Comparative Study of Glucose Homeostasis, Lipids and Lipoproteins, HDL Functionality, and Cardiometabolic Parameters in Modestly Severely Obese African Americans and White Americans With Prediabetes: Implications for the Metabolic Paradoxes

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OBJECTIVE

To determine whether modestly severe obesity modifies glucose homeostasis, levels of cardiometabolic markers, and HDL function in African Americans (AAs) and white Americans (WAs) with prediabetes.

RESEARCH DESIGN AND METHODS

We studied 145 subjects with prediabetes (N = 61 WAs, N = 84 AAs, mean age 46.5 ± 11.2 years, mean BMI 37.8 ± 6.3 kg/m^2). We measured fasting levels of lipids, lipoproteins, and an inflammatory marker (C-reactive protein [CRP]); HDL functionality (i.e., levels of paraoxonase 1 [PON1]); and levels of oxidized LDL, adiponectin, and interleukin-6 (IL-6). We measured serum levels of glucose, insulin, and C-peptide during an oral glucose tolerance test. Values for insulin sensitivity index (Si), glucose effectiveness index (Sg), glucose effectiveness at zero insulin (GEZI), and acute insulin response to glucose (AIR$_g$) were derived using a frequently sampled intravenous glucose tolerance test (using MINMOD software).

RESULTS

Mean levels of fasting and incremental serum glucose, insulin, and C-peptide tended to be higher in WAs versus AAs. The mean Si was not different in WAs versus AAs (2.6 ± 2.3 vs. 2.9 ± 3.0 × 10^{-4} × min^{-1} [μU/mL]$^{-1}$). Mean values for AIR$_g$ and disposition index as well as Sg and GEZI were lower in WAs than AAs. WAs had higher serum triglyceride levels than AAs (116.1 ± 55.5 vs. 82.7 ± 44.2 mg/dL, P = 0.0002). Mean levels of apolipoprotein (apo) A1, HDL cholesterol, PON1, oxidized LDL, CRP, adiponectin, and IL-6 were not significantly different in obese AAs versus WAs with prediabetes.

CONCLUSIONS

Modestly severe obesity attenuated the ethnic differences in Si, but not in Sg and triglyceride levels in WAs and AAs with prediabetes. Despite the lower Si and PON1 values, AAs preserved paradoxical relationships between the Si and HDL/apoA1/triglyceride ratios. We conclude that modestly severe obesity has differential effects on the pathogenic mechanisms underlying glucose homeostasis and atherogenesis in obese AAs and WAs with prediabetes.

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Type 2 diabetes, prediabetes, and obesity are associated with several metabolic derangements, including insulin resistance (IR) and β-cell dysfunction (1–4). Previous studies (5–11) have demonstrated ethnic/racial differences in β-cell and insulin sensitivity in African Americans and white Americans and in other populations. Consequently, African Americans are 1.6 times more likely to have diabetes and impaired glucose tolerance than white Americans. These abnormalities include altered hepatic glucose production and insulin-mediated and non–insulin-mediated glucose disposal (5,7,9–11). The proposed causes for the ethnic disparities include genetic and environmental factors (e.g., obesity and lack of physical activity).

Previous studies (1,10) have shown that IR is associated with low levels of HDL cholesterol (HDL-C), high levels of triglycerides (TGs), and increased levels of oxidized LDL in nonblack populations. The lower levels of HDL-C and LDL oxidation have been implicated in coronary artery diseases (CADs) (12–15). The CAD-associated outcomes are more common in African Americans than in white Americans (16,17). Although African Americans are more obese (18–21) and manifest more IR than white Americans, African Americans have paradoxically higher HDL-C and apolipoprotein (apo) A1 levels and lower TG levels when compared with age-, weight-, and sex-matched white Americans (22–27). Despite the favorable lipid profile (higher HDL levels/lower TG levels, more buoyant LDL particle size), African Americans are two to four times more likely to experience cardiovascular disease (CVD) and its associated morbidity and mortality (16,17). The reasons for these metabolic and CVD differences in African Americans and white Americans are unknown.

It is generally well established that HDL-C is antiatherogenic and cardioprotective, but the mechanisms remain debatable (12–15). In this regard, previous studies (12–15) have attributed the antiatherogenic properties of HDL-C predominantly to reversed cholesterol transport. However, several recent studies (20–22) have suggested that LDL oxidation plays a major role in the pathogenesis of atherosclerosis and that HDL protects LDL from oxidation. In this context, paraoxonase 1 (PON1), which cosegregates in HDL particles in the circulation, is reported (20–22) to

be partly responsible for the qualitative functions of HDL, such as its antioxidant and anti-inflammatory properties. We have postulated that the higher CVD mortality and morbidity in African Americans can be partly due to defective HDL-associated PON1. In this regard, we have demonstrated (22) that the level of PON1 is 50% lower while levels of oxidized-LDL and C-reactive protein (CRP) were higher in healthy, nondiabetic postmenopausal African American women when compared with healthy white American counterparts. These studies suggested that HDL-C may be dysfunctional in African Americans and perhaps less cardioprotective. But the effects of severe obesity on HDL functionality (PON1) and cardiometabolic markers were not examined in these studies. Given the epidemic of obesity and overweight in African Americans, in our current study we sought to investigate the effects of modestly severe obesity on 1) glucose homeostasis (insulin and C-peptide dynamics), insulin sensitivity (insulin sensitivity index [Si]), and non–insulin-mediated glucose disposal (glucose effectiveness index [Sg] and glucose effectiveness at zero insulin [GEZI]); 2) lipids and lipoproteins; 3) HDL functionality (PON1); and 4) nontraditional cardiometabolic biomarkers in white Americans and African Americans with prediabetes.

