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The contribution of race and diabetes status to metabolic flexibility in humans

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Abstract

Factors controlling metabolic flexibility (MF), the ability of the body to switch from fat to carbohydrate oxidation in response to feeding or with insulin administration, are being actively investigated. We sought to determine the effects of race (African American vs Caucasian) and diabetes status (nondiabetic vs type 2 diabetes mellitus individuals) on MF to glucose in humans. Respiratory quotient (RQ) and macronutrient substrate utilization were evaluated by indirect calorimetry during baseline (fasting) and hyperinsulinemic-euglycemic clamp (insulin infusion of 120 $mU \cdot m^{-2} \cdot min^{-1}$); ΔRQ (MF) = clamp RQ − fasting RQ. The study included 168 human subjects of different races (55 African Americans, 113 Caucasians), sex (73 men, 95 women), ages (18-73 years), body mass index (19.3-47.7 kg/m^2), and diabetes status (89 nondiabetic, 79 type 2 diabetes mellitus subjects). Metabolic flexibility was negatively correlated ($P < .01$) with age ($r = -0.41$), fasting RQ ($r = -0.22$), fasting glucose ($r = -0.55$), insulin ($r = -0.40$), and triglyceride ($r = -0.44$) concentrations; whereas a positive association was observed with insulin sensitivity ($r = 0.69$, $P < .0001$). Insulin sensitivity, fasting RQ, triglyceride concentrations, diabetes status, and race accounted for 71% of the variability in MF with insulin sensitivity being the main determinant factor (model $R^2 = 0.48$, $P < .0001$). After controlling for the significant predictors, MF was higher in African Americans vs Caucasians (mean ± SEM 0.080 ± 0.004 vs 0.069 ± 0.002, $P = .008$) and in nondiabetic vs type 2 diabetes mellitus subjects ($P = .003$). This study confirms that insulin sensitivity is the major contributor to MF in humans, but provides the novel findings that African Americans have significantly greater MF than Caucasians even after adjusting for insulin sensitivity and diabetes status.

1. Introduction

Metabolic flexibility (MF) is characterized by increased fat oxidation in skeletal muscle during fasting conditions and the ability to switch from fat to carbohydrate oxidation in response to a meal or insulin [1]. Factors that control MF are felt to reside at the mitochondrial level, as prior research suggests that insulin resistance and metabolic inflexibility are potentially caused by mitochondrial impairments in obesity and type 2 diabetes mellitus [2,3]. Previous research suggested that lean individuals had greater MF than obese individuals [4]. Specifically, lean individuals were able to successfully switch from primarily oxidizing fat during the fasting state (lower respiratory quotient [RQ]) to glucose during the insulin-stimulated state (higher RQ). In addition, there were reports of reduced MF in nondiabetic individuals with a family history of type 2 diabetes mellitus [5] and individuals with type 2 diabetes mellitus [6] when compared with nondiabetic individuals without a family history of type 2 diabetes mellitus and nondiabetic obese individuals. The reduced MF that was observed in the individuals with type 2 diabetes mellitus was mainly explained by the glucose disposal rate [6]. Galgani and colleagues [7] suggested that the glucose disposal rate, baseline fasting RQ, and steady-state plasma free fatty acid concentrations were important contributing factors to MF. Although the effects of body mass index (BMI) and diabetes status on MF have been observed, the contribution of race to MF has been less explored.

African Americans have a higher prevalence of obesity [8] and type 2 diabetes mellitus [9] than Caucasians. The reasons for this disparity are not precisely known, but some possible explanations may be that African Americans have lower skeletal muscle fatty acid oxidation [10], resting metabolic rate [11], insulin sensitivity [12], and higher 24-

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hour RQ [13]. To our knowledge, only one study [14] has reported results on race and MF. Specifically, Berk et al [14] observed that obese African American women were not able to efficiently switch between fat oxidation during the fasting state and carbohydrate oxidation during a fed and insulin-stimulated state, suggestive of reduced MF in this African American population. This study was restricted to a small group of premenopausal, nondiabetic, obese, and healthy women. Whether these effects are considered to be applicable to the general population encompassing a wide range of phenotypes and levels of glycemia are unknown. Thus, we sought to determine the effect of race and diabetes status on MF in a larger cohort of African Americans and Caucasians consisting of both sexes, a wide range for BMI and insulin sensitivity, and diabetes status (nondiabetic vs type 2 diabetes mellitus individuals).

