Insulin Sensitivity Differs Among Ethnic Groups With a Compensatory Response in β-Cell Function

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OBJECTIVE — A drastic difference is evident in the prevalence of type 2 diabetes among ethnic groups. We examined the role of β-cell function and insulin sensitivity in this disparity among 4 ethnic groups.

RESEARCH DESIGN AND METHODS — β-Cell function and insulin sensitivity were assessed in 77 healthy glucose-tolerant subjects using a hyperglycemic clamp (18 Asian-Americans, 9 African-Americans, 34 Caucasians, and 16 Mexican-Americans).

RESULTS — A wide range of variation was evident in clinical features of the studied subjects. Insulin sensitivity index and the second-phase insulin response differed among the 4 groups ($P = 0.0023$ and $P = 0.0082$, respectively), whereas the first-phase insulin response was marginally different ($P = 0.1090$). Stepwise regression analysis revealed that ethnicity was an independent determinant for the insulin sensitivity index ($P = 0.0014$) after adjusting for sex, age, diastolic blood pressure, waist-to-hip ratio, and BMI. Also, a compensatory response of β-cell function was observed among the ethnic groups.

CONCLUSIONS — In this study, we observed a drastic difference in insulin sensitivity among the different ethnic groups and observed that their β-cell function compensates for the prevailing insulin sensitivity. The difference in the prevalence of abnormal glucose tolerance in different ethnic groups could be a result of differences in insulin sensitivity.

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Type 2 diabetes and its complications are a major cause of morbidity and mortality in adults. In 1992, patients with diabetes constituted 4.5% of the U.S. population but accounted for 14.6% of total U.S. health care expenditures (1). Approximately 1 in 7 health care dollars is currently spent on caring for diabetic individuals, and 95% of these patients have type 2 diabetes (1). However, a marked interracial variability exists in the prevalence of abnormal glucose tolerance in the U.S. population (2). The prevalence rates range from 14.1 to 18.8 to 22.7% for Caucasians, African-Americans, and Mexican-Americans, respectively. Substantial progress has been made toward identifying population-based risk factors in the development of type 2 diabetes that may explain these ethnic disparities around the world (3–8). Although these diabetic risk factors appear to operate in all ethnic groups, whether specific groups are inherently different in the ways they respond to these risk factors (which may lead to their differential susceptibility to diabetes) is unknown.

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Abbreviations: GCRC, General Clinical Research Center; IRAS, Insulin Resistance Atherosclerosis Study; OGTT, oral glucose tolerance test; UCLA, University of California, Los Angeles; WHR, waist-to-hip ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Type 2 diabetes is an imbalance between β-cell function and insulin sensitivity (9). Because both β-cell dysfunction and insulin resistance have been shown to be inherited defects (10–12), either defect could account for the ethnic differences in the prevalence of type 2 diabetes. Although insulin resistance has been demonstrated in various minority ethnic groups in the U.S. when compared with Caucasians (4,13–16), much less is known regarding differences in β-cell function (17,18). Understanding the ethnic disparity in the pathophysiology of type 2 diabetes will likely lead to novel methods of therapy and prevention.

To investigate whether a difference exists in either insulin sensitivity or β-cell function among the 4 major ethnic groups in the U.S., we recruited 77 glucose-tolerant subjects. Insulin sensitivity index and β-cell function were assessed using a hyperglycemic clamp technique. We found that Caucasians were more insulin sensitive than Asian-Americans, African-Americans, and Mexican-Americans, and we found a compensatory response in β-cell function among the ethnic groups.

RESEARCH DESIGN AND METHODS

Study subjects

The study was approved by the Human Subject Protection Committee of the University of California, Los Angeles (UCLA). Written informed consent was obtained from all participants before they entered the study. Through an advertisement in the UCLA campus newspaper, healthy subjects who received no medical treatment were invited to undergo a screening test after an overnight fast. It included an oral glucose tolerance test (OGTT) with 75 g glucose and a brief physical examination as previously described (19,20). Only subjects who were noted to be glucose tolerant (fasting plasma glucose level <6.1 mmol/l, interval plasma glucose level <11.1 mmol/l, and 2-h plasma glucose level <7.7 mmol/l) and normotensive (blood pressure <140/90 mmHg) were invited back for the assessment of β-cell function and insulin sensi-

