Effects of Rosglitazone on Plasma Adiponectin, Insulin Sensitivity, and Insulin Secretion in High-Risk African Americans With Impaired Glucose Tolerance Test and Type 2 Diabetes

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We examined the metabolic effects of rosiglitazone therapy on glucose control, insulin sensitivity, insulin secretion, and adiponectin in first-degree relatives of African Americans with type 2 diabetes (DM) with impaired glucose tolerance (IGT) and DM for 3 months. The study was comprised of 12 first-degree relatives with IGT, 17 newly diagnosed DM, and 19 healthy relatives with normal glucose tolerance (NGT). Oral glucose tolerance test (OGTT) was performed before and after 3 months of rosiglitazone therapy (4 to 8 mg/d) in patients with IGT and DM. Serum glucose, insulin, C-peptide, and adiponectin levels were measured before and 2 hours during OGTT in the NGT and patients with IGT and DM. Insulin resistance index (HOMA-IR) and β-cell function (HOMA-%B) were calculated in each subject using homeostasis model assessment (HOMA). Rosglitazone improved the overall glycemic control in the IGT and DM groups. Following rosiglitazone, the β-cell secretion remained unchanged, while HOMR-IR was reduced in DM by 30% (4.12 ± 1.95 *v* 6.33 ± 3.54, $P < .05$) and the IGT group (3.78 ± 2.45 *v* 4.81 ± 3.49, P = not significant [NS]). Mean plasma adiponectin levels were significantly ($P < .05$) lower in the DM (6.74 ± 1.95 μg/mL) when compared with the NGT group(9.61 ± 5.09). Rosiglitazone significantly ($P < .001$) increased adiponectin levels by 2-fold in patients with IGT (22.2 ± 10.97 μg/mL) and 2.5-fold greater in DM (15.68 ± 8.23 μg/mL) at 3 months when compared with the 0 month. We conclude that adiponectin could play a significant role (1) in the pathogenesis of IGT and DM and (2) the beneficial metabolic effects of thiazolidinediones (TZDs) in high-risk African American patients.

TYPE 2 DIABETES (DM) is characterized by insulin resistance and β-cell dysfunction.[1-3] Recently, adipocytokines have been associated with the development of DM[4-21] Adiponectin, a 244-aa peptide, solely produced and secreted by adipose tissues, has been reported to improve insulin sensitivity and predict the development of DM and atherosclerosis.[5-19] The regulation of adiponectin has been extensively studied in vitro and in vivo.[22-30] Factors that have been implicated in the plasma levels and synthesis of adiponectin include gender (females > males), obesity, (intra-abdominal visceral adiposity), tumor necrosis factor-alpha(TNF-α),[26] and peroxisome proliferator-activated receptor gamma (PPARγ) agonists.[27,28]

Nondiabetic, first-degree relatives of parents with DM have genetic predisposition to insulin resistance.[3] The mechanism of the insulin resistance in the first-degree relatives remains debatable. In this regard, Peline et al[5] and Lihn et al[6] have recently shown that nondiabetic first-degree relatives of Caucasian patients with DM have lower adiponectin levels, independent of obesity. This would suggest (albeit unproven) that lower adiponectin levels are genetically determined and appear to antecede the development of IGT and DM.[28] A major risk factor for insulin resistance is also ethnicity and/or race, independent of family history of DM and obesity. Thus, while adiponectin levels have been studied in several ethnic/racial populations, such as Caucasians,[6-8] Pima Indians,[9-11] Japanese,[4,10] and Asians,[30] we are aware of a single cross-sectional study in which adiponectin levels were measured in nondiabetic African American subjects.[29] Hulver et al[29] found that adiponectin levels were similar in morbidly obese (body mass index [BMI] = 47kg/m^2) African Americans and white Americans. However, adiponectin was lower in nonobese (BMI = 27kg/m^2) African Americans when compared with their white American counterparts. This study suggested possible ethnic and racial differences in the levels or regulation of adiponectin. Because African Americans have greater prevalence and incidence of obesity, insulin resistance, and DM when compared with white Americans,[31-35] it is imperative that we investigate the role of adiponectin in the pathogenesis of glucose intolerance in African Americans.

