Beneficial Metabolic Effects of Chronic Glipizide in Obese African Americans With Impaired Glucose Tolerance: Implications for Primary Prevention of Type 2 Diabetes

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We examined the long-term metabolic effects of glipizide gastrointestinal therapeutic system (GITS), a potent sulfonylurea (SU), in impaired glucose-tolerant (IGT), first-degree relatives of African American patients with type 2 diabetes. To this end, we assessed glucose homeostasis, beta-cell function, insulin sensitivity (Si), and glucose effectiveness (Sg) in patients with IGT before and at yearly intervals for 24 months of GITS or an identical placebo in a randomized, double-blind manner. Eighteen IGT patients were randomized to receive either glipizide GITS (GITS, 5 mg/d, n = 9; mean age, 43.3 ± 8.7 years; mean body mass index [BMI], 32.9 ± 6.3 kg/m^2) or identical placebo (PLAC, n = 9; mean age, 41.5 ± 5.7 years; mean BMI, 39 ± 4.2 kg/m^2) for 24 months. Each of the subjects underwent oral glucose tolerance test (OGTT) and frequently sampled intravenous glucose tolerance test (FSIGT) at baseline and yearly intervals for 2 years. Si and Sg were determined by Bergman's minimal model method. The ability of beta cell to compensate for peripheral insulin resistance was calculated as the disposition index (DI). Chronic administration of glipizide GITS attenuated serum glucose responses to oral glucose challenge at 12 and 24 months when compared to baseline (0 months). In contrast, serum glucose levels at fasting and during OGTT tended to increase in the IGT/PLAC group at 12 and 24 months when compared to baseline. Serum insulin ($P < .05$ to 0.01) and serum C-peptide levels progressively increased in the GITS group at 12 and 24 months versus 0 months. In contrast, serum insulin and C-peptide responses remained unchanged in the IGT/PLAC group. During FSIGT, chronic GITS was associated with significant improvement in the blunted acute first insulin release in the IGT patients at 12 and 24 months. These parameters remained blunted in the IGT/PLAC group. We found that Si increased in the IGT/GITS group at 12 months ($P < .01$) and 24 months($P < .05$) versus baseline, but deteriorated in the IGT/PLAC group. Similarly, the DIs significantly ($P < .01$) increased following GITS therapy at 12 and 24 months when compared to baseline. In contrast, DI did not change from baseline values in the IGT/PLAC group throughout the study period. Chronic GITS partially restored the ability of beta cells to compensate for peripheral insulin resistance (as assessed by DIs). GITS was well tolerated without any symptoms suggestive of either hypoglycemia or significant weight gain. In summary, long-term chronic glipizde GITS administration improved glucose homeostasis by increasing beta-cell responsiveness to glucose, improving Si, as well as significantly improved DI, but not Sg, in high-risk, obese African Americans with IGT. Our study demonstrated that GITS appears to prime beta cells to intravenous glucose stimulation resulting in restoration of physiologic acute first- and second-phase insulin secretion in African Americans with IGT. We conclude that GITS might be considered as a useful agent in the primary prevention of type 2 diabetes in high-risk, obese African American patients with IGT.

THE PREVALENCE of type 2 diabetes has increased in several populations to epidemic proportions.[1-5] Beta-cell dysfunction and insulin resistance characterize the hyperglycemia found in patients with impaired glucose tolerance (IGT) and type 2 diabetes in several populations.[6-11] The earliest etiologic lesion in the development of IGT and type 2 diabetes is unknown, but it is presumed to be genetic with strong familial and environmental components. The disease has a long latency period with well-described precursors and predictors in the prediabetic phase. This provides an opportunity to introduce or implement diabetes prevention programs in high-risk populations.[12-15]

The prevalence of diabetes and its associated complications is higher in minority populations residing in the United States.[3-5] This is particularly so for African Americans, who have an extraordinary propensity for type 2 diabetes and the related long-term complications when compared to white Americans.[3-5] We[6,16] and others[17] have previously demonstrated that African Americans with and without IGT and type 2 diabetes manifest higher peripheral hyperinsulinemia and greater insulin resistance when compared to their white counterparts. Thus, nondiabetic African Americans with IGT could be targeted for primary diabetes prevention. In this regard, the Diabetes Prevention Program (DPP) demonstrated that lifestyle modification (diet and exercise with the goal of losing 7% of the baseline weight) and metformin reduced the incidence of type 2 diabetes in patients with IGT by 58% and 31%, respectively, in all US ethnic populations including African Americans.[12] Furthermore, Buchanan et al[14] have reported that troglitazone reduced the incidence of type 2 diabetes in previous gestational Latino/Hispanic women, a population with tremendous propensity for type 2 diabetes. However, oral sulfonylurea (SU) agents were not included in the DPP, perhaps for the fear of severe or fatal hypoglycemia. Thus, whether long-acting SU could prevent or delay the development of type 2 diabetes in high-risk African Americans remains uncertain.

Therefore, we tested the hypothesis that SU could reverse the early beta-cell dysfunction and ultimately improve glucose

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homeostasis in high-risk African American patients with IGT. To this end, we investigated the metabolic effects of a glipizide gastrointestinal therapeutic system (glipizide GITS; Glucotrol XL, Pfizer Pharmaceutical Inc, New York, NY) and an identical placebo in first-degree relatives of African American patients with type 2 diabetes who had IGT treated for 24 months in a randomized, double-blind manner .

