Changes in systemic and subcutaneous adipose tissue inflammation and oxidative stress in response to exercise training in obese black African women

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Key points

- Inflammation and oxidative stress are interrelated during obesity and contribute to the development of insulin resistance; and exercise training represents a key component in the management of these conditions.
- Black African women, despite high gluteal subcutaneous adipose tissue (SAT) and less visceral fat, are less insulin sensitive than their white counterparts.
- Exercise training improved systemic oxidative stress in obese black women, which was related to gynoid fat reduction and not insulin sensitivity.
- Inflammatory markers changed depot-specifically in response to exercise training, increasing in gluteal SAT without changing in abdominal SAT.
- The increase of inflammatory state in gluteal SAT after exercise training is suggested to result from tissue remodelling consecutive to the reduction of gynoid fat but does not contribute to the improvement of whole-body insulin sensitivity in obese black South African women.

Abstract  Inflammation and oxidative stress are interrelated during obesity and contribute to the development of insulin resistance. Exercise training represents a key component in the management of obesity. We evaluated the effects of 12 weeks’ combined resistance and aerobic exercise training on systemic and abdominal vs. gluteal subcutaneous adipose tissue (SAT) inflammatory and oxidative status in obese black South African women. Before and after the intervention, body composition (dual energy X-ray absorptiometry), cardio-respiratory fitness ($\text{VO}_2\text{peak}$), serum and SAT inflammatory and oxidative stress markers were measured from 15 (control group) and 20 (exercise group) women and insulin sensitivity ($\text{SI}$; frequently sampled...
intravenous glucose tolerance test) was estimated. Following the intervention, VO$_{2peak}$ (9.8%), body fat composition (1–3%) and S$_i$ (9%) improved, serum thiobarbituric acid reactive substances (TBARS) decreased (6.5%), and catalase activity increased (23%) in the exercise compared to the control group ($P < 0.05$), without changes in circulating inflammatory markers. The mRNA content of interleukin-10, tumour necrosis factor $\alpha$, nuclear factor $\kappa B$ and macrophage migration inhibitory factor increased in the gluteal SAT exercise compared to the control group ($P < 0.05$), with no changes in abdominal SAT. These changes of inflammatory profile in gluteal SAT, in addition to the reduction of circulating TBARS, correlated with the reduction of gynoid fat, but not with the improvement of S$_i$. The changes in systemic oxidative stress markers and gluteal SAT inflammatory genes correlated with the reduction in gynoid fat but were not directly associated with the exercise-induced improvements in S$_i$.

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Introduction

Obesity is associated to insulin resistance (IR) and the risk for developing type 2 diabetes (Blüher, 2013). One of the most accepted mechanisms linking obesity and IR is the pathological expansion of adipose tissue (AT) (Blüher, 2013). During continuous energy intake exceeding energy expenditure, adipocytes progressively store excess lipids in the form of triglycerides, increasing their size and/or number. However the pathophysiological expansion of AT is mainly exerted via an increase in cell size, which has been associated with alteration of immune cell populations and an increasing pro-inflammatory state (Jung et al. 2008). Activation of pro-inflammatory pathways may not only inhibit adipogenesis (Gustafson et al. 2009), but also stimulate reactive oxygen species (ROS) production (Devries et al. 2008). For instance, tumour necrosis factor $\alpha$ (TNF$\alpha$) activates NADPH oxidase resulting in ROS production, and interferon $\gamma$ (IFN$\gamma$) has been shown to be one of the most potent activators of macrophage-induced ROS production (Huang et al. 2015). On the other hand, elevated ROS concentrations can lead to IR via activation of inflammatory pathways (such as nuclear factor $\kappa B$; NFkB) and inhibitory phosphorylation of the insulin receptor (Ouchi et al. 1999; Bloch-Damti & Bashan, 2005; Bashan et al. 2009). Notably, hypoxia associated with AT hypertrophy also increases macrophage infiltration, fibrosis and oxidative stress (Bays et al. 2008), resulting in cell damage, activation of stress signalling pathways, inflammatory processes and IR (Devries et al. 2008). Inflammation and oxidative stress are hence interrelated during obesity and are both suggested to be independent contributors to the development of IR (Goedecke et al. 2013a; Huang et al. 2015).

