

Effect of exercise training on insulin sensitivity, hyperinsulinemia and ectopic fat in black South African women: a randomized controlled trial

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Abstract

Objective: We investigated the effects of a 12-week exercise intervention on insulin sensitivity (S_I) and hyperinsulinemia and associated changes in regional and ectopic fat.

Research design and methods: Healthy, black South African women with obesity (mean age 23 ± 3.5 years) and of *isiXhosa* ancestry were randomised into a 12-week aerobic and resistance exercise training group ($n = 23$) and a no exercise group (control, $n = 22$). Pre and post-intervention testing included assessment of S_I , insulin response to glucose (AIRg), insulin secretion rate (ISR), hepatic insulin extraction (FE_L) and disposition index (DI) ($\text{AIRg} \times S_I$) (frequently sampled i.v. glucose tolerance test); fat mass and regional adiposity (dual-energy X-ray absorptiometry); hepatic, pancreatic and skeletal muscle fat content and abdominal s.c. and visceral adipose tissue volumes (MRI).

Results: Exercise training increased $VO_{2\text{peak}}$ (mean \pm s.d.: 24.9 ± 2.42 to 27.6 ± 3.39 mL/kg/min, $P < 0.001$), S_I (2.0 (1.2 – 2.8) to 2.2 (1.5 – 3.7) ($\text{mU/l})^{-1} \text{min}^{-1}$, $P = 0.005$) and DI (median (interquartile range): 6.1 (3.6 – 7.1) to 6.5 (5.6 – 9.2) $\times 10^3$ arbitrary units, $P = 0.028$), and decreased gynoid fat mass (18.5 ± 1.7 to $18.2 \pm 1.6\%$, $P < 0.001$) and body weight (84.1 ± 8.7 to 83.3 ± 9.7 kg, $P = 0.038$). None of these changes were observed in the control group, but body weight increased ($P = 0.030$). AIRg, ISR and FE_L , VAT, SAT and ectopic fat were unaltered after exercise training. The increase in S_I and DI were not associated with changes in regional or ectopic fat.

Conclusion: Exercise training increased S_I independent from changes in hyperinsulinemia and ectopic fat, suggesting that ectopic fat might not be a principal determinant of insulin resistance in this cohort.

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Introduction

Insulin resistance and hyperinsulinemia are more frequently found in black African women compared to white women (1). However, the mechanisms that underlie the high prevalence of insulin resistance and hyperinsulinemia and type 2 diabetes in black South African (SA) women have not been fully elucidated.

Notably, black African women exhibit a unique phenotype that contradicts the established determinants of insulin resistance typically shown in white populations. Compared to their white counterparts, black African women have less visceral adipose tissue (VAT) (2), a proven determinant of insulin resistance (3), and more peripheral s.c. adipose tissue (SAT) (2), typically regarded as protective (4). Similarly, black African women have less hepatic fat and equivalent i.m. fat compared to their white counterparts (5). Hyperinsulinemia found in black Africans has been ascribed to low insulin sensitivity (S_I), with low hepatic insulin extraction and/or high insulin secretion rate (ISR) (6). Studies in black African populations have reported that low hepatic insulin extraction was not associated with hepatic fat (7, 8), while insulin response/ β -cell function was positively associated with pancreatic fat (9, 10). However, these were cross-sectional studies from which we cannot infer causality.

Exercise can decrease the risk for developing type 2 diabetes (11), most likely through its ability to improve S_I (12). In addition, exercise training has been shown to reduce the insulin response, after an oral glucose load, in healthy adults with obesity (13), although this response may be modified by the baseline insulin secretory capacity (14). Further, exercise training may also reduce skeletal muscle (15), hepatic (16) and pancreatic fat (17), which may explain exercise-induced alterations in S_I and hyperinsulinemia. However, an exercise-intervention study that evaluates the chronic training effects on S_I and hyperinsulinemia, as well as on skeletal muscle, hepatic and pancreatic fat, has not been completed in a black African population who present with a unique phenotype. Accordingly, the current study hypothesizes that exercise training would increase S_I and decrease hyperinsulinemia in black SA women with obesity, which would be associated with favorable changes in ectopic and regional fat distribution.

Methods

The study design and detailed methods have been published previously (18) and are described in brief below.

The CONSORT diagram for the work described here is provided in Fig. 1.

