UNCOVERING PHYSIOLOGICAL MECHANISMS FOR HEALTH DISPARITIES IN TYPE 2 DIABETES

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Type 2 diabetes (T2D) prevalence in the United States is significantly higher in African Americans vs Whites. Yet, the physiological mechanisms contributing to this health disparity have been poorly described. To design effective strategies to reduce this disparity, there is a need to determine whether racial differences in diabetes prevalence are attributable to modifiable or non-modifiable factors. This review synthesizes and critically evaluates the potential physiological and genetic mechanisms that may contribute to the higher susceptibility of African Americans to T2D. These mechanisms include: 1) obesity and fat distribution; 2) metabolic flexibility; 3) muscle physiology; 4) energy expenditure and fitness; and 5) genetics. We focus on the clinical significance of findings and limitations of the recent literature. (*Ethn Dis*. 2015;25[1]:31–37)

Key Words: Cardiorespiratory Fitness, Energy Expenditure, Genetics, Glucose Homeostasis, Muscle Physiology, Obesity, Race Differences

INTRODUCTION

African Americans (AAs) have a 1.9-fold higher incidence of type 2 diabetes (T2D) compared to Whites,[1] a disparity observed throughout the lifespan.[2] The etiologies and mechanisms explaining the race differences in T2D prevalence are largely unknown. T2D is a complex disease affected by multiple genetic and physiological factors, which may interact with environmental and behavioral triggers to create disparities.[3] In order to design targeted prevention and treatment strategies, there is a need to determine whether observed race differences in diabetes prevalence are attributable to modifiable or non-modifiable differences in physiology and genetics.[4] The objective of this review is to synthesize the mechanisms that may explain the disparities in T2D among AAs and Whites. The mechanisms include: 1) obesity and fat distribution; 2) metabolic flexibility; 3) energy expenditure and fitness; 4) muscle physiology; and 5) genetics.

In 2013, we assembled a writing group of scientists with expertise in ethnic minority health, body composition, physical activity, exercise physiology, and genetic epidemiology to discuss race differences in the physiological and genetic drivers of T2D. Each scientist was assigned a specific area to describe and performed a selective literature review according to his/her expertise. Although environmental and socioeconomic factors are important influences on health disparities, the review focused on physiological and genetic manifestations which may contribute to these factors. Our review article is a preliminary step to encourage further research into the physiological and genetic drivers of health disparities in T2D, so that there will be documented effect sizes for a future meta-analysis or systematic review. This article compares two race groups: Africans and the descendants of Africans, referred to here as African Americans, with those of predominantly European ancestry, referred to here as Whites. Race refers to groups with shared biological or genetic characteristics, whereas ethnicity refers to groups with cultural similarities.[4]

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OBESITY AND FAT DISTRIBUTION

Obesity is a recognized risk factor for T2D.[4] The prevalence of obesity reported in 2012 was higher among AA women (58.6%) and men (38.8%) compared to White women (33.4%) and men (36.4%).[5] Given the association between obesity and insulin resistance, it is plausible that race differences in obesity may partially contribute to the observed race differences in T2D.

In addition to generalized adiposity, the anatomic depot where fat is stored is an important risk factor for T2D. Subcutaneous adiposity is associated with cardiometabolic risk in both AAs and Whites, but the associations are attenuated when visceral adipose tissue

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Table 1. Empirical evidence of race differences in glucose metabolism and metabolic inflexibility in adults[a]

Reference	Sample	Method	Results: African Americans Relative to Whites		
			Fasting or 2-h Post-load Glucose or Insulin[b]	Insulin Sensitivity	β-cell Function
42	60 women premenopausal	IVGT		↓ IS	↑ AIR
12	13,287 nondiabetic	Fasting insulin	> fasting insulin (women) = fasting insulin (men)		
64	74	Hyperglycemic clamp	< first and second-phase insulin response	↓ IS	↑ β-cell function ↑ glucose clearance
65	34 obese	Insulin-modified FSIVGT	= fasting insulin = fasting glucose	↓ IS	↑ AIR ↑ glucose disposal
10	366	2-h OGTT	> 2-h post-load insulin		
66	723 nondiabetic	2-h OGTT; insulin-modified FSIVGT	> fasting insulin > 2-h post-load insulin = fasting glucose = 2-h post-load glucose	↓ IS	↑ AIR = glucose effectiveness
67	272 nondiabetics; first-degree relatives of individuals with T2D	2-h OGTT			↑ AIR (NGT only) ↑ β-cell function (NGT only)
68	62 healthy	2-h OGTT; tolbutamide-modified, FSIVGT	< glucose peak response = glucose = C-peptide levels	↓ IS index ↓ basal and postprandial hepatic insulin extraction ↓ post-prandial insulin	↑ basal insulin
69	333 obese nondiabetic	2-h OGTT FSIVGT	= fasting insulin = 2-h post-load insulin < 2-h post-load glucose	↓ IS	↑ AIR ↑ glucose disposal
70	2105 women nondiabetic	HOMA		↓ HOMA % IS	↑ HOMA % β-cell function

