Impaired Insulin Sensitivity, Insulin Secretion, and Glucose Effectiveness Predict Future Development of Impaired Glucose Tolerance and Type 2 Diabetes in Pre-Diabetic African Americans

Implications for primary diabetes prevention

KWAME OSEI, MD
SCOTT RHINESMITH, MD
TRUDY GAILLARD, RN, CDE
DARA SCHUSTER, MD

OBJECTIVE — We examined the determinants of impaired glucose tolerance (IGT) and type 2 diabetes in first-degree relatives of African-American type 2 diabetic patients over 5–8 years (median 6).

RESEARCH DESIGN AND METHODS — A total of 81 healthy subjects (age 41.5 ± 4.8 years; BMI 31.3 ± 3.6 kg/m^2) participated in the study. Each subject underwent an oral glucose tolerance test (OGTT) and a frequently sampled intravenous glucose tolerance test at baseline. Insulin sensitivity index (S_i) and glucose effectiveness index (S_g) were determined by the minimal model method. Homeostasis model assessment (HOMA) was used to estimate insulin resistance (HOMA-IR) and β-cell function (HOMA-%B). A total of 18 subjects progressed to either IGT or type 2 diabetes (progressors), whereas 19 subjects maintained normal glucose tolerance (nonprogressors).

RESULTS — Comparing the progressors and nonprogressors, mean fasting serum glucose levels (95 ± 8 vs. 80 ± 14 mg/dl, $P < 0.01$) and 2-h serum glucose levels (149 ± 27 vs. 100 ± 60 mg/dl, $P < 0.01$) as well as 2-h serum insulin levels (117 ± 81 vs. 72 ± 87 μU/ml, $P < 0.01$) during OGTT were higher at baseline. Mean acute first-phase insulin secretion (205 ± 217 vs. 305 ± 230 μU/ml), HOMA-%B (148 ± 60 vs. 346 ± 372, $P < 01$), S_i (1.61 ± 1.13 vs. 2.48 ± 1.25 × $10^{-4} \cdot min^{-1}$ [μU/ml]$^{-1}$), and S_g (1.48 ± 0.61 vs. 2.30 ± 0.97 × $10^{-2} \cdot min^{-1}$) were lower in the progressors than in the nonprogressors at baseline. Mean HOMA-IR (3.31 ± 1.64 vs. 2.36 ± 1.64) was significantly greater in the progressors than the nonprogressors. At the time of diagnosis of glucose intolerance (IGT + diabetes), HOMA-%B (101 ± 48 vs. 148 ± 60, $P < 0.001$) and HOMA-IR (5.44 ± 2.55 vs. 3.31 ± 1.64, $P < 0.003$) deteriorated in the progressors versus baseline.

CONCLUSIONS — We conclude that nondiabetic, first-degree relatives of African-American type 2 diabetic patients who progressed to IGT and type 2 diabetes manifest triple defects (decreased insulin secretion, insulin action, and glucose effectiveness) that antecede the disease.

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β-Cell dysfunction, insulin resistance, and increased (absolute or relative) hepatic glucose production characterize the hyperglycemia found in patients with established impaired glucose tolerance (IGT) and type 2 diabetes (1–10). The earliest etiologic lesion underlying the development of IGT and type 2 diabetes is unknown, but it is presumed to be genetic with strong familial and environmental components (10–18). Prevention of type 2 diabetes could not only prevent the long-term morbidity and mortality associated with the disease but could have tremendous economic impact for individuals and the nation (19–21).

Previous investigators reported quantitative and qualitative changes in tissue insulin resistance (in the liver, adipose tissue, and skeletal muscles) and/or blunted acute first-phase secretion as metabolic predictors of IGT and diabetes in prospective, longitudinal studies in Pima Indians (7,10,13), Mexican Americans (18), and Caucasians (5,12,14–17). We are not aware of similar studies in African Americans, a population with extraordinary propensity for developing IGT and type 2 diabetes. In this regard, African Americans (22–30) and other high-risk populations (12–18) manifest greater prevalence and incidence of type 2 diabetes and its long-term complications compared with their white counterparts. In the same regard, these metabolic differences extend to African-American children and adolescents (28,29). We and others (18,20–27) have previously provided cross-sectional data on β-cell function, insulin sensitivity index (S_i), and glucose effectiveness index (S_g) in African Americans with newly diagnosed IGT and type 2 diabetes. We have also shown that blacks, in general,

