Moderate-Intensity Aerobic Training Program Improves Insulin Sensitivity and Inflammatory Markers in a Pilot Study of Morbidly Obese Minority Teens

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We initiated a pilot study to investigate the effects of 8 wks of aerobic exercise training (ET) on insulin sensitivity and inflammatory markers in obese and insulin-resistant minority adolescents. Eleven morbidly obese (BMI 41.4 ± 1.8 kg/m²) minority adolescents were entered into a supervised ET intervention (~180 min/wk at 40–55% VO₂PeakR [(VO₂Peak−VO₂Rest)/VO₂Rest]). The effects of training on insulin sensitivity (S_I), inflammation and other metabolic syndrome features were examined. Results: Insulin action improved in response to training, as indicated
Moderate-Intensity Aerobic Training Program

by a ~37% increase in $S_I$ ($p = .018$). Plasma levels of several proinflammatory cytokines were reduced in response to ET, as indicated by significant decrements in sTNF-R, CCL2, MPO, IL-6, resistin, and leptin, with no significant changes in hsCRP. ET induced reductions in BMI and percent total body fat. Conclusions: The present study supports the efficacy of ET interventions on metabolic syndrome features in morbidly obese minority youth.

Nosotros iniciamos un estudio piloto para investigar los efectos de 8 semanas de entrenamiento con ejercicios aeróbicos (EA) sobre la sensibilidad insulinica y los marcadores inflamatorios en un grupo minoritario de adolescentes abesos con resistencia a la insulina. Once adolescentes con obesidad mórbida (IMC 41, 4+1.8kg/m²) fueron asignados a un grupo de intervención que realizo un EA supervisado (~180 min/semana al 40-55%VO₂ picoR [(VO₂Pico–VO₂Reposo)/VO₂Reposo]). Se analizo el efecto del entrenamiento sobre la sensibilidad insulinica (IS), inflamación y otras características del síndrome metabólico.

RESULTADOS: El incremento del 37% en la SI ($p=0.018$) indica que la acción de la insulina mejora en respuesta al entrenamiento. Como indican la disminución significativa de sTNF-R, CCL2, MPO, IL-6, resistina, and leptina, y la falta de cambios significativos en hsCR, los niveles plasmáticos de varias citoquinas proinflamatorias se redujeron en respuesta al EA. Además, el entrenamiento produjo una reducción del IMC y del porcentaje de grasa corporal. CONCLUSIONES: Los resultados del presente estudio apoyan la eficacia de una intervención con EA sobre las características del síndrome metabólico en un grupo minoritario de adolescentes con obesidad mórbida.

Pediatric obesity is associated with clusters of metabolic syndrome phenotypes, including: insulin resistance, hypertension, dyslipidemia, chronic low-grade systemic inflammation, endothelial dysfunction, and impaired fibrinolysis (3,15,17,30,39,41). Pediatric obesity and associated metabolic syndrome phenotypes contribute to early-onset atherosclerosis and result in an increased lifetime risk of cardiovascular disease (CVD) and type 2 diabetes (T2D) (30). The epidemiological and economic impacts of pediatric obesity are projected to increase in magnitude as obese youth become obese adults, with an increasing proportion of adults requiring early life-long treatment for obesity-associated comorbidities (10,26).

