

β -cell function in black South African women: Associations with insulin clearance and ectopic fat

Melony Cathlin Fortuin-de Smidt (✉ mcfortuindesmidt@gmail.com)

University of Cape Town <https://orcid.org/0000-0003-3488-7781>

Amy E Mendham

University of Cape Town Division of Exercise Science and Sports Medicine

Jon Hauksson

Umea Universitet

Ali Alhamud

University of Cape Town

Darko Stefanovski

University of Pennsylvania

Olah Hakim

King's College London

Jeroen Swart

University of Cape Town Division of Exercise Science and Sports Medicine

Louise M Goff

King's College London

Steven E Kahn

University of Washington

Tommy Olsson

Umea Universitet

Julia H Goedecke

University of Cape Town Division of Exercise Science and Sports Medicine

Research

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Abstract

Background: The role of ectopic fat, insulin secretion and clearance in the preservation of β -cell function in black African women with obesity who typically present with hyperinsulinemia is not clear. We aim to examine the associations between disposition index (DI, an estimate of β -cell function), insulin secretion and clearance and ectopic fat deposition.

Methods: This is a cross-sectional study of 43 black South African women (age 20-35 years) with obesity (BMI 30-40 kg/m²) and without type 2 diabetes that measured the following: DI, insulin sensitivity (S_I), acute insulin response (AIRg), insulin secretion rate (ISR), hepatic insulin extraction and peripheral insulin clearance (frequently-sampled intravenous glucose tolerance test); pancreatic and hepatic fat, visceral adipose tissue (VAT) and abdominal subcutaneous adipose tissue (aSAT) volume (magnetic resonance imaging), intramyocellular (IMCL) and extramyocellular fat content (EMCL) (magnetic resonance spectroscopy).

Results: DI correlated positively with peripheral insulin clearance before (β 55.80, $p=0.002$) and after adjusting for hepatic insulin extraction. Higher DI was associated with lower VAT, pancreatic fat and soleus fat, but VAT explained most of the variance in DI (32%). Additionally, higher first phase ISR ($p=0.033$) and lower hepatic insulin extraction ($p=0.022$) associated with lower VAT, independent from S_I , rather than with ectopic fat.

Conclusion: Peripheral insulin clearance emerged as an important correlate of DI, independent from hepatic insulin extraction. However, VAT was the main determinant of a lower DI above ectopic fat depots. Importantly, VAT, but not ectopic fat, was associated with both lower insulin secretion and higher hepatic insulin extraction, independent from S_I , and may provide a novel explanation of these findings in black South African women with obesity.

Background

The acute insulin response (AIRg) relative to the prevailing level of insulin sensitivity (S_I) described by the disposition index (DI), estimates β -cell function, which is a key component in the pathogenesis of type 2 diabetes (T2D) [1]. These measures are derived from mathematical modelling using plasma glucose and insulin levels obtained from a frequently sampled intravenous glucose tolerance test (FSIGT) [2]. The primary events in the development of T2D may differ between black Africans and their white counterparts. Indeed, black Africans without T2D present with lower S_I and hyperinsulinaemia, characterised by greater fasting insulin and AIRg in comparison to white individuals [3]. In some cases the AIRg response is exaggerated for the level of S_I [4], resulting in a higher DI. Determinants of S_I in black African populations have been studied extensively but there is limited evidence on the determinants of hyperinsulinemia and its components, namely insulin secretion rate (ISR) and insulin clearance.

The relative contribution of first phase ISR and insulin clearance to a high AIRg, independent from S_I , is essential to our understanding of the pathogenesis of T2D in African populations. However, this has only been reported in African American children [5], with no studies in black African adults with obesity and without T2D. A lower hepatic insulin extraction is found in black African women [6] which contributes towards a high AIRg [5], but how it relates to DI is unknown. Further, while the liver is the main organ involved in insulin clearance and clears approximately 50-70% of insulin during first pass through the liver [7], insulin is also cleared by peripheral tissue such as the kidneys, muscle and adipose tissue, amongst others. Polidori *et al.* developed a model to determine both hepatic (FE_I) and peripheral insulin clearance (CLp) [8]. This model was used in two studies that included African American adults [6,8], but the association of CLp with β -cell function measures was not assessed and needs further clarification.

An important link between alterations in DI and its components, may be ectopic fat accumulation in the visceral compartment (VAT), liver, skeletal muscle and pancreas. Few studies have assessed associations between measures of β -cell function and VAT [9–11] and ectopic fat deposition [12,13] in African Americans, but no studies have been undertaken in an African cohort, which is required to determine if this phenotype is robust. Indeed, studies from Africa and the USA have consistently shown that black populations presents with lower ectopic fat accumulation compared to white populations [12,14,15], together with hyperinsulinemia [3] and paradoxically a higher prevalence of T2D. Whether black African populations exhibit a greater sensitivity to ectopic fat accumulation or whether ectopic fat is not an important correlate of β -cell function and its components requires further elucidation. Accordingly, this study, aimed to evaluate the correlates of β -cell function, assessed by DI, focusing on hyperinsulinemia (insulin secretion, FE_L and CLp) and its association with ectopic fat depots in black South African women with obesity.

Methods

Research design

This study was a cross-sectional analysis of baseline data obtained from a randomized controlled exercise intervention study, for which the study design and methods have been published previously [16]. Participants were recruited from low socio-economic areas in Cape Town, South Africa. Ethical permission was obtained from the University of Cape Town Human Research Ethics Committee. The trial was registered in the Pan African Clinical Trial Registry (PACTR201711002789113).

