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Ethnic differences in glucose disposal, hepatic insulin sensitivity, and endogenous glucose production among African American and European American women

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ABSTRACT

Intravenous glucose tolerance tests have demonstrated lower whole-body insulin sensitivity (S_I) among African Americans (AA) compared with European Americans (EA). Whole-body S_I represents both insulin-stimulated glucose disposal, primarily by skeletal muscle, and insulin's suppression of endogenous glucose production (EGP) by liver. A mathematical model was recently introduced that allows for distinction between disposal and hepatic S_I. The purpose of this study was to examine specific indexes of S_I among AA and EA women to determine whether lower whole-body S_I in AA may be attributed to insulin action at muscle, liver, or both. Participants were 53 nondiabetic, premenopausal AA and EA women. Profiles of EGP and indexes of Disposal S_I and Hepatic S_I were calculated by mathematical modeling and incorporation of a stable isotope tracer ([6,6-$^2H_2$]glucose) into the intravenous glucose tolerance test. Body composition was assessed by dual-energy x-ray absorptiometry. After adjustment for percentage fat, both Disposal S_I and Hepatic S_I were lower among AA ($P = .009$ for both). Time profiles for serum insulin and EGP revealed higher peak insulin response and corresponding lower EGP among AA women compared with EA. Indexes from a recently introduced mathematical model suggest that lower whole-body S_I among nondiabetic AA women is due to both hepatic and peripheral components. Despite lower Hepatic S_I, AA displayed lower EGP, resulting from higher postchallenge insulin levels. Future research is needed to determine the physiological basis of lower insulin sensitivity among AA and its implications for type 2 diabetes mellitus risk.

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1. Introduction

Compared with European Americans (EA), African Americans (AA) are twice as likely to be diagnosed with type 2 diabetes mellitus (T2D) [1]. In particular, AA women have higher prevalence rates of T2D than any other sex-ethnic group [2]. The reasons for this disparity are not clear, but ethnic differences in tissue sensitivity to insulin may play a role.

Author contributions: BAG designed the study and supervised all aspects of the project. ACE analyzed the data and prepared the manuscript. JAA performed data analyses and provided input into manuscript preparation. WMG performed mathematical modeling of the data. FO served as study physician and provided conceptual advice. All authors contributed to the interpretation and implications of these results as well as the review of the manuscript.

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Indexes of whole-body insulin sensitivity (S_I) and glucose effectiveness (S_g) can be estimated by mathematical modeling of glucose and insulin values from an intravenous glucose tolerance test (IVGTT) [3,4]. Previous studies that have estimated S_I by the traditional 1-compartment minimal model have consistently shown lower whole-body S_I among healthy AA compared with EA, independent of body composition [5-8]. However, the 1-compartment model is not ideal for comparing groups such as EA and AA that differ regarding the magnitude of the postchallenge insulin response [9] because of overestimation of the effects of glucose itself (S_g) in subjects with a higher insulin response [10,11]. Furthermore, the 1-compartment minimal model assesses S_I only at the whole-body level. Whole-body S_I comprises insulin action both to promote glucose uptake as well as to suppress endogenous glucose production (EGP) by the liver [12]. Whether lower S_I among AA represents impairment in glucose uptake or hepatic glucose production is not known. Discerning whether lower S_I among AA relates to hepatic or peripheral glucose regulation could help elucidate the etiology behind racial/ethnic differences in T2D.

When a stable isotope tracer is included in the IVGTT, a 2-compartment model can be used to provide an index of disposal-specific S_I and a more reliable index of S_g [13,14]. In 2005, researchers expanded on the traditional 2-compartment minimal model by describing EGP from tracer-labeled IVGTT data [15]. In 2009, Tokuyama and colleagues [16] further developed the 2-compartment model framework by introducing model-derived S_I indexes specific to hepatic glucose regulation. Thus, these latest advances in 2-compartment modeling offer the opportunity to provide novel data comparing disposal-specific S_I, hepatic S_I, and hepatic glucose production in AA and EA.

The aim of this study was to describe insulin action and hepatic glucose metabolism among nondiabetic, premenopausal women of AA and EA ancestry using a recently introduced integrated model [16] with the goal of determining whether lower S_I among AA may be attributed to either hepatic or peripheral sensitivity to insulin.