Inflammatory processes are associated with the presentation of metabolic syndrome features in both animal models of obesity (44) and in adolescent populations, where C-reactive protein levels are positively associated with BMI and other metabolic syndrome features (15). In obesity, adipocyte inflammogenicity results in chronic low-grade systemic inflammation due to the elevated expression of proinflammatory cytokines and proteins. Elevated adipocyte expression of chemokine (C-C motif) ligand 2 (CCL2/MCP-1) is commonly observed in obese states and contributes to proinflammatory macrophage recruitment to sites of adipocyte necrosis (12). Macrophage recruitment perpetuates adipocyte inflammogenicity, as well as local and systemic insulin resistance via increasing the secretion of proinflammatory cytokines such as tumor necrosis factor $\alpha$ (TNF-$\alpha$), interleukin 6 (IL-6), and resistin (19,36). The elevated secretion of proinflammatory cytokines from adipocytes further contributes to local and systemic inflammation and insulin resistance. Overall, the endocrine, paracrine and autocrine actions of adipokines, observed in obese states, are suggested to disrupt multiorgan cell signaling mechanisms and lead to a metabolically unfavorable systemic phenotype (35). Moderate levels of aerobic training have been demonstrated to attenuate adipocyte inflammogenicity.
and peripheral markers of inflammation in rodent models of obesity (27,43). While numerous studies have observed that regular aerobic exercise training attenuates multiple metabolic syndrome components, such as insulin resistance, hypertension, and dyslipidemia in pediatric populations (3,7,13,31,37,42), the effects of aerobic training on multiple systemic markers of inflammation are less thoroughly investigated. In addition, the effects of structured aerobic training programs on inflammatory cytokines and other metabolic syndrome components are less well investigated in morbidly obese minority adolescents. Morbidly obese adolescents (BMI >40 kg/m²) represent an extremely high-risk population in which examination of the efficacy of various lifestyle treatment regimens on CVD and T2D risk factors warrants investigation. We therefore initiated a pilot study to determine the effects of a structured aerobic exercise training (ET) program on insulin sensitivity and inflammatory markers in morbidly obese and insulin-resistant urban adolescent minorities. We were unable to include a control group due to ethical concerns voiced by the IRB, and included a 2-wk dietary stabilization period before initiation of the intervention. We hypothesized that ET would increase insulin action and decrease plasma markers of inflammation in this high-risk population.

**Methods**

**Study Design**

Our pediatric minority study was designed and powered after the STRRIDE study, which examined the effects of three exercise training protocols differing in intensity and volume on middle-aged (40–65 yrs), sedentary, overweight to moderately obese (BMI 25–35 kg/m²), dyslipidemic, but otherwise healthy adults. Sample size calculations (statistical power) were based upon intervention-induced changes in insulin action observed in adults in STRRIDE (21). A sample size of \( n = 11 \) was calculated to provide sufficient power (\( \beta = 0.80, \alpha = 0.05 \)) to determine changes in insulin sensitivity using the low-volume/moderate-intensity training program. Additional participants were enrolled to account for dropouts and to potentially provide gender/ethnicity stratification groups. While this sample size is small, the possible risks of IVGTT testing in such overweight youth required recruitment only to the point of sufficient powering.

**Participants**

Participants at high-risk for insulin resistance were recruited through our outpatient adolescent clinic and through local advertisements. Written consent and assent were obtained from all participants and their legal guardian. The protocol was reviewed and approved by the IRBs of Children’s National Medical Center, National Institutes of Health (intramural), and Georgetown University Medical Center. Adolescents (age 14–18 yrs) reported as sedentary (regular exercise <2 times/wk and <20 min/session), BMI-for-age \( 3^\text{rd} \)5th percentile, and free of conditions known to affect glucose metabolism or preclude regular exercise, underwent oral glucose tolerance testing (OGTT) and medical screening for further eligibility determination. The inclusion criteria for insulin resistance were defined as: 1) fasting insulin >17 \( \mu \text{U/mL} \); 2) 100 mg/dL < fasting plasma glucose< 126 mg/dL; and/or 3) 140 mg/dL.
< 2-hr OGTT plasma glucose< 200 mg/dL. Participants presenting with insulin resistance and meeting other aforementioned criteria were enrolled in the study. All participants were encouraged to maintain current dietary intake to examine the effects of ET independent of diet-induced weight loss.

Anthropometrics and Body Composition

Weight was measured on a digital scale and recorded to the nearest 0.1 kg. Height was measured on a calibrated stadiometer and recorded to the nearest 0.1 cm. Body composition assessment was performed by dual X-ray absorptiometry (DXA) Hologic QDR 4500A (Hologic; Bedford, MA).

Cardiorespiratory Fitness Assessment

Exercise testing was performed using a modified Balke treadmill protocol intended for use in obese pediatric populations (38). Peak oxygen consumption (VO₂peak) was measured via expired gases (Medical Graphics; St. Paul, MN). The criteria for reaching VO₂peak were designed based upon methods by Rowlands designed for exercise testing in pediatric populations and included volitional exhaustion and at least one of the following criteria: 1) plateau or decrease in VO₂ upon increased workload; 2) RER >1.00; and/or 3) a heart rate of >195 bpm (38).

