Insulin Response in Relation to Insulin Sensitivity An appropriate beta-cell response in black South African women

Citation for published version:

Digital Object Identifier (DOI):
10.2337/dc08-2048

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Publisher's PDF, also known as Version of record

Published In:
Diabetes Care

General rights
Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.
Insulin Response in Relation to Insulin Sensitivity

An appropriate β-cell response in black South African women

Julia H. Goedecke, PhD 1,2
Joel A. Dave, MB, CHB, PhD 3
Mirjam V. Faulenbach, MD 4
Kristina M. Utschneider, MD 4
Estelle V. Lambert, PhD 4
Sacha West, PhD 3
Malcolm Collins, PhD 1,2
Tommy Olsson, MD 5
Brian R. Walker, MD 6
Jonathan R. Seckl, MB, PhD 6
Steven E. Kahn, MB, CHB 6
Naomi S. Levitt, MB, CHB 6

OBJECTIVE — The purpose of this study was to characterize differences in the acute insulin response to glucose (AIRg) relative to insulin sensitivity (Sg) in black and white premenopausal normoglycemic South African women matched for body fatness.

RESEARCH DESIGN AND METHODS — Cross-sectional analysis including 57 black and white South African women matched for BMI, Sg, AIRg, and the disposition index (AIRg × Sg) were performed using a frequently sampled intravenous glucose tolerance test with minimal model analysis, and similar measures were analyzed using an oral glucose tolerance test (OGTT). Body composition was assessed by dual-energy X-ray absorptiometry and computed tomography.

RESULTS — Sg was significantly lower (4.4 ± 0.8 vs. 9.4 ± 0.8 and 2.9 ± 0.8 vs. 6.0 ± 0.8 × 10^{-5} min^{-1} pmol/l, P < 0.001) and AIRg was significantly higher (1,028 ± 229 vs. 469 ± 246 pmol/l, P < 0.001), despite similar body fatness (30.9 ± 1.4 vs. 29.7 ± 1.3 and 46.8 ± 1.2 vs. 44.4 ± 1.3%) in the normal-weight and obese black women compared with their white counterparts, respectively. Disposition index, a marker of β-cell function, was not different between ethnic groups (3,811 ± 538 vs. 2,966 ± 518 and 3,646 ± 483 vs. 2,353 ± 518 × 10^{-7} min, P = 0.10). Similar results were obtained for the OGTT-derived measures.

CONCLUSIONS — Black South African women are more insulin resistant than their white counterparts but compensate by increasing their insulin response to maintain normal glucose levels, suggesting an appropriate β-cell response for the level of insulin sensitivity.

Diabetes Care 32:860–865, 2009

Type 2 diabetes is a significant contributor to morbidity and mortality worldwide and was ranked as the seventh leading cause of death among individuals of all ages in South Africa in 2000 (1). The relatively high prevalence of diabetes has been accompanied by a high prevalence of obesity in South-African women (2), as 87% of all type 2 diabetes in South Africa has been attributed to excess body weight (3).

For reasons that have not yet been explained, both black South African and African American women are more insulin resistant than their adiposity-matched Caucasian counterparts (4–8). Insulin resistance in African Americans has been associated with hyperinsulinemia (6–8), due in part to reduced hepatic insulin extraction (7,8). In contrast, insulin resistance in black South African women has been associated with insulinopenia (5,9,10). However, the women in the previous studies were either not matched for glucose tolerance (5,10) or glucose tolerance and insulin sensitivity were not measured (9), making interpretation of β-cell function difficult. Thus, it is an open question whether β-cell function, assessed using state-of-the-art methods, differs in normoglycemic South African women of different ethnicities who are otherwise well matched.

It has become clear that insulin sensitivity is an important modulator of the β-cell response (11). The relationship between insulin sensitivity and insulin response is hyperbolic in nature, such that as insulin sensitivity decreases, normal β-cells will increase their insulin response to maintain normoglycemia. This hyperbolic relationship allows for the product of insulin sensitivity and insulin response to be calculated, with the resultant parameter being termed the disposition index. The disposition index is highly heritable and correlates strongly with glucose tolerance such that individuals with the lowest disposition index are at increased risk for or already have type 2 diabetes (12).

By estimating the disposition index, we aimed to better define β-cell function in black and white South African women matched for body fatness. Further, we aimed to compare these measures with estimates of glucose metabolism obtained using an oral glucose tolerance test (OGTT).