2. Methods

2.1. Participants

Fifty-three nondiabetic, premenopausal women were categorized by ethnicity as AA or EA based on self-report and assertion that both parents shared the same ethnicity as the participant. Normal glucose tolerance was verified by 2-hour oral glucose tolerance testing, and premenopausal status was confirmed by serum follicle-stimulating hormone concentration less than or equal to 35 IU/mL in addition to self-report of regular menstrual cycles. Exclusion criteria included history of polycystic ovary disease, hypoglycemia, and any medication known to influence glucose metabolism (including oral contraceptives). All participants provided oral and written consent, and the study was approved by the Institutional Review Board for Human Use at the University of Alabama at Birmingham.

2.2. Protocol

For 3 days before testing, participants were instructed to consume approximately 250 g carbohydrates. The evening before testing, they reported to the General Clinical Research Center. After a 12-hour overnight fast, metabolic parameters were determined by insulin-modified IVGTT. Body composition was assessed by dual-energy x-ray absorptiometry (DXA; Lunar Prodigy, GE Healthcare, Madison, WI), and scans were analyzed with software version 1.5.

2.3. Intravenous glucose tolerance test

For the IVGTT, flexible intravenous catheters were placed in the antecubital spaces of both arms. Blood was sampled 3 times over 15 minutes; and averages of these 3 fasting samples were used to determine fasting glucose, insulin, and C-peptide concentrations. At time zero, a bolus of glucose (50% dextrose, 270 mg/kg, plus [6,6-$^2H_2$]glucose, 30 mg/kg) was infused intravenously. Insulin (0.02 U/kg) was administered intravenously over a 5-minute period from 20 to 25 minutes after the glucose injection. Blood was sampled at the following times (minutes) following glucose administration: 2, 3, 4, 5, 6, 8, 10, 12, 15, 19, 20, 21, 22, 24, 26, 28, 30, 35, 40, 45, 50, 55, 60, 70, 80, 100, 120, 140, 180, 210, and 240, for a total of 34 samples). Sera were stored at –85°C until laboratory analysis of glucose and insulin.

Acute insulin response to glucose (AIRg), the integrated incremental area under the curve for insulin during the first 10 min of the IVGTT, was calculated using the trapezoidal method. An integrated 2-compartment mathematical model [16] was used to estimate the time course of EGP in milligrams per kilogram per minute. Endogenous glucose production primarily reflects hepatic glucose production [17,18]. Indexes of S_I specific to glucose disposal (Disposal S_I) and hepatic insulin action (Hepatic S_I) were calculated [16]. The same model was used to derive indexes of disposal and hepatic S_g (Disposal S_g and Hepatic S_g) as estimates of the ability of glucose itself to promote disposal and suppress EGP, respectively. Details of the integrated 2-compartment minimal model have been previously described by Tokuyama et al [16], and indexes from the model are summarized by the following equations:

$$\mathrm{EGP}(t) = k_{\mathrm{out}}[1 - H_2(t)]G_{\mathrm{L}}(t)$$

$$\text{Disposal } S_g = S^{2^*}{}_{\mathrm{G}} = V_1\left(k_p + k_{21}k_{02} / (k_{02} + k_{12})\right)$$

$$\text{Disposal } S_I = S^{2^*}{}_{\mathrm{I}} = V_1 s_k k_{21} k_{12} / (k_{02} + k_{12})^2$$

$$\text{Hepatic } S_g = hS^2{}_{\mathrm{G}} = -\partial \mathrm{EGP}(t) / \partial G(t) = k_{\mathrm{in}} / 4G_b$$

$$\text{Hepatic } S_I = hS^2{}_{\mathrm{I}} = \partial^2 \mathrm{EGP}(t) / \partial G(t)\, \partial I(t) = S_I^2 * hS^2{}_{\mathrm{G}} / \left(S^{2^*}{}_{\mathrm{G}+} hS^2{}_{\mathrm{G}}\right)$$

IC_{50} is representative of insulin action required for 50% inhibition of EGP. H_2 represents a function of insulin's

inhibitory effect on EGP ($H_2 = x(t)/[IC50 + x(t)]$), and G_L signifies available glucose in the liver.

V_1 is the volume of the accessible compartment; s_k is a parameter of insulin action; and k_p, k_{02}, k_{12}, and k_{21} are rate constant parameters.

Basal glucose is quantified by G_b, whereas k_{in} and k_{out} are rate constants of hepatic glucose production and hepatic glucose loss, respectively.

Data were modeled using SCIENTIST software (version 2.01; Micromath Research, St. Louis, MO). For each participant, Disposal S_I and Hepatic S_I from the 2-compartment model were summed to yield a value for Total S_I. A surrogate index for fasting hepatic insulin resistance was calculated by multiplying basal EGP by fasting insulin concentration as previously described [19].

