Anti-Inflammatory Effect of Exercise, via Reduced Leptin Levels, in Obese Women With Down Syndrome

Francisco J. Ordonez, Gabriel Fornieles-Gonzalez, Alejandra Camacho, Miguel A. Rosety, Ignacio Rosety, Antonio J. Diaz, and Manuel Rosety-Rodriguez

Recent studies have reported that obese young people with Down syndrome suffer from low-grade systemic inflammation. Whereas this condition may be improved in the general population by regular exercise, the problem has received no attention in the case of people with intellectual disability. Therefore, the authors’ aim was to assess the influence of aerobic training on plasma adipokines in obese women with Down syndrome. Twenty obese young women with Down syndrome volunteered for this study, 11 of whom were randomly assigned to a 10-wk aerobic-training program. They attended 3 sessions/wk, which consisted of warm-up exercises followed by the main activity on a treadmill (30–40 min) at a work intensity of 55–65% of peak heart rate and ended with a cooling-down period. The control group included 9 women with Down syndrome matched for age, sex, and body-mass index. Fat-mass percentage and distribution were measured, and plasma adipokine levels (leptin and adiponectin) were assessed. In addition, each participant performed a maximal graded continuous treadmill exercise test. These parameters were assessed pre- and postintervention. Aerobic training produced a significant increase in participants’ maximal oxygen uptake (20.2 ± 5.8 vs.23.7 ± 6.3 ml · kg⁻¹ · min⁻¹; p < .001), and plasma leptin levels were significantly reduced in the intervention group (54.2 ± 6.7 vs.45.7 ± 6.1 ng/ml; p = .026). Further significant correlations between plasma leptin and indices of obesity were found. In contrast, no significant changes were found in adiponectin levels (p > .05). None of the tested parameters changed in the control group. In conclusion, a 10-week training program reduced leptin levels in obese young women with Down syndrome.

Keywords: intellectual disability, aerobic training, obesity, adiponectin

Obesity is a major public health problem among people with intellectual disabilities (ID). It can reduce their quality of life and increases health care costs (de Winter, Bastiaanse, Hilgenkamp, Evenhuis, & Echteld, 2012). Among subjects with ID, people with Down syndrome are significantly more at risk for being obese (de Winter et al., 2012).

There is increasing evidence from both clinical and experimental studies indicating the association of visceral obesity with a proinflammatory status (Inadera, 2008). Recent studies have reported that obese people with Down syndrome suffer from low-grade systemic inflammation, which has been proposed as a pathogenic mechanism of several disorders (Corsi et al., 2009; de Winter, Magilsen, van Alfen, Willemsen, & Evenhuis, 2011). Previous studies showing increased levels of soluble intercellular adhesion molecule-3 and soluble vascular cell adhesion molecule-1 in plasma also reported the presence of a moderate dysfunction of endothelial cells in subjects with Down syndrome (Licastro et al., 2006).

Adipokines and acute-phase proteins are important mediators of these adverse effects; therefore, normalization of their levels has been proposed as a therapeutic target (Athyros, Tziomalos, Karagiannis, Anagnostis, & Mikhailidis, 2010). For example, the beneficial effects of high-dose statin therapy on inflammatory markers are well known (Singh, Devaraj, Jialal, & Siegel, 2008). Similarly, several studies have reported that resistance-training programs at low to moderate intensity may reduce proinflammatory adipokines (leptin) and acute-phase proteins in overweight and obese women without ID (Arikawa, Thomas, Schmitz, & Kurzer, 2011; Polak et al., 2006). However, to the best of our knowledge, no research has been published concerning people with ID.

These are strong arguments in favor of strengthening the role of preventive strategies such as exercise to reduce future health care costs arising from the increasing life expectancy of people with disabilities (Tenenbaum, Chavkin, Chavkin, Wexler, Korem, & Merrick, 2012). However, it is widely accepted that physical activity entails an inherent risk of injury, especially for those with ID, as the risk may be compounded by preexisting disability (Ramirez et al., 2009). This is particular important, since
injuries and discomfort may lead participants to interrupt their training programs, increasing dropout rates and sedentary lifestyles (Mahy, Shields, Taylor, & Dodd, 2010). To avoid these problems, suitable preparticipation physical examination and the design of specific training programs that are adapted to the needs of individuals with ID would appear to be essential (Mahy et al. 2010; Ramirez et al. 2009).

Consequently, this study was designed to determine the effect of a 10-week aerobic training program on plasma levels of adiponectin and leptin in obese women with Down syndrome.

