A Systematic Review of Beta Cell Function in Adults of Black African Ethnicity

M. Ladwa, O. Hakim, S. A. Amiel, and L. M. Goff

Diabetes Research Group, Department of Diabetes, School of Life Course Sciences, Faculty of Life Sciences & Medicine, King’s College London, London, UK

Correspondence should be addressed to M. Ladwa; meera.ladwa@kcl.ac.uk

Received 23 April 2019; Revised 16 July 2019; Accepted 11 August 2019; Published 20 October 2019

Background. Understanding ethnic differences in beta cell function has important implications for preventative and therapeutic strategies in populations at high risk of type 2 diabetes (T2D). The existing literature, largely drawn from work in children and adolescents, suggests that beta cell function in black African (BA) populations is upregulated when compared to white Europeans (WE).

Methods. A systematic literature search was undertaken in June 2018 to identify comparative studies of beta cell function between adults (>age 18 years) of indigenous/diasporic BA and WE ethnicity. All categories of glucose tolerance and all methodologies of assessing beta cell function in vivo were included.

Results. 41 studies were identified for inclusion into a qualitative synthesis. The majority were studies in African American populations (n=30) with normal glucose tolerance (NGT)/nondiabetes (n=25), using intravenous glucose stimulation techniques (n=27). There were fewer studies in populations defined as only impaired fasting glucose/impaired glucose tolerance (IFG/IGT) (n=3) or only T2D (n=3). Although BA broadly exhibited greater peripheral insulin responses than WE, the relatively small number of studies which measured C-peptide to differentiate between beta cell insulin secretion and hepatic insulin extraction (n=14) had highly variable findings. In exclusively IGT or T2D cohorts, beta cell insulin secretion was found to be lower in BA compared to WE.

Conclusions. There is inconsistent evidence for upregulated beta cell function in BA adults, and they may in fact exhibit greater deficits in insulin secretory function as glucose intolerance develops.

1. Background

Populations of black African (BA) ethnicity have a higher prevalence [1, 2] and earlier age of onset [3, 4] of type 2 diabetes (T2D) compared to those of white European (WE) ethnicity. While there is evidence that part of the disparity is due to environmental and cultural factors (such as socioeconomic status and diet) [5, 6], studies which adjust for these variables have found persistently higher rates of T2D and poorer glycaemic control in BA populations [7, 8], suggesting that ethnic-specific pathophysiological differences also play a role.

It has been hypothesised that in BA populations, beta cell function is upregulated or exaggerated in comparison to WE [9, 10], possibly mediated by lower adiponectin levels [11, 12], greater sensitivity of the beta cell to free fatty acid (FFA) stimulation [13, 14], or dietary factors such as an increased fat-to-carbohydrate ratio [15, 16]. This appears to be borne out by a meta-analysis of ethnic differences in insulin secretion by Kodama et al. [17], which concludes that BA exhibit a higher acute insulin response to glucose (AIRg, as measured by the intravenous glucose tolerance test) compared to WE. It has been speculated that this state of “upregulated” beta cell function plays a role in the increased risk of T2D in BA by predisposing to premature beta cell exhaustion [9].

There is no widely accepted “gold standard” method of assessing beta cell function in vivo. The most common techniques measure insulin response following the stimulation of the beta cell by glucose, either intravenously (as in the case of the hyperglycaemic clamp, graded glucose infusion, or intravenous tolerance test, which may be modified by intravenous insulin or tolbutamide) or orally (following the oral glucose tolerance test (OGTT) or the mixed meal tolerance test...
(MMTT)) [18]. Other techniques use intravenous arginine or glucagon to provoke a robust insulin secretory response [18]. Surrogate indices are also used, which may be derived from fasting glucose and insulin, such as the homeostatic model assessment of beta cell function (HOMA%B), or from the OGTT/MMTT, such as the insulinogenic index or the corrected insulin response (CIR) [18]. Each method has its strengths and limitations; for example, oral glucose and mixed meal tests are highly physiological while intravenous techniques allow specific assessment of the beta cell by excluding the modulating effect of the incretin hormones [18, 19].

There are two important factors to consider when assessing the evidence for “upregulated” beta cell function in BA. Firstly, “beta cell function” implies the concept of the beta cell adequately meeting its physiological role of maintaining glucose homeostasis; that is, it requires assessment of insulin secretion not in isolation but in the context of prevailing insulin sensitivity. Secondly, peripheral insulin levels are determined by both the rate of insulin secretion and the rate of hepatic insulin extraction (HIE), as insulin is secreted by the pancreatic beta cell into the portal vein and undergoes first pass metabolism in the liver before entering the systemic circulation [20]. As C-peptide is cosecreted with insulin into the portal vein in equimolar quantities and undergoes negligible hepatic extraction, measurements of plasma C-peptide are a better reflection of beta cell insulin secretion than plasma insulin levels [21].

The purpose of this systematic review is to examine the evidence for the impact of BA ethnicity on physiological differences in beta cell function in adulthood, taking into account both adjustments made for insulin sensitivity and the differentiation between beta cell insulin secretion and HIE. Unlike previous reviews, it examines adults only, as paediatric populations with impaired glucose regulation are likely to represent a more extreme phenotype. Furthermore, this review will include studies employing a variety of methodologies, in order to obtain a more comprehensive review of ethnic differences in beta cell function.

2. Methods and Procedures

2.1. Search Strategy. The study was formulated with reference to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [22].

A modified “PICO” (Population, Intervention, Comparison, Outcome) framework was used. As the relevant topic is ethnic difference rather than intervention, “Phenomenon of Interest” was substituted for “Intervention” and “Outcome.”

Using this framework, the following question was generated: “how does beta cell function in adults of black African ethnicity differ from that of adults of white European ethnicity across all ranges of glucose tolerance?”

The Ovid Medline database was searched in June 2018 to identify potentially relevant publications. Keywords included “African”, “Caribbean”, “beta cell function”, “acute insulin response (AIR)”, “disposition index (DI)”, “insulinogenic index”, and “insulin secretion”. The complete search string may be found in the appendix. No limits were set in terms of publication date or language.

Inclusion and exclusion criteria were predetermined in order to systematically select studies.

(i) Inclusion criteria

(a) Population: adults (over 18 years of age) of black African ethnicity. To include both indigenous populations and those of the diaspora, e.g., African Americans, African-Caribbean, and indigenous African. Both male and female. Across all ranges of glucose tolerance: normal glucose tolerant, impaired glucose tolerant, impaired fasting glucose, and type 2 diabetic

(b) Phenomenon of interest: beta cell function. Indices included were HOMA%B, insulin secretion, AIR (acute insulin response), EIR (early insulin response), insulinogenic index, corrected insulin response (CIR), disposition index (DI), beta cell responsivity to glucose (Phi1, Phi2, and Phi total), insulin secretion rate (ISR), and insulin secretory function (ISF)

(c) Comparison population: adults of white European ethnicity. To include whites, Caucasians, non-Hispanic whites, and white Europeans

(ii) Exclusion criteria

(a) Population: population contains only subjects < 18 years

(b) Phenomenon of interest: no assessment of beta cell function, e.g., only genetic data collected, only insulin clearance assessed, only fasting insulin/C-peptide without model assessment

(c) Comparison population: no direct statistical comparison to WE population (or data not reported in comparison to WE population)

Two investigators (ML and OH) independently screened the search results to determine study inclusion to minimise bias. In the first step, studies were eliminated if the abstract indicated that at least one criterion was not met. In the second step, full-text manuscripts were obtained from the remaining studies to assess them against the inclusion and exclusion criteria. The references of included studies were also reviewed to identify further suitable studies.

If data from the same study were reported in multiple publications, only the publication with the greatest number of participants in the analyses was included.

2.2. Quality Assessment. The Newcastle-Ottawa scale [23] (developed as a quality assessment tool for nonrandomised studies) was used to determine the quality and risk of bias of the selected papers. A modified version of the scale for cross-sectional studies (mNOS) was formulated (see the appendix).
3. Results

The selection of the included studies is shown in Figure 1. A total of 182 articles were screened; after the study selection process, 41 studies met the prespecified eligibility criteria and were included in the qualitative synthesis.

The characteristics of the included studies are shown in Table 1. The majority were studies of African American populations (n = 30), but other study populations included indigenous black African (n = 5) [24–28], immigrant black African (n = 2) [29, 30], UK African-Caribbean (n = 3) [31–33], and a mixture of the above (n = 1) [34]. The total number of subjects of BA ethnicity in the included studies was 4619. The smallest cohort of BA subjects was 7 [24] and the largest was 752 [35]. The majority of studies (n = 25) were in NGT or nondiabetic populations only; three studies were in prediabetic (IFG/IGT) populations only [35–37], and three studies were in populations with T2D only [30, 32, 38]. Ten studies were in a population known to be of mixed glucose tolerance [31, 39–47].