RESEARCH DESIGN AND METHODS

The study comprised 145 modestly severely obese (BMI >30 kg/m^2) subjects, 61 white Americans (50 females, 11 males), and 84 African Americans (78 females, 6 males, mean age 46.5 ± 11.2 years, age range 25–70 years) with prediabetes, as defined by the American Diabetes Association (28). Prediabetic patients were defined as individuals with impaired fasting glucose levels (100–125 mg/dL), and impaired glucose tolerance (2-h glucose level 140–199 mg/dL), and A1C level of 5.7–6.4% (38.8–46.6 mmol/mol). We excluded patients with type 2 diabetes and a BMI <30 kg/m^2, uncontrolled hypertension (blood pressure [BP] ≥140/90 mmHg), and hyperlipidemia (total cholesterol >200 mg/dL, LDL >130 mg/dL, TGs ≥200 mg/dL). Patients with severe renal, liver, and thyroid dysfunction were also excluded. Patients receiving treatment with antilipid medications

(e.g., statins, fibric acid) or estrogen, current smokers, patients who had experienced recent weight loss within the past 6 months, and patients requiring the use of exogenous antioxidant vitamin supplementation were also excluded. Patients signed a written informed consent, which was approved by The Ohio State University Biomedical Research Committee Institutional Review Board.

General Studies
The subjects reported to the Clinical Research Center (CRC)/Center for Clinical and Translational Science after an overnight fast of 10–12 h duration. Height, weight, waist circumference, hip circumference, and waist-to-hip ratio were measured. BP measurements were obtained at 10 min intervals three times in a sitting position. Fasting blood was obtained for measurement of serum insulin, C-peptide, glucose, total cholesterol, TGs, HDL-C, LDL cholesterol (LDL-C), apoA1, apoB100, interleukin-6 (IL-6), CRP, PON1, and oxidized LDL and adiponectin. Body composition parameters were measured using bioelectrical impedance analysis (RJL Systems) and DEXA (Lunar; GE Healthcare).

Metabolic Studies
Patients underwent an oral glucose tolerance test (OGTT) and a frequently sampled intravenous glucose tolerance test (FSIVGTT) on 2 separate days at the CRC.

OGTT
Each subject was instructed to ingest at least 250 g of carbohydrate in their regular meals for at least 3 days before the test. With the subject in the supine position, an intravenous needle was inserted after a 10- to 12-h overnight fast into the forearm vein and kept patent with 0.9% normal saline infusion. Blood samples were drawn for the measurement of serum glucose, insulin, and C-peptide levels. The subjects then ingested 75 g of oral glucose load (Fisherbrand UN-DEX; Fisher Diagnostics, Middletown, VA) over a 2-min period. Blood samples were drawn at $t = 0$, 30, 60, 90, and 120 min for measurement of serum glucose, insulin, and C-peptide levels.

FSIVGTT
With the subject in the supine position, two intravenous needles were inserted into the forearm veins and kept patent with a 0.9% normal saline infusion. One intravenous line was used to draw blood

samples, and the other was used to administer the intravenous glucose and exogenous insulin, as previously described (2–4). Four blood samples were obtained at $t = -20, -10, -5$, and 0 min for measurement of basal serum glucose, C-peptide, and insulin concentrations. The average of the four samples was considered the basal level. Thereafter, 0.3 g/kg glucose (50 mL of 50% dextrose water) was infused over a 1-min period. At $t = 19$ min, intravenous insulin (0.05 units/kg; Humulin; Eli Lilly, Indianapolis, IN) dissolved in 30 mL of 0.9% normal saline solution was infused over 60 s. Blood samples were obtained at frequent intervals ($t = 2, 3, 4, 5, 6, 8, 10, 12, 16, 19, 22, 24, 25, 27, 30, 40, 60, 70, 90, 120, 140, 150, 160$, and 180 min) for measurement of serum glucose, C-peptide, and insulin levels (3,5,6).

Analytical Methods

All the blood samples were centrifuged at $-4°C$, and the supernatant was collected and stored at $-20°C$ and $-80°C$. All the metabolic assays of each subject were run in a single batch to minimize interassay variability. The serum glucose levels were measured by the glucose oxidase method (model 2300; YSI Life Sciences, Yellow Springs, OH). Serum insulin and C-peptide levels were measured by standard radioimmunoassay techniques. The coefficients of variation were 6% and 10%, respectively. The lower limit of the C-peptide assay was 0.1 ng/mL, and the intra-assay and interassay coefficients of variation were 7% and 13%, respectively. The A1C level was measured by the cationic, microcolumn chromatographic technique (Bayer, Inc.). The normal reference range was 4.0–5.6% (20.2–37.7 mmol/mol). The serum levels of cholesterol, HDL-C, and TGs were measured using enzymatic methods. LDL-C was calculated using the Friedwald equation, as follows: LDL-C = total cholesterol − HDL-C − TGs/5 for serum TGs <400 mg/dL. apoAI and apoBl00 levels were measured using nuclear magnetic resonance (LipoScience, Raleigh, NC). Adiponectin (Quantikine; R&D Systems, Minneapolis, MN) and oxidized LDL (Mercodia, Uppsala, Sweden) were measured using ELISA. CRP was measured using nephelometry (Synchron LX Systems).

Measurement of PON Enzyme Activity

PON1 was measured as previously described in our laboratory (22).