Study design and participants

In this randomized controlled exercise intervention, black SA women were recruited from a low socioeconomic community in Cape Town. Inclusion criteria were: obesity (BMI 30–40 kg/m²), both parents of *isiXhosa* descent (self-reported), 20–35 years old, 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. Participants were excluded if they had any known diseases (e.g. HIV, hypertension, diabetes (random blood glucose >11.1 mmol/L, HbA1c >6.5%)), were pregnant or lactating, smoking or had any other orthopaedic or medical problems that prevented or restricted exercise participation. University of Cape Town Human Research Ethics Committee provided ethical permission. The trial was registered in the Pan African Clinical Trial Registry (PACTR201711002789113). Written informed consent was obtained prior to screening and testing procedures. Eligible participants were blocked randomized (2–4 participants) into an exercise ($n=23$) and control group ($n=22$). Three women in the exercise group and seven in the control group did not complete the trial, as described previously (18).

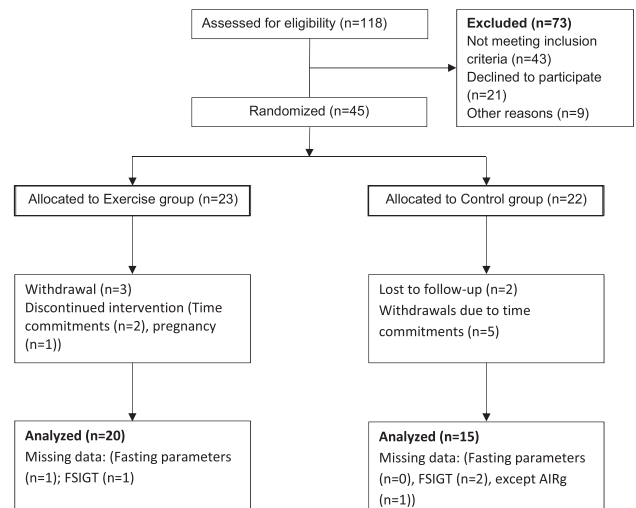


Figure 1
CONSORT participant flow diagram (adapted from Goedecke *et al.* (18)).

Table 1 Details of the combined aerobic and strength exercise training program.

	Weeks											
	1	2	3	4	5	6	7	8	9	10	11	12
Session frequency, times/week	4	4	4	4	4	4	4	4	4	4	4	4
Total session duration (min)	40	40	40	40	45	45	50	50	55	55	60	60
Aerobic training												
Session duration (min)	30	30	28	28	33	30	35	32	37	37	40	40
Intensity, % HR _{peak}	75-80	75-80	75-80	75-80	75-80	75-80	75-80	75-80	75-80	75-80	75-80	75-80
Strength training												
Session duration (min)	10	10	12	12	12	15	15	18	18	18	20	20
Repetitions and sets	10×3	15×3	10×3	15×3	10×3	15×3	20×3	20×3	10×3	15×3	10×3	15×3
Weights, kg	-	-	1	1	1.5	1.5	1.5	1.5	2	2	2.5	2.5
Intensity, % HR _{peak}	60-70	60-70	60-70	60-70	60-70	60-70	60-70	60-70	60-70	60-70	60-70	60-70

HR, heart rate; Weights, refers to the weight of the dumbbells.

Exercise intervention

The exercise group participated in 12-weeks of aerobic and resistance training, 40–60 min, 4 days per week (Table 1) and every session was supervised by a qualified clinical exercise specialist. The intervention included aerobic-based exercises (dance, running, skipping and stepping) performed at a moderate-vigorous intensity (75–85% peak heart rate, HR_{peak}) and progressive (body weight, bands and free weights) strengthening exercises to achieve a prescribed intensity of 60–70% HR_{peak} (Table 1). Based on the results of focus group discussions conducted in black SA women (19), the intervention utilized a combination of exercises to ensure greater enjoyment and adherence.

A heart rate monitor (Polar Electro, Kempele, Finland) was used to ensure participants achieved the desired exercise intensity and attendance was recorded for each session. The control and exercise groups were instructed to continue with habitual activity and dietary patterns.

Anthropometrics and body fat distribution

Anthropometric measurements included weight, height, hip and waist circumferences. Whole body composition was measured by dual-energy X-ray absorptiometry (DXA; Discovery-W®, software version 12.7.3.7; Hologic, Bedford, MA, USA), in the morning after an overnight fast, for the analyses of total body (whole body minus head) fat mass and fat-free soft tissue mass, as well as trunk, leg, android and gynoid fat mass (20).

Cardiorespiratory fitness

Peak oxygen consumption (VO_{2peak}) was measured using a walking treadmill-based (C, Quasar LE500CE, HP Cosmos, Nussdorf-Traunstein, Germany), graded exercise test designed for sedentary participants that are not familiar with gym-based equipment. The test started at 3 km/h at 2% gradient and the gradient was increased by 2% every 2 min until a gradient of 16% were reached. Thereafter, the speed and gradient were increased alternatively (0.5 km/h and 1%, respectively) to volitional exhaustion (21). VO_{2peak} was measured by indirect calorimetry (CPET, Cosmed, Rome, Italy) and heart rate was monitored continuously (Polar Electro Oy, Kempele, Finland) to determine HR_{peak}.

