

β -Cell Function Is a Major Contributor to Oral Glucose Tolerance in High-Risk Relatives of Four Ethnic Groups in the U.S.

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First-degree relatives of individuals with type 2 diabetes are at increased risk of developing hyperglycemia. To examine the prevalence and pathogenesis of abnormal glucose homeostasis in these subjects, 531 first-degree relatives with no known history of diabetes (aged 44.1 ± 0.7 years; BMI 29.0 ± 0.3 kg/m²) underwent an oral glucose tolerance test (OGTT). Newly identified diabetes was found in 19% ($n = 100$), and impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) was found in 36% ($n = 191$). Thus, only 45% ($n = 240$) had normal glucose tolerance (NGT). The homeostasis model assessment of insulin resistance (HOMA-IR) was used to estimate insulin sensitivity; β -cell function was quantified as the ratio of the incremental insulin to glucose responses over the first 30 min during the OGTT ($\Delta I_{30}/\Delta G_{30}$). This latter measure was also adjusted for insulin sensitivity as it modulates β -cell function ($[\Delta I_{30}/\Delta G_{30}]/\text{HOMA-IR}$). Decreasing glucose tolerance was associated with increasing insulin resistance (HOMA: NGT 12.01 ± 0.54 pmol/mmol; IFG/IGT 16.14 ± 0.84 ; diabetes 26.99 ± 2.62 ; $P < 0.001$) and decreasing β -cell function ($\Delta I_{30}/\Delta G_{30}$: NGT 157.7 ± 9.7 pmol/mmol; IFG/IGT 100.4 ± 5.4 ; diabetes 57.5 ± 7.3 ; $P < 0.001$). Decreasing β -cell function was also identified when adjusting this measure for insulin sensitivity ($[\Delta I_{30}/\Delta G_{30}]/\text{HOMA-IR}$). In all four ethnic groups (African-American, $n = 55$; Asian-American, $n = 66$; Caucasian, $n = 217$; Hispanic-American, $n = 193$), IFG/IGT and diabetic subjects exhibited progressively increasing insulin resistance and decreasing β -cell function. The relationships of insulin sensitivity and β -cell function to glucose disposal, as measured by the incremental glucose area under the curve (AUCg), were examined in the whole cohort. Insulin sensitivity and AUCg were linearly related so that insulin resistance was associated with poorer glucose disposal ($r^2 = 0.084$, $P < 0.001$). In contrast, there was a strong inverse curvilinear relationship between β -cell function and AUCg such that poorer insulin release was associated with poorer

glucose disposal ($\log[\Delta I_{30}/\Delta G_{30}]$: $r^2 = 0.29$, $P < 0.001$; $\log([\Delta I_{30}/\Delta G_{30}]/\text{HOMA-IR})$: $r^2 = 0.45$, $P < 0.001$). Thus, abnormal glucose metabolism is common in first-degree relatives of subjects with type 2 diabetes. Both insulin resistance and impaired β -cell function are associated with impaired glucose metabolism in all ethnic groups, with β -cell function seeming to be more important in determining glucose disposal. *Diabetes* 51:2170–2178, 2002

Insulin resistance and impaired β -cell function are widely recognized as features of type 2 diabetes (1–5). It has been debated whether insulin resistance (6), β -cell dysfunction (7,8), or both (9–11) constitute the primary abnormality in type 2 diabetes and whether one defect precedes the other in the natural history of the disease (7,10,12–14).

First-degree relatives of individuals with type 2 diabetes are at increased risk of developing hyperglycemia (14–16). Studies of these subjects have reported greater insulin resistance (6,8,14,17–20) or decreased β -cell function (7,8,19) among first-degree relatives in comparison with controls. In addition to the genetic risk associated with a family history of the disease, it is apparent that genetic predisposition related to ethnicity is a major determinant of diabetes risk. African-Americans (15,21), Asian-Americans (22,23), Hispanic-Americans (21,24), and Native Americans (25–27) have been shown to be at increased risk of developing type 2 diabetes compared with Caucasians. Studies have compared the pathogenesis of type 2 diabetes among ethnic groups to determine whether this process is similar. Some have found differences in insulin sensitivity (28–32) and/or β -cell function (28,30,33) among different ethnic groups, whereas others have found no difference in either insulin sensitivity (33) or β -cell function (32). As many of these studies comparing different ethnic groups have used relatively small numbers of subjects or fewer ethnic groups, they are somewhat limited. Thus, it is unclear whether the pathogenesis of type 2 diabetes does or does not differ among ethnic groups.

The American Diabetes Association's Genetics of NIDDM (GENNID) Study was designed to phenotype and obtain genetic material from families with at least two first-degree relatives with diabetes, the goal being to provide the necessary material needed to identify genes linked to type 2 diabetes (34). The study recruited African-Americans, Asian-Americans, Caucasians, and Hispanic-Americans. As

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ADA, American Diabetes Association; AUCg, glucose area under the curve; IFG, impaired fasting glucose; HOMA, homeostasis model assessment; HOMA-IR, HOMA of insulin resistance; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test.