From the Ohio State University College of Medicine and Public Health, Columbus, Ohio.
Address correspondence and reprint requests to Kwame Osei, MD, FACE, FACP, Ohio State University College of Medicine and Public Health, 491 McCampbell Hall, Columbus, OH 43210. E-mail: osei-1@medtr.osu.edu.
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Abbreviations: HIE, hepatic insulin extraction; HOMA, homeostasis model assessment; HOMA-%B, HOMA-derived β-cell function; HOMA-IR, HOMA-derived insulin resistance index; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test.

have decreased S_i, β-cell dysfunction, and S_g at the time of diagnosis of IGT and type 2 diabetes (31,32). However, we were unable to determine the metabolic predictors or determinants of IGT and/or type 2 diabetes in obese African Americans or whether these predictors differed from those of white Americans. These are important issues for future primary prevention of IGT and type 2 diabetes in African Americans. In this regard, the Diabetes Prevention Program demonstrated that lifestyle modification with diet and exercise, with the goal of losing 7% of baseline weight, significantly decreased the risk of type 2 diabetes by 58% in several racial groups, including African Americans with IGT (19). These findings were consistent with those found in other populations (20,21).

The objective of the present study was to systematically determine the primary defects in the pathogenesis of IGT and type 2 diabetes in healthy, glucose-tolerant, first-degree relatives of African-American type 2 diabetic patients.

RESEARCH DESIGN AND METHODS

— During 1994–1996, we undertook a metabolic study to examine the natural history of the pathogenic mechanism(s) in IGT and type 2 diabetes in glucose-tolerant, first-degree relatives of African-American patients with type 2 diabetes who were residing in Franklin County in central Ohio. Informed written consent approved by the institutional review board for human biomedical research at Ohio State University, Columbus, Ohio, was obtained from each subject.

The baseline clinical characteristics of our African-American subjects are shown in Table 1. The first-degree relatives comprised 81 subjects with normal glucose tolerance (NGT): age 41.5 ± 4.8 years, BMI 31.3 ± 3.6 kg/m^2. The subjects were invited at 1- to 3-year intervals to undergo an oral glucose tolerance test (OGTT). In 18 subjects (age 45.4 ± 8.2 years, BMI 35.4 ± 5.9 kg/m^2), IGT (n = 8) and type 2 diabetes (n = 10) developed during follow-up. These subjects were designated as progressors. We found that 19 nondiabetic subjects who also underwent OGTT at the end of 5–8 years (median 6) maintained NGT during follow-up. The latter group was designated as nonprogressors. During screening, the following subjects were excluded: *1*) those taking medications known to influence glucose and insulin metabolism; *2*) those with liver, heart, lung, and kidney diseases; *3*) those with established diabetes taking antidiabetic medications; and *4*) those who participated in endurance or strenuous exercise or indulged in regular competitive sport. Strenuous exercise was defined as weight lifting, wrestling, racquetball, marathon, jogging, etc., at least three times per week.

Table 1—*Baseline clinical and metabolic characteristics of high-risk African Americans with NGT*

Clinical characteristics	
n	81
Age (years)	41.5 ± 4.8
Sex ratio (women/men)	54/27
Body weight (kg)	89.9 ± 10.3
Height (m)	1.68 ± 0.1
BMI (kg/m^2)	31.3 ± 3.6
Lean body mass (kg)	61.7 ± 7.0
Body fat mass (%)	37.4 ± 4.3
Waist-to-hip ratio	0.90 ± 0.10
Metabolic parameters	
OGTT	
Fasting serum glucose (mg/dl)	78.3 ± 8.9
2-h serum glucose (mg/ml)	95 ± 11
Fasting serum insulin (μU/ml)	13.7 ± 1.9
2-h serum insulin (μU/ml)	78 ± 4.9
Fasting serum C-peptide (ng/ml)	2.68 ± 0.35
2-h serum C-peptide (ng/ml)	9.31 ± 1.13
IVGTT	
AIR_{peak} at t = 5 min	
Peak glucose (mg · dl^{-1} · min^{-1})	221 ± 32
Peak insulin (μU/ml)	108 ± 88
Peak C-peptide (ng/ml)	6.85 ± 3.20
Acute first phase (AIR_{FSIGTT})	
Glucose (mg · dl^{-1} · min^{-1})	1,217 ± 245
Insulin (μU · ml^{-1} · min^{-1})	354 ± 23
C-peptide (ng · ml^{-1} · min^{-1})	17 ± 0.16
Insulin sensitivity indexes	
S_i ($\times 10^{-4} \times$ min^{-1} [μU/ml]$^{-1}$)	2.48 ± 0.33
S_g ($\times 10^{-2} \times$ min^{-1})	2.48 ± 0.31
HOMA-IR	2.56 ± 1.4
HOMA-%B	391 ± 54

