The Impact of an Insulin Sensitizer, Troglitazone, on Glucose Metabolism in African Americans at Risk for Type 2 Diabetes Mellitus: A Placebo-Controlled, 24-Month Randomized Study

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African Americans (AA) have greater prevalence of type 2 diabetes mellitus (DM), and nondiabetic AA have demonstrated increased insulin resistance when compared with Caucasian Americans (CA). The objective of this study was to examine the impact of chronic use of an insulin sensitizer on glucose metabolism in normal glucose tolerant AA at risk for DM (previous gestational diabetes mellitus [GDM] or first-degree relative with DM). Forty-nine high-risk AA received 200 mg/d troglitazone (TRO) versus 81 age-, weight-, and body mass index (BMI)-matched high-risk AA who received placebo (PLA) for 24 months. Yearly anthropometric measurements, oral glucose tolerance test (OGTT) and frequently sampled intravenous glucose tolerance test (FSIVGTT) were performed. Biochemical parameters were monitored quarterly. There was no significant change in anthropometric measurements over 24 months in TRO versus PLA. There were no significant differences in serum glucose, insulin, or C-peptide incremental area under the curve (AUC) in TRO versus PLA at baseline or 24 months for OGTT and FSIVGTT. The insulin sensitivity (S_I) for TRO and PLA increased from baseline to 24 months by 17% and 16%, respectively. The TRO demonstrated a 26% increase in insulin/glucose ratio versus 1% increase in the PLA at 24 months. The disposition index (DI) increased 33% from baseline in TRO versus 21% increase in PLA. Modest improvement in glucose metabolism was seen in TRO when compared with PLA. TRO was well tolerated without significant reported adverse events. Based on our current data, the treatment of normal glucose tolerant high-risk AA with thiazolidinedione (TZD) may be beneficial to "reset" and protect glucose metabolism by improving insulin responses. Because of the potential drug-related risks associated with use of TZD and the proven positive impact of diet and exercise in prevention of DM, studies of longer duration with examination of other potentially beneficial parameters, such as cardiovascular indices and inflammatory markers will be necessary to justify the cost in the nondiabetic population.

AFRICAN AMERICANS (AA) demonstrate higher rates of type 2 diabetes mellitus (DM) when compared with Caucasian Americans (CA). In addition, certain ethnic and racial populations demonstrate higher rates of impaired glucose tolerance (IGT) and insulin resistance.[1] We and others have demonstrated that AA are more insulin resistant as reflected by a lower insulin sensitivity (insulin-dependent glucose transport or SI), but manifest a greater glucose effectiveness (insulin-independent glucose tranport or SG) than CA, irrespective of family history of diabetes.[2-6] Indeed, several previous studies have demonstrated that fasting hyperinsulinemia and 2-hour postprandial glucose levels, as well as obesity, could predict the future development of DM in several ethnic groups, including CA, Hispanic Americans, and Pima Indians with IGT.[7,8] Most importantly, the rate of progression to diabetes in IGT varies by race and ethnicity depending on the prevalence of obesity in that population.[8,9] In this regard, understanding the risk factors and the metabolic predictors of the disease is crucial for impacting disease progression.

Type 2 DM is characterized by overproduction of glucose by the liver, peripheral insulin resistance, and β-cell dysfunction.[1,10-12] Based on these known defects, several approaches have been adopted to delay or prevent the onset of DM.[13-16] These approaches have included diet, exercise, and pharmacologic interventions. Hu et al[17] and The Nurses' Health Study have shown that individuals who ingest lower amounts of fat are less obese and manifest lower rates of DM. This study also indicated that lifetime exercise is associated with decreased incidence of DM. The recent reports from the Finnish Diabetes Prevention Study and the Diabetes Prevention Program (DPP) support the effectiveness of lifestyle intervention and exercise on the prevention of DM in individuals with IGT.[20,21] Lastly, over the past 30 years, various oral antidiabetic medications have been used in an attempt to prevent DM in patients with IGT or those at risk for DM.[22] However, the inherent risk of hypoglycemia has prevented the use of insulin secretagogues as a mode of prevention of DM in high-risk subjects. Hence, the use of oral antidiabetic medications, such as biguanides, TZDs, and α glycosidase inhibitors, with only rare occasion of hypoglycemia, has regenerated the interest in impacting the rate of progression to DM in high-risk patients. The recently published DPP results demonstrated a reduction in new diabetes by 31% with the use of metformin.[21]