TABLE 1
Glucose tolerance status of 531 first-degree relatives of subjects with type 2 diabetes with previously unknown glucose tolerance

Fasting glucose (mmol/l)	2-h glucose (mmol/l)			Total
	NGT (<7.8)	IGT (7.8–11.1)	Type 2 diabetes (>11.1)	
Normal (<6.1)	240	141	33	414
IFG (6.1–6.9)	8	42	19	69
Type 2 diabetes (≥ 7.0)	2	8	38	48
Total	250	191	90	531

part of the phenotyping of the individuals not known to have type 2 diabetes, an oral glucose tolerance test (OGTT) was performed. We used the results of this test to address a number of questions related to glucose tolerance, insulin sensitivity, and β -cell function in these individuals with a first-degree relative with type 2 diabetes. First, what is the prevalence of normal glucose tolerance (NGT), impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and diabetes in these high-risk subjects not previously known to have diabetes? Second, do insulin sensitivity and β -cell function differ in these subjects on the basis of their glucose tolerance status, and how do they contribute to glucose disposal? Third, is there a difference in insulin sensitivity and/or β -cell function in first-degree relatives on the basis of ethnicity?

RESEARCH DESIGN AND METHODS

Subjects. The design and methods used in the GENNID Study have been described in detail elsewhere (34). The study was conducted at eight centers in the United States and recruited families with at least two siblings who had type 2 diabetes. In addition, at least three first-degree relatives and one unaffected spouse of an affected member from each family were included. At each site, the study was approved by the local Institutional Review Board and written informed consent was obtained from each participant.

A total of 531 subjects are included in the present report. They were selected from the 1,291 subjects who were sampled during phase I of the GENNID Study if they had no previous diagnosis of diabetes, at least one first-degree relative with type 2 diabetes, complete OGTT and anthropometric data, and ethnicity self-identified as African-American, Asian-American, Caucasian, or Hispanic-American.

Study methods. Age and ethnicity were as reported by the subject. Body weight, height, waist and hip measurements, and blood pressure were each measured three times using a common protocol (34), and the average value was used.

All previously undiagnosed subjects underwent a 75-g OGTT in the morning after a 10-h overnight fast. Samples for glucose and insulin measurements were drawn into tubes containing EDTA at baseline and every 30 min after glucose ingestion up to and including 120 min. For this report, subjects were classified as having NGT, IFG, IGT, or diabetes on the basis of the American Diabetes Association (ADA) criteria for fasting and 2-h glucose levels (35).

Assays. Plasma glucose was measured using a hexokinase method (Glucose/HK, Boehringer Mannheim, Indianapolis, IN). Plasma insulin concentrations

were measured by radioimmunoassay using LINCO antibody 1012 (Linco Research, Ellisville, MO). This antibody cross-reacts with intact proinsulin (38%), des 31, 32 proinsulin (47%), and des 64, 65 proinsulin (72%).

Calculations and statistical analysis. BMI was calculated as weight/height² (kg/m²). The incremental glucose (ΔG_{30}) and insulin (ΔI_{30}) responses were calculated as the difference between the values 30 min after glucose intake and those before glucose intake. The trapezoidal rule was used to calculate the incremental area under the curve for glucose (AUC_g) for the duration of the OGTT. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated from fasting glucose and insulin levels as described by Matthews et al. (36) using the equation resistance = [glucose] \times [insulin]/22.5, which is equivalent to the originally described equation [insulin]/[22.5e^{-ln(glucose)}].

Statistical analysis was performed using SPSS version 10.0 (SPSS, Chicago, IL). Data are presented as means \pm SE. Continuous measures were adjusted for age and sex. Comparisons between groups were performed by ANOVA, except when comparing two groups with normal data distribution, in which case the Student's *t* test was used. The χ^2 test was used for dichotomous variables. Pearson correlation coefficients were calculated for pairs of continuous variables. $P \leq 0.05$ was considered significant.

RESULTS

Glucose tolerance status and demographics. Using ADA criteria based on a single OGTT, only 45% ($n = 240$) of the subjects were classified as having NGT (Table 1). Among the remaining subjects, 2% ($n = 8$) had IFG, 27% ($n = 141$) had IGT, 8% ($n = 42$) had IFG and IGT, and 19% ($n = 100$) had previously undiagnosed diabetes. In those individuals with diabetes, this classification was based on the fasting glucose alone in 10%, the 2-h glucose alone in 52%, and both in 38%. Subjects who had IFG and/or IGT and did not have diabetes by either the 2-h or fasting glucose levels, respectively ($n = 191$), were combined. Thus, there were three groups for additional analysis: NGT, IFG/IGT, and diabetes.

The characteristics of the study subjects subdivided on the basis of their glucose tolerance are listed in Table 2. The proportion of subjects with NGT, IFG/IGT, and diabetes did not vary by sex. Each group was middle-aged, overweight, and normotensive, with each of these parameters increasing with decreasing glucose tolerance.

TABLE 2
Characteristics of the 531 subjects (215 men and 316 women)

	NGT	IFG and/or IGT*	Diabetes	<i>P</i>
<i>n</i>	240	191	100	
M/F	102/138	73/118	40/60	0.668
Age (years)	38.6 \pm 0.9	44.3 \pm 1.1	56.9 \pm 1.5	<0.001
BMI (kg/m ²)	27.8 \pm 0.4	29.6 \pm 0.5	30.5 \pm 1.0	<0.001
Waist/hip ratio	0.88 \pm 0.006	0.91 \pm 0.006	0.95 \pm 0.008	<0.001
Systolic blood pressure (mmHg)	115.1 \pm 1.0	121.6 \pm 1.1	131.0 \pm 1.8	<0.001
Diastolic blood pressure (mmHg)	72.6 \pm 0.7	76.1 \pm 0.8	79.4 \pm 1.2	<0.001
Fasting glucose (mmol/l)	5.18 \pm 0.03	5.64 \pm 0.04	7.36 \pm 0.27	<0.001
2-h glucose (mmol/l)	6.21 \pm 0.07	8.99 \pm 0.08	13.99 \pm 0.4	<0.001

Data are means \pm SE. *Excluding those with diabetes.