From the 1Department of Human Biology, UCT/MRC Research Unit for Exercise Science and Sports Medicine, University of Cape Town, Cape Town, South Africa; the 2South African Medical Research Council, Cape Town, South Africa; the 3Endocrine Unit, Department of Medicine, University of Cape Town, Cape Town, South Africa; the 4Division of Metabolism, Endocrinology and Nutrition, Department of Medicine, VA Puget Sound Health Care System and University of Washington, Seattle, Washington; the 5Department of Medicine, Umeå University, Umeå, Sweden; and the 6Endocrinology Unit, Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, Scotland.

Corresponding author: Julia H. Goedecke, julia.goedecke@uct.ac.za.

Received 13 November 2008 and accepted 30 January 2009.

Published ahead of print at http://care.diabetesjournals.org on 5 February 2009. DOI: 10.2337/dc08-2048.

© 2009 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See http://creativecommons.org/licenses/by-nc-nd/3.0/ for details.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
sities. Additional inclusion criteria were: 1) age 18–45 years, 2) no known diseases and not taking medication for diabetes, hypertension, HIV infection/AIDS, or any other metabolic disease, 3) not currently pregnant, lactating, or postmenopausal, and 4) of South African ancestry. The study was undertaken in accordance with the guidelines of the Declaration of Helsinki and was approved by the Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town.

Before participating in the study, procedures and risks were explained to the subjects, all of whom gave written informed consent to participate in the study.

Testing procedures

Body composition assessment. Basic anthropometric measurements, including weight, height, and waist (at the level of the umbilicus) and hip (largest gluteal area) circumferences were taken. Body fat was measured using dual-energy X-ray absorptiometry (Discovery-W, software version 4.40; Hologic, Bedford, MA). Body composition of subjects that exceeded the scanning region (n = 15 [26%]) was calculated using the arm-replaced method (13). The coefficients of variation for measurements of fat-free tissue mass and fat mass were 0.7 and 1.7%, respectively. Abdominal visceral and subcutaneous adipose tissue areas were measured using computed tomography (Xpris helical scanner; Toshiba, Tokyo, Japan) at the level of L4–L5 lumbar vertebrae.

Blood sampling and measurement of glucose tolerance, insulin sensitivity, and insulin release. Subjects completed an insulin-modified frequently sampled intravenous glucose tolerance test (FSIGT). After an overnight fast, cannulae were inserted into the antecubital vein of each arm. One arm was used for intravenous glucose and insulin infusions and the contralateral arm was used for blood sampling. The arm used for blood sampling was heated to arterialize venous blood. Baseline samples were taken at −15, −5, and −1 min before a bolus of glucose (50% dextrose; 11.4 g/m² body surface area) was infused intravenously over 60 s beginning at time 0 min. At 20 min, human insulin (0.02 unit/kg, Actrapid; Novo Nordisk) was infused over 5 min at a constant rate. Samples for determination of plasma glucose and serum insulin concentrations were drawn at 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 23, 24, 25, 27, 30, 33, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, 180, 200, 220, and 240 min. This sampling schedule allows for the identification of parameters using the minimal model of glucose kinetics (14) and the acute insulin response to glucose (AIRg). The samples were centrifuged at 3,000 rpm for 10 min at 4°C, the plasma was stored at −20°C for subsequent analysis of glucose concentrations, and the serum was stored at −80°C for the subsequent analysis of insulin concentrations.

On a separate day, a fasting venous blood sample was drawn for the determination of plasma glucose and serum insulin levels. Subjects then underwent a 75-g OGTT, during which blood was drawn at 30-min intervals for 2 h for the measurement of plasma glucose and serum insulin concentrations.

Biochemical analysis

Plasma glucose concentrations were determined using the glucose oxidase method (YSI 2300 STAT Plus; YSI, Yellow Springs, OH). Serum insulin concentrations were determined by immunochromiluminometric assays using the ADVIA Centaur (Bayer Diagnostics). The intrasay and interassay coefficients of variation for plasma glucose and serum insulin concentrations were 0.6 and 2.5 and 4.5 and 12.2%, respectively.

Calculations

Glucose and insulin data from the FSIGT were used to calculate indexes of insulin sensitivity (S0) and glucose effectiveness (SG) (the ability of glucose to promote its own uptake at basal insulin levels) using Bergman’s minimal model of glucose kinetics (14). AIRg was calculated as the mean incremental insulin response above basal between 2 and 10 min after the intravenous glucose bolus was started. β-Cell function was determined as the disposition index, which was calculated as the product of S0 and AIRg (11). The glucose disappearance constant (Kg), a measure of intravenous glucose tolerance, was calculated as the slope of the natural log of glucose from 10 to 19 min, expressed as percent change per minute.

