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Research Article

Salient Features of Insulin Resistance in African Americans

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Abstract

Insulin resistance (IR) is a central mechanism in the development of type 2 diabetes mellitus and metabolic syndrome, both of which disproportionately affect African Americans. This review synthesizes current evidence on the multifactorial causes of IR, emphasizing the intersection of molecular, epigenetic, and social structural determinants. At the cellular level, white adipose tissue dysfunction, characterized by impaired mitochondrial activity, oxidative stress, and chronic inflammation has emerged as a key driver of systemic insulin desensitization. Despite mitochondrial damage, adaptive mechanisms such as increased biogenesis and mitophagy can temporarily preserve metabolic balance. However, persistent metabolic stress and environmental exposures overwhelm these defences, leading to progressive insulin resistance. Among African Americans, the biological burden is magnified by social and structural factors, including chronic psychosocial stress, dietary inequities, and intergenerational epigenetic programming linked to systemic inequities. Together, these mechanisms illustrate that insulin resistance is not solely a metabolic defect, but a biocultural process shaped by both molecular pathways and lived social environments. Understanding these overlapping influences are crucial to developing targeted interventions that address the biological and social roots of metabolic disparities. Furthermore, that in African Americans the biological burden is increased by social and structural factors including chronic psychological stress dietary inequities, and intergenerational epigenetic programming linked systemic inequalities; Sirtuin 1 may be repressed in African Americans.

Key Words: insulin resistance; African Americans; type 2 diabetes mellitus; adipose tissue distribution; mitochondrial dysfunction; chronic inflammation; epigenetics; social determinants of health; metabolic disparities; hyperinsulinemia

List of Abbreviations:

AKT – Protein kinase B

ATP – Adenosine triphosphate BAT – Brown adipose tissue BMI – Body mass index

CER – Ceramides

COX5B – Cytochrome c oxidase subunit 5B

DAG – Diacylglycerols

eIF2 – Eukaryotic initiation factor 2

eIF4-p70S6K – Eukaryotic initiation factor 4/p70 S6 kinase pathway

ESRD – End-stage renal disease

FH – Fumarate hydratase

FtMt – Mitochondrial ferritin

GLUT-4 – Glucose transporter type 4

HDL – High-density lipoprotein

HOMA-IR – Homeostatic model assessment of insulin resistance

HPA axis – Hypothalamic-pituitary-adrenal axis

HPG axis – Hypothalamic-pituitary-gonadal axis

IL-6 – Interleukin-6

IL-8 – Interleukin-8

IR – Insulin resistance

IRS – Insulin receptor substrate

mTOR – Mechanistic target of rapamycin

MeSH – Medical Subject Headings MnSOD – Manganese superoxide dismutase

OGTT – Oral glucose tolerance test

PA-1 – Plasminogen activator inhibitor-1

PKC – Protein kinase C

PON-2 – Paraoxonase-2

Prx-3 – Peroxiredoxin-3

ROS – Reactive oxygen species

SAAT – Subcutaneous abdominal adipose tissue

SAT – Subcutaneous adipose tissue

SSPG – Steady-state plasma glucose

TAZ – Transacylase Tafazzin

T2DM – Type 2 diabetes mellitus

TIMM8A – Translocase of inner mitochondrial membrane 8A
TIMM17B – Translocase of inner mitochondrial membrane 17B

TNF-α – Tumour necrosis factor-alpha

UCP-1 – Uncoupling protein-1

VAT – Visceral adipose tissue

VAT/SAT ratio – Visceral-to-subcutaneous adipose tissue ratio

WAT – White adipose tissue

Introduction

Insulin resistance (IR) does not exist in isolation. The aberration of molecular signalling that underlies IR initiates a cascade of compensatory disturbances across cellular pathways, ultimately leading to widespread systemic dysfunction. This phenomenon represents a pressing global health concern. According to the World Obesity Federation's Obesity Atlas 2025, global obesity rates are projected to reach 17% in men and 22% in women by 2030, equating to nearly 3 billion adults, or roughly half of the world's adult population, living with a body mass index (BMI) of 25 kg/m² or higher [1].

In the United States, obesity is defined as a BMI of 30 kg/m² or greater and affects an estimated 38.4% of adult men and 41.3% of adult women as of 2025 [1,2]. While the biochemical mechanisms of insulin resistance have been increasingly elucidated, the underlying causes of its development, and the reasons certain populations are more predisposed remain incompletely understood. This review aims to consolidate recent peer-reviewed evidence to define insulin resistance within a modern mechanistic framework, examine current hypotheses regarding its origins, and explore the biological and social structural factors that may explain why some populations, particularly African Americans, exhibit higher susceptibility to this metabolic aberration.