Data are means ± SD. AIR_{FSIGTT}, acute insulin response to a frequently sampled intravenous glucose tolerance test; IVGTT, intravenous glucose tolerance test.

Study protocol

After a 10- to 12-h overnight fast, the subjects reported to the General Clinical Research Center of the Ohio State University Medical Center in Columbus, Ohio. Body weight and height were measured with the subject wearing a very light gown and no shoes. The body fat distribution was measured as the waist-to-hip circumference ratio. Waist circumference was measured at the level of the umbilicus (with the subject standing) and hip circumference at the level of the greater trochanter (with the patient standing). Body composition (lean body mass and body fat) was measured using bioelectrical impedance analyzer (33). All subjects answered a simple questionnaire regarding physical activity. The activity level was described as *1*) sedentary (no extra physical activity apart from walking and activity of daily living) or *2*) moderate (tennis, brisk walking, swimming, etc., at least three times per week).

Metabolic studies

OGTT. Each subject was instructed to ingest at least 250 g of carbohydrate in their regular meals for at least 3 days before the test. With the subject in the supine position, an intravenous needle was inserted after a 10- to 12-h overnight fast

Table 2—*Baseline clinical and metabolic characteristics of high-risk African Americans with normal glucose tolerance who were followed for 5–8 years and those who dropped out during the study period*

	Progressors	Nonprogressors	Dropouts	*P* value: Progressors vs. dropouts	*P* value: Nonprogressors vs. dropouts
n	18	19	44		
Age (years)	45.5 ± 8.2	42.1 ± 8.2	39.7 ± 8.7	0.029	0.416
Sex ratio (women/men)	14/4	16/3	18/26		
BMI (kg/m^2)	35.4 ± 5.9	33.5 ± 7.0	33.4 ± 4.4	0.130	0.475
Waist-to-hip ratio	0.91 ± 0.10	0.88 ± 0.06	0.92 ± 0.01	0.722	0.021
Systolic blood pressure (mmHg)	127 ± 14	125.6 ± 20	122.9 ± 7	0.138	0.5557
Diastolic blood pressure (mmHg)	78 ± 12	81.2 ± 14.1	77.7 ± 7.5	0.980	0.01
Metabolic parameters					
Fasting serum glucose (mg/dl)	95 ± 8	80 ± 14	88 ± 16	0.083	0.064
Fasting serum insulin (μU/ml)	15.1 ± 8.1	11.54 ± 7.85	18.36 ± 8.71	0.185	0.055
Fasting serum C-peptide (ng/ml)	3.04 ± 0.85	2.64 ± 1.17	3.03 ± 0.92	0.990	0.194
Minimal model parameters					
S_i ($\times 10^{-4} \times \text{min}^{-1}\,[\mu\text{U/ml}]^{-1}$)	1.61 ± 1.13	2.67 ± 1.27	2.48 ± 1.34	0.01	0.600
S_g ($\times 10^{-2} \cdot \text{min}^{-1}$)	1.48 ± 0.61	2.30 ± 0.97	2.21 ± 0.72	0.01	0.684

Data are means ± SD.

into the forearm vein and kept patent with 0.9% normal saline infusion. Blood samples were drawn for serum glucose, insulin, and C-peptide levels. The subjects then ingested 75 g of oral glucose load (Glucola, Baltimore, MD) over a 2-min period. Blood samples were drawn at t = 0 and 120 min for serum glucose, insulin, and C-peptide levels. Glucose tolerance status of the subjects was defined using the World Health Organization criteria (34)