**Material and Methods**

Twenty sedentary, premenopausal, obese women with Down syndrome (18–30 years) volunteered for this study (Table 1). Participants were living at home and had good health status. A preparticipation physical examination was conducted to rule out the presence of any underlying diseases that could affect physical performance. Participants’ intelligence quotient (IQ), determined by the Stanford-Binet Scale, ranged between 50 and 69, and they were diagnosed as having mild ID. Eleven of them were randomly assigned to the intervention group to participate in a 10-week aerobic-training program of three sessions/week, using a motorized treadmill. Each ergometer conditioning session consisted of 10–15 min of warm-up exercises followed by the main activity (30–40 min, increasing by 2.5 min every 2 weeks), during which participants exercised at 55–65% of peak heart rate (increasing the rate by 2.5% every 2 weeks), and a 5- to 10-min cooling-down period.

To ensure that the training workload was appropriate, all participants wore a wireless heart-rate monitor (Sport Tester PE3000, Polar Electro, Kempele, Finland). Before starting the training program, they underwent a pretraining period during which they were taught the correct use of the treadmill.

The control group included 9 women with Down syndrome matched for age, sex, and body-mass index who did not take part in any training program. To control the potential confounding effect of diet, parents were carefully instructed to avoid quantitative or qualitative differences. Furthermore, a food-consumption frequency questionnaire, recorded by parents for 3 days (2 weekdays and 1 weekend day), was obtained both pre- and postintervention. No significant changes were reported between the intervention and control groups at the beginning of the study (1,928 ± 241 vs. 1,896 ± 258 kcal/day; \( p > 0.05 \)). Descriptive but nonsignificant differences were found at the end of the study period between the two groups (2,008 ± 226 vs. 1,937 ± 262 kcal/day; \( p > 0.05 \)).

Furthermore, participants had no harmful habits (smoking or alcohol) or took any medication that could affect appetite regulation or physical performance.

This research was conducted in full accordance with ethical principles, including those established in the World Medical Association Declaration of Helsinki (version 2002). Written informed consent was obtained from all participants’ parents or legal representatives, and the protocol was approved by an institutional ethics committee.

All participants (\( N = 20 \)) performed a maximal continuous incremental test on a treadmill. In the first stage, they walked at a speed of 4.0 km/hr for 2 min. The grade was then increased by 2.5% every 2 min until a grade of 12.5% was reached. The grade was then held constant and the speed was increased by 1.6 km/hr every minute until exhaustion. This protocol has been widely used to determine \( V_{O2\text{max}} \) and \( HR_{\text{max}} \) in people with Down syndrome (Fernhall et al., 2001; Mendonca & Pereira, 2009).

Fat-mass percentage was assessed by bioelectrical-impedance analysis (Tanita TBF521). To determine waist-to-hip ratio (WHR), both waist circumference and hip circumference were measured with an anthropometric tape (Holtain Ltd). Waist circumference was measured at a level midway between the lowest rib and the iliac crest. Hip circumference was measured around the widest portion of the buttocks. Blood samples were collected from the antecubital vein. The whole blood was centrifuged at 3,000 rpm for 20 min in a clinical centrifuge. The plasma was separated and stored at −80 °C until further analysis.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Participants’ Age, Height, Weight, Body Composition, and Fitness in Experimental (( n = 11 )) and Control Groups (( n = 9 )) at Baseline</th>
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<tbody>
<tr>
<td><strong>Experimental group</strong></td>
<td><strong>Control group</strong></td>
</tr>
<tr>
<td>Age (years)</td>
<td>24.7 ± 3.6 (19.4–29.1)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>152.3 ± 5.1 (148.2–156.5)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>69.8 ± 5.7 (62.9–73.8)</td>
</tr>
<tr>
<td>Fat mass (%)</td>
<td>38.9 ± 4.0 (36.3–39.6)</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>94.7 ± 3.3 (93.7–96.2)</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>1.12 ± 0.01 (1.06–1.15)</td>
</tr>
<tr>
<td>Maximum oxygen uptake (ml · kg(^{-1}) · min(^{-1}))</td>
<td>20.2 ± 5.8 (17.1–25.7)</td>
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</tbody>
</table>
Plasma levels of adiponectin and leptin were assessed by immunoenzymatic methods using commercial ELISA kits (R&D, Minneapolis, MN, USA). All outcomes at the individual level were assessed first at baseline and second 72 hr after the end of the intervention.

The results were expressed as $M \pm SD$ with 95% confidence intervals (95% CI). Kolmogorov-Smirnov’s test was applied to verify normal distribution of results. Statistical analysis of the data was performed using Student’s $t$ test for paired data. Pearson’s correlation coefficient ($r$) was used to determine potential associations among tested parameters. The significance of the changes observed was ascertained to be $p < .05$.

### Results

Compared with baseline results, $VO_{2\max}$ was significantly increased (20.2 ± 5.8 vs. 23.7 ± 6.3 ml · kg$^{-1}$ · min$^{-1}$; $p = .0007$), suggesting an improvement in the intervention group’s physical fitness.