Participants

Black African (self-reported ancestry with both parents of *isiXhosa* descent) women with obesity (BMI 30-40 kg/m²) that fulfilled the following inclusion criteria were enrolled: age 20-35 years, stable weight (<5 kg change in weight in the last 6 months), using injectable contraception (depot medroxyprogesterone acetate, 400 mg) for a minimum of 2 months prior to testing. Different type of hormonal contraception (injectables compared to oral contraception) have differential effects on fasting glucose and insulin levels [17]. In Khayelitsha, where most of our participants reside, 83% of women use injected contraceptives and in the majority (75%), the method of contraception is determined by the healthcare provider [18]. Therefore, to minimize the effect of hormonal fluctuations on our study findings our inclusion criteria ensured participants were all using the same contraceptive method based on the standard of care in the public health system. Participants were excluded if they had any known diseases (e.g. HIV, hypertension, diabetes), were pregnant, lactating or smoking. After written informed consent was obtained, patients were screened for inclusion.

Body composition

Anthropometry included weight, height, hip and waist circumferences measured using standardized methods. Whole body composition was measured by dual-energy X-ray absorptiometry (DXA; Discovery-W®, software version 12.7.3.7; Hologic, Bedford, MA) for the analyses of sub-total body (whole body minus head) fat mass and fat-free soft tissue mass, as well as trunk and leg mass (expressed as percent of sub-total body fat mass) [19].

Ectopic and central fat quantification

Pancreatic, hepatic and skeletal muscle (soleus, tibialis anterior) fat content, VAT and abdominal subcutaneous adipose tissue (aSAT) volumes were analysed using a 3 Tesla whole-body human magnetic resonance imaging scanner (MRI; MAGNETOM Skyra; Siemens Medical Solutions, Erlangen, Germany) using a two-point Dixon method

as described previously [16]. Soleus and tibialis anterior intra-myocellular (IMCL) and extra-myocellular (EMCL) fat content were determined by magnetic resonance spectroscopy (MRS) using a point-resolved spectroscopy sequence with the following parameters: TR/TE 3000/33 ms, bandwidth 2000 Hz, 80 averages with voxel dimensions of $15 \times 15 \times 15 \text{ mm}^3$.

For the determination of hepatic, pancreatic and skeletal muscle fat, VAT and aSAT obtained by MRI, a fat fraction map was created, calculated as the fat signal over the sum of the water and fat signals. A region of interest (ROI) was drawn on 7 consecutive slices in the right lobe of the liver. In the soleus and tibialis anterior muscles, an ROI was drawn on 7 consecutive slices with a method adapted from Machann *et al.* [20]. Pancreatic fat was determined by drawing one circular 1 cm^2 ROI in the head, body and tail of the pancreas to calculate the average [21]. The methods for determining VAT and aSAT volumes were previously published [22]. The above mentioned methods, to quantify hepatic [23], pancreatic [24] and skeletal muscle fat [25] and VAT and aSAT [26], have previously been reported to have high precision.

Determination of S_I and β -cell function

A FSIGT allows for the determination of the acute insulin response after an intravenous glucose load [27]. After 20 minutes insulin is infused to suppress endogenous insulin production which enables the evaluation of the effect of insulin on glucose disappearance. A FSIGT was used in this study because it provides measures of the AIR_g as well as S_I and it is less labour intensive compared to the clamp method and it does not require a steady state. Additionally, the FSIGT shows good correlation to the hyperglycemic clamp [28]. The FSIGT was conducted after an overnight fast (10-12 h). Glucose (50% dextrose, 11.4 g/m^2 body surface area) was infused at 0 min over a 60 s period. At 20 min, human insulin (0.02 unit/kg; NovoRapid, Novo Nordisk Limited, Cape Town, SA) was infused over 5 min at a constant rate. Thirty-two blood samples were drawn over 240 minutes for the determination of plasma glucose and serum insulin and C-peptide.

Biochemical analyses

Fasting whole blood was collected and analysed for HbA1c using high-performance liquid chromatography (Meharini Diagnostics, Florence, Italy). Plasma glucose concentrations were measured using a colorimetric assay (Randox (Pty) Ltd, Gauteng, South Africa). Serum insulin and C-peptide concentrations were determined by an immunochemiluminometric assay (IMMULITE 1000 immunoassay system, Siemens Healthcare (Pty) Ltd, Midrand, South Africa).

Mathematical modelling

The minimal model of glucose kinetics was used to calculate S_I , AIR_g and glucose effectiveness [29]. S_I is a measure of the fractional disappearance of glucose for a given insulin concentration achieved by uncoupling the glucose and insulin responses. Glucose effectiveness is a measure of the ability of glucose to enhance its own uptake. AIR_g is the incremental area under the insulin curve in response to intravenous glucose over the first 10 minutes, and reflects the first phase insulin response. DI is a measure of the insulin response to glucose relative to the prevailing level of S_I ($\text{AIR}_g \times S_I$) which gives an index of whether the insulin response is adequate for the level of S_I [1]. The ISR was determined by C-peptide deconvolution using a 2-compartmental model with standard kinetic parameters for individuals with obesity [30]. The incremental area-under curve (AUC), above baseline, for ISR, glucose, insulin and C-peptide were calculated using the trapezoidal rule for the first 10 minutes and the entire 240 min of the FSIGT, and are referred to as the first phase AUC ($\text{ISR}_{\text{first phase}}$) and the total AUC ($\text{ISR}_{\text{total}}$), respectively.

FE_L and CLp were calculated using a method previously described by Polidori *et al.*[8]. Hepatic insulin clearance were described using both linear and saturable kinetics. The linear model estimated a single parameter for hepatic insulin clearance (FE_L) while the saturable model estimated two parameters (V_{max} and K_m). The linear model described hepatic insulin clearance well (fractional standard deviation <5%) in 91% (39/ 43) of participants. In addition, the linear model described the plasma insulin values with a mean normalized root square error (NMRSE) \pm SD of $8.3 \pm 2.14\%$. The parameters of the models were estimated using WinSAAM [31].