Procedure

In this assay, arylesterase/PON catalyzes the cleavage of phenyl acetate, resulting in phenol formation. The rate of formation of phenol is measured by monitoring the increase in absorbance at 410 nm at 25°C. The working reagent consists of 20 mmol/L Tris/HCl buffer, pH 8.0, containing 1 mmol/L $CaCl_2$ and 4 mmol/L phenyl acetate as the substrate. Samples diluted 1:50 in buffer are added, and the change in absorbance is recorded after a 20-s lag time. One unit of arylesterase activity is equal to 1 μmol/L phenol formed per minute. The activity is expressed in units per liter, based on the extinction coefficient of phenol of 1,310 $M^{-1} \cdot cm^{-1}$ at 410 nm, pH 8.0, and 25°C.

Calculations

Results are expressed as mean $\pm$ SD, unless stated otherwise. BMI was calculated as weight (in kilograms) divided by height (square meters). Si, Sg, acute insulin response to glucose (AIR_g), disposition index (DI), and GEZI were calculated using the Bergman MINMOD Millennium version 6.1 software program. The Sg was defined as the ability of glucose to mediate its own disposal at the basal insulin level. GEZI was defined as glucose-mediated glucose disposal at a theoretical zero insulin concentration as follows: GEZI = Sg − BI, where BI is basal insulin effect (3,5,6). AIR_g was defined as the incremental area under the curve for glucose-mediated insulin release from t = 0–10 min during an FSIVGTT. The DI was calculated as Si × AIR_g. The DI reflects the ability of β-cell secretion to compensate for the prevailing peripheral IR. In addition, IR and β-cell function were also calculated using HOMA (2,3,29). HOMA-derived IR (HOMA-IR) index was calculated as follows: fasting insulin (μU/mL) × fasting plasma glucose (mmol/mL)/22.5. HOMA-derived β-cell function (HOMA-B) was also calculated as follows: 20 × fasting insulin (μU/mL)/fasting glucose (mmol/mL) − 3.5 (29).

Statistical Analyses

Statistical analyses were performed using SAS version 9.1. Results are expressed as the mean $\pm$ SD, unless otherwise stated. The nonparametric data are analyzed using the χ^2 and Mann-Whitney ranked tests. The Student unpaired t test and multiple t tests

are used to analyze the data within and between the groups. The Spearman univariate linear regression was used to determine the relationships among BMI and Si; HOMA-IR and AIR_g; and PON1, oxidized LDL, and CRP. Multiple regression analyses were performed using linear square regression models to examine the relationships among BMI and Si and cardiometabolic markers after adjusting for fasting glucose level, insulin level, age, sex, and ethnicity. $P < 0.05$ is considered statistically significant.

RESULTS

Clinical and biochemical parameters are shown in Table 1. The mean age of the group was 46.5 $\pm$ 11.2 years. Mean ages in white Americans versus African Americans were not different. The mean body weight was not significantly different in white Americans and African Americans (102.1 $\pm$ 21.1 vs. 107.2 $\pm$ 20.1 kg, respectively; P = NS). However, white Americans had significantly lower mean BMIs than African Americans (35.0 $\pm$ 8.8 vs. 38.0 $\pm$ 7.9 kg/m^2, P = 0.04). White Americans had higher waist-to-hip ratio (0.93 $\pm$ 0.1 vs. 0.90 $\pm$ 0.1, P = 0.03), a higher percent lean body mass (55.7 $\pm$ 5.9% vs. 53.5 $\pm$ 4.7%, P = 0.02), and a lower percent body fat (43.9 $\pm$ 5.2% vs. 46.6 $\pm$ 4.6%, P = 0.002). The mean A1C level was lower in white Americans versus African Americans (5.5 $\pm$ 0.5% vs. 5.9 $\pm$ 0.4% [36.6 $\pm$ 3.7 vs. 41.0 $\pm$ 2.0 mmol/mol], $P < 0.0001$). White Americans had higher HOMA-IR (4.3 $\pm$ 2.8 vs. 3.2 $\pm$ 1.9, P = 0.02) and higher HOMA-B (66.7 $\pm$ 53.5 vs. 45.3 $\pm$ 26.6, P = 0.01) than African Americans. Mean systolic BP (125.3 $\pm$ 12.1 vs. 129.7 $\pm$ 15.8 mmHg, P = 0.06) and diastolic BP (77.4 $\pm$ 8.3 vs. 80.6 $\pm$ 10.3 mmHg, P = 0.04) were lower in white Americans versus African Americans with prediabetes.

Mean serum glucose, insulin, and C-peptide profiles during an OGTT are shown in Fig. 1. Mean fasting serum glucose levels were not different in modestly severely obese white Americans and African Americans with prediabetes (98.1 $\pm$ 10.6 vs. 96.3 $\pm$ 12.2 mg/dL, P = NS). The mean serum glucose level was significantly (P = 0.05–0.004) higher at 30 and 90 min, but not at 120 min, in white Americans than in African Americans (Fig. 1A). White Americans had significantly higher fasting serum insulin

Table 1—Clinical and biochemical parameters of modestly severely obese white Americans and African Americans with prediabetes