Frequently sampled intravenous glucose tolerance. With the subject in the supine position, two intravenous needles were inserted into the forearm veins and kept patent with 0.9% normal saline infusion. One intravenous line was used to draw blood samples, and the other was used to administer the intravenous glucose and exogenous insulin, as previously described (22,23,26,27,35–38). Four blood samples were obtained at $t = -20$, -10, -5, and 0 min for basal serum glucose, C-peptide, and insulin concentrations. The average of the four samples was considered the basal level. Thereafter, 0.3 g/kg glucose (50 ml of 50% dextrose water) was infused over a 1-min period. At t = 19 min, intravenous insulin (0.05 units/kg, Humulin; Eli Lilly, Indianapolis, IN) dissolved in 30 ml of 0.9% normal saline was infused over 60 s. Blood samples were obtained at frequent intervals (t = 2, 3, 4, 5, 6, 8, 10, 12, 16, 19, 22, 24, 25, 27, 30, 40, 60, 70, 90, 120, 140, 150, 160, and 180 min) for serum glucose, C-peptide, and insulin levels. All samples were centrifuged at 4°C, and the sera were frozen and stored at −20°C until assayed.

Longitudinal follow-up of subjects

The subjects were seen at 3- to 4-month intervals for interviews over 5–8 years. We inquired about participation in new dietary and exercise programs as well as concurrent illness (e.g., hypertension requiring medications, antilipid medications, and medications that are known to influence glucose and insulin metabolism). Body weight and height were obtained in each subject as described above. During each visit, the subjects completed questionnaires regarding their diet and exercise habits. Specifically, we interviewed each subject with respect to their knowledge of diabetes and the related symptoms of hyperglycemia. Blood samples were obtained for routine biochemistry and hematologic parameters. OGTT protocols were repeated at 1- to 3-year intervals in the subjects for 5–8 years. A total of 37 subjects were restudied at a median of 6 years. IGT had developed in eight subjects and type 2 diabetes had developed in 10 subjects. Both the IGT and diabetes groups constituted the glucose intolerance group and comprised the progressors. A total of 19 subjects who were similarly followed but did not progress to IGT or type 2 diabetes (but maintained NGT) were also studied. This group was empirically designated as nonprogressors. A total of 44 obese subjects dropped out of the study during follow-up for several reasons, including the following. *1*) Nineteen subjects opted out of the study to participate in active weight reduction programs involving exercise, low-calorie diet, high-protein diet, etc. *2*) Seven subjects developed hypertension requiring antihypertensive medications known to influence glucose and insulin metabolism that were prescribed by the primary care providers. *3*) Seven subjects began new jobs that limited their flexibility to participate in a long-term study. *4*) Nine subjects moved out of Franklin County to other states. *5*) One subject had a stroke, and another subject had cardiac arrhythmia requiring implantation of a cardiac pacemaker. Table 2 shows the baseline clinical and biochemical characteristics of the 44 subjects who dropped out and the 37 subjects who remained in the study. At baseline, mean age, BMI and fasting glucose, insulin and C-peptide, as well as S_i and S_g were not significantly different in the subjects who maintained NGT (nonprogressors) or the entire group when compared with those subjects who dropped out.

Analytical methods

Serum glucose concentrations were measured by the glucose oxidase method using a glucose autoanalyzer (Beckman Instruments, Fullerton, CA). The serum

Table 3 —*Clinical and metabolic characteristics of 18 high-risk African Americans who progressed to IGT and/or type 2 diabetes and 19 healthy subjects who did not progress at the end of 8 years*