The advent of new "insulin sensitizers," thiazolidinedione drugs (TZD) for the management of DM, provides a unique opportunity to design a program to potentially impact progression to IGT and DM by potentially affecting the underlying pathophysiology of insulin resistance and hyperinsulinemia. Studies with one such drug, troglitazone (TRO)[23-26] (Parke Davis, Morris Plains, NJ) have demonstrated its ability to sensitize various tissues to insulin action, as well as suppress the basal hepatic glucose production with very little associated hypoglycemia.[24,27] In the Troglitazone in the Prevention of Diabetes (TRIPOD) study, TRO was effective in reducing insulin resistance and preventing the conversion of IGT to DM

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in Latin Americans with prior gestational diabetes.[28] Moreover, TZD has been shown to reduce free fatty acids, an important mechanism for improving insulin action and peripheral glucose disposal.[23] These effects make TZD theoretically an ideal intervention for individuals at risk for development of DM. However, the short-term benefits of TRO in AA and the long-term benefits of TRO in nondiabetic, high-risk populations, and IGT remain unknown.

Therefore the objectives of this study were to examine the impact of low-dose TRO on (1) peripheral insulin resistance as measured by glucose, insulin, and C-peptide responses to oral glucose tolerance test (OGTT) and frequently sampled intravenous glucose tolerance test (FSIVGTT), (2) insulin sensitivity (S_I) and glucose effectiveness (S_G), (3) lipids and lipoproteins, and (4) anthropometric parameters in nondiabetic AA first-degree relatives of patients with DM.

SUBJECTS, MATERIALS, AND METHODS

This study was a double blinded, placebo-controlled, antidiabetic drug intervention study in AA at risk for DM using low-dose TRO 200 mg/d.

Study Protocol

Location. All of the studies were performed at the Clinical Research Center of The Ohio State University Hospitals after a 10- to 12-hour fast. Before each study, subjects were instructed to ingest at least 300 g carbohydrates in their regular meals for 3 days. Intense exercise activities (marathon running, biking, etc) were avoided.

Inclusion criteria. Healthy AA individuals from both sexes, age range, 30 to 60 years who were former gestational diabetes mellitus (GDM) or first-degree relative of an individual with DM, percent ideal body weight 90% to 160%, able to give written informed consent, and willing to be monitored for at least 3 to 5 years were included in the study.

Exclusion criteria. Minors, age less than 18 years, severe hypertensive, clinical diabetes on antidiabetic medications, on medications known to influence insulin, glucose, and lipoprotein metabolism, prisoners, unable to give wriften informed consent, morbidly obese subjects participating or contemplating on participating in a weight reduction program within 5 years, allergies to sulfur compounds, and pregnant females were excluded.

Dietary regimen. The subjects were instructed on a diet with a composition of 45% to 50% carbohydrate, 30% to 35% fat, and 10% to 15% protein in total energy content. The aim of the diet was weight maintenance throughout the study period, while teaching healthier eating habits.

Anthropometric measurements. Body weight was measured to the nearest 0.5 kg. Body mass index (BMI) was calculated as the weight (kg)/height (m^2). The skinfold thickness was measured in triplicate at midtriceps, midbiceps, trunk-midpoint between acromion and olecranon processes, inferior angle of the scapula midpoint between the acromion process, and iliac crest. Waist-to-hip ratio (WHR) was used to indirectly identify the location of the fat distribution in the body. The WHR < 0.8 is considered normal, while values > 1 are taken as upper body obesity or android habitus. The percent lean body mass was obtained by the bioelectrical impedance analyzer (BIA) technique.[29,30] Casual blood pressure was measured using mercury sphygmomanometer during the admission at the research center.