Parameters	WAs	AAs	P value
Subjects (n)			
Total	61	84	
Male	11	6	
Female	50	78	
Age (years)	44.7 ± 11.9	46.4 ± 10.2	0.36
Weight (kg)	102.1 ± 21.1	107.2 ± 20.1	0.14
BMI (kg/m^2)	35.0 ± 8.8	38.0 ± 7.9	0.04
Height (cm)	167.5 ± 7.9	166.9 ± 7.2	0.68
% Lean body mass (%)	55.7 ± 5.9	53.5 ± 4.7	0.02
WHR	0.93 ± 0.1	0.90 ± 0.1	0.03
% Body fat (%)	43.9 ± 5.2	46.6 ± 4.6	0.0022
Systolic BP (mmHg)	125.3 ± 12.1	129.7 ± 15.8	0.06
Diastolic BP (mmHg)	77.4 ± 8.3	80.6 ± 10.3	0.04
A1C			
%	5.5 ± 0.5	5.9 ± 0.4	<0.0001
mmol/mol	36.6 ± 3.7	41.0 ± 2.0	<0.0001
HOMA-IR (%)	4.3 ± 2.8	3.2 ± 1.9	0.02
HOMA-B (%)	66.7 ± 53.5	45.3 ± 26.6	0.01

Values are mean ± SD, unless otherwise indicated. AA, African American; WA, white American; WHR, waist-to-hip ratio.

levels (17.2 ± 10.9 vs. 13.1 ± 7.2 μU/mL, $P = 0.03$), but serum insulin levels were nonsignificantly higher at 30, 60, and 120 min (Fig. 1B). However, white Americans had significantly ($P = 0.03$–0.001) higher corresponding fasting and post–glucose challenge serum C-peptide levels during the OGTT (Fig. 1C).

Parameters measured during the FSIVGTT are shown in Table 2. During the FSIVGTT, mean serum glucose, insulin, and C-peptide responses were not different. Mean Si was similar in white Americans versus African Americans (2.6 ± 2.3 vs. 2.9 ± 3.0 × 10^{-4} × min^{-1} [μU/mL]$^{-1}$, P = NS). Although the AIR$_g$ tended to be lower, the mean DI was significantly lower in modestly severely obese white Americans than in modestly severely obese African Americans. In addition, mean Sg and GEZI values were significantly lower in white Americans than African Americans with prediabetes.

Serum lipid and lipoprotein levels are shown in Table 3. Despite comparable Si values, white Americans had significantly higher fasting serum TG levels (116.1 ± 55.5 vs. 82.7 ± 44.2 mg/dL, $P = 0.0002$) and cholesterol/HDL ratio (4.0 ± 1.2 vs. 3.7 ± 0.9, $P = 0.11$). Modestly severely obese white Americans had slightly lower HDL-C and apoA1 levels than African Americans with prediabetes. Furthermore, mean levels of

apoB100, total cholesterol, LDL-C, and non–HDL-C were not different in modestly severely obese white Americans versus African Americans.

Table 3 shows nontraditional cardiometabolic parameters in modestly severely obese white Americans and African Americans with prediabetes. Mean HDL functionality (as assessed by PON1 measurement), oxidized LDL, as well as IL-6 and adiponectin levels were not significantly different in white Americans and African Americans. Although CRP levels tended to be 30% lower in white Americans than in African Americans (6.7 ± 7.0 vs. 8.7 ± 9.8 mg/dL, respectively), the mean differences were not statistically significant.

Correlation Coefficients

We examined the relations among body composition, cardiometabolic parameters, and HDL functionality. The percent lean body mass and the percent fat mass and BMI did not correlate with Si, Sg, AIR$_g$, DI, and levels of lipids, lipoproteins, and PON1 after adjusting for age, sex, and fasting glucose and insulin levels in any of our ethnic groups.

CONCLUSIONS

African Americans experience type 2 diabetes and the associated cardiovascular morbidity and mortality disproportionately more than white Americans (16,17).

However, the exact contributions of obesity to type 2 diabetes and coronary heart disease in African Americans remain debatable. Thus, whether severe obesity differentially modifies the metabolic mediators and precursors of prediabetes, type 2 diabetes, and CVD in African Americans and white Americans remains to be investigated. Given the increasing epidemic of obesity and its potential impact on glucose regulation, prediabetes, and type 2 diabetes among US ethnic and racial populations, we felt it was imperative to perform a comprehensive assessment of clinical and metabolic characteristics of modestly severely obese African Americans and white Americans with prediabetes. Thus, in the current study, we recruited individuals with a BMI >30 kg/m^2 who had prediabetes. These patients had greater than class III obesity with a mean BMI of >35 kg/m^2 and lean body fat >40% in both groups. We found that BMI and the percent body fat were greater in African Americans than in white Americans with prediabetes.

Pathogenic mechanisms underlying prediabetes, impaired glucose tolerance, and type 2 diabetes are characterized by abnormalities in β-cell secretion, hepatic glucose production, and glucose disposal (i.e., insulin-mediated [Si] and non–insulin-mediated [Sg and GEZI] glucose disposal) in patients with prediabetes and type 2 diabetes. These abnormalities are more prevalent in African Americans than white Americans. We (2,3,6,11) and others (4,9,10) have previously shown greater IR (lower Si or higher HOMA-IR) and hyperinsulinemia as well as hepatic glucose overproduction or hepatic IR in healthy nonobese and mildly obese African Americans than white Americans (9). These abnormalities antedated the development of prediabetes and type 2 diabetes in African Americans by decades (2). In the current study, we observed that modestly severely obese African Americans tended to have somewhat lower fasting and post–glucose challenge serum glucose levels when compared with white Americans with prediabetes. However, paradoxically, African Americans had greater A1C levels than white Americans. This finding is similar to those in recent reports (30,31).