2.4. Laboratory analyses

All analyses were performed in the Core Laboratories of the General Clinical Research Center, Nutrition Obesity Research Center, and Diabetes Research and Training Center. Glucose was measured in 10 μL sera using the Ektachem DT II analyzer (Johnson and Johnson Clinical Diagnostics, Rochester, NY). This analysis had a mean intraassay coefficient of variation (CV) of 0.61% and a mean interassay CV of 1.45%. Insulin was measured by radioimmunoassay (Linco Research, St Charles, MO; now Millipore, Billerica, MA). This assay has a sensitivity of 3.35 μIU/mL, mean intraassay CV of 3.49%, and mean interassay CV of 5.57%. C-peptide was measured by radioimmunoassay (Siemens Healthcare Diagnostics, Los Angeles, CA) in duplicate 25-μL aliquots. Sensitivity for this assay is 0.318 ng/mL, mean intraassay CV is 3.57%, and mean interassay CV is 5.59%. Serum concentrations of free fatty acids (FFA) were measured with NEFA-C assays (Wako Diagnostics, Richmond, VA) [20]. This assay has an intraassay CV of 3.89%, and the interassay CV is 5.87%. Minimum assay sensitivity was 0.0014 mEq/L. [6,6-$^2H_2$] glucose enrichment for each of the 34 blood samples listed above was analyzed by gas chromatography mass as previously described [21]. Briefly, serum samples were deproteinized, evaporated, and prepared with *N*,*O*-bis[trimethylsilyl]trifluoroacetamide and 1% trimethylchlorosilane. Derivatives were analyzed on an Agilent (Santa Clara, CA) 6890 gas chromatograph coupled to a 5973 mass spectrometer in electron impact mode. This analysis uses a standard curve prepared with in-house control serum samples and monitoring of $M + 0$ and $M + 2$ ions. Mole fractions were calculated from total area counts. The CV of the [6,6-$^2H_2$]glucose among the fasting samples was 1.75%.

2.5. Statistical analysis

Ethnic group differences for age, body mass index (BMI), k_{in}, k_{out}, and IC_{50} were compared by nonparametric Mann-Whitney *U* tests; percentages of overweight subjects in each group were compared by the Fisher exact test; and independent *t* tests were used to determine between-group differences for all other variables of interest. Variables were Log_{10} transformed for normality when appropriate. Analyses of covariance were performed to examine group differences in S_I and S_g indexes with adjustment for percentage body fat.

Mann-Whitney *U* tests and independent *t* tests were used to identify ethnic differences in glucose, insulin, and EGP at individual time points over the duration of the IVGTT. Composite scores for glucose, insulin, and EGP time courses were calculated as incremental area under the curve (AUC) by the trapezoidal method.

Statistical tests were performed with SPSS software (version 19.0; Chicago, IL) and GraphPad Prism (version 5.0; La Jolla, CA). All tests were 2-sided with a type I error rate of .05.