Plasma leptin levels were significantly decreased at the end of the training program (54.2 ± 6.7 vs. 45.7 ± 6.1 ng/ml; $p = .026$). In contrast, no significant changes were found in the intervention group’s levels of adiponectin (36.7 ± 5.4 vs. 39.1 ± 5.6 ng/ml; $p = .058$).

Regarding anthropometric measurements, both fat-mass percentage (38.9% ± 4.6% vs. 35.0% ± 4.2%; $p = .041$) and WHR (1.12 ± 0.006 vs. 1.00 ± 0.005 cm; $p = .038$) were also reduced. These results are summarized in Table 2. Furthermore, a significant positive association was found between leptin and WHR ($r = .51$; $p < .001$). A significant, but negative, correlation was found between adiponectin and waist circumference ($r = -.39$; $p = .038$). These correlations and their directions are shown in Table 3. Finally, neither sports-related injuries nor withdrawals from the program were reported during the entire study period in the intervention group.

With respect to the control group, no significant changes were found in plasma levels of leptin (55.8 ± 6.9 vs. 55.4 ± 7.0 ng/ml; $p = .071$) or adiponectin (35.0 ± 5.7 vs. 35.3 ± 5.5 ng/ml; $p = .086$).

### Discussion

The main finding of this study was that aerobic training significantly reduced plasma leptin levels in obese young women with Down syndrome. Similar results regarding the anti-inflammatory effect of a 3-month aerobic-training program have been reported in obese young women without ID (Gueugnon et al., 2012; Polak et al., 2006). Furthermore, a 14-week combination of aerobic training and modest caloric restriction reduced plasma levels of leptin in obese adult women (Kerksick et al., 2010).

It should be emphasized that the protocol reported here was only 10 weeks long, a duration that may be considered more feasible and practical for participants and leaders. Furthermore, the current design comprised three sessions/week, whereas previous training programs have consisted of five sessions/week (Polak et al., 2006).

In this regard, reducing the number of sessions per week but increasing the total number of weeks has also been reported to facilitate good compliance with training programs. For example, Elmahgoub et al. (2011) concluded that exercising twice a week for 15 weeks...

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**Table 2**  Influence of a 10-Week Training Program on Plasma Levels of Adipokines (Adiponectin and Leptin) and Anthropometric Measurements in Obese Young Women With Down Syndrome ($n = 11$)

<table>
<thead>
<tr>
<th></th>
<th>Preintervention</th>
<th>Postintervention</th>
<th>$p$</th>
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</thead>
<tbody>
<tr>
<td>Adiponectin (ng/ml)</td>
<td>36.7 ± 5.4 (31.3–40.8)</td>
<td>39.1 ± 5.6 (35.2–44.6)</td>
<td>.058</td>
</tr>
<tr>
<td>Leptin (ng/ml)</td>
<td>54.2 ± 6.7 (49.8–61.3)</td>
<td>45.7 ± 6.1 (40.7–48.8)</td>
<td>.026</td>
</tr>
<tr>
<td>Fat mass (%)</td>
<td>38.9 ± 4.0 (36.3–39.6)</td>
<td>35.0 ± 3.8 (33.6–35.9)</td>
<td>.041</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>94.7 ± 3.3 (93.7–96.2)</td>
<td>91.5 ± 3.1 (90.6–93.2)</td>
<td>.030</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>1.12 ± 0.01 (1.06–1.15)</td>
<td>1.00 ± 0.01 (0.97–1.03)</td>
<td>.038</td>
</tr>
</tbody>
</table>

**Table 3**  Correlations Between Plasma Levels of Adipokines (Adiponectin and Leptin) and Anthropometric Measurements in Obese Young Women With Down Syndrome ($n = 11$)

<table>
<thead>
<tr>
<th></th>
<th>Fat mass</th>
<th>WHR</th>
<th>WC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adiponectin</td>
<td>- .34*</td>
<td>- .37*</td>
<td>- .39*</td>
</tr>
<tr>
<td>Leptin</td>
<td>.46*</td>
<td>.51*</td>
<td>.50*</td>
</tr>
</tbody>
</table>

Note. WHR = waist-to-hip ratio; WC = waist circumference.

* $p < .05$.
(30 sessions) had the same beneficial health effects as exercising three times a week for 10 weeks (30 sessions) in overweight and obese adolescents with ID in short-term training programs. Furthermore, to facilitate the sustainability of these health programs, it is essential to target not only the participants but also their parents, caregivers, and educators (Elinder, Bergström, Hågborg, Wihlman, & Hagström, 2010). However, these have received little attention to date, so there is an urgent need for further studies based on a cluster-randomized intervention design.

