Ethnic Differences in Insulin Resistance and Its Consequences in Older Mexican American and Non-Hispanic White Women

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Background. This study was initiated to test the hypothesis that older, healthy, nondiabetic Mexican American women would be relatively resistant to insulin-mediated glucose disposal, hyperinsulinemic, and dyslipidemic as compared to a matched group of non-Hispanic White (NHW) women.

Methods. The study, cross-sectional in nature, involved 14 Mexican American and 19 NHW healthy, normotensive, nondiabetic, postmenopausal women of similar age and body mass index. It took place in the General Clinical Research Center at Stanford Medical Center. Measurements were made of fasting plasma glucose, insulin and lipid concentrations, and plasma glucose and insulin concentrations following a 75 gram oral glucose challenge. Resistance to insulin-mediated glucose disposal was estimated by the steady-state plasma glucose (SSPG) concentration achieved at the end of a 3 hour constant infusion of glucose, insulin, and somatostatin.

Results. Mexican American women had significantly greater glucose \( (p < .001) \) and insulin \( (p < .001) \) responses to the oral glucose challenge than did the NHW women. Resistance to insulin-mediated glucose disposal was increased in Mexican American women (SSPG 195 ± 25 mg/dl compared to 137 ± 18 mg/dl in NHW; \( p < .001 \)). While total cholesterol, low density lipoprotein (LDL)-cholesterol, and triglyceride concentrations were not significantly different in the two ethnic groups, high density lipoprotein (HDL)-cholesterol was significantly lower in the Mexican American women (51 mg/dl vs 61 mg/dl; \( p = .04 \)).

Conclusion. Older Mexican American women are more insulin resistant, glucose intolerant, and hyperinsulinemic, and have a lower HDL-cholesterol than a matched group of non-Hispanic White peers. These results were observed despite the exclusion of individuals with non-insulin dependent diabetes mellitus (NIDDM).

Several recent publications have emphasized the fact that the prevalence of non-insulin dependent diabetes (NIDDM) varies widely in different ethnic groups (1–5). For example, approximately 5,096 of Pima Indians in the age group 30–64 have NIDDM (1). Other ethnic groups in whom high prevalences of NIDDM are reported include Nauruans (2), Mauritians (3), Asian Indians (4), and Mexican Americans (5). This latter group, which constitutes a significant and increasing proportion of the elderly population of the United States, has a three- to fivefold excess prevalence of non-insulin dependent diabetes compared to non-Hispanic Whites (2–5). The prevalence of diabetes increases with age in Mexican Americans, as in all ethnic groups, such that over the age of 60 more than 1 in 4 are diabetic (9). Diabetes therefore causes a substantial burden of chronic health problems among the Mexican American elderly.

Resistance to insulin-mediated glucose uptake appears to be a primary pathophysiological abnormality predisposing to NIDDM (10). One would, therefore, expect insulin resistance to be more common in populations at increased risk for NIDDM. This view has been supported by results of large community-based studies among Mexican Americans, using fasting and post-glucose hyperinsulinemia as a surrogate marker of insulin resistance (11,12). More recently, Haffner et al. (13) have published direct evidence that insulin sensitivity was decreased in a relatively small number of young, nondiabetic Mexican Americans as compared to a matched group of non-Hispanic Whites (NHW). The present study was initiated to expand the inquiry concerning insulin action in Mexican Americans, but focused on comparing insulin-mediated glucose disposal in healthy, postmenopausal women over the age of 60, all of whom had a nondiabetic oral glucose tolerance test (14). By examining an age group with an increased prevalence of NIDDM, and by only studying those individuals who had not yet developed NIDDM, the ability to still discern a difference in insulin-mediated disposal would emphasize the importance of ethnicity in modulation of this phenomenon.

