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Are risk factors for conversion to NIDDM similar in high and low risk populations?

S.M. Haffner, H. Miettinen, M. P. Stern

Department of Medicine, Division of Clinical Epidemiology, University of Texas Health Science Center, San Antonio, Texas, USA

Summary Mexican Americans have an increased risk of non-insulin-dependent diabetes mellitus (NIDDM) relative to non-Hispanic whites which is only partially explained by their excess overall obesity and unfavourable body fat distribution. Non-diabetic Mexican Americans have hyperinsulinaemia and insulin resistance relative to non-Hispanic whites. We therefore hypothesized that the insulin resistance might be a more important predictor of NIDDM in high-risk populations characterized by obesity and insulin resistance, while compromised insulin secretion might be a more important risk factor for NIDDM in low-risk populations. We assessed the ability of ethnicity (Mexican American vs non-Hispanic white), age, overall adiposity (body mass index [BMI]), unfavourable body fat distribution (as assessed by waist-to-hip ratio [WHR]), glucose tolerance (impaired glucose tolerance vs normal glucose tolerance), fasting insulin and compromised insulin secretion (as assessed by increment in insulin to the increment in glucose over the first 30 min of an oral glucose tolerance test ($\Delta I_{30}/\Delta G_{30}$)) to predict future NIDDM. In the 8-year follow-up of the San Antonio Heart Study, NIDDM developed in 11.7 % (107/914) of Mexican Americans and in 5.0 % (18/362) of non-Hispanic whites ($p < 0.001$). Multivariate predictors of NIDDM by multiple logistic regression analysis included increased age, BMI, WHR, fasting insulin and impaired glucose tolerance and decreased insulin secretion. The strongest independent predictors of NIDDM were high fasting insulin and decreased insulin secretion. These risk factors predicted NIDDM equally well in high and low-risk populations. [Diabetologia (1997) 40: 62–66]

Keywords Mexican Americans, insulin, obesity, NIDDM.

Numerous studies have shown that Mexican Americans have an increased prevalence [1–4] and incidence [5] of non-insulin-dependent diabetes mellitus (NIDDM) relative to non-Hispanic whites. The Mexican American population is characterized by increased adiposity [1–4, 6], a more centralized distribution of body fat [6, 7], hyperinsulinaemia [8–10] and insulin resistance [11, 12].

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Corresponding author: Dr. S. Haffner, Department of Medicine, Division of Clinical Epidemiology, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, Texas 78284–7873, USA

Abbreviations: NIDDM, Non-insulin-dependent diabetes mellitus; WHO, World Health Organization.

Metabolic factors have been shown to be important risk factors for the development of NIDDM. Both insulin resistance [13, 14] and hyperinsulinaemia [13, 15–19] have been shown to predict NIDDM. Likewise, decreased insulin secretion in response to various stimuli may predict NIDDM. A low acute insulin response has been found to predict NIDDM in Pima Indians [13], but not in children of two Caucasian diabetic parents [14]. A low 30-min increment in insulin relative to the 30-min increment in glucose ($\Delta I_{30}/\Delta G_{30}$) during an oral glucose tolerance test predicts conversion to NIDDM, especially in subjects with impaired glucose tolerance [20–23]. A low insulin response 60 min after an intravenous glucose challenge also predicted NIDDM [24, 25]. A low 2-h insulin in response to an oral glucose load also

predicts conversion to NIDDM in impaired glucose tolerance subjects [17, 18]. We have recently shown that both increased fasting insulin (a proxy for insulin resistance) and decreased $\Delta I_{30}/\Delta G_{30}$ (a proxy for decreased insulin secretion) predict the development of NIDDM in Mexican Americans [23].

Weir [26] has suggested that risk factors for NIDDM may differ in different populations. Obese subjects with a family history of diabetes are characterized by insulin resistance [27, 28], while lean Caucasian subjects with a family history of diabetes may be characterized by decreased insulin secretion [29]. We thus examined whether risk factors for the development of NIDDM might differ in Mexican Americans (a high-risk population for NIDDM) and non-Hispanic whites (a low-risk population for NIDDM). Most previous studies of metabolic risk factors for NIDDM have been in high-risk populations [13–18, 23] with a few exceptions [19, 21, 24, 25]. Previous studies in high-risk populations (which are generally obese and characterized by insulin resistance) have generally emphasized increased insulin resistance as a predictor of NIDDM while studies in low-risk populations have often emphasized decreased insulin secretion. In a few cases such as in Swedish subjects both low insulin secretion and insulin resistance predicted the development of NIDDM [24, 25]. However, no study has previously compared risk factors for the development of NIDDM in high and low-risk populations.