Thiazolidinediones (TZDs) have become an important addition to the drug armamentarium for the treatment and prevention of IGT and DM.[4,36-38] TZDs primarily improve insulin sensitivity in the liver and peripheral skeletal muscles (without direct effects on β-cell secretion) by activating the PPARγ. Thus, the recent demonstration that TZDs increase adiponectin levels and adipose tissue gene expression, as well as suppress TNF-α,[26-28,39] raises the question as to whether the metabolic and vascular properties of TZDs can be partly ascribed to TZD-induced hyperadiponectinemia. However, whether adiponectin serves as the putative link or factor that mediates TZD's metabolic effects in obesity-prone, insulin-resistant, African Americans remains uncertain.

Therefore, in the present study, we sought to investigate the effects of a potent TZD, (rosiglitazone; GSK Pharmaceutical, Philadelphia, PA) on adiponectin, glucose homeostasis, insulin action, and insulin secretion, as well as lipid and lipoprotein levels in African Americans with IGT and DM before and after 3 months of rosiglitazone treatment.

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Table 1. Adiponectin Insulin Action and β=Cell Function in African Americans With NGT, IGT, and DM Before and After Rosiglitazone therapy 3 months

Parameter	Controls Baseline	IGT		DM	
		Baseline	Rosiglitazone	Baseline	Rosiglitazone
N	19	12	—	17	—
Age (yr)	49.1 ± 7.8	51.0 ± 9.3	—	49.0 ± 8.44	—
Body weight (kg)	86.8 ± 16.4	105.7 ± 27.8	105.9 ± 28.7	102.7 ± 14.6	101.8 ± 14.2
BMI (kg/m^2)	32.45 ± 6.69	40.16 ± 9.363	38.8.45 ± 8.79.3	35.8 ± 4.4	35.91 ± 3.88
Body fat mass (%)	42.2 ± 12.4	48.6 ± 12.8	49.2 ± 10.2	48. ± 5.12	49.42 ± 5.08
Blood pressure (mm Hg)					
Systolic	129 ± 14	139 ± 17.8	140 ± 17.5	136 ± 17	128 ± 15.9
Diastolic	77 ± 11.6	81.1 ± 8.50	76.4 ± 11.5	82 ± 11.7	75 ± 12
Metabolic parameters					
Fasting glucose (mg/dL)	85.2 ± 12.2	111.7 ± 3.5	100.1 ± 18.3	164.0 ± 71.76	127.1 ± 51.6‡
2-h PP glucose (mg/dL)	85.6 ± 20.1	162.1 ± 22.5	122.1 ± 41.2	289.2 ± 102.3	199.6 ± 105.0‡
Fasting insulin (μU/mL)	13.01 ± 9.32	15.40 ± 9.16	17.32 ± 9.39	14.9 ± 8.43	13.71 ± 5.04
2-h PP insulin (μU/mL)	72.75 ± 87.7	69.5 ± 43.7	72.50 ± 49.36	89.72 ± 50.18	71.9 ± 54.4‡
Fc-peptide (ng/mL)	3.68 ± 1.44	3.61 ± 1.34	3.79 ± 1.42	4.88 ± 2.26	3.88 ± 1.23
2-h C-peptide (ng/mL)	10.10 ± 4.12	11.31 ± 2.31	11.72 ± 3.66	9.48 ± 3.53	10.66 ± 4.32
HbA_{1c} (%)	5.7 ± 0.5	6.06 ± 0.53	5.60 ± 0.39	7.77 ± 2.10	6.96 ± 2.01
HOMA-IR	2.81 ± 2.01	4.81 ± 3.49‡	3.78 ± 2.45	6.33 ± 3.54‡	4.12 ± 1.95‡
HOMA-%B	252 ± 187	132 ± 62	191.2 ± 169	110.6 ± 84	106.9 ± 61.6
Adiponectin (μg/mL)					
Fasting	9.61 ± 5.09	10.21 ± 6.89	22.42 ± 10.97‡	6.74 ± 1.95†	15.68 ± 8.23‡
2-h PP	10.56 ± 5.32	10.04 ± 6.56	23.02 ± 10.97*	6.56 ± 1.89†	15.82 ± 6.61*
Lipids and lipoproteins (mg/dL)					
Total cholesterol	191.2 ± 26.1	203.6 ± 36.9	209.2 ± 33.3	223.4 ± 31.3	219.2 ± 72.0
Triglycerides	77.3 ± 32.81	155.12 ± 131	153.0 ± 123.5	163.3 ± 89.1	113.8 ± 62.9
HDL-C	51.42 ± 12.3	48.7 ± 13.8	48.2 ± 14.4	37.7 ± 7.6*	41.7 ± 10.5
LDL-C	124.3 ± 21.9	123.7 ± 26.5	143.2 ± 22.4	150.0 ± 4	164.5 ± 70.5