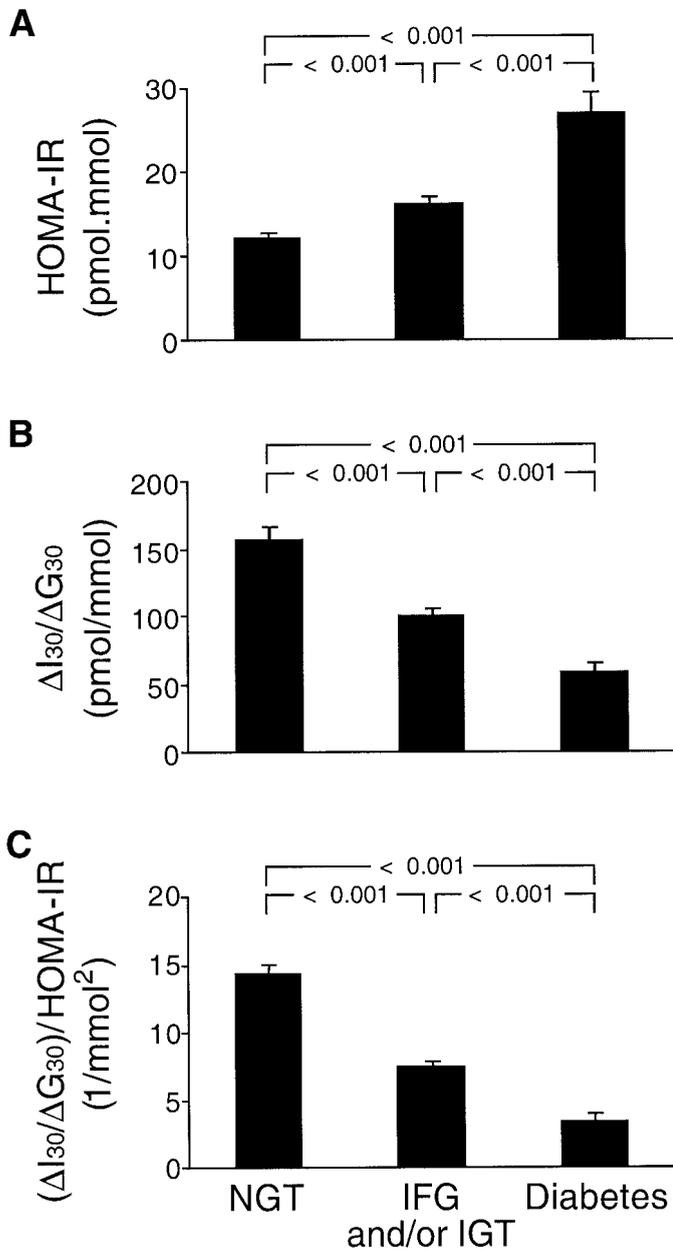


FIG. 1. Insulin sensitivity determined by the HOMA-IR (A) and β-cell function quantified as ΔI₃₀/ΔG₃₀ (B) and (ΔI₃₀/ΔG₃₀)/HOMA-IR (C) from an OGTT in 531 first-degree relatives with NGT (*n* = 240), IFG/IGT (*n* = 191), and diabetes (*n* = 100). Individuals who had IFG or IGT and had diabetes by the 2-h or fasting glucose criteria, respectively, were classified as having diabetes. As glucose tolerance declined, insulin resistance increased and β-cell function deteriorated.

Estimates of insulin sensitivity and β-cell function. Decreasing glucose tolerance was associated with increasing insulin resistance as measured by the HOMA-IR (NGT 12.01 ± 0.54 pmol/mmol; IFG/IGT 16.14 ± 0.84; diabetes 26.99 ± 2.62; *P* < 0.001; Fig. 1). Similarly, fasting insulin, a surrogate measure of insulin sensitivity, also increased significantly with decreasing glucose tolerance (NGT 50.8 ± 2.3 pmol/l; IFG/IGT 61.6 ± 3.0; diabetes 78.8 ± 6.0; *P* < 0.001) and was highly correlated with the HOMA-IR (*r* = 0.898, *P* < 0.001).

Decreasing glucose tolerance was also associated with decreasing β-cell function as measured by the ratio of the incremental insulin to glucose responses over the first 30

min (ΔI₃₀/ΔG₃₀) during the OGTT (NGT 157.7 ± 9.7 pmol/mmol; IFG/IGT 100.4 ± 5.4; diabetes 57.5 ± 7.3; *P* < 0.001).