2. Subjects and methods

2.1. Subjects

The study population comprised 168 individuals (55 African Americans, 113 Caucasians) with a wide range of characteristics. The characteristics included the following: (1) sex (73 men, 95 women), (2) ages (18-73 years), (3) BMI (19.3-47.7 kg/m^2), and (4) diabetes status (89 nondiabetic, 79 type 2 diabetes mellitus individuals). If the subject had a history of type 2 diabetes mellitus, he/she was required to be on dietary therapy only, that is, drug naïve, with a fasting plasma glucose between 125 mg/dL (6.94 mmol/L) and 175 mg/dL (9.72 mmol/L). Diabetes status was confirmed by an oral glucose tolerance test. Exclusions were as follows: (1) medications known to affect glucose metabolism; (2) untreated thyroid or chronic liver, renal, or cardiovascular disease; and (3) a history of drug and/or alcohol abuse, or psychiatric disease prohibiting adherence to study protocol. The study protocol was approved and conducted in strict compliance with Pennington Biomedical Research Center's (PBRC's) Institutional Review Board for human subjects.

2.2. Study design

After subjects gave written consent, they underwent a physical examination, resting electrocardiogram, 75-g oral glucose tolerance test, and routine blood and urine chemistries. After passing screening criteria, subjects had body fat and fat-free mass measured by dual-energy x-ray absorptiometry (Hologic QDR 4500A, Bedford, MA). All evaluations were performed after a 12-hour overnight fast. Individuals were then admitted to the PBRC inpatient unit the evening before their testing day. After admission, the subjects consumed a eucaloric standardized meal with a macronutrient composition of 50% carbohydrates, 35% fat, and 15% protein prepared by the metabolic kitchen. The following morning, after a 12-hour fast, each participant had insulin sensitivity and MF assessed.

2.3. Insulin sensitivity

Hyperinsulinemic-euglycemic clamps [15] were performed to assess insulin sensitivity. After a 12-hour overnight fast, an intravenous catheter was placed in an antecubital vein for infusion of insulin and glucose. A second catheter was inserted in a dorsal vein of the contralateral arm for blood withdrawal. The hand was placed between a heating pad for arterialization of venous blood sampling. During the 45-minute fasting state, blood samples were collected every 15 minutes. Insulin was then administered at a primed-continuous infusion rate of $120 \cdot mU \cdot m^{-2} \cdot min^{-1}$ for 2 hours and blood samples were collected every 5 minutes during this period. Arterialized serum glucose was measured periodically and a variable infusion of dextrose (20% solution) was given to maintain serum glucose concentrations at approximately 100 mg/dL (5.6 mmol/L). During the steady state (last 30 minutes of clamp), the mean rate of exogenous glucose infusion was corrected for changes in glycemia and divided by fat-free mass to assess insulin sensitivity.

2.4. Metabolic flexibility

Resting metabolic rate (RMR), RQ, and substrate oxidation of carbohydrate and fat were determined by indirect calorimetry using a Deltatrac II instrument (Sensor Medics, Helsinki, Finland) [16]. The ventilated hood technique was used. Indirect calorimetry (ie, RMR, RQ, and substrate utilization) was assessed 45 minutes before the insulin/glucose infusion (fasting state of clamp) and after the insulin/glucose infusion (ie, last 45 minutes of the clamp). The adaptation period under the hood was the first 15 minutes and data were collected during the last 30 minutes (ie, the average values were used). The ratio of the respiratory gases ($RQ = CO_{2produced}/O_{2consumed}$) was analyzed and used to predict changes in carbohydrate and fat substrate utilization. Whole-body MF to glucose was calculated as the change in RQ from the fasting to insulin-stimulated states (ΔRQ = insulin-stimulated RQ − fasting RQ). The change in carbohydrate and fat oxidation was calculated similarly to the ΔRQ. Fat and carbohydrate oxidation was calculated as described by Jequier et al [16]. Urinary nitrogen excretion was estimated based on an assumption that protein metabolism was 15% of RMR.