Intravenous Glucose Tolerance Testing

After a 12-hr overnight fast, fasting blood samples were obtained and a 3-hr Frequent-Sampled Intravenous Glucose Tolerance Test (FSIVGTT) was performed beginning between 0700 and 0800 hr, to control for diurnal variation in plasma analytes. Participants were instructed to refrain from taking NSAIDs 48 hr before testing. SI was calculated from FSIVGTT testing as the incremental glucose disappearance under the insulin curve according to the minimal model methods of Bergman (9) and analyzed by use of MINMOD Millennium pharmacokinetic modeling software (version 6.02, MINMOD; Pasadena, CA) according to methods we have described previously (21). The post-training test took place 24–48 hr after the last exercise session during the follicular phase of menstruation for female participants. The FSIVGTT was performed at the Georgetown University Medical Center, while all other visits were performed at Children’s National Medical Center.

Biochemical Assays

Insulin was analyzed by enzyme-linked immunoabsorbant assay (Mercodia; Uppsala, Sweden). Glucose was analyzed using a YSI 2300 STAT Plus glucose analyzer (YSI; Yellow Springs, OH). CRP was analyzed by immunonephelometry using a CardioPhase hsCRP reactivity kit (Dade Behring; Newark, DE). Plasma cytokines were measured by multiplex cytometric bead assay (Bender MedSystems; Vienna, Austria). Total PAI-1, t-PA and fibrinogen were measured by use of enzymatic immunoassay (Trinity Biotech; Jamestown, NY). All assays were performed according to the manufacturers’ instructions. The molar ratio of PAI-1:t-PA was calculated as described previously (4).
Aerobic Exercise Training

Due to lack of a control arm, participants entered into the study first had a 2-wk dietary stabilization period in which participants monitored their diet through use of 3-day 24-hr recalls, before the start of the exercise intervention. After the dietary stabilization period, participants were instructed not to make any changes to their diet and this was assessed by use of 3-day 24-hr recalls throughout the study. Participants then completed 8 wks of supervised ET after a one-month training acclimation period. Heart rate corresponding to percent peak oxygen reserve \([\% \text{VO}_2\text{Peak}R = (\text{VO}_2\text{Peak} - \text{VO}_2\text{Rest})/\text{VO}_2\text{Rest}]\) observed during baseline treadmill testing was used for exercise prescription. All exercise sessions were supervised by trained personnel at Children’s National Medical Center and exercise intensity was monitored by heart rate observed (Polar Electro Heart Rate Monitors; Woodbury, NY). During the 4-wk training acclimation period, exercise intensity and duration was increased each week by 5% \(\text{VO}_2\text{Peak}R\) and 5 min, respectively. Participants subsequently exercised at 40–55% \(\text{VO}_2\text{Peak}R\) for ~180 min/week (2–4 days/wk), to expend ~1200 kcal/wk for eight consecutive weeks. Training sessions were preceded by a 5-min warm-up and ended with a 5-min cool-down and stretching exercises. Body weight was assessed once weekly in conjunction with a questionnaire designed to assess medical, dietary and lifestyle changes warranting study exclusion. Exercise modes included cycle ergometer, elliptical trainer, stair stepper and treadmill. Initial sessions were done using the cycle ergometer, with later sessions primarily transitioning to the treadmill and elliptical trainer.

Statistics

Comparisons between baseline and final measures were made using the Wilcoxon signed-rank test, based on the conservative assumption of non-normally distributed variables (due to the small sample size). Statistical significance was defined as \(p < .05\). Data are presented as mean ± SEM.

Results

Participants

Of 152 screened adolescents, 32 participants met the inclusion criteria for insulin resistance (OGTT) and other inclusion criteria. Twenty-five participants completed all baseline testing visits and 11 participants completed the entire study; transportation difficulties to and from the facility were the major reason for drop-out. Comparison of drop-outs with those completing the study indicated no significant differences in baseline body mass, fasting plasma glucose and insulin, \(\text{VO}_2\text{Peak}R\) or percent total and truncal body fat. Of the 11 participants eligible for analysis, 2 were male (1 Black/1 Latino) and 9 were female (7 Black/2 Latina). Participants were postpubertal (Tanner growth stage >IV); the average age at enrollment was 15 ± 0.31yrs. The exercise session adherence rate for participants completing the intervention was ~87%, with no subject missing more than three exercise sessions. On average, participants completed 724 MET-min/wk of exercise by training for
~180 min/wk at an intensity of ~55% VO$_2$Peak R, which is equivalent to ~70% VO$_2$Peak (Table 5).