Metabolic Studies

Fasting blood was taken for routine chemistry; lipids and lipoproteins, hematologic and liver function profile at 3-month intervals. The OGTT and FSIVGTT were performed at baseline and yearly during study participation.

OGTT. The OGTT was used to identify IGT and DM as assessed by the National Diabetes Data Group (NDDG)[31] and World Health Organization (WHO)[32] criteria. A standard OGTT with 75 g glucose (Koladex, Custom Laboratories, Baltimore, MD) was performed in each subject. Blood samples were drawn before and after the glucose load at 0, 30, 60, 90, 120, 150, 180, 210, and 240 minutes for glucose, insulin and C-peptide.

FSIVGTT. The FSIVGTT was used to measure the first and second phases of insulin release and secretion.Two angiocatheters were placed in the antecubital veins, one for the administration of glucose and insulin and the other for blood sampling from the contralateral arm. Baseline glucose, insulin, and C-peptide levels were obtained at -20, -5, and 0 minutes. At time $= 0$ minutes, intravenous glucose 0.3 g/kg, (50% dextrose in water) was administered over a 1-minute period. A dose of intravenous insulin (0.05 μ/kg for BMI <30 kg/m^2 and 0.1 μ/kg for BMI >30 kg/m^2) was given at time $= 20$ minutes. Blood samples for glucose and insulin levels were drawn at time $t = -20$, -5, 0, 2, 5, 8, 10, 16, 19, 22, 25, 30, 40, 60, 90, 120,150, and 180 minutes. The blood samples were centrifuged at 4°C; sera were stored at -20°C until assayed.

Follow-up program. The subjects were randomly selected to receive TRO or placebo (PLA). This randomization was blinded to the investigator. A 3-month supply of the medication was dispensed, and the subjects were asked to return all unused pills and pill container at their next study visit. The subjects were seen at 3-month intervals for at least 24 months. During each visit, weight, blood pressure, and skinfold measurements were performed. The unused pills were counted and recorded. If there was a discrepency in the number of pill left, this was addressed.

Analytical methods. Serum glucose was measured by the glucose oxidase method (Yellow Spring Instruments [YSI], Yellow Springs, OH). Glycosylated hemoglobin (HbA_{1c}) was measured using high-performance liquid chromotography (HPLC) technique (Tosoh Medics, San Francisco, CA). The normal reference value range is between 4.2% to 6.2% in our laboratory. Serum insulin levels were measured by coated-tube radioimmunoassay technique, and C-peptide levels were measured by standard double-antibody radioimmunoassay technique in the Core Laboratories at The Ohio State University Hospitals, Columbus, OH. The sensitivity for the insulin assay is 1.2 μU/mL and for C-peptide, 0.01 ng/mL. The intra- and interassay coefficients of variation (CV) are 6% and 10% for insulin and 7.9% and 5.3% for C-peptide, respectively.

Calculations

For the OGTT and FSIVGTT, both absolute and integrated incremental areas under the curves (AUC) were calculated using trapezoidal rule for serum glucose, insulin, and C-peptide levels. Acute first and second phases of insulin release were taken as the sum of incremental area above the baseline between $t = 0$ to 5 minutes and $t = 8$ to 19 minutes, respectively. Serum cholesterol, triglycerides, and high-density lipoprotein-cholesterol (HDL-C) were measured using enzymatic methods. The low-density lipoprotein-cholesterol (LDL-C) was calculated using Friedwalds equation: LDL-C = total cholesterol $-$ [HDL-C $-$ (triglycerides/5)]. The disposition index (DI) is a measure of the activity of the β cells adjusted for insulin resistance.[25,26] It was calculated as the SI $\times$ acute insulin release (AIR).[33] Hepatic insulin extraction was calculated as the molar ratio of C-peptide (AUC-OGTT)/insulin (AUC-OGTT).[34] Insulin/glucose ratio was calculated as the ratio of AUC for acute first phase of glucose and insulin release during FSIVGTT (0 to 5 minutes). The calculation of SI and SG was performed using the MINIMOD software program developed by Bergman et al.[35]