2.5. Statistical analysis

Baseline characteristics of African Americans vs Caucasians stratified by presence and absence of diabetes were reported. Two-sample t tests were used to compare the means of metabolic and physiologic parameters for African Americans vs Caucasians within diabetes status strata. Pearson correlation was used to assess the relationships between MF and measured variables. A stepwise multiple regression analysis was then performed to determine the best predictors of MF. This provided a platform for evaluating the MF association with each predictor variable adjusted for all

other predictors in the regression model. Differences between the groups during the fasting and insulin-stimulated states (including the change) were evaluated by repeated-measures analysis of variance. Statistical significance was assumed at $P \leq .05$. All statistical analyses were performed using SAS version 9.1.3 (SAS Institute, Cary, NC).

3. Results

3.1. Subject characteristics

Table 1 lists the metabolic and physiologic parameters for the entire cohort. None of the parameters for the women were significant except that the nondiabetic

Table 1

A. Baseline characteristics of the African Americans vs Caucasian women in the study sample

	No diabetes		Type 2 diabetes mellitus		Overall range
	African American n = 25	Caucasian n = 30	African American n = 15	Caucasian n = 25	
BMI status, kg/m^2 (<25/≥ 25)	6/19	10/20	0/15	3/22	–
Age, y	39 ± 2	44 ± 3	55 ± 2	58 ± 1	18-73
Body weight, kg	89.6 ± 4.2	85.6 ± 4.4	88.5 ± 3.2	83.5 ± 2.8	52.3-140.1
BMI, kg/m^2	32.8 ± 1.5	32.1 ± 1.5	33.0 ± 1.2	31.8 ± 1.0	20.1-46.6
Body fat, %	38.2 ± 1.7	40.1 ± 1.3	41.2 ± 0.8	40.2 ± 1.1	21.7-51.2
Fat mass, kg	36.3 ± 2.9	36.2 ± 2.7	37.0 ± 1.9	34.7 ± 1.8	12.8-71.8
Fat-free mass, kg	54.7 ± 1.4	50.9 ± 1.8	52.2 ± 1.6	50.4 ± 1.2	36.3-75.9
Fasting					
Glucose, mg/dL	94.7 ± 1.5	95.7 ± 1.5	117.5 ± 5.2	125.4 ± 3.4	76.8-165.3
Insulin, μU/mL	13.3 ± 1.3	11.4 ± 1.1	18.1 ± 2.8	22.5 ± 3.7	3.2-82.3
FFA, mmol/L	0.56 ± 0.03	0.56 ± 0.04	0.57 ± 0.03	0.58 ± 0.03	0.06-1.13
Triglycerides, mg/dL	74.9 ± 5.5	145.1 ± 13.2*	140.3 ± 20.7	164.8 ± 13.3	33.0-356.0
Cholesterol, mg/dL	192.6 ± 8.1	209.3 ± 6.6	206.0 ± 10.6	210.2 ± 6.8	121.0-304.0
LDL, mg/dL	114.8 ± 7.4	122.9 ± 6.1	113.6 ± 7.2	120.3 ± 6.0	54.4-217.6
HDL, mg/dL	62.8 ± 2.6	57.4 ± 2.5	64.3 ± 4.8	57.0 ± 2.3	38.5-101.2
Steady state					
Glucose, mg/dL	102.2 ± 1.2	101.7 ± 0.9	96.5 ± 1.3	98.8 ± 0.9	83.8-112.7
Insulin, μU/mL	235.8 ± 7.8	226.8 ± 8.5	234.2 ± 9.8	241.6 ± 13.4	151.2-423.7
Insulin sensitivity, mg·kg FFM^{-1}·min^{-1}	11.7 ± 0.6	11.7 ± 0.7	6.2 ± 0.4	6.4 ± 0.4	3.0-19.5