MATERIALS AND METHODS

Populations

The study group consisted of 18 subjects who were first-degree relatives of African American patients with type 2 diabetes and manifested IGT during an oral glucose tolerance test (OGTT). The subjects were recruited during community screening for diabetes in the first-degree relatives (offspring and siblings) of African American patients with type 2 diabetes. The categories of glucose tolerance were defined or classified according to the World Health Organization (WHO) criteria,[18] which was the classification at the time of initial screening of the subjects in 1996. Patients with IGT were defined as those with fasting serum glucose less than 140 mg/dL and 2-hour serum glucose after a 75-g oral glucose challenge greater than 140 mg/dL, but less than 199 mg/dL. We excluded individuals who had diabetes (newly or previously diagnosed) who were taking medications known to influence glucose and insulin metabolism. We also excluded subjects with liver, heart, lung, and kidney diseases and those who participated in endurance exercise or indulged in regular competitive sports. All of the subjects answered a simple questionnaire on physical activity. The activity level was described as (a) sedentary (no extra physical activity apart from walking and activity of daily living), (b) moderate (tennis, brisk walking, swimming, etc at least 3 times per week), and (c) strenuous (weight lifting, wrestling, racket ball, marathon, jogging, etc at least 3 times per week). Subjects who participated in an endurance or competitive sport were excluded. Informed written consent approved by the Institutional Review Board for Human Biomedical Research at the Ohio State University, Columbus, OH was obtained from each subject after the risks entailed in the study have been thoroughly explained.

Study Protocol

After a 10- to 12-hour overnight fast, the subjects reported to the clinical research center of the Ohio State University Medical Center. Body weight and height were measured with the subject wearing a very light gown and without shoes. Body mass index (BMI) was calculated as weight (kilograms) divided by square of height (meters). Lean body mass and body fat composition were measured by bioelectrical impedance analyzer.[19] Body fat distribution was measured as the waist-to-hip circumference ratios. Waist circumference was measured at the level of the umbilicus (with the subject in standing position) and hip circumference at the level of the greater trochanter (in the standing position).

Metabolic Studies

With the subject in the supine position, an intravenous needle was inserted into the forearm vein and kept patent with 0.9% normal saline infusion.

OGTT

Each subject was instructed to ingest at least 250 g of carbohydrate in their regular meals for at least 3 days prior to the test. After a 10- to 12-hour overnight fast, blood samples were drawn for serum glucose, insulin, and C-peptide at t = 0 minutes. The subjects then ingested 75 g of oral glucose load (Glucola, Baltimore, MD; 250 mL) over a 2-minute period. Blood samples were drawn at t = 30, 60, 90, and 120 minutes for serum glucose, insulin, and C-peptide concentrations. Glucose tolerance status of the subjects was defined by the WHO criteria.[18]

Table 1. Baseline Clinical and Metabolic Characteristics of First-Degree Relatives of African American Patients With Type 2 Diabetes With IGT

Parameter	Placebo (n = 9)	GITS (n = 9)	*P* Value
Clinical characteristics			
Age (yr)	41 ± 4.7	43.3 ± 8.7	NS
Body weight (kg)	108.9 ± 18.8	95.8 ± 16.3	NS
BMI (kg/m^2)	39.0 ± 4.2	32.9 ± 6.3	.02
LBM (kg)	51.3 ± 13.9	61.6 ± 7.6	.01
BFM (%)	48.7 ± 7.1	38.3 ± 7.5	.01
WHR	0.93 ± 0.37	0.88 ± 0.07	NS
Metabolic parameters			
Glucose (mg/dL)			
Fasting	83 ± 8	88 ± 12	NS
30 min	142 ± 20	150 ± 20	NS
2-h PP	160 ± 20	153 ± 14	NS
Insulin (μU/mL)			
Fasting	15.5 ± 6.4	13.4 ± 6.5	NS
30 min	44.6 ± 18.6	63.6 ± 29.0	NS
2-h PP	96 ± 38	94 ± 58	NS
C-peptide (ng/mL)			
Fasting	2.93 ± 1.20	3.20 ± 2.13	NS
30 min	5.60 ± 2.24	7.07 ± 2.82	NS
2-h PP	10.29 ± 4.01	11.29 ± 4.40	NS

NOTE. Values are mean ± SD. Metabolic parameters were obtained before and during standard oral glucose tolerance test.

Abbreviations: BMI, body mass index; LBM, lean body mass; BFM, body fat mass; WHR, waist-to-hip circumference ratio; PP, postprandial; NS, not significant.

Frequently Sampled Intravenous Glucose Tolerance

Following a 10- to 12-hour overnight fast, subjects were admitted to the research center for a frequently sampled intravenous glucose tolerance test (FISGT). Two intravenous needles were inserted into the forearm veins and kept patent with 0.9% normal saline infusion with the subject in supine position. One intravenous line was used to draw blood samples and the other to administer the intravenous glucose and exogenous insulin as previously described.[8,16,17,20,21] Four blood samples were obtained at t = −20, −10, −5, and 0 minutes for basal serum glucose, C-peptide, and insulin concentrations. The average of the 4 samples was taken as the basal level. Thereafter, 0.3 g/kg glucose as 50% dextrose water was infused over a 1-minute period: At t = 19 minutes, intravenous insulin (0.05 U/kg Humulin, Eli Lilly, Indianapolis, IN) dissolved in 30 mL of 0.9% normal saline was infused over 60 seconds. Blood samples were obtained at frequent intervals at t = 2, 5, 8, 10, 12, 14, 16, 19, 22, 24, 25, 27, 30, 40, 60, 70, 90, 120, 140, 150, 160, and 180 minutes for serum glucose, C-peptide, and insulin concentrations. All samples were centrifuged at 4°C and the sera frozen and stored at −20°C until assayed.

