JIM Review Symposium

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doi: 10.1111/joim.13090

Obesity in African-Americans: The role of physiology

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Abstract. Gower BA, Fowler LA (University of Alabama at Birmingham, Birmingham, AL, USA). Obesity in African-Americans: The role of physiology (Review Symposium). *J Intern Med* 2020; **288**: 295–304.

The disproportionate obesity in African American (AA) women has a physiologic basis and can be explained by the interactive effects of insulin secretion, insulin clearance, insulin sensitivity and the glycaemic load of the diet. This review will present data supporting a physiologic basis for obesity propensity in obesity-prone AA women that resides in their unique metabolic/endocrine phenotype: high beta-cell responsiveness, low hepatic insulin extraction and relatively high insulin sensitivity, which together result in a high exposure of tissues and organs to insulin. When combined with a high-glycaemic (HG) diet (that stimulates insulin secretion), this underlying propensity to obesity becomes manifest, as ingested calories are diverted from energy production to storage. Our data indicate that both weight loss and weight loss maintenance are optimized with low-glycaemic (LG) vs HG diet in AA. Whether greater obesity in AA is mechanistically related to their greater prevalence of type 2 diabetes is debatable. This review provides data indicating that obesity is not strongly related to insulin resistance in AA. Rather, insulin resistance in AA is associated with relatively low adipose tissue in the leg, consistent with a genetic predisposition to impaired lipid storage. Greater bioenergetic efficiency has been reported in AA and, via resultant oxidative damage, could plausibly contribute to insulin resistance. In summary, it is proposed here that a subset of AA women are predisposed to obesity due to a specific metabolic/endocrine phenotype. However, greater diabetes risk in AA has an independent aetiology based on impaired lipid storage and mitochondrial efficiency/oxidative stress.

Keywords: insulin, African American, glycaemic load, obesity, insulin sensitivity, diet, carbohydrate.

Ethnic disparity in obesity prevalence

According to recent data from the Centers for Disease Control and Prevention (https://www.cdc.gov/obesity/data/prevalence-maps.html), obesity (BMI> 30 kg m^2) is more widespread in African Americans (AA) relative to Caucasians or European Americans (EA). However, this greater obesity prevalence amongst AA is confined to women. When data are examined by race and sex, the prevalence of obesity nationwide is 55% amongst AA women, compared to 37% amongst AA men, and 38% for both sexes in EA (https://www.cdc.gov/nchs/data/databriefs/db288.pdf). We will present data in this review to support the hypothesis that the disproportionate burden of obesity seen in AA women reflects the combined effects and unique contributions of physiologic factors related to race and sex.

In addition to being more obese, it is well documented that AA lose less weight than EA in clinical weight loss trials [1-7]. Although the reason for this disparity is not clear, it has been observed that the AA participants in these trials also engage in less physical activity [1]. Finally, data from NHANES indicate that long-term weight loss maintenance is lower amongst AA (15%) when compared to EA (19%) [8]. As will be discussed in this review, we believe that the selective partitioning of energy to storage at the expense of ATP production, specifically in AA women, may explain all of these observations.

Metabolic basis for predisposition to obesity in AA

Our data suggest that AA have a predisposition to obesity due to their unique metabolic phenotype, which is characterized by relative hyperinsulinaemia. We showed in 1998 that, for a given oral

glucose dose, healthy AA children had twofold higher peak peripheral insulin concentrations than EA children, despite significantly lower circulating glucose [9]. This pattern was then replicated with intravenous administration of glucose, which showed ~ 4-fold higher peripheral insulin (Fig. 1) and ~ 2-fold higher C-peptide in AA [10]. The higher C-peptide concentrations suggested that insulin secretion is twofold higher in AA, whilst the higher molar ratio of C-peptide to insulin suggested that insulin clearance is lower in AA. Lower clearance was subsequently verified with mathematical modelling of C-peptide and insulin data, which indicated that hepatic extraction of insulin was significantly lower in AA [11]. These patterns of secretion and clearance are maintained across the lifespan in healthy, nondiabetic women [12,13]. In all cases, insulin secretion is disproportionate to insulin sensitivity. When the acute insulin response to glucose (AIRg) is plotted against insulin sensitivity, AIRg is higher in AA vs EA at any given level of insulin sensitivity [10]. Even when pair-matched for insulin sensitivity, AIRg remains higher in AA compared to EA [14]. Thus, higher insulin amongst AA is not simply a compensatory response for insulin resistance, and it results in a higher tonic level of 'insulin action'.