B. Baseline characteristics of the African American vs Caucasian men in the study sample

	No diabetes		Type 2 diabetes mellitus		Overall range
	African American n = 11	Caucasian n = 23	African American n = 4	Caucasian n = 35	
BMI status, kg/m^2 (<25/≥25)	6/5	9/14	0/4	4/31	–
Age, y	31 ± 3	41 ± 3	58 ± 2	59 ± 1	18-69
Body weight, kg	91.6 ± 9.0	92.8 ± 3.8	100.1 ± 8.2	95.2 ± 2.3	59.0-144.6
BMI, kg/m^2	29.0 ± 3.0	29.3 ± 1.4	31.1 ± 2.5	31.0 ± 0.7	19.3-47.7
Body fat, %	20.8 ± 4.0	26.7 ± 1.8	24.0 ± 2.9	28.6 ± 0.8	7.8-46.6
Fat mass, kg	22.8 ± 6.2	26.4 ± 2.6	25.1 ± 5.1	27.8 ± 1.3	5.1-60.9
Fat-free mass, kg	70.7 ± 3.7	67.7 ± 1.5	76.9 ± 3.4	67.5 ± 1.3‡	53.6-96.8
Fasting					
Glucose, mg/dL	95.6 ± 2.5	97.4 ± 1.1	133.3 ± 10.2	124.2 ± 2.8	82.5-158.5
Insulin, μU/mL	8.3 ± 1.6	13.0 ± 1.8	11.9 ± 2.2	16.1 ± 1.2	2.9-37.4
FFA, mmol/L	0.53 ± 0.06	0.48 ± 0.04	0.64 ± 0.09	0.54 ± 0.03	0.21-1.07
Triglycerides, mg/dL	86.4 ± 10.6	152.6 ± 19.9†	164.8 ± 33.1	147.5 ± 13.8	32.0-383.0
Cholesterol, mg/dL	165.5 ± 9.8	204.1 ± 8.5†	187.5 ± 2.1	191.7 ± 8.1	99.0-356.0
LDL, mg/dL	96.6 ± 7.2	127.8 ± 6.9†	110.0 ± 6.3	113.5 ± 7.2	43.0-248.8
HDL, mg/dL	51.5 ± 3.2	45.7 ± 1.7	44.5 ± 2.2	48.8 ± 1.8	30.6-73.8
Steady state					
Glucose, mg/dL	101.2 ± 2.1	102.5 ± 0.8	94.9 ± 4.7	98.0 ± 0.6	82.5-111.0
Insulin, μU/mL	209.5 ± 12.9	227.0 ± 8.3	199.4 ± 34.2	217.7 ± 7.2	119.3-288.8
Insulin sensitivity, mg·kg FFM^{-1}·min^{-1}	11.4 ± 0.8	9.1 ± 0.6†	4.8 ± 1.4	5.7 ± 0.4	2.2-16.8

Multipliers for conversion to International System of Units: glucose, 0.0556 (millimoles per liter); insulin, 7.175 (picomoles per liter); triglycerides, 0.0113 (millimoles per liter); cholesterol, LDL, and HDL, 0.0259 (millimoles per liter). Data are reported as unadjusted values and mean ± SEM. FFA indicates free fatty acid; HDL, high-density lipoprotein.

* African Americans vs Caucasians without diabetes, $P < .0001$.

† African Americans vs Caucasians without diabetes, $P < .03$.

‡ African Americans vs Caucasians with diabetes, $P = .03$.

African Americans had lower triglyceride levels than the Caucasians. The nondiabetic men who were African American had lower triglyceride, cholesterol, and low-density lipoprotein levels and higher insulin sensitivity when compared with the Caucasians. In addition, the African American men with type 2 diabetes mellitus had a higher fat-free mass than the Caucasian men with type 2 diabetes mellitus.

3.2. Relationships between MF and metabolic parameters

For the entire cohort, MF was inversely related to age ($r = -0.41$, $P < .0001$), fasting RQ ($r = -0.22$, $P = .005$), fasting glucose ($r = -0.55$, $P < .0001$), insulin ($r = -0.40$, $P < .0001$), and triglyceride ($r = -0.44$, $P < .0001$) concentrations, but positively correlated with insulin sensitivity ($r = 0.69$, $P < .0001$). When evaluating the correlation coefficients for each race separately, MF remained negatively and significantly correlated to age, fasting glucose, insulin, and triglyceride concentrations and positively correlated to insulin sensitivity for both racial groups. In Caucasians only, MF was negatively and significantly correlated to fasting RQ. In addition, when race was evaluated by sex, MF was positively correlated to insulin sensitivity in the African American and Caucasian women and also the Caucasian men. (Fig. 1A and B). However, only a trend existed for the African American men (Fig. 1B).