Table 1. Baseline Clinical Characteristics

	Placebo (n = 81)	Troglitazone (n = 49)
Age (yr)	41 ± 1	39 ± 1
Gender (M/F)	21/60	8/41
Weight (kg)	90 ± 10	89.5 ± 13
BMI (kg/m^2)	31 ± 4	32 ± 5
% Body fat	37 ± 4	38 ± 6
WHR	0.90 ± 0.1	0.89 ± 0.1
Glucose (mg/dL) fasting	78 ± 9	79 ± 12
Insulin (μU/mL) fasting	14 ± 2	12 ± 2
C-peptide (ng/mL) fasting	2.7 ± 0.4	2.8 ± 0.5

Statistical Analysis

Results are expressed as mean ± SEM, unless otherwise stated. Probability (P) value less than .05 was considered significantly different. For nonparametric data, statistical analyses were performed by Mann-Whitney U test and χ^2 tests. The parametric parameters were evaluated using Student's t test (unpaired).

RESULTS

One hundred and thirty healthy AA subjects were studied. The population was comprised of TRO (n = 49) receiving 200 mg/d TRO and PLA (n = 81) receiving placebo. The sampling was weighted in favor of the PLA group to determine progression to IGT or DM. The groups were first-degree relatives of patients with DM or former GDM patients with normal glucose tolerance. Socioeconomic status was similar between the 2 groups as assessed by a standardized questionnaire. Compliance was estimated at 79% for TRO and 82% for PLA. There was no difference in attrition rate between the 2 groups. There were no statistically significant gender differences in the parameters studied.

Anthropometric Measurements

At baseline, there were no differences in age, height, weight, BMI, WHR, or skinfold thickness among the 2 groups (Table 1). Change in weight (TRO 2.8 ± 6 kg *v* PLA 1.4 ± 0.8 kg), BMI, or skinfold thickness was not significant at 24 months in TRO versus PLA.

OGTT

Using incremental AUC, there were no significant differences in serum glucose, insulin, or C-peptide AUC in TRO versus PLA at baseline, 12, or 24 months (Figs 1 and 2). The glucose, insulin, and C-peptide profiles demonstrated no significant differences in baseline or peak levels in TRO versus PLA. However, there was a trend for increasing glucose, insulin, and C-peptide levels in PLA over time, while this increase was not seen in TRO.

FSIVGTT

The baseline glucose, insulin, and C-peptide levels were no different in TRO versus PLA. There were no significant differences in first or second phase glucose, insulin, or C-peptide responses over time in TRO versus PLA. Peak glucose, insulin, and C-peptide levels, after intravenous glucose load, did not change significantly over time for either group. The change in first phase AUC response in glucose (decreased 9% *v* increase 4%), insulin (increased 20% *v* increase 6%), and C-peptide (increased 25% *v* increase 14%) in TRO versus PLA. The change in second phase AUC response included glucose (decreased 7% *v* increase 6%), insulin (decreased 8% *v* decreased 8%), and C-peptide (decreased 2% *v* decreased 4%). The TRO demonstrated improved glucose metabolism with lower first and second phase glucose levels and a more brisk first phase response, while PLA demonstrated higher first and second phase glucose with modest increased first phase and decreased second phase insulin and C-peptide responses.

Minimal Model Parameters

The baseline SI for TRO was statistically greater than PLA (3.21 ± 0.63 *v* 2.47 ± 0.33 $min^{-1} \cdot \mu U^{-1} \cdot mL^{-1}$). At 12 months (3.55 ± 0.92 *v* 2.98 ± 0.52 $min^{-1} \cdot \mu U^{-1} \cdot mL^{-1}$) and