The early insulin response during the OGTT, also known as the insulinoergic index, was calculated as the ratio of the change in insulin to the change in glucose from 0 to 30 min (Δinsulin0–30/Δglucose0–30). The oral disposition index (DI0), a measure of β-cell function derived from the OGTT, was calculated as 

\[ \text{DI}_0 = \frac{\Delta \text{insulin}_{0-30}}{\Delta \text{glucose}_{0-30}} \times 1/\text{fasting insulin} \]

Three subjects (one normal-weight and two obese black women) had a negative Δinsulin0–30/Δglucose0–30 measurement and were excluded from analyses including this parameter.

Statistics

Results are presented as means ± SEM. Two-way ANCOVA, adjusting for age, was used to compare anthropometric and metabolic measures between normal-weight and obese women of different ethnicity, with Bonferroni post hoc analyses. Repeated-measures ANOVA with Tukey post hoc analyses was used to explore differences in the glucose and insulin responses during the OGTT over time. Data were normalized by log transformation for statistical analyses when required. Data were analyzed using STATISTICA (version 7; StatSoft, Tulsa, OK). P < 0.05 was considered significant.

RESULTS

Subject characteristics

On average, the obese women were significantly older than the normal-weight women (P = 0.002) (Table 1). Consequently, all subsequent analyses were covaried for age. By design, all measures of body composition and regional fat deposition were significantly greater in the obese than in the normal-weight women (Table 1). There was a difference in stature between the black and white women (Table 1), with the black women being on average 10 cm shorter than the white women (P < 0.001) and weighing significantly less (P = 0.039). However, the black and white groups were well matched for BMI and body fat. Although there were no ethnic differences in waist circumference and waist-to-hip ratio, obese black women had less visceral adipose tissue (P = 0.006) but more subcutaneous adipose tissue (P = 0.013) than obese white women.

Glucose tolerance, insulin sensitivity, and insulin response to glucose

The glucose profile during the FSIGT was similar in black and white women, whereas the insulin profile after glucose injection was greater in black women (Fig. 1). S0 was significantly lower and AIRg was significantly higher in black women than in white women (Table 2) and in obese women than in normal-weight women in both ethnic groups (P < 0.001). Ethnic differences in S0 and AIRg persisted after adjustment for differences in age, BMI, and waist circumference.
in visceral adipose tissue and subcutaneous adipose tissue areas. Disposition index \((S_I/H_{AIRg})\) was not significantly different between ethnic and BMI groups, as was also the case for \(S_g\). However, obese black women had better \(K_g\) than obese white women \((P = 0.044)\).

Glucose and insulin levels in response to the oral glucose challenge are presented in Table 2 and Fig. 2. All subjects had normal glucose tolerance by American Diabetes Association criteria. Two-hour plasma glucose levels were significantly higher in normal-weight black than in normal-weight white women \((5.0 \pm 0.3\) vs. \(3.8 \pm 0.3\) mmol/l, \(P = 0.016)\), with no differences between the obese black and white women \((5.7 \pm 0.2\) vs. \(4.8 \pm 2.3\) mmol/l, \(P = 0.132)\). Fasting serum insulin levels were greater in black women than in white women \((P < 0.001)\) and in obese women than in normal-weight women \((P < 0.001)\). The insulinogenic index \([\Delta \text{insulin}_{0-30}/\Delta \text{glucose}_{0-30}]\) was significantly higher in both normal-weight and obese black women than in their white counterparts (Table 2). With adjustment for the effect of insulin sensitivity to modulate the insulin response, \(DI_o = [\Delta \text{insulin}_{0-30}/\Delta \text{glucose}_{0-30}] \times 1/\text{fasting insulin}\) was not different between the BMI and ethnic groups.

**CONCLUSIONS** — In the present study, we assessed for the first time in a sample of normoglycemic black and white South African women matched for BMI the relationship between insulin sensitivity and insulin response, which describes the ability of the \(\beta\)-cells to compensate for insulin resistance \((11)\). We found that insulin resistance in the black women was associated with an appropriately greater insulin response to maintain normoglycemia compared with that in their white counterparts. Thus, the disposition index, which measures \(\beta\)-cell function, did not differ in black and white South African women.

