fasting insulin was significantly associated with conversion to type II diabetes in the former (OR = 3.32, 95% CI = 1.39–7.93) but not in the latter (OR = 2.01, 95% CI = 0.76–5.34) group, although as noted above, the IGT results may represent a lack of statistical power due to small numbers ($n = 61$).

Fifty-six (12%) individuals in the population at risk for developing diabetes were simultaneously in the top quartile of both the insulin and the glucose distribution. Of these high-risk individuals, 14 (25%) developed diabetes over 8 yr. In contrast, only 3.3% of the remaining low-risk individuals developed diabetes over this period, for a relative risk of 7.6. The fraction of total cases that can be attributed to being at high risk as defined here (i.e., the population-attributable risk percent [PAR%]) can be calculated from the formula

$$PAR\% = 1 - (RRP_h + P_l)^{-1}$$

where RR is 7.6, P_h is proportion at high risk (0.12), and P_l is proportion at low risk (0.88). Solving this equation gives PAR% = 44.2%, which means that a small subset of the population (12%), readily identifiable by their glucose and insulin values, contribute nearly half of the future type II diabetes cases (and perhaps more with continuing follow-up).

DISCUSSION

This study shows that fasting insulin predicts conversion to type II diabetes in Mexican Americans, which confirms earlier work in Pima Indians (14,20,21) and Nauruans (15), both of which are exceedingly high-risk populations for this disorder (4,15). Because Mexican Americans have a lower prevalence of type II diabetes than either Pima Indians or Nauruans (~15 vs. 40%) and because Mexican Americans are predominantly Caucasian in origin (24), these results suggest that hyperinsulinemia may also be an important precursor of type II diabetes in lower-risk populations. Indeed, a preliminary report has suggested that fasting insulin levels predict conversion to type II diabetes in a low-risk White population, namely Paris policemen with IGT (31). In addition, elevated fasting C-peptide concentrations but not insulin concentrations predicted conversion to type II diabetes in Japanese Americans (32). Finally, preliminary data suggest that insulin resistance measured by an intravenous glucose tolerance test also predicts conversion to type II diabetes in predominantly White offspring of diabetic parents (22).

Among subjects with IGT, most of whom have high absolute insulin concentrations, those with relatively lower 2-h post–glucose load values are more likely to convert to diabetes than those with relatively higher values (14,15,31,33). In Pima Indians with IGT (14), both high fasting and relatively low 2-h insulin concentrations predicted conversion, suggesting that both increased insulin resistance (as reflected by high fasting values) and deteriorating ability to maintain insulin hypersecretion (reflected by relatively lower 2-h values) play a role in conversion. In our study, high fasting insulin predicted conversion in both the NGT and the IGT groups. Unfortunately, 2-h insulin values were not available on this cohort, so we could not assess the possibility of a superimposed secretory defect among IGT subjects. These studies support the insulin resistance/pancreatic exhaustion hypothesis, which states that as a result of chronic insulin resistance, compensatory hypersecretion of insulin develops to maintain glucose homeostasis and that eventually diabetes mellitus develops when pancreatic hypersecretion fails. The evidence in favor of this hypothesis has been reviewed by M.P.S. (34). The apparent paradox of an association between high postload insulin concentrations and conversion from normal glucose tolerance and between falling postload insulin concentrations and conversion from IGT could be resolved by postulating that those who convert from IGT are already experiencing a deterioration in their ability to compensate for insulin resistance by maintaining high levels of insulin secretion, i.e., they are undergoing incipient pancreatic exhaustion.

Several lines of evidence suggest that insulin resistance may be inherited. Lillioja et al. (35) showed that insulin resistance is a familial trait in nondiabetic Pima Indians, and Bogardus et al. (36) showed that it has a trimodal distribution in this population, suggesting an autosomal codominant mode of inheritance. Also, nondiabetic Mexican Americans with a parental history of diabetes have higher insulin con-

centrations than nondiabetic Mexican Americans without such a history (37). These differences in insulin concentration persist even after adjustment for BMI glucose concentration, and both upper and central adiposity (37). Recently, two different restriction-fragment–length polymorphisms of the insulin-receptor gene (a candidate gene for type II diabetes) have been reported to be associated with type II diabetes in Whites (38) and Mexican Americans (39). These findings offer further support for the concept that insulin resistance is inherited, although it remains to be shown that either polymorphism is associated with functional disturbances of the insulin receptor.

The magnitude of the effect of obesity on diabetes incidence estimated from this study (RR = 1.97) is similar to that reported by Saad et al. (RR = 2.4; 14), Keen at al. (RR = 2.1; 11), and Modan et al. (RR = 1.6; 40). As in reports on very obese Pima Indians (14) and Nauruans (15), our study of moderately obese Mexican Americans indicates that the effect of obesity is no longer statistically significant after adjustment for insulin and glucose. These findings suggest that the effect of obesity may be mediated by insulin resistance. Also, as in previous reports (11,14), we found a markedly increased risk of type II diabetes with increasing baseline glucose concentrations. The increased risk in the highest quartile of fasting glucose (≥95.5 mg/dl) relative to the lowest three quartiles was 13.2; the increased risk in subjects who had IGT at baseline was 6.17 compared with subjects who had NGT at baseline. We also found an increase in incidence of diabetes with increasing central adiposity, thereby confirming an earlier report in Swedish men (13), although in that study, the assessment of body-fat distribution was based on the ratio of waist-to-hip circumference. Insulin concentrations were not reported in the Swedish study.

The observation that BMI is not a significant independent predictor of type II diabetes in multivariate analysis should not be interpreted as implying that adiposity plays no role in the development of diabetes in Mexican Americans. In crude (i.e., unadjusted) analyses, obese Mexican Americans have an increased incidence of diabetes relative to lean Mexican Americans. However, in developing a public health strategy to prevent diabetes, it might be preferable to concentrate on individuals who have high insulin and glucose concentrations rather than those who are obese but without these metabolic abnormalities. Nearly half of future diabetic individuals are located in that subset of the population who are simultaneously in the highest quartile of both fasting insulin and fasting glucose concentrations. In these individuals, techniques to improve insulin sensitivity, including behavioral modifications, e.g., weight reduction and increased physical activity, might be applied. Identification of candidates for intervention on the basis of fasting insulin and glucose concentrations, rather than on the basis of obesity per se, would circumvent intervention attempts on subjects who, although obese, are relatively insulin sensitive and thus at less risk for type II diabetes. Further work on metabolic predictors of type II diabetes should be performed in high- and/or intermediate-risk populations, e.g., Native Americans, Mexican Americans, and offspring of diabetic parents, to assist in the development of an effective public health strategy to identify at-risk subjects.

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