The studies comprised 17 all-female cohorts [25–28, 37, 41, 43, 48–56], 3 all-male cohorts [24, 29, 30], and 21 mixed-sex cohorts. Where sex of subject was reported by ethnicity, the majority in both BA (3350 of 4395, or 76%) and WE (6630 of 10900, or 61%) subjects were female. There was evidence of sex-specific differences in insulin secretion within the BA population, with females exhibiting a greater insulin response compared to males [33, 57].

A variety of methodologies were employed to assess beta cell function, with some studies employing multiple methods. These included models based on fasting parameters (n = 5) [32, 36, 37, 41, 58] and measurements using data from oral glucose and mixed meal stimulation tests (n = 21), such as poststimulation insulin and/or C-peptide concentrations [24, 25, 28, 31, 37, 38, 50], corrected insulin response (CIR) [35, 42], insulinogenic index [27, 36, 40, 44, 55], and insulin and/or C-peptide area under the curve (AUC) [26, 29, 30, 34, 42, 48, 59, 60]. Of the studies using intravenous stimulation (n = 27), some studies employed multiple methods within the same study, most commonly the insulin-modified IVGTT (n = 15) [27, 36–39, 43–45, 49, 51–54, 56, 58]. Studies also employed the nonmodified IVGTT (n = 6) [33, 46, 59–62], the tolbutamide-modified IVGTT (n = 4) [43, 44, 51, 63], the hyperglycaemic clamp (n = 4) [30, 47, 64, 65], and the arginine-stimulated response (n = 2) [47, 60]. One study [25] used combined tolbutamide and glucagon intravenous stimulation.

Nineteen studies reported measurements of insulin secretion corrected for insulin sensitivity, with adjustment by HOMA-IR [28, 40], M value from hyperinsulinaemic-euglycaemic clamp [59, 62], insulin sensitivity index (ISI) [38, 42, 43], or by calculation of the disposition index (AIR × SI) [27, 33, 36, 37, 44, 45, 47, 53, 54, 58, 60, 61]. According to the prespecified quality criteria, one study was at high risk of bias (n = 1) [24] while the remainder were at low risk of bias (n = 40).

As the study population sizes are very different, the cumulative n has been calculated and presented for Tables 2 and 3; however, due to the high degree of variability in study populations and methodologies, this is intended to be indicative rather than for direct quantitative comparison.
| Study                          | Methods | Study design       | Ethnicity                          | Population of interest | Gender %M/F | Glucose tolerance | Comparison population | Findings                                                                                                                                  | mNOS |
|-------------------------------|---------|--------------------|------------------------------------|------------------------|-------------|-------------------|-----------------------|------------------------------------------------------------------------------------------------------------------------------------------|------|
| Rubenstein et al. [24]        | OGTT    | Cross-sectional    | Native black South African, no FHx of T2D | 7                      | 30 ± 6      | 100/0  NGT        | White South African, no FHx of T2D | Similar fasting insulin levels, but lower serum insulin in response to oral glucose and lower renal insulin clearance in BA compared to WE | 5    |
| Shires et al. [25]            |         | Cross-sectional    | Obese native black South African   | 10                     | 39.4 ± 1.7  | 0/100  Nondiabetic | Obese white South African | Serum insulin and C-peptide levels significantly lower in BA compared to WE 30 mins after oral glucose and 30 mins after tolbutamide and glucagon | 6    |
| Cruickshank et al. [31]       | OGTT    | Cross-sectional    | UK Afro-Caribbean                  | 106                    | 56.6 ± 6.0 (F), 57.0 ± 5.0 (M) | 50/50  NGT, IGT, and T2D | White European         | No statistically significant difference between C-peptide and insulin concentrations post oral glucose; however, difference in profiles led investigators to suggest impaired hepatic processing of insulin in BA. | 6    |
| Osei et al. [48]              | OGTT    | Case control       | African American (first-degree relatives of T2D and controls) | 24 relatives and 8 controls Total = 32 | 32 ± 2 (relatives) and 27 ± 2 (controls) | 0/100  NGT | White American (first-degree relatives of T2D and controls) | In both first-degree relatives and controls, iAUC insulin and C-peptide were significantly higher in BA compared to WE | 9    |
| UK Prospective Diabetes Study Group [32] |         |                     | UK Afro-Caribbean                  | 387                    | 51.6 ± 7.4 (M), 50.2 ± 7.2 (F) | 57/43  T2D | UK Caucasian       | Lower HOMA%B in BA compared to WE, adjusted for age and BMI. BA had higher fasting plasma glucose and higher HbA1c vs. WE. | 9    |
| Osei et al. [63]              |         | Cross-sectional    | African American                   | 32                     | —           | 0/100  NGT        | White American         | Higher insulin levels in BA but similar C-peptide levels compared to WE | 9    |
| Haffner et al. [39]           | Insulin-modified IVGTT | Prospective cohort            | African American                   | 187 NGT, 101 IGT Total = 288 | 54.2 ± 0.7  | 43/57  NGT and IGT | Non-Hispanic white      | Higher AIR in BA compared to WE when adjusted for age, sex, BMI, and WHR. Greater insulin resistance in BA by SI OGTT: no difference in fasting and 2 h insulin. AIR higher in BA. No ethnic difference in SI. Adjusted for age, sex, obesity and WHR, fasting glucose, and therapy | 9    |
| Haffner et al. [38]           | OGTT    | Prospective cohort            | African American (overweight and obese) | 153                    | 57.1 ± 0.7  | 45/55  T2D | Non-Hispanic white (overweight and obese) | | |
| Study                        | Methods                  | Population of interest | Comparison population | Glucose tolerance | Gender | Mean age | Findings                                                                 |
|-----------------------------|--------------------------|------------------------|-----------------------|-------------------|--------|----------|--------------------------------------------------------------------------|
| Osei et al. [34]            | OGTT                     | Cross-sectional        | Native Ghanaian, US immigrant, and African American | 147               |        |          | Higher peak and AUC insulin in BA compared to WE, no difference in C-peptide to insulin molar ratio (BA lower than WE)             |
| Chiu et al. [64]            | Hyperglycaemic Clamp     | Cross-sectional        | African American      | 26                |        | 22.5 ± 0.7 | No difference in insulin, but C-peptide and C-peptide to insulin ratio lower in BA compared to WE, similar BMI in both ethnic groups |
| Melby et al. [49]           | Insulin-modified IVGTT   | Cross-sectional        | African American      | 9                 |        | 20.6 ± 0.2 | Higher AIR in BA and lower insulin sensitivity in BA and lower insulin sensitivity in BA for both ethnic groups |
| Chen et al. [65]            | Hyperglycaemic Clamp     | Cross-sectional        | African American      | 11                |        | 42.4 ± 0.2 | Higher first and second phase insulin response in BA, lower insulin sensitivity index in BA and lower insulin sensitivity index in BA. Similar age, BMI, and percentage body fat between ethnicities |
| Jensen et al. [40]          | OGTT                     | Cross-sectional        | African American      | 55                |        | 41.8 ± 1.9 | Insulinogenic index adjusted for insulin sensitivity higher in NGT BA vs. WE. No difference in IFG/IGT and T2D between ethnicities |
| Punzeder et al. [28]        | MMTT                     | Cross-sectional        | African American      | 17                |        | 31.9 ± 2.6 | Higher insulin levels at 30 mins post meal in obese BA compared to obese WE, no difference in insulin and insulin to glucose ratio between ethnicities |
| Velasquez-Mier et al. [42]  | OGTT Cross-sectional     | Cross-sectional        | African American      | 16                |        | 36 ± 2       | Similar BMI and fat mass by DXA between ethnic groups for both obese groups |