The distribution of AT is more important than total body fat mass in determining the individual obesity-related risk for cardio-metabolic diseases. Visceral adipose tissue (VAT) has the highest expression and secretion of pro-inflammatory cytokines compared to subcutaneous adipose tissue (SAT) depots and has been closely associated with IR (Després, 1993). Depending on the location, SAT also contributes to the development of oxidative and inflammatory phenotype (Manolopoulos et al. 2010; Smith & Kahn 2016). Indeed, compared to peripheral SAT, abdominal SAT has a higher inflammatory profile and has been shown to be negatively associated to insulin sensitivity mainly in Caucasian populations (Goedecke et al. 2009b; Manolopoulos et al. 2010). In contrast, gluteo-femoral SAT is proposed to be ‘protective’ against the obesity-associated complications in obese individuals (Manolopoulos et al. 2010). Importantly, these relationships are modified by ethnicity (Goedecke et al. 2013a). Black African women have more gluteo-femoral SAT and less VAT compared to their body mass index (BMI)- and age-matched white counterparts (Rush et al. 2007), but are less insulin sensitive (Goedecke et al. 2009a). Linked to this, the gluteal AT depot of black African women has been shown to contain larger adipocytes (Keswell et al. 2012) and have higher expression of genes induced by hypoxia, fibrosis and inflammation (Kotze-Horstmann et al. 2016), compared to white women. These findings suggest that the regulatory pathways underlying depot-specific AT metabolism and function and the associations with whole body metabolism need to be investigated within specific ethnic groups. Further, studies using animal models have shown that adipose tissue from trained mice transplanted into untrained mice improved their peripheral insulin sensitivity (Stanford et al. 2015; Smith & Kahn 2016), and the knockout of insulin receptor in adipose tissue of mice (FIRKO mice) protected these animals against obesity-related glucose intolerance (Blüher et al. 2002). We therefore hypothesized that gluteal AT function might be altered in obese black African populations and that it potentially represents a link between obesity and IR in this ethnic group. In order to understand this causal
molecular links between depot-specific AT function and development of IR in black African women, there is a need for intervention studies. These can form a basis for more targeted prevention and/or treatment of obesity and associated complications in this ethnic group particularly at high risk for cardio-metabolic diseases (Abraham et al. 2015).

Exercise training represents a key component of the treatment of obesity and has been well established to improve whole-body glucose metabolism and insulin sensitivity via its action, predominantly on skeletal muscle (Colberg et al. 2010; Ruth, 2012; Stanford et al. 2015). However, long term exercise training has also been shown to induce beneficial adaptations in other tissues, including AT (Bonadonna et al. 1993; Stanford et al. 2015). Hence, exercise training can be used as a model to understand systemic and depot-specific AT inflammation and oxidative stress on one hand, and insulin sensitivity/resistance on the other hand. In addition, it is not known whether the improvement in whole-body insulin sensitivity induced by exercise training is related to changes in systemic and/or AT inflammation and oxidative stress. Therefore, this study aimed to (i) assess the effects of 12 weeks’ exercise training on systemic and depot-specific SAT (abdominal vs. gluteal) inflammatory and oxidative stress status; and to (ii) examine whether these changes are related to changes in insulin sensitivity in obese black South African women. We hypothesized that exercise training will reduce systemic and SAT inflammation and oxidative stress, and this will be associated with improvements in insulin sensitivity ($S_I$).

Methods

Ethical approval

This study was approved by the Human Research Ethics Committee at the University of Cape Town (HREC REF: 827/2016) and registered to the Pan African Clinical Trial Registry (trial registration: PACTR201711002789113). The study was performed in accordance with the principles of the Declaration of Helsinki (1964, amended last in Fortaleza Brazil, 2013), ICH Good Clinical Practice (GCP) and the laws of South Africa. Participants provided written informed consent before participation in the screening and the research study.

Study design and participants

The detailed protocol and methods for this randomized controlled research study have been previously published (Goedecke et al. 2018) and are briefly summarized here. Forty-five obese black South African women (20–35 years old, BMI: 30–40 kg m$^{-2}$) were randomized into control ($n = 22$) and experimental (exercise $n = 23$) groups. Ten participants did not complete the intervention (dropout: $n = 7$ in control and $n = 3$ in exercise group) due to time commitment or loss of follow-up. The greater dropout in the control group could be attributed to their loss of interest due to their failure to be assigned to the exercise group, despite the assurance that they could participate in a 12-week exercise training programme following the 12-week control period. Consequently, the final number of participants was 15 in the control and 20 in the exercise group. They were recruited from a low socioeconomic community and were included in the study if they were of isiXhosa ancestry (both parents), not having known metabolic or inflammatory diseases (e.g. HIV tuberculosis, active hepatitis, or rheumatoid arthritis), not taking any medications, non-smoker, not pregnant or lactating and on injectable contraception.

Intervention and testing procedures

Intervention. The 12-week exercise training intervention consisted of supervised combined aerobic and resistance training progressing from 40 to 60 min, 4 days per week by a trained facilitator. This training type was based on previous studies showing that combined aerobic and resistance training affected adipose tissue mass, glucose metabolism and insulin sensitivity to a greater extent than aerobic training alone, in addition to the improvement of cardio-metabolic fitness (Belay et al. 2013; Sanal et al. 2013; Dickie et al. 2016). Exercises included cardiovascular exercises in the form of aerobic dance, running, skipping and stepping that were performed at a moderate-vigorous intensity (75–80% peak heart rate; $HR_{peak}$). Resistance exercises consisted of participants using their own body weight and progressed to the use of equipment (e.g. bands and light free weights). These exercises mainly included squats, lunges, bicep curls, push-ups and shoulder press with a prescribed intensity of 60% to 70% $HR_{peak}$. Attendance was recorded at each training session, and a heart rate monitor (Polar A300, Kempele, Finland) was worn by participants to ensure the prescribed exercise intensity was maintained throughout the 12-week period.