Note: Values are mean ± SD. Rosiglitazone therapy for 3 months.
*$P < .05$ *v* controls; †$P < .0$ *v* controls; ‡$P < .01$, 3 months *v* baseline.

SUBJECTS, MATERIALS AND METHODS

Populations

The participants were first-degree relatives of African Americans with DM. There were 12 patients with impaired glucose tolerance (IGT) test and 17 with newly diagnosed, drug naïve, patients with DM. Nineteen first-degree relatives with normal glucose tolerance (NGT) test served as healthy controls. 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.

All the subjects had fasting serum glucose measured after a 10- to 12-hour fast to qualify for the study. After at least 10 minutes bed rest, 2 blood pressure readings were taken using zero-centered sphygmomanometer at 10-minute intervals in the sitting position. Each subject was weighed to the nearest gram and the height was measured to the nearest centimeter. Body composition was measured using dual energy x-ray absorptiometer (DEXA, Lunar, WI). The subjects who qualified for the study then underwent a standard oral glucose tolerance test (OGTT). The clinical characteristics of our African Americans with varying degrees of glucose tolerance are shown in Table 1. We excluded patients with symptoms of hyperglycemia, such as polyuria, polydipsia, polyphagia, excessive thirst, recent weight loss, blurred vision, etc during screening. The following subjects were also excluded: (1) those taking medications known to influence glucose and insulin metabolism; (2) those individuals with liver, heart, lung, and kidney diseases; (3) those with established diabetes on antidiabetic medications; and (4) those who participated in endurance exercise or indulged in regular competitive sports.

Metabolic Studies

All the subjects were admitted to the Endocrine/Diabetes Clinical Research Unit of The Ohio State University, Columbus, OH after a 10- to 12-hour overnight fast. With the subject in the sitting position, an intravenous needle was inserted into a forearm vein. Blood samples were drawn for serum glucose, insulin, C-peptide, and plasma adiponectin levels. Fasting lipids and lipoproteins and glycosylated hemoglobin (HbA_{1c}) levels, as well as routine kidney and liver function tests, were obtained.

OGTT

The subjects ingested 75 g (250 mL) oral glucose load (Glucola, Baltimore, MD) over a 2-minute period. Blood samples were obtained at t = 0 minutes and 2 hours after oral glucose load for serum glucose, insulin, C-peptide, and plasma adiponectin levels. The categories of glucose tolerance were defined according to the Expert Committee on the Diagnosis of Diabetes.[40]

Longitudinal Study

The patients with IGT and DM received rosiglitazone (4 mg/d) for the initial 4 weeks in the morning before breakfast. The dose was then increased to 8 mg/d single dose in the morning from 4 to 12 weeks. The subjects were seen at the outpatient clinical research unit at 4 weekly intervals following a 10- to 12-hour overnight fast. Each subject was instructed to perform self-glucose monitoring using a portable glucose meter. Fasting blood was drawn for fasting glucose, lipids and liporproteins, and liver and renal function tests and HbA_{1c} levels at the

baseline (0 month) and after 3 months of rosiglitazone therapy. The serum OGTT was repeated at 3 months of rosiglitazone treatment.