**Table 1: Continued.**
### Table 1: Continued.

| Study | Methods | Study design | Ethnicity | Population of interest | Gender %M/F | Glucose tolerance | Comparison population | n | Findings |
|-------|---------|--------------|-----------|------------------------|-------------|-------------------|------------------------|----|----------|
| Stefan et al. [59] | OGTT, MMTT, and IVGTT | Cross-sectional | African American | 30 | 31 ± 1 | 66/33 | NGT | White American | 30 | Higher AIR after IVGTT in BA, when adjusted for insulin sensitivity by M-Low (from 2-step hyperinsulinaemic-euglycaemic clamp). BA and WE matched for age, sex, BMI, WHR, and percentage body fat. No ethnic difference in AUC insulin post OGTT or MMTT. |
| Torrens et al. [41] | Fasting glucose and insulin to derive HOMA%B | Prospective cohort | African American | 746 | 46 ± 2.7 | 0/100 | Nondiabetic; included subjects with IFG | Non-Hispanic white | 1359 | HOMA%B higher in BA after controlling for alcohol consumption, waist circumference, triglycerides, and prevalence of IFG. Higher AIR in BA, which persisted when adjusted for insulin sensitivity index and measures of adiposity and skeletal muscle. |
| Albu et al. [43] | Insulin- or tolbutamide-modified IVGTT | Cross-sectional | African American | 32 | 36.8 ± 1.3 | 0/100 | NGT and IGT | White American | 28 | Higher AIR in BA, which persisted when adjusted for insulin sensitivity index and measures of adiposity and skeletal muscle. |
| Boule et al. [61] | IVGTT | Pre/postinterventional | African American | 173 | 32.9 (30.8-35.0) (F) 33.1 (30.2-36.0) (M) | 37/63 | Nondiabetic | White American | 423 | AIRg and DI higher and SI lower in BA vs WE. |
| Reimann et al. [28] | OGTT | Cross-sectional | Black South African (with and without abdominal obesity) | 86 | 27 (23, 30) (without abdominal obesity) 32 (28, 35) (with abdominal obesity) | 0/100 | Nondiabetic | White South African (with and without abdominal obesity) | 90 | No ethnic difference in age, BMI, or insulin resistance by HOMA-IR. 2 h C-peptide post glucose significantly higher in BA vs. WE in the group with abdominal obesity. No ethnic difference in post glucose C-peptide in the lean group. |
| Elbein et al. [44] | OGTT | Insulin- or tolButamide-modified IVGTT | Case control | African American | 159 | 38.4 ± 9.2 | 34/66 | NGT and IGT | European American | 344 | No ethnic difference in age, BMI, or insulin resistance by HOMA-IR. 2 h C-peptide post glucose significantly higher in BA vs. WE in the group with abdominal obesity. No ethnic difference in post glucose C-peptide in the lean group. |
| Herman et al. [35] | OGTT | RCT (data obtained before randomisation) | African American | 752 | 50.5 ± 10.1 | 26/74 | IGT | White American | 2117 | Higher CIR in BA in the context of greater insulin resistance in BA by HOMA IR and higher BMI. |
| Study                        | Methods                          | Study design | Ethnicity                          | Population of interest | Gender | Glucose tolerance | Comparison population | n  | Findings                                                                 |
|-----------------------------|----------------------------------|--------------|------------------------------------|------------------------|--------|------------------|------------------------|-----|--------------------------------------------------------------------------|
| Rasouli et al. [60]         | OGTT IVGTT Arginine stimulation test in subgroup | Cross-sectional | African American (obese, with and without family hx of T2D) | 121 | 38 (36-39) | 41/59 | NGT | White American (obese, with and without family hx of T2D) | 212 | No difference in 2 h OGTT insulin or insulin area under the curve, but higher AIRg in BA. No difference in A1max, lower DI max. BA had lower SI but higher disposition index. No difference in age, BMI, or WHR between ethnic groups. Higher insulinogenic index 30 mins in BA, but no difference when adjusted for insulin sensitivity. Higher AIR and lower SI in BA, adjusted for visceral and subcut adipose volume. No ethnic difference in DI. No ethnic difference in BMI, WHR, or body fat % by DXA. AIRg higher and SI lower in BA. No ethnic difference in age and BMI. |
| Goedecke et al. [27]       | OGTT Insulin-modified IVGTT      | Cross-sectional | Native black South African (lean and obese) | 29 | 24 ± 2 (lean) and 28 ± 1 (obese) | 0/100 | NGT | White South African (lean and obese) | 28 | Higher AIRg and DI higher in BA. AIRg remained higher after adjusting for SI. |
| Willig et al. [51]          | Insulin- or tolbutamide-modified IVGTT | Cross-sectional | African American                  | 87 | 35.3 ± 4.5 | 0/100 | Nondiabetic | European American | 68 | Higher X0 (acute C-peptide secretion), Ph1 and Ph1(tot) in BA after adjusting for age. Lower SI in BA, after adjusting for body fat % by DXA. |
| Chandler-Laney et al. [52]  | Insulin-modified IVGTT           | Cross-sectional | African American (premenopausal), (postmenopausal) | 43 | 25.9 ± 3.4 (premenopausal), 55.7 ± 4.2 (postmenopausal) | 0/100 | NGT | European American | 63 | AIRg and DI higher in BA. AIRg and DI higher after adjusting for SI. Lowered WHC and higher body fat % in BA. Higher fasting insulin and insulinogenic index (30 mins) in BA. Similar BMI and WHR in both ethnic groups. Higher AIRg and DI in BA, lower SI. Ethnic groups matched for age, sex, BMI, and BP. Adjusted for HbA1c. |
| Goree et al. [53]           | Insulin-modified IVGTT           | Cross-sectional | African American                  | 42 | 24.8 ± 3.3 (premenopausal), 56.6 ± 5.1 (postmenopausal) | 0/100 | NGT | European American | 64 | AIRg and DI higher in BA. AIRg and DI higher after adjusting for SI. Lowered WHC and higher body fat % in BA. Higher fasting insulin and insulinogenic index (30 mins) in BA. Similar BMI and WHR in both ethnic groups. Higher AIRg and DI in BA, lower SI. Ethnic groups matched for age, sex, BMI, and BP. Adjusted for HbA1c. |
| Chow et al. [54]            | Insulin-modified IVGTT           | Cross-sectional | African American                  | 17 | 36 ± 9 | 0/100 | Nondiabetic | White American | 17 | AIRg and DI higher in BA, SI lower. Matched for age and BMI. Lowered WHC and higher body fat % in BA. Higher fasting insulin and insulinogenic index (30 mins) in BA. Similar BMI and WHR in both ethnic groups. Higher AIRg and DI in BA, lower SI. Ethnic groups matched for age, sex, BMI, and BP. Adjusted for HbA1c. |
| Ladson et al. [55]          | OGTT                             | Case control  | African American with PCOS        | 36 | 27.9 ± 5.0 | 0/100 | Nondiabetic | White American with PCOS | 63 | Higher fasting insulin and insulinogenic index (30 mins) in BA. Similar BMI and WHR in both ethnic groups. Higher AIRg and DI in BA, lower SI. Ethnic groups matched for age, sex, BMI, and BP. Adjusted for HbA1c. |
| Szczepaniak et al. [45]     | Insulin-modified IVGTT           | Cross-sectional | African American                  | 20 | 37 ± 3 | 35/65 | NGT and IGT | Non-Hispanic white | 30 | Higher AIRg and DI in BA, lower SI. Ethnic groups matched for age, sex, BMI, and BP. Adjusted for HbA1c. |
| Study | Methods | Study design | Ethnicity | Population of interest | Gender | Glucose tolerance | Comparison population | Findings |
|-------|----------|--------------|-----------|------------------------|--------|-------------------|-----------------------|----------|
| Goff et al. [33] | IVGTT | Cross-sectional | UK Afro-Caribbean | 35 | 42.6 ± 7 (F) 44.9 ± 9.7 (M) | 29/71 | Nondiabetic | UK white | When adjusted for age and BMI: higher AIRg and lower Si in BA. No ethnic difference in DI. Within each HbA1c group, BA had higher AIRg and DI. Similar insulin sensitivity between ethnic groups by hyperinsulinaemic-euglycaemic clamp. |
| Ebenibo et al. [62] | IVGTT | Prospective cohort | African American | 142 | 40.2 ± 10.7 (HbA1c < 5.7%), 46.5 ± 8.9 (HbA1c 5.7-6.4%) | 25/75 | NGT | White American | 138 | Higher HOMA%B in BA. Lower SI and higher AIR and DI in BA, adjusted for age, sex, and BMI. |
| Ferguson et al. [58] | Insulin-modified IVGTT | Pre/postinterventional | African American | 42 | 26 (median), 9 (IQR) (F) 27 (median), 18 (IQR) (M) | 45/55 | Nondiabetic | European American | 106 | HOMA%B lower in BA. OGTT fasting and post glucose C-peptide levels lower in BA, no difference in insulinogenic index. Higher AIRg in BA (not significant), similar SI, and significantly higher DI in BA. BA had higher BMI and higher body fat % by DXA. |
| Healy et al. [36] | OGGT Insulin-modified IVGTT | Cross-sectional | African American (obese) | 84 | 46.4 ± 10.2 | 7/93 | Prediabetic (IFG and IGT) | White American (obese) | 61 | No significant ethnic difference in insulin or C-peptide iAUC post feeding. |
| Goff et al. [29] | MMTT plus high-fructose or high-glucose feeding | Cross-sectional | UK black African | 9 | 38.3 ± 2.0 | 100/0 | Nondiabetic | UK white | 417 | Higher AIR in BA. Lower insulin sensitivity by hyperinsulinaemic-euglycaemic clamp in blacks. BA younger and higher BMI. |
| Owei et al. [46] | IVGTT | Prospective cohort | African American (with parental T2D) | 184 | 43.2 ± 10.0 | Not reported by ethnicity | NGT and IGT | European American (with parental T2D) | 151 | Higher acute insulin response and DI in BA, late-phase insulin tended to be higher in BA. No ethnic difference in insulin sensitivity index. |
| Shah et al. [47] | Hyperglycaemic clamp Arginine-stimulated insulin response | Cross-sectional | African American | 24 | Not reported by ethnicity | Not reported by ethnicity | NGT, IGT, and T2D | White American | 74 | |
### Table 1: Continued.

