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Sex differences in insulin sensitivity and insulin response with increasing age in black South African men and women

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ABSTRACT

Aims: Black Africans are disproportionally affected by type 2 diabetes, but the pathophysiology is poorly understood. The study aimed to examine the effect of sex and age on insulin sensitivity and insulin response in black South African adults.

Methods: This cross-sectional study included a random sample of 179 men and 260 women aged 25–74 years with normal glucose tolerance from 5 peri-urban townships in Cape Town, SA. Insulin sensitivity (insulin sensitivity index, $ISI_{0,120}$) and response (insulinogenic index, IGI), and the disposition index (DI, $ISI_{0,120} \times IGI$), derived from an oral glucose tolerance test, were measured.

Results: Although men were older (median [interquartile range]: 39 [30–48] vs. 35 [29–44], $P = 0.021$) and had significantly lower BMI than women (22.6 [20.0–25.3] vs. 31.0 [25.9–35.7] kg/m^2, $P = 0.001$), DI was not different ($P = 0.740$), but $ISI_{0,120}$ was higher ($P = 0.007$) and IGI was lower ($P = 0.074$) in men than women, adjusting for age and BMI. With increasing age, DI (β (95%CI): −24.4 (−36.3 to −12.5), $P < 0.001$) and IGI (β (95%CI): −4.9 (−7.5 to −2.2), $P < 0.001$) decreased similarly in both sexes, but $ISI_{0,120}$ did not change (β (95%CI): 0.005 (−0.20 to 0.03), $P = 0.675$).

Conclusion: Black South African women with normal glucose tolerance have lower insulin sensitivity than their male counterparts, but increase their insulin response to maintain normoglycemia. With increasing age, insulin sensitivity remains unchanged, but the insulin response decreases at a similar rate in men and women.

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1. Introduction

In accordance with the global spread of type 2 diabetes [1], in South Africa there is a high and growing prevalence, particularly in urban-dwelling black African populations [2]. Black Africans with diabetes have higher rates of associated comorbidities, and are 2–3 times more likely to die from these diseases than their white counterparts [3]. It is therefore important to understand the pathophysiology contributing to the development of type 2 diabetes in this population.

The pathogenesis of type 2 diabetes is dependent on the combination of reduced insulin sensitivity and β-cell dysfunction. The relationship between insulin sensitivity and insulin responses, measured using a frequently sampled intravenous glucose tolerance test (FSIGT), has been shown to be hyperbolic in nature, such that as insulin sensitivity decreases, normal β-cells will increase their insulin response in order to maintain normoglycemia [4]. This hyperbolic relationship allows for the product of insulin sensitivity and insulin response to be calculated, with the resultant parameter termed the disposition index (DI). Subsequently, analogous measures of β-cell function based on oral glucose tolerance test (OGTT)-derived measures of insulin sensitivity and response have been validated [5,6], and shown to predict the development of type 2 diabetes over 10 years, independent of age, sex, body mass index (BMI), family history, and glucose concentrations [6]. However, to our knowledge, there are no studies that have explored the hyperbolic relationship between insulin sensitivity and response within a black population.

Studies in South Africa and the USA have shown that black women, predominantly premenopausal, are more insulin resistant, have lower hepatic insulin extraction, and a greater insulin response than their white counterparts [7–10]. However, it is not known whether the compensatory β-cell response in relation to the prevailing level of insulin resistance in black women persists with increasing age. Peer et al. [2] showed that the prevalence of type 2 diabetes in black South Africans increased significantly with increasing age, with the disease being present in as many as 34.7% and 39.3% of women and men over the age of 65 years, respectively. Despite the high prevalence of type 2 diabetes in black South African men and them having a significantly lower prevalence of obesity compared to women (10.6% vs. 39.2%) [11], it is not known whether their insulin sensitivity and response differ from that of black South African women, and whether the impact of age on these measures is the same or different.

We hypothesized that black South African women, due to their high prevalence of obesity, are more insulin resistant and have greater insulin responses compared to black South African men, and that with increasing age, β-cell function will decline similarly in women and men. Therefore, from this cross-sectional study of urban-dwelling black South African women and men aged 25–74 years, we aimed to answer the following questions: (i) Does insulin sensitivity and insulin response differ between black men and women? (ii) Does insulin sensitivity and insulin response differ with increasing age?

2. Subjects, materials and methods

2.1. Study population and sampling procedure

The study population consisted of participants from the Cardiovascular Risk in Black South African (CRIBSA) study, which was a cross-sectional study comprising a random sample of black South Africans residing in the peri-urban areas of Langa, Guguletu, Crossroads, Nyanga and Khayelitsha in Cape Town. The study design and methods have been previously described [2]. Participants were excluded from this secondary analysis if they were taking any medication for diabetes ($n = 232$); were diagnosed with type 2 diabetes ($n = 28$), impaired glucose tolerance or impaired fasting glucose ($n = 90$); had incomplete OGTT data ($n = 229$); or a negative insulinogenic index (IGI) ($n = 95$). Only participants with normal glucose tolerance (NGT), and who were not taking any other medications that may alter insulin sensitivity, were included, resulting in a total study sample of 179 men and 260 women aged between 25 and 74 years. Sensitivity analysis comparing the characteristics of the participants who were included in the analysis vs. those who were excluded due to incomplete OGTT data, showed that apart from a greater proportion of men included in the analysis (42.6% vs. 32.1%, $P = 0.016$), there were no differences in age, family history of diabetes or anthropometry between groups (data not shown). The study was conducted in accordance with the guidelines of the Declaration of Helsinki and was approved by the Human Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town. All participants signed an informed consent form after the procedures and risks were explained to them.

2.2. Blood sample collection and determination of glucose tolerance, insulin sensitivity and insulin release

After an overnight fast, a venous blood sample was taken followed by the performance of a standard OGTT using 75 g of anhydrous glucose in 250 ml of water. Blood samples were drawn at 30 min and 120 min for the measurement of plasma glucose and serum insulin concentrations.

Plasma glucose concentrations were determined using the glucose oxidase method (Cobas 6000-module C501, Roche) and insulin concentrations by immune-chemiluminometric assays using ADVIA Centaur (Siemens, Germany, Mannheim, Germany). The inter- and intra-assay coefficient of variation for plasma glucose and serum insulin concentrations were 0.8 and 2.1% and 6.6% and 9.8%, respectively.

Participants were categorized based on WHO criteria as having normal glucose tolerance (NGT) if the fasting plasma glucose was <6.1 mmol/l and 2-h plasma glucose was <7.8 mmol/l. Insulin sensitivity was estimated using the insulin sensitivity index ($ISI_{0,120}$) [12], homeostasis model assessment of insulin sensitivity (HOMA2-%S) (https://www.dtu.ox.ac.uk) and 1/fasting insulin. These three measures of insulin sensitivity were chosen because they represent both fasting (HOMA-S and 1/fasting insulin) and post-prandial ($ISI_{0,120}$) measures of insulin sensitivity. The early insulin response