Table 1 – Participant characteristics and metabolic parameters

	EA (n = 30)	AA (n = 23)	*P* value	*P* value adjusted for % fat
Age (y)	26.02 ± 3.45 (19.3-32.9)	24.27 ± 4.13 (18.0-29.9)	.141	
Weight (kg)	69.86 ± 12.82 (52.6-103.0)	73.27 ± 16.05 (51.9-111.8)	.442	
BMI (kg/m^2)	25.22 ± 4.33 (18.7-35.2)	26.62 ± 5.84 (18.5-38.6)	.440	
BMI > 25 (%)	(43.3%)	(43.5%)	1.000	
FFM (kg)	41.14 ± 5.09 (32.6-49.7)	42.72 ± 4.32 (36.1-50.9)	.212	
FM (kg)	25.56 ± 9.79 (9.8-50.9)	27.06 ± 13.36 (10.9-57.8)	.954	
Percentage body fat (%)	35.92 ± 7.91 (16.4-49.9)	35.31 ± 10.34 (21.0-52.0)	.814	
k_{in} (mg/[kg min])	2.66 ± 0.40 (2.23-3.82)	2.63 ± 0.45 (1.47-3.73)	.872	
k_{out} (min^{-1})	0.027 ± 0.004 (0.020-0.038)	0.027 ± 0.005 (0.021-0.043)	.693	
IC_{50} (min^{-1})	0.013 ± 0.002 (0.011-0.018)	0.016 ± 0.012 (0.010-0.071)	.844	
Basal FFA (mEq/L)	0.50 ± 0.16 (0.13-0.79)	0.56 ± 0.15 (0.38-0.96)	.143	.141
Basal glucose (mg/dL)	90.71 ± 6.32 (77.0-105.0)	88.86 ± 7.97 (79.0-112.6)	.311	.326
Basal insulin (μU/mL)	10.29 ± 4.56 (4.0-26.0)	12.18 ± 4.26 (7.0-23.2)	.062	**.027**
Basal C-peptide (nmol/L)	1.64 ± 0.0.48 (0.64-2.66)	1.52 ± 0.52 (0.66-2.72)	.359	.328
AIRg (μU/mL × 10 min)	481.45 ± 384.28 (66.8-1958.5)	1178.03 ± 799.80 (262.0-3080.7)	**<.001**	**<.001**
Basal EGP (mg/[kg min])	1.33 ± 0.20 (1.12-1.91)	1.32 ± 0.23 (0.73-1.86)	.702	.737
Basal EGP × basal insulin	13.59 ± 6.02 (5.47-35.17)	16.10 ± 6.64 (7.68-35.87)	.112	**.048**
Disposal S_g (×10^2/min)	0.736 ± 0.235 (0.337-1.342)	0.586 ± 0.189 (0.249-1.214)	**.020**	**.008**
Hepatic S_g (×10^2/min)	0.57 ± 0.09 (0.460-0.871)	0.538 ± 0.109 (0.315-0.838)	.156	.152
Disposal S_I (min^{-1} · 10^{-4})/μU/mL	10.51 ± 4.54 (3.49-20.53)	7.46 ± 3.81 (1.66-20.31)	**.009**	**.002**
Hepatic S_I (min^{-1} · 10^{-4})/μU/mL	4.46 ± 1.71 (2.29-10.22)	3.42 ± 1.34 (0.94-6.52)	**.009**	**.005**
Total S_I (min^{-1} · 10^{-4})/μU/mL	14.97 ± 6.13 (5.77-30.75)	10.88 ± 4.97 (2.60-26.13)	**.009**	**.002**

Mean ± SD and range. FFM indicates fat-free mass; FM, fat mass.

3. Results

Participant characteristics and metabolic parameters are displayed as mean ± SD by ethnic group in Table 1. Groups were similar in age, body weight, and body composition. Both Hepatic S^I and Disposal S^I were lower for AA ($P = .009$ for both), and these ethnic differences intensified with adjustment for body composition. On average, Hepatic S^I accounted for approximately 30% Total S^I in both EA (range, 24.5-39.6) and AA (range, 22.2-42.2). Hepatic S^g did not differ between ethnic groups, but Disposal S_g was significantly lower among AA independent of body composition ($P = .020$). The AIRg was more than 2-fold higher among AA ($P < .001$); and after adjustment for percentage body fat, the surrogate index of fasting hepatic insulin resistance [19] was higher for AA ($P = .048$). Time profiles for serum total glucose, glucose enrichment, insulin, C-peptide, and EGP are shown in Fig. 1. Total glucose concentrations did not differ between groups at any point during the test (panel A), but AA demonstrated higher peak insulin levels (panel C) ($P < .05$ for minutes 3-22 following the glucose challenge). Area under the curve for insulin was