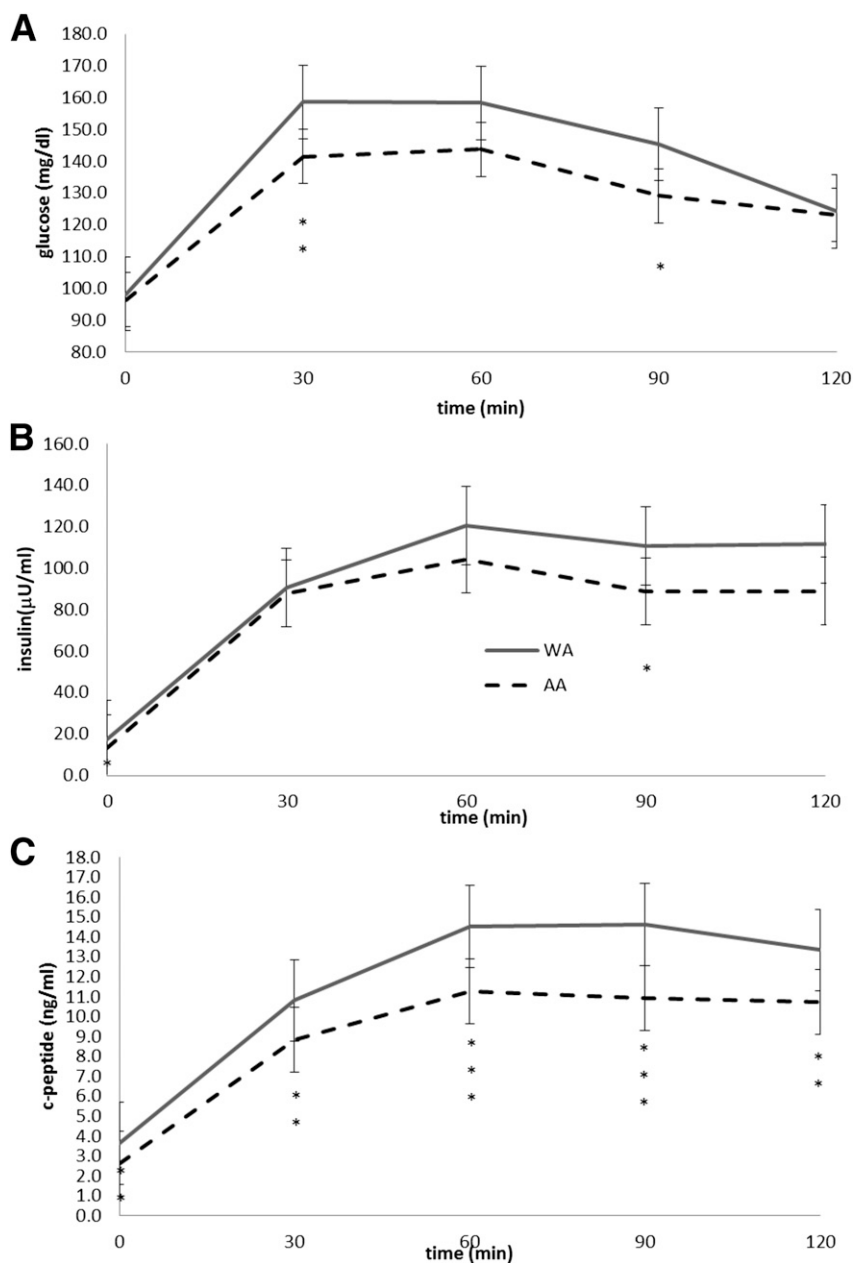In the current study, we found that the mean fasting and post–glucose

Figure 1—Mean $\pm$ SD serum glucose (A), insulin (B), and C-peptide (C) levels during OGTT in modestly severely obese African Americans and white Americans with prediabetes. *$P < 0.03$–0.04, **$P < 0.01$–0.001, ***$P < 0.02$–0.008, African Americans vs. white Americans with prediabetes. AA, African American; WA, white American.

challenge levels, as well as the corresponding serum insulin and C-peptide levels, tended to be lower in modestly severely obese African Americans than white Americans with prediabetes. In this context, in a previous study (2,3,5) in mildly obese or overweight African Americans, we demonstrated that prediabetic subjects had antecedent poor β-cell function (as assessed by serum insulin and C-peptide levels). This was not the case in the current study of modestly severely obese African Americans.

In the current study, the serum insulin and C-peptide response during the OGTT, when corrected for prevailing glucose (insulinogenic index, insulin/glucose, or C-peptide/glucose ratios; data not shown) levels were similar in African Americans and white Americans with prediabetes. To examine in detail β-cell function and insulin sensitivity in modestly severely obese African Americans and white Americans with prediabetes, we performed FSIVGTT in both groups. We found that AIR$_g$ and DI

were higher in African Americans than white Americans with prediabetes. Thus, our modestly severely obese African Americans with prediabetes had astonishingly fairly well preserved β-cell function and the ability to compensate for the prevailing skeletal muscle IR when compared with white American counterparts.

Obesity is a major cause of IR in the general population and patients with type 2 diabetes (1–4). Unlike previous reports, we found no significant differences in Si values in modestly severely obese African Americans and white Americans with prediabetes. It should be noted that previous studies (2,3,5,6,11) have shown that in vivo total body glucose disposal consists of both insulin-mediated (Si) and non–insulin-mediated or glucose-mediated (Sg or GEZI) glucose disposal. In this regard, we have previously demonstrated that, while Si is lower, Sg is higher in healthy African Americans with and without a family history of type 2 diabetes (11). Contrary to the Si, we were therefore intrigued that obese African Americans with prediabetes had significantly higher Sg and GEZI values when compared with white American counterparts. Our data suggest that the greater Sg and GEZI values could serve as important compensatory mechanisms to maintain normal or nearly normal glucose tolerance in modestly severely obese African Americans with prediabetes. The mechanism of the putative greater Sg and GEZI values, however, remains to be elucidated in obese and nonobese African Americans with and without prediabetes.