Twenty-Four–Month Longitudinal (phase II) Follow-up Study

After satisfying study entry requirements and baseline studies, the subjects were randomized in a double blind, placebo-controlled manner to receive either GITS (5 mg/d) or identical placebo (PLAC) for 24 months. The clinical characteristics of the 2 subgroups of African Americans with IGT are listed in Table 1. Group 1 (IGT/GITS, n = 9) consisted of subjects with IGT receiving GITS, and group 2 (IGT/

PLAC, n = 9) subjects with IGT receiving placebo. Participants were seen at the clinical research center at 3- to 4-month intervals for 24 months. The participants were instructed to take their respective medications 15 to 30 minutes before breakfast every day. However, on the morning of the days of metabolic studies, subjects were instructed to omit all medications. During each visit, body weight and height were obtained as described above. The subjects answered questionnaires regarding their diet and exercise habits. Specifically, we interviewed each subject with respect to their knowledge on diabetes and the related symptoms of hyperglycemia and hypoglycemia. The subjects were not required to monitor their blood sugar levels using self/home glucose monitoring (SHGM). Thus, symptoms suggestive of hypoglycemia (eg, nervousness, excessive hunger, tremors, confusion, etc) were recorded in a logbook, but there was no ascertainment by blood glucose levels. Furthermore, all subjects were counseled by our research dietitian on American Diabetes Association (ADA) recommended dietary intake in an effort to maintain their baseline weight. In addition, subjects completed daily physical activity and dietary questionnaire to ensure that they were not participating in new exercise or weight reduction program. Routine biochemical and hematological parameters were obtained at baseline and 3- to 4-month intervals. During each visit, each subject received bottles of either the active medication or placebo. Adherence with the medications was assessed by counting the pills in each labeled container with serial codes. We also examined the participant logbook to confirm the number of pills consumed by the participants. Subjects in each group consumed more than 80% of the assigned number of pills per month as a measure of acceptable adherence. The OGTT and FSIGT protocols were repeated at yearly intervals for 2 years.

Analytical Methods

Serum glucose concentrations were measured by the hexokinase method using a glucose autoanalyzer (Yellow Spring Instruments, Yellow Springs, OH). Serum insulin and C-peptide levels were determined by a standard double-antibody radioimmunoassay technique at The Core Laboratories of The Ohio State University Hospitals. The sensitivity of the insulin assay was 2.5 μU/mL. The intra- 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- and interassay CVs were 7% and 13%, respectively.

Calculations and Statistical Analyses

Results are expressed as mean ± SD unless stated otherwise. BMI was calculated as weight (kilograms) divided by square of the height (meters). Obesity was taken as BMI greater than 30 kg/m^2 for females and males. The acute first and second phases of insulin release (AIR) were calculated as the incremental areas of insulin curves (AUCs) from t = 0 to 5 minutes and t = 8 to 19 minutes using the trapezoidal rule, respectively. The early-phase insulin and C-peptide levels during OGTT were taken as the difference between the values at 30 minutes and baseline (0 minutes). We calculated the incremental AUC for serum glucose, insulin, and C-peptide levels during OGTT as the incremental areas above the baseline values using the trapezoidal rule. Peripheral insulin reflects both beta-cell secretion and insulin clearance. We estimated the hepatic insulin extraction (HIE) or insulin clearance based on the assumptions that (1) insulin and C-peptide are cosecreted in equimolar proportions into the portal circulation, and (2) while insulin is extracted by the liver, C-peptide is not metabolized by the liver. HIE was calculated as the molar ratios of the steady-state, fasting C-peptide and insulin levels at t = 0 minutess. HIE after oral glucose challenge was calculated as the molar ratio of incremental AUC for C-peptide and insulin values as previously described.[16]

Insulin sensitivity index (Si) and glucose effectiveness (Sg) were calculated using Bergman's Minmod software program.[22] The ability of beta cells to compensate for Si was calculated as the disposition index (DI). We calculated the DI using 2 methods: DI_{ivgtt} = Si × AIR, where AIR was defined as the incremental acute first-phase insulin response between t = 0 to 5 minutess during FSIGT; and DI_{ogtt} = Si × AUC for insulin.[8,10,16,20,21]

Stepwise linear regression and 2-way analyses of covariance (ANCOVAs) were used to adjust for the effects of age, sex, body weight, and WHR on the various metabolic parameters. Nonparametric data were analyzed using chi-square and Mann-Whitney rank tests. Statistical analyses were performed using Student's *t* test (paired and unpaired) and analysis of variance (ANOVA), where appropriate, with Bonferroni correction for post-hoc testing. For comparison of the mean data with unequal variance, the Neuman-Keuls multiple *t* test was used. *P* values less than .05 were considered statistically significant

RESULTS

The first-degree relatives of African American patients with type 2 diabetes who had newly diagnosed IGT tolerated glipizide GITS without any symptoms suggestive of hypoglycemia or hyperglycemia. GITS was not associated with significant weight gain when compared with the PLAC group. We found no biochemical or hematological abnormalities with the chronic use of GITS in our IGT patients when compared with the PLAC group

Clinical Characteristics

As shown in Table 1, mean body weight was lower in the IGT/GITS group than in the IGT/PLAC group, but differences did not reach statistical significance. Despite double-blind randomization, we found that mean lean body mass was significantly greater in the IGT/GITS than in the IGT/PLAC group. In contrast, mean body fat mass and percent body fat were lower in the IGT/GITS than in IGT/PLAC group (Table 1). During follow-up, the mean body weight, BMI, and body composition indices did not significantly change at 12 and 24 months in any of the groups when compared with baseline values (Table 2).

Metabolic Studies

Despite the significant differences in BMI, lean body mass, and percent body fat at baseline, we found no statistically significant differences in fasting and post–glucose challenge serum glucose, insulin, and C-peptide levels in the obese, IGT/GITS, and IGT/PLAC groups at baseline. Accounting for BMI, body fat, and lean body mass by ANCOVA, we found no differences in these metabolic parameters, perhaps due to the small sample size.