The control group was instructed to maintain their normal daily physical activity patterns, and not start any exercise training programme, which was verified through monthly monitoring using accelerometry (ActivPAL3c, PAL Technologies Ltd, Glasgow, UK). Both groups were instructed to maintain their usual dietary intake, which was evaluated every 4 weeks by a food frequency questionnaire as previously described (Clamp et al. 2019). Before and after the 12-week intervention, body composition, cardiorespiratory fitness and $S_I$ were measured, and blood and fat samples were collected for further analyses.
Body composition. Basic measures of anthropometry (weight, height, waist and hip circumference) were collected and whole-body composition was measured by dual-energy X-ray absorptiometry (DXA; Discovery-W, software version 12.7.3.7; Hologic, Bedford, MA, USA). Regional body fat distribution (gynoid, and android fat mass) was characterized (Goecke et al. 2013b) and VAT and SAT areas estimated (Micklesfield et al. 2012).

Cardiorespiratory fitness. Cardiorespiratory fitness was determined by measuring peak oxygen consumption (VO2peak) using a walking treadmill-based (C, Quasar LE500CE, HP Cosmos, Nussdorf-Traunstein, Germany) graded exercise test that increased in gradient by 2% every minute until 16%, following by an alternate increase in speed (0.5 km h−1) and gradient (1%) until volitional exhaustion. Pulmonary gas exchange was measured by determining O2 and CO2 concentrations and ventilation to calculate VO2 consumption and respiratory exchange ratio (RER) using a metabolic gas analysis system (CPET, Cosmed, Rome Italy).

Fasting blood samples and frequently sampled intravenous glucose tolerance. At least 72 h from the last exercise training session, the participants stayed overnight at the laboratory where they were given a standardized evening meal at 20.00 h and then fasted overnight (10 h). At 07.00 h, fasting blood samples were collected for biochemical analyses. Participants then underwent a frequently sampled intravenous glucose tolerance test (FSIGT) to measure S0 using Bergman’s minimal model of glucose kinetics (Bergman et al. 1979). Fasting IR was estimated using homeostasis model assessment of IR (HOMA-IR) (Levy et al. 1998).

Biochemical analyses. Plasma glucose concentrations were determined using a colourimetric assay (Randox, Gauteng, South Africa) and serum and high-sensitivity C-reactive protein (CRP) were measured using immunochemiluminometric assays (IMMULITE 1000 immunoassay system, Siemens Healthcare, Midrand, South Africa). Inflammatory cytokines (interleukin (IL)-6, IL1-βα, IL-8, IL-10, IL-15, monocyte chemotactic protein (MCP)1, interferon γ (IFNγ) and tumour necrosis factor α (TNFα)) were measured using Milliplex MAP MAG Human Cytokine kit (Merck, Johannesburg, South Africa) and xMAP technology (Luminex, Austin, TX, USA) according to the manufacturer’s instruction. The serum concentrations of IL-1βα, IL-6, IL-10 and IL-15 were below the detectable range and were excluded from the analysis. Serum concentrations of leptin and high molecular weight adiponectin were analysed using commercially available ELISA kits according to the manufacturer’s instructions (EMD Millipore Corp., St Charles, MO, USA). Systemic oxidative stress was evaluated in the serum by measuring concentrations of thiobarbituric acid reactive substances (TBARS), oxygen radical absorbance capacity (ORAC), superoxide dismutase (SOD) and catalase activities via enzyme assays (Maarman, 2014) using a microplate data acquisition program (Synergy HT, Gen5 2.01; BioTek Instruments, Inc., Winooski, VT, USA).

Adipose tissue gene expression.

Tissue collection. SAT samples were collected after 4–6 h of fasting, and at least 48 h after the last exercise training session. Abdominal samples from the region around the umbilicus and gluteal samples from the right upper outer quadrant were obtained by mini-liposuction (Evans et al. 2011). After local anaesthesia with lignocaine hydrochloride (2%, Intramed, Port Elizabeth, South Africa), 200 ml of normal saline with 20 ml 2% lignocaine was infused using an infiltration cannula (Lamis 14 ga × 15 cm, Byron Medical Inc., Tucson, AZ, USA). An aspiration cannula (Coleman, 12 ga × 15 cm, Byron Medical Inc.) attached to a 10 ml syringe was used to aspirate fat. Approximately 2–3 cm3 of fat was extracted from each site, washed with normal saline until no blood was visible, immediately frozen in liquid N2 and stored at −80°C.