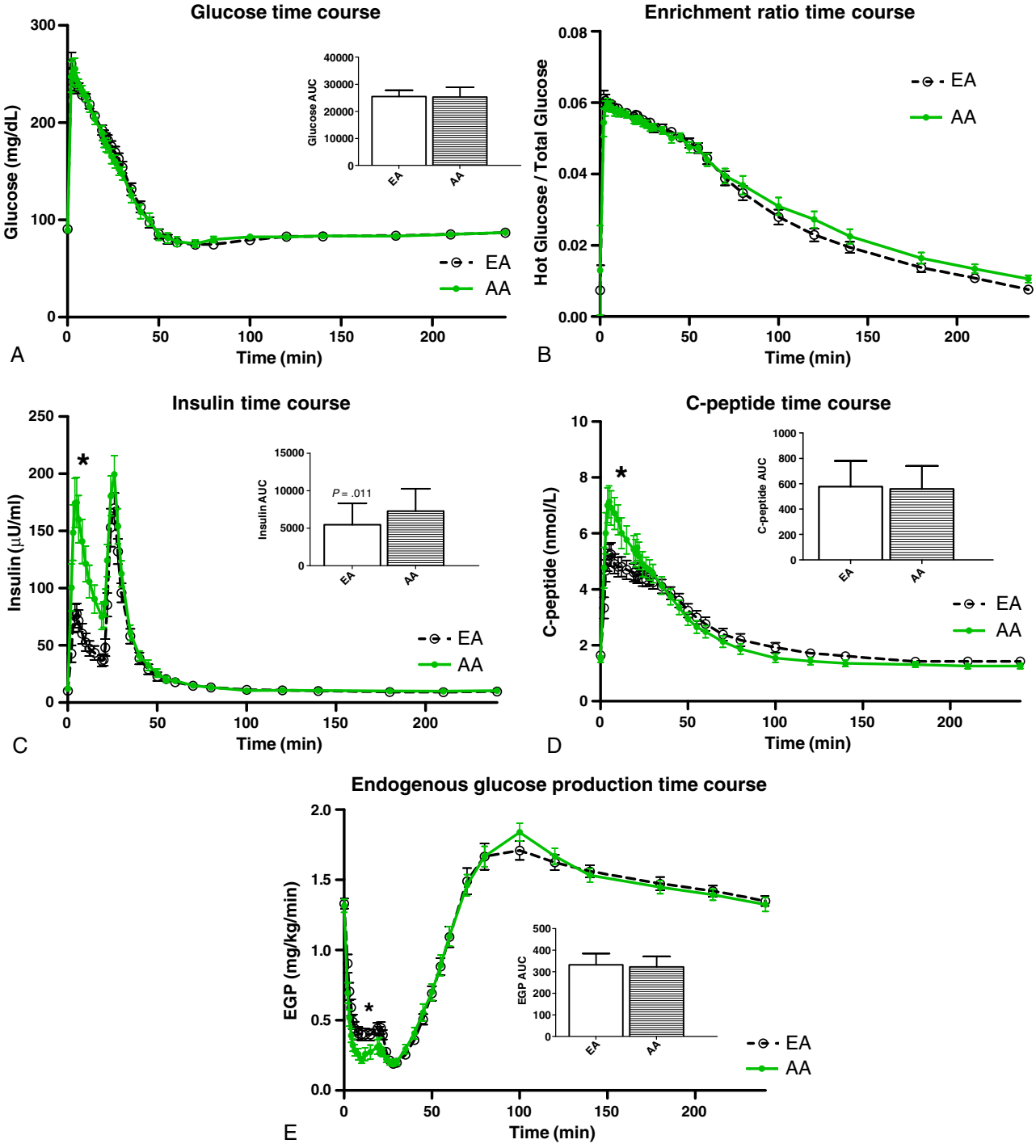

Fig. 1 – Time courses for glucose (A), isotope enrichment (B), insulin (C), C-peptide (D), and EGP (E). *P < .05.

also greater for AA compared with EA ($P = .01$). C-peptide measurements were available for 50 of the 53 participants. Panel D displays higher postchallenge C-peptide concentrations among AA ($P < .05$ for minutes 4-10). Endogenous glucose production among AA was significantly lower ($P < .05$) from minutes 2 to 22 of testing (Panel E). Although total AUC of EGP did not differ between ethnic groups, AUC for the first 30 minutes of testing was significantly lower for AA ($P = .016$). Serum concentrations of FFA were similar between groups at baseline, and circulating FFA did not differ between groups at any point of blood sampling (data not shown).

4. Discussion

It is well established that AA are at higher risk than EA for developing T2D. Previous studies quantifying S_I by IVGTT and the traditional 1-compartment minimal model [22] have repeatedly reported lower whole-body S_I among AA participants, independent of body composition [5-8]. However, T2D is a disease involving multiple organs and tissues; and whole-body S_I represents a composite of both peripheral and hepatic components. Whether lower S_I among AA relates to lower Disposal S_I (insulin-mediated glucose uptake), lower Hepatic S_I (suppression of EGP in response to insulin concentration), or both has not previously been investigated. The results presented here indicate that *both* Disposal S_I and Hepatic S_I were lower among a cohort of healthy, premenopausal AA vs EA women. In addition, a surrogate index of basal hepatic insulin resistance was higher among AA. However, despite the lower Hepatic S_I, AA demonstrated lower model-derived EGP following a glucose challenge. Lower EGP among AA was concomitant with higher insulin and C-peptide concentrations. The physiological basis for lower S_I in AA remains to be determined.