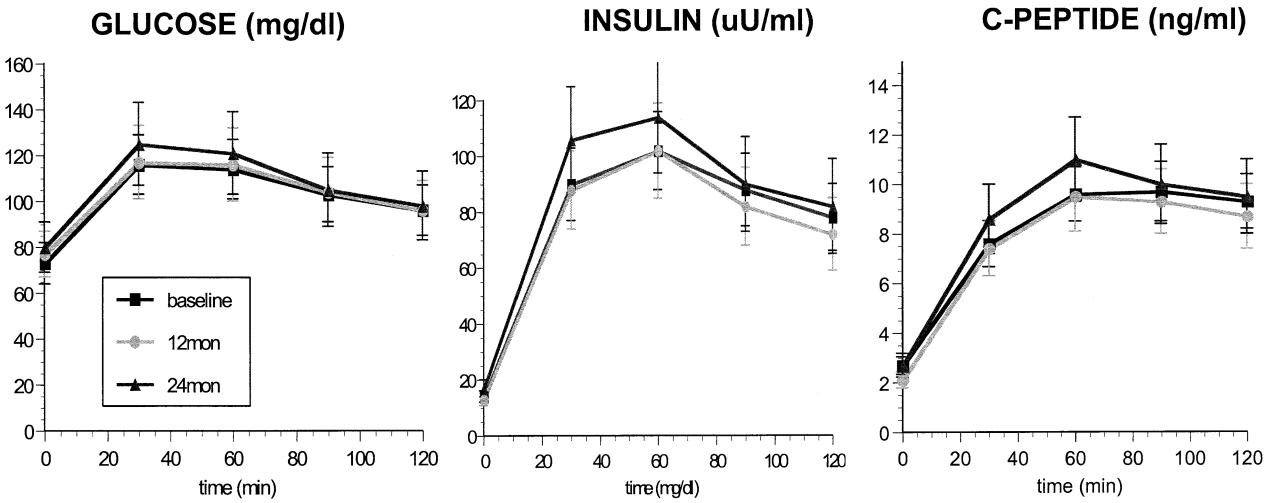

Fig 1. Glucose, insulin, and C-peptide responses to OGTT over 24 months in PLA group.

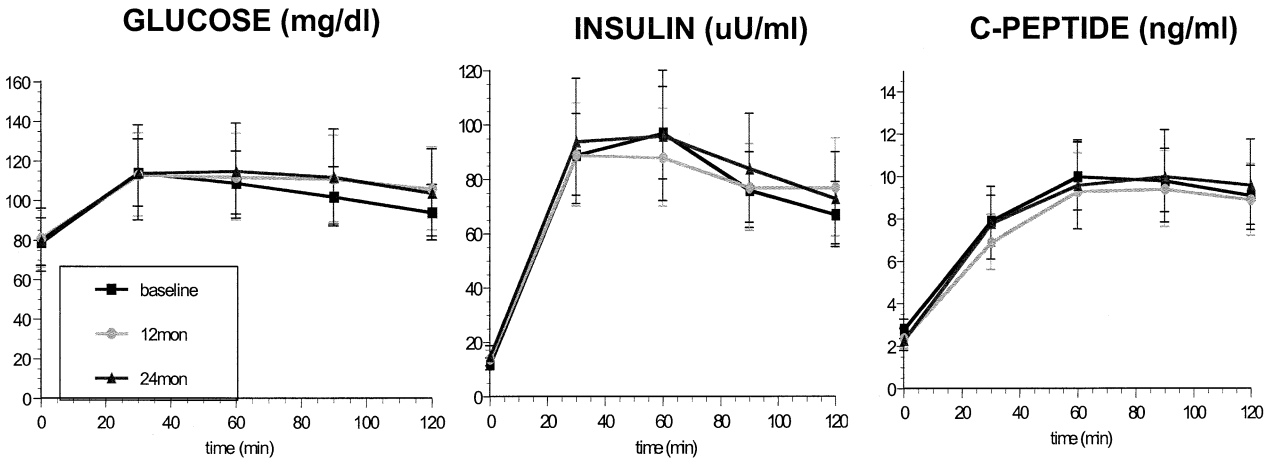

Fig 2. Glucose, insulin, and C-peptide responses to OGTT over 24 months in TRO group.

24 months (3.85 ± 1.01 *v* 2.94 ± 0.54 $min^{-1} \cdot \mu U^{-1} \cdot mL^{-1}$), there was no statistical difference in SI in TRO versus PLA. The SI progressively increased in the TRO group and PLA from 0 to 24 months. Despite the fact that the TRO started out significantly higher, continued improvement was seen over time. The mean SG was similar at baseline (2.54 ± 0.6 *v* $2.48 \pm 0.3 \times 10^{-2}$/min) and month 24 ($2.48 \pm 0.6$ *v* $2.39 \pm 0.4 \times 10^{-2}$/min) in the TRO versus PLA, with no appreciable change over time.