**Anthropometrics**

No changes in mean daily caloric intake were observed during the dietary stabilization period or throughout the study. Changes in anthropometric variables in response to 8 wks of training are presented in Table 1. Favorable changes in body mass and composition were observed in response to training, including a ~2 kg reduction in body mass, a ~0.8 kg/m$^2$ reduction in BMI, a ~3.5% reduction in percent total body fat, and a ~2.0% increase in lean body mass ($p < .05$). A trend toward a decrease in percent truncal body fat was observed (~3.7%; $p = .059$).

**Cardiorespiratory Fitness**

Peak oxygen consumption (VO$_2$Peak) did not change in response to training (22.7 ± 1.48 vs. 23.3 ± 1.84 mL/kg/min, $p = .415$). Peak heart rate was reduced after training (187 ± 4 vs. 178 ± 4 bpm, $p = .038$) at the highest workload achieved (6.48 ± 0.42 vs. 6.67 ± 0.52 METs, $p = .414$; Table 4).

**Insulin Action**

Upon enrollment, the majority of participants met the inclusion criterion for elevated fasting insulin (fasting plasma insulin >17 μU/mL) and presented with normal fasting glucose (fasting plasma glucose <100 mg/dL). Of the 11 participants successfully completing the exercise intervention, 7 participants’ FSIVGTT data were used for analysis due to the inability to maintain continuous catheter access during FSIVGTT administration for 4 participants, resulting in missed time points critical to $S_I$ modeling and pre vs. post comparisons. A ~37% improvement in $S_I$ was observed in response to training ($p < .05$; Table 2). Changes in $S_I$ did not correlate with any training-induced changes in body mass or composition. Fasting plasma insulin and glucose, insulin secretion (AIRG), and glucose effectiveness (SG) did not change significantly in response to training.

### Table 1  Changes in Body Mass and Composition in Response to Training

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>N</th>
<th>Baseline</th>
<th>Final</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean ± SEM</td>
<td>Mean ± SEM</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>11</td>
<td>41.4 ± 1.8</td>
<td>40.6 ± 1.8</td>
<td>0.005*</td>
</tr>
<tr>
<td>Body mass (kg)</td>
<td>11</td>
<td>116.2 ± 7.6</td>
<td>114.2 ± 7.5</td>
<td>0.004*</td>
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<tr>
<td>Lean body mass (kg)</td>
<td>10</td>
<td>61.7 ± 4.1</td>
<td>62.9 ± 4.2</td>
<td>0.028*</td>
</tr>
<tr>
<td>Total Body Fat (%)</td>
<td>10</td>
<td>43.4 ± 2.0</td>
<td>41.9 ± 1.9</td>
<td>0.009*</td>
</tr>
<tr>
<td>Truncal Body Fat (%)</td>
<td>10</td>
<td>43.3 ± 2.0</td>
<td>41.7 ± 2.2</td>
<td>0.059†</td>
</tr>
</tbody>
</table>

*p < 0.05, †p < 0.10 between baseline and final paired comparisons.
**Table 2  Changes in Indices of Metabolic Syndrome in Response to Training**