Methods

A comprehensive literature review was conducted to synthesize current evidence on the biological, molecular, and socio-structural determinants of insulin resistance (IR) in African American populations. Searches were performed in NIH National Library of Medicine, PubMed, Google Scholar, MDPI and Science Direct for peer-reviewed articles published from 2010 to 2025, ensuring inclusion of both foundational and recent studies. Key search terms included combinations of: "insulin resistance," "type 2 diabetes," "African American," "Black," "race," "ethnic differences," "adipose tissue," "inflammation," "mitochondrial dysfunction," "HPA axis," "cortisol," "epigenetics," and "social determinants of health." Boolean operators and Medical Subject Headings (MeSH) were applied to optimize search specificity.

Studies were included if they reported data on insulin sensitivity or related metabolic pathways in African American adults, either alone or in comparison to other racial/ethnic groups, and if outcomes were assessed using validated measures (e.g., HOMA-IR, hyper insulinemic-euglycemic clamp, SSPG, or oral glucose tolerance tests). Exclusion criteria comprised studies lacking racial/ethnic subgroup analysis, animal-only studies without clear human relevance, as well as non-peer-reviewed publications.

Articles were screened by title and abstract for relevance, followed by full-text review. Data extracted included study design, participant characteristics, insulin sensitivity measures, and key findings regarding mechanistic contributors to IR. Findings were synthesized thematically across molecular, physiological, and social domains, emphasizing adipose tissue function, mitochondrial and oxidative stress pathways, hormonal regulation, genetic and epigenetic factors, and environmental or social determinants.

To address potential bias, study limitations were evaluated, including variability in insulin resistance measurement, sample size, and adjustment for confounders such as socioeconomic status, diet, and physical activity. The review emphasizes interpretation of racial and ethnic differences within a biocultural framework, considering both biological and social contributors to metabolic outcomes.

Known Mechanisms of Insulin Resistance

Adiposity and Lipo-toxicity

Current evidence strongly links insulin resistance to obesity; a disease state closely tied to excessive adiposity. However, this relationship is not uniform, as accumulating research demonstrates that adiposity is not the metabolic monolith it was once regarded as; the type and function of adipocytes play a more critical role than total fat mass alone. Adipocytes exist along a functional continuum, comprising three principal types: white, brown, and beige (or Brite) adipocytes [3].

White adipocytes, the predominant form in adults, primarily function to store energy in the form of triglycerides and cholesterol esters while secreting adipokines such as leptin and adiponectin. These cells are most strongly implicated in the development of insulin resistance and related metabolic disorders [3]. In contrast, brown adipocytes, localized in supraclavicular, mediastinal, and paravertebral regions, contain multiple small lipid droplets and are enriched with mitochondria expressing uncoupling protein-1 (UCP-1). This protein enables thermogenesis during cold exposure through sympathetic activation. Importantly, brown adipose tissue (BAT) activity declines with increasing BMI, fasting glycemia, and age, contributing to the loss of metabolic flexibility [3].

Beige or Brite adipocytes represent an intermediate phenotype located within white adipose depots. They share the thermogenic and mitochondrial features of brown adipocytes and can be induced by external stimuli such as cold exposure, physical activity, or hormonal signalling [3]. The ability of white adipose tissue (WAT) to undergo "browning" toward a more metabolically active state has thus become a focus of therapeutic interest in combating obesity-related insulin resistance.

In obese individuals, white adipocytes can comprise over 50% of total adipose tissue, compared to approximately 10% in lean individuals [4]. This expansion is not merely quantitative but also qualitative: adipose tissue functions as a major endocrine organ, influencing systemic

metabolism through its secretion of adipokines, cytokines, and free fatty acids. Dysregulation of these secretory pathways contributes to chronic low-grade inflammation and impaired insulin signalling.

As white adipocytes hypertrophy beyond sustainable limits, several pathological processes ensue, including increased fibrosis, mitochondrial dysfunction, localized hypoxia, and disrupted adipokine secretion [5,6]. The resulting accumulation of toxic lipid intermediates and oxidative stress drives cellular injury and systemic inflammation phenomenon broadly described as lipo-toxicity. This lipotoxic state perturbs insulin signalling at both the receptor and post-receptor levels, manifesting as insulin hypersecretion and resistance. Central to these disturbances is mitochondrial dysfunction, which both amplifies and results from lipotoxic stress, linking adipocyte overload to impaired oxidative metabolism and insulin resistance, as discussed in the following section.