Insulin is a highly lipogenic hormone. Thus, it seems reasonable to hypothesize that higher insulin action could promote fat deposition. We tested this hypothesis in two cohorts of obesity-prone, weight-reduced AA and EA premenopausal women [15,16]. The women were part of two studies to probe the physiologic basis for obesity predisposition. As such, they were recruited to be overweight and to have a family history of overweight in at least one first-degree relative. All women underwent a diet-induced weight loss intervention (all food provided) until reaching BMI < 25 kg m^2. At this time, in the first study, a second group of normal weight women was recruited, matched for age, race and BMI to the weight-reduced women. The 'lean controls' had no personal or family history of overweight or obesity. Women were then followed for one year to track change in body composition (per cent fat from dual-energy X-ray absorptiometry, DXA) under free-living conditions. These data were examined for predictors of fat gain, looking specifically at insulin-related variables (insulin sensitivity, AIRg, fasting insulin), race and free-living diet. Regarding diet, we focused specifically on dietary glycaemic load, as this measure reflects both the quantity and quality of carbohydrates that are consumed and would be relevant to insulin secretion.

During the weight loss phase of the study, all women showed an increase in insulin sensitivity (Fig. 2), with no difference between race groups [17]. After one year, the women gained 5.3 ± 3.0% body fat on average. Fat gain was greater in AA vs EA women and was significantly associated with insulin sensitivity [15] (main effect of insulin sensitivity $P < 0.05$, Fig. 3). When the data were analysed within each race group, the AA women continued to demonstrate a significant main effect of insulin sensitivity. A significant interaction

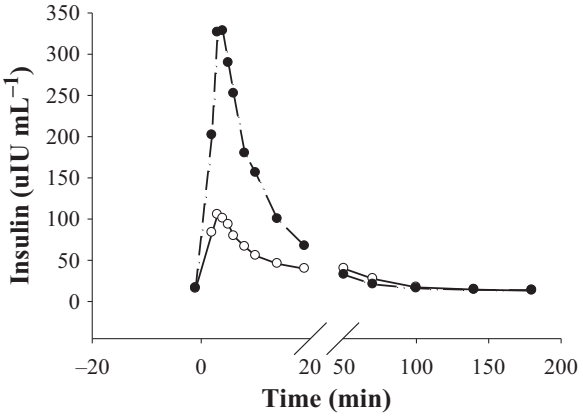

Fig. 1 *Higher insulin following iv glucose in AA● vs EA○; modified from [10].*

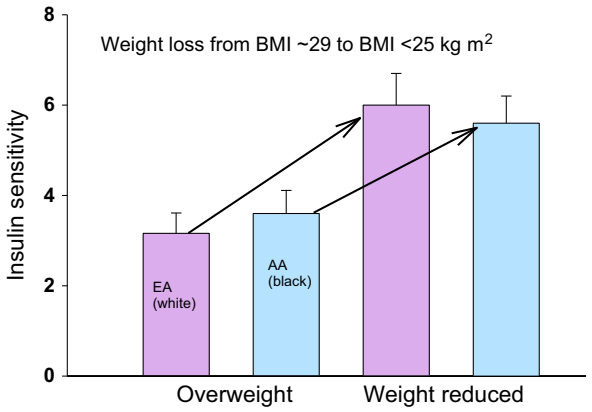

Fig. 2 *Weight loss results in an increase in insulin sensitivity in both EA and AA [17].*

between insulin sensitivity and diet glycaemic load (GL) also was observed; those women who were insulin sensitive and ate a high-GL diet gained the most body fat [16] (Fig. 4). No significant predictors of fat gain were observed in the EA women.