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Baseline Mean ± SEM</th>
<th>Final Mean ± SEM</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insulin Action</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$S_1$ (mU·L$^{-1}$·min$^{-1}$)</td>
<td>7</td>
<td>1.00 ± 0.15</td>
<td>1.37± 0.26</td>
<td>0.018*</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>11</td>
<td>85.6 ± 4.46</td>
<td>82.1 ± 3.98</td>
<td>0.213</td>
</tr>
<tr>
<td>Fasting insulin (μU/mL)</td>
<td>11</td>
<td>20.6 ± 2.86</td>
<td>20.2 ± 2.80</td>
<td>0.929</td>
</tr>
<tr>
<td>AIRG (mU/mM)</td>
<td>7</td>
<td>2.18 ± 0.63</td>
<td>1.54 ± 0.29</td>
<td>0.176</td>
</tr>
<tr>
<td>$S_G$ (10$^2$/min)</td>
<td>7</td>
<td>2.50 ± 0.43</td>
<td>2.92 ± 0.57</td>
<td>0.499</td>
</tr>
<tr>
<td><strong>Blood Pressure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>11</td>
<td>129 ± 4</td>
<td>122 ± 5</td>
<td>0.109</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>11</td>
<td>71 ± 3</td>
<td>64 ± 2</td>
<td>0.018*</td>
</tr>
<tr>
<td><strong>Plasma Lipids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>11</td>
<td>151 ± 10.7</td>
<td>152 ± 12.1</td>
<td>0.788</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>11</td>
<td>96 ± 9.1</td>
<td>98 ± 10.2</td>
<td>0.726</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>11</td>
<td>35 ± 2.5</td>
<td>36 ± 2.7</td>
<td>0.788</td>
</tr>
<tr>
<td>VLDL cholesterol (mg/dL)</td>
<td>11</td>
<td>20 ± 3.8</td>
<td>19 ± 3.5</td>
<td>0.858</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>11</td>
<td>99 ± 19.0</td>
<td>95 ± 17.2</td>
<td>0.657</td>
</tr>
<tr>
<td><strong>Fibrinolytic Potential and Hemostatic Activation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t-PA (ng/mL)</td>
<td>10</td>
<td>6.34 ± 0.51</td>
<td>7.32 ± 0.85</td>
<td>0.028*</td>
</tr>
<tr>
<td>PAI-1 (ng/mL)</td>
<td>10</td>
<td>25.75 ± 4.46</td>
<td>22.79 ± 3.02</td>
<td>0.575</td>
</tr>
<tr>
<td>PAI-1:t-PA molar ratio</td>
<td>10</td>
<td>5.47 ± 0.79</td>
<td>4.46 ± 0.52</td>
<td>0.241</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>10</td>
<td>10.48 ± 1.60</td>
<td>12.00 ± 1.25</td>
<td>0.422</td>
</tr>
</tbody>
</table>

*p < 0.05 between baseline and final paired comparisons.

**Inflammatory Markers**

Significant decrements in soluble tumor necrosis factor receptors (sTNF-R; $-14.0 ± 4.0\%$), CCL2 ($-15.8 ± 4.6\%$), myeloperoxidase (MPO; $-21.0 ± 6.1\%$), IL-6 ($-22.8 ± 5.6\%$), resistin ($-14.5 ± 4.5\%$), and leptin ($-13.8 ± 6.2\%$) were observed ($p < .05$; Table 3). There were no significant changes in hsCRP, soluble CD40 ligand (sCD40L), soluble intercellular adhesion molecule 1 (sICAM-1), or osteoprotegerin (OPG). There were no significant correlations between training-induced changes in inflammatory markers and changes in body mass, lean body mass, percent total and truncal body mass, or $S_1$.

**Other Obesity-Associated Phenotypes**

Blood Pressure and Plasma Lipids: A significant reduction in resting diastolic blood pressure (DBP) was observed in response to training ($p < .05$); resting systolic blood pressure (SBP) appeared to be reduced, but did not reach statistical significance ($p = .109$). No significant changes in fasting plasma lipids levels were observed in
response to training. Fibrinolytic Potential and Hemostatic Activation: In response to training, a ~15% increase in t-PA antigen was observed ($p < .05$). PAI-1 antigen, fibrinogen and the molar ratio of PAI-1 to t-PA did not decrease significantly in response to training. (Table 3)

## Discussion

The goal of our study was to determine if morbidly obese, insulin-resistant, urban pediatric minorities would improve insulin action, inflammation and other metabolic syndrome features with controlled exposure to moderate intensity ET. The level of activity in the intervention (180 min/wk) is about half of that recommended for youth ages 6–17 yrs (1). The number of participants studied was small ($n = 11$), however

