Metabolic Effects of Chronic Glipizide Gastrointestinal Therapeutic System on Serum Glucose, Insulin Secretion, Insulin Sensitivity, and Hepatic Insulin Extraction in Glucose-Tolerant, First-Degree Relatives of African American Patients With Type 2 Diabetes: New Insights on Mechanisms of Action

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We examined the long-term metabolic effects of a potent sulfonylurea (SU), glipizide gastrointestinal therapeutic system (glipizide GITS) in normal glucose-tolerant (NGT), first-degree relatives of African American patients with type 2 diabetes in a randomized, placebo-controlled, double-blind manner for 24 months and 6 months after discontinuation of glipizide GITS. Fifty NGT African American first-degree relatives (n = 50)) were randomized to receive either glipizide GITS (GITS, 5 mg/d) or identical placebo (PLAC). The NGT consisted of NGT/GITS (n = 16; mean age, 43.1 ± 8.7years; body mass index [BMI], 34.8 ± 10) and NGT/PLAC (n = 34; 45.5 ± 9.7 years; BMI, 31.3 ± 3.1years). Each of the subjects underwent an oral glucose tolerance test (OGTT) and frequently sampled intravenous glucose tolerance test (FSIGT) at baseline and at yearly intervals for 2 years. Insulin sensitivity (Si) and glucose effectiveness (Sg) were determined by Bergman's minimal model method. Hepatic insulin extraction (HIE) was calculated as the molar ratio of C-peptide and insulin. The mean fasting serum glucose, insulin, and C-peptide levels in the NGT/GITS were not different from that of the NGT/PLAC. After oral glucose challenge, mean serum glucose responses slightly increased (*P* = not significant [NS]) at 12 and 24 months in the NGT/GITS group when compared with the baseline, 0 month, but remained unchanged in the NGT/PLAC group. In addition, serum insulin and C-peptide responses significantly increased in the NGT/GITS group, but were unchanged in the NGT/PLAC group at 12 and 24 months versus 0 month. The HIE, during OGTT, decreased by 30% from the baseline (0 month) values in the NGT/ GITS, but remained unchanged in the NGT/PLAC group at 12 and 24 months. Mean Si decreased by 30% from the baseline in the NGT/GITS group by 12 and 24 months, but remained unchanged in the NGT/PLAC group. However, the disposition index (DI) remained normal in the NGT/GITS and the NGT/PLAC groups. The DI data in the NGT/GITS group suggested that β cells maintained the ability to compensate for the lower Si during the chronic GITS administration in our high risk African Americans. Chronic GITS was well tolerated without any symptoms of either hypoglycemia or weight gain in the NGT/IGTS group. After discontinuation of GITS, the altered metabolic parameters significantly improved, returning to baseline values in the NGT/IGTS group in 6 months. In summary, chronic glipizide GITS administration (5 mg/d) was associated with increased β-cell secretion, peripheral hyperinsulinemia, reduced Si, and reduced HIE in glucose-tolerant, first-degree relatives of African American patients with type 2 diabetes. These metabolic changes were reversible within 6 months after discontinuation of glipizide GITS. Our study defines a unique mode of action of glipizide GITS in African Americans at high risk for type 2 diabetes. We conclude that the use of glipizide GITS in the primary prevention of type 2 diabetes in nondiabetic first-degree relatives of patients with type 2 diabetes impaired glucose homeostasis.

TYPE 2 DIABETES is a genetic disease with strong environmental components.[1,2] At the time of diagnosis, β-cell dysfunction and insulin resistance characterize the hyperglycemia found in patients with impaired glucose tolerance (IGT) and type 2 diabetes in several populations.[3-7] It is well established that both β-cell dysfunction and insulin resistance, which are paramount dual lesions in the pathogenesis of type 2 diabetes, are genetically inherited.[2] It is also well established that first-degree relatives of patients with type 2 diabetes have alterations in glucose metabolism and insulin resistance and hence have a higher propensity to develop type 2 diabetes when compared with those without a family history of diabetes.[2,8-10] Thus, prediabetic first-degree relatives of patients with type 2 diabetes seem to be ideal subjects for primary diabetes prevention programs.