Insulin secretion, insulin clearance and insulin sensitivity

Prior to the testing day, participants slept overnight at the laboratory and consumed a standardized meal at 20:00 h (Energy: 2,456 kJ, 21 g protein (14% energy), 49 g carbohydrate (33% energy) and 32 g fat (48% energy)), followed by an overnight fast (10–12 h). In the morning, fasting blood samples were drawn for measurement of HbA1c, insulin, glucose and C-peptide, and insulin-modified frequently sampled i.v. glucose tolerance test (FSIGT) was performed. Glucose (50% dextrose; 11.4 g/m²×body surface area) was infused at 0 min over a 60 s period followed at 20 min by an infusion of human insulin (0.02 unit/kg; NovoRapid, Novo Nordisk Limited) over 5 min at a constant rate. Thirty-three blood samples were drawn for the measurement of insulin, glucose and C-peptide at standardised time points over 240 min, following the start of glucose administration. Post-intervention testing occurred 72 h following the last exercise training session.

Mathematical modelling

The minimal model of glucose kinetics was used to calculate: S_I , glucose effectiveness (S_g), the acute insulin response to glucose (AIR_g), and disposition index ($DI = S_I \times AIR_g$) (22). A two-compartment model was used to determine the ISR using standard kinetic parameters taking into account obesity (23). The total area-under-curve (AUC) for glucose, insulin and C-peptide, derived from the FSIGT and ISR, was calculated using the trapezoidal rule. Hepatic and peripheral insulin clearance was determined as previously described (24). WinSAAM was used to estimate these model parameters (25). Hepatic insulin clearance can either be explained by a linear or a saturable model. Both models were run on all participants. The model with the lowest Akaike Information Criteria (26) was chosen as the preferred model. The linear model provided a single parameter (FE_{L_i}) to explain hepatic insulin extraction (post-glucose load), compared to two parameters (V_{max} and K_m) provided by the saturable model. In order to compare FE_{L_i} , only participants in whom the linear model was preferred pre-and post-intervention were included in the analysis ($n=21$).

Ectopic fat

A standardized meal (Energy: 2553 kJ, protein: 20.9 g; carbohydrates: 83.0 g; fat: 22.2 g) was consumed 2–4

h prior to ectopic fat determination. MRI was used to determine hepatic, pancreatic and skeletal muscle (soleus, tibialis anterior) fat content using a 3 Tesla whole-body human MRI scanner (MAGNETOM Skyra; Siemens Medical Solutions). A three-point Dixon volume interpolated breath-hold gradient recalled echo sequence were used: TR 3.97 ms, TE1 1.23 ms, TE2 2.46ms, flip angle 9 degrees, number of averages 1, bandwidth 1040 Hz/px, field of view 450×366 mm, matrix size 195×320×144 and a slice thickness of 2 mm. The three-point Dixon method has been validated before using a fat/water phantom and was found to be accurate and reproducible even at low levels of fat in liver, pancreas and skeletal muscle (27).

A MATLAB algorithm was used to separate the water and fat signals and to create a fat fraction map calculated as the fat signal over the sum of the water and fat signals. Region of interests (ROIs) were manually drawn using OsiriX (liver, muscle) and HOROS V 1.1.7 (pancreas, VAT, abdominal SAT). The precision of manual methods in fat quantification are not significantly different compared to semi-automated methods (28, 29). An ROI was drawn on seven consecutive slices of the right lobe of the liver, avoiding ducts and blood vessels, and over the largest cross-sectional area of soleus and tibialis anterior muscles, adapted from Machann *et al.* (30). The ROI included the intermuscular fat but excluded the fatty septa between muscles. Pancreatic fat was determined by drawing one circular 1 cm² ROI in the head, body and tail of the pancreas. This method was used to avoid inclusion of VAT (31). Abdominal VAT and SAT volumes were determined by calculating the sum of the VAT and SAT areas from five images in a 15 cm region from the level of L1-5 and then multiplied by 3 (32). The above-mentioned methods were found to have high precision in previous studies (28, 29, 33, 34).

Biochemical analyses

HbA1c was analysed using HPLC (Meharini Diagnostics, Florence, Italy). Plasma glucose was measured using a colorimetric assay (Randox (Pty) Ltd, Gauteng, South Africa). Serum insulin and C-peptide were determined by an immunochemiluminometric assays (IMMULITE 1000 immunoassay system, Siemens Healthcare (Pty) Ltd, Midrand, South Africa). Pre- and post-intervention samples for a participant were run in the same assay. Coefficient of variation for assays ranged from 6 to 8.5%.