### Table 3 Changes in Inflammatory Markers in Response to Training

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>n</th>
<th>Baseline Mean ± SEM</th>
<th>Final Mean ± SEM</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>hsCRP (mg/L)</td>
<td>10</td>
<td>2.53 ± 0.86</td>
<td>2.09 ± 0.54</td>
<td>0.574</td>
</tr>
<tr>
<td>sCD40L (pg/mL)</td>
<td>11</td>
<td>62.13 ± 12.01</td>
<td>72.43 ± 15.14</td>
<td>0.213</td>
</tr>
<tr>
<td>sTNF-R (ng/mL)</td>
<td>11</td>
<td>0.66 ± 0.05</td>
<td>0.55 ± 0.02</td>
<td>0.016*</td>
</tr>
<tr>
<td>OPG (pg/mL)</td>
<td>11</td>
<td>11.74 ± 3.00</td>
<td>9.14 ± 2.09</td>
<td>0.314</td>
</tr>
<tr>
<td>CCL2 (pg/mL)</td>
<td>11</td>
<td>441.69 ± 17.87</td>
<td>367.28 ± 17.64</td>
<td>0.008*</td>
</tr>
<tr>
<td>MPO (ng/mL)</td>
<td>11</td>
<td>32.90 ± 3.46</td>
<td>24.50 ± 1.72</td>
<td>0.013*</td>
</tr>
<tr>
<td>sICAM-1 (ng/mL)</td>
<td>11</td>
<td>480.82 ± 40.10</td>
<td>454.08 ± 45.83</td>
<td>0.374</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>11</td>
<td>4.67 ± 0.46</td>
<td>3.45 ± 0.23</td>
<td>0.008*</td>
</tr>
<tr>
<td>Resistin (ng/mL)</td>
<td>11</td>
<td>10.43 ± 1.55</td>
<td>8.58 ± 1.21</td>
<td>0.004*</td>
</tr>
<tr>
<td>Leptin (ng/mL)</td>
<td>11</td>
<td>45.18 ± 4.33</td>
<td>37.48 ± 3.59</td>
<td>0.026*</td>
</tr>
</tbody>
</table>

*p < 0.05 between baseline and final paired comparisons.

### Table 4 Changes in Cardiovascular Fitness Variables in Response to Training

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>n</th>
<th>Baseline Mean ± SEM</th>
<th>Final Mean ± SEM</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$VO_2^{Peak}$ (mL/kg/min)</td>
<td>10</td>
<td>22.7 ± 1.48</td>
<td>23.3 ± 1.84</td>
<td>0.415</td>
</tr>
<tr>
<td>$VO_2^{Peak}$ (mL/kg FFM/min)</td>
<td>10</td>
<td>47.4 ± 2.28</td>
<td>42.3 ± 3.20</td>
<td>0.059</td>
</tr>
<tr>
<td>RER $^{Peak}$</td>
<td>10</td>
<td>1.13 ± 0.04</td>
<td>1.01 ± 0.02</td>
<td>0.007*</td>
</tr>
<tr>
<td>HR $^{Peak}$ (bpm)</td>
<td>9</td>
<td>187 ± 4</td>
<td>178 ± 4</td>
<td>0.038*</td>
</tr>
<tr>
<td>METs $^{Peak}$ (kcal/kg/hr)</td>
<td>10</td>
<td>6.48 ± 0.42</td>
<td>6.67 ± 0.52</td>
<td>0.414</td>
</tr>
</tbody>
</table>

*Note. p < 0.05 between baseline and final paired comparisons.*
our study was sufficiently powered based upon findings from the previous STRRIDE study. Further, the possible risks of FSIVGTT testing in such highly overweight individuals required enrollment only to the point of sufficient powering. The main findings were that insulin action and several of markers of systemic inflammation improved significantly with training. Findings of improvements in insulin action in response to training are consistent with pediatric studies conducted previously demonstrating improvements in both direct and surrogate measurements of insulin sensitivity (3,7,13,24,32,42). There has been little investigation of the effects of controlled doses of ET in urban pediatric minorities utilizing direct measures of insulin sensitivity and assessing changes in multiple inflammatory cytokines. Thus, a novel aspect of our study was determination of the efficacy of controlled doses of low-volume, moderate-intensity aerobic training (the equivalent of ~3 hr of brisk walking per week) on SI and multiple markers of obesity-associated inflammation in morbidly obese minority adolescents.

In comparison with pediatric studies using direct measures of insulin sensitivity, our observed ~37% improvement in insulin sensitivity is similar to that of Conwell et al. who reported a ~32% increase in SI by FSIVGTT in obese youth (BMI 34.5 ± 1.3kg/m², age 8–18 yrs) after a 10-wk home-based physical activity program which consisted of health education encouraging more steps per day (13); however, a direct comparison between study intensities cannot be made. van der Heijden et al. observed a greater (~59 ± 19%) improvement in peripheral insulin sensitivity in obese postpubertal Latino adolescents (BMI 33.2 ± 0.9kg/m², age 15.6 ± 0.4 yrs; 42). The greater improvement is likely due to the intervention used [12-wks of high-intensity (~85% VO₂peak) aerobic training, plus a 7-day low carbohydrate diet before testing], as well as the different methodology for determining insulin action (stable isotope-labeled IVGTT). Fasting insulin and glucose levels did not significantly change in response to training. Gutin et al. also did not observe changes in fasting insulin in 12 obese Black girls (age 7–11 yrs) after 5 weeks of mixed-modality aerobic training, despite a ~1.4% reduction in total body fat as determined by DXA (18). In contrast to these findings, Ferguson et al. observed significant reductions in fasting insulin levels, without changes in fasting glucose levels, in Black, White and Asian children (age 7–11 yrs) after 4 months of game-based aerobic training (16). Our participants presented with hyperinsulinemia at baseline (average fasting insulin: 20.6 ± 2.86 mU/mL) and very low insulin sensitivity indices (average S₁: 1.00 ± 0.15 mU·L⁻¹·min⁻¹). Reduced fasting insulin in response to training is indicative of enhanced insulin sensitivity as less insulin is required to maintain euglycemia. Despite improvements in insulin sensitivity, our participants did not normalize S₁ in response to training which may have contributed to the preservation of hyperinsulinemic states and lack of training response.