It is well known that IGT and type 2 diabetes have ethnic and racial predilection.[11-13] In this regard, African Americans and other minority populations in the US have an extraordinary propensity for type 2 diabetes and the related long-term complications when compared with white Americans.[12,13] The reasons for the high propensity for type 2 diabetes in African Americans are uncertain, but have been partly ascribed to the higher prevalence of obesity in African Americans when compared with white Americans. In addition, others and we have previously demonstrated that African Americans manifest high peripheral hyperinsulinemia and insulin resistance and reduced hepatic insulin extraction (HIE) (as assessed by C-peptide: insulin molar ratios and hyperglycemic clamp) when compared with their white counterparts.[14-20] Moreover, at the time of initial diagnosis, high risk African Americans with IGT and type 2 diabetes manifest moderate to severe insulin resistance and severe β-cell dysfunction and lower disposition index (DI).[7] Our studies suggest that β-cell secretion (as assessed by serum C-peptide) may be defective in the face of insulin resistance in glucose-tolerant, nondiabetic first-degree relatives of African American patients with type 2 diabetes. Thus, we have postulated that augmentation of the β-cell secretion using a sulfonylurea (SU) could improve β-cell secretory function

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and perhaps prevent the development of IGT and/or type 2 diabetes. In this regard, there is increasing interest to use pharmacologic intervention to prevent type 2 diabetes in various populations at high risk for the disease. These medications include insulin sensitizers, such as troglitazone[21-23] and metformin.[24] However, oral SU agents have not been enthusiastically endorsed or recommended as antidiabetic drugs in the prevention of type 2 diabetes for the fear of potential severe or fatal hypoglycemia. Thus, whether SU could prevent or delay the development of type 2 diabetes in nondiabetic high risk African Americans remains uncertain.

Glipizide is an effective second generation SU with demonstrable safety and tolerability for the past 20 years.[25-27] Oral glipizide gastrointestinal therapeutic system (GITS) is designed to release the active medication in a delayed manner with effective glucose-lowering properties, as well as lower incidence of hypoglycemia when compared with intermediate-acting glipizide and glyburide.[27] Therefore, we investigated the mechanism(s) of chronic glipizide GITS in the primary prevention of type 2 diabetes in first-degree relatives of African American patients with type 2 diabetes and who had normal glucose tolerance (NGT) in a double-blind, placebo-controlled, randomized study for 24months and then 6 months after discontinuation of GITS.

SUBJECTS, MATERIALS, AND METHODS

Populations

The study comprised of 50 free living African Americans who were first-degree relatives of African American patients with type 2 diabetes residing in Franklin County, central Ohio. 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. African Americans were defined as those individuals who (1) had both biologic parents as African Americans, (2) grandparents were of black African origin based on history of transatlantic slave trade, and (3) identified themselves as belonging to the black race, ethnicity, and culture.

After satisfying study entry requirements, subjects were enrolled in the 24-month longitudinal study. Each subject underwent a standard oral glucose tolerance test (OGTT). The categories of glucose tolerance were defined or classified according to the World Health Organization (WHO) Criteria,[28] which was the classification at the time of initial screening of the subjects in 1996. Although the criteria for fasting serum glucose values differ, ie, 140 mg/dL and 126 mg/dL for WHO(1985) and new American Diabetes Association (ADA) (1997) criteria, respectively, we used the 2-hour serum glucose levels as the major criteria for the definition of glucose tolerance in our study independent of the fasting serum glucose levels.

The NGT group was randomized in a double-blind, placebo-controlled manner to receive either GITS (5 mg/d) or identical placebo (PLAC). The clinical characteristics of the 2 subgroups of African Americans with NGT are shown in Table 1; group I: (NGT/GITS, n = 16) NGT receiving GITS and group 2: (NGT/PLAC, n = 34) NGT receiving placebo. The NGT/PLAC group was oversampled in the approximate ratio of 2:1 when compared with the NGT/GITS group to detect potential progression from NGT to IGT and perhaps type 2 diabetes. 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 had 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. The body mass index (BMI) was calculated as the weight (kg) divided by square of height (m). The lean body mass and body fat composition were measured by bioelectrical impedance analyzer. The body fat distribution was measured as the waist-to-hip circumference ratios (WHR). The waist circumference was measured at the level of the umbilicus (with the subject in standing position) and the hip circumference at the level of the greater trochanter (in the standing position). The subjects answered a simple questionnaire on diet and physical activity. Subjects who participated in endurance or competitive sports were excluded.

Metabolic studies. With the subject in the supine position, an intravenous needle ("heparin lock") 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 before the test. After a 10- to 12-hour overnight fast, blood samples were drawn for serum glucose, insulin, and C-peptide. The subjects then ingested a 75-g oral glucose load (Glucola, 250 mL; NERL Diagnostics, East Richmond, RI) over a 2-minute period in the sitting position. 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.[28]

Frequently Sampled Intravenous Glucose Tolerance

With subject in the supine position, 2 intravenous needles ("heparin lock") 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 to administer the intravenous glucose and exogenous insulin as previously described.[6,29,30] 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 gm/kg glucose (50 mL 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 0.9% normal saline was infused over 60 seconds. Blood samples were obtained at frequent intervals at 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 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

The subjects received GITS (5 mg/d) or identical placebo in a double-blind, randomized manner. The study subjects, the study staff, and the investigators were blinded to the medications. The subjects were seen at the clinical research center at 3 to 4 monthly intervals for at least 24 months. Body weight and height were obtained in each subject as described above. The subjects answered a questionnaire regarding their diet and exercise habits. Specifically, we interviewed each subject with respect to their knowledge of diabetes and the related symptoms of hyperglycemia and hypoglycemia. In addition, the subjects completed daily physical activity questionnaires. The OGTT and frequently sampled intravenous glucose tolerance (FSIGT) protocols were repeated at yearly intervals. Routine biochemical and hematologic parameters were obtained at 3-month intervals. During the visits, the subjects received bottles with serial numbers and codes containing either an active medication or placebo. Medication compliance was

assessed by counting the pills in each labeled container. The medication bottles were collected at each visit for tablet counting by the study staff. We also examined the logbook for the number of pills consumed by each participant. The medication compliance was over 80% for both GITS and placebo.