Physical activity and dietary monitoring

Energy expenditure of both groups was estimated using accelerometry (ActiGraph GTX3+, LLC, Pensacola, Florida), worn for 24 h a day over a 7-day period at baseline, 4, 8 and 12 weeks. Energy expenditure was compared between the exercise (non-exercise days) and the control group. Dietary intake was measured by a registered dietician using a 24-h dietary intake recall and a 3-day dietary record (2 weekdays and 1 weekend day) at baseline, 4 and 8 and 12 weeks.

Statistical analysis

Data was analysed using STATA 12.0 (College Station, TX, USA). Data were expressed as mean ± s.d. or median and interquartile range (IQR) for normally and skewed data, respectively. The latter were transformed to achieve normality prior to mixed-model analysis in which the random and fixed effects referred to inter-subject variability and differences between the groups, respectively. Fisher’s least significant difference *post hoc* test was used when appropriate. Linear regression determined associations between changes in main outcomes and changes in predictors in the combined group and to check for group interactions. A *P* value of ≤0.05 was regarded as statistically significant. The sample size determination, based on the change in normalized glucose clearance determined by euglycemic hyperinsulinemic clamp (35), using a power of 80% and a significance level of *P*<0.05 was six participants per group. A per protocol analysis was performed on those with both pre- and post-intervention data available (*n*=15 control and *n*=20 exercise group).

Results

Exercise adherence and effect of exercise on cardiorespiratory fitness

Mean exercise session attendance was 79% (range 52–100%) at a mean intensity of 79.6 ± 4.0 %HR_{peak}. An improvement in cardiorespiratory fitness (VO_{2peak}) was observed in the exercise group (2077 ± 211 to 2278 ± 231 mL/min, *P*<0.001 and 24.9 ± 2.42 to 27.6 ± 3.39 mL/kg/min, *P*<0.001), while no change was observed in the control group (2099 ± 282 to 2032 ± 196 mL/min, *P*=0.286 and 23.9 ± 2.97 to 23.0 ± 2.64 mL/kg/min, *P*=0.309).

Dietary and physical activity

Energy intake, macronutrient composition of the diets, and total energy expenditure (non-exercise days in the exercise group) did not differ within or between groups at baseline, 4, 8 and 12 weeks (Supplementary Table 1, see section on [supplementary materials](#) given at the end of this article).

Effect of exercise training on metabolic outcomes

No differences in metabolic outcomes were observed between groups at baseline. Exercise training improved the AUC of glucose_{total} (group × time *P*=0.020) (Supplementary Fig. 1). S_i improved in the exercise group (*post hoc* *P*=0.005), improving in 15 out of 19 participants, with no change in the control group (*post hoc* *P*=0.711) (Fig. 2). In contrast, the AUC for insulin and C-peptide did not change with exercise training (Supplementary Fig. 1). Accordingly, no changes were observed in AIR_g (Fig. 2), ISR, hepatic insulin extraction and peripheral insulin clearance. As S_i improved with no reciprocal change in AIR_g, DI increased after exercise training (*post hoc* *P*=0.028) (Table 2).

Effect of exercise training on body composition and body fat distribution and ectopic fat content

A small but significant reduction in body weight was observed after exercise training (mean Δ -0.82 kg, *post hoc* *P*=0.038), whereas the control group gained body weight (mean Δ +1.0 kg, *post hoc* *P*=0.030) and abdominal SAT (mean Δ +285.5 cm³, *post hoc* *P*=0.008). While exercise training did not alter total fat mass, fat-free soft tissue

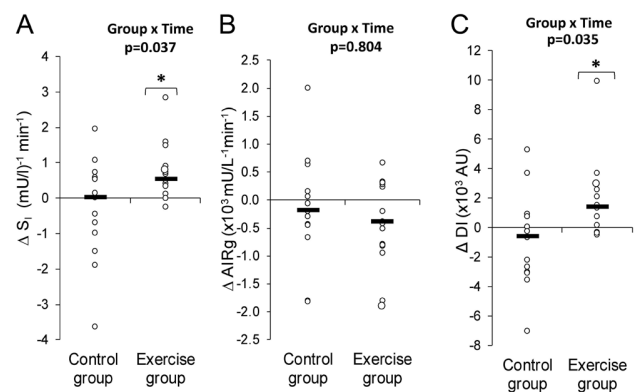


Figure 2 Changes in (A) insulin sensitivity (S_i), (B) acute insulin response to glucose (AIR_g) and (C) disposition index (DI) in the control and exercise groups. Thick black line – median, empty circles – individual changes. **Post hoc* test *P* ≤ 0.05.