Statistical analysis

Data were analysed using STATA 12 .0 (College Station, TX, USA). Data analysis included those that completed a FSIGT (n=43). The cohort was divided into tertiles based on the DI, calculated as $S_I \times AIRg$: DI_{Low} , $DI_{Intermediate}$ and DI_{High} . Normally and non-normally distributed data were expressed as mean \pm standard deviation (SD) and median (25-75th percentile), respectively. Differences between DI tertiles was determined using one-way ANOVA with a Bonferroni *post hoc test* or Kruskal Wallis test with the Dunn *post hoc test* for normally and non-normally distributed data, respectively. Correlations were conducted using Pearson (normally distributed variables) and Spearman (non-normally distributed variables). Linear regression was performed with the transformed variables to determine the association between DI components and central fat depots, adjusted for S_I , where applicable.

Results

Subject Characteristics of the overall sample and by DI tertiles

A hyperbolic relationship between S_I and $AIRg$, the main components of DI, is presented in Figure 1 for the overall sample (A) and in each of the DI tertiles (B). The cohort had a median age of 23 (IQR 21-27) years and a mean BMI of $33.2 \pm 2.8 \text{ kg/m}^2$. Participant characteristics by DI tertile, as an estimate of β -cell function, are displayed in Table 1. The group with the highest DI, were the most insulin sensitive (*post hoc* $p=0.001$) and had the highest glucose effectiveness (*post hoc* $p<0.001$) compared to the group with the lowest DI. $AIRg$ and $ISR_{first\ phase}$ showed no decline across DI tertiles (*post hoc* $p=0.060$ and $p=0.071$, respectively). In addition the group with the highest DI had the highest CLp (*post hoc* $p=0.001$) and lowest FE_L (*post hoc* $p=0.049$) compared to those in the lowest DI tertile. Further, the highest DI had the lowest pancreatic and hepatic fat, and the lowest VAT and VAT-aSAT ratio, compared to those with the lowest DI.

Correlations of DI with $AIRg$, S_I and ISR

DI was positively associated with both its immediate components ($AIRg$: $\rho=0.372$, $p=0.014$; S_I : $\rho=0.459$, $p=0.020$) and $ISR_{first\ phase}$ ($\rho=0.350$, $p=0.021$).

Associations of DI and its components with CLp and FE_L

Further, in univariate analysis, DI was positively associated with CLp and inversely with FE_L which explained 23.4% and 16.8% of the variance in DI, respectively (Table 2). However, when both CLp and FE_L were placed in the model only CLp remained a significant positive determinant of DI. S_I was not associated with FE_L ($p=0.065$) and CLp ($p=0.881$) in the univariate model (Table 2). The association between S_I and FE_L became significant when adjusted for CLp ($p=0.038$). $AIRg$ was associated with CLp in the univariate analysis but after adjusting for FE_L and S_I this association was diminished (Table 2).

Contributions of FE_L and $ISR_{\text{first phase}}$ to AIRg

In addition, we used linear regression models to determine the relative contributions of FE_L and $ISR_{\text{first phase}}$ to AIRg, without and with adjustment for S_I (Table 3). In the univariate models, $ISR_{\text{first phase}}$ and FE_L explained 81.9% and 57.6%, of the variance in AIRg, respectively. S_I explained 32% of the variance in AIRg (data not shown). In the multivariate model, FE_L and $ISR_{\text{first phase}}$ were independently associated with AIRg, adjusted for S_I .

DI and its components - associations with body fat distribution and ectopic fat

DI was not associated with fat mass (%), leg fat mass or aSAT (data not shown) but was negatively associated with VAT and the VAT-aSAT ratio (β -167.4, $p < 0.001$). The unadjusted associations between DI and ectopic fat depots and VAT, are shown in Figure 2. DI was inversely correlated with pancreatic fat, total soleus fat and both soleus IMCL and EMCL. DI was not associated with tibialis anterior fat (β -2.59, $p = 0.887$). In univariate analysis, VAT explained 32% of the variance in DI, while soleus IMCL explained 18.7%, soleus EMCL 10.9% and pancreatic fat 12%. Adjusting for age and fat mass (%) in multivariable models did not alter the models. Accordingly, the negative associations of DI with pancreatic fat (β -62.9, $p = 0.030$), VAT (β -0.037, $p < 0.001$), soleus fat (β -50.0, $p = 0.049$), soleus IMCL (β -41.3, $p = 0.012$) and soleus EMCL (β -32.0, $p = 0.047$) remained. We explored the associations between DI and ectopic fat, independent of VAT and found that the associations of DI with pancreatic fat, hepatic fat, soleus fat and soleus IMCL were ameliorated to non-significance ($p > 0.05$) (data not shown). Instead, VAT remained a significant determinant of DI independent of any of the ectopic fat depots (data not shown).

The components of DI (S_I , AIRg, $ISR_{\text{first phase}}$, FE_L and CLp) were not associated with fat mass (%) or ectopic fat sites ($p > 0.05$) (data not shown). Rather, significant associations were found between the components of DI and central fat measures (Table 4). A lower S_I was associated with higher VAT but not aSAT, while higher AIRg was associated with higher aSAT and lower VAT-aSAT. When adjusting for S_I , a higher AIRg was associated with only a lower VAT and VAT-aSAT. Only after adjusting for S_I , an inverse association emerged between $ISR_{\text{first phase}}$ and VAT. We further showed that FE_L was positively associated with VAT only after adjusting for S_I . CLp was not associated with any central fat depots (data not shown).

Lastly, we explored the associations between VAT and ectopic fat depots (Supplementary Table 1). VAT was positively associated with pancreatic fat (ρ 0.417, $p = 0.007$) and soleus IMCL (ρ 0.403, $p = 0.014$), but was not associated with soleus EMCL (ρ 0.121, $p = 0.474$) and hepatic fat (ρ 0.300, $p = 0.060$). Moreover, pancreatic fat was positively associated with hepatic fat (ρ 0.540, $p < 0.001$).