Insulin sensitivity is known to be a critical modulator of the insulin response to a stimulus, with insulin resistance increasing insulin release (37). Thus, we also adjusted ΔI₃₀/ΔG₃₀ for the degree of insulin sensitivity because this varied across glucose tolerance categories. Dividing ΔI₃₀/ΔG₃₀ by the HOMA-IR gave an adjusted measure of β-cell function (ΔI₃₀/ΔG₃₀/HOMA-IR) that accounted for variation in insulin sensitivity. This measure also declined significantly with progressive reductions in glucose tolerance (NGT 14.4 ± 0.5 mmol⁻²; IFG/IGT 7.6 ± 0.4; diabetes 3.5 ± 0.5; *P* < 0.001) in keeping with a decline in β-cell function.

We also separately subdivided the NGT and IFG/IGT groups and performed additional analyses on these subgroups. First, we subdivided the 240 subjects with NGT into two groups based on the median value for AUC_g to determine whether differences in insulin sensitivity and/or β-cell function could explain differences in postchallenge glucose within this group (*n* = 120 per group). Using this approach, we found no difference in the HOMA-IR (11.3 ± 0.7 pmol/mmol vs. 12.8 ± 0.8; *P* = 0.092) or ΔI₃₀/ΔG₃₀ (171.7 ± 13.6 pmol/mmol vs. 141.5 ± 14.4; *P* = 0.305) in those individuals who fell above the median versus those who fell below. In contrast, β-cell function adjusted for insulin resistance (ΔI₃₀/ΔG₃₀/HOMA-IR) was significantly lower in those individuals who were above the median (16.7 ± 1.0 mmol⁻² vs. 12.1 ± 0.8; *P* = 0.001), compatible with a reduction in β-cell function even in NGT subjects with greater postchallenge glycemia. Second, we examined the IFG/IGT group by subdividing them into a group with IFG with or without IGT (*n* = 50) and one that had IGT alone (*n* = 141). In this analysis, we found that the IFG with or without IGT group were more insulin resistant as determined by the HOMA-IR (23.4 ± 2.3 pmol/mmol vs. 14.0 ± 0.8; *P* < 0.001) and had poorer β-cell function (ΔI₃₀/ΔG₃₀/HOMA-IR: 4.0 ± 0.4 mmol⁻² vs. 8.7 ± 0.5; *P* < 0.001).

Effect of ethnicity on insulin sensitivity and β-cell function. The study included 55 African-American, 66 Asian-American, 217 Caucasian, and 193 Hispanic-American subjects (Table 3). The proportion of men and women did not vary between ethnic groups (*P* = 0.128). However, there were significant differences in age (*P* < 0.001) between ethnic groups.

When ethnic groups were analyzed separately, decreasing glucose tolerance was associated with increasing insulin resistance in all groups (African-American *P* = 0.027; Asian-American *P* < 0.001; Caucasian *P* < 0.001; Hispanic-American *P* < 0.001; Fig. 2). Comparisons between subjects with similar glucose tolerance from different ethnic groups revealed significant differences in insulin resistance in the NGT and IFG/IGT subjects but not among subjects with diabetes. Asian-Americans with NGT or IFG/IGT were less insulin resistant than all other ethnic groups (NGT: *P* = 0.020 vs. African-American, *P* = 0.002 vs. Caucasian, *P* = 0.001 vs. Hispanic-American; IFG/IGT: *P* = 0.009 vs. African-American, *P* = 0.002 vs. Caucasian, *P* < 0.001 vs. Hispanic-American), whereas Caucasians were less insulin resistant than Hispanic-Americans (NGT

TABLE 3
Demographic and glucose tolerance status of 531 first-degree relatives of subjects subdivided on the basis of ethnicity

	African-American	Asian-American	Caucasian	Hispanic-American
<i>n</i>	55	66	217	193
No. of families	22	15	63	46
M/F	21/34	33/33	93/124	68/125
Age	41.8 ± 1.9	53.4 ± 2.0	45.4 ± 1.1	40.2 ± 1.1
BMI (kg/m ²)	30.8 ± 1.0	24.5 ± 0.5	29.4 ± 0.5	29.4 ± 0.4
Waist-to-hip ratio	0.90 ± 0.01	0.90 ± 0.01	0.91 ± 0.006	0.90 ± 0.006
Fasting glucose (mmol/l)	6.07 ± 0.39	5.91 ± 0.14	5.66 ± 0.07	5.73 ± 0.09
2-h glucose (mmol/l)	9.28 ± 0.67	9.41 ± 0.46	8.38 ± 0.22	8.59 ± 0.23
% NGT	42	30	48	48
% IFG and/or IGT *	31	46	36	35
% Diabetes	27	24	16	17

Data are means ± SE unless otherwise indicated. *Subjects with either fasting >7.0 mmol/l or 2-h glucose >11.1 mmol/l were classified as having diabetes.

$P = 0.001$; IFG/IGT $P = 0.012$). Ethnic differences persisted even after adjustment for BMI.