Mitochondrial Dysfunction

Mitochondrial dysfunction has emerged as a critical molecular contributor within the obesity–insulin resistance–metabolic syndrome spectrum [7, 8]. Although it may not represent the primary initiating factor in insulin resistance, mounting evidence suggests that mitochondrial impairment is central to the development and progression of metabolic pathology [9]. In aging-associated obesity, repression of mitochondrial electron transport chain complex IV subunit COX5B has been observed, correlating with reduced oxidative capacity and increased adiposity [10].

Obese individuals also exhibit decreased expression of the thioredoxin-dependent mitochondrial peroxidase Peroxiredoxin 3 (Prx-3), diminished activity of Paraoxonase 2 (PON-2), and overexpression of ferritin mitochondrial protein (FtMt)a key regulator of mitochondrial iron homeostasis [10]. Together with specific epigenetic modifications, these alterations enhance reactive oxygen species (ROS) production, promoting insulin resistance, β-cell hyperplasia, and adipocyte dysfunction [10, 11, 12, 13].

At the molecular level, mitochondrial impairment disrupts fatty acid β-oxidation, resulting in intracellular accumulation of lipid intermediates such as diacylglycerols (DAG) and ceramides (CER). These lipid species directly interfere with insulin signalling: DAG activates protein kinase C (PKC), which translocate to the plasma membrane and inhibits insulin receptor phosphorylation, while CER suppresses AKT activation, thereby impairing downstream insulin signalling [14, 15, 16].

Despite these deleterious effects, adipocytes retain intrinsic mechanisms that safeguard mitochondrial integrity and preserve metabolic stability. Interestingly, mitochondrial damage in white adipocytes does not invariably lead to metabolic dysfunction. For instance, mice with adipose-specific deletion of fumarate hydratase (FH) display distorted mitochondria and decreased ATP production yet remain resistant to obesity and insulin resistance, though this protection diminishes under thermoneutral conditions. Similarly, deletion of manganese superoxide dismutase (MnSOD) triggers a compensatory increase in mitochondrial biogenesis and respiratory capacity, protecting against diet-induced metabolic dysfunction [17, 18, 19].

Collectively, these findings underscore the dual nature of mitochondrial dysfunction in adipose tissue: while chronic dysfunction fosters ROS accumulation and impaired insulin signalling, adaptive mitochondrial stress responses such as mitophagy and mitochondrial stress signalling can preserve metabolic resilience and delay disease progression. These mitochondrial dynamics not only influence adipocyte function but also interact with the regional distribution of body fat, linking cellular energy metabolism to the anatomical determinants of insulin resistance discussed in the following section.

Location of Body Fat and Insulin Resistance

Although an elevated body mass index (BMI) is strongly correlated with the prevalence of obesity, emerging clinical and molecular evidence indicates that the distribution of adipose tissue serves as a more reliable predictor of metabolic dysfunction. The anatomical site of fat deposition, rather than total adiposity alone, is now recognized as a critical determinant of insulin resistance and the subsequent progression to metabolic syndrome. This concept, initially described as sex-dependent adiposity distribution, refers to the tendency for males to accumulate central or visceral fat, whereas females more commonly exhibit iliofemoral or peripheral fat deposition [20]. Clinically, individuals with central or abdominal obesity display a higher incidence of insulin resistance, dyslipidaemia, and cardiovascular morbidity compared to those with peripheral fat accumulation.

At the molecular level, visceral adipose tissue (VAT) and subcutaneous adipose (SAT) demonstrate distinct metabolic and endocrine characteristics. VAT is primarily composed of hypertrophic adipocytes that exhibit reduced insulin sensitivity, heightened lipolytic activity, and increased secretion of proinflammatory cytokines such as TNF-α and IL-6. In contrast, SAT contains smaller, more insulin-sensitive adipocytes that maintain a greater capacity for lipid storage and secrete higher levels of adiponectin [11, 20].

Interestingly, even within SAT, regional variation exists; abdominal subcutaneous adipocytes exhibit metabolic profiles resembling those of VAT, underscoring the influence of local tissue environment on adipocyte function. Collectively, these findings demonstrate that the pathogenicity of adipose tissue extends beyond its total volume to encompass its regional distribution, cellular phenotype, and secretory behaviour.