Discussion

The correlates of β -cell function, a critical factor in the pathogenesis of T2D, are incompletely understood, especially in black African populations who present with a phenotype of low S_I , hyperinsulinemia and low ectopic fat deposition. Our study extends existing evidence by demonstrating that DI was positively associated with CLp. Notably, the major correlate of AIRg was $ISR_{\text{first phase}}$, above insulin clearance. VAT emerged as the strongest correlate of DI, above and independent of pancreatic fat and soleus fat. Additionally, we showed that a lower VAT also associated with a higher $ISR_{\text{first phase}}$ and lower FE_L . Thus, our findings suggest that VAT is a more important correlate of a lower DI than ectopic fat in this cohort, not only through its association with a lower S_I , but also through its relation with the AIRg downstream components, ISR and FE_L .

DI associates with peripheral insulin clearance

Our study, not only distinguishes between FE_L and CLp, which has only been done in a few studies in adults without T2D [6,8,32], but we also demonstrated for the first time a positive association between DI and CLp. The reason for this relationship is unclear. Nevertheless, considering DI is based on the product of S_I and AIRg, we can postulate two scenarios. Firstly, a higher DI may be due to a hyperinsulinemia relative to the level of S_I . However, hyperinsulinemia has been associated with lower insulin clearance in both adipose tissue [33] and muscle [34], due to reduced affinity of insulin receptors at these sites, and is therefore an unlikely explanation for our finding of a higher CLp relative to higher DI. Secondly, a higher DI could be due to a greater S_I in relation to the level of AIRg. In this scenario, a higher CLp may be due to enhanced binding of insulin to insulin receptors in peripheral tissues. Although a positive association has been demonstrated between S_I and hepatic insulin clearance [35], no association between insulin internalization, a measure of insulin clearance, and S_I was observed in rat adipocytes [33], whereas the association between S_I and insulin clearance in muscle is unknown. However, in support of the second scenario, we showed that those with the highest DI and CLp were also more insulin sensitive, but only exhibited a slightly higher AIRg compared to those with lower DI and CLp. Nevertheless, CLp was not associated with S_I in our study, but rather with the insulin secretory component. Further, we may also consider that the observed association between DI and CLp is in compensation for a lower FE_L , but this association remained independent of FE_L . We also evaluated the associations of CLp with ectopic fat deposition as possible explanation for the association with DI, but found that CLp was not associated with skeletal muscle fat. Skeletal muscle fat has been associated with reduced S_I [36], which may also affect CLp in the muscle. Further study is justified to evaluate the relationship between CLp and S_I in the muscle, considering that the muscle is only secondary to the kidney in the proportion of insulin cleared in the periphery [37]. Of note, CLp in our study is much higher compared to another study conducted in black American women [6]. However, the acute insulin response in our cohort was twice as high as that observed in Piccinini *et al*, and may contribute to this discrepancy.

Associations between DI and ectopic fat

Preservation of β -cell function is critical for delaying the onset of T2D. We, therefore, investigated, firstly, whether ectopic fat accumulation may explain the variance in DI and secondly, we assessed the associations of ectopic fat with the components of DI. Our study demonstrated that a higher DI was associated with a lower pancreatic and soleus fat but these associations were not independent from VAT. A similar observation was found in overweight African American and Hispanic adolescents (13 to 25 years old) without T2D [38]. In contrast a positive association between DI and pancreatic fat, adjusted for BMI and VAT, was shown in black African American women [13]. However, this study included participants with and without T2D, which may explain the incongruent findings. Our study extends the literature by showing that pancreatic fat was not associated with $ISR_{\text{first phase}}$ or with FE_L in black Africans. Notably, a positive association was found between pancreatic fat and VAT in our study. Our findings therefore suggest that pancreatic fat may only be a marker of VAT accumulation and may not be detrimental to β -cell function in this cohort.

Contribution of hepatic insulin clearance and ISR to AIRg

The ability to maintain DI and prevent deteriorating glucose tolerance depends on the balance between AIRg and S_I [1]. However, there is no consensus on the mechanism of maintaining a higher AIRg, which is frequently observed in black African populations [3,4]. Some studies reported that a lower hepatic insulin clearance alone is responsible for a higher AIRg [39,40], while others showed that both lower hepatic insulin clearance and higher ISR contribute towards a higher AIRg [4,6]. Notably, AIRg may be out of proportion for the level of S_I , and to assess the relative contribution of $ISR_{\text{first phase}}$ and insulin clearance to AIRg in this context, we need to adjust for S_I . Accordingly, a lower FE_L and higher

$ISR_{\text{first phase}}$ were the main independent contributors towards a higher AIRg, but $ISR_{\text{first phase}}$ explained more of the variance in AIRg. Lowering hepatic insulin clearance is an important compensatory mechanism to reduce the strain on the pancreatic β -cells, which has been shown in canines [41]. Indeed, we also noted a higher DI is associated with a lower FE_L which may be explained by the negative association between AIRg and FE_L . Further, we showed that a higher ISR associates with AIRg, independently of lower FE_L and S_I , suggesting that despite a lower FE_L , pancreatic β -cells may continue to secrete insulin at a higher rate, which may be detrimental to the longevity of the β -cell in this cohort.

Associations of ISR and hepatic insulin clearance with ectopic fat

The current study further examined the associations between the components of AIRg and ectopic fat. Previously, reduced hepatic insulin clearance and increased insulin secretion, have been associated with hepatic fat accumulation [42]. An association between fasting hepatic insulin clearance and hepatic fat was studied in African American women [15], but the association between stimulated hepatic insulin clearance, which is a more physiological response, and hepatic fat has not been previously investigated in black African populations without T2D. We showed that hepatic fat was not associated with FE_L and ISR in black South African women with obesity. Therefore, in black African populations, hepatic fat may not be an important correlate of hepatic insulin clearance and insulin secretion prior to T2D, and also not in those with early T2D [43]. Instead, we found that a lower $ISR_{\text{first phase}}$ and higher FE_L were associated with higher VAT. This highlights a novel mechanism to explain the association between AIRg and VAT since to the best of our knowledge, no previous study has evaluated the effect of central fat depots on FE_L . In addition, evidence on the associations between central fat depots and ISR, determined by C-peptide deconvolution are also limited in black African populations [11]. We add to the literature by showing a negative association between VAT and $ISR_{\text{first phase}}$ independent of S_I , in premenopausal black South African women. Interestingly, black African women have lower VAT compared to other ethnicities [3,4], but they have a greater propensity to increase VAT over time, with the greatest increase occurring in the 20-29-year age group [44]. However, further studies are needed to confirm the effect of VAT on ISR in this cohort.