| Study | Methods | Study design | Ethnicity | Population of interest | Gender | Glucose tolerance | Comparison population | Findings | mNOS |
|-------|---------|--------------|-----------|------------------------|--------|-------------------|------------------------|----------|------|
| Osei et al. [37] | Fasting parameters to determine HOMA%B OGGT Insulin-modified IVGTT | Cross-sectional | African American | Overweight/obese | 67 | 46.3 ± 10.3 | Prediabetic (IFG and IGT) | Overweight/obese white American | 28 | HOMA%B no ethnic difference OGGT: fasting C-peptide and peak C-peptide lower in BA, fasting and mean insulin tended to be higher IVGTT: AIR higher in BA, not significant. DI significantly higher in BA. BA had higher BMI and higher percentage body fat by DEXA. Insulin sensitivity by Si same between ethnic groups |
| Piccininiet al. [56] | Insulin-modified IVGTT | Cross-sectional | African American | | 18 | 25 ± 4 | NGT | European American | 29 | Insulin secretion rate (ISR) as modelled by C-peptide higher in BA vs. WE MMTT: fasting and AUC C-peptide lower in BA, no difference in insulin AUC HC: second-phase C-peptide lower in BA, no difference in insulin iAUC. Groups matched for age, BMI, HbA1c, and duration of diabetes |
| Mohandas et al. [30] | MMTT Hyperglycaemic clamp | Cross-sectional | UK black African | | 19 | 54.1 ± 7.7 | T2D (recently diagnosed) | UK white | 15 | |

AIR: acute insulin response; BA: black African; BMI: body mass index; CIR: corrected insulin response; DI: disposition index; DXA: dual-energy X-ray absorptiometry; FHx: family history; HIE: hepatic insulin extraction; HOMA%B: homeostatic model assessment of beta cell function; HOMA-IR: homeostatic model assessment of insulin resistance; iAUC: incremental area under the curve; IG: impaired glucose tolerance; IVGTT: intravenous glucose tolerance test; mNOS: modified Newcastle-Ottawa scale; MMTT: mixed meal tolerance test; NGT: normal glucose tolerance; OGGT: oral glucose tolerance test (refers to 2-hour post 75 g oral glucose); PCOS: polycystic ovarian syndrome; RCT: randomised controlled trial; Si: insulin sensitivity index; T2D: type 2 diabetes; WBISI: whole-body insulin sensitivity index; WE: white European; WHR: waist-hip ratio.
3.1. Overall Findings. The majority—thirty-four out of forty-one studies—found evidence of a higher peripheral insulin response in people of BA compared to WE ethnicity.

3.1.1. Adjustment for Adiposity. Some studies (n = 14) controlled for measures of adiposity, whether using surrogate measurements such as waist circumference or waist-hip ratio [28, 38, 39, 41, 60], or using hydrostatic weighing [49] or DXA to assess percentage body fat [27, 36, 37, 42, 52, 55, 59], or using CT imaging to assess volume of visceral and subcutaneous fat deposits [54]. All 14 studies consistently demonstrated that hyperinsulinaemia of BA persisted after adjustment for adiposity.

3.1.2. Adjustment for Insulin Sensitivity. The relative hyperinsulinaemia of BA ethnicity persisted in the majority of studies which adjusted for the prevailing insulin sensitivity (n = 15), while a minority (n = 2) of studies found that hyperinsulinaemia was an appropriate compensatory response to higher insulin resistance [27, 33].

### Table 2: Ethnic comparison of insulin responses.

| Models based on fasting measures (HOMA%B) | BA > WE | No significant ethnic difference | BA < WE |
|------------------------------------------|---------|----------------------------------|---------|
| (HOMA%B)                                 | [41] (NGT and IFG) | [37] (IFG/IGT) | [32] (T2D) |
|                                          | [58]    | [36] (IFG/IGT)                  |         |
| Cumulative n (fasting)                   | 2253    | 95                               | 4709    |

| Oral nutrient stimulation                |         |                                  |         |
|------------------------------------------|---------|----------------------------------|---------|
| (NGT)                                    | [40]    | [60]                            | [24]    |
|                                          | [42]    | [27]                            |         |
|                                          | [35]    | [36] (IFG/IGT)                  |         |
|                                          | [55]    | [37] (IFG/IGT)                  |         |
|                                          | [44] (NGT and IGT) | [38] (T2D) |         |
|                                          | [28] (in obese only) | [30] (T2D) |         |
| Cumulative n (oral)                      | 4541    | 2068                            | 33      |

| IV glucose stimulation                   |         |                                  |         |
|------------------------------------------|---------|----------------------------------|---------|
| (NGT and IGT)                            | [46]    | [30] (T2D)                      |         |
|                                          | [45] (NGT and IGT) | [43] (NGT and IGT) |         |
|                                          | [58]    | [62]                            |         |
|                                          | [47] (NGT, IGT, and T2D) | [38] (T2D) |         |
|                                          | [36] (IFG/IGT) | [37] (IFG/IGT) |         |
|                                          | [53]    | [60]                            |         |
|                                          | [51]    | [49]                            |         |
|                                          | [44] (NGT and IGT) | [36] (IFG/IGT) |         |
|                                          | [61]    | [43] (NGT and IGT) |         |

Cumulative n (IV) 4461 34 18

NGT and nondiabetic subjects, unless otherwise specified. Cumulative n fasting, oral, and IV refer to the total number of participants (BA and WE) in the studies using fasting measures, oral nutrient stimulation, and intravenous glucose stimulation techniques, respectively (note that each study may be presented in more than one category). BA: black African; WE: white European; NGT: normal glucose tolerance; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; T2D: type 2 diabetes.
3.1.3. Models Based on Fasting Measures. Five studies calculated HOMA%B using fasting glucose and fasting insulin. Two studies, one in a non-diabetic and one in a mixed NGT/IFG population, found higher HOMA%B in BA [41, 58], one study in an IFG/IGT population found no significant ethnic difference [37], and two studies in IFG/IGT and type 2 diabetic populations found that HOMA%B was lower in BA compared to WE [32, 36].

3.1.4. Insulin Response Post Oral Glucose or Meal. Of the 21 studies reporting indices of insulin secretion based on oral glucose or meal tests (Table 2), the majority found no ethnic difference in insulin response between BA and WE (n = 10).

Seven studies found a greater insulin response in BA [34, 35, 42, 44, 48, 50, 55] while two studies found a lower response [24, 25]. Two studies had different results in stratified cohorts, with a greater insulin response in BA in NGT subjects but no ethnic difference in IGT or T2D subjects [40] and a greater insulin response in BA in obese subjects but no ethnic difference in lean subjects [28].

Only three studies [26, 29, 30] employed the mixed meal test, while one study found a higher insulin levels at 30 mins post meal in BA [26]; none of these studies found significant ethnic differences in the incremental area under the curve for insulin post meal.

3.1.5. Insulin Response Post Intravenous Glucose. A consistent picture emerges from the 25 studies which assessed insulin response to intravenous glucose (Table 2), with the overwhelming majority finding that the insulin response was greater in those of BA compared to WE ethnicity, across all categories of glucose tolerance (n = 23). One study in a T2D population found no ethnic difference [30], and one study in an NGT population found the response was lower in BA compared to WE [25].

3.1.6. Beta Cell Insulin Secretion Using C-Peptide Measurements. Fourteen out of forty-one studies used C-peptide measurements in their assessment of beta cell function (see Table 3). Most used oral glucose stimulation techniques (n = 9), with a minority using intravenous techniques (n = 3) [52, 56, 63] or a combination of both oral and intravenous stimulation (n = 2) [25, 30]. In NGT cohorts, findings were conflicting, with some studies finding that beta cell insulin secretion was higher in BA vs. WE (n = 4) [28, 48, 52, 56] while others found it was lower (n = 2) [25, 50] or that there was no significant difference (n = 2) [28, 29, 34, 63]. In exclusively IGT or T2D cohorts, beta cell insulin secretion by C-peptide measurement was found to be consistently lower in BA compared to WE, albeit the number of studies was very small (n = 3, comprising a total of 170 BA subjects) [30, 36, 37]. In two populations of mixed glucose tolerance, no significant difference was found [31, 42].

4. Discussion

4.1. Overall Findings. This systematic review is aimed at examining the evidence for “upregulated” beta cell function in adults of black African ethnicity; in particular, it sought to account for prevailing insulin sensitivity and to differentiate between insulin secretion and hepatic insulin extraction.

Overall, the results show that adults of black African ethnicity—whether indigenous or of the diaspora—have a greater peripheral insulin response compared to those of white European ethnicity. Their relative hyperinsulinaemia does not appear to be accounted for either by differences in insulin sensitivity or differences in adiposity.

Hyperinsulinaemia in black African populations appears to be a highly conserved trait [34] which has been demonstrated in prepubertal children [66] and which may be driven by both genetic and epigenetic factors [67]. It has been hypothesised that a robust insulin response may have evolved in this population to promote tissue growth, which is in keeping with the observation that BA youths tend to be taller than their white counterparts [68] and that BA populations have increased bone density [69–71] and muscle mass [72, 73] compared to WE.