These observations suggested that something unique about AA women permits insulin sensitivity and diet to drive fat gain under free-living conditions. The most likely phenotypic variable to explain these relationships is the strikingly high AIRg displayed by AA women. To test this hypothesis, we stratified the women by AIRg (high vs low, based on the median). In this analysis, women with high AIRg and high insulin sensitivity gained the most weight (Fig. 5) [16]. In this model, race was not a significant determinant of fat gain. Thus, when data were stratified by AIRg and insulin sensitivity, 'race' was no longer relevant. This observation suggests that that race can be 'deconstructed' into physiologic variables that explain free-living gain in body fat.

However, not all AA women are overweight or obese. The prevalence of obesity in the US amongst non-Hispanic black women is 55% [18]. Because we recruited a group of lean women, we were able to explore phenotypic variables that confer resistance to obesity. In AA women, AIRg was identical between obesity-prone (506 ± 92 μIU $mL^{-1} \times$ 10 min) and never-overweight (536 ± 87 μIU $mL^{-1} \times 10$ min); however, insulin sensitivity was significantly lower in the never-overweight women (4.09 ± 0.53 vs $5.48 \pm 0.77 \times 10^{-4}$ min^{-1}/(μIU mL^{-1})), $P < 0.05$; Fig. 6) [16]. Thus, in the context of inherently high insulin, it appears that relative insulin resistance is protective against weight gain. It is noteworthy that amongst the EA

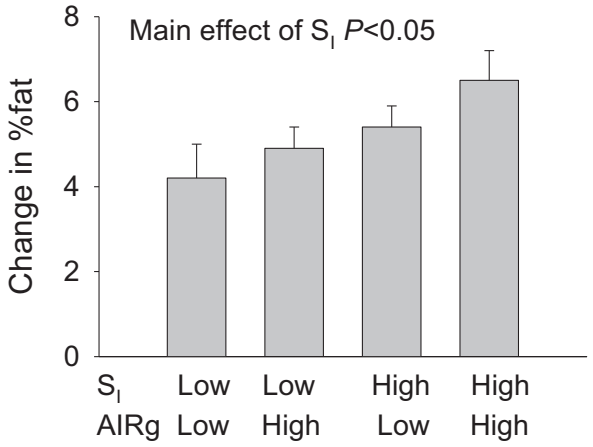

Fig. 3 *Among formerly obese, weight-reduced AA and EA women, change in %fat over 1 yr was greatest in those with relatively high levels of both SI and AIRg. Participants were categorized based on median SI and AIRg. 75% of AA were in the high AIRg group.*

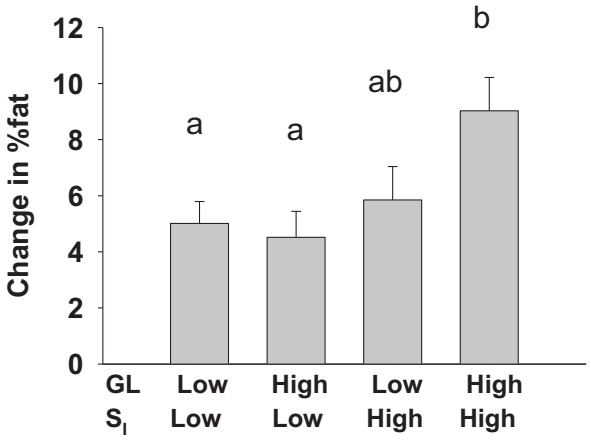

Fig. 4 *Among formerly obese, weight-reduced AA women, those who were relatively insulin sensitive and consumed a free-living diet relatively high in glycemic load (GL) gained the most fat over one year [16].*