Posttreatment Follow-up

After 24 months, all normal subjects stopped their respective active medications and were converted to only the placebo arm in a double-blind manner. These NGT subjects were restudied after 6months. Each subject underwent OGTT and FSIGT, as well as anthropometric measurements (vide supra).

Analytical Methods

Serum glucose concentrations were measured by the glucose oxidase method using glucose autoanalyzer (Yellow Spring Instruments, Yellow Springs, OH). The 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 (CV) were 6% and 10%, respectively. The lower limit of the C-peptide assay was 0.47 ng/mL and the intra- and interassay CV were 7% and 13%, respectively.

Calculations and Statistical Analyses

Results are expressed as mean ± SD or unless stated otherwise. The BMI was calculated as weight (kg) divided by square (m) of the height in meters. Obesity was defined as BMI $>$ 30 kg/m^2 for females and males. Hypoglycemia was defined as serum glucose $<$ 50 mg/dL. However, we recorded symptoms suggestive of hypoglycemia in all our subjects, although our participants were not instructed on or required to monitor their capillary glucose levels using a glucose meter We examined phases of acute insulin release in the NGT/GITS and NGT/PLAC groups. The acute first phase of insulin release (AIR) was calculated as the area of insulin curve (AUC) from t = 0 to 5 minutes and the second phase AUC between t = 8 to 19 minutess using trapezoidal rule. The early phase insulin and C-peptide levels during OGTT were taken as the difference between the 30-minute and baseline values. We calculated the incremental AUC for serum glucose, insulin, and C-peptide during OGTT as the incremental area above the baseline values using trapezoidal rule. HIE was calculated as the molar ratios of C-peptide and insulin levels at fasting, as well as during the OGTT as previously described.[14,15] We empirically designated HIE to reflect hepatic insulin extraction based on the known kinetics of both insulin and C-peptide levels with the pitfalls and limitations in the nonsteady state.[31]

Insulin sensitivity index (Si) and glucose effectiveness (Sg) were calculated using Bergman's Minmod software program.[6,29,30] β-cell compensation for insulin resistance was estimated using the DI as follows: DI = Si × AIR during FSIGT. Step-wise linear regression and 2-way analyses of covariance (ANOCOVA) were used to adjust for the effects of age, sex, body weight, and WHR on the various metabolic parameters. The nonparametric data were analyzed using χ^2 and Mann-Whitney Rank Test. Statistical analyses were performed using Student's *t* test (unpaired) and analysis of variance (ANOVA), where appropriate, with Bonferroni method for post hoc testing. For comparison of the mean data with unequal variance, Neuman-Keuls Multiple *t* test was used. Probability (*P*) value less than .05 was considered statistically significant

RESULTS

Chronic glipizide GITS administration was well tolerated in the NGT group without any significant symptoms of hypoglycemia, any systemic or constitutional symptoms, or changes in biochemical parameters. Of interest is that chronic GITS was not associated with any significant weight gain in the NGT/GITS subjects followed for 24 months. There were no changes in the liver, hematologic, or renal function tests in any of the groups during the 24-month follow-up.

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

Parameter	Placebo (n = 34)	GITS (n = 16)
Clinical characteristics		
Age (yr)	45.5 ± 9.7	43.3 ± 8.7
BW (kg)	89.2 ± 10.3	94.64 ± 25.8
BMI (kg/m^2)	31.3 ± 3	34.8 ± 10.0
LBM (kg)	62.5 ± 7	58.1 ± 12.1
BFM (%)	37.4 ± 4.3	41.7 ± 9.8
WHR	0.89 ± 0.10	0.89 ± 0.08
Metabolic Parameters		
Glucose (mg/dl)		
Fasting	79 ± 9	89 ± 12
2-h postglucose	95 ± 11	98 ± 25
Insulin (μU/mL)		
Fasting	13 ± 7.2	10.0 ± 5.8
2-h postglucose	78 ± 22	80 ± 32
C-peptide (ng/mL)		
Fasting	2.68 ± 1.30	2.65 ± 1.39
2-h postglucose	9.31 ± 1.13	9.13 ± 4.30

NOTE. Values are mean ± SD.