RNA extraction, reverse transcription and real-time PCR. Total RNA was extracted from SAT samples using the RNeasy Mini lipid kit (Qiagen Ltd, Germantown, MD, USA). The yield and purity were determined spectrophotometrically using a microplate data acquisition program (Synergy HT, Gen5 2.01; BioTek Instruments, Inc.) and the RNA integrity was checked using 1% agarose gel electrophoresis. The extracted RNA (1.2 µg) was reverse transcribed to cDNA using High-Capacity cDNA Reverse Transcription Kit with RNase inhibitors (Thermo Fisher Scientific, Waltham, MA, USA). Real-Time PCR (RT-PCR) was performed in triplicate for each sample using the Applied Biosystems QuantStudioTM 3 Real-Time PCR system with predesigned Taqman assays from Thermo Fisher Scientific (Warrington, UK). A standard curve was constructed for each primer probe set using a serial dilution of cDNA pooled from all samples. SAT mRNA content was quantified for the adipokines adiponectin (Hs00605917_m1) and leptin (Hs00961622_m1); macrophage markers macrophage migration inhibitory factor (MIF, Hs00236988_g1), MCP1 (Hs00234140_m1); chemokines and cytokines: IL-10 (Hs00961622_m1), toll like receptor 4 (TLR4, Hs01060206_m1), NFXB1 (Hs00765730_m1), TNFα (Hs00174128_m1); and oxidative stress markers: nitric oxide synthase 3 (NOS3, Hs01574665_m1), catalase (CAT, Hs00156308_m1) and SOD (Hs00533490_m1).
These genes were specifically chosen because of their extensive documented association with alteration of AT function and IR during obesity. Endogenous (‘housekeeping’) genes were evaluated by comparing ribosomal protein lateral stalk subunit PO (RPLPo; Hs99999902_m1) and low-density lipoprotein receptor-related protein 10 (LRP10; Hs00204094_m1) against the full study cohort using the NormFinder algorithm (v0.953, Denmark). RPLPo was identified as the most stable gene. We further compared the mRNA levels of RPLPo within and between both depots pre- and post-exercise training and found no difference between the depots at baseline and in response to the exercise training. The expression levels of the target genes were normalized to RPLPo as the endogenous control. The expression of these genes was presented as the ratio of abundance of the gene of interest: abundance of RPLPo.

Statistical analyses

The data are expressed as mean ± standard deviation (SD) for normally distributed data, and median interquartile range for skewed data. Normality was testing using the Shapiro–Wilks test and skewed data were transformed prior to analysis. The data were transformed if from the normality test, P values were lower than 0.05 and transformations were performed after checking the best normalized option, which was mostly log transformation. The equality of variance of the groups was checked using Levene’s test and there was homogeneity of variances. The difference between the groups in response to exercise training was analysed using a two-way analysis of variance (ANOVA) with repeated measures on transformed data, and post hoc analysis was conducted when there was a significant main or interaction effect. Student’s paired t-test was used to compare gene expression between the two depots at baseline. Pearson’s correlation was used to evaluate the association between the changes in systemic and SAT inflammatory and oxidative stress markers, body composition, S1 and HOMA-IR. Significance levels were set at P < 0.05 and the analyses were performed using Stata software version 13.1 (StataCorp, College Station, TX, USA).

Results

Compliance, body composition and cardio-metabolic response to the intervention

A total of 48 exercise training sessions were conducted, in which participants attended 79 ± 13 (range: 52–100)% at a mean intensity of 79.7 ± 4.0 (range: 71–85)% HRpeak. Participants’ dietary intake did not change in either group throughout the intervention, as previously reported (Clamp et al. 2019).

A summary of participant characteristics at baseline and in response to the intervention is presented in Table 1. At baseline, the cardio-respiratory fitness, body composition and S1 did not differ between the groups. Following the intervention, VO2peak increased in the exercise group and was unchanged in the control group (P < 0.01 for group × time interaction). The exercise group had significantly reduced body weight, BMI and waist circumference (P < 0.01), while these parameters were increased in the control group (P < 0.01). In addition, gynoid fat (% fat mass (FM)) decreased in the exercise group (P < 0.01) only, but android fat (%FM), VAT and SAT did not change in either group. S1 increased in the exercise group and did not change in the control group (P < 0.05 for group × time interaction). No changes in fasting glucose, insulin or HOMA2-IR were observed in either group in response to the intervention.

Systemic inflammatory and oxidative stress markers in response to the intervention

Circulating inflammatory markers (CRP, TNFα, MCP1 and IL-8), as well as leptin and adiponectin concentrations did not differ between the groups in response to the exercise training (P > 0.05) (Table 2). In contrast, markers of oxidative stress were altered in response to the exercise training and were unchanged in the control group. Specifically, after post hoc analyses (following a trend or significant main effect), circulating TBARS concentrations decreased (P = 0.001) while catalase activity increased (P = 0.022) in the exercise group only. There was a tendency for SOD activity to increase (P = 0.067) in the exercise group and there were no changes in total antioxidant capacity (ORAC) in either group in response to the intervention (Table 2).