Decreasing glucose tolerance was also associated with a decreasing insulin response as measured by $\Delta I_{30}/\Delta G_{30}$ among Caucasian ($P < 0.001$) and Hispanic-American ($P < 0.001$) subjects. This insulin response, which was not adjusted for insulin sensitivity, was lower in Asian-Americans than in other ethnic groups among both NGT and IFG/IGT subjects (NGT: $P = 0.031$ vs. Caucasian, $P = 0.008$ vs. Hispanic-American; IFG/IGT: $P = 0.009$ vs. African-American, $P = 0.003$ vs. Caucasian, $P < 0.001$ vs. Hispanic-American). Caucasians also had lower unadjusted insulin responses than African-Americans (NGT $P = 0.006$) and Hispanic-Americans (NGT $P < 0.001$; IFG/IGT $P = 0.007$). However, as insulin sensitivity is a determinant of β -cell function and insulin sensitivity differed between ethnic groups, adjustment of $\Delta I_{30}/\Delta G_{30}$ for insulin sensitivity by dividing by the HOMA-IR ($(\Delta I_{30}/\Delta G_{30})/\text{HOMA-IR}$) revealed that β -cell function declined in all ethnic groups (African-American $P < 0.001$; Asian-American $P = 0.021$; Caucasian $P < 0.001$; Hispanic-American $P < 0.001$) as glucose tolerance decreased. After the insulin response was adjusted for insulin sensitivity, β -cell function did not seem to differ between ethnic groups with similar glucose tolerance, except that African-American subjects had better function than Caucasian subjects with NGT ($P = 0.026$).

Relationship among insulin sensitivity, β -cell function, and the plasma glucose response. The relationships between the incremental AUCg after an oral glucose load, insulin sensitivity, and β -cell function were then examined in the whole cohort. As illustrated in Fig. 3, these relationships differed when insulin sensitivity and β -cell function were examined. Regression analysis of insulin sensitivity and AUCg demonstrated that insulin sensitivity was related to AUCg in a linear manner, but this relationship was weak ($r^2 = 0.084$, $P < 0.001$; Fig. 3A). In contrast, the relationship between β -cell function quantified as either $\Delta I_{30}/\Delta G_{30}$ or $(\Delta I_{30}/\Delta G_{30})/\text{HOMA resistance}$ was nonlinear in nature (Fig. 3B and C). Therefore, we log-transformed the independent (β -cell function) variables and examined their relationship with AUCg. There was an inverse relationship between β -cell function and the postchallenge glucose such that poorer insulin release was associated with poorer glucose disposal ($\log[\Delta I_{30}/$

$\Delta G_{30}]$: $r^2 = 0.29$, $P < 0.001$; $\log[(\Delta I_{30}/\Delta G_{30})/\text{HOMA resistance}]$: $r^2 = 0.45$, $P < 0.001$).

To examine further the contribution of insulin sensitivity and β -cell function to postchallenge glycemia, we performed stepwise regression analysis using the HOMA-IR and $\Delta I_{30}/\Delta G_{30}$ as the independent variables and AUCg as the dependent variable. In this analysis, $\Delta I_{30}/\Delta G_{30}$ explained 29.2% ($P < 0.001$) of the variance in AUCg and the HOMA-IR explained an additional 11.0% ($P < 0.001$).

DISCUSSION

It is widely recognized that there are a number of risk factors for type 2 diabetes, including family history (14–16) and ethnicity (15,21–24,38). Although these are known risk factors, to the best of our knowledge, the present study represents the first comparison of a large number of subjects who are first-degree relatives of individuals with type 2 diabetes and represent four different ethnic groups. Because of the presence of these risk factors, it is not completely surprising that we found that the majority of first-degree relatives of individuals with type 2 diabetes had abnormal glucose tolerance. What is more surprising is that after differences in age, sex, and insulin sensitivity were adjusted for, insulin resistance and decreasing β -cell function were characteristic findings in both impaired glucose metabolism and diabetes among all ethnic groups, and the nature of the change in these two parameters was similar in all ethnic groups. These findings therefore strongly suggest that the pathogenesis of type 2 diabetes is similar among all at-risk groups in the United States, with insulin resistance and β -cell dysfunction both being important contributors to this process.

The prevalence of 19% of previously undiagnosed diabetes in this sample of individuals 18–91 years of age (average age 44.1 years) is much higher than that previously reported in the U.S. population as a whole. In the Third National Health and Nutrition Examination Survey, 1988–1994, of individuals 40–74 years of age, the prevalence of previously undiagnosed diabetes was 7.3% (21). Similarly, a high prevalence of impaired glucose metabolism was found among subjects in this study (2% IFG, 27% IGT, 8% IFG and IGT). However, the prevalence of IGT in this study is much higher than that found among first-degree relatives in other studies (14,18,19). The reason for