Table 2 Participant characteristics before and after the 12-week intervention period.

	Control group		Exercise group		C/E [†]	Group	Time	Group × Time
	Pre	Post	Pre	Post				
Age (years)	23 (21–27)	-	22 (21–24)	-	15/20	0.748	-	-
Body weight (kg)	87.8 ± 10.9	88.8 ± 11*	84.1 ± 8.7	83.3 ± 9.7*	15/20	0.267	0.030	0.003
Height (m)	1.62	-	1.57	-	15/20	0.016	-	-
BMI (kg/m ²)	33.4 ± 2.7	33.8 ± 2.8*	34.1 ± 2.8	33.8 ± 3.1*	15/20	0.430	0.038	0.003
Waist circumference (cm)	100.0 (97.0–112.0)	103.0 (98.5–116.5)*	103.2 (97.9–108.1)	99.5 (94.0–103.3)* [†]	15/20	0.911	0.013	<0.001
Waist-to-hip ratio	0.88 (0.83–0.93)	0.89 (0.86–0.95)	0.89 (0.87–0.94)	0.87 (0.86–0.91)	15/20	0.202	0.078	0.015
FFSTM (kg)	37.7 (35–41)	38.2 (35–41)	37.1 (34–39)	37.1 (34–40)	14/20	0.293	0.223	0.324
Body fat mass (%)	49.8 (47–54)	50.9 (48–52)	49.9 (49–52)	49.9 (48–51)	14/20	0.981	0.480	0.471
Trunk fat (%FM)	45.8 ± 4.7	45.6 ± 4.7	48.0 ± 4.6	47.7 ± 4.7	14/20	0.170	0.568	0.845
Leg fat (%FM)	42.5 ± 5.0	42.9 ± 5.3	39.8 ± 5.0	39.8 ± 4.8	14/20	0.103	0.386	0.607
Android fat (%FM)	8.0 ± 1.3	7.9 ± 1.5	8.3 ± 1.0	8.1 ± 1.0	14/20	0.572	0.163	0.860
Gynoid fat (%FM)	19.4 ± 2.3	19.6 ± 2.3	18.5 ± 1.7	18.2 ± 1.6* [†]	14/20	0.129	0.323	0.002
Visceral fat (cm ³)	903.1 ± 431.0	953.1 ± 403.9	920.0 ± 322.1	906.2 ± 346.9	13/20	0.850	0.177	0.178
Abdominal s.c. fat (cm ³)	5298.9 ± 1853.8	5584.4 ± 1956.9*	5489.3 ± 1053.4	5447.7 ± 1260.7	13/20	0.850	0.008	0.018
HbA1c (%)	5.2 ± 0.35	5.3 ± 0.38	5.2 ± 0.32	5.2 ± 0.29	15/19	0.676	0.794	0.884
HbA1c (mmol/mol)	33 ± 2.2	34 ± 2.4	33 ± 2.0	33 ± 1.84	15/19	-	-	-
Fasting glucose (mmol/L)	5.0 ± 0.66	5.1 ± 0.79	5.5 ± 0.84	5.1 ± 0.98	15/19	0.102	0.829	0.217
Fasting insulin (pmol/L)	78.6 (58.4–85.2)	79.2 (64.5–117.6)	88.5 (38.6–114.6)	75.3 (63.2–102.6)	15/19	0.942	0.979	0.773
Fasting C-peptide (pmol/L)	575.9 (484.9–787.8)	586.7 (448.5–916.9)	620.6 (362.4–804.3)	643.8 (458.4–852.3)	15/19	0.949	0.900	0.943
ISR _{basal} (pmol/min)	74.8 (63.0–102.4)	76.3 (58.3–119.2)	80.7 (47.1–102.4)	83.7 (59.6–110.8)	13/19	0.681	0.795	0.715
HOMA2 %IR	1.8 (1.4–2.2)	2.0 (1.1–2.9)	2.2 (1.0–2.9)	1.9 (1.4–2.6)	15/19	0.939	0.993	0.943
HOMA2 %B	143.5 (98.9–235.6)	132.1 (117.9–208.6)	131.5 (89.9–182.7)	145.7 (97.6–199.7)	15/19	0.287	0.907	0.227
S ₁ × 10 ⁻⁴ (mU/l) ⁻¹ min ⁻¹	2.01 (1.29–3.24)	1.83 (1.65–32.64)	2.04 (1.20–2.77)	2.17 (1.45–3.69)*	13/19	0.094	0.711	0.037
AI _{Rg} × 10 ³ (mU/l) ⁻¹ min ⁻¹	2.43 (2.10–4.28)	2.70 (1.91–4.21)	3.16 (1.72–4.72)	3.33 (1.68–4.33)	14/19	0.609	0.404	0.804
DI × 10 ³	7.80 (4.53–8.78)	5.92 (5.34–8.25)	6.10 (3.61–7.12)	6.53 (5.56–9.22)*	13/19	0.151	0.294	0.035
Sg × 10 ⁻² (min ⁻¹)	2.4 ± 0.97	2.2 ± 0.66	2.3 ± 0.98	2.6 ± 0.79	13/19	0.795	0.574	0.226
ISR _{total} (pmol/min)	12,608 (10,214–14,534)	10,879 (9068–15,866)	12,697 (9331–14,831)	12,731 (9891–15,506)	13/19	0.949	0.459	0.549
ISR/Glucose _{total}	10.5 (8.4–13.4)	9.8 (6.9–11.9)	9.3 (6.5–10.9)	10.0 (6.9–11.6)	13/19	0.257	0.221	0.048
C-peptide/Insulin _{basal}	8.1 (6.47–9.37)	7.5 (7.31–8.71)	7.0 (6.39–9.09)	7.7 (7.01–8.41)	15/19	0.957	0.916	0.711
FE ₁ (%)	56.4 ± 8.3	53.6 ± 13.6	52.4 ± 9.0	54.2 ± 10.7	10/11	0.358	0.408	0.328
Clp (mL/kg/min)	86.2 (74.7–131.9)	89.3 (76.7–94.6)	105.4 (97.8–158.6)	101.0 (73.1–155.4)	10/11	0.138	0.734	0.718