Materials and Methods

Subjects

Healthy postmenopausal women were recruited from the San Francisco Bay area by advertisements in local English and Spanish language newspapers, and contact with church and community groups. Fourteen Mexican American and 19
non-Hispanic White (NHW) women of similar age and body mass index were enrolled in the study. “Mexican American” was defined as persons who were born in Mexico or whose parents or grandparents originated in Mexico. All subjects were judged to be in good general health, with no evidence of disease on the basis of history, physical examination, complete blood count, routine biochemical screening, and electrocardiogram. They were normotensive (blood pressure < 160/90) and taking no medication known to affect carbohydrate or lipid metabolism. Similar proportions of the two groups were taking estrogen hormone replacement (2 of 14 Mexican American women and 3 of the 19 NHW). All subjects were questioned about their habitual diet and level of activity. None of the volunteers was following a specific diet; weight had been stable for the past 6 months, and dietary composition approximated the conventional American diet in both groups. No subject was engaged in a regular program of exercise, and estimates of daily level of physical activity were similar in the two groups. This project was approved by the Stanford Human Subjects Committee, and all women gave informed consent in their language of choice. Characteristics of the 14 Mexican American and 19 NHW women studied are presented in Table 1. They were well-matched for age, body mass index (BMI), ratio of the waist-to-hip girth (W/H ratio), and blood pressure.

**Measurements**

*Oral glucose tolerance test (OGTT).* — After an overnight fast, blood was drawn for measurement of plasma glucose (15) and insulin (16) concentrations before and 30, 60, 120, and 180 minutes after the ingestion of a 75 g oral glucose challenge. Only volunteer subjects with a non-diabetic OGTT by the World Health Organization (WHO) criteria were included in the study (14). Two of the women in each group had a diagnosis of impaired glucose tolerance by WHO criteria.

*Insulin suppression test.* — Resistance to insulin-mediated glucose disposal was estimated by a modification of the insulin suppression test originally described by our research group (17,18). After an overnight fast, intravenous catheters were placed in a superficial antecubital vein in each arm. One arm was used for a continuous 180 min infusion of glucose (240 mg/m2/min), somatostatin (5 μg/min), and insulin (25 mU/m2/min). Venous blood samples for glucose and insulin were obtained from the contralateral arm every 30 min (to 150 min), and then every 10 min for the last half-hour of the infusion. The mean of these last four values was used to calculate the steady-state plasma glucose (SSPG) and insulin (SSPI) concentrations. Under these experimental conditions, endogenous insulin secretion is suppressed by somatostatin and the SSPI concentration achieved is comparable in all individuals. Consequently, the SSPG concentration provides a measure of insulin-mediated glucose disposal: the higher the SSPG, the more insulin-resistant the individual.

*Plasma lipids.* — Venous blood for measurement of triglyceride (19) and cholesterol (20) concentration was obtained after an overnight fast on two occasions. In addition, plasma was separated by ultracentrifugation (21) for measurement of low density lipoprotein (LDL) and high density lipoprotein (HDL) cholesterol concentrations.

**Statistical analysis.** — Values for continuous variables are expressed as a mean ± standard error (SEM). The areas under the glucose and insulin curves following the oral glucose challenge were calculated using the trapezoidal method. Comparisons of the fasting lipid and lipoprotein values of the two groups were performed using the two-tailed, unpaired Student's t-test. Differences between the SSPG concentration and glucose and insulin responses in the two ethnic groups were compared by two-way analysis of variance (ANOVA) using SAS software (SAS Inc., Cary, NC). Correlations between insulin resistance and other variables were analyzed using Pearson's correlation coefficients.

**RESULTS**

Fasting plasma glucose and insulin concentrations were similar in the two ethnic groups. However, it can be seen in Figure 1 that both the plasma glucose and insulin responses to oral glucose were greater in the Mexican American women ($p < .001$, two-way ANOVA). Mexican American women also had greater total integrated glucose (370 ± 18 mg/dl×h vs 325 ± 13 mg/dl×h, $p < .05$) and insulin (237 ± 47 μU/ml×h vs 130 ± 16 μU/ml×h, $p < .02$) responses when compared by unpaired t-test.
Figure 2 shows the steady-state plasma insulin (SSPI) and glucose (SSPG) concentrations of the two groups during the insulin suppression test. The SSPI concentrations were similar in both groups of women; 59 ± 7 μU/ml in Mexican Americans and 54 ± 3 μU/ml in NHW. Despite the almost identical SSPI levels, SSPG concentrations were significantly higher in the Mexican American women (195 ± 25 mg/dl vs 137 ± 18 mg/dl; p < .001).