AIR, acute insulin response to intravenous glucose; FSIVGT, frequently sampled intravenous glucose tolerance test; HOMA, homeostatic model assessment; IS, insulin sensitivity; IVGT, intravenous glucose tolerance test; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; T2D, type 2 diabetes.

[a] Table is partially adapted from Golden, et al, 2012.[71]

[b] ↓ indicates variable is lower, ↑ higher, = equivalent, in African Americans compared to Whites.

(VAT), the fat depot that has been most associated with insulin resistance,[6] is taken into account.[7] There is consistent evidence that Whites have higher levels of VAT than AAs,[8] even when controlling for differences in absolute levels of fat mass.[9] These findings are somewhat paradoxical as one would predict higher levels of diabetes among Whites rather than AAs given the association of T2D with VAT.

METABOLIC FLEXIBILITY

Hyperinsulinemia and insulin resistance are more common among AAs vs Whites, even after controlling for obesity and lifestyle factors (Table 1). African Americans typically have higher fasting glucose regardless of diabetes status[3] and higher insulin responses to a 2-hr glucose challenge.[10] Non-diabetic AAs (n=288) vs Whites (n=435) were more insulin resistant and hyperinsulinemic during a 2-h oral glucose tolerance test, and these differences were not entirely explained by adiposity or lifestyle.[11] In a longitudinal study, both obese and non-obese AA women (n=1930) had higher fasting insulin than White women (n=5395).[12] At follow-up, a two-fold higher incidence of T2D was observed in non-obese AA vs White women and 30% higher incidence in obese AA vs White women. Incidence for T2D was 30% higher in non-obese AA vs White men.[12]

African Americans have a lower hepatic clearance of insulin, potentially compounding the health disparity in glucose homeostasis;[11,13] they also demonstrate reduced metabolic flexibility,[14] characterized by the absence of fat oxidation in skeletal muscle during fasting and a reduced ability to switch between fat and carbohydrate oxidation (termed flexibility) after feeding.

One exception to the otherwise consistent health disparities in T2D prevalence is that no race differences in T2D incidence existed across the three arms (lifestyle, metformin, or placebo) in the Diabetes Prevention Program.[15] Participants (n=3234) had impaired glucose tolerance at baseline, so the health disparity may occur in the early stages of T2D.

ENERGY EXPENDITURE AND FITNESS

Total daily energy expenditure (EE) adjusted for fat free mass (FFM) is lower in AAs compared to Whites, though

Table 2. Empirical evidence of race differences in skeletal muscle properties

Reference	Sample	Method to Assess Skeletal Muscle Properties	Results: African Americans Relative to Whites	
			Fiber Type Proportion[a]	Enzyme Activity
45	46 men sedentary and matched for age, height, body weight, and body mass index	Muscle biopsy of vastus lateralis at rest	↓ type I ↑ type IIa = type IIb	↑ 30 to 40% phosphagenic and glycolytic metabolic pathways = oxidative enzymes
46	28 men	Muscle biopsy of vastus lateralis	= type I = type IIa = type IIb	
47	18 men untrained, healthy	^{31}P-NMR spectroscopy in flexor carpi radialis muscle during exercise		↑ relative decrease in muscle pH ↑ inorganic phosphate/phosphocreatine ratio
49	53 women	Muscle biopsy of rectus abdominus at rest	↓ type I (obese) = type I (lean) ↑ type IIb (obese) = type IIb (lean)	
72	12 men runners	Muscle biopsy of vastus lateralis at rest	= type I	↑ 50–54% oxidative enzymes = phosphofructokinase activity

[a] ↓ indicates variable is lower, ↑ higher, = equivalent, in African Americans compared to Whites.