Analytical Methods

Serum glucose concentrations were measured by the glucose oxidase method using glucose autoanalyzer (Yellow Spring Instruments, Yellow Spring, 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, Columbus, OH. 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. Plasma adiponectin levels were measured by an enzyme-linked immunosorbent assay (ELISA) method (B-Bridge International). The lower limit of adiponectin sensitivity was 0.77 μg/mL. The inter and intra-assay CV were 5.76% and 3.65%, respectively. The HbA_{1c} level was measured by the immunobased method (DCA 2000, Bayer, Indianapolis, IN). The normal reference range was 3.6% to 6.1%. The serum cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides were measured using enzymatic methods.

Calculations and Statistical Analyses

Results are expressed as mean ± SD unless stated otherwise. The BMI was calculated as weight (kg) divided by height square (m). Insulin resistance and β-cell function were calculated using homeostasis model assessment (HOMA).[41] Insulin resistance index was calculated using the homeostasis model assessment (HOMA-IR) as follows: fasting insulin (μU/mL) × fasting plasma glucose (mmol/mL)/22.5. HOMA-derived, β-cell function (HOMA %B) was also calculated by the formula: 20 × fasting insulin (μU/mL)/fasting glucose (mmol/mL) − 3.5. The low-density lipoprotein cholesterol (LDL-C) was calculated using Friedwald's equation: LDL-C = total cholesterol − HDL-C − triglyceride/5, for serum triglycerides less than 400 mg/dL.

Statistical analyses were performed using Student's t test (paired) within the group analyses and unpaired t test between the groups and analysis of variance (ANOVA) with repeated measures, where appropriate. Bonferroni method was used for post hoc testing. The nonparametric data were analyzed using χ^2. The relationships of adiponectin, HOMA-IR, HOMA-%B, fasting insulin, blood pressure, body composition variables, as well as lipids and lipoproteins, were calculated using least square method, as well as stepwise linear regression. 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

The mean body weight and BMI were significantly higher in the IGT and DM than in the NGT group. During rosiglitazone therapy, the mean body weight and BMI were not significantly changed in the IGT and DM groups. Rosiglitazone treatment was well tolerated without any discernable weight gain or clinical pitting edema. Rosiglitazone had no adverse effects on liver function nor associated hematologic parameters in the IGT and DM groups. As shown in Table 1, the mean systolic and diastolic blood pressures tended to be greater in patients with IGT and DM than in the healthy controls. Rosiglitazone therapy was associated with lowering of both systolic and diastolic blood pressures, but the difference did not reach statistical significance.

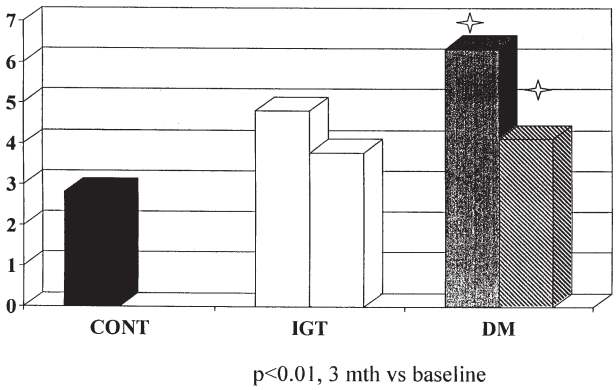

Fig 1. HOMA -IR before and after rosiglitazone therapy in African Americans with IGT and DM. *P < .05 before and after rosiglitazone treatment for DM.

Effects of Rosiglitazone on Glucose Homeostasis, Insulin Secretion and Insulin Resistance in African Americans With IGT and DM

As shown in Table 1, the IGT and DM groups were significantly more insulin resistant and had decreased β-cell function when compared with the NGT group at baseline. Fasting serum glucose did not change in the IGT during the rosglitazone treatment when compared with 0 month. However, the 2-hour serum glucose levels during OGTT were significantly decreased during rosiglitazone treatment in the IGT group. In contrast, both fasting and 2-hour serum glucose levels during OGTT were significantly decreased during rosiglitazone treatment in the DM group (Table 1). Furthermore, HbA_{1c} slightly, but not significantly, decreased in the IGT and DM groups, but significantly so during rosiglitazone therapy in the IGT group.