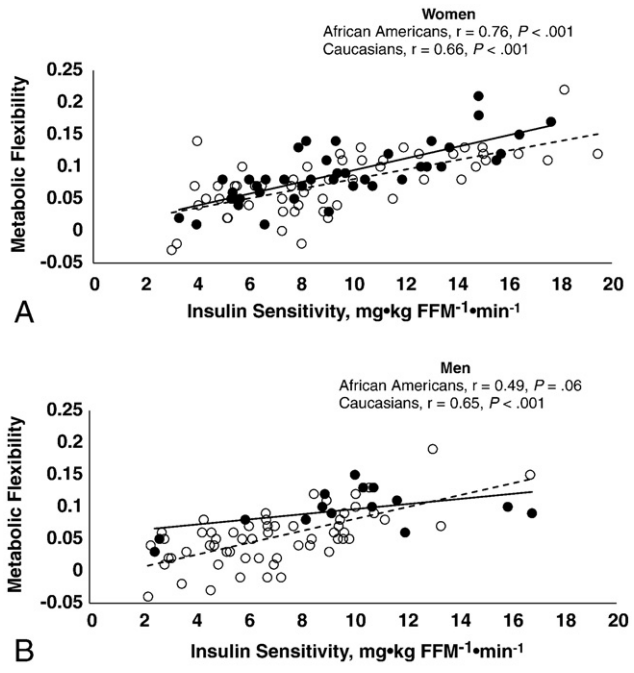

Fig. 1. Correlation analysis between MF (insulin-stimulated RQ − fasting RQ) and insulin sensitivity. A, Women (n = 95). B, Men (n = 73). African Americans, black circles and solid black line; Caucasians, open circles and dashed line.

Table 2
Predictors of MF

	Partial R^2	Model R^2	Parameter estimate ± SEM	P value
Insulin sensitivity, mg·kg FFM^{-1}·min^{-1}	0.48	0.48	0.0067 ± 0.0007	<.0001
Fasting RQ	0.14	0.62	−0.5114 ± 0.0585	<.0001
Triglycerides, mg/dL	0.05	0.67	−0.0001 ± 2.8E-05	<.0001
Diabetes status				
No diabetes vs type 2 diabetes mellitus	0.02	0.70	0.0179 ± 0.0052	.0004
Race				
African Americans vs Caucasians	0.01	0.71	−0.0112 ± 0.0045	.0131

Linear statistical model (stepwise multiple regression) with 5 variables for predicting MF.

3.3. Metabolic flexibility

3.3.1. Predictors

Age, sex, diabetes status, fasting RQ, insulin sensitivity, fasting glucose, insulin, and triglyceride concentrations were the included variables in the stepwise multiple regression analysis. The only variables that remained significant in the model were insulin sensitivity, fasting RQ, triglyceride concentrations, diabetes status, and race (Table 2). Sex was not a significant predictor of MF. The predictors of MF explained 71% of the variability in MF with 48% being attributed to insulin sensitivity. Similar results were found after applying the same analysis to the change in nonprotein RQ (results not reported).

3.3.2. Race

After adjustments for diabetes status, fat, and fat-free mass, the fasting RQ between the races did not differ (Fig. 2A). However, after insulin stimulation, there was a difference between the racial groups. The ΔRQ (ie, MF) was greater for African Americans vs Caucasians and remained significantly greater after controlling for insulin sensitivity, fasting RQ, triglyceride concentrations, and diabetes status (adjusted values: 0.080 ± 0.004 vs 0.069 ± 0.002; Fig. 2B, raw data or unadjusted values graphed).

3.3.3. Diabetes status

After adjustments for race, fat, and fat-free mass, the fasting RQ between individuals without diabetes and with type 2 diabetes mellitus did not differ. However, there was a difference between the groups after insulin stimulation (adjusted values: no diabetes, 0.928 ± 0.005; type 2 diabetes mellitus, 0.866 ± 0.004; $P < .0001$). Metabolic flexibility was higher in subjects without diabetes vs subjects with type 2 diabetes mellitus (unadjusted values: 0.099 ± 0.004 vs 0.044 ± 0.004, $P < .0001$) and remained significant after adjusting for all the metabolic predictors of MF (adjusted values: 0.083 ± 0.003 vs 0.065 ± 0.004, $P = .003$).