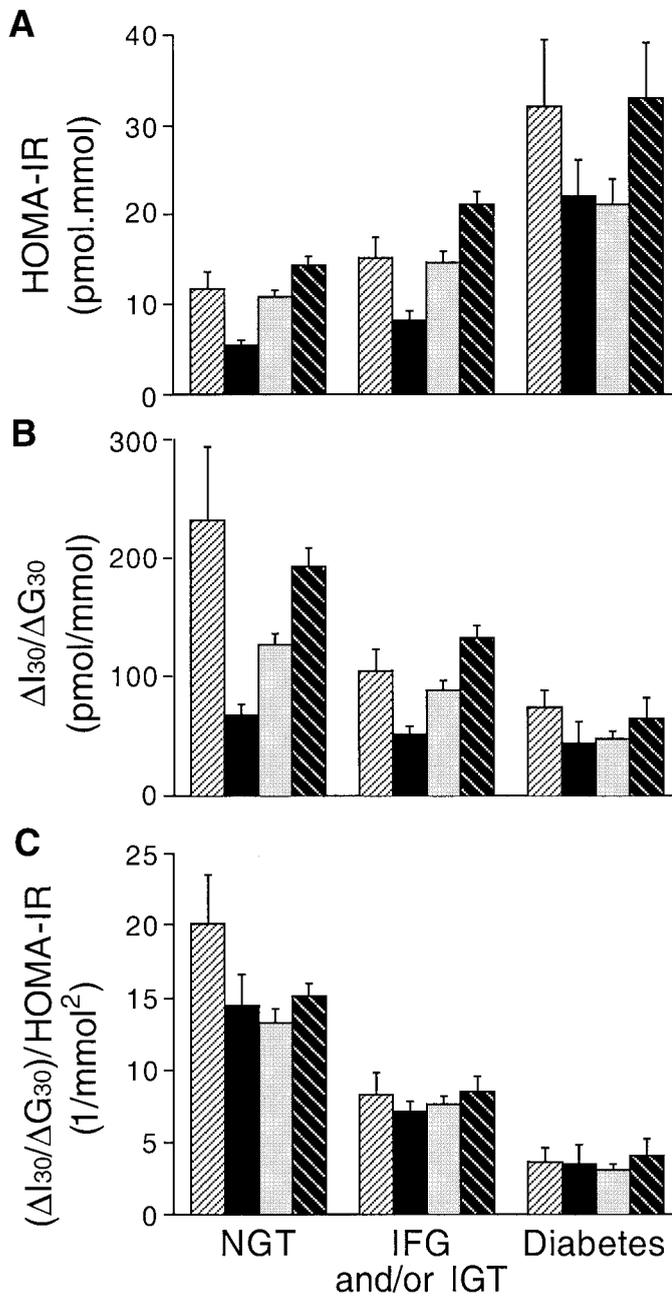


FIG. 2. Insulin sensitivity determined by the HOMA-IR (A) and β -cell function quantified as $\Delta I_{30}/\Delta G_{30}$ (B) and $(\Delta I_{30}/\Delta G_{30})/HOMA-IR$ (C) from an OGTT in 531 first-degree relatives of whom 55 were African-American (▨), 66 were Asian-American (■), 217 were Caucasian (□), and 193 were Hispanic-American (▩). Individuals who had IFG or IGT and had diabetes by the 2-h or fasting glucose criteria, respectively, were classified as having diabetes.

this difference may be that these previous studies were performed in cohorts of Caucasian subjects in whom ethnic risk would be less. Because IFG and IGT are risk factors for the subsequent development of type 2 diabetes (35) and the rate of progression from IGT to diabetes can be nearly 6% per year (38,39), the prevalence of type 2 diabetes within this study group will likely only increase.

The high prevalence of abnormal glucose tolerance in this group allowed us to determine whether there were differences in the pathogenic mechanisms responsible for the decline in glucose tolerance in this cohort of high-risk