The findings of this study, therefore, do not support the concept that insulin

### Table 1—Subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>Normal-weight black</th>
<th>Normal-weight white</th>
<th>Obese black</th>
<th>Obese white</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n)</td>
<td>13</td>
<td>14</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Age (years)</td>
<td>24 ± 2</td>
<td>26 ± 2</td>
<td>28 ± 1</td>
<td>31 ± 2</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>158.8 ± 1.8*</td>
<td>169.6 ± 1.8*</td>
<td>157.1 ± 1.6†</td>
<td>167.2 ± 1.8†</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>59.2 ± 3.1*</td>
<td>64.8 ± 3.0†</td>
<td>94.1 ± 2.9*</td>
<td>98.8 ± 2.8*</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.4 ± 1.0*</td>
<td>22.6 ± 0.9†</td>
<td>38.0 ± 0.9*</td>
<td>35.2 ± 0.9*</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>30.9 ± 1.4*</td>
<td>29.7 ± 1.3†</td>
<td>46.8 ± 1.2*</td>
<td>44.4 ± 1.3†</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>76.7 ± 2.8*</td>
<td>80.1 ± 2.8†</td>
<td>113.6 ± 2.6*</td>
<td>105.7 ± 2.8†</td>
</tr>
<tr>
<td>WHR</td>
<td>0.77 ± 0.02*</td>
<td>0.78 ± 0.02†</td>
<td>0.90 ± 0.02*</td>
<td>0.85 ± 0.02†</td>
</tr>
<tr>
<td>VAT (cm²)</td>
<td>60.4 ± 11.5*</td>
<td>59.9 ± 10.7†</td>
<td>101.5 ± 11.1†</td>
<td>143.8 ± 11.1††</td>
</tr>
<tr>
<td>Total SAT (cm²)</td>
<td>176.7 ± 22.3*</td>
<td>175.5 ± 20.7†</td>
<td>591.3 ± 21.4†‡</td>
<td>492.2 ± 21.4†‡</td>
</tr>
</tbody>
</table>

Values are unadjusted means ± SEM. All \(P\) values were adjusted for age. *,†,‡Matching superscript symbols represent groups that are significantly different from each other, \(P < 0.01\). SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; WHR, waist-to-hip ratio.

Figure 1—Plasma glucose and serum insulin responses during an FSIGT in normal-weight (A) and obese (B) black (●) and white (○) women.
resistance in nondiabetic black South African women is associated with insulinopenia, previously attributed to a reduction in β-cell mass (16). Rather, the results of this study correspond to those reported in African Americans, in whom insulin resistance is associated with hyperinsulinemia (6–8). The higher AIRg in African Americans has been attributed to perinsulinemia (6–8). The higher AIRg in black women (5,10) has been attributed with impaired type 2 diabetes (12). However, intravenous glucose tolerance testing is expensive and time consuming, reducing its use in resource-limited countries such as South Africa. Alternatively, the DIo can be calculated from the hyperbolic relationship between the early insulin response and insulin sensitivity during a standard OGTT (15). Although less precise than FSIGT-derived measures, DIo has been

<table>
<thead>
<tr>
<th>Table 2—Glucose tolerance, insulin sensitivity, and release</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal-weight black</td>
</tr>
<tr>
<td>n</td>
</tr>
<tr>
<td>FSIGT</td>
</tr>
<tr>
<td>$S_i \times 10^{-5}$ min$^{-1}$ [pmol/l]</td>
</tr>
<tr>
<td>AIRg (pmol/l)</td>
</tr>
<tr>
<td>Disposition index $\times 10^{-5}$ min$^{-1}$</td>
</tr>
<tr>
<td>$S_e \times 10^{-1}$ min</td>
</tr>
<tr>
<td>$K_e$ (%/min)</td>
</tr>
<tr>
<td>OGTG</td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)</td>
</tr>
<tr>
<td>Fasting insulin (pmol/l)</td>
</tr>
<tr>
<td>$\Delta$ insulin$<em>{0–30}$/glucose$</em>{0–30}$</td>
</tr>
<tr>
<td>DIo (mmol/l)</td>
</tr>
</tbody>
</table>

Values are unadjusted means ± SEM. All $P$ values were adjusted for age. *,†,‡,§Matching superscript symbols represent groups that are significantly different from each other, $P < 0.05$, **$P < 0.01$. 