As shown in Table 1, mean fasting and 2-hour serum insulin during OGTT were not significantly changed after 3 months of treatment with rosiglitazone in the IGT and DM groups.). The serum C-peptide levels followed a trend similar to those of serum insulin responses in both IGT and DM groups (Table 1). Rosiglitazone had no significant effects on β-cell function as assessed by HOMA-%B in the IGT and DM groups. As shown in Table 1 and Fig 1, rosiglitazone treatment decreased slightly the HOMA-IR in the IGT when compared with the baseline value (P = not significant [NS]). In contrast, in the DM group, rosiglitazone significantly decreased the HOMAR-1R when compared with the baseline (0 month) values.

Effects of Rosiglitazone on Adiponectin in African Americans With IGT and DM

Mean plasma adiponectin levels at fasting and 2 hours during OGTT were significantly lower in the DM group than in the IGT and NGT at baseline. As shown in Table 1 and Fig 2, rosiglitazone treatment significantly increased plasma adiponectin levels at fasting from 10.21 ± 6.89 to 22.42 ± 10.97 μg/mL in the IGT (P < .01) and from 6.74 ± 1.95 μg/mL to 15.68 ± 8.23 μg/mL (P < .01) in the DM group at 3 months, respectively. As shown in Table 1, the mean adiponectin levels at 2 hours did not differ from the corresponding fasting levels

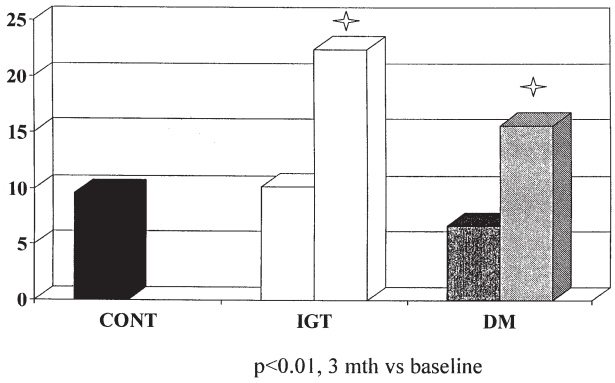

Fig 2. Adiponectin levels before and after rosiglitazone therapy in African Americans with IGT and DM during OGTT. *$P < .01$ before and after rosiglitazone treatment for both IGT and DM.

before and after rosiglitazone treatment in the either IGT and DM groups during OGTT.

Effects of Rosiglitazone on Lipid and Lipoprotein Levels in African Americans With IGT and DM

The mean fasting serum cholesterol, triglycerides, and LDL-C levels did not differ in the IGT and DM groups when compared with that of the NGT group at baseline (Table 1). However, mean HDL-C levels were significantly lower in the DM when compared with the IGT and NGT groups. Following 3 months of rosiglitazone therapy, HDL-C increased while triglycerides decreased, but the mean differences did not reach statistical significance in the IGT and DM groups (Table 1).

DISCUSSION

TZDs are known to improve insulin resistance and overall glucose control in patients with DM.[37-39,41] In the present study, rosiglitazone monotherapy improved the overall glycemic control as assessed by fasting and 2-hour postprandial glucose and HbA_{1c} mostly in the DM group. The β-cell function (absolute and incremental serum insulin, C-peptide levels, and HOMA-%B) was however not significantly changed by rosiglitazone therapy in the African American patients with IGT and DM. Because rosiglitazone treatment was associated with lower fasting and/or 2-hour serum glucose during OGTT despite similar insulin and C-peptide levels at 3 months in the DM group, it could be inferred that rosiglitazone enhanced β-cell responsiveness to glucose stimulation by an as yet ill-defined mechanism. We should note that it is well established that β-cell dysfunction is the proximate cause for the glucose intolerance in patients with IGT and DM. Although the reasons for the β-cell dysfunction in IGT and DM groups is uncertain, both genetic and environmental factors have been implicated.[3] Whether adiponectin has a significant role in β-cell function remains unknown. We found that β-cell function, as expressed by HOMA %B and fasting serum insulin and C-peptide, negatively correlated with adiponectin levels in African Americans. Although, we cannot ascertain cause and effect relations of adiponectin on β-cell function, it is possible that adiponectin could directly or indirectly affect β-cell function or could be a marker of β-cell dysfunction in genetically prone individuals.