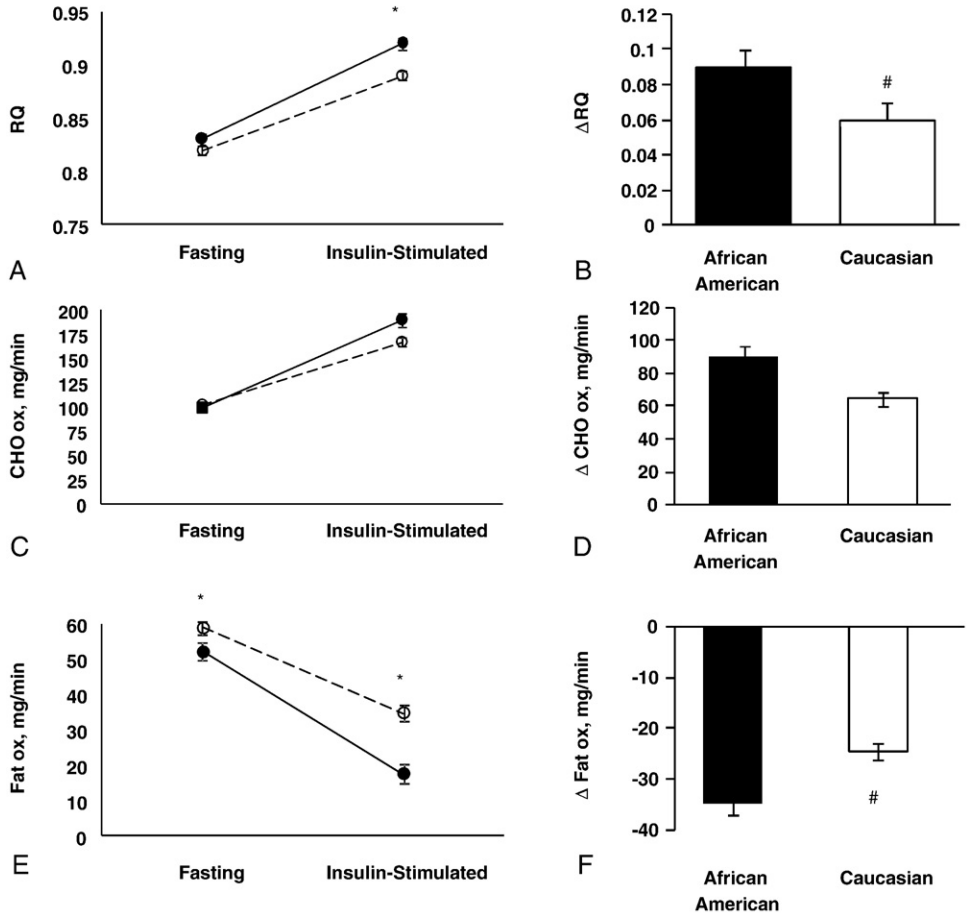

Fig. 2. The raw data (unadjusted values) are presented in the figure for RQ, carbohydrate oxidation, and fat oxidation. However, the *P* value is based on the adjusted values. A, C, and E, Fasting and insulin-stimulated conditions in African Americans (black circle and black line, n = 55) vs Caucasians (open circle and dotted line, n = 113); $^{*}P \leq .03$, adjusted for diabetes status, fat, and fat-free mass. B, D, and F, Change (Δ) in RQ, carbohydrate oxidation, and fat oxidation in African Americans and Caucasians; $\#P \leq .02$, adjusted for insulin sensitivity, fasting variable (RQ, carbohydrate, or fat), fasting triglyceride concentrations, and diabetes status. CHO indicates carbohydrate; ox, oxidation.

3.4. Carbohydrate and fat oxidation

The fasting and insulin-stimulated carbohydrate oxidation did not differ after adjusting for diabetes status, fat, and fat-free mass (Fig. 2C). In addition, there were no racial differences in the Δcarbohydrate oxidation (Fig. 2D). The fasting and insulin-stimulated fat oxidation was different between the African Americans and Caucasians (Fig. 2E). The Δfat oxidation was higher for African Americans vs Caucasians and remained significantly higher after controlling for insulin sensitivity, fasting fat oxidation, fasting triglyceride concentrations, and diabetes status (adjusted values: −31.48 ± 1.60 vs −25.77 ± 1.06; Fig. 2F, raw data or unadjusted values graphed).

3.5. Resting metabolic rate

After adjusting for diabetes status, sex, fat mass, fat-free mass, and age, the fasting RMR (adjusted: 1486 ± 33 vs 1668 ± 18, $P < .0001$) was lower for African Americans vs Caucasians. After insulin stimulation, the RMR (adjusted: 1561 ± 33 vs 1738 ± 18, $P < .0001$) remained lower for African Americans vs Caucasians. The ΔRMR was not statistically significant between the racial groups.