### Table 5 Subject Training Program

<table>
<thead>
<tr>
<th>Duration (min/wk)</th>
<th>Training Intensity (%VO₂peak)</th>
<th>Training Intensity (%VO₂peak)</th>
<th>METs</th>
<th>MET-hr/wk</th>
<th>MET-min/wk</th>
<th>Example Treadmill Program</th>
<th>Example Elliptical Program</th>
</tr>
</thead>
<tbody>
<tr>
<td>180</td>
<td>55%</td>
<td>70%</td>
<td>4.3</td>
<td>12</td>
<td>724</td>
<td>3.5 mph; 4% incline</td>
<td>55–65 rpm; level 1–5</td>
</tr>
</tbody>
</table>

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Moderate-Intensity Aerobic Training Program

In agreement with our hypothesis of the anti-inflammatory effects of exercise, we observed significant reductions in the adipokines sTNF-R, CCL2, MPO, IL-6, resistin and leptin in our minority teen group. Findings of improvements of peripheral markers of inflammation are consistent with improvements in other components of obesity-associated metabolic dysregulation ($S_t$, diastolic blood pressure) as elevated proinflammatory adipokine secretion is suggested to contribute to the pathogenesis of insulin resistance and atherosclerosis. However, we did not observe significant correlations between changes in these variables, likely due to our small sample size. Findings from the current study are of interest as participants were morbidly obese and it has been suggested that diet-induced moderate weight loss does not reverse the inflammatory state in severely/morbidly obese adults over a 3-month period (40). The ability to reverse plasma markers of inflammation in morbidly obese teens through an exercise intervention, suggests that younger participants may be more flexible, and more easily reverse the proinflammatory state.

TNF-α is a proinflammatory cytokine that is secreted from adipose tissue in obese states. Neutralization of adipocyte-derived TNF-α has been shown to attenuate obesity-associated insulin resistance (20). Plasma levels of TNF-α and sTNF-R are elevated in patients with ongoing inflammation (20) and in overweight youth (29). IL-6 is another cytokine that is elevated in obesity and thought to impair insulin signaling (25). Although we observed concurrent reductions in plasma IL-6 and sTNF-R levels and improvements in insulin action, changes in these variables did not show statistically significant correlations. High sensitivity (hs) CRP is another commonly used marker for the proinflammatory state in metabolic syndrome. Despite the observed reductions in multiple proinflammatory cytokines, we did not observe reductions in hsCRP levels in response to training. In contrast to our findings, Rosenbaum et al. (37) and Balagopal et al. (3) did observe significant decrements in CRP levels in pediatric populations in response to school and home-based moderate intensity exercise programs. Differences between findings from these studies and others (24,32,42) may be due to the addition of dietary modifications as Camhi et al. observed significant decrements in hsCRP in response to diet and diet plus physical activity interventions, but not in interventions only utilizing physical activity (11). Our findings thus support the suggestion of others, where examination of the effects of exercise training on multiple plasma cytokines may be a better method of assessing changes in obesity-associated systemic inflammation than isolated measures of hsCRP (14).