Plasma lipid and lipoprotein concentrations of the two groups are illustrated in Table 2. These data demonstrate that total plasma cholesterol, LDL-cholesterol, and triglyceride (TG) concentrations were not significantly different in the two ethnic groups. However, HDL-cholesterol concentration was lower in the Mexican American women (51 mg/dl vs 61 mg/dl in the NHW women; p = .04).

Since previous studies had demonstrated significant relationships between insulin resistance and plasma glucose, insulin, triglyceride, and HDL-cholesterol concentrations (10), we examined this issue in our study group. The results of the correlation coefficients between SSPG concentration (insulin resistance) and six metabolic variables are presented in Table 3. These data demonstrate the presence of significant relationships between SSPG and both the plasma glucose and insulin responses to the oral glucose challenge, as well as the plasma TG and VLDL-cholesterol concentrations. On the other hand, there was no relationship between SSPG and either total or LDL-cholesterol concentration. It should be noted that the significant relationships were present within each ethnic group. The only possible exception to this generalization is that the magnitude of the relationship between SSPG and TG was decreased in the Mexican American subjects. Whether this represents a true ethnic difference, or is simply a function of the relatively small sample size and variability inherent in measurement of TG concentration, cannot be determined.

**DISCUSSION**

The results have shown that the older Mexican American women studied were insulin resistant, glucose intolerant, and hyperinsulinemic when compared to similarly aged NHW women. Furthermore, these results are not readily explained by differences in degree of overall or regional obesity, blood pressure, or estrogen use. Although our results are similar to the observations by Haffner et al. (13), they compared young (average age of 31 years) Mexican Americans to NHW. By studying women over the age of 60 years, we have selected an age group in which one would expect 25–50% of the Mexican American women to have NIDDM (22). The fact that older Mexican American women, who had not developed NIDDM, were more insulin resistant than NHW women, provides additional and persuasive evidence of the importance of ethnicity in modulation of insulin-mediated glucose disposal. Since insulin resistance has been documented in both young and older Mexican women, it seems highly unlikely that our findings are due to an accentuated decline in insulin-mediated glucose disposal with age in this ethnic group. Additional support for this view can be derived from knowledge of the epidemiology of NIDDM in Mexican Americans and non-Hispanic Whites.

The first recognizable metabolic defect in the development of NIDDM in both Mexican Americans (23) and non-Hispanic Whites (24) is insulin resistance. Despite this qualitative similarity between the two ethnic groups, the prevalence of NIDDM is approximately 3.5 times greater in Mexican Americans (8), and this difference is independent of age. Thus, although aging is associated with a modest decline in insulin-mediated glucose disposal (25–27), there is no reason to believe that this phenomenon is greater in Mexican Americans. Finally, the importance of ethnicity in determining differences in insulin action can also be derived from recent studies from our group (28), in which we were able to show that Asian Indian men and women were insulin resistant and hyperinsulinemic compared to NHW of both genders.

<table>
<thead>
<tr>
<th>Variable (mg/dL)</th>
<th>Non-Hispanic White</th>
<th>Mexican American</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol (CHOL)</td>
<td>200 ± 11</td>
<td>205 ± 12</td>
<td>0.80</td>
</tr>
<tr>
<td>LDL-CHOL</td>
<td>108 ± 8</td>
<td>114 ± 11</td>
<td>0.60</td>
</tr>
<tr>
<td>HDL-CHOL</td>
<td>61 ± 4</td>
<td>51 ± 4</td>
<td>0.04</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>116 ± 18</td>
<td>143 ± 24</td>
<td>0.40</td>
</tr>
</tbody>
</table>

Table 2. Fasting Plasma Lipids and Lipoprotein Concentrations (Mean ± SEM)