Gene expression in subcutaneous adipose tissue

We compared the expression of specific genes between the depots at baseline to evaluate depot-specific inflammatory and oxidative profiles (Table 3). Leptin mRNA content was higher in gluteal SAT (gSAT) compared to abdominal SAT (aSAT; P < 0.01) with no difference in adiponectin mRNA content (Table 3).

In response to exercise training, gSAT IL-10 mRNA increased in the exercise group (P < 0.001) but remained unchanged in the control group (P = 0.016 for group × time interaction) (Fig. 1). There was a significant group effect for gSAT NFKB1 and TNFα mRNA (P = 0.011 and P = 0.025, respectively), such that the expression of these genes was significantly higher in the exercise compared to the control group at 12 weeks (P < 0.01) (Fig. 1). Of...
Table 1. Changes in body composition, cardio-respiratory fitness and insulin sensitivity in response to the 12-week exercise intervention in exercise and control groups

| Variable                      | Exercise (n = 20)     | Control (n = 15)    |   | Group | Time | Group × time |
|-------------------------------|-----------------------|---------------------|---|-------|------|--------------|
| **Cardio-respiratory fitness**|                       |                     |   |       |      |              |
| VO_{peak} (ml min^{-1})       | 2077 ± 211            | 2278 ± 231*         |   | 0.100 | 0.130| 0.001        |
| VO_{peak} (ml kg^{-1})        | 24.9 ± 2.2            | 27.6 ± 3.4*         |   | 0.003 | 0.078| <0.001       |
| **Body composition**          |                       |                     |   |       |      |              |
| Weight (kg)                   | 84.1 ± 2.2            | 83.3 ± 2.2*         |   | 0.187 | 0.787| 0.003        |
| BMI (kg m^{-2})               | 34.1 ± 0.6            | 33.8 ± 0.6*         |   | 0.695 | 0.898| 0.003        |
| WC (cm)                       | 103.6 ± 1.8           | 100.4 ± 1.8**       |   | 0.331 | 0.700| <0.001       |
| Body fat mass (%)             | 50.2 ± 0.8            | 50.1 ± 0.8          |   | 0.782 | 0.698| 0.471        |
| Android FM (%FM)              | 8.3 ± 0.3             | 8.1 ± 0.3           |   | 0.608 | 0.033| 0.860        |
| SAT (cm²)                     | 18.5 ± 0.4            | 18.2 ± 0.4*         |   | 0.095 | 0.139| 0.002        |
| VAT (cm²)                     | 137 ± 8               | 132 ± 8             |   | 0.619 | 0.266| 0.509        |
| SAT (cm²)                     | 529 ± 19              | 523 ± 19            |   | 0.823 | 0.640| 0.535        |
| **Fasting glycaemia and insulin sensitivity** |       |                     |   |       |      |              |
| Fasting glucose (mmol l^{-1}) | 5.5 ± 0.8             | 5.1 ± 1.0           |   | 0.645 | 0.169| 0.217        |
| Fasting insulin (µIU ml^{-1}) | 14.8 (6.4–19.1)       | 12.6 (10.5–17.1)    |   | 0.977 | 0.811| 0.773        |
| HOMA2-IR                      | 2.2 (1.0–2.9)         | 1.9 (1.4–2.6)       |   | 0.916 | 0.956| 0.943        |
| S_{i} × 10^{-4} (µmol L^{-1} min^{-1}) | 2.0 (1.2–2.8)       | 2.2 (1.5–3.7)*      |   | 0.422 | 0.145| 0.045        |

Values are means ± SD for normally distributed variables and median (interquartile range) for non-normally distributed variables. **P < 0.01 and ***P < 0.001 represent the difference between the groups after the intervention and #P < 0.05, represents the difference post vs. pre in the exercise group. BMI, body mass index; FM, fat mass; HOMA2-IR, homeostatic model assessment of insulin resistance; SAT, subcutaneous adipose tissue; S_{i}, insulin sensitivity; VAT, Visceral adipose tissue; VO_{2} max, maximal oxygen uptake, used as a measure of cardio-respiratory fitness; WC, waist circumference.

Table 2. Changes in systemic inflammation and oxidative stress in response to the 12-week exercise intervention in exercise and control groups