This study provides a novel contribution to the literature by comparing specific indexes of S_I between EA and AA. Previous studies describing lower whole-body S_I among AA by 1-compartment modeling [5-8] were unable to tease apart specific effects of insulin on glucose disposal and glucose production, and inherent limitations of the 1-compartment model warrant caution about its estimation of S_g [9-11]. Incorporation of a stable isotope tracer of glucose into the IVGTT in combination with 2-compartment modeling provides a more accurate estimate of S_g as well as discrimination of disposal-specific S_I and S_g [12-14]. Based on a description of endogenous glucose kinetics by Krudys et al [15], Tokuyama et al [16] recently expanded modeling of the glucose system to provide new indexes of Hepatic S_I and Hepatic S_g that correspond to the effects of insulin and glucose on EGP specifically. Using this new integrated mathematical model, we report for the first time that both Disposal S_I and Hepatic S_I appear lower in AA compared with EA. Moreover, although the ability of glucose per se to suppress EGP (Hepatic S_g) did not differ between groups, the action of glucose to facilitate its own disposal (Disposal S_g) appeared lower among AA.

Lower Disposal S_I and Disposal S_g among AA women may relate to inherent differences in aspects of skeletal muscle function. A previous study among premenopausal women reported lower muscle oxidative capacity among AA vs EA, as well as an independent correlation between in vivo mitochondrial function and whole-body S_I [23]. Our group also recently demonstrated that disposal-specific S_I was independently associated with systemic markers of oxidative stress in AA but not EA [24]. In contrast, infiltration of skeletal muscle by lipid was related to decreased S_I among EA but not AA [25-27]. Taken together, these observations suggest that mitochondrial dysfunction and consequent oxidative stress may compromise muscle function and consequent glucose disposal in AA women.

The source of lower Hepatic S_I among AA is not clear. Previous studies in animals [28] and humans [29,30] have related compromised hepatic insulin resistance to accumulation of visceral adipose tissue, with increased free fatty acids into portal circulation as a proposed mechanism [30,31]. However, AA have been shown to have lower hepatic triglyceride content [32,33]; and it is well established that AA women tend to deposit less fat as visceral adipose [5,34-37]. Among our cohort, neither fasting nor postchallenge FFA concentrations differed between AA and EA; and ethnic differences in Hepatic S_I intensified with adjustment for percentage body fat. Although it is possible that hepatic triglycerides or portal FFA may have contributed to differences between groups, these analyses were beyond the scope of this study. Thus, although it seems likely that lower Hepatic S_I among AA is attributable to factors other than body composition, the source of this difference awaits further study.

Despite significantly lower Hepatic S_I, time course comparisons revealed lower EGP among AA during the early period of testing. Little data are available regarding ethnic differences in EGP, but one study examining basal hepatic glucose production among obese adolescents similarly reported lower EGP in AA compared with EA [38]. Although the physiological mechanism for lower EGP in AA is not known, higher insulin is likely influential. The model-derived estimate of EGP involves both IC_{50} and insulin response. IC_{50} did not significantly differ between the 2 groups, suggesting that greater suppression of EGP resulted from the relatively robust early insulin response of AA. Fasting insulin concentration was higher in AA vs EA in this sample; and average AIRg was approximately 2-fold higher in AA, as previously reported [6,8,39]. First-phase insulin secretion has been identified as a determinant of EGP [40], and higher C-peptide concentrations in AA concurrent with higher AIRg suggest that early insulin secretion was higher in AA vs EA [41]. Further research is indicated to explain the interrelationships of fasting and postchallenge insulin and EGP as well as the physiological significance of these relationships for diabetes risk within healthy, nondiabetic individuals.

Major strengths of this study were incorporation of a stable isotope tracer and application of recent advances in mathematical modeling to differentiate peripheral and hepatic S_I. However, this mathematical model has yet to be validated against model-independent measures of S_I; so our analysis may be subject to limitations inherent to model-derived indexes of S_I [9,12]. Additional limitations included modest sample size and cross-sectional design. Although we adjusted for percentage body fat and confirmed equal distribution of normal-weight and overweight women in each group, we lacked statistical power for further subgroup analysis of normal-weight vs overweight participants.

In conclusion, the present results indicate that the lower whole-body S_I previously reported among healthy AA may be due to both disposal and hepatic components. Further research is indicated to determine why AA women exhibit lower S_I and higher risk for T2D despite their lower post-challenge EGP, and future studies using model-independent methods are needed to determine the physiological basis of lower S_I among AA.

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Conflict of Interest

The authors have no conflicts of interest

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