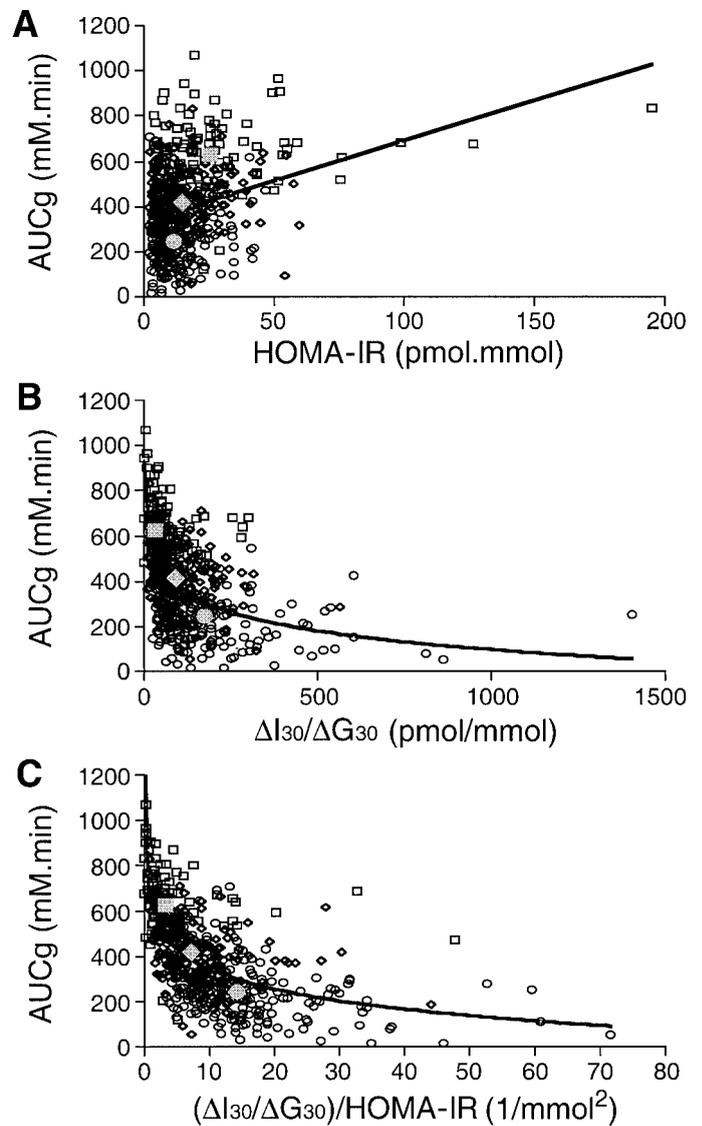


FIG. 3. Relationship of insulin sensitivity determined by the HOMA-IR (A), β -cell function quantified as $\Delta I_{30}/\Delta G_{30}$ (B) and $(\Delta I_{30}/\Delta G_{30})/HOMA-IR$ (C) to glucose disposal after an oral glucose load quantified as AUCg in 531 first-degree relatives. The relationship between insulin sensitivity and glucose disposal is linear in nature ($r^2 = 0.084$, $P < 0.001$), whereas that between β -cell function and glucose disposal is nonlinear and best described by a log-linear fit ($\Delta I_{30}/\Delta G_{30}$: $r^2 = 0.29$, $P < 0.001$; $(\Delta I_{30}/\Delta G_{30})/HOMA$ resistance: $r^2 = 0.45$, $P < 0.001$). The means for each glucose tolerance category (NGT [shaded circle], IFG/IGT [shaded diamond], and diabetes [shaded square]) are illustrated.

individuals. The approach to phenotyping individuals in this cohort used measures derived from the OGTT to determine insulin sensitivity and β -cell function rather than measures derived from more complicated tests. Insulin sensitivity was quantified using the HOMA-IR, which is based on the fasting insulin and glucose values, and with fasting insulin. Both of these measures have been shown to correlate with sophisticated measures of insulin sensitivity across different glucose tolerance categories, including diabetes, and therefore seem suitable for studies involving large numbers of subjects (37,40–42). We found that insulin sensitivity was reduced among subjects with IFG and/or IGT compared with those with NGT, and it was even lower in individuals with diabetes. Furthermore,

subjects with IFG were more insulin resistant than those with IGT and a normal fasting glucose. This finding that insulin sensitivity is reduced in subjects with reduced glucose tolerance is in accordance with other studies (5,6,13,14) that have suggested that insulin resistance is necessary for the development of diabetes but runs counter to other studies that have suggested that insulin resistance may be a less common factor in the pathogenesis of diabetes than β -cell function (7).

Using the early insulin response as a measure of β -cell function, we found that this parameter was also diminished among those with IFG and/or IGT and was even lower among those with diabetes, suggesting that β -cell dysfunction, like insulin resistance, is already present when glucose intolerance is identifiable on an OGTT and declines progressively with decreased glucose tolerance. The highly significant differences in β -cell function among the three groups suggest that it is a critical component in the pathogenesis of type 2 diabetes (2,3,5,13) rather than a late secondary defect as suggested by some (14). It is interesting that in an analysis of the subjects with IFG/IGT, we also found that individuals with IFG with or without IGT had reduced β -cell function compared with those who had IGT and a normal fasting glucose.

Differences between ethnic groups in insulin resistance and β -cell function have been suggested in a number of studies (28–33), whereas others have found no differences in these parameters (33). However, these studies have been limited because they typically have examined only up to three different ethnic groups or included smaller numbers of subjects. Thus, these conclusions regarding the pathogenesis of type 2 diabetes in different ethnic groups may be somewhat limited. In contrast, in this study, we documented that African-American, Asian-American, Caucasian, and Hispanic-American subjects all become more insulin resistant as glucose tolerance declines. Although the degree of insulin resistance differed between ethnic groups even after adjustment for BMI, with Asian-Americans being markedly less resistant than all other ethnic groups and Caucasians being less resistant than Hispanic-Americans, the change in resistance observed in each group suggests that insulin resistance is likely to be a characteristic feature in the pathogenesis of type 2 diabetes in all ethnic groups. Similarly, we found that β -cell function decreased in all groups as glucose tolerance declined. Using the insulinogenic index ($\Delta I_{30}/\Delta G_{30}$), we found that β -cell function decreased significantly with decreasing glucose tolerance only among Caucasian and Hispanic-American subjects. However, because the amount of insulin secreted by the β -cell is very dependent on the prevailing degree of insulin sensitivity, assessment of β -cell function accounting for differences in insulin sensitivity is critical when evaluating β -cell function (3,5,37,43). Thus, adjusting $\Delta I_{30}/\Delta G_{30}$ for the level of insulin sensitivity may be a better measure of β -cell function as without it, it may be difficult to determine whether a lower $\Delta I_{30}/\Delta G_{30}$ indicates true β -cell dysfunction or the impact of differences in insulin sensitivity.

Indeed, use of $(\Delta I_{30}/\Delta G_{30})/\text{HOMA-IR}$ in this study provides a different interpretation of β -cell function than $\Delta I_{30}/\Delta G_{30}$. With the use of $(\Delta I_{30}/\Delta G_{30})/\text{HOMA-IR}$, β -cell function decreased in all ethnic groups as glucose toler-

ance declined, and there were no significant differences between ethnic groups when this measure of β -cell function was used, except for that between African-American and Caucasian subjects with NGT ($P = 0.028$). Because a total of 18 separate analyses were conducted between ethnic groups for this variable, this difference may simply be the result of multiple comparisons. This approach of interpreting β -cell function derived from the OGTT relative to insulin sensitivity is similar to that used with more sophisticated tests of these two parameters (3,37,44). From these analyses has come the concept of the disposition index (insulin sensitivity \times β -cell function) and the progressive loss of β -cell function in individuals with IGT and diabetes (3,37,44,45). Thus, on the basis of the current analyses in which insulin sensitivity was accounted for when interpreting β -cell function during an OGTT, decreased β -cell function seems to be an important contributor to the pathogenesis of type 2 diabetes in all ethnic groups. Furthermore, it seems that all ethnic groups demonstrate evidence of β -cell dysfunction when glucose intolerance exists and this dysfunction is more severe in the presence of diabetes.