| Variable                  | Exercise (n = 20)     | Control (n = 15)    |   | Group | Time | Group × time |
|---------------------------|-----------------------|---------------------|---|-------|------|--------------|
| **Inflammatory markers and adipokine** |                       |                     |   |       |      |              |
| CRP (mg l^{-1})           | 5.0 (2.1–11.5)        | 4.6 (2.8–9.0)       |   | 0.575 | 0.151| 0.225        |
| TNFα (pg ml^{-1})         | 4.1 (3.3–7.8)         | 4.6 (4.0–6.3)       |   | 0.461 | 0.816| 0.515        |
| MCP1 (pg ml^{-1})         | 283.6 (237.5–370.3)   | 302.8 (235.4–431.1) |   | 0.042 | 0.206| 0.358        |
| IL-8 (pg ml^{-1})         | 2.3 (0.2–4.1)         | 2.3 (1.7–5.1)       |   | 0.382 | 0.859| 0.377        |
| Leptin (ng ml^{-1})       | 62.5 (47.3–81.5)      | 63.4 (46.7–79.1)    |   | 0.305 | 0.900| 0.613        |
| Adiponectin (µg ml^{-1})  | 3.3 (1.9–5.0)         | 2.1 (1.3–3.3)       |   | 0.060 | <0.001| 0.793       |
| **Oxidative stress markers** |                       |                     |   |       |      |              |
| TBARS (µmol l^{-1})       | 0.49 (0.44–0.52)      | 0.46 (0.43–0.49)**  |   | 0.797 | 0.168| 0.003        |
| Catalase (UI mg^{-1})     | 0.80 (0.37–1.51)      | 1.04 (0.74–1.74)*   |   | 0.842 | 0.201| 0.091        |
| SOD (UI ml^{-1})          | 0.21 (0.14–0.52)      | 0.32 (0.17–0.48)#   |   | 0.300 | 0.049| 0.672        |
| ORAC (nmol l^{-1} min^{-1}) | 919.3                 | 1012.5              |   | 0.554 | 0.826| 0.918        |

Values are median (interquartile range). **P < 0.01, *P < 0.05 and #P < 0.1 represent the difference between pre vs. post in the exercise group after the intervention (post hoc). CRP, C-reactive protein; IL-8, interleukin 8; MCP1, monocyte chemoattractant protein 1; SOD, superoxide dismutase; TBARS, thiobarbituric acid reactive substances; TNFα, tumour necrosis factor α; ORAC, oxygen radical absorbance capacity.

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not different at baseline between the depots and did not shown). The levels of NOS3 this was not an effect of the exercise training (data not tended to decrease in the control group (P < 0.037 for group × time interaction) and was significantly lower in the control group at 12 weeks (P = 0.001; Fig. 1).

While leptin mRNA content did not change in response to exercise training, adiponectin mRNA (in both depots) tended to decrease in the control group (P < 0.1), but this was not an effect of the exercise training (data not shown). The levels of NOS3, SOD and CAT mRNA were not different at baseline between the depots and did not change in response to the intervention (data not shown).

Correlations between changes in inflammatory markers and changes in body composition and insulin sensitivity/resistance over the intervention period

As the relationship between the changes in inflammatory and oxidative stress markers and changes in body composition and insulin sensitivity/resistance over the 12-week period did not differ between groups (no interaction effect), we combined the groups (n = 35) for the correlation analyses. We found that increases in gSAT MCP1 and TNFα mRNA were associated with a decrease in BMI (P < 0.01), while an increase of gSAT IL-10 and MIF mRNA correlated with the decline in gynoid fat mass (%FM) (P < 0.05 and P < 0.001 respectively). No significant associations were found between changes in aSAT gene expression and changes in body composition. No significant associations were found between changes in systemic inflammatory markers and changes in body composition. These relationships were not different between the groups (no interaction effect).

The changes in systemic and SAT inflammatory markers were not associated with changes in S_f. However, the change of circulating TNFα and MCP1 concentrations were positively associated with changes of HOMA2-IR and this remained significant when adjusting for changes in BMI or gynoid fat mass (%FM) (P < 0.05). In addition, changes of aSAT IL-10 and TLR4 mRNA content were positively associated with changes of HOMA2-IR after adjusting for changes in BMI (P = 0.018 and P = 0.014) or in gynoid fat mass (%FM) (P = 0.009 and P = 0.011), respectively. Notably, changes in gSAT inflammatory markers were not associated with changes in HOMA2-IR over the 12-week intervention period (data not presented).

Correlations between changes in oxidative stress and inflammatory genes

When exploring the associations between transcript levels of oxidative stress markers and inflammatory markers in the SAT depots, we found that gSAT levels of MIF, NFKB1 and TNFα mRNA were positively correlated with gSAT SOD1 (MIF r = 0.289 P = 0.114; NFKB1 r = 0.459 P = 0.010; TNFα r = 0.422 P = 0.018) and CAT (MIF r = 0.399 P = 0.026; NFKB1 r = 0.568 P < 0.001; TNFα r = 0.537 P = 0.002) mRNA content. There were no significant correlations between inflammatory and oxidative markers in aSAT, and no associations between SAT mRNA and circulating levels of systemic markers of inflammation and oxidative stress.