Total Glucose Homeostasis

The TRO group demonstrated a 26% increase versus 1% increase in the PLA group from baseline to 24months in insulin/glucose ratio (Fig 3). DI, as a measure of pancreatic compensation for insulin resistance, increased 33% from baseline in TRO versus 21% increase in PLA (Fig 4). Hepatic insulin extraction was not significantly different over time or when comparing TRO versus PLA.

Lipid Profiles

There was no statistically significant difference at baseline for total cholesterol (177 ± 6 *v* 179 ± 4 mg/dL), LDL (110 ± 6 *v* 108 ± 5 mg/dL), HDL (47 ± 2 *v* 50 ± 2 mg/dL), or triglycerides (101 ± 10 *v* 109 ± 20 mg/dL) in TRO and PLA, respectively. Similar changes in the lipid profile were seen in the nondiabetic AA as has been demonstrated in diabetic patients, including increased total cholesterol, LDL-C, and HDL-C. The LDL-C increased from baseline → 12 → 24 months for both TRO (108 → 109 → 122) and PLA (110 → 113 → 123). There was no significant difference in the change

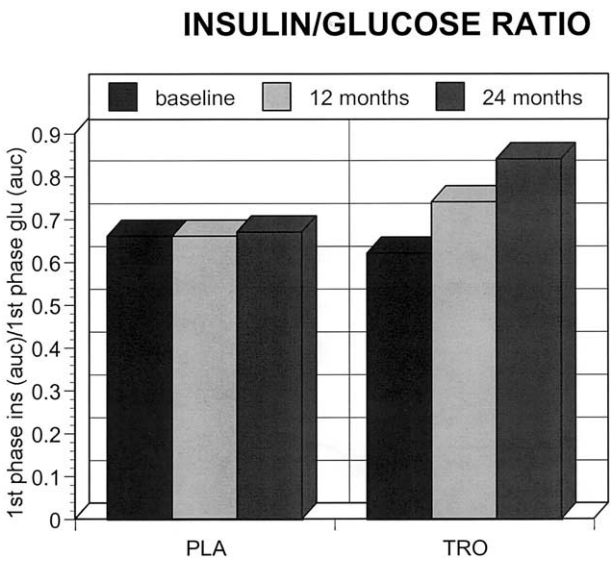

Fig 3. Insulin/glucose ratio for PLA and TRO groups at baseline, 12, and 24 months.

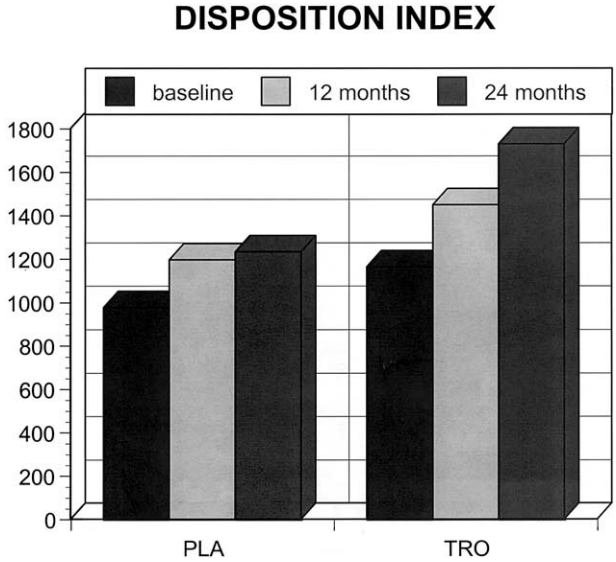

Fig 4. DI for PLA and TRO groups at baseline, 12, and 24 months.

over time when comparing TRO versus PLA for any of the lipid parameters.