This mechanistic interplay between adipose tissue distribution and its endocrine output forms the foundation for the chronic low-grade inflammatory milieu observed in obesity. The differential secretion of adipokines, cytokines, and chemokines from visceral versus subcutaneous depots provides an important link between adiposity patterning and the development of systemic insulin resistance, an interaction explored in greater detail in the following section.

Endocrine/Inflammation Influences

Historically, adipocytes were viewed primarily as passive energy reservoirs, storing fatty acids and glycerol as triglycerides. However, accumulating evidence now establishes that adipose tissue; whether white, beige, or brown functions as a dynamic endocrine organ. Adipocytes secrete a wide array of hormones and bioactive molecules, including steroid hormones (e.g., estrogen, cortisol), energy-regulatory hormones such as leptin, and multiple cytokines such as tumour necrosis factor-α (TNF-α), plasminogen activator inhibitor-1 (PAI-1), and angiotensinogen [21,22].

Leptin plays a central role in regulating satiety, reducing appetite, and increasing energy expenditure through its actions on the adrenal glands, thyroid, and the hypothalamic–pituitary–gonadal (HPG) axis [23].

Physiologically, leptin serves as a protective mechanism against obesity; individuals experiencing starvation consistently display reduced leptin levels compared with those who are well nourished. Experimental mice models reinforce this role: leptin deficiency or receptor knockout in mice results in marked adiposity, severe insulin resistance, and uncontrolled hyperphagia all of which are reversed by exogenous leptin administration [20,24,25]. Yet in human obesity, circulating leptin levels are typically elevated. This paradox reflects leptin resistance, in which the hypothalamus becomes insensitive to leptin's regulatory signals. Hypothesized mechanisms include impaired leptin receptor signalling, increased C-reactive protein binding to leptin, and decreased histone deacetylase activity, all contributing to persistent overeating and weight gain despite hyperleptinemia [26].

Obesity, insulin resistance, and related metabolic disorders are also characterized by a chronic, low-grade systemic inflammatory state. This inflammation is partly driven by increased leukocyte infiltration into adipose tissue and elevated expression of pro-inflammatory cytokines particularly interleukin-6 (IL-6) and TNF-α [21]. TNF-α and its receptors play complex roles: while some in vivo work suggests protective functions against early insulin resistance [27], the predominant evidence indicates that elevated TNF-α contributes to metabolic dysfunction. Obesity-associated adipocyte hypertrophy is frequently accompanied by upregulation of TNF-α expression, although this is not observed uniformly across all populations [27,29,30]. TNF-α interferes with insulin action by reducing insulin-stimulated glucose disposal, promoting lipolysis, and inducing serine phosphorylation of insulin receptor substrate (IRS) proteins, thereby impairing downstream insulin signalling [22–30]. In addition, TNF-α stimulates the expression of other cytokines, including IL-6 and IL-8, further amplifying inflammatory processes implicated in insulin resistance.

IL-6, classically known to be pro-inflammatory, is produced substantially by adipocytes, and its circulating level is reliably elevated along the obesity–insulin resistance spectrum [22–30]. IL-6 directly reduces the expression of GLUT-4 mRNA and its associated transporter which are critical components for glucose uptake and thus directly contributing to insulin signalling defects. While IL-6 does not exert strong acute lipolytic effects on subcutaneous adipocytes, it rapidly diminishes insulin action by increasing the binding of the p85 subunit to IRS proteins, enhancing their ubiquitination and degradation. Notably, this mechanism is distinct from the serine phosphorylation pathway induced by TNF-α [22–30].

Together, these endocrine and inflammatory alterations illustrate how adipose tissue dysfunction drives systemic metabolic impairment. Importantly, the degree to which these mechanisms operate and the extent to which specific cytokines or hormonal pathways contribute to insulin resistance can vary among populations. These population-level differences are particularly relevant when examining insulin resistance in African Americans, a group disproportionately affected by obesity-related metabolic disease. Understanding how endocrine and inflammatory pathways manifest across diverse biological and social contexts sets the stage for the next section, which focuses on the measurable differences in insulin resistance in African Americans compared to other ethnic/racial groups.

Insulin Resistance in African Americans

Relevance

Although there has been a broader push to eliminate race-based approaches in medicine, race continues to influence clinical decision-making and health outcomes, often to the detriment of racial and ethnic minority groups. These long-standing assumptions about innate physiological differences based on appearance can negatively affect patient care. At the same time, racial disparities in health outcomes persist. Thus, while race is a social construct, it remains important to study how genetics, phenotype, social stressors, and environmental exposures intersect to shape disease risk among populations that experience disproportionate burdens of chronic illness [31,32].