more pronounced in women[16,17] and equivalent in overweight adults.[16] Possible alterations in FFM may explain race differences in resting EE (REE), with FFM (when adjusted per kg) being less metabolically active in AAs vs Whites.[18] Specifically, the mass of metabolically active organs, including the liver, heart, and brain, was smaller among AAs compared to Whites, when adjusted for total fat, FFM, sex, and age, and these metabolically active organs attenuated the race differences in REE.[18] Similarly, Hunter et al[19] observed less trunk FFM and lower total daily and REE in AA premenopausal women compared to White women. African Americans reduced their REE to a greater extent during weight loss[20] while also having lower REE and physical activity EE in both the overweight and normal weight state.[21] Furthermore, lab-based studies suggest that AAs require fewer calories for their body size to maintain body weight.[22] In sum, lower daily EE, including lower physical activity, and smaller volumes of metabolically active organs, may be important metabolic factors predisposing AAs, especially women, to obesity and T2D.[22]

Low cardiorespiratory fitness (CRF) is an independent risk factor for T2D incidence.[23,24] Data from epidemiological studies[25–31] and controlled trials[32–36] suggest that CRF levels are lower in AAs compared to Whites. Furthermore, a greater proportion of AAs had low CRF compared to Whites.[27,32,37,38] The potential etiologies for the observed race differences in CRF are likely multi-focal but may be related to lower physical activity levels,[39] and, as described below, differences in muscle fiber type distribution, compared to Whites.[36,40]

MUSCLE PHYSIOLOGY

Considering that skeletal muscle is the most insulin-sensitive tissue and the primary site of insulin resistance,[41] multiple muscle parameters are associated with glucose metabolism, including total muscle volume,[42] muscle mitochondrial function,[43] and type and diameter of muscle fiber and capillary density.[44] Importantly, race differences in skeletal muscle properties have been observed between Whites and AAs.[40] Muscle oxidative capacity was lower among premenopausal AA women (n=22) compared to White women (n=37), and when controlled for VAT, mitochondrial function independently predicted insulin sensitivity.[43]

Muscle fiber composition (ie, the proportion of type I vs type II fibers) contributes to the pathogenesis of T2D because these fibers differ both metabolically and physiologically.[44] As much as 45% of the phenotypic and metabolic profile of skeletal muscle and its fiber composition is explained by genetic factors.[40] Several empirical studies observed that AAs have a higher proportion of type II vs type I fibers compared to Whites[45–48] (Table 2). A higher proportion of type II fiber contributes to lower oxidative enzyme activity and fat oxidation, [41] which could promote ectopic fat accumulation, lower insulin sensitivity, and worsen glucose control. The race difference in fiber type composition may explain the lower fat oxidation and higher lipid deposition in physically inactive AAs compared to Whites,[40,47] contributing to insulin resistance and T2D.[41]

The literature on race differences in muscle physiology is limited by the following: 1) small sample sizes across few studies, 2) discrepancy between

fiber type composition and enzymatic activity, and 3) a dearth of longitudinal data indicating that skeletal muscle properties are a causal factor of disease.[40] Evidence suggests that AAs have lower oxidative activity and higher glycolytic activity due to fiber type composition, but discrepancies across studies exist (Table 2). Obesity status may partially explain the race differences in fiber type composition: AAs had a lower percentage of type I fibers and greater percentage of type IIb fibers.[49] However, when stratified by obesity status, the race differences in fiber type were observed in obese women but not lean women. Therefore, environmental and genetic factors may modulate the race differences in muscle physiology and its relation to T2D.

GENETICS

Few studies have reported on familial aggregation or heritability of T2D in AAs,[50] despite heritability estimates ranging from 26–73% in Whites.[51,52] The genetic contributions to T2D are not well understood in non-European populations, particularly AA populations, due to their low representation in genome-wide association studies (GWAS). With the exception of the *KCNQ1* locus which was identified in the Japanese population,[53,54] all of the well-replicated risk variants were first identified in populations of Northern European ancestry.