Mean (±s.d.) for normally distributed variables and median (interquartile range) for non-normally distributed variables, non-normally distributed variables were transformed. P values are derived from mixed model analysis.

*Significant *post hoc* difference (pre- vs post-intervention) within group P ≤ 0.05, †Significant *post hoc* difference (Exercise vs Control) between groups P ≤ 0.05, †C/E = number of participants in control (C)/exercise (E) group.

AI_{Rg}, acute insulin response to glucose; AUC, area under curve; Clp, peripheral insulin clearance; DI, Disposition Index; FE₁, fractional hepatic insulin extraction; FFSTM, fat free soft tissue mass; FM, fat mass; HOMA, homeostasis model of assessment; IR, insulin resistance; ISR, insulin secretion rate; Sg, glucose effectiveness; S₁, insulin sensitivity.

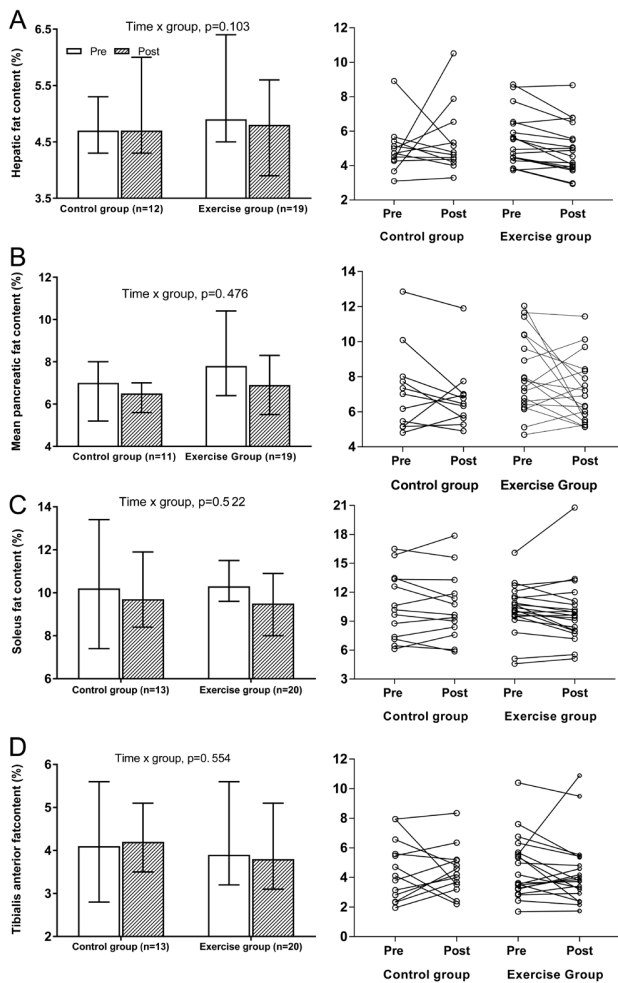


Figure 3

Individual changes from pre- to post-exercise training in (A) hepatic, (B) pancreatic, (C) soleus and (D) tibialis anterior fat in control and exercise group.

mass, abdominal SAT and VAT, there was a significant decrease in gynoid fat mass (%) ($P < 0.001$) in the exercise group only. After exercise training the pancreatic (7.8 (6.4–10.4)% to 6.9 (5.5–8.3)%), hepatic (4.9 (4.5–6.4)% to 4.8 (3.9–5.6)%), soleus (10.3 (9.5–11.5)% to 9.6 (8.0–10.9)%) and tibialis anterior (3.9 (3.2–5.6)% to 3.8 (3.1–5.1)%) fat, remained unaltered (Fig. 3 and Table 2).