Insulin resistance is central to the development of metabolic dysfunction, including glucose intolerance, dyslipidaemia, type 2 diabetes, hypertension, and cardiovascular disease. Each of these conditions and their resulting morbidity and mortality disproportionately affects African Americans compared with individuals of European ancestry. According to CDC data, non-Hispanic Black or African American adults experienced a 24% higher diabetes diagnosis rate than the overall U.S. population in 2024. In 2021, they developed end-stage renal disease from diabetes at 2.19 times the national rate, and by 2022 their diabetes-related mortality was 40% higher than the total population [33,34]. These persistent disparities underscore the importance of examining the biological, environmental, and structural contributors to insulin resistance specifically within African American communities.

Genetic and Epigenetic Factors

Although race does not reflect discrete biological categories, individuals of African ancestry may carry genetic or epigenetic patterns that contribute to differences in metabolic disease risk. Several studies have identified DNA methylation sites that differ significantly in African Americans. Chilunga et al. identified three uniquely methylated loci cg14013695, cg00456326, and cg20259981 with HOXA5 (cg14013695)

showing consistent hypomethylation across African and Mexican American populations and potential involvement in metabolic regulation [35]. The locus OSR1 (cg00456326), a tumour suppressor gene implicated in renal and gastric cancers, was found to be hypermethylated in African Americans. Although its precise role in insulin resistance is unclear, it correlates with altered phosphorylation responses to insulin [35,36].

More broadly, studies examining subcutaneous adipose tissue reveal 6,774 uniquely methylated genes in African Americans, many located in CpG regions implicated in obesity and insulin signalling [37,38]. Follow-up analyses show that insulin resistance in both adipose and skeletal muscle is tightly linked to altered expressions of genes involved in mTOR, eIF2, eIF4/p70S6K, and pathways regulating leukocyte chemotaxis such as NINJ1 [37,38]. Comparisons with European Americans, with and without diabetes, show only modest differences in methylation (2–3%), suggesting that even small epigenetic changes can influence metabolic phenotypes [28,39].

Body Fat Distribution and Skeletal Muscle Characteristics

As with European Americans, abdominal adiposity in African Americans correlates with reduced insulin sensitivity. However, the strength and nature of this association differ across ancestry groups. Early work by

Karter et al. demonstrated similar glucose tolerance across ethnicities but found stronger associations between waist circumference and fasting insulin among European Americans, indicating that abdominal fat may exert ethnicity-specific metabolic effects [40].

More recent studies challenge assumptions of inherent ethnic differences in physiological insulin sensitivity. For example, direct comparisons between West African and European men revealed no differences in whole-body or tissue-specific insulin sensitivity. Instead, ethnic differences emerged in ectopic lipid deposition: intramyocellular and intrahepatic lipids were strongly associated with reduced insulin sensitivity only in White European men, not in West African men. Similarly, suppression of lipolysis correlated with intrahepatic and visceral fat exclusively in Europeans [41,42].

Studies in women show analogous complexity. In African American and Caucasian women, fasting glucose and triglycerides correlated with insulin resistance, but the triglyceride association remained significant only in African American women after adjustment. HDL cholesterol and the TG/HDL ratio were robust predictors of insulin sensitivity in African American women but not in Caucasians. Additionally: BMI and percent body fat predicted insulin resistance only in Caucasian women, visceral adipose tissue predicted lower insulin sensitivity in both groups, thigh fat was metabolically protective only in Caucasian women, and adipocyte size showed minimal associations except among insulin-sensitive African American women [43].

Comparative work using diverse body composition measures has found that, for European Americans, higher BMI, total fat mass, subcutaneous abdominal adipose tissue, leg fat, and liver fat all predict lower insulin sensitivity (As shown in Figure 1). In African Americans, however, central fat is more strongly linked to insulin resistance, while peripheral fat correlates with preserved insulin sensitivity, patterns opposite to those observed in Europeans. Importantly, higher lean mass predicted lower insulin sensitivity in African Americans, suggesting that skeletal muscle may not convey the same protective metabolic effects seen in European ancestry populations [44].