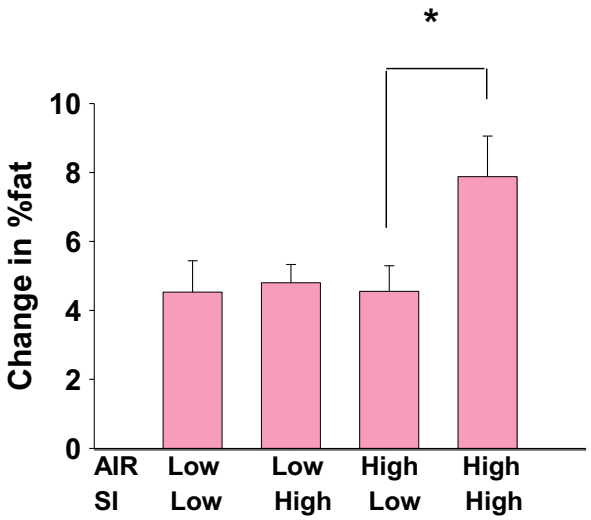

Fig. 5 *Among formerly obese, weight-reduced AA women, those who had a high acute insulin response (AIR) and a high insulin sensitivity index (SI) gained the most fat over one year (*P < 0.05) [16].*

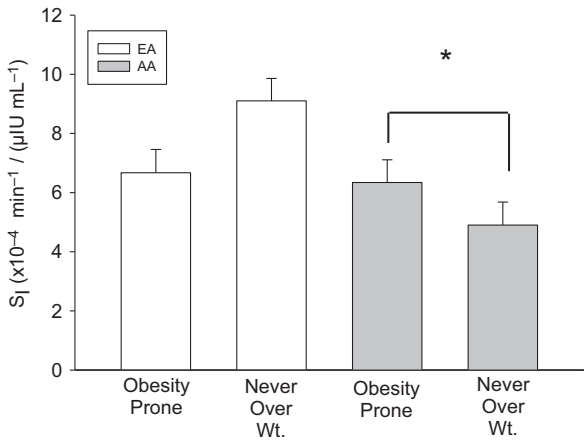

Fig. 6 *Formerly overweight (obesity-prone) AA women were more insulin sensitive than never overweight AA women (*P < 0.05), whereas obesity-prone EA women did not differ from never overweight EA women.* P < *0.05 for the group x ethnicity/race interaction [16].*

women (who have low AIRg), insulin sensitivity did not differ between obesity-prone and never-overweight.

Taken together, it seems clear that the predisposition to obesity requires a combination of high AIRg and high insulin sensitivity. Elevations in both insulin sensitivity and the acute insulin response to glucose (AIRg) have repeatedly been implicated in weight or fat gain [19]. Improved or greater baseline insulin sensitivity was associated with greater future weight gain [20,21]. Naturally occurring conditions where insulin sensitivity is elevated, such as PTEN haploinsufficiency [22] and early pregnancy [23], are associated with weight gain. When the independent and interactive effects of insulin sensitivity and AIRg on weight gain were examined in offspring of parents with type 2 diabetes (T2D) over an interval of 24 y, the combination of high insulin sensitivity and high AIRg resulted in the greatest weight gain [24].

Further, as shown in Fig. 4, in order to fully express the obese phenotype, the diet must have a high GL (high in total and/or highly processed carbohydrates). An HG diet will stimulate greater insulin secretion. Thus, the predisposition to obesity requires the interaction of three variables (two phenotypic and one environmental): AIRg × insulin sensitivity x diet GL.

Although AIRg and insulin sensitivity may be inherent phenotypic characteristics that are not modifiable, diet is an environmental variable that is modifiable. Recent meta-analyses support the concept that carbohydrate restriction generally yields greater weight loss than fat restriction [25,26]. A low-glycaemic diet will minimize postprandial [27] and perhaps fasting [25] insulin secretion, which may minimize the impact of high insulin sensitivity on fat deposition. We retrospectively analysed data from a controlled feeding study to determine if diet composition differentially affected weight loss based on race. In this study, all food was provided for a 16-week diet intervention consisting of two phases; 8 weeks of eucaloric feeding followed by 8 weeks of energy restriction at an individualized deficit of 1000 kcal day^{-1}. After the diet intervention, weight (fat) loss was greater with the LG (vs HG/low-fat) diet ($P = 0.005$) amongst all participants combined [28]. However, the difference between diets was far more striking within AA (men and women combined), who showed greater loss of fat mass with the LG diet ($P < 0.01$); the diet difference in EA approached significance ($P = 0.059$) (Fig. 7) [29]. These results suggest that AA are particularly sensitive to the influence of diet composition on body composition, perhaps due to their inherently high AIRg. Further, because all food was controlled and provided at an individualized energy deficit, these results also suggest that 'a calorie is not a calorie'. It appears that diet composition affects metabolic processes that ultimately determine energy balance, energy partitioning, or both.