4. Discussion

In this study, we confirmed that insulin sensitivity was the main predictor of whole-body MF to glucose as previously reported [6]. In addition, metabolic factors such as fasting RQ and fasting triglyceride concentrations contributed to MF. Although the contribution was small, diabetes status and race were also significant determinant factors. Specifically, our data suggest that in response to an insulin/glucose infusion, MF was higher in African Americans and nondiabetic individuals as opposed to Caucasians and type 2 diabetes mellitus individuals.

Racial differences were also observed in another study [14]. However, Berk et al [14] concluded that African Americans had reduced MF (ie, metabolic inflexibility)

when compared with Caucasians and did not suppress fatty acid oxidation in response to a dose of insulin. In addition, African Americans had a defect in substrate switching when dietary fat was increased, whereas this switch was apparent in Caucasians. Comparison of the current study data to previous data [14] was not feasible because of the definition of MF, dose of insulin to evaluate MF, fasting RQ between races, sample size, and phenotype of the population.

The current study evaluated MF as the change in RQ from the fasting to insulin-stimulated states (ΔRQ = insulin-stimulated RQ − fasting RQ) and this change was not evaluated in the reported study of Berk et al [14]. The goal of our study was to evaluate insulin sensitivity with the use of a 1-step high-dose insulin infusion (120 $mU \cdot m^{-2} \cdot min^{-1}$). With the high-dose insulin infusion, suppression of free fatty acids should be maximal. However, the objective of the study conducted by Berk et al [14], as discussed above, was to assess lipolysis by infusing 2 lower insulin doses (2 and 8 $mU \cdot m^{-2} \cdot min^{-1}$). The average insulin levels for the study of Berk et al [14] were approximately 6 μU/mL (40.8 pmol/L) for the lower insulin dose and 17 μU/mL (125 pmol/L) for the higher dose. Thus, there were marked differences in insulin levels evaluated between the 2 studies. Due to the current study's high insulin levels (average >200 μU/mL) during the steady state, we were not able to evaluate the suppression of free fatty acids between the 2 studies. Unlike the previous study [14], the current study did not detect any racial differences at the fasting RQ. It has been suggested that fasting RQ can be influenced by the diet consumed before the testing procedure [17-19]. In addition, the study by Berk et al [14] was limited to a specific population of 18 participants (9 African Americans and 9 Caucasians) that were premenopausal and obese women, whereas the current study included a larger population of men and women with different ranges of age, BMI, and insulin sensitivity.

Another important finding in the present study was that insulin sensitivity accounted for majority of the total variability in MF as previously reported [6]. In addition, a smaller portion of the variability was contributed from diabetes status (nondiabetic vs type 2 diabetes mellitus individuals), fasting triglyceride concentrations, fasting RQ, and race. However, Galgani et al [6] did not observe race and diabetes status as being significant predictors of MF. In the current and previous [6] studies, during a hyperinsulinemic-euglycemic clamp, MF was greater for nondiabetic vs type 2 diabetes mellitus individuals. After controlling for the main predictor of MF (ie, insulin sensitivity), the differences between the groups remained significant for the current study and disappeared in the previous study [6]. The discrepancy in these findings could possibly be due to the previous study's [6] smaller sample size (42 nondiabetic and 59 diabetic individuals) that may have limited the power to examine a change between groups and the ability of the regression model to detect other determinants of MF.

The strengths of the current study were the large number of individuals with a broad range of insulin sensitivity, stratification of race, and the detection of 71% of the variability in MF. Although 71% of the total variability in MF was explained in our analytical model, we recognize that other variables not tested in the current study may be contributors to MF. In addition, we evaluated one facet of whole-body MF, which was the ability of the body to switch from fat to carbohydrate oxidation after an insulin/glucose infusion (hyperinsulinemic-euglycemic clamp). Metabolic flexibility to a high-carbohydrate and high-fat meal and/or diet was not evaluated, but they have been suggested as other measurements of MF [5,13,20].

In conclusion, our data support previous findings that suggest insulin sensitivity is the main contributor of MF in humans. However, the novelty of these data is that race and diabetes status are also significant contributors, although the contribution is considered small in comparison to insulin sensitivity. We demonstrated that African Americans have a higher MF after insulin stimulation than Caucasians. These differences remained after controlling for the known physiologic factor (ie, insulin sensitivity) modulating MF. Thus, this study provides evidence that racial differences and diabetes status should be considered when evaluating MF. The mechanisms and genetic factors contributing to the racial disparity in MF are not precisely known and further mechanistic and genetic research studies are warranted.

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