OGTT. Mean fasting serum glucose levels were similar in the IGT/GITS group when compared with the IGT/PLAC group at 0 months (Table 1). Mean serum fasting glucose levels remained unchanged in the IGT/GITS group but significantly ($P < .05$) increased in the IGT/PLAC group at 24 months (Table 3). During follow-up, mean serum glucose responses to oral glucose load were attenuated in the IGT/GITS group, but rather tended to increase in the IGT/PLAC group at t = 60, 90, and 120 minutes at 12 and 24 months (P = 05 by ANOVA) when compared to those at 0 months (Table 3). We found that serum glucose responses to oral glucose challenge were lower in the IGT/GITS group than in the IGT/PLAC group at t = 90

Table 2. Body Composition Characteristics of First-Degree Relatives of African American Patients With IGT Treated With Glipizide GITS and Placebo for 24 Months

Parameter	Group		*P* Value
	Placebo	Glipizide GITS	Glipizide GITS *v* Placebo
Body weight (kg)			
0 months	108.9 ± 18.8	95.8 ± 16.3	.136
12 months	100.1 ± 19.0	85.5 ± 21.3	.157
24 months	110.0 ± 18.0	92.5 ± 27.7	.146
Body mass index (kg/m^2)			
0 months	39.6 ± 4.2	32.9 ± 6.3	.010
12 months	40.4 ± 7.0	29.9 ± 9.0	.018
24 months	43.5 ± 7.1	32.6 ± 11.0	.022
Lean body mass (%)			
0 months	51.3 ± 13.9	61.7 ± 7.5	.057
12 months	51.3 ± 5.8	63.6 ± 8.3	.001
24 months	53.2 ± 4.9	64.0 ± 11.3	.001
Body fat mass (%)			
0 months	48.7 ± 7.1	38.3 ± 7.5	.012
12 months	48.8 ± 5.9	36.42 ± 8.3	.001
24 months	46.8 ± 4.8	36.0 ± 11.3	.001

NOTE. Values are mean ± SD. *P* = NS for 12 and 24 months *v* 0 months for both GITS and placebo groups, respectively.

and 120 minutess, but the differences reached only borderline statistical significance. Comparing the IGT/GITS with the IGT/PLAC group, mean serum glucose levels were significantly ($P < .05$) lower at 90 and 120 minutes in the IGTS/GITS than in the IGT/PLAC group at 12 and 24 months (Table 3). Mean glucose AUC values at 12 and 24 months remained unchanged in the IGT/GITS group, but tended to increase in the IGT/PLAC group when compared with the respective baseline values (Table 4).

Mean fasting serum insulin levels were similar in the IGT/GITS and IGT/PLAC groups at baseline. During follow-up, mean serum fasting insulin levels significantly increased in the IGT/GITS group at 12 and 24 months. Fasting serum insulin levels also increased in the IGT/PLAC group when compared to the respective baseline. The significant increases in the IGT/GITS group at 24 months ($P < .05$) were perhaps due to the effects of the active medication, since fasting glucose remained unchanged, while that of the IGT/PLAC group was more likely due to deterioration in fasting glucose levels. As shown in Table 3, mean serum insulin responses during OGTT rose to significantly ($P < .05$, ANOVA) greater levels at t = 30, 60, and 90 minutes at 24 months in the IGT/GITS group when compared to values at 0 months. However, serum insulin responses did not change in the IGT/PLAC group when compared to baseline (Table 3). We found that serum insulin profiles were significantly ($P < .05$) different in IGT/GITS group when compared to the IGT/PLAC group during the OGTT. Mean serum C-peptide responses during OGTT followed trends similar to serum insulin profiles in both the IGT/GITS and IGT/PLAC groups, respectively. The mean AUCs for serum insulin values were not different in the IGT/GITS and IGT/PLAC groups at baseline. While the mean AUC for serum insulin increased significantly in the IGT/GITS group, the mean AUC for C-peptide did not change significantly in the IGT/IGTS group at 12 and 24 versus 0 months (Table 4). The mean AUC for serum insulin and C-peptide rather deteriorated in the IGT/PLAC group at 12 and 24 months versus 0 months. Comparing the IGT/GITS with the IGT/PLAC group, mean serum insulin levels were significantly ($P < .05$) higher at 30 and 60 minutes in the IGT/GITS than in the IGT/PLAC group at 24 months (Table 3). Similarly, when comparing the IGT/GITS with the IGT/PLAC group, mean serum C-peptide levels during OGTT were higher but not statistically significantly different at 12 and 24 months in the IGT/GITS than in the IGT/PLAC group.

HIE. Mean HIE during OGTT decreased by 28.9% at 24 months when compared with baseline in the IGT/GITS group. In the PLAC group, mean HIE during OGTT decreased by only 9.8% at 24 months from baseline values. Thus, we found significant differences in HIE during OGTT in the IGT/GITS group at 24 months when compared to the IGT/PLAC group (28.9% *v* 9.8%, $P < .05$).

FSIGT. During the FSIGT, mean serum glucose responses to glucose load were attenuated in the IGT/GITS (Fig 1A, left panel), but tended to increase in the IGT/PLAC group (Fig 1A, right panel) at 12 and 24 months. Indeed, the mean peak glucose levels at t = 5 minutes in the IGT/GITS group tended to be lower than in the IGT/PLAC group (242 *v* 330 mg/dL, respectively; Fig 1A left panel). In addition, as shown in Fig 1A, right panel, the mean serum glucose levels at t = 16 minutes in the IGT/GITS group were lower than in the IGT/PLAC group (200 *v* 255 mg/dL, respectively). The blunted acute first-phase of insulin (Fig 1B, left panel) and C-peptide (Fig 1C, left panel) responses to intravenous glucose load improved significantly during FSIGT at 12 and 24 months in the IGT/GITS group when compared to baseline values at 0 months. As shown in Fig 1B and C, left panels, both serum insulin and C-peptide responses to intravenous glucose progressively increased at 12 and 24 months in the IGT/GITS group, but remained unchanged and blunted in the IGT/PLAC group. Although, the subjects did omit their GITS dose on the morning of the test, we demonstrated partial restoration or restitution of acute first insulin and C-peptide responses (t = 0 to 5 minutes) to intravenous glucose load in the IGT/GITS group (Fig 1B and C, left panels). This was seen also in the early release of insulin, with peaks occurring in 5 minutes, and in overall secretion profiles, similar to those of healthy controls.[8,16] Between t = 8 to 19 minutes, serum insulin levels remained slightly elevated (by 1.5-fold) and did not return to fasting values in the IGT/GITS group at the end 12 and 24 months. In contrast, the acute first-phase insulin release to intravenous glucose stimulation remained severely blunted at t = 0 to 5 minutes in the IGT/PLAC group throughout the study period (Fig 1B and C, right panels). Furthermore, we observed progressive increases in acute second-phase insulin release (insulin and C-peptide) between t = 8 to 19 minutes; these values were 2.5-fold greater than the fasting values, perhaps due to persistent hyperglycemia (Fig 1B and C, right panels) in the IGT/PLAC group. The acute first and second phases of insulin secretion and profiles did not change and remained

