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Type 2 diabetes mellitus risk in middle-aged black South African women: dissecting the role of menopause, HIV infection and adipose tissue biology

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2022

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ABSTRACT

Background:

The prevalence of type 2 diabetes (T2D) mellitus in sub-Saharan Africa has increased in recent decades and is projected to increase more than any region in the world. Black African women are at greater risk of T2D due to the higher rates of obesity and insulin resistance compared to white European women. The risk of T2D increases with menopause and is hypothesised to be due to changes in reproductive hormones, body fat distribution and adipose tissue biology. As life expectancy increases, more South African women living with human immunodeficiency virus (HIV) will be transitioning through menopause into post-menopause as they live longer on antiretroviral therapy (ART). Thus, aim of this thesis is twofold, firstly to examine the differences in body fat distribution and insulin sensitivity and response, measured using oral glucose tolerance tests (OGTT) and frequently sampled intravenous glucose tolerance tests (FSIGT), between pre- and post-menopausal women living with and without HIV. Secondly, to explore how abdominal and gluteal adipose tissue expression of adipokines, inflammatory, glucocorticoid and lipid metabolism genes differ by menopause and HIV and how these gene associate with insulin sensitivity. To address these aims, this thesis has 3 results chapters with the following objectives; 1) to compare conventional body composition and insulin sensitivity and response assessment methods to more precise measures, 2) to investigate the effect of menopause and HIV status on glycaemia, insulin sensitivity and response in black African women, 3) and to determine the difference in adipokines, inflammatory, glucocorticoid and lipid metabolism gene expression between abdominal and gluteal subcutaneous adipose tissue (SAT) depots and how they relate to insulin sensitivity, in pre- and post-menopausal women with and without HIV.

Methods:

This thesis was nested within a larger cohort study investigating the determinants of T2D risk in middle-aged black South African men and women: dissecting the role of sex hormones, inflammation and glucocorticoids. For the main study, all the men (n=502) and women (n=527) participants were recruited and provided informed consent, and completed a series of questionnaires including a demographic and food frequency questionnaire (FFQ). Body fat and its distribution were associated using anthropometry and dual energy x-ray absorptiometry (DXA); glycaemia and insulin sensitivity and response were measured from

fasting blood samples and an OGTT. For this thesis, a sub-sample of 92 of the women who met the following inclusion criteria were included and recruited to additionally undergo FSIGT and abdominal and gluteal adipose tissue biopsies. The inclusion criteria were: (1) age and menopause status: pre-menopausal women 40-45 years and post-menopausal women 55-65 years old; (2) HIV status: HIV negative women or women living with HIV (LWHIV); (3) BMI 20-40 kg/m^2; (4) not diabetic. The 92 women who were recruited were divided into four groups based on HIV and menopause status: (1) pre-menopausal HIV-negative (PRE-; n=21); (2) pre-menopausal women LWHIV (PRE+; n=11); (3) post-menopausal HIV-negative (POST-; n=42); (4) post-menopausal women LWHIV (POST+; n=18). From the gluteal and abdominal fat biopsies, adipose tissue expression of adipokines, inflammatory, glucocorticoid and lipid metabolism gene expression were measured. The frequently sampled intravenous glucose tolerance test was conducted in 82 of these participants to estimate insulin sensitivity (S_I), acute insulin response to glucose (AIRg) and beta cell function (disposition index, DI). The OGTT-derived outcomes included, insulin sensitivity measured by Matsuda Index, insulin response measured by Insulinogenic index (IGI) and beta cell function measured by oral disposition index (DI_O).