Other investigators have observed the interactive effect of AIRg with diet. Amongst obese young adults, those with high 30-minute insulin following an oral glucose challenge (analogous to AIRg) were uniquely sensitive to diet glycaemic load on free-living weight gain over 18 months. When randomized to a low GL diet, young adults with high 30-min insulin spontaneously lost weight (average of 5.8 kg) and kept it off for the duration of the study (18 months) despite not being told to energy restrict. In contrast, when randomized to a high-glycaemic (low-fat) diet, this group showed minimal weight loss that was not sustained [30]. Similarly, in a small sample of the CALERIE study, healthy overweight participants aged 24-42 y with high 30-min insulin lost more weight if randomized to an LG diet [31]. These observations suggest that individuals with high postprandial insulin may have a chronic 'brake' on lipid mobilization that is

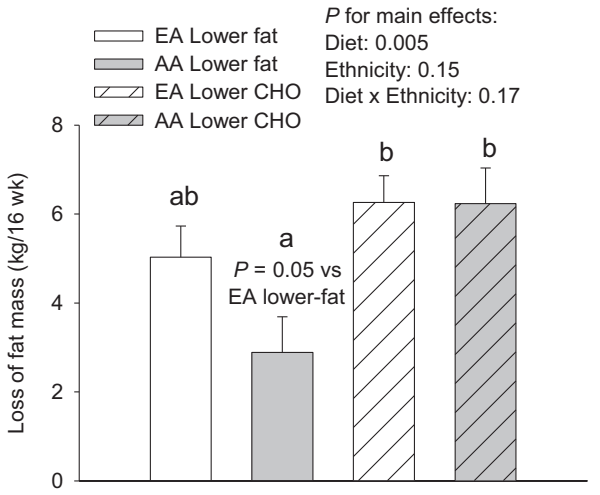

Fig. 7 *AA (men and women combined) lost more body fat when provided with a lower carbohydrate (low glycemic) diet when compared to a lower-fat diet (P < 0.05; different lowercase letters indicate significant differences between groups). The diet effect in EA was not significant. The race specificity of the diet effect may have been due to higher AIRg in AA (1415 + 917 μIU/ml x 10 min) vs EA (824 + 628 μIU/ml x 10 min; P < 0.01). All food was provided for 8 weeks at energy balance followed by 8 weeks at a 1000 kcal/d energy deficit [29].*

acutely relieved when diet glycaemic load is reduced.

The unique propensity to obesity amongst AA women is due in part to being female. Compared to men, women have higher insulin sensitivity [32], which is one of the critical components of the equation that determines obesity propensity. This is likely due to the insulin-sensitizing effects of oestradiol [33]. Further, as noted by us and others, serum oestradiol is higher in AA when compared to EA females [34,35]. Oestradiol has a number of adipogenic effects that may reflect its insulin-sensitizing actions. Oestradiol treatment in humans increases insulin-mediated suppression of lipolysis [36] and deposition of subcutaneous adipose tissue [37], and decreases whole-body and regional lipolysis [38,39]. In a longitudinal, observational study, we observed that AA girls, when compared to their EA counterparts, showed a dramatically accelerated deposition of subcutaneous fat at menarche, a time associated with an increase in oestradiol, concentrations of which were positively associated with AIRg [34]. Taken together, these observations suggest that AA females may be uniquely prone to obesity as a result of the combined effects of higher AIRg, lower insulin clearance and elevated oestradiol, which may enhance insulin sensitivity.