Table 3. Serum Glucose, Insulin, and C-Peptide Levels Before and After Oral Glucose Challenge in African Americans With IGT Treated With Glipizide GITS or Placebo for 24 Months

Parameter	Minutes				
	0	30	60	90	120
Serum glucose (mg/dL)					
Placebo 0 months	83 ± 18	142 ± 20	177 ± 32	176 ± 25	160 ± 19
Placebo 12 months	99 ± 19*	150 ± 36	183 ± 38	190 ± 34	182 ± 35
Placebo 24 months	99 ± 18*	149 ± 44	186 ± 52	187 ± 52	179 ± 52
GITS 0 months	88 ± 12	150 ± 30	176 ± 29	172 ± 30	153 ± 14
GITS 12 months	83 ± 10§	150 ± 18	177 ± 21	163 ± 23‡	152 ± 30‡
GITS 24 months	87 ± 21§	147 ± 29	177 ± 31	167 ± 23‡	143 ± 30‡
Serum insulin (μU/mL)					
Placebo 0 months	15.5 ± 6.4	44.6 ± 18.4	76.4 ± 25.0	93.0 ± 37.0	96.0 ± 38.0
Placebo 12 months	21.7 ± 8.4	69.7 ± 26.4	95.4 ± 36.7	103.8 ± 40.1	116.2 ± 44.9
Placebo 24 months	22.7 ± 8.6¶	65.4 ± 20.4	76.9 ± 38.9	89.8 ± 44.8	94.5 ± 42.8
GITS 0 months	13.4 ± 6.5	63 ± 29	86 ± 44	102 ± 52	94 ± 58
GITS 12 months	15.0 ± 6.3	72 ± 20	104 ± 52	105 ± 55	107 ± 50
GITS 24 months	25.3 ± 13¶	125 ± 88.0†§	125 ± 79†§	139 ± 105	143 ± 105
Serum C-peptide (ng/mL)					
Placebo 0 months	2.93 ± 1.2	5.60 ± 2.24	8.03 ± 3.11	10.16 ± 3.98	10.29 ± 4.01
Placebo 12 months	3.26 ± 2.20	6.24 ± 2.35	8.02 ± 3.07	10.02 ± 3.04	10.91 ± 4.23
Placebo 24 months	3.35 ± 1.30	5.97 ± 1.96	8.55 ± 3.0	9.87 ± 2.87	10.65 ± 2.77
GITS 0 months	2.20 ± 1.1	6.78 ± 2.64	8.26 ± 3.14	9.32 ± 2.40	10.02 ± 4.08
GITS 12 months	3.20 ± 1.75	7.07 ± 2.82	10.39 ± 4.19	12.06 ± 4.66	11.29 ± 4.40
GITS 24 months	3.70 ± 2.13	8.88 ± 5.52	11.45 ± 4.07	12.64 ± 4.05	11.30 ± 4.43

NOTE. Values are mean ± SD.
*$P < .05$, 12 and 24 months *v* 0 months in the placebo group.
†$P < .05$, 12 months *v* 0 months in the GITS group.
‡$P < .05$, GITS *v* placebo.
§$P < .05$, GITS *v* placebo.
¶$P < .05$, 24 months *v* 0 months.

blunted in the IGT/PLAC group throughout the study period when compared with the IGT/GITS group responses at 12 and 24 months, respectively.

Minimal model parameters. The mean Si values were not different in the IGT/GITS group compared to the IGT/PLAC group (Table 5 and Fig 2) at 0 months. Mean Si increased at 12 months ($P < .01$) and 24 months ($P < 5$) by 90% and 62%, respectively, when compared to baseline values in the IGT/GITS group. During follow-up, Si significantly increased by 2-fold in the IGT/GITS group when compared to the IGT/PLAC group at 12 and 24 months. In contrast, mean Si values significantly deteriorated in the IGT/PLAC group at 12 and 24 months when compared to baseline (Fig 2 and Table 5). Mean Sg values were similar in the IGT/GITS versus IGT/PLAC group at baseline. Sg did not change significantly either within or between groups throughout the study period (Table 5).

DI. Mean DI_{ivgtt} values were not different in the IGT/GITS group compared the IGT/PLAC group (Table 5 and Fig 2) at 0 months. As shown in Table 5, GITS improved the DI_{ogtt} and

Table 4. Areas Under the Curve During OGTT in African American Subjects With IGT Receiving Placebo or GITS for 24 Months

Parameter	Month		
	0	12	24
Glucose area (mg/dL × min)			
Placebo	8,613 ± 3,158	8,071 ± 3,077	9,120 ± 3,202
GITS	7,980 ± 2210	8,248 ± 1468	7,886 ± 2,035
Insulin area (μU/mL × min)			
Placebo	6,235 ± 2,493	7,535 ± 2,960	5,988 ± 3,033
GITS	7,516 ± 3,992	8,451 ± 3,084	11,194 ± 8,154*†
C-peptide area (ng/mL × min)			
Placebo	623 ± 560	550 ± 235	539 ± 204
GITS	726 ± 273	650 ± 90	768 ± 291†

NOTE. Values are mean ± SD.
*$P < .05$, 24 months *v* 0 months for the GITS group.
†$P < .05$, at 24 months in the GITS *v* placebo group.