Table 3. Correlation Coefficients (R) Between Insulin Resistance (SSPG) and Glucose, Insulin, and Lipid Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Combined R</th>
<th>Non-Hispanic White R</th>
<th>Mexican American R</th>
</tr>
</thead>
<tbody>
<tr>
<td>OGTT glucose area</td>
<td>0.6***</td>
<td>0.6**</td>
<td>0.6*</td>
</tr>
<tr>
<td>OGTT insulin area</td>
<td>0.7***</td>
<td>0.7***</td>
<td>0.8***</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0.11</td>
<td>0.25</td>
<td>-0.08</td>
</tr>
<tr>
<td>LDL-CHOL</td>
<td>0.13</td>
<td>0.06</td>
<td>-0.08</td>
</tr>
<tr>
<td>HDL-CHOL</td>
<td>-0.5**</td>
<td>-0.4</td>
<td>-0.5</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>0.6***</td>
<td>0.8***</td>
<td>0.5</td>
</tr>
</tbody>
</table>

*p < .05; **p < .01; ***p < .001.
The fact that insulin resistance varies as a function of ethnicity does not necessarily mean that the differences have a genetic basis. For example, obesity is more common among Mexican Americans, and 30% of women aged above 60 have a BMI >30 kg/m² (29). However, the excess prevalence of NIDDM is not wholly accounted for by the higher prevalence of obesity and unfavorable distribution of body fat in this population (30,31). Similarly, differences in degree of obesity, as estimated in this study, cannot account for our observation that Mexican American women were more insulin resistant than NHW. On the other hand, we estimated visceral obesity by the ratio of waist-to-hip girth, and it is possible that a more sensitive estimate would have revealed an ethnic difference.

It should also be noted that we did not attempt to quantify dietary intake and physical activity in the subjects. However, as part of the medical history we estimated the habitual diet and level of physical activity. In this context, weight had been stable for at least several months in all individuals, and the diet history of all subjects was similar to that of the average American diet. Furthermore, there is evidence that fairly wide variations in dietary composition have essentially no effect on insulin-mediated glucose disposal (32,33). Finally, no subject was engaged in a regular program of exercise, and the variations in level of habitual physical activity of the experimental subjects would not be anticipated to substantially modify in vivo insulin action.

Familial clustering of insulin resistance has been demonstrated in three different ethnic groups: Pima Indians (34), Europeans (35), and Mexican Americans (36). This familial aggregation of insulin resistance could be due to a shared genetic background, a common environment, or both. Although it is not possible to definitively choose between these alternatives, available data permit an argument to be made in support of the view that genetic differences contribute to at least some portion of the ethnic difference in insulin resistance between Mexican Americans and NHWs. Native Americans have a greatly increased prevalence of NIDDM (37), and Mexican Americans are estimated to have 31% of the gene pool of Native Americans origin (38). The high frequency of Native American-derived genes in the contemporary Mexican American population predicts a higher prevalence of insulin resistance and NIDDM, assuming that genetic factors are important in the etiology of NIDDM. Furthermore, within the Mexican American population, the prevalence of NIDDM in different income neighborhoods in San Antonio paralleled the percentage of Native American mixture (39). Thus, there is certainly experimental support for the view that ethnic differences in insulin resistance and prevalence of NIDDM in the Mexican American population have at least some genetic basis.

In NHW and Asian Indian populations, insulin resistance and compensatory hyperinsulinemia are also associated with an increase in plasma TG and a decrease in HDL-cholesterol concentration (10,28). This association was similarly observed in the present study, in that Mexican American women had significantly lower HDL-cholesterol concentrations. Furthermore, this ethnic difference could not be attributed to estrogen replacement (40) in that very few experimental subjects were receiving hormone replacement therapy. Plasma TG concentrations were also higher in the Mexican American women, although the difference did not reach statistical significance. Due to our small sample size, however, it may be difficult to demonstrate significance since plasma TG concentrations have a wide skewed distribution, and show a larger intra-individual variation than other lipid variables measure (41). In addition, there were statistically significant correlations between SSPG (insulin resistance) and the plasma glucose and insulin responses to oral glucose, and the plasma TG and HDL-cholesterol concentration in the population as a whole. Furthermore, the relationships (with the exception of the plasma TG concentration) were significant in each group when considered alone. However, it should be noted that neither total nor LDL-cholesterol correlated with insulin resistance.

In conclusion, an older group of Mexican American women, with normal glucose tolerance, were found to be relatively insulin resistant, hyperglycemic, hyperinsulinemic, and dyslipidemic when compared to a matched group of NHW women. It is suggested that these findings are at least partly due to differences at the genetic level.

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REFERENCES


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