None of these observations suggests that the first law of thermodynamics is not valid. Positive energy imbalance is the ultimate cause of obesity. However, it is clear that endocrine factors, particularly those involving insulin, play a predisposing role. 'Excessive' insulin action can result in a disproportionate allocation of energy to storage as fat, as opposed to source of fuel (ATP production). Preferential partitioning of energy to adipose tissue would result in low energy availability [40] (e.g. for physical activity) and possibly increase perceptions of fatigue and hunger, which in turn would facilitate energy intake and further energy storage as fat. The theoretical basis for this logic has been discussed [41]. Most clinical weight loss trials prescribe a low-fat (high carbohydrate) diet for the purpose of limiting total energy. It is likely that such a diet is counterproductive for AA, or for any individual with an exaggerated insulin response to exogenous carbohydrates. Based on the information provided in this review, we suggest that a first and highly feasible step into the realm of precision medicine would be to provide a low-glycaemic diet to individuals with high insulin action, such as most AA. High insulin action could be assessed as the 30-minute insulin response to an oral glucose load. Although this would not capture insulin sensitivity, it may be sufficient to identify most patients with an 'insulin-driven' metabolism.

Metabolic basis for predisposition to diabetes in AA

In addition to being at elevated risk for obesity, African Americans are also at greater risk for type 2 diabetes (T2D) [42]. Although it is tempting to assume that these two traits are associated in a cause-and-effect manner, with obesity 'causing' T2D, this may not be true. Statistical adjustment for obesity does not entirely explain the excess risk for T2D In epidemiological studies [43,44]; thus,it is clear that other variables, such as inherently greater insulin resistance, play a role.

Insulin sensitivity/resistance

Whether AA are more insulin resistant than EA is not clear. Data showing lower insulin sensitivity in AA compared to EA are abundant in the literature [12,45-50]; however, data demonstrating a lack of

an ethnic influence on insulin sensitivity also exist [51-54]. Our own data illustrate that this discrepancy may be due to obesity predisposition or obesity resistance. As discussed above and shown in Fig. 5, insulin sensitivity does not differ by ethnicity amongst obesity-prone women. However, insulin sensitivity is lower in constitutionally lean AA women compared to constitutionally lean EA women. Based on this, we hypothesize that, amongst AA, insulin resistance confers protection from obesity. A corollary of this hypothesis is that there are two genetically distinct groups of AA, those who are inherently insulin resistant (and likely to be lean) and those who are inherently insulin sensitive (and thereby prone to obesity). It is possible that differing distributions and ranges of participant BMI values amongst studies contribute to the discrepancy in the literature regarding whether insulin sensitivity is lower in AA when compared to EA.

We recently conducted a study to explore the association between obesity and insulin sensitivity in a diverse group of nondiabetic, healthy, young (19–45 years), AA and EA individuals (NCT03043235) [55]. We recruited men and women across the BMI spectrum from lean to obese. We assessed body fat percentage and distribution by DXA and MRI. Insulin sensitivity was measured using the euglycaemic clamp at a dose of 120 mU m^{-2} min^{-1} to assure that the insulin sensitivity measure reflected skeletal muscle glucose uptake (as opposed to hepatic glucose production). The goal of the study was to examine body fat-by-race interactions between the association of total or regional adipose tissue or organ/muscle lipid with insulin sensitivity.

Results indicated that the association between per cent body fat and insulin sensitivity was stronger in EA compared to AA, with a significant race-by-% fat interaction ($P < 0.01$, Fig. 8). This observation suggests that obesity plays a larger role in the development of insulin resistance in EA. The data shown in Figs 5 and 2 suggest that insulin sensitivity (in the context of high AIRg) promotes obesity in AA (but not EA), whereas obesity leads to a decrease in insulin sensitivity regardless of race. Taken together, the data support the hypothesis that insulin resistance in EA is due to weight gain, whereas insulin resistance in AA is to some extent an inherent, perhaps genetically determined, phenotypic characteristic that could limit the accrual of body fat, particularly in women.