Figure 2—Plasma glucose and serum insulin responses to a 75-g oral glucose load in normal-weight (△, △) and obese (●, ○) black (△, ●) and white (△, ○) women. *$P < 0.05$ for black versus normal weight; #$P < 0.05$ for black versus white obese.
Insulin sensitivity, insulin response, and ethnicity

shown to be predictive of the development of diabetes over 10 years, even beyond that of fasting or 2-h post-OGTT glucose levels (15). The data from the current study, in which the insulinogenic index was higher and insulin sensitivity was lower in black than in white women, suggest that the degree of \( \beta \)-cell compensation in our sample of black women was appropriate, as \( DI_0 \) was not different based on ethnicity.

Based on the finding of similar disposition index values in the black and white women in this study, one would assume a similar risk for type 2 diabetes in these two population groups. However, the prevalence of type 2 diabetes in South Africa is higher in the black population than in the white population (24). A similar scenario is presented in African Americans, who have a higher prevalence of type 2 diabetes but display a similar or higher disposition index than their Caucasian counterparts (6,7). The mechanisms underlying the increased risk of type 2 diabetes in black populations from South Africa and the U.S. is not known. Joffe et al. (16) proposed a scheme for the pathogenesis of type 2 diabetes in the black population of Southern Africa, in which a reduction of \( \beta \)-cell mass (due to childhood malnutrition and/or genetic factors), followed by an accelerated phase of \( \beta \)-cell decompensation induced by a variable period of peripheral insulin resistance, would ultimately lead to insulinopenic type 2 diabetes. However, to our knowledge, there is no evidence of a reduction in \( \beta \)-cell mass in the general black population. In fact, exaggerated glucose-stimulated insulin secretion appears to be a characteristic of individuals with normal glucose tolerance who are at risk for type 2 diabetes (Pima Indians and African Americans) (25).

A limitation of our study is that the subjects were not randomly drawn from the population but comprised volunteers who had responded to a recruitment advertisement. Thus, there is the possibility that they may not be representative of the population at large. However, our finding of insulin resistance in black women is in keeping with previous observations reported from South Africa (4,5). The reasons for the differences in insulin sensitivity and insulin responses and whether they apply to the general population are unclear. Aside from genetic differences, environmental and lifestyle differences exist between the black and white South African populations, and it is quite possible that these may have an impact on measures associated with glucose metabolism. For example, we found that black South African women had lower socioeconomic status, consumed more dietary fat, and had more subcutaneous and less visceral fat than their white counterparts and that these factors explained in part some of the differences in insulin sensitivity (J. H. Goedecke, unpublished observations). However, even after adjustment for differences in fat distribution, the ethnic differences in \( S_i \) and \( AIR_2 \) were not obviated. Identification of other factors and the mechanisms by which they may be operating to affect glucose metabolism is clearly needed. In addition, longitudinal studies are required to determine whether the \( \beta \)-cell will continue to compensate in the black women with increasing age or whether it will fail over time, leading to disturbances in glucose tolerance.

In summary, we have demonstrated that black South African women are more insulin resistant than their white counterparts but compensate by increasing their insulin response to maintain normal glucose levels. These findings refute previous suggestions that insulin resistance in black South African women is associated with relative insulinopenia but rather suggest an appropriate \( \beta \)-cell response for the level of insulin sensitivity. Future studies are required to explore the mechanisms underlying the high degree of insulin resistance in apparently healthy black populations and to establish whether their hyperinsulinaemic response to insulin resistance is in fact associated with increased or decreased risk of diabetes with increasing age.

Acknowledgments — This study was funded by the Medical Research Council of South Africa (Career Development Award for J.H.G.), the National Atomic Energy Agency, the National Research Foundation of South Africa and Royal Society SA-U.K. Science Networks Programme, the University of Cape Town, the British Heart Foundation, the Wellcome Trust, and the U.S. Department of Veterans Affairs.

No potential conflicts of interest relevant to this article were reported.

We thank the research volunteers for their participation in this study and fieldworker Nandipha Sinyanya for subject recruitment and translation. We are extremely grateful to Hendriena Victor for coordinating the study, and together with Judy Belonje, for technical expertise. Jack Bergman and Naomi Fenton of Symington Radiology are thanked for performing the computed tomography scans and Linda Bewerunge is thanked for performing the dual-energy X-ray absorptiometry scans.

References

5. van der Merwe MT, Crowther NJ, Schlapfhopf GP, Boyd HH, Gray IP, Joffe BI, Lonroth PN. Lactate and glycerol release from the subcutaneous adipose tissue of obese urban women from South Africa; important metabolic implications. J Clin Endocrinol Metab 1998;83:4084–4091