One of the first studies to examine T2D GWAS loci in AAs tested single nucleotide polymorphisms (SNPs) in twelve European-based GWAS loci in 993 AAs with T2D and 1,054 controls and found only one SNP near *TCF7L2* associated with T2D after adjustment for admixture.[55] A study of AA adults (2,652 T2D cases, 1,393 controls) observed that five of 17 GWAS SNPs showed evidence of nominal ($P<.05$) associations with T2D.[56] Notably, in these AAs, the previously defined risk allele in *ADAMST9* was protective of T2D (ie, the effect was opposite to that in European populations). Similarly, 32 GWAS SNPs were tested in a cohort of 1,496 AAs and only three SNPs (*JAZF1*, *BCL11A*, *WFS1*) showed nominally significant associations with T2D.[57] Eight of 19 common SNPs reproducibly associated with T2D risk in European populations significantly replicated in a case-control study of AAs (1,077 cases and 1,469 controls).[58] Of 40 established, European-based T2D loci, 23 showed directionally consistent associations with seven loci significantly associated with T2D among six GWAS of AAs, consisting of 2,806 cases and 4,265 controls.[59] Thus, the results above that only examined established T2D SNPs in AAs have led to limited replication thus far.

A recent meta-analysis of T2D association results across eight studies of AAs (1,986 T2D cases, 7,695 controls) identified novel study-wide significant associations for SNPs in *HMGA2* and replicated SNPs within *TCF7L2*.[60] Reasons for the lack of a statistically significant association in AAs at the remaining loci have been postulated: the risk allele is relatively invariant or rare in populations of African ancestry, low linkage disequilibrium between the index signal and the functional allele, recent positive selection of select SNPs in AAs, lack of statistical power, and population-specific effects in Europeans only.[58,59]

Extending GWAS to AAs is important because new genes may be identified as a result of genetic variation private to populations of African descent, differences in allele frequencies and in linkage disequilibrium patterns, differences in the relative impact of risk factors to disease, or differences in gene-environment interactions.[61] A GWAS of over 8,000 AAs from five population-based cohorts found no significant loci for T2D and replicated only one T2D loci previously identified in Whites (*TCF7L2*).[61] A recent case-control GWAS of T2D in AAs (965 cases, 1,029 controls) that included one replication and three validation cohorts found one SNP significantly associated and four suggestive ($P< 2.5\times10^{-5}$) SNPs, with no overlap with T2D GWAS loci previously identified in European populations.[62] These results suggest the susceptibility loci in AAs may be shared as well as distinct from those identified in other racial populations.

In order to ameliorate the health disparity in type 2 diabetes, we need to better understand the race differences in physiological and genetic contributors to this disease.

In summary, T2D genetic markers appear to differ between racial groups; however, given the lack of familial aggregation studies and very few GWAS in AAs, further research is required to determine if genetic differences contribute to disparities in T2D prevalence between AAs and Whites.

CONCLUSIONS AND FUTURE RESEARCH DIRECTIONS

In order to ameliorate the health disparity in T2D, we need to better understand the race differences in physiological and genetic contributors to this disease. Race differences in several physiological factors may substantially contribute to the higher susceptibility of AAs to T2D. African Americans have more total and subcutaneous adiposity, though less visceral adiposity, and are more likely to be insulin resistant with impaired β-cell activity. Additionally, AAs have lower REE and lower TDEE (also reflecting

less energy expenditure through physical activity energy expenditure).[41] Finally, several susceptibility loci for T2D have been identified that may aggregate in the AA population, though more research is needed in both GWAS and epigenetic studies of changes in gene expression due to environmental exposures.

Given the current uncertainty as to the physiological mechanisms linked to glucose homeostasis, and the observed race differences in socioeconomic status, access to health care, and lifestyle behaviors,[4] it is clear that more research is required to understand the role of physiology in explaining race differences in insulin resistance and T2D. Given the preliminary nature of much of the available research, it was not possible to provide a ranking of the relative importance of the potential mechanisms. The direction of causality for these relationships is controversial, as race disparities in socioeconomic status and health care access may contribute to physiological differences, which in turn may be influenced by behaviors. Further, environmental factors may amplify genetic predispositions to T2D. An urgent need exists for basic, population-based, and translational studies to explore the physiological mechanisms that may explain the higher incidence of T2D among AAs, particularly given their disproportionate burden of health care costs.[63] Mechanistic studies should determine the physiological basis of lower insulin sensitivity and β-cell physiology among AAs and its association with T2D development. Finally, studies should evaluate if race-specific criteria are needed for diagnostic criteria (eg, fasting glucose). In summary, the increased prevalence of T2D in AAs in the United States warrants immediate and targeted attention. In order to treat and prevent this insidious disease, there is a need to determine how differences in physiological or genetic composition may enhance or detract from interventional efforts.

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