However, there are several areas where this systematic review has demonstrated limitations or inconsistencies in our established understanding. There appear to be four key
areas of methodology which affect the outcomes of each study: the use of C-peptide measurements to assess insulin secretion; the use of oral or intravenous methods to stimulate beta cell response; the glucose tolerance status of the study population; and, possibly, the sex of the population.

4.2. Effect of C-Peptide Measurement. Only 14 out of the 41 studies measured C-peptide responses and were therefore able to differentiate between insulin secretory function and hepatic insulin extraction. This is of great importance, given that the evidence suggests that HIE is significantly lower in black compared to white ethnic populations [56, 66]. While the majority of studies found peripheral hyperinsulinemia in BA adults, the use of C-peptide levels as a measure of beta cell insulin secretion gave rise to highly variable findings. Although direct quantitative comparison is not possible due to the heterogeneity of populations and methods used, the cumulative n presented in Table 3 suggests that the weight of evidence based on C-peptide measurements does not support the finding of beta cell upregulation in BA adults. This is in contrast to the work in children and adolescents, which has found both increased beta cell insulin secretion and reduced HIE in BA [15, 74, 75]. Whether BA adults exhibit increased beta cell secretion or whether their hyperinsulinaemia is driven predominantly by reduced HIE remains an unresolved question.

The differences between the findings in children and adults may be due to an age-related decline in beta cell function [76, 77], with reduced HIE playing a relatively more dominant role in hyperinsulinemia of BA adults. It is interesting that HIE appears to be an important physiological process underlying ethnic differences in glucose metabolism. It has been previously noted that HIE is the primary cause of hyperinsulinemia in subjects with more severe glucose intolerance [78] and that it may be an important determinant of future T2D in BA [79]. While reduced HIE is traditionally understood to be associated with visceral adiposity and increased levels of hepatic fat [80, 81], in BA populations there is conversely evidence of lower intrahepatic lipid compared to WE [82–85]. Therefore, the mechanism of reduced HIE in BA is yet to be fully determined, but potential routes of investigation include the role of inflammatory and vascular mediators [86, 87].

4.3. Effect of IV versus Oral Methods of Beta Cell Stimulation. Where previous reviews have been drawn from mainly intravenous studies [9, 17], here the inclusion of multiple methodologies of beta cell function assessment gives a more complex picture. Studies examining the response to intravenous glucose administration provide highly consistent evidence for hyperinsulinaemia in BA, whereas studies using oral glucose or meal ingestion have much more variable findings. The discrepancy between intravenous and oral studies has been previously noted in the literature [9] and remains largely unexplained. Differences in the incretin response are one possible mechanism, but there are no consistent findings from the few studies which have investigated ethnic differences in the incretin pathway [42, 88–90].

These observations call into question whether the ethnic differences seen during intravenous studies are clinically relevant if they cannot be reliably demonstrated under physiological conditions. In particular, the small subset of studies using arguably the most physiological method of assessment, i.e., the mixed meal tolerance test, did not find any ethnic differences in insulin response. Further investigation is needed to determine the mechanisms which lead to the route of delivery and the magnitude of the glucose load provoking different insulin responses in BA adults.

4.4. Effect of Glucose Tolerance Status. It should be noted that not all studies measured glucose tolerance as part of their protocols; hence, while the population was defined as “healthy” or “nondiabetic” it is conceivable that participants with impaired glucose regulation were included in the sample. Furthermore, many studies were comprised of cohorts of mixed glucose tolerance. Therefore, an attempt to examine ethnic differences by glucose tolerance was limited by the small number of relevant studies.

While there were only three studies which assessed insulin secretory function by C-peptide measurements in IGT/IFG or T2D cohorts where glucose tolerance was strictly defined [30, 36, 37], all three of these indicated that BA adults with impaired glucose tolerance and T2D exhibit greater insulin secretory deficits compared to WE. Interestingly, this is in direct contrast to data from paediatric populations, which demonstrates elevated insulin secretory function in BA across all categories of glucose tolerance [10, 75, 91, 92].

It may be that impaired glucose regulation in the paediatric/youth population represents a more extreme or aggressive phenotype compared to adults. In youth, glucose intolerance is likely to be associated with severe obesity [93] which promotes beta cell hypersecretion of insulin, whereas age-related beta cell decline in BA adults may account for their relatively greater insulin secretory deficits as they progress to T2D. The findings of this review raise the question of whether the beta cells of BA adults are more vulnerable to dysfunction than their WE counterparts as obesity and insulin resistance prevail.

4.5. Effect of Gender. Although sex-specific differences were not explored by the majority of the studies, two studies found evidence that BA females exhibit greater hyperinsulinaemia compared with BA males [33, 57]. Enhanced postprandial insulin secretion in females compared to males has also been demonstrated in other ethnic groups, including white Americans [94] and East Asians [95]. While there was a predominance of female subjects in both ethnic groups (61% of WE and 76% of BA subjects across all included studies), the relatively higher proportion of females in the BA cohorts may have led to an overestimation of ethnic differences.

5. Conclusions

While BA have a hyperinsulinaemic response to glucose, reduced hepatic insulin extraction rather than differences in beta cell function may be the primary determinant of ethnic differences in diabetes pathophysiology in adulthood. The
available literature is predominantly drawn from female, NGT/nondiabetic subjects, and there are relatively few stud-
ies which look at exclusively IFG/IGT or T2D populations
or which take differences in HIE into account. Furthermore,
with the exception of responses to intravenous glucose, the
reported direction and magnitude of differences in insulin
responses to glucose challenges are not consistent across
all studies. The methodology employed—namely, whether
intravenous or oral techniques are used, whether C-peptide
levels are assessed, and/or whether the glucose tolerance
status of the population is studied—appears to have a signif-
icant impact on the findings made. The mechanisms of
hyperinsulinaemia in BA adults, and how these may relate
to their increased risk of T2D, therefore remain unclear.

The cumulative evidence demonstrates that further work
is needed to determine these mechanisms, using rigorous
methodology to differentiate between insulin secretion and
insulin clearance, adjusting for insulin sensitivity, using both
oral and intravenous techniques and examining subjects
according to strictly defined categories of glucose tolerance.

Appendix

A. Search Strategy for Ovid Medline

(1) exp African Continental Ancestry Group/
(2) afr*.mp.
(3) ghana*.mp.
(4) nigeria*.mp.
(5) caribbean.mp.
(6) beta cell function.mp.
(7) insulin secretion.mp.
(8) insulin clearance.mp.
(9) acute insulin response.mp.
(10) beta cell respons*.mp.
(11) insulinogenic index.mp.
(12) exp European Continental Ancestry Group/
(13) white european.mp.
(14) non-hispanic white.mp.
(15) caucasian.mp.
(16) exp DIABETES MELLITUS/ or exp Adult/
(17) diab*.mp.
(18) glucose toleran*.mp.
(19) non-diab*.mp.
(20) healthy.mp.
(21) 1 or 2 or 3 or 4 or 5
(22) 6 or 7 or 8 or 9 or 10 or 11
(23) 12 or 13 or 14 or 15
(24) 16 or 17 or 18 or 19 or 20
(25) 21 and 22 and 23 and 24

B. Newcastle-Ottawa Scale, Modified for Cross-
Sectional Studies

The most appropriate statements are selected. Studies can
score a maximum of 10 stars.

B.1. Selection: Maximum 5 Stars

(1) Representativeness of the sample
   (a) Truly representative of the average in the target
       population (all subjects or random sampling)*
   (b) Somewhat representative of the average in the
       target population (nonrandom sampling)*
   (c) No description of the sampling strategy

(2) Selected group of users
   (a) Selection of individuals to exclude factors that
       will bias results (e.g., medications affecting glu-
       cose metabolism)*
   (b) No relevant/systematic selection

(3) Sample size
   (a) Justified and satisfactory (power calculation
       included)*
   (b) Not justified

(4) Diagnosis
   (a) Characterisation of the diagnosis of diabetes sub-
       type**
   (b) Diabetes subtype is provided*
   (c) No information regarding diabetes subtype

B.2. Comparability: Maximum 2 Stars

(1) The subjects in different outcome groups are compar-
able, based on the study design or analysis. Con-
 founding factors are controlled:
   (a) The study controls for the most important factor
       (BMI)**
   (b) The study controls for any additional factor (e.g.,
       age, sex, insulin sensitivity, and diet)*

B.3. Outcome: Maximum 3 Stars

(1) Ascertainment of the method
The authors have no competing interests to declare.

Conflicts of Interest

The authors have no competing interests to declare.

Abbreviations

AIRg: Acute insulin response to glucose
BA: Black African(s)
CIR: Corrected insulin response
DXA: Dual-energy X-ray absorptiometry
DI: Disposition index
HIE: Hepatic insulin extraction
HOMA%B: Homeostatic model assessment of beta cell function
HOMA-IR: Homeostatic model assessment of insulin resistance
iAUC: Incremental area under the curve
IFG: Impaired fasting glucose
IGT: Impaired glucose tolerance
IVGTT: Intravenous glucose tolerance test
MMTT: Mixed meal tolerance test
OGTT: Oral glucose tolerance test
Si: Insulin sensitivity index
T2D: Type 2 diabetes
WBISI: Whole-body insulin sensitivity index
WE: White European(s).