Table 1—*Clinical features by ethnic groups*

	Asian-Americans	African-Americans	Caucasians	Mexican-Americans	*P*
n	18	9	34	16	
Sex (F)	11 (61)	4 (44)	21 (62)	10 (63)	NS
Age (years)*	23 (20–25)	26 (22–30)	27 (25–29)	25 (22–28)	0.043
BMI (kg/m^2)*	22.92 (21.45–24.50)	25.50 (20.76–31.32)	23.98 (22.59–25.46)	26.48 (24.50–28.61)	NS
WHR (cm/cm)*	0.75 (0.73–0.77)	0.80 (0.75–0.86)	0.79 (0.77–0.83)	0.82 (0.79–0.86)	0.017
Systolic blood pressure (mmHg)	112 (106–117)	116 (108–125)	114 (110–118)	116 (110–122)	NS
Diastolic blood pressure (mmHg)	64 (60–69)	63 (58–68)	68 (66–71)	69 (65–73)	NS
Fasting lipid profile					
Triglycerides (mmol/l)	0.79 (0.59–0.99)	0.65 (0.38–0.93)	0.87 (0.70–1.04)	1.07 (0.70–1.46)	NS
Total cholesterol (mmol/l)	4.32 (3.96–4.65)	4.29 (3.80–4.78)	4.01 (3.75–4.27)	4.42 (4.01–4.81)	NS
HDL cholesterol (mmol/l)	1.47 (1.29–1.63)	1.29 (1.01–1.55)	1.27 (1.14–1.40)	1.29 (1.11–1.45)	NS
LDL cholesterol (mmol/l)	2.46 (2.15–2.79)	2.72 (2.28–3.13)	2.33 (2.09–2.56)	2.64 (2.30–2.97)	NS
Hyperglycemic clamp					
Fasting plasma glucose (mmol/l)	4.76 (4.59–4.93)	4.68 (4.41–4.95)	4.80 (4.71–4.88)	4.74 (4.55–4.93)	NS
Fasting plasma insulin (pmol/l)*	61 (50–74)	67 (53–86)	64 (58–71)	78 (65–93)	NS
Steady-state plasma glucose (mmol/l)	10.01 (9.91–10.11)	9.75 (9.49–10.01)	9.99 (9.85–10.14)	9.97 (9.84–10.09)	NS
First-phase insulin response (pmol/l)*	1,723 (1,164–2,551)	1,745 (1,113–2,736)	1,402 (1,151–1,708)	2,172 (1,840–2,565)	NS
Second-phase insulin response (pmol/l)*	533 (401–709)	495 (311–789)	358 (296–433)	592 (480–728)	0.008
Insulin sensitivity index ($\mu mol \cdot l^{-1} \cdot m^{-2} \cdot min^{-1} \cdot pmol^{-1} \cdot l^{-1}$)*	4.17 (3.09–5.64)	5.04 (2.97–8.56)	6.87 (5.71–8.27)	3.74 (2.77–5.07)	0.002

Data are *n*, *n* (%), or means (95% CIs). *Data are geometric means (95% CIs).

tivity using a modified hyperglycemic clamp technique (21). To minimize the effect of smoking, subjects were asked to refrain from smoking for at least 12 h before the study. Briefly, after an overnight fast and rest in the General Clinical Research Center (GCRC) at UCLA, participants received a bolus of 50% dextrose solution based on their body surface area (11.4 g/m^2) at 0 min. Body surface area (in meters squared) was calculated from height (in centimeters) and weight (in kilograms) with the following: $[(\text{height in cm} \times \text{weight in kg})/3{,}600]^{0.5}$ (20). Continuous infusion of 30% dextrose solution began at 15 min at variable rates that were adjusted every 5 min based on prevailing plasma glucose levels to maintain a plasma glucose level of ~10 mmol/l toward 180 min. The first-phase insulin response was the sum of plasma insulin levels during the first 10 min (at 2.5, 5, 7.5, and 10 min), and the second-phase insulin response was the average of plasma insulin levels at 130, 140, 150, 160, 170, and 180 min. No correlation was evident between the amount of bolus that was given and either the first- or second-phase insulin responses (P = 0.1764 and P = 0.1604, respectively). Insulin sensitivity index was calculated by dividing the average glucose infusion rate during the last 60 min of the clamp by the average plasma insulin level during the last 60 min of the clamp. Fasting plasma glucose and insulin levels were the average of 3 samples before glucose loading (OGTT and hyperglycemic clamp). Plasma glucose, insulin, and lipid levels were assayed as previously described (19). Ethnicity was defined as reported ethnicity by each participant. Maternal history of diabetes was noted in 2 Asian-Americans, 1 African-American, 4 Caucasians, and 0 Mexican-Americans. Paternal history of diabetes was noted in 4 Asian-Americans, 1 African-American, 4 Caucasians, and 5 Mexican-Americans. The distribution of parental history of diabetes was not different among the ethnic groups (P = 0.5667 for maternal and P = 0.4711 for paternal history of diabetes).