Associations between S_I and ectopic fat

We also assessed the association between S_I and ectopic fat and found no association between S_I and skeletal muscle or hepatic fat. These findings suggest that these ectopic fat depots are not important correlates of S_I in our study. However, we should consider that we measured whole body S_I , which could have diluted the associations with hepatic and soleus fat. Indeed, a small South African study found that in black South African women, hepatic fat was associated with hepatic S_I but not peripheral S_I [14]. Furthermore, total soleus fat and soleus IMCL were associated with peripheral S_I , but not hepatic S_I [14]. Nevertheless, lower S_I was associated with higher VAT which may contribute to the observed inverse association between DI and VAT in this cohort.

A major strength of this study is that ISR and both hepatic and peripheral clearance were determined using mathematical modelling, which has never been done before in an African cohort. Further we assessed pancreatic, hepatic and skeletal muscle ectopic fat depots, as well as VAT and aSAT volumes using MRI. However, limitations of this study were that we did not determine glucose tolerance, and we did not distinguish between hepatic and peripheral S_I . We have not corrected for multiple correlation which may have produced false positive associations. However, the focus was to explore the possible significant associations between variables and therefore we wanted to minimize false negative associations. In addition, these findings are applicable to premenopausal, black South African women with obesity and may not be extrapolated to men or other races.

In conclusion, an original finding from this study was that DI was associated with CLp, independent from FE_L . Further, while both FE_L and $ISR_{\text{first phase}}$ independently contributed towards hyperinsulinemia, $ISR_{\text{first phase}}$ was more important. Ectopic fat was not an important independent correlate of DI and its components. Rather, a key finding was that higher VAT was the principal correlate of a lower DI, above other ectopic fat depots. Additionally, the associations of higher VAT on the downstream components of DI, a lower $ISR_{\text{first phase}}$ and higher FE_L may contribute to lower DI prior to T2D onset but requires further elucidation. Accordingly, the prevention of VAT accumulation, especially in young black African women should be an important target for β -cell preservation.

Declarations

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Author contributions

AM, JG, TO conceived and designed the study. MF, AM, JG, JS performed study procedures. MF, AA, JH, OH performed MRI fat quantification. MF, DS performed mathematical modelling. MF prepared figures and drafted the manuscript. MF, AM, JG were involved in data analysis. MF, AM, JG, TO, JS, SK, JH, DS, LG, AA, OH read and edited the manuscript and approved the final version. MF, AM and JG are the guarantors of this work and, as such, has full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Availability of data and materials

The data and materials used to support the findings in this study is available from the corresponding author upon a reasonable request.

Ethics approval and consent to participate

Ethical approval was obtained from the University of Cape Town Human Research Ethics Committee (reference number 799/2015). This study formed part of a randomized controlled trial that was registered in the Pan African Clinical Trial Registry (PACTR201711002789113). All study participants provided written informed consent to participate in the study. The study was conducted in accordance to ethical principles outlined in the Declaration of Helsinki.

Consent for publication

All the study participants provided written informed consent to participate in the study.

Competing interest

All the authors have nothing relevant to disclose.

Author details

¹Division of Exercise Science and Sports Medicine, Department of Human Biology, University of Cape Town, Cape Town, South Africa, ²Non-Communicable Diseases Research Unit, South African Medical Council, Tygerberg, South Africa, ³Department of Radiation Sciences, Radiation Physics and Biomedical Engineering, Umeå University, Umeå, Sweden,

⁴Department of Human Biology, MRC/UCT Medical Imaging Research Unit, University of Cape Town, Cape Town, South Africa, ⁵The Al-Amteaz Centre for MRI Solution and Development, Tripoli, Libya, ⁶Department of Clinical Studies, New Bolton Center, University of Pennsylvania, School of Veterinary Medicine, Kennett Square, Pennsylvania, USA, ⁷Department of Diabetes, School of Life Course Sciences, Faculty of Life Sciences & Medicine, King's College London, London, UK, ⁸Division of Metabolism, Endocrinology and Nutrition, Department of Medicine, Veterans Affairs Puget Sound Health Care System, University of Washington, Seattle, WA, USA, ⁹Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden

Abbreviations

AI_{Rg}: Acute insulin response to glucose; aSAT: Abdominal subcutaneous adipose tissue; AUC: Area under curve; BMI: Body mass index; CL_p: Peripheral insulin clearance; DI: Disposition index; DXA: Dual-energy X-ray absorptiometry; EMCL: Extramyocellular lipid; FE_L: Fractional hepatic insulin extraction; FSIGT: Frequently sampled intravenous glucose tolerance test – insulin modified; IMCL: Intramyocellular lipid; ISR: Insulin secretion rate; MRI: Magnetic resonance imaging; MRS: Magnetic resonance spectroscopy; S_I: Insulin sensitivity; T2D: Type 2 Diabetes; VAT: Visceral adipose tissue