The large cohort of subjects with varying glucose tolerance enabled us to examine the relationship of insulin sensitivity and β -cell function to the magnitude of the glycemic response after oral glucose ingestion. Using the approaches we have described here to assess insulin sensitivity and β -cell function, we found the latter to be more highly correlated with glucose tolerance. This observation even held within the NGT group in whom subdivision of the 240 subjects on the basis of the glucose excursion after oral glucose ingestion demonstrated that the half with the greater glucose response had lower β -cell function, compared with the half with the lower glucose excursion in whom β -cell function was better. Examination of the data from the whole study cohort demonstrates that the impact of β -cell function on glucose disposal becomes even more dramatic as β -cell function declines so that small changes in this measure in individuals with reduced glucose tolerance can have dramatic effects on glucose metabolism. This finding is compatible with recent longitudinal data from the Pima Indians that have demonstrated that the progression over time from NGT to IGT and then to diabetes is associated with a marked decline in β -cell function in response to intravenous glucose and very little change in insulin sensitivity (45). Thus, early-phase insulin secretion seems to be critical to the maintenance of normal glucose disposal and is likely to have this effect by regulating hepatic glucose output. Support for this concept comes from studies performed using the OGTT and meal tolerance tests in subjects with IGT and diabetes, respectively, in whom the lack of early-phase insulin secretion was associated with impaired suppression of hepatic glucose production and poorer glucose tolerance (46,47). Furthermore, when individuals with type 2 diabetes had their early-phase insulin response restored with exogenous insulin administration, it was demonstrated that restoration of the early response was associated with greater suppression of hepatic glucose output and better glucose tolerance (48,49). Finally, in addition to these studies in which nutrients were administered orally, a study performed in healthy subjects in

which insulin secretion in response to intravenous glucose was suppressed with somatostatin demonstrated that the loss of the first-phase response was associated with impaired suppression of hepatic glucose output (50).

Among the individuals in whom diabetes was found, the criterion used for this categorization was a fasting glucose of ≥ 7.0 mmol/l in 10%, a 2-h glucose of >11.1 mmol/l in 52%, and both values in 38%. Recognizing the caveat that the ADA criteria require duplicate tests for the diagnosis of diabetes (35) and the results from an OGTT are not always consistent from test to test (51), use of the fasting glucose alone for screening rather than the OGTT-based 2-h glucose measure would have resulted in 52% of those with type 2 diabetes in the present cohort being undiagnosed. Other studies have also found that the fasting criteria alone results in a much lower percentage of individuals with type 2 diabetes being diagnosed compared with when the 2-h OGTT value is also used (52–55). These findings among a number of different population groups raise the interesting question of whether the approach to the diagnosis of diabetes needs to be reexamined.

There are a number of potential limitations to our study. First, the study was restricted to first-degree relatives of individuals with type 2 diabetes with some of the subjects being from the same families. It is possible that the pathogenic mechanism responsible for type 2 diabetes differs between first-degree relatives and individuals who are not as genetically predisposed to development of type 2 diabetes. However, we believe that this is highly unlikely as diabetes is likely to be a polygenic disorder and therefore a genetic interaction is probable in most individuals, with the genetic causes in the vast majority of individuals having not yet been identified. The large numbers of families from different ethnic groups that were included in our study decreases the likelihood that the findings related to insulin resistance and β -cell dysfunction hold true only in a subset of individuals. It is always possible that the pathogenesis may differ somewhat depending on the genes responsible, but we believe that the similarity found among the four ethnic groups that we have studied will hold true. Second, there were significant differences in age between ethnic groups: African-American and Hispanic-American subjects were younger on average than Caucasian subjects, and Asian-American subjects were older. This difference was related to the fact that the probands in the African-American and Hispanic-American groups were younger, resulting in a lower age for the sampled previously unaffected relatives. Because we adjusted all comparisons for age, this should have ensured that the observed differences are not the effect of differences in age. Finally, the insulin assay used has significant cross-reactivity with proinsulin, which has been shown to be disproportionately elevated among subjects with type 2 diabetes (56–58). As the proportion of immunoreactive insulin that is composed of proinsulin increases with decreasing glucose tolerance (56,59,60), if anything, we have likely underestimated the magnitude of the reduction in β -cell function in terms of the release of fully processed insulin.

In conclusion, we found that decreased glucose tolerance was associated with increased insulin resistance and decreased β -cell function in all ethnic groups. The magni-

tude of the change in β -cell function was similar in all groups once adjustment was made for the effect of insulin sensitivity on β -cell function, whereas the degree of insulin resistance varied between ethnic groups. Thus, it seems that major contributors to the pathogenesis of type 2 diabetes are likely to be similar in all ethnic groups in the United States, with β -cell function being a major determinant of glucose disposal after an oral glucose load.

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