Statistical analysis

Differences in continuous variables between the groups of subjects were tested with either 1-way analysis of variance or Student's t test when appropriate. Differences in proportions were evaluated by a χ^2 test. The continuous variables that failed the normality test were logarithmically transformed before analysis. The transformed variables were age, BMI, waist-to-hip ratio (WHR), plasma insulin level, first-phase insulin response, second-phase insulin response, and insulin sensitivity index. To examine the influence of confounding variables, a stepwise regression analysis was used. Backward stepwise analysis with alpha-to-enter of 0.10 and alpha-to-remove of 0.10 was used to exclude variables that had little or no influence on the parameter under analysis. SYSTAT 8.0 for Windows from SPSS (Chicago) was used for statistical analysis. Data are arithmetic means (95% CIs) unless otherwise specified. A 2-tailed P value of <0.05 was considered significant.

RESULTS

— Of the 77 subjects, 18 were Asian-Americans, 9 were African-Americans, 34 were Caucasians, and 16 were Mexican-Americans. Compared with the other ethnic groups, Asian-Americans were the leanest according to WHR (P = 0.0169). Although no differences were noted statistically in most clinical features, a wide range of variation was noted in plasma glucose and insulin levels during the OGTT. Only the differences in age (P = 0.0429), WHR (P = 0.00169), 120-min postchallenge insulin level (P = 0.0295), and insulin area under the curve (P = 0.0460) reached the defined statistical level. Marginal differences ($0.0500 > P > 0.1000$) were noted for BMI (P = 0.0847), diastolic blood pressure (P = 0.0622), fasting insulin level (P = 0.0899), and 90-min postchallenge insulin level (P = 0.0658).