Abbreviations: BW, body weight; BMI, body mass index; LBM, lean body mass; BFM, body fat mass; WHR, waist-to-hip circumference ratio; NGT, normal glucose tolerance.

The clinical characteristics of the subjects are shown in Table 1. The mean body weight, BMI, and percent body fat were not significantly different in the NGT/GITS group when compared with the NGT/PLAC group. These parameters remained unchanged in both groups at the end of 12 and 24 months.

OGTT

The serum glucose, insulin, and C-peptide responses to oral glucose challenge in high risk African Americans with NGT are shown in Table 2 and Fig 1. The mean fasting serum glucose, insulin, and C-peptide levels in the NGT/GITS were not significantly different from that of the NGT/PLAC at baseline (Table 1). The mean fasting serum glucose tended to increase during the 24-month follow-up in the NGT/GITS group (Fig 1A), but was unchanged in the NGT/PLAC group (Fig 1A). Surprisingly, mean serum glucose responses (peak and AUC) during the OGTT in the NGTS/GITS group slightly increased at 24 months when compared with 0 month (Table 2 and Fig 1A), but these parameters remained unchanged in NGT/PLAC group (Table 2 and Fig 1A). In addition, the corresponding serum insulin and C-peptide responses during the OGTT significantly increased in the NGT/GITS group at 12 and 24 months when compared with the baseline (Table 2 and Fig 1A-C), but were unchanged in the NGT/PLAC (Table 2 and Fig 1B and C).

Mean HIE during fasting and after oral glucose challenge was similar in the NGT/IGTS and NGT/PLAC groups at base-

Table 2. Metabolic Parameters in African American Subjects With NGT Treated With Placebo or GITS for 24 Months

Group	Placebo (n = 34)			GITS (n = 16)		
	0	12	24 mo	0	12	24 mo
OGTT						
Glucose area (mg/dL × min)						
NGT	3,259 ± 498	3,478 ± 570	3,686 ± 635	2,357 ± 420	3,847 ± 673	5,138 ± 2,310*
Insulin area (μU/mL × min)						
NGT	8,459 ± 1,166	7,859 ± 1,306	8,763 ± 1,583	7,407 ± 4,238	9,593 ± 4,556	12,836 ± 2310*
C-peptide area (ng/mL × min)						
NGT	681 ± 82	690 ± 98	758 ± 116	736 ± 297	729 ± 238	902 ± 466*
FSIGT (acute first phase)						
Glucose (mg/dL × min)						
NGT	608 ± 16	626 ± 20	662 ± 23	599 ± 28	650 ± 36	689 ± 41
Insulin (μU/mL × min)						
NGT	347 ± 33	340 ± 40	393 ± 51	363 ± 98	531 ± 98*	613 ± 146*
C-peptide (ng/mL × min)						
NGT	15.42 ± 1.25	18.30 ± 2.22	18.95 ± 2.11	17.15 ± 2.66	24.88 ± 3.79*	28.60 ± 4.38*

NOTE. Values are mean ± SD.
*$P < .05$, 12 and 24 *v* 0 mo.

line, 0 month. During the follow-up, the HIE significantly ($P < .05$) decreased in the NGT/GITS subjects at 12 and 24 months from baseline (0 month) (Fig 2A), but remained unchanged in NGT/PLAC groups (Fig 2B).

FSIGT

As shown in Fig 3A, the serum glucose responses were similar in the NGT/IGTS and NGT/PLAC groups after intra-