Discussion

This is, to the best of our knowledge, the first study in women of African ancestry that has evaluated changes in AT and systemic inflammatory and oxidative stress markers in response to an exercise training intervention. The 12 weeks of combined aerobic and resistance exercise training resulted in significant improvements in S_f, cardio-respiratory fitness and body composition, but did not reduce circulating markers of inflammation. In contrast,
circulating TBARS concentrations, a by-product of lipid peroxidation by ROS, decreased with a concomitant increase in circulating antioxidant enzyme activity (mainly catalase). Notably, exercise training resulted in an increase in gSAT IL-10, TNFα, NFKB1 and MIF mRNA content with no changes in aSAT inflammatory gene expression. These changes in systemic oxidative stress markers and gSAT inflammatory genes did not correlate with the improvement in SI, but were rather associated with the reduction of gynoid fat mass. Moreover, changes in aSAT IL-10 and TLR4 mRNA were positively associated with changes in HOMA2-IR in response to the intervention and these were independent of changes in body composition.

The effect of exercise training on systemic inflammation in obese cohorts has been extensively studied but findings remain controversial. Some studies showed a reduction of systemic inflammatory markers after exercise training (Cordova et al. 2011; Trachta et al. 2014) while others found no changes of these markers (Libardi et al. 2012; Lakhdar et al. 2013). We did not find changes of

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**Figure 1. Effect of exercise training on gluteal (gSAT) and abdominal subcutaneous adipose tissue (aSAT) inflammatory gene expression**

Data presented as individual plot on the right and mean (SD) on the left. 
*P < 0.05 and **P < 0.01: pre vs. post within groups following the intervention (time effect).
1P < 0.05: interaction between groups over the period of intervention. 6P < 0.01: differences between groups at post-intervention (i.e. group effect at 12 weeks).
Control group n = 15, both depots and exercise group n = 20 in aSAT and n = 18 in gSAT at post-training. IL-10, interleukin-10; MIF, macrophage migration inhibitory factor; NFKB1, nuclear factor κB; TNFα, tumour necrosis factor α.
circulating leptin, adiponectin, CRP, TNFα, MCP1 and IL-8 concentrations after 12 weeks of exercise training. This may relate to the duration of the intervention and/or the limited effects that exercise training has on weight loss and body fat-mass. We found a small (~1 kg) but significant decrease in body weight in the exercise group, whereas body weight, BMI and waist circumference increased in the control group, which is reflective of the typical changes in body weight expected in this group of young women (Chandler et al. 2016).

Contrary to our findings, Cordova et al. showed a reduction of cytokine levels (IFNy, IL-6 and TNFα) after 8 months of resistance training in obese women (Cordova et al. 2011) and Trachta et al showed a decrease in circulating CRP with a decline in body fat of 4.1% after 3 months of aerobic exercise training (Trachta et al. 2014). Accordingly, these differences in exercise duration and total fat mass reduction could explain why we and others (Libardi et al. 2012; Lakhdar et al. 2013) did not find any significant changes in systemic inflammation.

Inflammation and oxidative stress are interrelated during obesity, both contributing to the development of IR (Huang et al. 2015). While we showed no changes in inflammatory markers, we found a decrease in TBARS and an increase in antioxidant enzyme activity. Likewise, Oh et al. showed an increase of glutathione peroxidase after 6 months of aerobic training that was accompanied by a reduction of body weight (Oh et al. 2013). In contrast, 8 weeks of high intensity exercise training without changes in body weight did not improve oxidative stress and inflammatory state in obese adolescents (Kelly et al. 2007). Catalase and SOD represent the primary antioxidant protection against the harmful effects of ROS, and contribute to a lower oxidative stress and cell damage (Bradley & Carl, 1984). The accumulation of modified ‘ROS-damaged’ proteins can lead to IR by activating inhibitor of NF-κB (IkB) via p38 mitogen-activated protein kinase (MAPK), followed by the activation of NFκB (Bashan et al. 2009). Elevated ROS can also activate serine/threonine phosphorylation of insulin receptor substrate-1 (IRS1) leading to IR (Bloch-Damti & Bashan, 2005; Bashan et al. 2009). However, we did not show an association between the changes in circulating TBARS levels, catalase and SOD activities and the improvement of $S_i$. The maintenance of a balanced oxidative stress status seems to reflect the beneficial effect of exercise training on body fat, but not a direct mechanism in the improvement of $S_i$ in these women.

The distribution of body fat (abdominal vs. peripheral) is distinctively associated with metabolic risks, due to the different biological properties and metabolism of the different depots (Lacabini et al. 2019). When comparing the gene expression between aSAT and gSAT at baseline, we found a higher level of leptin mRNA in gSAT. Gluteal SAT has been shown to have larger adipocytes compared to aSAT in this population (Goedecke et al. 2013a) and a strong positive correlation between cell size and leptin mRNA has been reported (Skurk et al. 2012). These findings support the role of leptin as a signal of fat mass (and its effect on adipocyte metabolism).