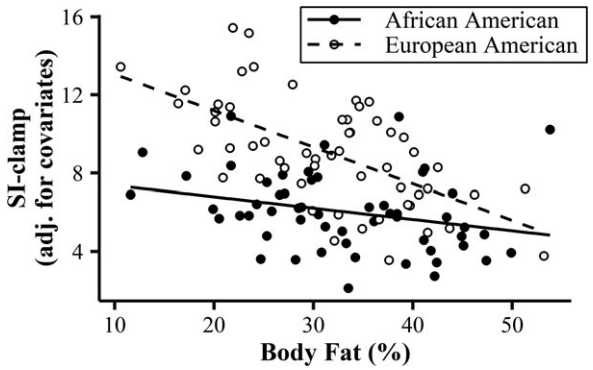

Fig. 8 *Percent body fat is more strongly associated with insulin sensitivity in EA than in AA ($P < 0.01$ for the race x %fat interaction; adjusted for sex and age).*

We next conducted multiple linear regression analyses to identify the best predictors of insulin sensitivity within each race group. Within EA, liver fat was the best inverse predictor of insulin sensitivity ($P < 0.001$), with total body fat making a significant independent contribution ($P < 0.01$). Within AA, body fat distribution was the best predictor of insulin sensitivity. The amount of fat in the legs was positively associated with insulin sensitivity ($P = 0.001$, Fig. 9) in a model that also contained subcutaneous abdominal adipose tissue (SAAT, $P < 0.05$) and intra-abdominal adipose tissue (IAAT, $P < 0.01$), both of which were inversely associated with insulin sensitivity. Liver fat was not associated with insulin sensitivity in AA ($P = 0.533$), and leg fat was not associated with insulin sensitivity in EA ($P = 0.342$). These results demonstrate that the determinants of insulin sensitivity differ based on race [55].

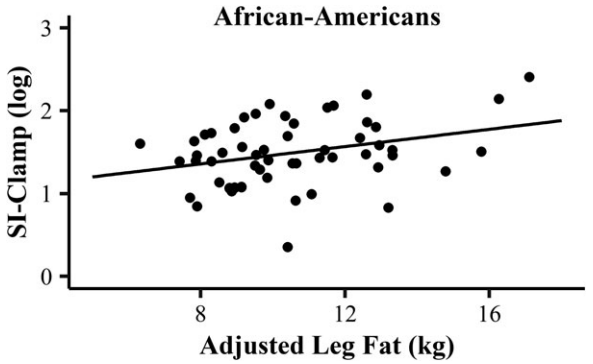

Fig. 9 *Greater leg fat associated with higher insulin sensitivity in African-Americans.*

The positive association between leg fat and insulin sensitivity observed in AA may reflect a genetic basis for insulin sensitivity, as discussed in the companion review by Hanieh Yaghootkar ('Ethnic differences in adiposity and diabetes risk – insights from genetic studies'). When our data are considered in light of these genetic studies, they suggest that AA, or at least a subset of AA, have a genetic form of insulin resistance [56]. This insulin resistance confers 'leanness', but may increase risk for T2D. In contrast, AA without this genetic insulin resistance (who are insulin sensitive) are at greater risk for obesity due to their inherently high insulin responsiveness. Thus, we put forth the hypothesis that there may be distinct trajectories amongst AA (Fig. 10), one (insulin resistant) directed towards relative leanness but perhaps greater disease risk and the other (insulin sensitive) directed towards relative obesity but perhaps protection from chronic disease. This scenario is over-simplified here for the purpose of illustrating the concept. It is more likely that genotypes and phenotypes exist on a continuum. Figure 10 illustrates the two hypothesized core trajectories upon which variation is superimposed. We believe the insulin resistance associated with the first phenotype is due to lipid intermediates within skeletal muscle, as we and others have shown that AA deposit more intermuscular adipose tissue and extramyocellular lipid [57,58]. Further, statistical adjustment for skeletal muscle area from MRI explains lower insulin sensitivity in AA [47]. We suggest that future research focus on identifying the specific lipid species that comprise muscle lipid in AA, determining whether these lipids may play a causal role in insulin resistance, and developing interventions that target reductions in specific lipid species.

Bioenergetic efficiency

Insulin resistance in AA also may be related in part to bioenergetic efficiency. AA, relative to EA, are more energetically efficient. Using indirect calorimetry and doubly labelled water, we determined that AA women had significantly lower sleeping energy expenditure (6.9%), resting energy expenditure (7.5%), total energy expenditure (9.6%) and maximal (during exercise; 13.4%) energy expenditure compared to EA women [59]. Oxygen consumption during performance of sub-maximal exercise also was lower in AA vs EA, suggesting a greater metabolic efficiency [60-62]. Similarly, oxygen consumption in vitro in isolated muscle fibres is uniformly lower in biopsies from AA women than in those from EA women [63]. Using ^{31}P-MRS, we observed that production of ATP during a planar flexion exercise likewise reflected greater energetic efficiency [64]. In this study, the ADP time constant, which reflects the efficiency of ATP production, statistically explained a portion of the lower insulin sensitivity in the AA women.