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Tables

Table 1: Characteristics of participants by disposition index tertile

	DI _{Low} (≤ 5073.4) n=15	DI _{Intermediate} (>5073.4 $-\leq 7933.2$) n=13	DI _{High} (>7933.2) n=15	P value
	Mean \pm SD/Median (IQR)			
Age and anthropometry				
Age (years)	24 (21-28)	22 (21-28)	23 (21-24)	0.455
Body weight (kg)	85.1 \pm 8.8	87.8 \pm 6.3	87.1 \pm 13.7	0.400
Body mass index (kg/m ²)	33.3 \pm 2.6	35.3 \pm 2.1	33.6 \pm 3.5	0.147
Waist circumference (cm)	103.1 \pm 5.3	103.9 \pm 8.5	105.8 \pm 11.0	0.705
Waist-hip ratio	0.89 (0.84-0.95)	0.89 (0.87-0.91)	0.90 (0.85-0.94)	0.899
Body composition and fat distribution				
Body fat mass (%)	50.1 \pm 2.8	51.3 \pm 3.1	50.4 \pm 4.5	0.660
Fat free soft tissue mass (kg)	36.9 (33.8-40.3)	37.4 (35.8-38.8)	38.7 (34.9-40.6)	0.791
Trunk fat mass (%)	47.9 \pm 4.7	47.3 \pm 4.0	46.5 \pm 4.7	0.684
Leg fat mass (%)	40.0 \pm 5.2	40.6 \pm 4.3	40.8 \pm 5.2	0.901
Android fat mass (%)	8.5 \pm 1.4	8.1 \pm 0.8	7.9 \pm 0.8	0.284
Gynoid fat mass (%)	18.5 \pm 1.8	18.7 \pm 2.0	18.4 \pm 2.5	0.942
VAT (cm ³)	1113.3 \pm 317.9	931.6 \pm 355.1	669.8 \pm 229.1 [†]	0.002
aSAT (cm ³)	5303.9 \pm 1116.8	5741.4 \pm 1105.2	5629.1 \pm 2191.8	0.747
VAT-aSAT	0.20 (0.16-0.24)	0.15 (0.11-0.21) [§]	0.13 (0.09-0.15) [†]	0.003
Ectopic fat				
Mean pancreatic fat (%)	8.0 (7.3-9.0)	7.4 (6.6-10.4)	6.2 (5.2-6.4) ^{†‡}	0.006
Hepatic fat (%)	5.6 (4.5-6.1)	5.9 (4.5-8.4)	4.5 (3.9-4.9) ^{†‡}	0.023
Soleus fat (%)	10.7 (10.1-11.4)	9.7 (8.8-11.6)	9.4 (6.8-10.3)	0.111
Tibialis anterior fat (%)	4.1 (3.3-5.7)	4.2 (3.5-5.4)	5.0 (2.6-6.1)	0.953
SIMCL (%)	2.9 (2.5-3.9)	2.9 (2.5-4.8)	2.1 (1.3-3.1) [†]	0.055
SEMCL (%)	4.5 (4.2-12.8)	5.1 (3.6-4.5)	4.3 (3.6-5.6)	0.410
TIMCL (%)	0.5 (0.3-0.8)	0.4 (0.3-0.5)	0.4 (0.3-0.5)	0.288
TEMCL (%)	2.9 (1.1-4.7)	2.6 (1.6-3.0)	2.5 (1.5-4.2)	0.815
Fasting metabolic parameters				
Fasting glucose (mmol/L)	5.4 \pm 0.9	5.0 \pm 0.9	5.2 \pm 0.6	0.411
Fasting insulin (pmol/L)	85.2 (63.9-119.1)	82.5 (78-113.7)	57.7 (38.6-88.5)	0.107
Fasting C-peptide (pmol/L)	605.7 (572.6-744.8)	733.2 (491.5-835.8)	466.7 (382.3-787.8)	0.218
C-peptide/insulin _{basal}	6.8 (6.3-8.4)	8.4 (6.4-9.3)	9.0 (7.7-10.9)	0.087
ISR _{basal} (pmol/min)	78.7 (74.4-96.8)	94.7 (62.9-102.4)	62.4 (49.-104.6)	0.567
HOMA2 IR%	2.1 (1.7-2.9)	2.0 (1.8-2.7)	1.4 (1.0-2.2)	0.149
HOMA2 B%	134.6 (97.5-204.3)	182.6 (130.4-213.2)	108.7 (85.2-149.1)	0.133
HbA1c and FSIGT-derived measures				
HbA1c	5.24 \pm 0.36	5.19 \pm 0.36	5.20 \pm 0.43	0.829
Disposition index (AU)	3780 (2989-4527)	6596 (6070-7119) [§]	9995 (9247-13882) ^{†‡}	<0.001
S _I (mU/l) ⁻¹ min ⁻¹	1.94 (1.1-2.8)	1.97 (1.4-3.1)	3.1 (2.2-4.5) ^{†‡}	0.008
AIR _g mU l ⁻¹ min ⁻¹	2159 (1465-3159)	2909 (2544-4870)	3561 (4278-4514)	0.064
S _g (min ⁻¹)	0.017 \pm 0.008	0.024 \pm 0.008	0.031 \pm 0.008 [†]	<0.001

ISR _{first phase} (pmol/min)	2692 (1909-4023)	3624 (2826-4999)	4049 (2758-4877)	0.060
ISR _{total} (pmol/min)	4246 (3231-8095)	5589 (4813-7913)	4272 (3261-6500)	0.365
FE _L (%)	61.6 ±11.9	54.5 ±8.7	51.4 ±9.4 †	0.042
CLp (ml/min/kg)	74.7 (61.3-105.3)	91.5 (77.1-125.8)	128.9 (92.3-168.2) †	0.009

Mean (\pm SD) for normally distributed variables and median (IQR) for non-normally distributed variables; DI - Disposition index, VAT - visceral adipose tissue, aSAT - abdominal subcutaneous adipose tissue, SIMCL - soleus intra-myocellular fat, SEMCL - soleus extra-myocellular fat, TIMCL - tibialis anterior intra-myocellular fat, TEMCL - tibialis anterior extra-myocellular fat, ISR - insulin secretion rate, HOMA - homeostatic model assessment 2 of insulin resistance (IR) and beta cell function (B), SI - insulin sensitivity, AIRg - acute insulin response to glucose, Sg - glucose effectiveness, FE_L - fractional hepatic insulin extraction; CLp - peripheral insulin clearance. P value derived from ANOVA or Kruskal Wallis, significant post-hoc differences: † High DI compared to low DI; ‡ High DI compared to intermediate DI; § Intermediate DI compared to low DI with $P \leq 0.05$ deemed as statistically significant.