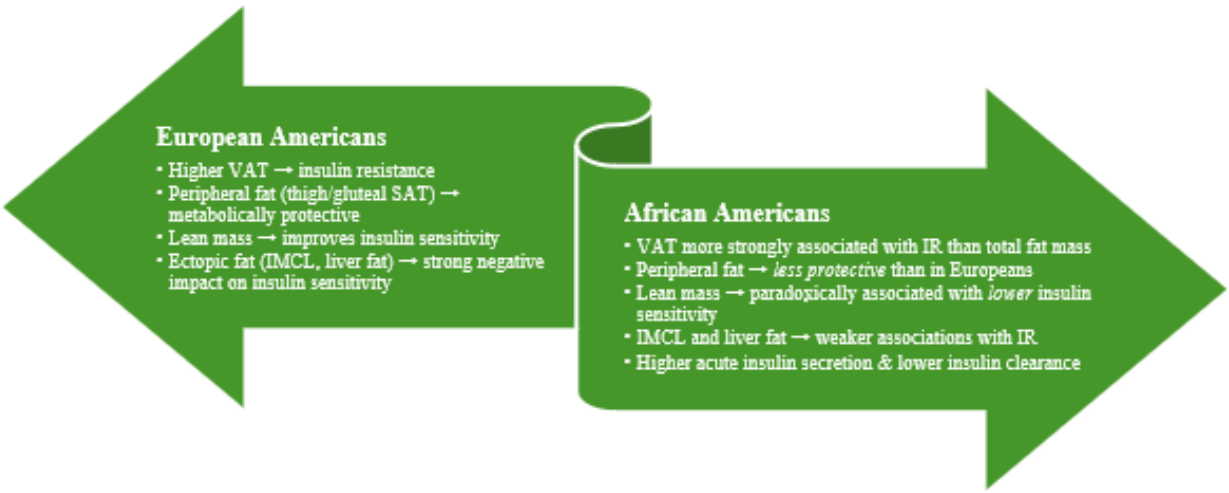

Figure 1: Body Fat Distribution Patterns and Their Metabolic Effects Across Populations.

This figure compares how adipose tissue distribution influences insulin resistance in European Americans versus African Americans. Among European Americans, greater visceral adipose tissue (VAT) and higher levels of ectopic fat such as intramyocellular and hepatic lipid are strongly associated with reduced insulin sensitivity, while peripheral subcutaneous fat and greater lean mass tend to be metabolically protective. In contrast, African Americans show a distinct pattern: VAT demonstrates a stronger relationship to insulin resistance than overall adiposity, peripheral fat is less protective, and increased lean mass is paradoxically linked to lower insulin sensitivity. Additionally, ectopic fat stores show weaker metabolic associations, while heightened insulin secretion and reduced insulin clearance characterize their physiologic response. These comparative schematic highlights ancestry-specific metabolic phenotypes that influence insulin resistance risk.

Collectively, these findings indicate that insulin resistance in African Americans may not adhere to the traditional lipocentric model developed primarily from European-ancestry research. Instead, ancestry-specific patterns of muscle metabolism, adipocyte biology, and lipid handling appear to shape metabolic risk. Moreover, differences in measurement tools such as reliance on fasting insulin or HOMA-IR may artificially magnify or obscure ethnic differences due to population-specific patterns of insulin secretion and clearance.

Mitochondrial Dysfunction

Mitochondrial dysfunction has recently emerged as a contributing factor to insulin resistance susceptibility. Early hypotheses suggested that individuals of African descent might possess unique mitochondrial genetic variations that predispose them to metabolic disease [45]. More recent research focuses on metabolic flexibility, the capacity of mitochondria to switch between available fuel sources depending on nutritional state. Impaired switching termed “metabolic inflexibility” is characteristic of the obesity–insulin resistance–type 2 diabetes continuum [46–50].

A key difference observed between African American and European American individuals is substrate preference: African Americans rely more heavily on glycolysis in both fasting and fed states, whereas

Europeans typically oxidize fat during fasting and carbohydrates after feeding, reflecting distinct mitochondrial phenotypes [51–54].

Furthermore, lower expression of mitochondrial transport and import proteins; Tafazzin (TAZ), TIMM8A, and TIMM17B has been documented in African American women and may contribute to reduced mitochondrial efficiency [47–49,55]. These mitochondrial differences are thought to contribute to lower resting energy expenditure among African Americans relative to European Americans, although the complexity of genetic–environment interactions make it difficult to attribute such findings directly to insulin resistance risk [56].

Endocrine Influences

Endocrine function and inflammatory regulation also appear to differ across populations and may contribute to varying insulin resistance risk. One area of focus is cortisol regulation. In a study of 310 adults with type 2 diabetes, higher morning cortisol levels were associated with poorer glycaemic control and impaired pancreatic insulin secretion, independent of ethnicity [57]. When contextualized with research on racial discrimination and cortisol patterns, the implications become significant for African Americans.