	Nonprogressors		Progressors GIT		*P* value		
Parameters	Baseline	After 6 years	Baseline	After 6 years	Nonprogressors: baseline vs. after 6 years	Progressors vs. nonprogressors: baseline	Progressors vs. nonprogressors: after 6 years
n	19	19	18	18			
Age (years)	42.1 ± 8.2	49.1 ± 7.9	45.4 8.2	51.6 8.5	0.011	NS	NS
Sex ratio (female/male)	16/3	16/3	14/14	14/4			
Body weight (kg)	84.7 ± 0.7	85.0 ± 3.0	98.7 ± 19	103.6 ± 20.9	NS	NS	0.073
Height (m)	1.64 ± 0.7	1.61 ± 0.7	1.66 ± 0.9	1.65 ± 0.1	NS	NS	NS
BMI (kg/m^2)	33.5 ± 7.0	32.4 ± 6.7	35.4 ± 5.9	37.7 ± 6.4	NS	NS	0.030
Waist-to-hip ratio	0.88 ± 0.06	0.88 ± 0.05	0.91 ± 1.10	0.93 ± 0.37	0.04	NS	NS
Systolic blood pressure (mmHg)	126.6 ± 20.0	129.1 ± 14.7	127 ± 14	138 ± 20	NS	NS	NS
Diastolic blood pressure (mmHg)	81.2 ± 14.1	82.8 ± 11.7	78 ± 12	82 ± 12	NS	NS	NS
Lipids and lipoproteins (mg/dl)							
Cholesterol	195 ± 32	191 ± 26	205 ± 31	235 ± 40	NS	NS	0.001
Triglycerides	82 ± 30	77 ± 32	128 ± 4	184 ± 60	NS	0.001	0.001
HDL cholesterol	57.9 ± 13.7	51.4 ± 12.3	44.5 ± 10.1	41.7 ± 11.7	NS	0.086	0.001
LDL cholesterol	150 ± 49	124 ± 22	135 ± 3	140 ± 53	NS	NS	NS

Data are means ± SD. Progressors GIT (glucose intolerance) represents patients in both the IGT and diabetes groups who progressed during the 5–8 years of follow-up.

insulin and C-peptide levels were determined by a standard double-antibody radioimmunoassay technique at The Core Laboratories of Ohio State University Hospitals. The sensitivity of the insulin assay was 2.5 μU/ml. The intra-assay and interassay coefficients of variation (CVs) were 6 and 10%, respectively. The lower limit of the C-peptide assay was 0.47 ng/ml, and the intra-assay and interassay CVs were 7 and 13%, respectively.

Calculations and statistical analyses

Results are expressed as means ± SD, unless stated otherwise. BMI was calculated as weight (kg) divided by height squared (m^2). Obesity was defined as BMI >30 kg/m^2 for both women and men. We examined the potential role of insulin clearance or hepatic insulin extraction (HIE) in the peripheral hyperinsulinemia in the progressors and nonprogressors using C-peptide–to–insulin molar ratios at fasting and at 2 h during OGTT at baseline and at 5–8 years. The acute first phase of insulin secretion was taken as the peak serum insulin and C-peptide levels at $t = 5$ min and area under the curve for acute first-phase insulin release between $t = 0$ and 5 min after the intravenous glucose load. We calculated the incremental area under the curve for serum glucose, insulin, and C-peptide levels during frequently sampled intravenous glucose tolerance tests as the areas above the baseline values using trapezoidal rule. S_i and S_g were calculated using Bergman's Minmod software program (35–38). Insulin resistance and β-cell function were also calculated using homeostasis model assessment (HOMA) (39). HOMA-derived insulin resistance index (HOMA-IR) was calculated as follows: fasting insulin (μU/ml) × fasting plasma glucose (mmol/ml)/22.5. HOMA-derived β-cell function (HOMA-%B) was also calculated, using the following formula: 20 × fasting insulin (μU/ml)/fasting glucose (mmol/ml) – 3.5 (39).

The nonparametric data were analyzed using χ^2 and Mann-Whitney rank test. Statistical analyses were performed using Student's unpaired *t* test between the groups and paired *t* test for intragroup analyses and ANOVA with repeated measures, where appropriate. Bonferroni method was used for post hoc testing. For comparison of the mean data with unequal variance, Neuman-Keuls multiple *t* test was used. $P < 0.05$ was considered statistically significant.

RESULTS — The clinical characteristics of the subjects are shown for the whole group in Table 1; characteristics during follow-up are shown in Tables 3 and 4. A total of 18 subjects who progressed to either IGT ($n = 8$) and type 2 diabetes ($n = 10$) had greater body weight, BMI, and waist-to-hip ratio than those of the nonprogressors at baseline. During follow-up, the progressors gained 5–10 kg body weight. In contrast, there was no change in body weight and BMI in the nonprogressors (Table 3).