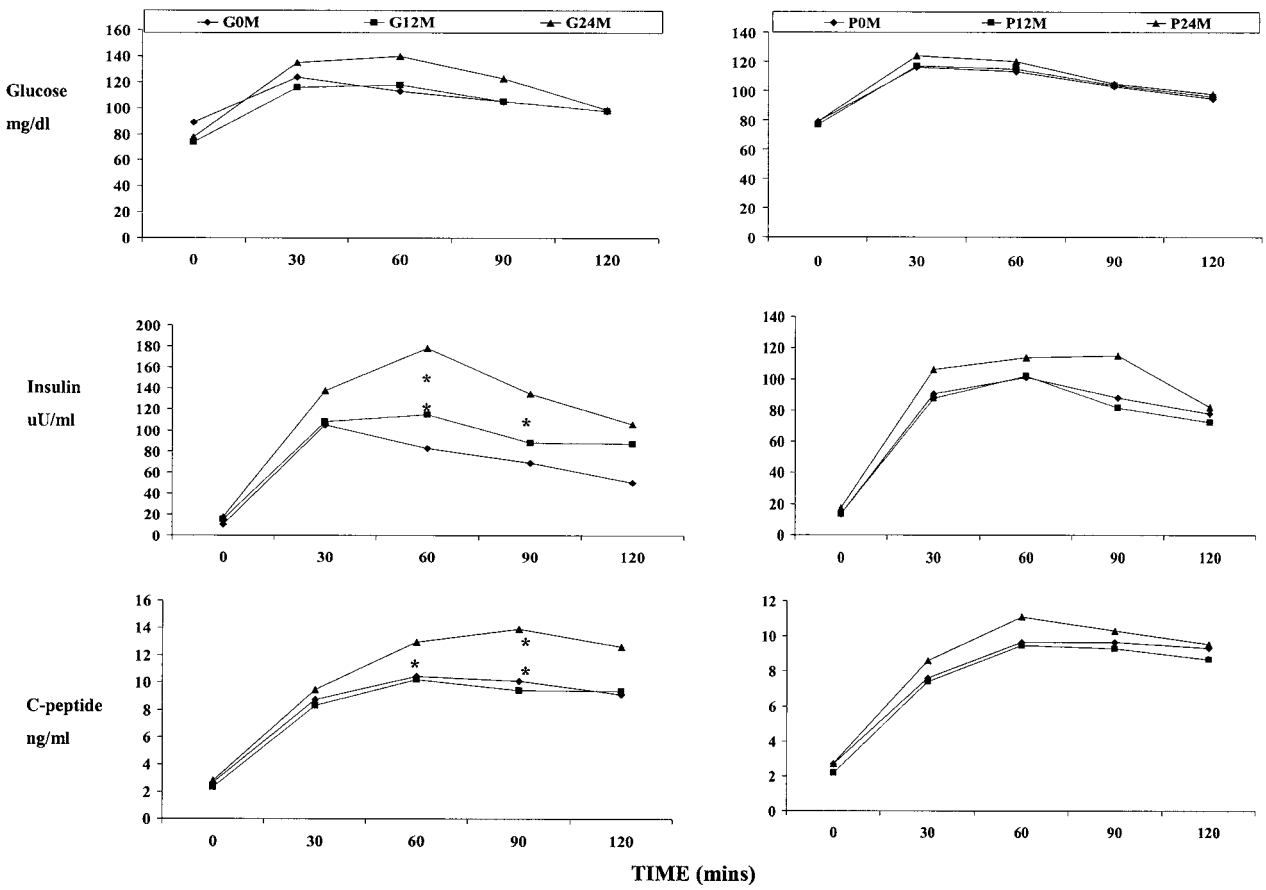

Fig 1. (A) Serum glucose, (B) insulin, and (C) C-peptide levels before and after oral glucose load in high-risk African Americans with NGT followed for 24 months during glipizide GITS (G) and placebo (P) administration. *$P < .05$ and **$P < .01$; 12 and 24 *v* 0 month by ANOVA.

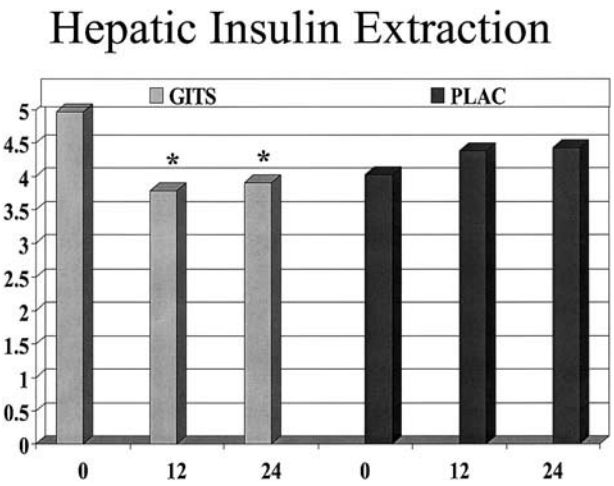

Fig 2. HIE in high-risk African Americans with NGT followed for 24 months on (A) glipizide GITS or (B) placebo (PLAC). *$P < .05$; 12 and 24 *v* 0 month.

venous glucose administration at baseline. However, the corresponding serum insulin and C-peptide responses were greater in the NGT/GITS group at 12 and 24 months versus 0 month (Fig 3B and C). Mean serum insulin and C-peptide responses did not change in the NGT/PLAC group (Fig 3B and C) during the 24-month follow-up.

Minimal Model Parameters

Mean Si was similar in the NGT/GITS versus NGT/PLAC (Table 3) at baseline, 0 month. However, surprisingly, Si decreased by 30% at 12 and 24 months when compared with the baseline (0 month) values in the NGT/GITS. Mean Si remained unchanged in the NGT/PLAC at 12 and 24 months when compared with the 0 month (Table 3). The mean Sg was similar at 0 month in the NGT/GITS versus NGT/PLAC values. During the follow-up, Sg did not change in any of the groups at 12 and 24 months (Table 3).

We assessed the ability of β cells to compensate for insulin resistance using DI. DI was not significantly different in the NGT/GITS group and NGT/PLAC at 12 and 24 months and when compared with the respective, baseline values (Table 3).