The typical lipid and lipoprotein profiles associated with obesity, type 2 diabetes, IR, and metabolic syndrome are characterized by higher serum TG and lower HDL-C levels. However, we (27) and others (1,23–26) have reported that insulin-resistant African Americans rather have normal or higher HDL-C and apoA1 levels, and lower serum TG levels than white American counterparts. In the current study, our modestly obese, insulin-resistant African Americans with prediabetes had significantly lower serum TG levels, a normal or higher HDL-C level and HDL/TG ratio, and apoA1 level when compared with their white American counterparts with similar IR (Si). Our findings suggest that the favorable lipid and lipoprotein

Table 2—Metabolic parameters measured during FSIVGTT with MINMOD software in modestly severely obese white Americans and African Americans with prediabetes

Parameters	WAs	AAs	P value
AIR_g ($\times$ min $[\mu U/L]^{-1}$)	531.0 ± 581.6	666.5 ± 516.4	0.26
DI	923.7 ± 542.4	1,502.4 ± 1,311.5	0.0034
Si ($\times 10^{-4} \times min^{-1}$ $[\mu U/mL]^{-1}$)	2.6 ± 2.3	2.9 ± 3.0	0.70
Sg ($\times 10^{-2}$/min)	2.0 ± 0.7	2.5 ± 1.3	0.01
GEZI ($\times 10^{-2}$/min)	1.7 ± 0.7	2.2 ± 1.3	0.03

Values are mean ± SD, unless otherwise indicated. AA, African American; WA, white American.

profiles in the obese and nonobese African Americans appear to be independent of the degree of obesity (22,23,27). We should note that the lower serum TG levels and the normal or higher HDL-C and apoA1 levels in African Americans are also found in other blacks of African ancestry residing in diverse geographic locations (5,8). The reasons for the IR and lipid/lipoprotein paradox in blacks are unknown. In this regard, ethnic and genetic interactions have been implicated in hepatic lipid and lipoprotein synthesis and clearance as possible mechanisms for the paradoxical differences in lipids/lipoproteins in obese and nonobese African Americans and blacks residing in diverse populations (23).

High-density lipoprotein has been regarded as an important antiatherogenic lipoprotein with several critical roles in lipid transport and atherogenesis (12–15). Recently, one of the potential mechanisms for these HDLs—antiatherogenic functions—has been attributed to PON1 activity, which is cosegregated with HDL in the circulation (20,21). PON1 inhibits the oxidation of LDL, suppresses inflammation, improves endothelial function and injury repair (antiapoptotic effect), and enhances reverse cholesterol transport activity (12–14,20,21). Thus, our recent findings that PON1 activity is 50% lower in nondiabetic, postmenopausal African American women than their white American counterparts were unexpected. Our previous study (22) also showed that oxidized LDL and CRP levels were higher in nondiabetic, postmenopausal African American women than in white Americans. These observations suggested that HDL was dysfunctional in African Americans and could play a critical role in atherogenesis in African Americans (22). However, our study and those by other investigators did not examine the potential effects of the severity of obesity on these cardiometabolic markers in African Americans and white Americans with prediabetes. We found in our present study of modestly severely obese subjects with prediabetes that PON1 and oxidized LDL levels were not different in white Americans and African Americans. This was surprising and unexpected. Therefore, we examined some of the additional qualitative functions of HDL such as subclinical inflammation (CRP) and adipocytokines (IL-6). In this regard, previous studies (32–34) have demonstrated higher serum CRP levels in obese African Americans than white Americans. We found in the current study that CRP and IL-6 levels were not statistically significant in modestly severely obese African Americans with prediabetes compared with their white American counterparts. Finally, serum adiponectin, a very potent adipose-derived insulin sensitizer, is associated with lower rates of type 2 diabetes, metabolic syndrome, and CAD. Serum adiponectin levels are lower in African Americans and patients with obesity and IR (35,36). In the current study, adiponectin levels tended to be lower but not significantly different in modestly severely obese African Americans and white Americans with prediabetes. Although the mechanism is unknown, we speculated that adaptive metabolic processes associated with a severe degree of obesity may be partly responsible.

Limitations of the Study

Although our study has several strengths, we also acknowledge some limitations. First, based on our previous studies, we had expected greater IR (Si) and hyperinsulinemia in African Americans with modestly severe obesity and prediabetes than their white American counterparts, but this was not the case. Second, our observation suggests a possible ethnic and racial threshold effect of obesity (BMI) on glucose homeostasis, insulin sensitivity, and lipid and lipoprotein metabolism, as well as cardiometabolic parameters. This hypothesis deserves further elucidation. Third, the study was cross-sectional, and hence cause-effect relations among the degree of obesity and cardiometabolic parameters could not be ascertained. Fourth, the respective putative mechanisms of the paradoxical relationships of IR versus TGs and HDL-C and HDL-C/TG ratio in obese African Americans could not be ascertained in our study. Fifth, we did not measure the visceral abdominal

Table 3—Fasting serum levels of lipids and lipoproteins, HDL functionality (PON1), inflammatory markers, and adipocytokines in modestly severely obese white Americans and African Americans with prediabetes