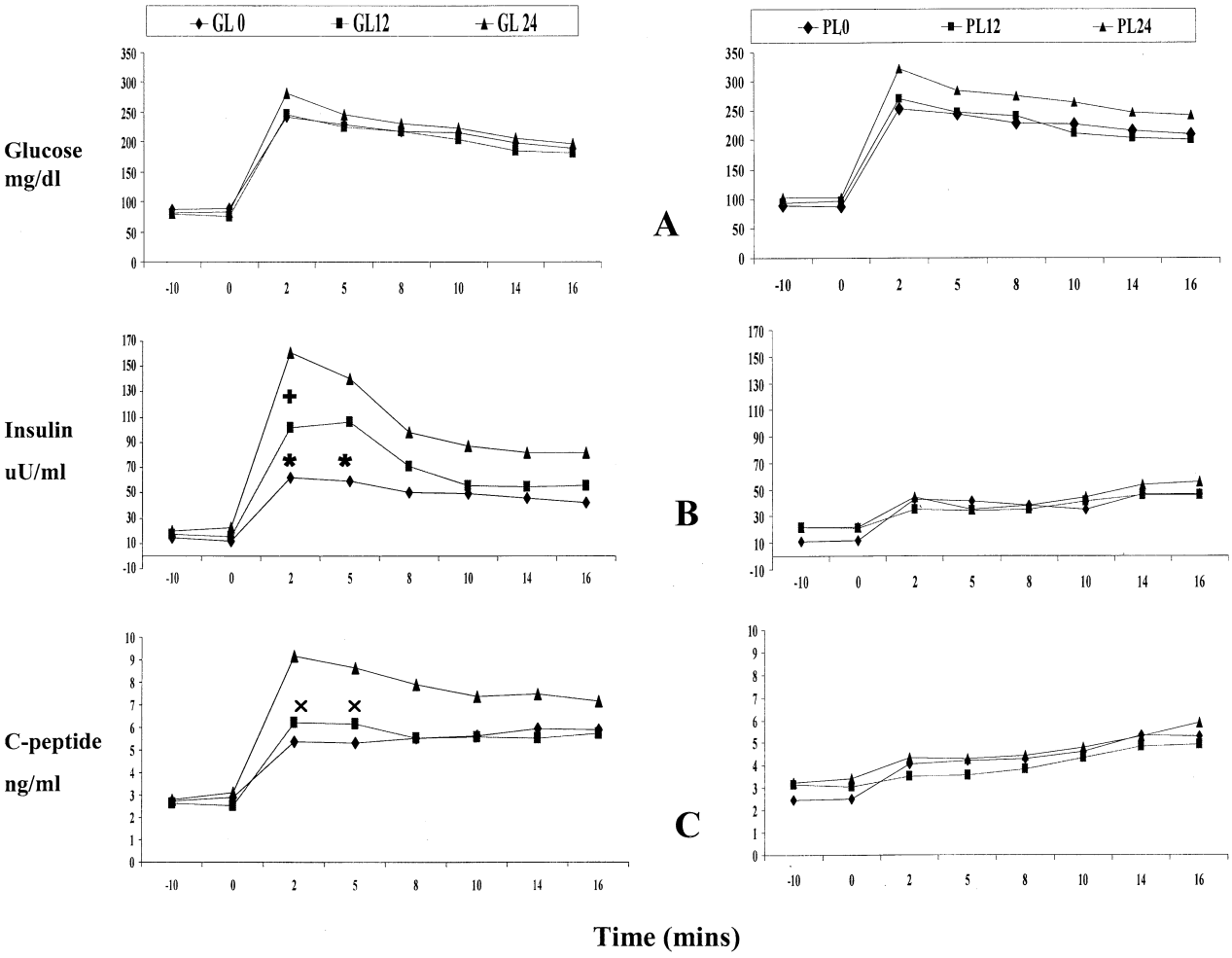

Fig 1. Serum glucose (A), insulin (B), and C-peptide (C) levels before and after intravenous glucose tolerance test in high-risk, obese African Americans with IGT receiving glipizide GITS (left panels) and placebo (right panels) for 24 months. *$P < .05$, 12 *v* 0 months; $^{+}P < 0.01$, 24 *v* 0 months; $^{\times}P < .05$, 24 *v* 0 months.

DI_{ivgtt} in the IGT patients at 12 and 24 months by 2-fold (Table 5 and Fig 3) when compared to baseline values. The respective DIs deteriorated in the IGT/PLAC group at 12 by 24 months (Table 5 and Fig 3). When comparing the groups, DI_{ivgtt} was significantly higher by 2- and 3-fold in the IGT/GITS group at 12 and 24 months when compared to the IGT/PLAC group.

DISCUSSION

We provide, to be best of our knowledge, the first long-term, feasibility study on tolerability, adverse side effects, and metabolic effects during glipizide GITS therapy in high-risk African Americans with IGT for 24 months. Our study demonstrated that (1) moderately severe dual pathogenetic defects, ie, insulin resistance and beta-cell dysfunction, exist in African American patients with IGT; and (2) chronic GITS administration reversed most of the metabolic abnormalities associated with IGT in obese African American patients. We found that chronic GITS improved glucose homeostasis during fasting and after oral and intravenous glucose challenge for 24 months. Most importantly, GITS significantly improved beta-cell responsiveness to glucose stimulation in our IGT patients These beta-cell responses were approximately 75% of that found in healthy, glucose-tolerant African Americans previously reported by our group.[8,16] The restoration of physiologic beta-cell responses to glucose stimulation by GITS could prevent progression of our IGT subjects to diabetes melitur, but this remains unproven in our high-risk African American subjects. We are aware of only 2 previous studies in which long-term SU has been shown to reduce the conversion of IGT to type 2 diabetes.[27,28] The latter study by Banerji et al[28] suggested that low-dose intermediate-release glipizide 2.5 mg daily for 24 months prolonged glycemic remission in black patients with prior non–insulin-dependent diabetes mellitus.