Table 2: Relationship of β -cell function and insulin sensitivity with hepatic and peripheral insulin clearance

Model	Variables	Sqrt DI		ln AIR _g		ln ISR _{first phase}		ln S _I	
		β (P value)	R ²	β (P value)	R ²	β (P value)	R ²	β (P value)	R ²
1.	FE _L (%)	-0.709 (0.010)	0.168	-0.016 (<0.001)	0.576	-0.011 (<0.001)	0.403	0.008 (0.065)	0.089
2.	ln CLp (ml/min/kg)	55.80 (0.002)	0.234	0.623 (0.004)	0.204	0.644 (<0.001)	0.293	-0.042 (0.881)	0.001
3.	FE _L (%)	-0.364 (0.222)	0.265	-0.015 (<0.001)	0.579	-0.009 (0.002)	0.430	0.010 (0.038)	0.115
	ln CLp (ml/min/kg)	42.78 (0.035)		0.086 (0.630)		0.335 (0.060)		0.320 (0.313)	
4.	FE _L (%)	-		-0.011 (<0.001)	0.765	-0.005 (0.023)	0.647	-	
	ln CLp (ml/min/kg)	-		0.206 (0.138)		0.438 (0.004)		-	
	ln S _I ((mU/l) ⁻¹ min ⁻¹)	-		-0.374 (<0.001)		-0.324 (<0.001)		-	

β - linear regression coefficient, Sqrt- square root, Ln - natural log, DI - disposition index, S_I - insulin sensitivity, AIRg - acute insulin response to glucose, ISR- insulin secretion rate, FE_L - fractional hepatic insulin extraction, CLp - peripheral insulin clearance; $p \leq 0.05$ regarded as statistically significant

Table 3: The contribution of insulin secretion and hepatic insulin extraction to acute insulin response to glucose

Model	Variables	Ln AIR _g			
		β-coefficient ± SE	Partial beta	P	Model R ²
1.	ln ISR _{first phase}	0.99 ± 0.07	-	<0.001	0.819
2.	Hepatic insulin extraction (%)	-0.016 ± 0.002	-	<0.001	0.576
3.	ln ISR _{first phase}	0.813 ± 0.091	0.701	<0.001	0.869
	Hepatic insulin extraction (%)	-0.007 ± 0.002	-0.314	0.001	
4.	ln ISR _{first phase}	0.667 ± 0.094	0.574	<0.001	0.898
	Hepatic insulin extraction (%)	-0.007 ± 0.001	-0.333	<0.001	
	ln S _I	-0.166 ± 0.053	-0.203	0.004	

Ln - natural log, AIR_g - acute insulin response to glucose, SE - Standard error, ISR - insulin secretion rate, S_I - insulin sensitivity

Table 4: Correlations of insulin sensitivity, secretion and clearance, with central adipose tissue depots

	Model 1				Model 2		
	β-coefficient (p value)				β-coefficient (p value)		
	ln S _I (mU/l) ⁻¹ min ⁻¹	ln AIR _g mU l ⁻¹ min ⁻¹	ln ISR _{first phase} (pmol/min)	FE _L (%)	ln AIR _g mU l ⁻¹ min ⁻¹	ln ISR _{first phase} (pmol/min)	FE _L (%)
VAT cm ³	-3.07 x10 ⁻⁴ (0.011)	-0.74 x10 ⁻⁴ (0.511)	-0.43 x10 ⁻⁴ (0.667)	0.008 (0.101)	-2.780 x10 ⁻⁴ (0.006)	-2.02 x10 ⁻⁴ (0.033)	0.013 (0.012)
aSAT cm ³	-0.33 x10 ⁻⁴ (0.248)	0.50 x10 ⁻⁴ (0.049)	0.21 x10 ⁻⁴ (0.365)	-0.001 (0.507)	0.34 x10 ⁻⁴ (0.114)	-0.01 x10 ⁻⁴ (0.957)	-0.0003 (0.823)
ln VAT-aSAT ratio	-0.320 (0.179)	-0.427 (0.042)	-0.220 (0.253)	23.9 (0.016)	-0.617 (<0.001)	-0.327 (0.054)	27.16 (0.006)

Unadjusted (Model 1) and adjusted for S_I (Model 2). S_I - Insulin sensitivity, AIR_g - acute insulin response to glucose, ISR - insulin secretion rate, FE_L - hepatic insulin extraction, VAT - visceral adipose tissue, SAT - abdominal subcutaneous adipose tissue. Ln - natural log transformed variable