	WAs	AAs	P value
Cholesterol (mg/dL)	186.2 ± 35.6	185.7 ± 35.6	0.93
TGs (mg/dL)	116.1 ± 55.5	82.7 ± 44.2	0.0002
HDL (mg/dL)	51.2 ± 15.2	52.7 ± 13.0	0.55
LDL (mg/dL)	114.9 ± 27.4	116.8 ± 32.0	0.72
Cholesterol/HDL ratio	4.0 ± 1.2	3.7 ± 0.9	0.11
Non–HDL-C (mg/dL)	138.1 ± 31.1	133.6 ± 34.7	0.42
apoA1 (mg/dL)	146.5 ± 30.4	153.0 ± 26.0	0.19
apoB (mg/dL)	92.3 ± 19.7	90.2 ± 22.8	0.56
PON1 (ng/dL)	0.6 ± 0.3	0.6 ± 0.3	0.89
Oxidized LDL (units/L)	48.7 ± 17.1	46.4 ± 12.5	0.47
CRP (mg/dL)	6.7 ± 7.0	8.7 ± 9.8	0.15
Adiponectin (μg/mL)	7.4 ± 3.7	6.5 ± 3.5	0.21
IL-6 (pg/mL)	1.3 ± 0.8	1.7 ± 1.6	0.07

Values are mean ± SD, unless otherwise indicated. AA, African American; WA, white American.

adiposity that is well established as an important determinant of IR in white Americans, but not in African Americans and other black populations (32–34). Sixth, there was a sex imbalance with more females than males (8–10:1) in both white Americans and African Americans. However, excluding males from our analyses did not change the mean values of the anthropometric and metabolic parameters or the relationships of BMI and the Si and cardiometabolic parameters in both ethnic groups. Finally, the genetic markers for the paradoxical relations of IR and CVD risks in African Americans are not known. Thus, an understanding of the genomic and/or proteomic basis of IR and glucose homeostasis, lipid and lipoprotein synthesis, and catabolism in modestly severely obese African Americans is warranted.

In summary, the current study demonstrated several metabolic paradoxes in modestly severely obese African Americans with prediabetes when compared with their white American counterparts. We found that modestly severely obese African Americans and white Americans with prediabetes had somewhat similar glucose responses and Si values, but required diverse regulatory mechanisms. While white Americans with prediabetes maintained glucose homeostasis via increased β-cell secretion, their African American counterparts had higher non–insulin-mediated glucose disposal. Second, modestly severely obese African Americans with prediabetes showed persistently lower Si and PON1 values as well as paradoxical relationships between Si and HDL-C and TG levels, and HDL-C/TG ratios. In contrast, the insulin-resistant modestly severely obese white Americans maintained the well-established relations between Si and HDL-C and TG levels, and HDL-C/TG ratios.

Conclusion

We conclude that the regulation of glucose homeostasis and lipid/lipoprotein metabolism appears to differ in modestly severely obese African Americans and white Americans with prediabetes. Furthermore, in the current study modestly severely obese African Americans had attenuation in some of the cardiometabolic parameters when compared with white Americans with prediabetes. Nevertheless, the modestly severely obese African Americans with prediabetes

retained the paradoxical relations of Si and HDL-C/TG ratios. We speculate that the pathogenetic mechanisms for glucose intolerance and perhaps atherogenesis appear to be different in modestly severely obese African Americans and white Americans with prediabetes. We suggest that longitudinal studies of underlying putative mechanisms and molecular targets for glucose homeostasis, lipid/lipoprotein metabolism, and HDL functionality in a large sample of obese African Americans and white Americans are warranted.

References

1. DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care 1991;14:173–194
2. Osei K, Rhinesmith S, Gaillard T, Schuster D. Impaired insulin sensitivity, insulin secretion, and glucose effectiveness predict future development of impaired glucose tolerance and type 2 diabetes in pre-diabetic African Americans: implications for primary diabetes prevention. Diabetes Care 2004;27:1439–1446
3. Osei K, Gaillard T, Schuster DP. Pathogenetic mechanisms of impaired glucose tolerance and type II diabetes in African-Americans. The significance of insulin secretion, insulin sensitivity, and glucose effectiveness. Diabetes Care 1997;20:396–404
4. Haffner SM, Howard G, Mayer E, et al. Insulin sensitivity and acute insulin response in African-Americans, non-Hispanic whites, and Hispanics