In the present study, our high-risk, obese African Americans with IGT had significantly lower or blunted acute serum insulin and C-peptide responses to glucose stimulation at 0 months, as assessed by the absolute and incremental values following intravenous glucose challenge. The blunted acute first-phase

Table 5. Minimal Model Parameters in African American Subjects With IGT Tolerance Receiving Placebo or GITS for 24 Months

Group	Month 0	12	24
Si ($\times 10^{-4} \cdot min^{-1}$ [μU/mL]$^{-1}$)			
Placebo	1.13 ± 0.50	1.27 ± 0.63	0.64 ± 0.44*
GITS	1.36 ± 0.54	2.60 ± 1.21‡‖	1.74 ± 1.26¶
Sg ($\times 10^{-2} \cdot min^{-1}$)			
Placebo	1.35 ± 0.58	1.47 ± 0.73	1.81 ± 0.63
GITS	1.53 ± 0.63	1.72 ± 0.90	1.97 ± 1.23
DI_{ogtt}			
Placebo	7,093 ± 2,893	9,569 ± 3,552	3,722 ± 1,947†
GITS	10,303 ± 5,190	21,988 ± 8,018‡‖	21,000 ± 10,274§‖
DI_{ivgtt}			
Placebo	76 ± 9	43 ± 8	22 ± 7†
GITS	80 ± 19	276 ± 77‡‖	244 ± 140§‖

NOTE. Values are mean ± SD.

Abbreviations: DI, disposition index; DI_{ogtt}, Si × AUC for insulin during oral glucose tolerance test; DI_{ivgtt}, Si × AIR insulin levels during intravenous glucose tolerance test.

*$P < .05$, 24 *v* 0 months for placebo.

†$P < .01$, 24 *v* 0 months for placebo.

‡$P < .05$, 12 *v* 0 months for GITS.

§$P < .05$, 24 *v* 0 months for GITS.

¶$P < .01$, GITS *v* placebo.

‖$P < .01$, GITS *v* placebo.

insulin release to glucose is regarded as an early pathogenetic lesion in both type 1 and type 2 diabetes. We found that the severity of beta-cell dysfunction was even more impressive when examined in the context of the prevailing insulin resistance as determined by the DI. Indeed, as shown in Table 5 and Fig 3, the DI values confirmed the inability of the beta cells in our African Americans with IGT to compensate for the peripheral insulin resistance.[8,16] At the time of diagnosis, the DIs were severely blunted and were 2-fold lower than that previously reported by our investigators in glucose-tolerant, African American subjects.[8,16] We found that chronic administration of GITS was associated with significant improvement in overall beta-cell secretion (total and acute first and second phase) and DIs with concomitant improvement in post-challenge hyperglycemia in the IGT group at 12 and 24 months. Of great interest, there was progressive improvement in beta-cell function from 12 to 24 months in the IGT/GITS group without clinical evidence of tachyphylaxis. Furthermore, while the peripheral insulin levels increased at fasting and following glucose challenge by at least 2- to 3-fold, there were no corresponding increases in serum C-peptide (1.05-fold) with GITS therapy, especially at 24 months. This suggests a possible reduction in insulin clearance or HIE during long-term GITS therapy. Theoretically, the reduced HIE could potentially enhance post-hepatic insulin delivery and hence contribute to peripheral hyperinsulinemia during GITS therapy. If confirmed in future studies, the mechanism(s) of the reduced HIE during glucose challenge by GITS will need to be elucidated.

Insulin secretagogues such as SU, repaglinide, and nateglinide directly stimulate insulin secretion as well as augment

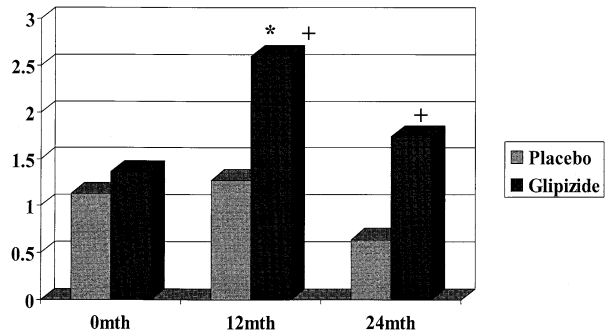

Fig 2. Si before and at 12 and 24 months treatment with glipizide GITS and placebo in obese African Americans with IGT. *$P < .05$, 12 and 24 months *v* 0 months for GITS; $^{+}P < .01$, GITS *v* placebo at 12 and 24 months.

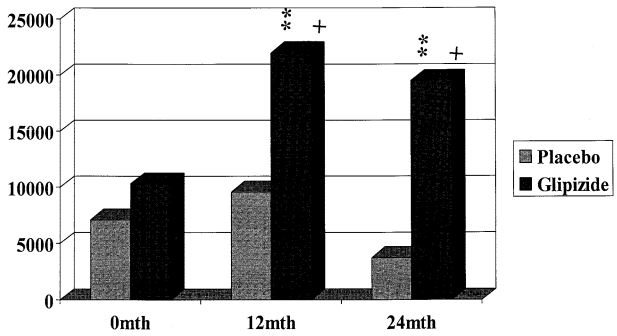

Fig 3. DI before and during 24 months treatment with glipizide GITS and placebo in obese African Americans with IGT. **$P < .01$, 12 and 24 months *v* 0 months for GITS; $^{+}P < .01$, GITS *v* placebo at 12 and 24 months.