After resting in the GCRC and fasting overnight, the 4 ethnic groups had similar

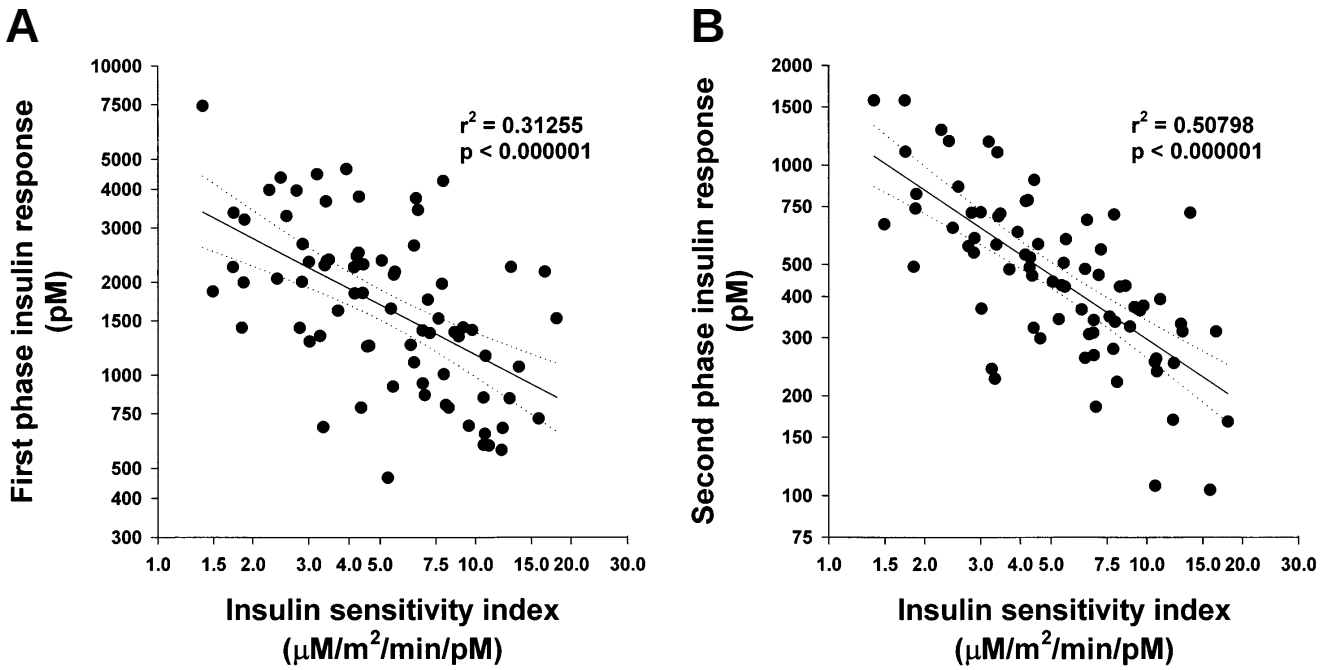

Figure 1—*Relationship between insulin sensitivity and β-cell function in 77 glucose-tolerant and normotensive subjects by simple regression analysis between insulin sensitivity index and first-phase insulin response (*A*) and between insulin sensitivity index and second-phase insulin response (*B*). • • •, 95% CIs; —, regression lines. Insulin sensitivity index and first- and second-phase insulin responses were logarithmically transformed before analysis.*

fasting plasma glucose and insulin levels before the hyperglycemic clamps were initiated (Table 1). During the hyperglycemic clamps, steady-state plasma glucose levels were achieved at similar levels among the 4 ethnic groups. Although only a marginal difference was noted in the first-phase insulin response among the 4 ethnic groups ($P = 0.1090$), a drastic difference was evident in the second-phase insulin response ($P = 0.0082$). However, the ethnic patterns were similar for both phases of insulin response and were highest in Mexican-Americans, were intermediate in Asian-Americans and African-Americans, and were lowest in Caucasians. When compared with the other 3 ethnic groups, Caucasians had the highest insulin sensitivity index ($P = 0.0023$).

In glucose-tolerant subjects, β-cells produced insulin in response to the prevailing insulin sensitivity to maintain plasma glucose levels within a relatively narrow range. As shown in Fig. 1, simple regression analyses revealed that both the first- and second-phase insulin responses correlated very well with the insulin sensitivity index ($P < 0.000001$ for both phases of insulin response). These results lead us to speculate whether the observed differences in insulin sensitivity index and second-phase insulin response, along with a marginal difference in first-phase insulin response, are an independent influence of ethnicity or whether some are primary and others are secondary.

To investigate whether ethnicity was an independent determinant for insulin sensitivity or β-cell function, a stepwise regression analytical approach was performed to examine the effect of potential confounding covariates on these parameters. We found that ethnicity was an independent determinant for the insulin sensitivity index ($P = 0.0014$) (Table 2). Ethnicity, along with sex, age, diastolic blood pressure, WHR, and BMI, accounted for 46.1% of the variation in the insulin sensitivity index. Ethnicity had no effect on the first-phase insulin response ($P = 0.2020$), and the first-phase insulin response was mainly affected by BMI ($P = 0.0117$). For the second-phase insulin response, 32.8% of the variation could be explained by BMI ($P = 0.0005$), age ($P = 0.0081$), and ethnicity ($P = 0.0735$).