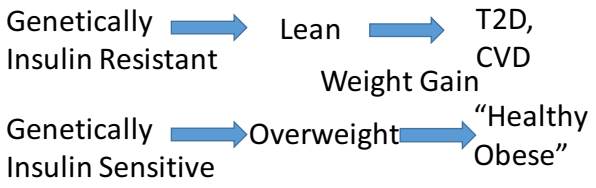

Fig. 10 *Hypothesized core trajectories for AA. With weight gain, individuals genetically predisposed to insulin resistance are prone to chronic disease. Based on Lotta et al. [56].*

Greater energetic efficiency at the mitochondrial level (a more 'coupled' electron transport chain) is expected to result in greater reactive oxygen species (ROS) production, particularly when fuel is present in excess. ROS, when not neutralized by anti-oxidants, can result in oxidative stress and tissue damage. AA are reported to have higher levels of oxidative stress, as reflected in lower glutathione and more oxidized glutathione, than EA [65]. In a sample of healthy, nondiabetic women, we observed that serum concentrations of protein carbonyls (a circulating marker of oxidative damage) were inversely associated with insulin sensitivity in AA but not EA women [66]. This study used deuterium-labelled glucose to specifically examine insulin-stimulated glucose uptake, which primarily reflects insulin sensitivity at skeletal muscle.

However, ROS production is not uniformly pathogenic. The ROS hydrogen peroxide (H_2O_2) acts as a signalling molecule in numerous biochemical reactions throughout the body. As such, greater energetic efficiency and ROS production in AA also may result in increased signalling events. This may be particularly relevant in the beta cells, where H_2O_2 is integral to insulin secretion. In cultured insulin-producing cells, elevation in H_2O_2 results in increased insulin secretion, whereas addition of anti-oxidants results in decreased insulin secretion [67]. Thus, greater mitochondrial coupling in AA, by way of increased ROS production, may result in greater insulin secretion for a given glucose stimulus, thereby explaining the strikingly

robust beta-cell responsiveness in AA. When combined with lower insulin clearance, this high beta-cell responsiveness results in sustained elevations in circulating insulin. This high level of insulin exposure may not only contribute to weight gain and obesity (as discussed), but also may down-regulate insulin responsiveness, which would be interpreted as lower insulin sensitivity during a euglycaemic clamp or intravenous glucose tolerance test. Thus, mitochondrial efficiency and ROS production could explain many of the observed phenotypic differences in insulin secretion and action between AA and EA.

In summary, we believe that the predisposition to obesity in many AA women is due to their high AIRg in combination with relatively high insulin sensitivity, which selectively partitions energy to fat. These effects are exacerbated by a high-glycaemic diet. AA men are not equally predisposed to obesity; the obesity propensity of women specifically may be due to oestrogen, which augments both insulin sensitivity and beta-cell mass [33,68]. Our research has shown that the increase in oestrogen at puberty was greater in AA vs EA girls, and that puberty had a disproportionate effect on fat gain in AA [34]. Thus, physiologic factors that determine insulin sensitivity and AIRg may render many AA women uniquely prone to obesity. It is unlikely, however, that obesity per se underlies greater prevalence of T2D in AA, as the association between obesity and insulin resistance is stronger in EA than in AA. Rather, in AA, greater mitochondrial efficiency may lead to production of ROS, which in turn enhances glucose-stimulated insulin secretion. This stress on the beta cell may ultimately lead to damage and/or dysfunction. At the level of skeletal muscle, mitochondrial efficiency and oxidative damage also may contribute to insulin resistance. Thus, mitochondrial efficiency may be the key variable underlying greater T2D risk in AA.

Conflict of interest

The authors declare no conflicts of interest.

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