Subjects 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 (Phase I) and from 1984 to 1988 (Phase II), we randomly selected households from low-income (barrio), middle income (transitional), and high income (suburban) census tracts in San Antonio [1, 8]. Mexican Americans were defined as individuals whose ancestry and cultural traditions are derived from a Mexican national origin [30]. This study was approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio. All subjects gave informed consent.

Beginning in October 1990, we began a 7 to 8-year follow-up of the Phase II cohort [23]. The results in this report are based on risk factors for the development of NIDDM in the first four of six census tracts (one upper, two low income, and one middle income) of the Phase II cohort. Subjects with diabetes at the baseline examination are excluded from the analyses presented in this report.

At the baseline and follow-up of the Phase II cohort, blood specimens were obtained after a 12 to 14-h fast for determination of serum insulin and plasma glucose concentrations. Plasma glucose was determined by a glucose oxidase method. We measured serum insulin with a solid phase radioimmunoassay (Diagnostic Products Corporation, Los Angeles, Calif., USA) which shows a relatively high degree of cross reactivity with proinsulin (about 70 to 100 %) [10]. At Phase II baseline and follow-up, a 75-g glucose equivalent load (Koladex or Orangedex, Custom Laboratories, Baltimore, MD, USA) was administered and blood specimens were obtained 2 h later for plasma glucose and serum insulin concentrations. Diabetes and impaired glucose tolerance were diagnosed according to World Health Organization (WHO) criteria [31]. Subjects who did not meet WHO plasma glucose criteria, but who were under treatment with oral antidiabetic agents or insulin were considered to have diabetes. Subjects on diet therapy or oral antihyperglycaemic therapy were considered to have NIDDM. Additionally, subjects on insulin therapy who were obese (body mass index ≥ 30 kg/m^2) and with an onset of diabetes greater than 40 years were also considered to have NIDDM. Other subjects taking insulin were considered to have possible insulin-dependent diabetes and were excluded from this report.

Anthropometric measurements (height, weight and waist and hip circumference) were made after participants had removed their shoes and upper garments and donned an examining gown [7]. Body mass index was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured at the level of the umbilicus and hip circumference at the level of the greater trochanter. The waist-to-hip ratio was used as a measure of upper body adiposity.

Statistical analysis

Statistical analyses were performed using the SAS statistical package (version 6.09). Statistical analyses included chi-squared test (Table 1), Mantel Haenszel odds ratio (Table 1), the Breslow-Day test of heterogeneity (Table 1) and multiple logistic regression analyses (Tables 2 and 3). The Breslow-Day test of heterogeneity is a test of statistical interaction. We also tested for statistical interaction (ethnicity $\times$ other risk factors such as fasting insulin) in multiple logistic regression analyses. None of these interaction terms was significant ($p > 0.05$). Multiple logistic regression analyses were performed using both dichotomous predictor variables (above and below the median for the independent variables) and continuous independent variables. Both of these approaches yielded similar results. Therefore, the statistically more powerful continuous independent variables (except for impaired vs normal glucose tolerance) were used in multiple logistic regression analyses. The dependent variable in multiple logistic regression analyses was the development of NIDDM. This report emphasizes fasting insulin as a measure of insulin resistance [32, 33] and the ratio of the 30 min change in insulin to the 30 min change in glucose ($\Delta I_{30}/\Delta G_{30}$) [34] during the oral glucose tolerance test as a measure of insulin secretion. We also tested ΔI_{30} and ΔG_{30} as separate independent variables in multiple logistic regression analyses (similar to Tables 2 and 3) and results were similar to those obtained with $\Delta I_{30}/\Delta G_{30}$ as a ratio. Only the latter is presented in this report.

Results

The mean age was 43.5 ± 0.3 years and the mean body mass index was 28.0 ± 0.3 kg/m^2. Table 1 shows the incidence of diabetes by ethnicity and selected variables. None of the tests for heterogeneity was statistically significant suggesting that the effect of risk factors on the risk of developing diabetes is similar among subjects with high and low-levels of risk factors (e. g. obese vs lean).