with NIDDM: the Insulin Resistance Atherosclerosis Study. Diabetes 1997;46:63–69
5. Osei K, Schuster DP. Metabolic characteristics of African descendants: a comparative study of African-Americans and Ghanaian immigrants using minimal model analysis. Diabetologia 1995;38:1103–1109
6. Osei K, Schuster DP. Decreased insulin-mediated but not non-insulin-dependent glucose disposal rates in glucose intolerance and type II diabetes in African (Ghanaian) immigrants. Am J Med Sci 1996;311:113–121
7. Osei K, Schuster DP, Owusu SK, Amoah AG. Race and ethnicity determine serum insulin and C-peptide concentrations and hepatic insulin extraction and insulin clearance: comparative studies of three populations of West African ancestry and white Americans. Metabolism 1997;46:53–58
8. Amoah AG, Owusu SK, Ayittey OM, Schuster DP, Osei K. Minimal model analyses of beta cell secretion, insulin sensitivity and glucose effectiveness in glucose tolerant, non-diabetic first-degree relatives of Ghanaian patients with type 2 diabetes and healthy control subjects. Ethn Dis 2001;11:201–210
9. Ellis AC, Alvarez JA, Granger WM, Ovalle F, Gower BA. Ethnic differences in glucose disposal, hepatic insulin sensitivity, and endogenous glucose production among African American and European American women. Metabolism 2012;61:634–640
10. Lee CC, Haffner SM, Wagenknecht LE, et al. Insulin clearance and the incidence of type 2 diabetes in Hispanics and African Americans: the IRAS Family Study. Diabetes Care 2013;36:901–907
11. Osei K, Schuster DP. Ethnic differences in secretion, sensitivity, and hepatic extraction of insulin in black and white Americans. Diabet Med 1994;11:755–762
12. Wilson PW. High-density lipoprotein, low-density lipoprotein and coronary artery disease. Am J Cardiol 1990;66:7A–10A
13. Lewis GF, Rader DJ. New insights into the regulation of HDL metabolism and reverse cholesterol transport. Circ Res 2005;96:1221–1232
14. Assmann G, Gotto AM Jr. HDL cholesterol and protective factors in atherosclerosis. Circulation 2004;109(Suppl. 1):III8–III14
15. Parthasarathy S. *Modified Lipoproteins in the Pathogenesis of Atherosclerosis.* Austin, TX, R.G. Landers, 1994
16. Gillum RF, Mussolino ME, Madans JH. Coronary heart disease incidence and survival in African-American women and men. The NHANES I Epidemiologic Follow-up Study. Ann Intern Med 1997;127:111–118
17. Gillum RF, Mussolino ME, Madans JH. Diabetes mellitus, coronary heart disease incidence, and death from all causes in African American and European American women: the NHANES I epidemiologic follow-up study. J Clin Epidemiol 2000;53:511–518
18. Flegal KM, Graubard BI, Williamson DF, Gail MH. Excess deaths associated with underweight, overweight, and obesity. JAMA 2005;293:1861–1867
19. Mokdad AH, Bowman BA, Ford ES, Vinicor F, Marks JS, Koplan JP. The continuing epidemics of obesity and diabetes in the United States. JAMA 2001;286:1195–1200

20. Parthasarathy S, Barnett J, Fong LG. High-density lipoprotein inhibits the oxidative modification of low-density lipoprotein. Biochim Biophys Acta 1990;1044:275–283

21. Aviram M, Rosenblat M, Bisgaier CL, Newton RS, Primo-Parmo SL, La Du BN. Paraoxonase inhibits high-density lipoprotein oxidation and preserves its functions. A possible peroxidative role for paraoxonase. J Clin Invest 1998;101:1581–1590

22. Gaillard T, Parthasarathy S, Osei K. HDL dysfunctionality (Paraoxonase) is worse in nondiabetic, postmenopausal African American than in white women. Diabetes Care 2011;34:e19

23. Sumner AE, Finley KB, Genovese DJ, Criqui MH, Boston RC. Fasting triglyceride and the triglyceride-HDL cholesterol ratio are not markers of insulin resistance in African Americans. Arch Intern Med 2005;165:1395–1400

24. Cowie CC, Howard BV, Harris MI. Serum lipoproteins in African Americans and whites with non-insulin-dependent diabetes in the US population. Circulation 1994;90:1185–1193

25. Li C, Ford ES, Meng YX, Mokdad AH, Reaven GM. Does the association of the triglyceride to high-density lipoprotein cholesterol ratio with fasting serum insulin differ by race/ethnicity? Cardiovasc Diabetol 2008;7:4

26. Haffner SM, D'Agostino R Jr, Goff D, et al. LDL size in African Americans, Hispanics, and non-Hispanic whites: the insulin resistance atherosclerosis study. Arterioscler Thromb Vasc Biol 1999;19:2234–2240

27. Gaillard T, Schuster D, Osei K. Differential impact of serum glucose, triglycerides, and high-density lipoprotein cholesterol on cardiovascular risk factor burden in nondiabetic, obese African American women: implications for the prevalence of metabolic syndrome. Metabolism 2010;59:1115–1123

28. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2011;34(Suppl. 1):S62–S69

29. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–419

30. Herman WH, Ma Y, Uwaifo G, et al.; Diabetes Prevention Program Research Group. Differences in A1C by race and ethnicity among patients with impaired glucose tolerance in the Diabetes Prevention Program. Diabetes Care 2007;30:2453–2457

31. Ziemer DC, Kolm P, Weintraub WS, et al. Glucose-independent, black-white differences in hemoglobin A1c levels: a cross-sectional analysis of 2 studies. Ann Intern Med 2010;152:770–777

32. Lovejoy JC, de la Bretonne JA, Klemperer M, Tulley R. Abdominal fat distribution and metabolic risk factors: effects of race. Metabolism 1996;45:1119–1124

33. Jennings CL, Lambert EV, Collins M, Joffe Y, Levitt NS, Goedecke JH. Determinants of insulin-resistant phenotypes in normal-weight and obese Black African women. Obesity (Silver Spring) 2008;16:1602–1609

34. Carroll JF, Fulda KG, Chiapa AL, et al. Impact of race/ethnicity on the relationship between visceral fat and inflammatory biomarkers. Obesity (Silver Spring) 2009;17:1420–1427

35. Hulver MW, Saleh O, MacDonald KG, Pories WJ, Barakat HA. Ethnic differences in adiponectin levels. Metabolism 2004;53:1–3

36. Ferris WF, Naran NH, Crowther NJ, Rheeder P, van der Merwe L, Chetty N. The relationship between insulin sensitivity and serum adiponectin levels in three population groups. Horm Metab Res 2005;37:695–701