A longitudinal study of adolescents aged 13–19 found that cumulative and peer-related racial discrimination were associated with a steeper diurnal cortisol slope; higher morning levels followed by a sharper decline throughout the day, which could be interpreted as dysregulation of the HPA axis [58]. This pattern corresponds to poorer glycaemic control and increased metabolic stress. Such findings highlight how social determinants can biologically embed through endocrine pathways.

Additional endocrine differences include higher insulin secretion and greater acute insulin responses among African Americans when challenged with insulin resistance. While initially compensatory, this hypersecretion may accelerate β-cell exhaustion, thereby increasing vulnerability to early insulin resistance and type 2 diabetes progression [59-61].

Taken together, these studies suggest that insulin resistance in African Americans arises from an interplay between environmental exposures (including chronic stress and discrimination), endocrine compensatory mechanisms, and distinctive metabolic responses. These interacting factors may accelerate the path toward insulin resistance and highlight the need for mechanistic models that account not only for biology but also for lived social experience.

Social Determinants of Health

A persistent structural challenge in the United States is the unequal distribution of wealth and opportunity across communities. This

inequitable system has been repeatedly shown to adversely affect population health. As discussed throughout this manuscript, socioeconomic conditions materially influence an individual's susceptibility to developing insulin resistance and are increasingly recognized as drivers of epigenetic changes that may perpetuate risk across generations.

The primary and most consequential of these determinants is equal access. African Americans and other marginalized populations are disproportionately concentrated in geographic areas with limited access to essential resources such as comprehensive healthcare services and full-service supermarkets. These environments often promote unhealthy lifestyle patterns, whether due to enduring legacies of discriminatory policies or contemporary systems that purport to address disparities but inadvertently reinforce them [62,63]. The influence of place is so pronounced that a person's ZIP code can often serve as a proxy indicator for their metabolic risk. For example, residence in areas with high supermarket density is associated with a lower risk of diabetes, whereas living in impoverished neighbourhoods confers a substantially elevated risk [64].

These disadvantaged regions commonly lack stable, high-quality food outlets offering fresh and nutritious options. In contrast, they tend to have a higher density of fast-food establishments and other sources of ultra-processed foods reenforcing dietary patterns that have been repeatedly shown to significantly increase the likelihood of developing insulin resistance and subsequent type 2 diabetes [65, 66]. Additionally, these communities often face limited access to safe and functional environments for physical activity, despite physical activity being a known protective factor capable of reducing insulin resistance by approximately 17 percent, independent of race, sex, or socioeconomic status [67].

Taken together, these social determinants underscore that insulin resistance does not arise solely from biological predisposition or individual behaviour but from structural conditions that shape daily living environments (As shown in Figure 2). Addressing the inequities in food access, healthcare availability, and opportunities for physical activity is therefore essential to reducing the disproportionate burden of insulin resistance and diabetes in marginalized communities. Interventions that prioritize resource redistribution, community-level infrastructure investment, and the dismantling of long-standing systemic barriers are likely to yield meaningful improvements in metabolic health and help disrupt the intergenerational transmission of risk.