Monitoring Parameters

Liver transaminases were not different at baseline or after 24 months (alanine transaminase [ALT] change 1.3 ± 1 *v* change 4 ± 0.8 U/L), (aspartate transaminase [AST] change 1.6 ± 0.9 *v* 4.4 ± 2 U/L) in TRO versus PLA.

DISCUSSION

Type 2 DM affects more than 15 million people in the US with greater frequency in ethnic populations such as AA, Mexican Americans, and Native Americans.[1] Type 2 DM has become epidemic in many of these ethnic populations.[1] Although the National Health and Nutrition Examination Survey (NHANES) III studies[1] demonstrated that the prevalence of both DM and IGT in AA between 20 and 74 years approaches 35%, none of these studies specifically addressed the cumulative risk of the disease in the AA at greater risk. Thus, in view of the socioeconomic implications of the disease and its related long-term complications in AA,[36-38] the prevention or delay of the onset of diabetes could not only lessen the economic cost associated with the disease, but could save lives and enormous morbidity. Early intervention, before the onset of symptomatic hyperglycemia, will be necessary to have significant impact on complications, in particular cardiovascular complications, based on the United Kingdom Prospective Diabetes Study (UKPDS).[10]

As previously mentioned, numerous modalities have been used, with some modest success, to delay/prevent the progression to DM in high-risk populations. Lifestyle modifications have been successful in the short term, but have been difficult to maintain longitudinally. Because of the presence of insulin resistance in high-risk AA, we attempted to intervene with the insulin sensitizer, TRO as a means of reducing one of the risk factors for the development of DM. Indeed, in the TRIPOD study, Buchanan et al[28] demonstrated a significant reduction in the conversion of IGT to DM in the Latino population.

Our study population of high-risk AA received low-dose TRO for at least 2 years. To the best of our knowledge, this is the longest study in the use of TRO in nondiabetic, normal glucose tolerant AA. The results of this study shed light on the impact of TZD in individuals with normal glucose tolerance, but at high risk of DM, as well as posed several new questions. The modest changes in glucose metabolism were consistent with the known drug action of TRO.[24,27] In the present study, the serum glucose, insulin, and C-peptide profiles were not different from baseline to 24 months in TRO or PLA, and the change in AUC was not statistically different. There were, however, some noteworthy trends. When examining the OGTT in TRO verssus PLA, we found that serum glucose, insulin, and C-peptide responses increased over the 24 months in the PLA group, whereas these trends were blunted with the TRO group. The FSIVGTT demonstrated similar results. We saw differences in the TRO versus PLA with improved first phase insulin and C-peptide responses and concomitant decreases in glucose levels. This improvement in first phase insulin response, we believe, indirectly reflects improved β-cell response.

The modest improvement in S_I for TRO was consistent with the changes in profiles. Despite starting out with a statistically higher S_I, the TRO continued to improve at both 12 and 24 months and did not appear to level off with regard to improvement of S_I. We saw no major changes in S_G from baseline to 24 months in any of the groups. This is consistent with the report by Prigeon et al[39]and Kemnitz et al[40] in TRO and pioglitazone, respectively.

In addition to the trends in improvement of S_I and AUC in TRO when compared with PLA, significant improvement was seen in more subtle parameters of glucose metabolism, including insulin/glucose ratios and DI for TRO when compared with PLA. The PLA group deteriorated over the course of the 2 years in this regard when compared with the TRO group. Improvement in DI has been previously demonstrated in IGT and polycystic ovarian syndrome females using TRO.[25,26] This study, to the best of our knowledge, is the first to demonstrate the improvement in nondiabetic, normal glucose tolerant, high-risk AA.

Should we have expected more dramatic changes in a healthy, normal glucose tolerant, high-risk population? The answer to this question is unknown. The DPP was one of the first studies to demonstrate that the drug therapy, metformin, was able to prevent the onset of diabetes[21] in individuals with IGT. Yet within this study of IGT, there were those who had lower BMI and fasting glucose who did not respond to drug intervention. In addition, despite this improvement in incidence of DM, the DPP demonstrated an increase in both HbA_{1c} and fasting plasma glucose over time for all groups studied indicating delay, but not true prevention.[21] Hence the present study poses the question, would earlier intervention prevent the progressive decline in glucose metabolism?