The mean fasting (95 ± 8 vs. 80 ± 14 mg/dl, $P < 0.01$) and 2-h (149 ± 41 vs. 89 ± 53 mg/dl, $P < 0.01$) serum glucose levels after oral glucose challenge in the progressors were significantly higher than those of the nonprogressors at baseline, respectively (Table 3). Mean fasting insulin levels were similar in the progressors and nonprogressors at baseline (15.1 ± 8.1 vs. 13.9 ± 1.9 μU/ml). However, the mean 2-h serum insulin levels during OGTT were significantly higher in the progressors than in the nonprogressors at baseline (117 ± 81 vs. 99 ± 60 μU/ml, $P < 0.01$). The mean fasting serum C-peptide levels were not different in the progressors and the nonprogressors. How-

Table 4—*Metabolic characteristics of 18 high-risk African Americans who progressed to IGT and/or type 2 diabetes and 19 healthy subjects who did not progressed at the end of 8 years*

	Nonprogressors		Progressors GIT		*P* value		
Metabolic parameters	Baseline	After 6 years	Baseline	After 6 years	Nonprogressors before vs. after 6 years	Progressor vs. nonprogressor baseline	GIT vs. progressors before vs. after 6 years
Fasting glucose (mg/dl)	80 ± 14	77 ± 10	95 ± 8	158 ± 74	0.035	0.011	0.001
2-h glucose (mg/dl)	100 ± 60	89 ± 53	149 ± 27	258 ± 112	0.541	0.001	0.001
Fasting insulin (μU/mll)	11.54 ± 7.85	13.01 ± 9.32	15.1 ± 8.1	17.4 ± 12	0.474	0.514	0.234
2-h insulin (μU/ml)	77.2 ± 71	72.7 ± 87	117 ± 81	99 ± 60	0.121	0.001	0.344
Fasting C-peptide (ng/ml)	2.64 ± 1.17	3.68 ± 1.44	3.04 ± 0.85	3.84 ± 1.38	0.135	0.149	NS
2 h C-peptide (ng/ml)	9.36 ± 6	0.10 ± 4.12	13.3 ± 5.11	10.17 ± 3.78	0.817	0.065	NS
AIR_{FSIGTT} (μU/min)	305 ± 230	—	203 ± 21	—		0.05	—
Acute C-peptide ($ng \cdot ml^{-1} \cdot min^{-1}$)	17 ± 16	—	8.65 ± 9.80	—		0.05	—
S_i ($\times 10^{-4} \times min^{-1}$ $[\mu U/ml]^{-1}$)	2.67 ± 1.25	—	1.61 ± 1.13	—		0.05	—
S_g ($\times 10^{-2} \cdot min^{-1}$)	2.30 ± 0.97	—	1.48 ± 0.61	—		0.05	—
HOMA-IR	2.36 ± 1.69	2.81 ± 2.06	3.31 ± 1.64	5.44 ± 2.55	0.578	0.459	0.003
HOMA-%B	364 ± 37	261 ± 90	148 ± 60	1 01 ± 48	0.298	0.020	0.001

Data are means ± SD. AIR_{FSIGTT}, acute insulin response to a frequently sampled intravenous glucose tolerance test. Progressors GIT (glucose intolerance) represents patients in both the IGT and diabetes groups who progressed during the 5–8 years of follow-up.

ever, the 2-h serum C-peptide levels during OGTT tended to be higher in the progressors than nonprogressors (Table 4).

We examined the acute phases of insulin release in the progressors and nonprogressors during intravenous glucose tolerance test at baseline (Table 4). The mean incremental peak serum insulin and C-peptide responses at $t = 5$ min were significantly lower in the progressors than the nonprogressors at baseline. Similarly, the acute first-phase insulin release in the progressors tended to be lower ($P < 0.05$) than in the nonprogressors (insulin: 203 ± 217 vs. 354 ± 230 μU/ml × min; C-peptide: 8.65 ± 9.86 vs. 17 ± 16 ng/ml × min). We found that the S_i (1.61 ± 1.13 vs. $2.67 \pm 1.25 \times 10^{-2} \cdot min^{-1}$ $[\mu U/ml]^{-1}$) and S_g (1.48 ± 0.61 vs. 2.30 ± $0.97 \times 10^{-2} \cdot min^{-1}$) were significantly lower in the progressors than the nonprogressors at baseline (Table 4). Mean HOMA-IR or insulin resistance index tended to be greater in the progressors than the nonprogressors at baseline (3.31 ± 1.64 vs. $2.36 \pm 1.69 \times 10^{-4} \cdot min^{-1}$ $[\mu U/ml]^{-1}$). However, as shown in Table 4, HOMA-%B was significantly lower in the nondiabetic subjects who progressed than those who maintained NGT, i.e., nonprogressors (148 ± 60 vs. 364 ± 372).