CONCLUSIONS — Epidemiological studies have documented the risk factors for diabetes among ethnic groups (3–7). However, with few exceptions (17,18), these studies have not been designed to examine the differences in insulin sensitivity and β-cell function simultaneously among specific ethnic populations. Because abnormal glucose tolerance affects both β-cell function and insulin sensitivity (22,23) and because hypertension is associated with insulin resistance (24), we enrolled only glucose-tolerant and normotensive subjects for the assessment of β-cell function and insulin sensitivity using the hyperglycemic clamp technique. We found that Caucasians were the most insulin sensitive compared with Asian-Americans, African-Americans, and Mexican-Americans and had a compensatory response in their β-cell function. Furthermore, pairwise comparisons showed no difference in insulin sensitivity index among Asian-Americans, African-Americans, and Mexican-Americans.

Because the association of obesity with insulin resistance is well established (4,14,25) and because we also noted differences in WHR among the 4 ethnic groups in the present study, we examined the influence of ethnicity on WHR. A stepwise regression analysis revealed that ethnicity had a modest effect ($P = 0.0279$) on WHR. In addition, ethnicity, along with sex ($P = 0.0005$) and age ($P = 0.0456$), explained 30.8% of the variation in WHR, whereas systolic and diastolic blood pressure had no effect on WHR. In contrast, ethnicity had no influence on BMI in this study. The difference in WHR was the result of a much lower adjusted WHR in Asian-Americans (0.7560) compared with African-Americans (0.7957),

Table 2—*Stepwise regression analysis of glycemic parameters*

Dependent variable	Covariate entered	Covariate removed	r^2	*P*
First-phase insulin response			0.082	
	BMI			0.0117
		Age		0.1851
		Ethnicity		0.2020
		Systolic blood pressure		0.5563
		Diastolic blood pressure		0.7592
		WHR		0.8093
		Sex		0.9876
Second-phase insulin response			0.328	
	BMI			0.0005
	Age			0.0081
	Ethnicity			0.0735
		WHR		0.4880
		Sex		0.6555
		Diastolic blood pressure		0.8172
		Systolic blood pressure		0.8486
Insulin sensitivity index			0.467	
	Ethnicity			0.0014
	Sex			0.0017
	Age			0.0023
	Diastolic blood pressure			0.0141
	WHR			0.0240
	BMI			0.0638
		Systolic blood pressure		0.4225

Caucasians (0.7964), and Mexican-Americans (0.8262). However, no difference was noted in the pairwise comparisons among African-Americans, Caucasians, and Mexican-Americans. Even though Asian-Americans had the lowest WHR, they were more insulin resistant than Caucasians. Thus, in Asian-Americans, the difference in WHR could not explain the observed differences in insulin sensitivity.

One of the unique features of the present study is the finding of less obesity but more insulin resistance in Asian-Americans compared with other ethnic groups. In contrast with other minority populations, such as American Indians, African-Americans, and Mexican-Americans, obesity and insulin resistance are the predominant features when compared with Caucasians, and insulin resistance, at least in part, is attributed to obesity (26). Although the underlying mechanism of this dissociation between obesity and insulin resistance in Asian-Americans is unknown, some have speculated that intra-abdominal or visceral adiposity plays a role in the pathogenesis of insulin resistance as shown in Japanese-Americans from King County, Washington (27–29). A systematic study comparing visceral adiposity and insulin resistance among ethnic groups is required to resolve this issue.

Because the luteal phase of the menstrual cycle and the use of oral contraceptives (30) have been implied to affect insulin sensitivity, we examined whether these 2 factors had any effect on the observed results. The present data set contained 46 women. Among them, 10 women used oral contraceptives. Among the remaining 36 women who did not use oral contraceptives, 24 women were in their last 14 days of their cycles. Female sex was further divided into 3 categories based on the phases of their cycles and the use of oral contraceptives. Including the male sex, a total of 4 categories were used in this covariate that replaced the original sex category in the stepwise regression analysis. We found that ethnicity remained an independent determinant for insulin sensitivity index ($P = 0.0024$) with a compensatory response in both the first-phase and second-phase insulin responses ($P = 0.1090$ and $P = 0.0844$). Therefore, we concluded that the phase of the menstrual cycle and use of birth control pills had little effect on our observation.