Recent studies have concluded that leptin may increase the generation of reactive oxygen species (Chetboun et al., 2012). This is particularly important since individuals with Down syndrome have generally been described as having high levels of oxidative stress, which has been associated with increased morbidity.

In a previous study, it was reported that a 12-week aerobic-training program reduced oxidative damage in obese subjects with Down syndrome (Ordonez et al., 2012; Rosety-Rodriguez et al., 2010). Data from the current study suggest that the improvement in redox status induced by regular exercise may be explained, at least in part, by the reduction in leptin levels.

The current data indicate that adiponectin levels are not significantly improved after a 10-week aerobic-training program. Similarly, no effects on levels of adiponectin were reported after a 12-week (Christiansen, Paulsen, Bruun, Pedersen, & Richelsen, 2010) or a 16-week (Arikawa et al., 2011) aerobic-training program in obese adults without ID. In contrast, a mixed protocol based on aerobic training plus resistance training showed more effective improvements in adiponectinemia in obese adolescents (de Mello et al., 2011). Accordingly, there is inconsistent support in the literature for increased adiponectin levels after short-term exposure to aerobic and/or resistance training in obese subjects.

Findings of decreased fat mass and body circumference as a result of exercise are consistent with previous studies (Mendonca & Pereira, 2009; Ordonez, Rosety, & Rosety-Rodriguez, 2006). In this respect, it is widely accepted that fat storage is not the sole function of adipose tissue, and the endocrine role of adipose tissue has become an active research area in recent years. In fact, the current results suggest that changes in body composition may have an influence on serum leptin levels. Therefore, another goal of this study was to identify significant associations between plasma leptin and indices of obesity to provide an easier, quicker, cheaper, and noninvasive method for assessing outcomes. The strongest correlation was found between leptin and WHR. Our findings not only confirmed that leptin correlates with indirect body fat-mass measures in obese women without ID (Ackermann et al., 2011; Bahceci et al., 2007) but also provided evidence that abdominal fat is significantly correlated to plasma levels of leptin.

Similarly, anthropometrical parameters such as body-mass index and WHR have been correlated with biomarkers of oxidative stress, both in people with Down syndrome (Camacho, Meletis, Rosety, & Ordoñez, 2010; Ordonez et al., 2006) and in obese women without ID (Crist et al., 2009). In fact, obesity has been described as a state of hyperoxidative stress, although the underlying mechanisms have not yet been elucidated. de Ferranti and Mozaffarian (2008) concluded that adipocyte dysfunction and its metabolic consequences (proinflammatory and pro-oxidative status) constitute a perfect storm that initiates and maintains adverse health effects in obese people.

As was hypothesized, peak VO₂max was also significantly increased after 10 weeks of exercise, although values were lower than those obtained for male adults with Down syndrome (Mendonca & Pereira, 2009).

Furthermore, it is widely known that people with Down syndrome exhibit low peak aerobic capacities and maximal heart rates compared with their healthy nondisabled peers. This finding may be explained by a lower walking economy that is mainly related to their inability to adapt efficiently to positive variations in walking speed (Mendonca, Pereira, Morato, & Fernhall, 2010). In addition, they present a different catecholamine response to exercise (Fernhall et al., 2009). Accordingly, the design of intervention programs based on regular exercise should take this chronotropic incompetence into account. If this is not done, sessions theoretically designed at moderate intensity that take the general population as the standard become exhausting for participants with Down syndrome, leading to undesired results and increased dropout rates.

To the best of our knowledge, this is the first study conducted exclusively on premenopausal women with ID, in attempt to obtain a homogeneous sample. To date, many studies that have focused on the influence of regular exercise on people with ID have recruited mixed (male and female) groups to increase sample size with the aim of strengthening research design and enhancing extrapolation of the results. In addition, a few studies have been conducted exclusively on males (Mendonca & Pereira, 2009; Ordonez et al., 2012; Rosety-Rodriguez et al., 2010). Less attention has been paid to women with Down syndrome, in spite of the higher prevalence of obesity in them (González-Agüero, Ara, Moreno, Vicente-Rodríguez, & Casajús, 2011). In fact, the higher fat-mass percentage they present may contribute to explaining why women with Down syndrome are observed to have a shorter life expectancy than men with the disability (Tyrer, Smith, & McGrother, 2007). Furthermore, it should be emphasized that the size of the current sample was similar to that of the largest samples reported in previous exercise intervention studies on people with trisomy 21.

Finally, we concluded that a 10-week aerobic-training program showed an anti-inflammatory effect via reduced serum leptin levels in obese young women with Down syndrome. Therefore, additional long-term, well-conducted studies are required to determine whether correction of this low-grade proinflammatory status improves clinical outcomes of people with trisomy 21.
References