Plasma leptin levels correlate to adiposity indices and are documented to decrease with weight loss (28). We observed significant reductions in plasma leptin levels; however, findings from the current study cannot rule out the effects of weight loss on changes in leptin levels. Resting diastolic blood pressure was also decreased in response to training in our pediatric population. Chronic hyperleptinemia is thought to play a causative role in obesity-associated hypertension by impairing renal sodium excretion and promoting vasoconstriction (8), which supports our findings of concurrent reductions in diastolic blood pressure and plasma leptin. Resistin is released from adipocytes and macrophages within the adipose tissue and is thought to impair insulin signaling (6). We observed decrements in peripheral resistin levels in response to ET in the current study. The effects of aerobic training on plasma resistin and leptin levels have been inconsistent in overweight pediatric populations. Jones et al. observed reductions in resistin levels without significant changes in leptin levels in overweight youth (BMI $31.8 \pm 5.2$ kg/m$^2$,
age 12–18 yrs) in response to a 32-wk monitored aerobic training program (22). Participants enrolled in the Jones et al. study showed no appreciable weight loss and lost ~7.4% of percent total body fat. In contrast to these findings, Ounis et al. observed significant increases in plasma resistin and reductions in leptin levels with an 8-wk caloric restriction and aerobic training program in obese adolescent females (33). This same study observed correlations between the leptin:adiponectin ratio and improvements in body composition and insulin sensitivity by HOMA (41).

In contrast to our findings, Kelly et al. did not observe changes in IL-6, TNF-α, leptin, or resistin in overweight youth (BMI 32.7 ± 2.6 kg/m², age 10.8 ± 0.67 yrs) in response to 8 wks of aerobic training, despite similar training duration (~200 min/wk) intensity (~70–80% VO₂peak) during the later portion of intervention (23). Changes in BMI or percent body fat were not observed among participants enrolled in the Kelly et al. study, which may explain the different findings between studies. In addition, differences between our findings and others may be due to a higher BMI of participants enrolled in this study relative to the aforementioned overweight/obese pediatric populations. A strength of the current study is that, to our knowledge, this is the first study conducted in a morbidly obese adolescent minority cohort. The effects of exercise training on CCL2 and MPO have not been extensively investigated in pediatric populations; we observed significant reductions in both inflammatory markers. Findings of reductions in CCL2 are, thus, consistent with observations of enhanced insulin action and decreased levels of adipogenic cytokines.

Findings from our study add to the literature supporting the anti-inflammatory effects of exercise and support the efficacy of aerobic training interventions in high-risk urban pediatric minorities. Discrepancies between our study and other pediatric interventions may be attributable to different entry criteria and baseline phenotypes, differences in training intensities, volumes and supervision, and different degrees of fat loss. This study is limited by lack of a sedentary control group; recruitment of insulin-resistant controls was deemed unethical by the governing IRBs. Findings of nonsignificant changes in peak oxygen consumption are an additional limitation of this study. Upon retesting, participants displayed significant reductions in RER and HR at the highest workload achieved. Further, a lower RER at the same relative workload suggests an improvement in cardiorespiratory fitness. This suggests that, on average, peak exertion was lower upon retesting. Others have suggested alternative approaches to exercise testing in obese pediatric populations as this population may display diminished motivation and increased perceptions of peripheral fatigue (34). An important area of future research may be to investigate methods to increase motivation and promote adherence in obese pediatric groups. While we had a relatively high dropout rate (>50%), we found no differences in baseline variables between those completing the study and drop-outs. The current study cannot fully rule out the effects of maturation on the observed variables as a sedentary control group was not included. It is notable that in a similar subject population (15.9 ± 0.5 yrs; Tanner stage IV; BMI 37.6 ± 3.3 kg/m²), Balagopal et al. observed no significant changes in insulin sensitivity, IL-6, hsCRP, fibrinogen, or soluble leptin receptor in sedentary controls over a three-month period (2,5), while a gain of ~1.4 kg body mass and 0.7% body fat was observed (2).
Summary

Our study was designed to examine the effects of structured ET on insulin sensitivity, systemic inflammation and other features of metabolic syndrome in severely obese, insulin resistant and previously sedentary urban minority adolescents. The current study suggests that moderate-intensity ET performed for ~180 min/wk can improve insulin action and attenuate markers of obesity-associated inflammation in morbidly obese minority teens. Findings from the current study do not differentiate between the effects of endurance training and weight loss on the metabolic syndrome features examined. Findings from the current study do support the efficacy of moderate-intensity ET in morbidly obese and insulin resistant minority adolescents. Our findings warrant future investigation of the efficacy of different training intensities, durations and volumes, as well as nutrition programs, on parameters of metabolic dysregulation in this extremely high risk minority group.

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References