Associations between changes in S_1 , AIRg, ISR, insulin clearance and changes in body composition, body fat distribution, ectopic fat and VO_{2peak}

Even though body fat distribution, except gynoid fat mass (%), and ectopic fat did not change significantly

after exercise training, the variability in the participants' responses allow us to assess the associations between the changes in metabolic outcomes and fat depots in response to the intervention. The exercise-induced increases in S_1 and DI were not associated with changes in body fat mass (%), gynoid fat mass (%), android fat mass (%) and ectopic fat (data not shown). Nevertheless, only in the control group (significant interaction by intervention group), significant associations were observed between changes in S_1 and changes in trunk fat mass (%) ($\beta -0.628, P < 0.001$) and leg fat mass (%) ($\beta 0.745, P = 0.002$). Further, in the combined group (control and exercise groups; no interaction by intervention group), an increase in S_1 was associated with a reduction in VAT ($\beta -0.002, P = 0.035$) and an increase in DI was associated with a reduction in trunk fat mass (%) ($\beta -842.7, P = 0.036$). Similarly, an increase in ISR_{total} was associated with a reduction in trunk fat mass (%) ($\beta -1237.8, P = 0.020$), but no significant associations occurred with changes in ectopic fat either in the combined or in the exercise or control groups (data not shown). No significant associations were observed between changes in AIRg and insulin clearance and changes in body fat distribution and ectopic fat (data not shown). No significant associations were found between any of the metabolic outcomes and change in VO_{2peak} (data not shown).

Discussion

For the first time, we comprehensively explored the effects of exercise training on S_1 , and hyperinsulinemia, as well as on pancreatic, hepatic and muscle fat and body fat distribution in black African women with obesity, who frequently present with low S_1 and hyperinsulinemia (36, 37). We showed that after 12 weeks of exercise training, S_1 increased but without any change in AIRg, and thus, showed a corresponding increase in DI. Further, the ISR and insulin clearance did not change after exercise training, which could explain the lack of change in AIRg. There were no changes in central or ectopic fat depots, but gynoid fat mass (%) decreased after exercise training. Notably, body fat distribution or ectopic fat changes were unrelated to the increase in S_1 or DI.

Evidence on the effect of exercise training on S_1 in black African populations are scarce. We, therefore, add to the literature by showing that exercise training improved S_1 in black South African women with obesity. However, the improvement of 6% in S_1 in our study is modest compared to earlier studies conducted in older African American women with obesity (58%) (38) and African American

adolescents with obesity (37%) (39). This discrepancy may be explained by the acute exercise effect on S_I which may last up to 72 h after a bout of exercise (40). The improvement in S_I in the earlier studies was demonstrated 14–18 h and 24–48 h, respectively (38, 39), after the last exercise session, compared to 72 h in our study. Another point to consider is the intensity of the exercise training since greater improvements in S_I have been observed with high intensity interval training compared to moderate intensity exercise training (41). Our study was performed at a moderate-high intensity (60–80% of VO_{2peak}) and used a combination of aerobic and strength training that has shown greater improvements in S_I compared to either of these modalities alone (42).

Notably, we showed improvements in S_I and the VO_{2peak} despite minimal weight loss (~1 kg). Similarly, improvements in both S_I and VO_{2peak} were observed in adults without obesity after 16 weeks of aerobic exercise training with marginal weight loss (0.5 kg), associated with augmented muscle mitochondrial enzyme activity and mitochondrial biogenesis gene expression, as well as increased GLUT4 mRNA and protein expression (43). Further, 12 weeks of moderate-intensity exercise training in men with obesity, improved both S_I and VO_{2peak} without weight loss with a contemporaneous reduction in systemic and skeletal muscle oxidative stress markers and an increased skeletal muscle antioxidant capacity (44). Therefore, both mitochondrial-related factors and the oxidative stress:antioxidant balance may be implicated in the improvement of S_I in our study. Further, the improvement of S_I in our study was not related to changes in central fat depots, since both VAT and abdominal SAT were unaltered after exercise training. In line with this, an increase in S_I was reported in overweight men after 6 weeks of exercise training with no concurrent reduction in VAT, but rather a reduction in fatty acid availability (45). The exercise-induced increase in S_I in our study may therefore be due to cellular changes within muscle and adipose tissue. Further research is required to address these hypotheses.