HIE

We examined the potential role of insulin clearance or HIE in the peripheral hyperinsulinemia found in the progressors and nonprogressors at baseline using C-peptide–to–insulin molar ratios during fasting and 2-h OGTT. Although we found that the HIE was 25% lower in the progressors than nonprogressors at baseline, these did not predict the development of either IGT or type 2 diabetes in the first-degree relatives of African-American patients with type 2 diabetes (data not shown).

Conversion and progression from NGT to IGT or type 2 diabetes (Table 4)

Of the 81 subjects, 18 progressed from NGT to either IGT or type 2 diabetes in 5–8 years. As shown in Table 4, the mean fasting and 2-h serum glucose during OGTT had deteriorated in the progressors. Specifically, the mean fasting serum glucose increased from 95 ± 18 mg/dl at baseline to 158 ± 74 mg/dl during follow-up ($P < 0.01$) in the progressors or converters. As shown in Table 4, the mean fasting serum insulin and C-peptide levels at the time of diagnosis of IGT/diabetes did not differ from those found in the progressors at baseline. In contrast, the mean serum insulin and C-peptide levels 2 h after oral glucose challenge decreased after 8 years when compared with their respective baseline values in the progressors. The mean insulin resistance index, as assessed by HOMA-IR (3.31 ± 1.64 vs. 5.44 ± 2.55), and β-cell function, as assessed by HOMA-%B (148 ± 60 vs. 101 ± 48), also deteriorated in the progressors from the respective baseline values (Table 4). Note that these parameters did not significantly change in the nonprogressors throughout follow-up.

CONCLUSIONS — We describe, to the best of our knowledge, the first study on the natural history of IGT and type 2 diabetes in first-degree relatives of African-American patients with type 2 diabetes. We hereby describe our observations in the present study in the following sections.

β-Cell function in African Americans with varying degrees of glucose tolerance

Previous studies have shown that β-cell dysfunction is a prerequisite for development of IGT and type 2 diabetes in several populations (5–9,20,31,37,38,40,41). Indeed, the blunted acute insulin release to glucose stimulation, but not to nonglucose stimuli, is considered an early lesion of β-cell dysfunction in patients with IGT and type 2 diabetes (7,15,40–42). This is consistent with our previous reports in African Americans with IGT and diabetes (26,31). Our present study showed that first-degree relatives of African-American patients with type 2 diabetes who progressed to either IGT and/or type 2 diabetes had decreased β-cell function before the diagnosis. The progressors from NGT to IGT and type 2 diabetes had 30% lower β-cell function, as assessed by the acute first-phase insulin release to intravenous glucose challenge, than the nonprogressors. During follow-up, β-cell function remained unchanged in the individuals who were nonprogressors. Our findings were also confirmed by β-cell function as assessed by HOMA-%B, which also deteriorated in the progressors but not in nonprogressors. We found that the subjects who progressed to IGT and type 2 diabetes had 58 and 55% reduction in β-cell function, respectively, from baseline values. We should note that these β-cell defects were more remarkable after intravenous glucose stimulation than oral glucose challenge. Indeed, during the oral glucose tolerance, the absolute differences in the serum insulin and C-peptide levels in the progressors and nonprogressors were very minimal despite the higher prevailing serum glucose levels in the progressors (Tables 3 and 4). Although the mechanism(s) of β-cell dysfunction and its progressive deterioration from NGT to IGT and type 2 diabetes in our high-risk African-American subjects remains uncertain, we are tempted to speculate that this may be a primary genetic defect.