Table 2 shows the results of multiple logistic regression analyses (separately for each ethnic group)

Table 1. Incidence of NIDDM by ethnicity and selected variables

	Mexican American		Non-Hispanic white	
	8-year incidence		8-year incidence	
	n	(%)	*n*	(%)
Age at baseline (years)				
25–44	39/522	7.5	6/204	2.9
45–65	68/392	17.3	12/158	7.6
RR (old/young)		2.31		2.62
	$p = 0.001$		$p = 0.043$	
Sex				
Male	38/362	10.5	9/171	5.3
Female	69/552	12.5	9/191	4.7
RR (female/male)		1.19		0.87
	$p = 0.357$		$p = 0.810$	
Body mass index (kg/m$^{2)}$				
Low (< 27.7)	37/476	7.8	9/253	3.6
High (≥ 28.7)	70/438	16.0	9/109	8.3
RR (high/low)		2.05		2.31
	$p = 0.001$		$p = 0.059$	
Waist-to-hip ratio[a]				
Low	34/483	7.1	5/213	2.3
High	73/431	16.9	13/149	8.7
RR (high/low)		2.38		3.78
	$p = 0.001$		$p = 0.006$	
Glucose tolerance				
Normal	46/733	6.3	7/320	2.2
Impaired	53/138	38.4	9/26	34.6
RR (IGT/NGT)		6.10		15.73
	$p = 0.001$		$p = 0.001$	
Fasting insulin (pmol)				
Low (< 78.7)	45/571	7.9	6/272	2.2
High (≥ 78.7)	62/343	18.1	12/96	12.5
RR (high/low)		2.29		5.68
	$p = 0.001$		$p = 0.001$	
$\Delta I_{30}/\Delta G_{30}$ (pmol/mmol)				
Low (< 281)	88/593	14.8	16/269	5.9
High (≥ 281)	19/321	5.9	2/93	2.2
RR (high/low)		0.40		0.37
	$p = 0.001$		$p = 0.146$	

RR, Relative risk; ΔI_{30}, change in insulin over first 30 min of a glucose tolerance test; ΔG_{30}, change in glucose over first 30 min of an oral glucose tolerance test

Note: Breslow Day test used to compute heterogeneity

[a] Cutoff point for women: 0.825; men: 0.938

Table 2. Multiple logistic regression analyses with the development of NIDDM as a dependent variable

Variable	Mexican Americans		non-Hispanic whites	
	Odds ratio	*p*-value	Odds ratio	*p*-value
Ln fasting insulin	2.81	< 0.001	5.12	< 0.001
Ln $\Delta I_{30}/\Delta G_{30}$	0.265	< 0.001	0.440	0.040

Age, gender, body mass index, waist-to-hip ratio and impaired glucose tolerance vs normal glucose tolerance were also included in the regression model.

$\Delta I_{30}/\Delta G_{30}$, Change in insulin to change in glucose over first 30 min of a glucose tolerance test

with the development of NIDDM as the dependent variable and fasting insulin and $\Delta I_{30}/\Delta G_{30}$ as independent variables. (In these models, age, body mass index, waist to hip ratio, gender and impaired glucose tolerance vs normal glucose tolerance were also included but are not shown in Table 2.) In Mexican Americans and non-Hispanic whites, both high fasting insulin and low $\Delta I_{30}/\Delta G_{30}$ predicted conversion to NIDDM. Fasting insulin was stronger in non-Hispanic whites and $\Delta I_{30}/\Delta G_{30}$ in Mexican Americans. However, the interaction terms (ethnicity × fasting insulin and ethnicity × $\Delta I_{30}/\Delta G_{30}$) were not statistically significant when the ethnic groups were pooled and an interaction term included in the model.

Table 3 presents a multiple logistic regression analyses in which the parameter estimates for all independent variables are shown. Age, Mexican American ethnicity, body mass index, waist to hip ratio, fasting insulin and impaired glucose tolerance were significantly positively related to NIDDM. A low $\Delta I_{30}/\Delta G_{30}$ was also significantly related to NIDDM. Gender was not significantly related to NIDDM.