Post-GITS Metabolic Studies in the NGT Groups

Thirty-four NGT/PLAC and 13 NGT/GITS subjects were restudied 6 months after discontinuation of the active GITS medication and switched to identical placebo in a double-blind

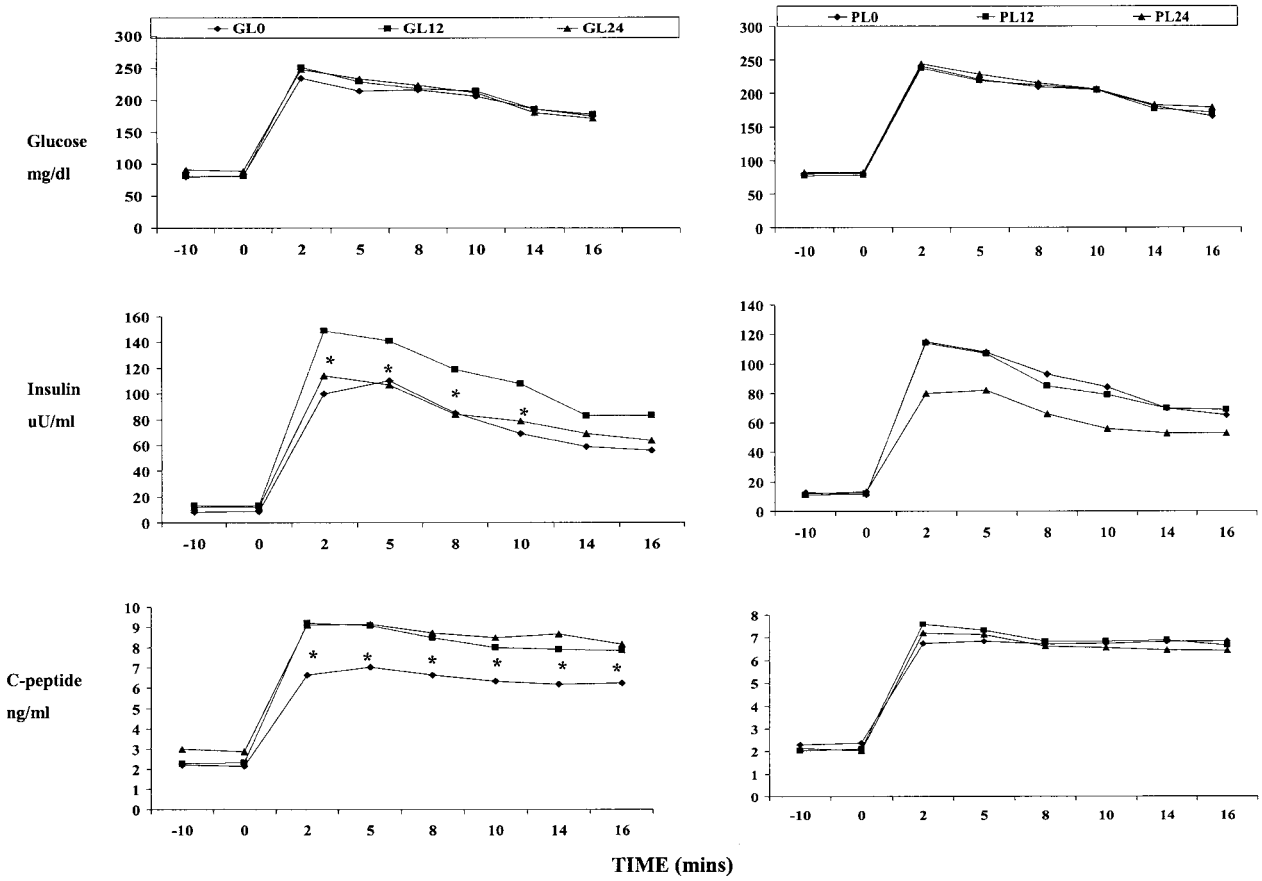

Fig 3. (A) Serum glucose, (B) insulin, and (C) C-peptide levels before and during IGT test in high-risk African Americans with NGT receiving glipizide GITS (P) and placebo (P) for 24 months. *$P < .05$ 12 and 24 *v* 0 month by ANOVA.