Insulin-resistant subjects commonly demonstrate alterations in lipids and lipoproteins that are potentially atherogenic. To this end, TRO has been reported to increase LDL-C and HDL-C in patients with DM, as well as change the composition of LDL-C, moving from a pattern with predominant small, dense LDL-C to a pattern with large, fluffy, less atherogenic LDL-C.[41] We found normal lipids and lipoproteins in our high-risk AA population. Treatment with TRO did not result in any significant changes in lipid parameters in TRO versus PLA. We did not examine composition of the LDL-C to determine shift from a more dense to a less dense particle.

TZDs have been associated with several side effects. The most notorious and severe side effect has been ascribed to the liver dysfunction with reported fatal outcomes.[42] In this study, TRO was well tolerated without reported adverse effects when compared with PLA. There was no evidence of increased liver transaminases in TRO versus PLA. There were no significant problems with hypoglycemia by laboratory testing or subjective reporting of symptoms.

Another important and common side effect of TZD treatment is weight gain. The TZD are reported to increase intravascular volume and stimulate adipocyte dedifferentiation, resulting in weight gain.[43] In addition, several recent reports[44] have indicated that weight gain is proportional to the reduction and improvement in hyperglycemia in patients with DM. The weight was essentially unchanged in our TRO group, consistent with the fact that no major changes were seen in glycemic control. The body fat content, body fat distribution did not

change as measured by BIA and waist/hip ratio. Finally, the known common side effect, edema, did not occur in our nondiabetic TRO group.[44]

In conclusion, we have conducted the first placebo-controlled, double-blinded, randomized study of TRO in nondiabetic normal glucose tolerant high-risk AA for 24 months. We found that TRO had a modest, positive impact on insulin sensitivity and glucose homeostasis in the setting of normal glucose tolerance. The findings included improvement in overall β-cell response to glucose, pancreatic compensation for insulin resistance, and improved S_I. The drug was well tolerated for the 2-year duration without significant reported adverse events. Based on our current data, the treatment of normal glucose tolerant high-risk AA with TZD may be beneficial to "reset" and protect glucose metabolism. Supporting this concept is Buchanan et al[46] who demonstrated similar findings in women with previous GDM. In this study, the use of TRO was associated with preservation of β-cell function and a decrease in the incidence of diabetes.

Final questions posed by the results of this study include (1) what is the optimal dose of TRO in nondiabetic individuals with normal glucose metabolism? Buchanan et al[46] demonstrated that 400 mg/d was well tolerated and had a signficant positive impact, but unlike our study population, had more severe glucose dysregulation and could be considered further down the path to diabetes, thus necessitating a larger dose of medication. On the other hand, 400 mg/d may be the optimal dose in individuals without frank hyperglycemia to gain the maximal positive response on the β cells. (2) Would these improvements in glucose metabolism impact the long-term rate of progression to DM in the high-risk AA population? Ongoing studies have clearly demonstrated that this class of drugs has positive benefits on β cells and insulin resistance, and the newer drugs in the class appear to be safer and better tolerated than TRO. Given the rate of increase of DM in AA and our ability to identify "at risk" groups and detect early abnormalities in glucose regulation, more research on prevention of DM in this population with the use of insulin sensitizers is warranted. (3) Would nondiabetic, high-risk individuals receive additional benefits from the use of TZD, in particular, reduction in cardiovascular inflammatory markers as seen in diabetic individuals on TZD? Further studies examining changes in these inflammatory markers in nondiabetic, high-risk individuals may provide a means to impact the increased risk of cardiovascular disease seen in impaired glucose tolerance and insulin-resistant states. In this regard, further long-term studies of TZD in nondiabetic, high-risk individuals is warranted. This population is ever expanding and treating before the onset of hyperglycemia may reduce the risk of comorbid conditons. Based on our research and the research of others, TRO does have a positive impact on glucose regulation and can be used safely in nondiabetic individuals. Additional research is needed, using the newer TZDs, to clarify whether the routine use of TZD in high-risk populations is beneficial.

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