Conflicts of Interest

The authors have no competing interests to declare.

References

[1] T. Tillin, N. G. Forouhi, P. McKeigue, N. Chaturvedi, and SABRE Study Group, “Southall And Brent REvisited: cohort profile of SABRE, a UK population-based comparison of cardiovascular disease and diabetes in people of European, Indian Asian and African Caribbean origins,” International Journal of Epidemiology, vol. 41, no. 1, pp. 33–42, 2012.

[2] F. L. Brancati, W. H. L. Kao, A. R. Folsom, R. L. Watson, and M. Szkel, “Incident type 2 diabetes mellitus in African American and white adults: the Atherosclerosis Risk in Communities Study,” Journal of the American Medical Association, vol. 283, no. 17, pp. 2253–2259, 2000.

[3] Statistics PH, Health Survey for England 2004: the Health of Minority Ethnic Groups– Headline Tables, National Statistics and Health and Social Care Information Centre, Leeds, England, 2005.

[4] K. Winkle, S. M. Thomas, S. Sivaprasad et al., “The clinical characteristics at diagnosis of type 2 diabetes in a multi-ethnic population: the South London Diabetes cohort (SOUL-D),” Diabetologia, vol. 56, no. 6, pp. 1272–1281, 2013.

[5] R. B. Lipton, Y. Uao, G. Cao, R. S. Cooper, and D. McGee, “Determinants of incident non-insulin-dependent diabetes mellitus among blacks and whites in a national sample: the NHANES I Epidemiologic Follow-up Study,” American Journal of Epidemiology, vol. 138, no. 10, pp. 826–839, 1993.

[6] L. B. Signorello, D. G. Schlundt, S. S. Cohen et al., “Comparing diabetes prevalence between African Americans and Whites of similar socioeconomic status,” American Journal of Public Health, vol. 97, no. 12, pp. 2260–2267, 2007.

[7] L. E. Eggede, M. Mueller, C. L. Echols, and M. Gebregziabher, “Longitudinal differences in glycemic control by race/ethnicity among veterans with type 2 diabetes,” Medical Care, vol. 48, no. 6, pp. 527–533, 2010.

[8] F. L. Brancati, P. K. Whelton, H. L. Kuller, and M. J. Klag, “Diabetes mellitus, race, and socioeconomic status. A population-based study,” Annals of Epidemiology, vol. 6, no. 1, pp. 67–73, 1996.

[9] T. S. Hannon, F. Bacha, Y. Lin, and S. A. Arslanian, “Hyperinsulinemia in African-American adolescents compared with their American white peers despite similar insulin sensitivity: a reflection of upregulated beta-cell function?,” Diabetes Care, vol. 31, no. 7, pp. 1445–1447, 2008.

[10] F. Bacha, N. Gungor, S. Lee, and S. A. Arslanian, “Type 2 diabetes in youth: are there racial differences in β-cell responsiveness relative to insulin sensitivity?”, Pediatric Diabetes, vol. 13, no. 3, pp. 259–265, 2012.

[11] F. Bacha, R. Saad, N. Gungor, and S. A. Arslanian, “Does adiponectin explain the lower insulin sensitivity and hyperinsulinemia of African-American children?,” Pediatric Diabetes, vol. 6, no. 2, pp. 100–102, 2005.

[12] K. Osei, T. Gaillard, and D. Schuster, “Plasma adiponectin levels in high risk African-Americans with normal glucose tolerance, impaired glucose tolerance, and type 2 diabetes,” Obesity Research, vol. 13, no. 1, pp. 179–185, 2005.

[13] K. S. Hughan, R. C. Bonadonna, S. Lee, S. F. Michaliszyn, and S. A. Arslanian, “β-cell lipotoxicity after an overnight intravenous lipid challenge and free fatty acid elevation in African American versus American white overweight/obese adolescents,” The Journal of Clinical Endocrinology and Metabolism, vol. 98, no. 5, pp. 2062–2069, 2013.

[14] S. F. Michaliszyn, R. C. Bonadonna, L. A. Sjaarda, S. Lee, L. Farchoukh, and S. A. Arslanian, “β-cell lipotoxicity in response to free fatty acid elevation in prepubertal youth: African American versus Caucasian contrast,” Diabetes, vol. 62, no. 8, pp. 2917–2922, 2013.

[15] S. A. Arslanian, R. Saad, V. Grishin, H. S. Caddick, and J. Janosky, “Hyperinsulinemia in African-American children: decreased insulin clearance and increased insulin secretion and its relationship to insulin sensitivity,” Diabetes, vol. 51, no. 10, pp. 3014–3019, 2002.

[16] L. L. Goree, P. Chandler-Laney, A. C. Ellis, K. Casaza, W. M. Granger, and B. A. Gower, “Dietary macronutrient composition affects β cell responsiveness but not insulin sensitivity,” The American Journal of Clinical Nutrition, vol. 94, no. 1, pp. 120–127, 2011.
[17] K. Kodama, D. Tojar, S. Yamada, K. Toda, C. J. Patel, and A. J. Butte, "Ethnic differences in the relationship between insulin sensitivity and insulin response: a systematic review and meta-analysis," *Diabetes Care*, vol. 36, no. 6, pp. 1789–1796, 2013.

[18] E. Ferrannini and A. Mari, "β-cell function in type 2 diabetes," *Metabolism: Clinical and Experimental*, vol. 63, no. 10, pp. 1217–1227, 2014.

[19] C. Cobelli, C. Dalla Man, G. Toffolo, R. Basu, A. Vella, and R. Rizza, "The oral minimal model method," *Diabetes*, vol. 63, no. 4, pp. 1203–1213, 2014.

[20] M. Ader, D. Stefanovski, S. P. Kim et al., "Hepatic insulin clearance is the primary determinant of insulin sensitivity in the normal dog," *Obesity*, vol. 22, no. 5, pp. 1238–1245, 2014.

[21] K. S. Polonsky and A. H. Rubenstein, "C-peptide as a measure of the secretion and hepatic extraction of insulin. Pitfalls and limitations," *Diabetes*, vol. 33, no. 5, pp. 486–494, 1984.

[22] D. Moher, A. Liberati, J. Tetzlaff, D. G. Altman, and for the PRISMA Group, "Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement," *The BMJ*, vol. 339, no. 1, article b2535, 2009.

[23] G. S. B. Wells, D. O'Connell, J. Peterson, V. Welch, M. Losos, and P. Tugwell, "The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses," http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.2013.

[24] A. H. Rubenstein, H. C. Sefelt, K. Miller, I. Bersohn, and A. D. Wright, "Metabolic response to oral glucose in healthy South African white, Indian, and African subjects," *The BMJ*, vol. 1, no. 5646, pp. 748–751, 1969.

[25] R. Shires, B. I. Joffe, and H. C. Sefelt, "Maximal pancreatic beta-cell stimulation and the counter-regulatory hormonal responses in South African black and white obese subjects," *South African Medical Journal*, vol. 67, no. 21, pp. 845–847, 1985.

[26] C. Punyadeera, N. J. Crowther, M. T. van der Merwe et al., "Metabolic response to a mixed meal in obese and lean women from two South African populations," *Obesity Research*, vol. 10, no. 12, pp. 1207–1216, 2002.

[27] J. H. Goedelke, J. A. Dave, M. V. Faulenbach et al., "Insulin response in relation to insulin sensitivity: an appropriate beta-cell response in black South African women," *Diabetes Care*, vol. 32, no. 5, pp. 860–865, 2009.

[28] M. Reimann, A. E. Schutte, H. W. Huisman et al., "Ethnic differences in C-peptide secretion but not in non-esterified fatty acid metabolism in pre-menopausal women with and without abdominal obesity," *Diabetes Research and Clinical Practice*, vol. 77, no. 1, pp. 62–69, 2007.

[29] L. M. Goff, M. B. Whyte, M. Samuel, and S. V. Harding, "Significantly greater triglyceridemia in Black African compared to White European men following high added fructose and glucose feeding: a randomized crossover trial," *Lipids in Health and Disease*, vol. 15, no. 1, p. 145, 2016.

[30] C. Mohandas, R. Bonadonna, F. Shoje-Moradie et al., "Ethnic differences in insulin secretory function between black African and white European men with early type 2 diabetes," *Diabetes, Obesity & Metabolism*, vol. 20, no. 7, pp. 1678–1687, 2018.

[31] J. K. Cruickshank, J. MacDuff, U. Drubra, J. Cooper, and M. Burnett, "Ethnic differences in fasting plasma C-peptide and insulin in relation to glucose tolerance and blood pressure," *The Lancet*, vol. 338, no. 8771, pp. 842–847, 1991.

[32] UK Prospective Diabetes Study Group, "UK Prospective Diabetes Study XII: differences between Asian, Afro-Caribbean and white Caucasian type 2 diabetic patients at diagnosis of diabetes," *Diabetic Medicine*, vol. 11, no. 7, pp. 670–677, 1994.