Figures

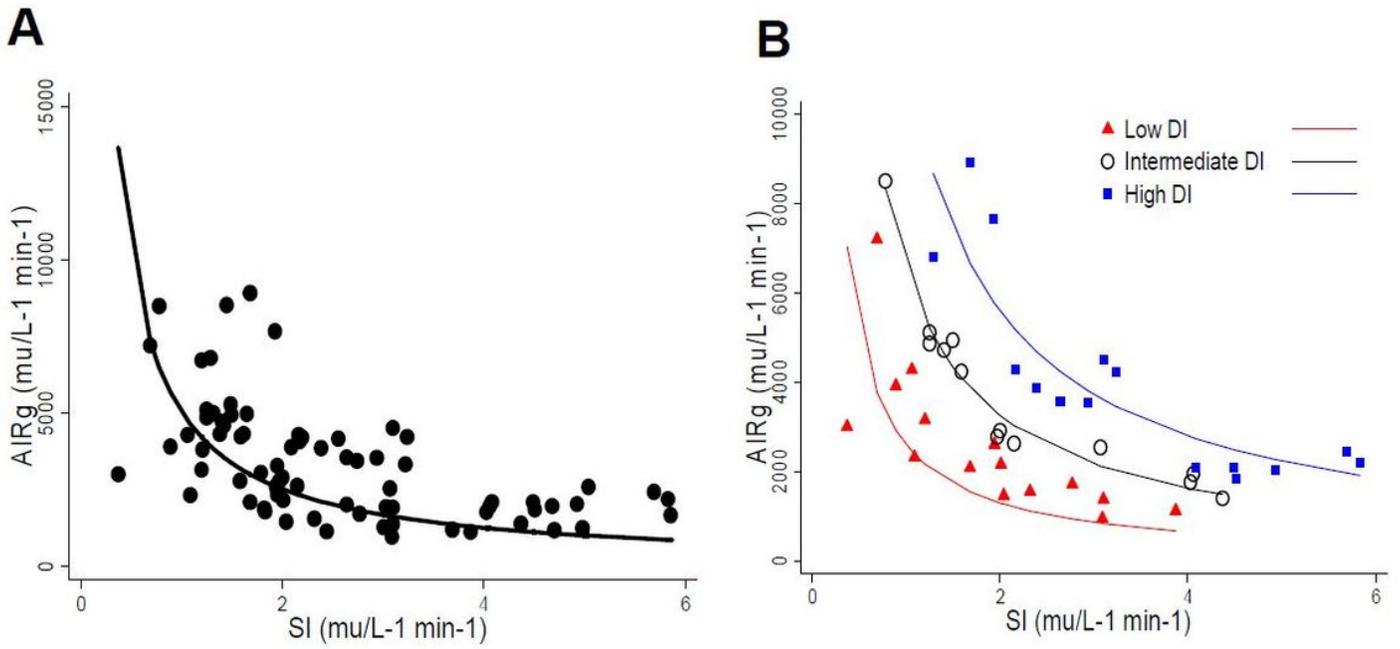


Figure 1

Hyperbolic association between insulin sensitivity (SI) and acute insulin response to glucose (AIRg) for overall sample (A) and by disposition index (DI) tertiles (B)

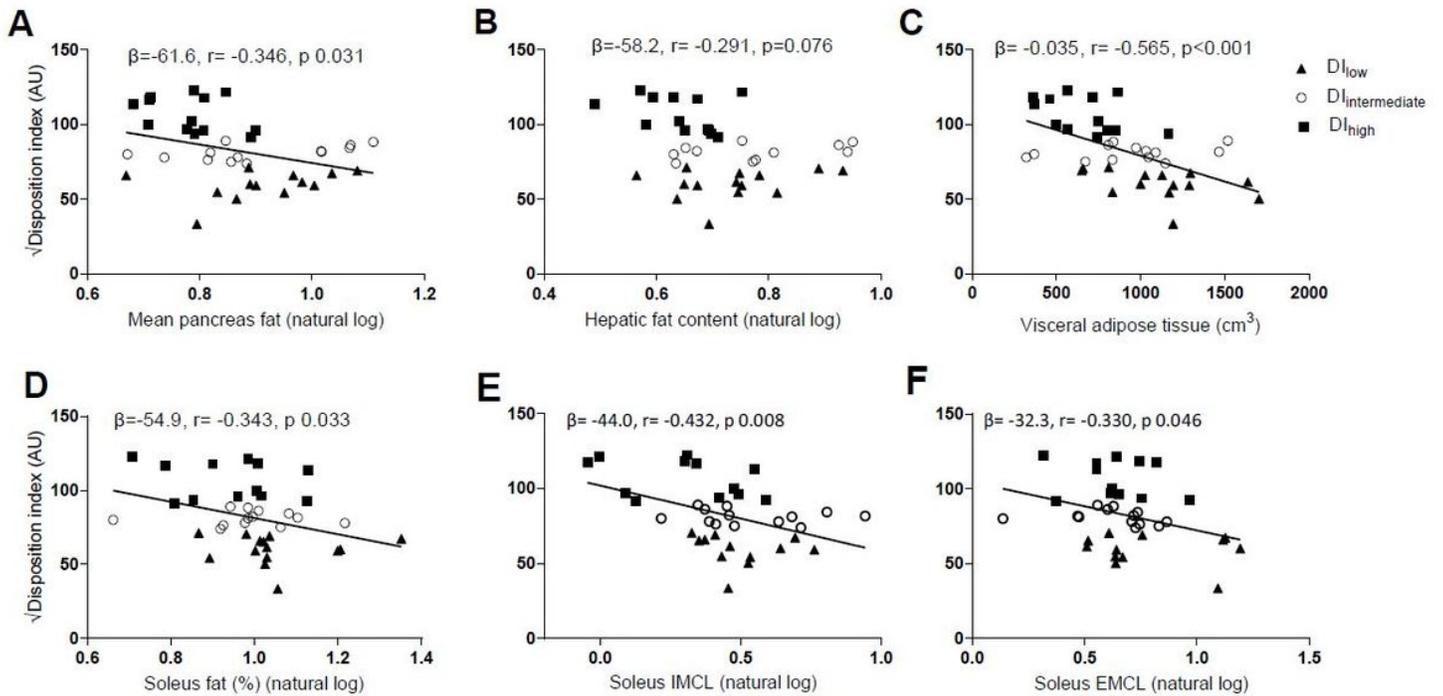


Figure 2

Disposition index (DI) associations: with (A) pancreatic fat (B) hepatic fat, (C) visceral adipose tissue, (D) soleus fat (E) soleus intra-myocellular fat (IMCL) and (F) soleus extra-myocellular fat (EMCL) in those with low DI (solid black triangles), intermediate DI (open circles) and high DI (solid black square). Regression line indicates significant association ($p < 0.05$) in the whole cohort, β (slope), r - correlation coefficients