Contrary to our hypothesis, we showed an increase in the gene expression of the inflammatory markers in gSAT at 12 weeks (post-intervention), which were associated with a reduction in gynoid fat mass, but not with an improvement in $S_i$. Noteworthy, the samples analysed in our study were collected 3 days after the last exercise training session to exclude the potential acute effects of the last bout of exercise training. The increase in inflammatory gene expression in the gSAT seems to be an adaptive response to fat mass reduction (Rutkowski et al. 2015), potentially representing a remodelling process occurring within this tissue. Indeed, the AT inflammatory state is modulated during expansion and/or remodelling of this tissue (Monteiro & Azevedo, 2010). Additionally, recent evidence showed that inflammation in the adipocyte microenvironment is required for extracellular matrix remodelling and angiogenesis (Cristancho & Lazar, 2011; Asterholm et al. 2014). Fat mass reduction driven by an overall reduction of stored triglycerides consecutive to lipolysis requires extensive remodelling of the tissue (Pasarica et al. 2009; Fischer et al. 2018). Exercise training increases basal and/or stimulated adipocyte lipolysis (Després et al. 1984; Teixeira et al. 2016). The free fatty acids released from adipocytes (from both basal and exercise-induced stimulated lipolysis) activate monocytes and create a paracrine loop between lipolysis and local inflammation (Suganami et al. 2005), increasing the inflammatory state in the fat depot. The increased IL-10 mRNA content in gSAT is supported by previous findings showing that the reduction of stored triglycerides in adipocytes is followed by an increased expression of lipolysis-associated M2 macrophage markers (Kosteli et al. 2010; Huang et al. 2014). IL-10 activates M2 macrophages for tissue repair and may also be a compensatory mechanism to cope with the increased inflammation. Increased inflammation can subsequently influence the oxidative stress state. Accordingly, we showed a strong positive association between the expression of inflammatory genes (MIF, NFKB1 and TNFα mRNA) and antioxidant enzymes (CAT and SOD1 mRNA) in gSAT. Inflammatory markers such as TNFα can trigger the activation of NADPH oxidase and the production of ROS (Huang et al. 2015), followed by increasing expression of antioxidant enzymes to buffer and maintain a ‘healthy’ oxidative stress balance (Perriette-Olson et al. 2016).
markers in response to 12 weeks of moderate exercise training – despite the expected improvements in body composition (Lakhdar et al. 2013). The changes in aSAT inflammatory status in response to exercise training might have been reflected at the post-transcriptional level. Further investigation is therefore required to evaluate the changes in protein content in both aSAT and gSAT depots after an exercise training programme.

Another important finding of this study was that although no improvements in HOMA2-IR were observed, we found a positive association between changes in HOMA2-IR and changes in aSAT IL-10 and TLR4 mRNA content in response to the exercise training. In contrast to whole body SI, estimated using the FSIGT, HOMA2-IR is based on fasting measures of insulin and glucose and is more representative of hepatic insulin resistance (Muniyappa & Madan 2018). Hence, we showed a linear relationship between abdominal inflammation and estimated hepatic IR. However, in order to show an improvement in hepatic IR following exercise training, a more profound and sustained alteration of aSAT inflammatory profile, which may only be achieved by a pronounced reduction in abdominal fat mass, may be required (Lakhdar et al. 2013). Furthermore, the concomitant absence of association between aSAT inflammatory profile and SI is supported by a previous study in which inflammation in this depot weakly correlated with SI (Marinou et al. 2014).

This is the first study which robustly measured the effect of exercise training on systemic and depot-specific SAT inflammation and oxidative stress in obese women of African ancestry, which makes the study unique and therefore our findings are relevant and novel. However, the limited number of evaluated genes and the lack of evaluation of protein levels represent the major limitations of this research work. Further studies exploring differences between SAT inflammatory markers at the translational level in response to exercise training are therefore needed. Notably, this study was restricted to young black South African women and therefore the findings cannot be directly translated to other groups of obese individuals with different phenotypes and/or age, sex, socioeconomic and health status.

**Conclusion**

A 12-week aerobic and resistance exercise training programme improved systemic oxidative stress markers and increased inflammatory mRNA profile in gSAT, without changes in aSAT. These changes were associated with the reduction of gynoid fat but were not correlated with the improvement in whole-body insulin sensitivity in obese black South African women. Further investigations are required to evaluate changes in protein levels and other regulatory pathways in AT that could determine the beneficial effects of exercise training on SI such as lipid and/or fatty acid metabolism.

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Additional information

Competing interests

The authors have no declared conflict of interest.

Author contributions

The experiments related to this research work were performed at the laboratory of the Division of Exercise Science and Sports Medicine of the University of Cape Town (South Africa). J.G., T.O., A.M. and D.K. conceived and design the study; P.N.N., J.G., A.M., M.F., D.K. and M.B. were involved in the acquisition, analysis and interpretation of data; P.N.N. drafted the manuscript; J.G., T.O., A.M., D.K., M.B., M.F. and P.N.N. read and critically revised the manuscript. All authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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Keywords

adipose tissue, exercise training, inflammation, insulin resistance, obesity, oxidative stress

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Statistical Summary Document.