Table 3. Multiple logistic regression analyses with the development of NIDDM as a dependent variable

Variable	B	SE(B)	Odds ratio	95% Confidence interval	*p*-value	Chi square
Age (years)	0.215	0.109	1.24	1.002, 1.535	0.048	3.90
Gender (male/female)	0.445	0.276	1.56	0.909, 2.677	0.107	2.60
Ethnic (MA/NHW)	0.1207	0.3086	1.48	1.12, 3.76	0.019	5.45
Body mass index (kg/m^2)	0.0496	0.0216	1.05	1.007, 1.096	0.022	5.28
Waist/hip ratio	0.389	0.154	1.48	1.09, 1.99	0.011	6.45
Ln fasting insulin	1.420	0.172	3.29	2.35, 4.63	< 0.001	46.3
$\Delta I_{30}/\Delta G_{30}$	− 1.12	0.174	0.322	0.219, 0.476	< 0.001	32.3
Impaired glucose tolerance (yes/no)	1.10	0.247	3.00	1.85, 4.88	< 0.001	19.6

MA, Mexican American; NHW, non-Hispanic white; $\Delta I_{30}/\Delta G_{30}$, change in insulin to change in glucose over the first 30 min of an oral glucose tolerance test

Discussion

We show that a similar pattern of risk factors for NIDDM operates in both high-risk populations for NIDDM characterized by obesity and insulin resistance and also in low-risk populations for NIDDM. In both Mexican Americans and non-Hispanic whites, increased fasting insulin significantly predicted the development of NIDDM. A low $\Delta I_{30}/\Delta G_{30}$ representing decreased insulin secretion in response to oral glucose predicted NIDDM significantly in Mexican Americans but not in non-Hispanic whites. However, the point estimate for the risk ratio for low $\Delta I_{30}/\Delta G_{30}$ (Table 1) was similar in the two ethnic groups, suggesting that the lack of association in non-Hispanic whites may be due to low statistical power. Moreover, when both ethnic groups were combined, and the interaction term for $\Delta I_{30}/\Delta G_{30} \times$ ethnicity was tested, this term was not statistically significant.

In previous reports, especially in non-diabetic relatives of subjects with NIDDM, there has been controversy about which defect (decreased insulin secretion or insulin resistance) is more important [26–29, 35, 36]. Our data suggest that both are important in the aetiology of NIDDM in both high and low-risk populations for NIDDM. Increased fasting insulin was a stronger predictor in terms of relative risk in non-Hispanic whites than in Mexican Americans which was contrary to our initial hypothesis that fasting insulin would be stronger in Mexican Americans. However, the Breslow-Day test for heterogeneity was not statistically significant ($p = 0.11$). These data are compatible with a recent report showing defects in both insulin secretion and resistance in identical twins discordant for NIDDM [36]. In previous studies, a low acute insulin response predicted the development of NIDDM in obese Pima Indians [13], but not in children of diabetic Caucasian parents [14]. In the Pima study, insulin secretion was a much weaker predictor of NIDDM than was decreased insulin sensitivity [13]. In two Swedish studies, both decreased insulin secretion (as judged by the 60-min insulin response to an intravenous glucose challenge) and insulin sensitivity (as judged by fasting insulin level) predicted the development of NIDDM [24, 25].

Relatively few studies have directly compared fasting insulin with insulin resistance in their relative ability to predict the incidence of NIDDM. Low insulin sensitivity (at the 10th percentile compared to the 90th percentile) was associated with a 30-fold relative risk of NIDDM, whereas high fasting insulin (at the 90th percentile compared to the 10th percentile) was associated with a 15-fold relative risk of NIDDM in Pima Indians [13].

In the present report, insulin was measured with an assay that cross-reacts with proinsulin. Several studies have shown that proinsulin is disproportionately elevated in subjects with NIDDM [10, 37–41]. The ratio of fasting proinsulin/fasting insulin, however, is only minimally elevated in subjects with impaired glucose tolerance in some studies [10, 39] and not at all in others [40]. At the time of the baseline survey (1984–1988), specific insulin assays were not available. However, the ratio of fasting proinsulin/specific insulin in Mexican Americans with impaired glucose tolerance (measured at the follow-up examination) [10] is only slightly higher than in Mexican American subjects with normal glucose tolerance (0.09 vs 0.07, respectively), but still very low, and thus unlikely to confound our measurement of insulin at baseline. Additionally, non-diabetic Mexican Americans have similar fasting proinsulin/insulin ratios to non-diabetic non-Hispanic whites [10].

In conclusion, we have shown that risk factors for NIDDM are similar in different populations having differing risks of NIDDM suggesting that for most subjects, similar pathophysiologic mechanisms may apply, although clearly the genetic basis may differ. In future studies, more sophisticated measures of insulin resistance (e.g. hyperinsulinaemic euglycaemic clamp or frequently sampled intravenous glucose tolerance test) and secretion (e.g. acute insulin response) should be performed, although these tests are expensive and thus might be restricted to high-risk subjects such as those with impaired glucose tolerance.

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