[33] L. M. Goff, B. A. Griffin, J. A. Lovegrove et al., "Ethnic differences in beta-cell function, dietary intake and expression of the metabolic syndrome among UK adults of South Asian, black African-Caribbean and white-European origin at high risk of metabolic syndrome," *Diabetes & Vascular Disease Research*, vol. 10, no. 4, pp. 315–323, 2013.

[34] K. Osei, D. P. Schuster, S. K. Owusu, and A. G. B. Amoah, "Race and ethnicity determine serum insulin and C-peptide concentrations and hepatic insulin extraction and insulin clearance: comparative studies of three populations of West African ancestry and white Americans," *Metabolism: Clinical and Experimental*, vol. 46, no. 1, pp. 53–58, 1997.

[35] W. H. Herman, Y. Ma, G. Uwaifo et al., "Differences in A1C by race and ethnicity among patients with impaired glucose tolerance in the Diabetes Prevention Program," *Diabetes Care*, vol. 30, no. 10, pp. 2453–2457, 2007.

[36] S. J. Healy, K. Osei, and T. Gaillard, "Comparative study of glucose homeostasis, lipids and lipoproteins, HDL functionality, and cardiometabolic parameters in modestly severely obese African Americans and White Americans with prediabetes: implications for the metabolic paradoxes," *Diabetes Care*, vol. 38, no. 2, pp. 228–235, 2015.

[37] K. Osei and T. Gaillard, "Ethnic differences in glucose effectiveness and disposition index in overweight/obese African American and white women with prediabetes: a study of compensatory mechanisms," *Diabetes Research and Clinical Practice*, vol. 130, pp. 278–285, 2017.

[38] S. M. Haffner, G. Howard, E. Mayer et al., "Insulin sensitivity and acute insulin response in African-Americans, non-Hispanic whites, and Hispanics with NIDDM: the Insulin Resistance Atherosclerosis Study," *Diabetes*, vol. 45, no. 1, pp. 63–69, 1996.

[39] S. M. Haffner, D. Ralph, M. F. Saad et al., "Increased insulin resistance and insulin secretion in nondiabetic African-Americans and Hispanics compared with non-Hispanic whites. The Insulin Resistance Atherosclerosis Study," *Diabetes*, vol. 45, no. 6, pp. 742–748, 1996.

[40] C. C. Jensen, M. Nnop, R. L. Hull, W. Y. Fujimoto, S. E. Kahn, and the American Diabetes Association GENNID Study Group, "β-cell function is a major contributor to oral glucose tolerance in high-risk relatives of four ethnic groups in the U.S.,” *Diabetes*, vol. 51, no. 7, pp. 2170–2178, 2002.

[41] J. I. Torres, J. Skurnick, A. L. Davidow et al., "Ethnic differences in insulin sensitivity and β-cell function in premenopausal or early perimenopausal women without diabetes: the Study of Women’s Health Across the Nation (SWAN)," *Diabetes Care*, vol. 27, no. 2, pp. 354–361, 2004.

[42] P. A. Velasquez-Meyer, P. A. Cowan, G. E. Umpierrez, R. H. Lustig, A. K. Cashion, and G. A. Burghen, "Racial differences in glucagon-like peptide-1 (GLP-1) concentrations and insulin dynamics during oral glucose tolerance test in obese subjects," *International Journal of Obesity and Related Metabolic Disorders*, vol. 27, no. 11, pp. 1359–1364, 2003.

[43] J. B. Albu, A. J. Kovera, L. Allen et al., "Independent association of insulin resistance with larger amounts of intermuscular adipose tissue and a greater acute insulin response to glucose in African American than in white nondiabetic
women,” The American Journal of Clinical Nutrition, vol. 82, no. 6, pp. 1210–1217, 2005.

[44] S. C. Elbein, W. S. Chu, S. K. Das et al., ”Transcription factor 7-like 2 polymorphisms and type 2 diabetes, glucose homeostasis traits and gene expression in US participants of European and African descent,” Diabetologia, vol. 50, no. 8, pp. 1621–1630, 2007.

[45] L. S. Szczepaniak, R. G. Victor, R. Mathur et al., ”Pancreatic steatosis and its relationship to β-cell dysfunction in humans: racial and ethnic variations,” Diabetes Care, vol. 35, no. 11, pp. 3777–3783, 2012.

[46] I. Owei, N. Umekwe, J. Wan, and S. Dagogo-Jack, “Plasma lipid levels predict dysglycemia in a biracial cohort of nondiabetic subjects: potential mechanisms,” Experimental Biology and Medicine, vol. 241, no. 17, pp. 1961–1967, 2016.

[47] S. S. Shah, C. E. Ramirez, A. C. Powers, C. Yu, C. A. Shibao, and J. M. Luther, ”Hyperglycemic clamp-derived disposition index is negatively associated with metabolic syndrome severity in obese subjects,” Metabolism: Clinical and Experimental, vol. 65, no. 6, pp. 835–842, 2016.

[48] K. Osei, D. A. Cottrell, and B. Harris, ”Differences in basal and poststimulation glucose homeostasis in nondiabetic first degree relatives of black and white patients with type 2 diabetes mellitus,” The Journal of Clinical Endocrinology & Metabolism, vol. 75, no. 1, pp. 82–86, 1992.

[49] C. L. Melby, R. C. Ho, K. Jeckle, L. Beal, M. Goran, and W. T. Donahoo, ”Comparison of risk factors for obesity in young, nonobese African-American and Caucasian women,” International Journal of Obesity and Related Metabolic Disorders, vol. 24, no. 11, pp. 1514–1522, 2000.

[50] X. Chen and T. O. Scholl, ”Ethnic differences in C-peptide/insulin/glucose dynamics in young pregnant women,” The Journal of Clinical Endocrinology and Metabolism, vol. 87, no. 10, pp. 4642–4646, 2002.

[51] A. L. Willig, K. R. Casazza, J. Divers et al., ”Uncoupling protein 2 Ala55Val polymorphism is associated with a higher acute insulin response to glucose,” Metabolism: Clinical and Experimental, vol. 58, no. 6, pp. 877–881, 2009.

[52] P. C. Chandler-Laney, R. P. Phadke, W. M. Granger et al., ”Adiposity and beta-cell function: relationships differ with ethnicity and age,” Obesity, vol. 18, no. 11, pp. 2086–2092, 2010.

[53] L. L. T. Goree, B. E. Darnell, R. A. Oster, M. A. Brown, and B. A. Gower, ”Associations of free fatty acids with insulin secretion and action among African-American and European-American girls and women,” Obesity, vol. 18, no. 2, pp. 247–253, 2010.

[54] C. C. Chow, V. Periwal, G. Csako et al., ”Higher acute insulin response to glucose may determine greater free fatty acid clearance in African-American women,” The Journal of Clinical Endocrinology and Metabolism, vol. 96, no. 8, pp. 2456–2463, 2011.

[55] G. Ladson, W. C. Dodson, S. D. Sweet et al., ”Racial influence on the polycystic ovary syndrome phenotype: a black and white case-control study,” Fertility and Sterility, vol. 96, no. 1, pp. 224–229.e2, 2011.

[56] F. Piccinini, D. C. Polidori, B. A. Gower, and R. N. Bergman, ”Hepatic but not extrahepatic insulin clearance is lower in African American than in European American women,” Diabetes, vol. 66, no. 10, pp. 2564–2570, 2017.

[57] T. R. Gaillard, D. P. Schuster, and K. Osei, ”Gender differences in cardiovascular risk factors in obese, nondiabetic first degree relatives of African Americans with type 2 diabetes mellitus,” Ethnicity & Disease, vol. 8, no. 3, pp. 319–330, 1998.

[58] J. F. Fergusson, R. Y. Shah, R. Shah, N. N. Mehta, M. R. Rickels, and M. P. Reilly, ”Activation of innate immunity modulates insulin sensitivity, glucose effectiveness and pancreatic β-cell function in both African ancestry and European ancestry healthy humans,” Metabolism: Clinical and Experimental, vol. 64, no. 4, pp. 513–520, 2015.

[59] N. Stefan, M. Stumvoll, C. Weyer, C. Bogardus, P. A. Tataranni, and R. E. Pratley, ”Exaggerated insulin secretion in Pima Indians and African-Americans but higher insulin resistance in Pima Indians compared to African-Americans and Caucasians,” Diabetic Medicine, vol. 21, no. 10, pp. 1090–1095, 2004.

[60] N. Rasouli, H. J. Spencer, A. A. Rashidi, and S. C. Elbein, ”Impact of family history of diabetes and ethnicity on β-cell function in obese, glucose-tolerant individuals,” The Journal of Clinical Endocrinology and Metabolism, vol. 92, no. 12, pp. 4656–4663, 2007.

[61] N. G. Boule, S. J. Weisnagel, T. A. Lakka et al., ”Effects of exercise training on glucose homeostasis: the HERITAGE Family Study,” Diabetes Care, vol. 28, no. 1, pp. 108–114, 2005.