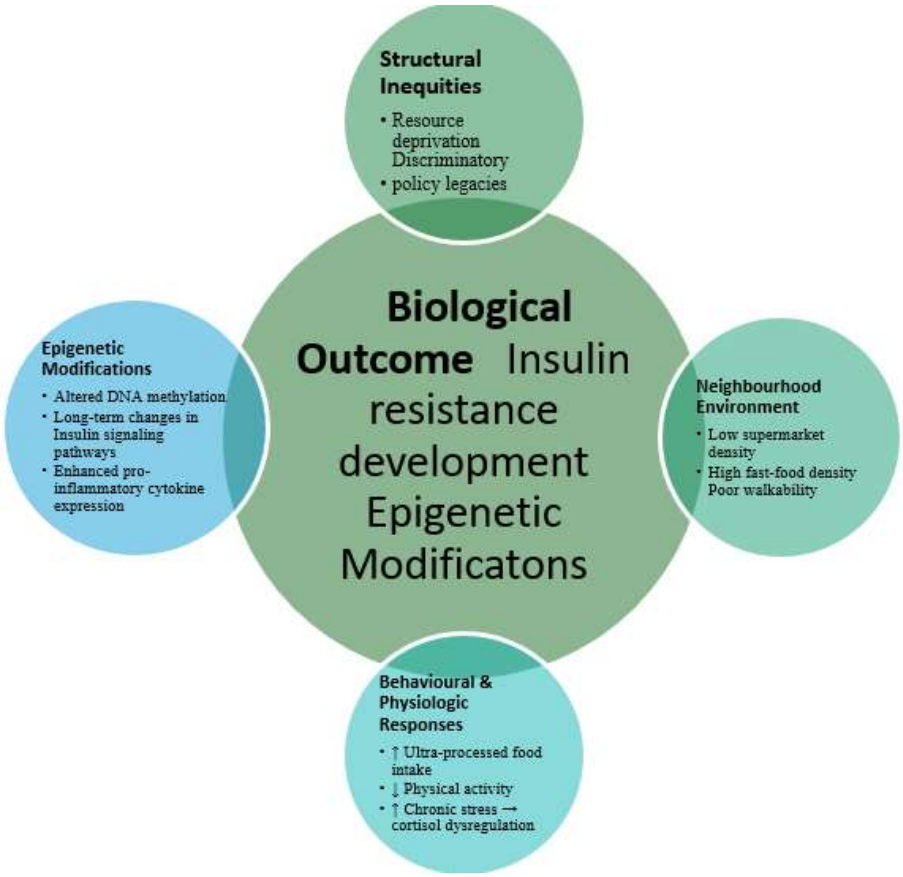

Figure 2: Social Determinants Pathways from Environment to Insulin Resistance.

This figure illustrates the multilevel pathway through which structural and neighbourhood-level inequities shape metabolic health in African Americans. Structural factors including segregation, resource deprivation, and discriminatory policies produce environmental conditions characterized by poor food access, low walkability, limited healthcare availability, and chronic psychosocial stress. These exposures drive behavioural and physiologic responses such as higher intake of ultra-processed foods, reduced physical activity, cortisol dysregulation, sleep disruption, and compensatory hyperinsulinemia. Over time, these stressors contribute to epigenetic modifications, including altered DNA methylation patterns and changes in key metabolic signalling pathways, which enhance inflammatory activity and predispose to insulin resistance. The cumulative result is heightened metabolic risk with the potential for intergenerational transmission.

Conclusion

Insulin resistance (IR) in African Americans emerges from the convergence of biological, environmental, and socio-structural determinants rather than from any singular genetic or metabolic anomaly. The evidence synthesized in this review demonstrates that mitochondrial dysfunction, chronic low-grade inflammation, and altered adipose tissue distribution form the biological foundation of IR. Yet, these processes are amplified by social and environmental context nutritional inequities, psychosocial stress, and chronic exposure to systemic discrimination that impose cumulative metabolic strain. The biological expression of stress, through dysregulated hypothalamic-pituitary-adrenal (HPA) axis activity, aberrant cortisol rhythms, and compensatory β-cell hypersecretion, exemplifies the biocultural embodiment of social adversity at the cellular level. Anti-Aging genes improve appetite regulation and reverse cell senescence and apoptosis in global populations (68,69,70). This suggest sirtuin1may be repressed in this population. Sirtuin 1 inhibitors may need to be consumed in African Americans.

While African Americans often display higher insulin secretion and reduced insulin clearance, these physiological features alone do not explain the disproportionate burden of IR and type 2 diabetes. Instead, the interplay between molecular vulnerabilities (e.g., epigenetic modifications in adipose and muscle tissue) and external stressors defines a unique metabolic milieu shaped by both ancestry and lived environment. Importantly, what have historically been interpreted as "racial" differences often reflect methodological variation in assessing insulin sensitivity and unmeasured confounding from structural senescence and apoptosis qualities rather than innate biological divergence.

Future research must move beyond reductionist racial comparisons toward integrative frameworks that couple precision molecular profiling with social epidemiology. This approach will clarify how gene–environment interactions and intergenerational epigenetic programming perpetuate metabolic disparities. Clinically, interventions that target both biological mechanisms, such as mitochondrial resilience and adipose tissue remodelling, and upstream social determinants, such as food access, chronic stress, and healthcare inequity, are most likely to reduce the disproportionate metabolic burden borne by African Americans.

Ultimately, insulin resistance is not merely a defect of metabolism but a reflection of embodied inequality. Recognizing its dual roots in molecular

biology and social structure is essential to designing equitable prevention and treatment strategies that address the true causes of metabolic disease disparities.

Authors' Contribution

Dr. Kanwal K. Gambhir conceived the idea and finalized the manuscript, Victor D. Ellis III drafted the first draft including all figures to fulfil the requirement of his senior year MSIV elective in endocrinology research Dr. Maurice B Fluitt edited the prefinal draft.

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