Table 3. Minimal Model Parameters in African American Subjects With NGT Who Were Receiving Either a Placebo or Glipizide GITS for 24 Months

Group	Placebo (n = 34)			GITS (n = 16)		
	0	12	24 mo	0	12	24 mo
Insulin sensitivity (Si × 10 × min^1 (μU/mL)$^{-1}$)						
NGT	2.47 ± 0.33	2.98 ± 0.32	2.94 ± 0.54	2.50 ± 0.62	1.81 ± 0.50	1.54 ± 0.46*
Glucose effectiveness (Sg × 10^{-2} min^{-1})						
NGT	2.48 ± 0.31	2.28 ± 0.35	2.39 ± 0.38	2.33 ± 0.56	2.16 ± 0.55	2.24 ± 0.45
Disposition index						
NGT	857 ± 111	1013 ± 130	1,155 ± 128	908 ± 61	961 ± 99	944 ± 67

NOTE. Values are mean ± SD.
*$P < .05$, 12 and 24 *v* 0 mo.

manner (Table 4). The BMI, lean body mass, and body fat mass were not significantly different in the NGT/PLAC and NGT/GITS subjects at the time of switching to placebo (Table 4). These parameters did not change during the 6-month follow-up. The mean serum glucose, insulin, and C-peptide responses, as well as HIE improved to near normal values comparable to the baseline values (Table 5). Furthermore, after the discontinuation of GITS, Si recovered 75% of normal values at 6 months (Table 5). The mean Sg remained unchanged 6 months after converting to the placebo in the NGT/GITS subjects.

DISCUSSION

We have conducted the first double-blind, placebo-controlled, randomized study to examine the metabolic, anthropometrics, as well as potential adverse effects of a long-acting SU, glipizide GITS, on glucose homeostasis and insulin metabolism in high risk, glucose-tolerant, African Americans with presumed insulin resistance and β-cell defect. The present study showed that low-dose GITS (5 mg/d) was well tolerated and surprisingly without symptoms of hypoglycemia or weight gain. We did not observe any systemic or constitutional symptoms that could be attributed to glipizide GITS. However, we observed several unexpected metabolic alterations during chronic GITS administration in our high-risk, but glucose-tolerant, first-degree relatives of patients with African Americans with type 2 diabetes followed for 24 months. We found that the serum glucose levels especially in response to oral and intravenous glucose loads in the NGT/GITS group either remained unchanged or slightly increased at 12 and 24 months, despite the higher serum insulin levels. These parameters remained unchanged in the NGT/PLAC group throughout 24 months. Most importantly, there were concomitant increases in peripheral serum insulin and C-peptide levels after both oral and intravenous glucose challenge in the NGT/GITS group, but not in the NGT/PLAC group at 12 and 24 months.

Blunted AIR to intravenous glucose is considered as an early β-cell lesion found in both IGT and type 2 diabetes.[2,5,7] Ravanam et al[32] reported improvement in glucose-stimulated acute insulin release during chronic glipizide treatment in patients with type 2 diabetes. However, systematic and sequential data on AIR in individuals receiving SU over 24 months are not available in individuals at risk for type 2 diabetes or patients with type 2 diabetes. In the present study, we found that AIR increased in the chronic GITS group at 12 and 24 months, but remained unchanged in the NGT/PLAC group (Table 2, Fig 3). We did not observe the so-called β-cell exhaustion or tachyphylaxis during chronic glipizide GITS administration in our high-risk African American population. Furthermore, we found

Table 4. Baseline Clinical and Metabolic Characteristics of High-Risk African Americans With NGT on GITS Switched to Placebo and Followed for 6 Months

Parameters	Placebo → Placebo	GITS → Placebo	*P* Value
No.	34	13	
Age (yr)	42.3 ± 1.4	46.3 ± 2.4	NS
Body weight (kg)	91.5 ± 10.3	96.8 ± 0.9	NS
Height (m)	1.68 ± 0.06	1.67 ± 0.01	NS
Body mass index (kg/m^2)	42.2 ± 1.3	46.2 ± 2.0	NS
Lean body mass (kg)	59.9 ± 1.7	59.3 ± 3.0	NS
Body fat mass (%)	40.1 ± 1.65	40.7 ± 3.0	NS
WHR	0.89 ± 0.10	0.87 ± 0.02	NS

NOTE. Values are mean ± SD. *P* = NS, GITS *v* placebo.
Abbreviation: NS, not significant.

Table 5. Metabolic Characteristics of Healthy First-Degree Relatives of African American Subjects Before and 6 Months After Glipizide (GITS) and Placebo

Parameters	Placebo → Placebo	Glipizide GITS → Placebo
Glucose area (mg/dL × min)		
Baseline	660 ± 180	633 ± 212
Post-treatment	746 ± 200	855 ± 262
Insulin area (μU/mL × min)		
Baseline	364 ± 67	385 ± 92
Post-treatment	371 ± 67	410 ± 20
Insulin sensitivity (Si × 10^- × min^{-1} [μU/mL]$^{-1}$)		
Baseline	2.42 ± 0.24	2.39 ± 0.41
Post-treatment	2.52 ± 0.33	1.67 ± 0.31*
Glucose effectiveness (Sg × 10^{-2} · min^{-1})		
Baseline	2.17 ± 0.65	1.93 ± 0.29
Post-treatment	2.17 ± 0.13	1.90 ± 0.23

NOTE. Values are mean ± SEM.
*$P < .05$ before and after glipizide GITS. Note that in the placebo group, the subjects continued taking their placebo pills. In the GITS group, the active drug was switched immediately to the identical placebo without a washout period for 6 months.