Insulin resistance is a hallmark of IGT and DM. The insulin resistance antecedes the development of DM by decades in patients with obesity and especially in nondiabetic first-degree relatives of patients with DM. In this regard, several investigators have suggested that insulin resistance is the primary defect in the pathogenesis of DM,[1] but this remains controversial.[1,4] Recently, Lihn et al[6] and Pelhme et al[8] showed that plasma adiponectin levels and its gene expression are significantly decreased in the nondiabetic first-degree relatives of patients with DM. These studies suggest that adiponectin could play a significant role in the pathogenesis of insulin resistance and its associated syndromes. Our present study in first-degree relatives of African American patients with DM who manifested IGT or DM confirmed moderate insulin resistance in both groups and that rosiglitazone improved the insulin resistance, especially in the DM groups. Indeed, the HOMA-IR was significantly reduced by 30% during rosiglitazone therapy in the DM group. This was independent of obesity. Of great interest is that rosiglitazone doubled the fasting and 2-hour plasma adiponectin levels at 3 months when compared with the values at 0 month in both IGT and DM groups. We found that adiponectin correlated negatively with HOMA-IR in our African Americans as a group ($r = -0.502$, $P = .048$). These relationships were not changed when examined in the NGT, IGT, and DM subgroups. Because the relationships of adiponectin with HOMA-IR were independent of circulating plasma glucose levels (fasting and 2-hour plasma glucose) and chronic glycemic control (HbA_{1c}), we have speculated that adiponectin could be important in the etiology of primary insulin resistance in African Americans predisposed to DM. Conversely, plasma adiponectin could serve as marker for insulin resistance in our African Americans.

Previous studies have suggested that lower adiponectin is associated with several cardiovascular diseases (CVD) and atherogenesis and appears to modify CVD risk factors. Indeed, plasma adiponectin levels are decreased in patients with hypertension and coronary artery diseases.[20,21] Although the reason for the protective actions of adiponectin deserves further elucidation, recent studies have shown that adiponectin inhibits intercellular adhesive molecule (ICAM), E-selectin, and TNF-α levels.[16] Thus, we examined the effects of rosiglitazone on lipids and lipoproteins in our study. We found that rosiglitazone slightly increased HDL-C levels and decreased triglycerides in African American patients with DM. Although, rosiglitazone could have several mechanisms, eg, lower free fatty acid levels, which are responsible for the beneficial effects on lipids and lipoproteins. It is theoretically possible that adiponectin could partly mediate these favorable effects on lipid and lipoprotein levels by TZDs. However, in contrast with other previous studies, we found no relationships between adiponectin and serum triglycerides and HDL-C level before and after rosiglitazone therapy (data not shown). We also found that rosiglitazone had some favorable effects on blood pressure by reducing the systolic and diastolic pressure in the patients

with DM (by median of systolic, 6 mm Hg and diastolic, 4 mm Hg). Because decreased adiponectin levels have been associated with hypertension, the TZD-induced increases in adiponectin levels could be implicated in the lowering of blood pressure responses during rosiglitazone. When taken together, rosiglitazone appears to have favorable effects on cardiovascular risk factors in African Americans with glucose intolerance. Finally, 3-month rosiglitazone treatment was well tolerated in African Americans with IGT and DM without body weight gain, increased percent body fat, peripheral edema, or dilutional anemia, despite significant improvement in insulin resistance and glucose parameters.

In summary, rosiglitazone was effective in improving long-term glucose control and insulin resistance in our African Americans with DM. Our study also demonstrated that adiponectin levels were lower in obese African Americans with DM. Rosiglitazone monotherapy was associated with doubling of plasma adiponectin levels, which correlated with β-cell function and insulin sensitivity indices. Even though, we cannot prove cause and effect relations of adiponectin on insulin sensitivity and β-cell secretion, our data suggest that adiponectin might be partly responsible for the beneficial metabolic effects of rosiglitazone. We speculate that increases in adiponectin levels and/or its gene expression could serve as the putative mediator of the pharmacologic actions of TZDs in the prevention and management of IGT and DM in high-risk African Americans.

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