We have previously demonstrated that the peripheral hyperinsulinemia found in African Americans is partly attributed to decreased HIE when compared with those of white Americans (24). Recently, Goran et al. (29) and Arslanian et al. (28) have reported a decreased insulin clearance in African-American children when compared with those of their white counterparts. However, the potential role of altered HIE in development of IGT and/or type 2 diabetes in African Americans remains uncertain. Therefore, we examined the potential contribution of altered insulin clearance or HIE (C-peptide-to-insulin molar ratios) in the peripheral hyperinsulinemia found in the progressors and nonprogressors at baseline during OGTT. The HIE was 25% lower in the progressors than nonprogressors at baseline. However, this did not predict the development of either IGT or type 2 diabetes in the first-degree relatives of African-American patients with type 2 diabetes (data no shown).

Insulin resistance in African Americans with varying degrees of glucose tolerance

Previous studies have shown that insulin resistance is found in significant proportions of patients with obesity, IGT, and type 2 diabetes in several populations (6–9,12–18,31,32). In this regard, we and others (22–30) have previously demonstrated moderate to severe insulin resistance in African-American patients with IGT and type 2 diabetes at the time of diagnosis, similar to other populations. Furthermore, we have previously reported a lower S_i in the nondiabetic African Americans than their white counterparts (22–25). Our present study demonstrated that African Americans who progressed to IGT or type 2 diabetes were significantly more insulin resistant than the NGT group (the nonprogressors) at baseline. In the longitudinal study, the insulin resistance worsened in the progressors but remained unchanged in the nonprogressors. We found that individuals who converted or progressed to IGT had a 21% reduction in insulin sensitivity. In contrast, subjects who progressed to type 2 diabetes had a 100% increase in HOMA-IR, suggesting worsening insulin resistance index in those who progressed to type 2 diabetes. Although the mechanism(s) underlying the insulin resistance in glucose-tolerant African-American subjects who progressed to IGT and type 2 diabetes is unknown, we believe the insulin resistance could be ascribed partly to genetic inheritance, as suggested by Vaag et al. (16) and Martin et al. (14). We should note that obesity, upper-body fat distribution, and physical activity have been implicated in the pathogenesis of insulin resistance in various populations. In the present study, we found that that the progressors to either IGT or type 2 diabetes were obese and gained ~5–10 kg during follow-up before development of either IGT or type 2 diabetes. The insulin resistance index did not change in the nonprogressors. Based on our present study, we believe prevention of modest weight gain in high-risk, glucose-tolerant, African-American subjects could possibly prevent conversion of NGT to IGT or type 2 diabetes, as demonstrated by the Diabetes Prevention Program (19).

Glucose effectiveness in African Americans with varying degrees of glucose tolerance

The ability of glucose to mediate its own glucose disposal as well as suppress basal hepatic glucose production at basal insulin level is referred to as glucose effectiveness (S_g). It is considered a major component in maintaining physiologic glucose tolerance in vivo in humans and experimental animals (22–24,29,34–38,43–45). Previous studies have shown that S_g is reduced in patients with IGT and type 2 diabetes in several populations (29,30, 35,39–41,46). We have previously demonstrated that S_g is slightly reduced in blacks with newly diagnosed IGT and type 2 diabetes when compared with healthy control subjects with NGT (31, 32). Our present study demonstrated that African Americans who also progressed to IGT and/or type 2 diabetes had 30% lower S_g before diagnosis at baseline. Our study is consistent with that of nondiabetic offspring of white American patients with type 2 diabetes who progressed to type 2 diabetes during 25 years of follow-up (14). In summary, this is the first study, to the best of our knowledge, to suggest that a reduced S_g seems to be essential for the early initiation of the pathogenesis of IGT and type 2 diabetes in African Americans at risk for IGT and type 2 diabetes.

In summary, the present study demonstrated that first-degree relatives of African Americans with NGT who progress to IGT and type 2 diabetes manifest insulin resistance (both S_i and HOMA-IR), β-cell dysfunction, decreased glucose effectiveness (S_g), and weight gain before diagnosis. We speculate that obese, high-risk African Americans, who are perhaps genetically prone to develop IGT and type 2 diabetes, seem to be distinct and manifest multiple defects. These defects could be targets for primary diabetes prevention pro-

grams using lifestyle modification (19–21) and/or pharmacological agents (47,48).

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