that the ability of β cells to compensate for peripheral insulin resistance as assessed by DIs (Tables 2 and 3) was maintained intact in the GITS group throughout the study period. Thus, we found no differences in the DI in the NGT/GITS when compared with the NGT/PLAC or the baseline values

We found that the subjects in the NGT/GITS group had progressive hyperinsulinemia in the face of intact or slightly increased serum glucose responses. Our study suggests that the NGT group receiving GITS experienced progressive insulin resistance. This was confirmed by the lower Si values in the NGT/GITS group when compared with NGT/PLAC group at 12 and 24 months. Indeed, we found that Si was decreased by 30% at 12 and 24 months during chronic GITS administration when compared with the baseline values. In contrast, mean Si was unchanged in the NGT/PLAC group throughout the study.

It is well established that insulin resistance has both genetic, familial, and environmental components with ethnic predilection.[2,8-10,14-19] Previous studies in obese patients with type 2 diabetes found that weight gain and physical inactivity exert negative impact on Si in several populations. Generally, chronic SU therapy has been associated with weight gain in patients with type 2 diabetes who achieve improved glycemic control in clinical practice. Thus, we assessed possible weight changes in the glucose-tolerant, first-degree relatives who received GITS for 24 months. We found no significant weight gain in the NGT/GITS group. Because physical activity and weight did not change in our study, we have therefore postulated the reduced peripheral insulin sensitivity during chronic GITS administration in our first-degree relatives could be partly ascribed to a GITS-induced systemic hyperinsulinemia, which perhaps downregulated the peripheral insulin receptors in our NGT/GITS subjects. Whether these findings in the NGT/GITS group are unique to the pharmacologic actions of GITS in glucose-tolerant, first-degree relatives of African American patients with type 2 diabetes remains uncertain.

Previous studies have shown that African Americans manifest a lower insulin clearance as assessed by serum C-peptide/insulin molar ratios (which indirectly reflects hepatic insulin extraction) or directly using hyperglycemic clamp when compared with white Americans.[15,19,20] These studies indicated that the reduced HIE contributed significantly to the greater peripheral hyperinsulinemia in African Americans than in white Americans. We found that the HIE was significantly decreased in the NGT/GITS at 12 and 24 months when compared with the baseline values, but remained unchanged in the NGT/PLAC group. Thus, while stimulation of β-cell secretion is the well-recognized hallmark of glipizide GITS action, we believe chronic GITS-mediated reduction in HIE perhaps contributed significantly to the peripheral hyperinsulinemia in high-risk African Americans with NGT. In this regard, previous studies have compared the peripheral insulin levels after immediate release glipizide and glyburide administration in humans[33,34] and experimental animals.[35] These acute studies demonstrated that serum C-peptide insulin molar ratios were reduced after administration of glipizide, but not glyburide. Thus, it appears that among the SUs, there are subtle differences in their effects on insulin secretion and subsequent insulin metabolism. The clinical significance of these findings in maintaining peripheral insulin levels and glucose homeostasis in patients with type 2 diabetes remains uncertain. Whether alteration in insulin clearance or hepatic insulin clearance also contributes to the peripheral hyperinsulinemia attributed to other non-SU secretagogues, such as netaglinide or metiglinide, remains unknown.

To determine the reversibility of metabolic changes associated with glipizide GITS in high-risk African Americans, the NGT subjects were restudied 6 months after discontinuation of glipizide GITS. We found that discontinuation of GITS resulted in either complete or near complete reversal of most of the metabolic alterations induced by glipizide GITS to baseline values (Table 4). At 6 months, while serum insulin C-peptide and HIE were restored to baseline values, the mean Si remained slightly reduced (by 25%) when compared with the baseline values in the NGT/GITS group. In contrast, the Si was similar in the NGT/PLAC group at 30 months when compared with that of the NGT/IGTS group. These findings strongly implicated a reversible, GITS-induced mechanism(s) or processes as being responsible for the impairment in glucose homeostasis, peripheral hyperinsulinemia (hypersecretion and reduced HIE), and insulin resistance in the NGT/GITS group.

In summary, in the present study, we found that chronic low-dose GITS administration over 24 months paradoxically impaired glucose homeostasis, induced hyperinsulinemia, as well as insulin resistance in our glucose-tolerant, obese first-degree relatives of African American patients with type 2 diabetes. Chronic GITS administration was also associated with significant reduction in hepatic insulin extraction in NGT subgroup, thus contributing to peripheral hyperinsulinemia in our high-risk African American subjects. Most importantly, these metabolic epiphenomena were reversible within 6 months after discontinuation of glipizide GITS. We conclude that chronic GITS impaired glucose homeostasis in nondiabetic, first-degree relatives of African American patients with type 2 diabetes.

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