To maintain glucose homeostasis in glucose-tolerant subjects, a dynamic balance between insulin sensitivity and β-cell function is needed to keep plasma glucose levels within a relatively narrow physiological range (9). We attempted to circumvent the entangled relationship between insulin sensitivity and β-cell function by including the insulin sensitivity index as a covariate for both the first- and second-phase insulin responses in the regression analysis. Insulin sensitivity index was the sole determinant for the first-phase insulin response ($R^2 = 0.3126$, $P < 0.0001$), whereas sex ($P = 0.2118$), BMI ($P = 0.4622$), WHR ($P = 0.6060$), age ($P = 0.6823$), diastolic blood pressure ($P = 0.7546$), ethnicity ($P = 0.7835$), and systolic blood pressure ($P = 0.9172$) were excluded from the model. For the second-phase insulin response, insulin sensitivity index ($P < 0.0001$), diastolic blood pressure ($P = 0.0389$), and systolic blood pressure ($P = 0.0594$) accounted for 54.0% of the variation, whereas BMI ($P = 0.2862$), age ($P = 0.3156$), sex ($P = 0.5266$), WHR ($P = 0.8043$), and ethnicity ($P = 0.8855$) were removed from the analysis. Furthermore, we also analyzed the effect of ethnicity on the insulin sensitivity index by considering the second-phase insulin response as 1 of the covariates. We found that second-phase insulin response ($P < 0.0001$), sex ($P = 0.0007$), diastolic blood pressure ($P = 0.0045$), WHR ($P = 0.0059$), ethnicity ($P = 0.0341$), and age ($P = 0.0799$) explained 63.8% of the variation in the insulin sensitivity index, while systolic blood pressure ($P = 0.2461$) and BMI ($P = 0.4569$) had no influence on the insulin sensitivity index. These results, along with the results shown in Table 2, illustrate that ethnicity has a stronger effect on the insulin sensitivity index ($P = 0.0014$) than either the first-phase ($P = 0.2020$) or second-phase ($P = 0.0735$) insulin response, which suggests that ethnicity affects primarily the insulin sensitivity index and that the observed differences in β-cell function are secondary to the differences in insulin sensitivity. However, disentangling the independent effects of insulin sensitivity and β-cell function in glucose-tolerant subjects is impossible because their β-cells compensate for the prevailing insulin sensitivity to maintain glucose homeostasis. Therefore, the rational interpretation of our observations is that insulin sensitivity differs among ethnic groups with a compensatory response in β-cell function.

Our observation that minority ethnic groups are more insulin resistant than Cau-

casians is consistent with many previously published reports (6,13,16,26,29). In contrast, our interpretation is different from the results of the Insulin Resistance Atherosclerosis Study (IRAS), which reported increased insulin resistance and increased acute insulin response in African-Americans and Mexican-Americans compared with Caucasians (17). Indeed, we did find a marginal difference in the unadjusted first-phase insulin response ($P = 0.1090$) and a significant difference in the unadjusted second-phase insulin response ($P = 0.0082$) among the 4 ethnic groups. Furthermore, the regression analysis suggests that the observed difference in β-cell function is secondary to the difference in insulin sensitivity index. In contrast, the IRAS study concluded that these high-risk minorities had increased insulin resistance and also increased insulin secretion. The latter should be a protective factor rather than a risk factor for the development of diabetes. Nonetheless, our study differs from the IRAS study in several ways. To assess insulin sensitivity and β-cell function, we used the hyperglycemic clamp technique, whereas the IRAS used the minimal model from the frequently sampled intravenous glucose tolerance test (17). In addition, subjects with a broad range of glucose tolerance were included in the IRAS (17), whereas we only enrolled glucose-tolerant subjects because abnormal glucose tolerance has been shown to affect insulin sensitivity and β-cell function (23). Because hypertension has been shown to be associated with insulin resistance (24), we only enrolled normotensive subjects; however, the IRAS did not account for differences in blood pressure (17). Furthermore, we studied Asian-American subjects, but the IRAS did not (17).

By using the hyperglycemic clamp technique to study glucose-tolerant and normotensive Americans who live in southern California, we have demonstrated that Caucasians are more insulin sensitive than Asian-Americans, African-Americans, and Mexican-Americans, and their β-cells compensate for the prevailing insulin sensitivity. Asian-Americans appear to have an ethnic propensity to insulin resistance that is not explained by obesity. The molecular basis for the difference in insulin sensitivity among the various ethnic groups remains to be explored.

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