insulin secretion following both oral and intravenous administration of glucose as part of their mechanisms of actions. The magnitude of beta-cell insulin secretion often depends on the potentiation by the prevailing or circulating glucose levels, as well as preservation of beta-cell critical mass. In the present study in African Americans with IGT, chronic GITS was associated with restoration of physiologic acute first- and second-phase insulin secretion during intravenous glucose stimulation in the absence of an acute exposure of the active drug. We should emphasize that, in the present study, the oral GITS was administered at least 24 hours prior to the beta-cell stimulation tests. In contrast to the IGT/GITS, we observed that the defective acute first-phase insulin secretion in the IGT/PLAC group persisted for 24 months. This was associated with a compensatory higher second-phase insulin secretion due to the increases in serum glucose levels after the intravenous glucose challenge between t = 8 to 19 minutes as shown in Fig 1A, right panel. Previous studies have shown that the blunted acute first-phase insulin is specific to intravenous glucose stimulation, but not to non-glucose stimulus, and serves as an early defect in the development of IGT and type 2 diabetes.[8,9] Our study showed that long-term GITS administration partially restored physiologic beta-cell responsiveness to intravenous glucose stimulation in patients with IGT. Thus, in addition to the direct beta-cell stimulatory effects by GITS and other SUs previously reported,[23-26] we documented that GITS provided a beta-cell priming effect to intravenous glucose stimulation, and hence restored to near normal, the physiologic acute phases of insulin release. We speculate that restoration of physiologic insulin release to glucose stimulation by GITS could be a major mechanism for the glucose lowering actions of GITS (and perhaps other insulin secretagogues) in patients with IGT and type 2 diabetes. Whether our findings are direct effects of GITS or an epiphenomenon associated with GITS therapy remain unknown. Our study somewhat supports the findings by Ravanam et al,[25] which showed that intermediate-release glipizide augmented acute insulin release during intravenous glucose tolerance tests in subjects who received glucose priming.

Insulin resistance is found in significant proportion of patients with IGT and type 2 diabetes.[6-11,16,17] The insulin resistance can be detected in nondiabetic, first-degree relatives of patients with type 2 diabetes prior to the development of type 2 diabetes. Hence, insulin resistance is believed to be the primary and earliest lesion underlying IGT and type 2 diabetes in several populations, although this remains debatable.[8,9] Our present study confirmed that at the time of diagnosis of IGT, obese, African American patients manifest 28% lower insulin sensitivity when compared to the healthy control subjects we have previously reported.[8] The magnitude of insulin resistance in the IGT group was similar to that reported in other high-risk populations.[6-10] In the present study, the Si was not significantly different in the IGT/GITS group when compared to the IGT/PLAC group, despite the significant differences in BMI, lean body mass, and percent body fat mass at baseline. However, when treated with GITS for 12 and 24 months, we found that the Si values significantly increased in IGT/GITS group, but deteriorated or remained unchanged in the IGT/PLAC group. We should note that there were no changes in the body weight, BMI, lean body mass, or percent body fat mass in the IGT/GITS and IGT/PLAC groups during the 24-month follow-up period. Because previous studies using euglycemic hyperinsulinemic clamp have not shown direct increases in the total glucose disposal rates in patients with type 2 diabetes during chronic SU therapy, we do not believe that GITS was directly responsible for the improvement in Si in our present study. We have therefore attributed the improvement in Si during GITS administration to possible elimination of glucose toxicity in our IGT patients. We should note that Greenfield et al[23] have reported that SU treatment improved in vivo insulin action in patients with established, non–insulin-dependent diabetes. The mechanism of the improved total glucose disposal was not elucidated in their study.

Previous studies have indicated that SUs cause weight gain and hypoglycemia. In this regard, pharmacologic insulin secretagogues eg, SUs, nagletinide, and repaglinide, have been associated with weight gain (average 2 to 4 kg) in patients who show significant glycemic lowering response (as assessed by fasting glucose and hemoglobin A_{1C}). In the present study, chronic GITS was not associated with weight gain in our obese patients with IGT despite improvement in insulin secretion and insulin sensitivity. Note that our patients had essentially normal fasting glucose (<110 mg/dL) at the time of diagnosis. The lack of severe fasting hyperglycemia could partly explain the absence of weight gain in our IGT/GITS group. Similarly, mean body weight was unchanged in the IGT/PLAC group.

Another concern in the use of SU and other insulin secretagogues in patients with type 2 diabetes is the fear of severe or fatal hypoglycemia. The incidence of all hypoglycemic events was estimated as 4% in SU-treated patients in United Kingdom Prospective Diabetes Study (UKPDS).[22] In this regard, we observed no significant symptoms suggestive of severe hypoglycemia in our obese IGT patients treated with glipizide GITS when compared to the IGT/PLAC group. The reasons for the lack of symptomatic hypoglycemia in our IGT patients are unclear. Indeed, in clinical trials, low-dose GITS, 5 mg/d, can induce hypoglycemia in some patients with type 2 diabetes.[26] We should note that our subjects were not required to perform self/home glucose monitoring. Thus, whether asymptomatic mild hypoglycemia occurred in some of our subjects remains uncertain and deserves further investigation in future studies. Finally, we did not observe any deterioration in the glycemic control in the IGT patients who received GITS, perhaps due to the shorter duration of observation and the small sample size. Nevertheless, our study suggests that GITS might be considered as potential agent for prevention of type 2 diabetes in high-risk patients with IGT.

In summary, chronic GITS at the dose used in the present study was well tolerated without symptoms of severe hypoglycemia nor weight gain in our obese African American patients with IGT. Chronic low-dose GITS therapy over 24 months prevented glycemic deterioration, improved beta-cell responses (acute phase and total) to glucose stimulation, and improved the DI. Chronic GITS therapy was also associated with improved insulin sensitivity, but not glucose effectiveness, in obese, IGT,

first-degree relatives of African American patients with type 2 diabetes. We found that chronic GITS partially restored the physiologic insulin secretion profile in our IGT patients. Thus, we have postulated that restoration of physiologic acute insulin secretion by GITS appears to be a paramount mechanism for its glucose-lowering effects and perhaps in the improvement in insulin sensitivity in our patients with IGT. Our preliminary study suggests that chronic GITS could be useful in the primary prevention of type 2 diabetes in obese African Americans with IGT. Long-term primary prevention trials using glipizide GITS involving large multiethnic populations with IGT are warranted.

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