Results:

The results are reported in 3 separate results chapters. Firstly, I compared conventional body composition and insulin sensitivity and response methods to methods that are more precise and strongly associated with gold standards. In this study, I showed that waist circumference was positively correlated with VAT (r_s =0.665), SAT (r_s=0.743) and android fat (r_s=0.834), but the strongest correlation was between hip circumference and gynoid fat mass (r_s =0.929). There was homoscedasticity between each of these correlations. For insulin sensitivity, there was a significant correlation between the OGTT-derived Matsuda Index and FSIGT-derived S_I (r_s =0.518) and for insulin response, there was a significant positive correlation between OGTT-derived IGI (OGTT) and FSIGT-derived AIRg (r_s =0.517). There was a weak but significant positive correlation between DI_O (OGTT) and DI (FSIGT) (r_s = 0.336). Furthermore, there was no proportional bias and there was homoscedasticity between the OGTT- and FSIGT-derived measures of insulin sensitivity, response and beta cell function. I then used both OGTT and FSIGT- derived measures of insulin sensitivity and response and beta cell function to explore associations with menopause and HIV status in chapter 4. In chapter 5, the OGTT-derived insulin sensitivity measure were used to examine the association between insulin sensitivity and adipose tissue function, since showed OGTT-

derived Matsuda Index showed a strong correlation and agreement with the FSIGT-derived S_I and indicates a more physiological response.

In the second study I investigated the effect of menopause and HIV status on glycaemia, insulin sensitivity and response in black African women. Results from the second study (chapter 4) reported that a greater proportion of HIV negative women presented with obesity compared to the women LWHIV (62% vs. 43%), and body fat % (BF%), fat mass index (FMI) and SAT were lower in women LWHIV compared to HIV negative women. Postmenopausal women had greater VAT compared to the premenopausal women (p=0.027). Despite no differences in glycaemia or insulin sensitivity, insulin response to glucose, derived from both OGTT and FSIGT, which were higher in women LWHIV (p=0.015 and 0.005, respectively). This hyperinsulinaemia shown was associated with higher insulin secretion and not due to differences in insulin clearance. Postprandial glycaemia was higher in post-menopausal women compared to their premenopausal counterparts and this was independent of the higher VAT in postmenopausal women (p=0.032).

In chapter 5, my results show that although insulin sensitivity was not different between the HIV and menopausal groups, women LWHIV had greater expression of adiponectin in both abdominal and gluteal depots (abdominal: p=0.057; gluteal: p=0.007), a corresponding lower expression of leptin (abdominal: p=0.005; gluteal: p=0.002), and lower abdominal cell size ratio compared to HIV negative women (p=0.001). Postmenopausal women had greater expression of M1 adipose tissue macrophages (abdominal: p=0.040; gluteal: p=0.018). Markers of systemic inflammation (hsCRP and IL-6) and adiposity (android fat, circulating leptin, abdominal LEP and gluteal LEP) were associated with lower insulin sensitivity. Gluteal adipogenic transcription factor (PPARγ) and PPARγ-responsive genes (LPL and adiponectin) were associated with higher insulin sensitivity.

Conclusion:

In conclusion, this study has provided evidence that postmenopausal women have greater postprandial glycaemia than premenopausal women, however this was independent of the higher VAT in postmenopausal women. This supports the hypothesis of a preferential increase in abdominal adiposity in postmenopausal women. This study demonstrates for the first time that insulin response to glucose was higher in women LWHIV, irrespective of their menopausal status. However, the cause and significance of this higher insulin response in

women LWHIV requires further investigation. Moreover, despite a tendency for lower insulin sensitivity, women LWHIV had greater expression of adiponectin in both abdominal and gluteal depots, a corresponding lower expression of leptin and lower abdominal cell size ratio compared to HIV negative women which requires further exploration. Lastly, irrespective of menopause and HIV status, gluteal adipogenic transcription factor and (PPARγ) and PPARγ-responsive genes (LPL and adiponectin) were associated with favourable insulin sensitivity, whereas markers of adiposity (android fat, circulating leptin, abdominal LEP and gluteal LEP) were associated with low insulin sensitivity. Thus, future research should explore biological pathways involved in SAT gene expression and insulin sensitivity in this population.