The lack of change in the ISR and hepatic insulin extraction was unexpected. Other exercise training studies have shown a reduction in stimulated insulin response (46, 47) or insulin secretion (17) in those with normal glucose tolerance. However, these studies were conducted in predominantly white older men and women known to have relatively lower baseline plasma insulin levels than those of black African ancestry. Notably, exercise-intervention studies that demonstrated reductions in AIRg either showed reduced body fat mass (46, 48, 49) or

reduced VAT (47). While no change in AIRg was observed in those with no significant change in VAT (47). These studies highlight a possible bi-directional relationship between hyperinsulinemia and body fat mass. In support, we showed in the combined group that a reduction in DI and ISR_{total} was associated with a reduction in trunk fat mass (%). While our 12-week exercise training program was unable to reduce hyperinsulinemia, despite increasing S_I , it produced a modest decrease in body weight (<1 kg) with no changes in central and ectopic fat depots. Notably, even in lifestyle intervention studies such as the Diabetes Prevention Program that included both exercise training and dietary changes, black African American women demonstrated smaller reductions in body weight compared to Black African American men and White and Hispanic men and women (50). It is possible that the inability to show greater exercise-induced changes in black women could be due to higher fasting and/or stimulated insulin levels. Insulin is a potent suppressor of lipolysis in adipose tissue and therefore limits free fatty acid mobilization (51). Even during exercise, excess insulin impedes the β -adrenergic stimulation of lipolysis (51). Thus, longer exercise training duration in combination with a dietary intervention, most likely a low carbohydrate and low glycemic diet (52), might be required to reduce hyperinsulinemia and consequently fat mass and central/ectopic depots in women with obesity and of black African ancestry.

A hyperbolic association has been described between AIRg and S_I , where a reduction in S_I results in compensatory increase in AIRg to maintain euglycemia (53). The stabilization point in black Africans occurs to the extreme left of the hyperbola (54), so that even a small increase in S_I could result in a reduction in AIRg. However, no change in AIRg was found in our study after exercise training. This might suggest that a high AIRg can occur independent from a low S_I and that perhaps a low S_I , found in black African population might not be the primary stimulus of a high AIRg. In support, a higher AIRg was found in normal-weight black compared to white children, matched for S_I (55). Furthermore, *in vitro* studies have shown that hyperinsulinemia may directly impact S_I through its effect on the insulin receptors (56) and/or indirectly through obesity-related sequelae (57). However, while exercise training can increase S_I independent to a loss in fat mass (44), a reduction in hyperinsulinemia may be required for sustained elevations in S_I .

Lastly, the significant reduction in gynoid fat mass (%) after exercise training is of major interest. We have previously reported lower adipogenesis (58) and higher

inflammation (59), fibrosis and hypoxia (60) in the gluteal fat depots of black SA women, compared to white women. Accordingly, the reduction in gynoid fat mass may have major beneficial long-term metabolic effects.

Our study has several strengths, including the randomized controlled design, using objective measures to ensure exercise intensity was maintained over the 12-week period. Monitoring of diet and habitual physical activity limited bias from these lifestyle behaviors on our observed findings. A limitation of our study is that we could not isolate the effect of exercise training on hepatic or adipose tissue insulin resistance because the FSIGT gives a measure of whole-body S_i . In addition, this study was conducted in black SA women and might not be generalizable to other ethnic groups or men.

In conclusion, we have demonstrated that in women known to present with hyperinsulinemia, 12 weeks of combined aerobic and resistance training increased S_i without concomitant changes in insulin secretion/clearance or central and ectopic fat depots. These findings suggest that ectopic fat might not be the primary determinant of insulin resistance in this cohort, rather intrinsic factors in the muscle and adipose tissue may explain the exercise-induced changes in S_i . Moreover, the greater insulin response found more frequently in black compared to white women, might not solely occur in compensation of a low S_i . Further, we found a reduction in gynoid fat that may have long-term beneficial effects in this study population.

Supplementary materials

This is linked to the online version of the paper at <https://doi.org/10.1530/EJE-19-0957>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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Author contribution statement

A M, J G, T O, L M conceived and designed the study. M F, A M, L C, L P, J G, J S performed study procedures. M F, J H, O H performed MRI fat

quantification. M F, D S performed mathematical modelling. M F prepared figures and drafted the manuscript. M F, A M, J G were involved in data analysis. M F, A M, J G, T O, S K, J H, D S, L G, L M, L K, L C, O H, J S read and edited the manuscript and approved the final version. M F, A M and J G 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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