[62] S. Ebenibo, C. Edeoga, J. Wan, and S. Dagogo-Jack, ”Glucoregulatory function among African Americans and European Americans with normal or pre-diabetic hemoglobin A1c levels,” Metabolism: Clinical and Experimental, vol. 63, no. 6, pp. 767–772, 2014.

[63] K. Osei and D. P. Schuster, ”Ethnic differences in secretion, sensitivity, and hepatic extraction of insulin in black and white Americans,” Diabetic Medicine, vol. 11, no. 8, pp. 755–762, 1994.

[64] K. C. Chiu, P. Cohan, N. P. Lee, and L. M. Chuang, ”Insulin sensitivity differs among ethnic groups with a compensatory response in beta-cell function,” Diabetes Care, vol. 23, no. 9, pp. 1353–1358, 2000.

[65] K. C. Chiu, L. M. Chuang, and C. Yoon, ”Comparison of measured and estimated indices of insulin sensitivity and β cell function: impact of ethnicity on insulin sensitivity and β cell function in glucose-tolerant and normotensive subjects,” The Journal of Clinical Endocrinology and Metabolism, vol. 86, no. 4, pp. 1620–1625, 2001.

[66] F. Piccinini, D. C. Polidori, B. A. Gower, J. R. Fernandez, and R. N. Bergman, ”Dissection of hepatic versus extra-hepatic insulin clearance: ethnic differences in childhood,” Diabetes, Obesity & Metabolism, vol. 20, no. 12, pp. 2869–2875, 2018.

[67] B. A. Gower, J. R. Fernandez, T. M. Beasley, M. D. Shriver, and M. I. Goran, ”Using genetic admixture to explain racial differences in insulin-related phenotypes,” Diabetes, vol. 52, no. 4, pp. 1047–1051, 2003.

[68] W. W. Wong, K. C. Copeland, A. C. Hergenroeder, R. B. Hill, J. E. Stuff, and K. J. Ellis, ”Serum concentrations of insulin, insulin-like growth factor-I and insulin-like growth factor binding proteins are different between white and African American girls,” The Journal of Pediatrics, vol. 135, no. 3, pp. 296–300, 1999.

[69] H. S. Nam, S. S. Kweon, J. S. Choi et al., ”Racial/ethnic differences in bone mineral density among older women,” Journal of Bone and Mineral Metabolism, vol. 31, no. 2, pp. 190–198, 2013.

[70] H.-S. Nam, M.-H. Shin, J. M. Zmuda et al., ”Race/ethnic differences in bone mineral densities in older men,” Osteoporosis International, vol. 21, no. 12, pp. 2115–2123, 2010.
References:

[71] A. J. van Ballegooijen, C. Robinson-Cohen, R. Katz et al., “Vitamin D metabolites and bone mineral density: the multi-ethnic study of atherosclerosis, “Bone, vol. 78, pp. 186–193, 2015.

[72] D. R. Wagner and V. H. Heyward, “Measures of body composition in blacks and whites: a comparative review,” The American Journal of Clinical Nutrition, vol. 71, no. 6, pp. 1392–1402, 2000.

[73] D. Liska, S. Dufour, T. L. Zern et al., “Inerethnic differences in muscle, liver and abdominal fat partitioning in obese adolescents,” PloS One, vol. 2, no. 6, article e569, 2007.

[74] G. I. Uwaifo, T. T. Nguyen, M. F. Keil et al., “A. Kotronen, S. Vehkavaara, A. Seppala-Lindroos, F. Bacha, R. Saad, N. Gungor, J. Janosky, and S. A. Arslanian, E. Reaven, G. Gold, and G. Reaven, “β induced insulin secretion by the β cell,” Journal of Gerontology, vol. 35, no. 3, pp. 324–328, 1980.

[75] E. Reaven, D. Curry, J. Moore, and G. Reaven, “Effect of age and environmental factors on insulin release from the perfused pancreas of the rat,” The Journal of Clinical Investigation, vol. 71, no. 2, pp. 345–350, 1983.

[76] E. Bonora, I. Zavaroni, C. Coscelli, and U. Butturini, “Decreased hepatic insulin extraction in subjects with mild glucose intolerance,” Metabolism: Clinical and Experimental, vol. 32, no. 5, pp. 438–446, 1983.

[77] C. C. Lee, S. M. Haffner, L. E. Wagenknecht et al., “Insulin clearance and the incidence of type 2 diabetes in Hispanics and African Americans: the IRAS Family Study,” Diabetes Care, vol. 36, no. 4, pp. 901–907, 2013.

[78] A. Kotronen, L. Juurinen, M. Tiikkainen, S. Vehkavaara, and H. Yki-Järvinen, “Increased liver fat, impaired insulin clearance, and hepatic and adipose tissue insulin resistance in type 2 diabetes,” Gastroenterology, vol. 135, no. 1, pp. 122–130, 2008.

[79] A. Kotronen, S. Vehkavaara, A. Seppala-Lindroos, R. Bergholm, and H. Yki-Järvinen, “Effect of liver fat on insulin clearance,” American Journal of Physiology Endocrinology and Metabolism, vol. 293, no. 6, pp. E1709–E1715, 2007.

[80] F. Bacha, R. Saad, N. Gungor, J. Janosky, and S. A. Arslanian, “Obesity, regional fat distribution, and syndrome X in obese black versus white adolescents: race differential in diabetogenic and atherogenic risk factors,” The Journal of Clinical Endocrinology and Metabolism, vol. 88, no. 6, pp. 2534–2540, 2003.

[81] R. Guerrero, G. L. Vega, S. M. Grundy, and J. D. Browning, “Ethnic differences in hepatic steatosis: an insulin resistance paradox?,” Hepatology, vol. 49, no. 3, pp. 791–801, 2009.

[82] C. Kim, S. D. Harlow, C. A. Karvonen-Gutierrez et al., “Racial/ethnic differences in hepatic steatosis in a population-based cohort of post-menopausal women: the Michigan Study of Women’s Health Across the Nation,” Diabetic Medicine, vol. 30, no. 12, pp. 1433–1441, 2013.

[83] J. A. Nazare, J. D. Smith, A. L. Borel et al., “Ethnic influences on the relations between abdominal subcutaneous and visceral adiposity, liver fat, and cardiometabolic risk profile: the international study of prediction of intra-abdominal adiposity and its relationship with cardiometabolic risk/intra-abdominal adiposity,” The American Journal of Clinical Nutrition, vol. 96, no. 4, pp. 714–726, 2012.

[84] C. C. Lee, C. Lorenzo, S. M. Haffner et al., “The association of inflammatory and fibrinolytic proteins with 5 year change in insulin clearance: the Insulin Resistance Atherosclerosis Study (IRAS),” Diabetologia, vol. 56, no. 1, pp. 112–120, 2013.

[85] A. Natali, R. Ribeiro, S. Baldi et al., “Systemic inhibition of nitric oxide synthesis in non-diabetic individuals produces a significant deterioration in glucose tolerance by increasing insulin clearance and inhibiting insulin secretion,” Diabetologia, vol. 56, no. 5, pp. 1183–1191, 2013.

[86] P. A. Velasquez-Meyer, P. A. Cowan, S. Perez-Faustinelli et al., “Racial disparity in glucagon-like peptide 1 and inflammation markers among severely obese adolescents,” Diabetes Care, vol. 31, no. 4, pp. 770–775, 2008.

[87] P. B. Higgins, J. R. Fernandez, W. T. Garvey, W. M. Granger, and B. A. Gower, “Entero-insular axis and postprandial insulin differences in African American and European American children,” The American Journal of Clinical Nutrition, vol. 88, no. 5, pp. 1277–1283, 2008.

[88] S. F. Michalizyn, S. Lee, F. Bacha et al., “Differences in β-cell function and insulin secretion in black vs. white obese adolescents: do incretin hormones play a role?,” Pediatric Diabetes, vol. 18, no. 2, pp. 143–151, 2017.

[89] S. Arslanian and C. Suprasongsin, “Differences in the in vivo insulin secretion and sensitivity of healthy black versus white adolescents,” The Journal of Pediatrics, vol. 129, no. 3, pp. 440–443, 1996.

[90] S. Arslanian, C. Suprasongsin, and J. E. Janosky, “Insulin secretion and sensitivity in black versus white prepubertal healthy children,” The Journal of Clinical Endocrinology and Metabolism, vol. 82, no. 6, pp. 1923–1927, 1997.

[91] T. Reinehr, “Clinical presentation of type 2 diabetes mellitus in children and adolescents,” International Journal of Obesity, vol. 29, Supplement 2, pp. S105–S110, 2005.

[92] R. Basu, C. Dalla Man, M. Campioni et al., “Effects of age and sex on postprandial glucose metabolism: differences in glucose turnover, insulin secretion, insulin action, and hepatic insulin extraction,” Diabetes, vol. 55, no. 7, pp. 2001–2014, 2006.

[93] I. Horie, N. Abiru, M. Eto et al., “Sex differences in insulin and glucagon responses for glucose homeostasis in young healthy Japanese women,” Journal of Diabetes Research, vol. 4, pp. 172–177, 2012.