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# How to Design an Exercise Program TO Reduce Inflammation in Obese People With Down Syndrome

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## 1. Introduction

*Obesity in people with Down syndrome: a big problem.*

Over the last decade, a significant increase in the life expectancy of people with Down syndrome (DS) has been observed. The higher life expectancy has caused a higher incidence of morbidity as they age [1]. Many of these disorders have been associated to obesity that is a major health problem in people with intellectual disabilities. Not only for its prevalence but also for its negative impact on their health status and quality of life.

In a more detailed way, it is widely accepted that obesity is a serious problem that is overwhelmingly prevalent in the general population. However, the magnitude of this problem is even worse in people with intellectual disability in general and Down syndrome in particular. A cross-sectional study with adult clients (n=470) of three Dutch intellectual disability care providing organizations and found that healthy behavior was low, with 98.9% of the participants having an unhealthy diet and 68.3% a lack of exercise [2]. In a more detailed way, women and people with Down syndrome were significantly more at risk of being obese [3].

Obesity and overweight are independent risk factors for chronic disease and have been shown to make a significant contribution to the reduced life expectancy of adults with intellectual disability. Further, the increased visceral fat in females with DS might indicate a higher risk of metabolic syndrome in this group [4].

Accordingly, recent studies have concluded that more attention needs to be paid to the rising fat mass percentages seen in individuals with Down syndrome in order to minimize negative, long-term health consequences [5,6].

In reviewing the current evidence, the effectiveness of interventions was judged on both the extent of and the maintenance of weight reduction.

It is widely accepted promoting appropriate levels of physical activity remains an important component for both weight loss and management and should have its place as a lifestyle and behavioral change in people with Down syndrome [7,8,9].

However, the interventions that have been conducted has achieved a degree of success in promoting weight reduction in the short term. There is less evidence about whether intervention programs can maintain weight loss effectively in the long term. In fact, current guidelines highlight the interventions that lead to modest, maintainable weight lose for people with intellectual disability will have significant benefits on both health and welfare.

The latter authors also concluded that much of the research on obesity in adults with Down syndrome has design weaknesses, including small sample sizes and a lack of controlled studies [10].

#### *Association between obesity and low-grade systemic inflammation*

Accumulating evidence derived from both clinical and experimental studies highlight obesity may be viewed as a chronic low-grade inflammatory disease as well as a metabolic disease [11,12]. Therefore, it is widely accepted adipose tissue is not merely a fat storage depot. In contrast, endocrine and paracrine aspects of adipose tissue have become an active research area in the last years.

Recent studies have reported that parenchymal and stromal cells (fibroblasts, endothelial cells and immune cells) in adipose tissue change dramatically in number and cell type during the course of obesity, which is referred to as "adipose tissue remodeling." In this regard, recent evidence suggests that the intimate crosstalk between mature adipocytes and stromal cells in adipose tissue plays a critical role in the dysregulation of adipocytokine production [13].

These findings were of particular interest since adults with intellectual disabilities experience high rates of obesity. Although Down syndrome has been traditionally considered an atheroma free model [14] recent studies have also reported individuals with intellectual disability suffer from low-graded systemic inflammation that has been proposed as a pathogenic mechanism of several disorders [15]. Previous studies showing increased levels of soluble intercellular adhesion molecule (sICAM-3) and soluble vascular cell adhesion molecule (sVCAM-1) in plasma, also suggested the presence of a moderate dysfunction of endothelial cells in subjects with Down syndrome [16].

Similarly, plasmatic concentrations of IL-6, IL-18 and CRP (C-reactive protein) levels were highly correlated with measures of total and visceral adiposity in obese adults with Prader-Willi Syndrome (PWS) [17]. The reported excessive visceral adiposity in subjects with PWS may be associated with decreased production and lower circulating levels of adiponectin

[18]. These data are of particular interest since increased low-grade inflammation is associated with increased arterial stiffness, a recognized marker for increased cardiovascular risk in people with Prader-Willi syndrome [19].

Importantly, some frequently diagnosed comorbidities could affect systemic inflammation in people with intellectual disability. In fact, obstructive sleep apnea, is a syndrome that has itself been linked to increased low-grade inflammation both in general population [20] and people with Prader-Willi syndrome [19].

Adipokines and acute phase proteins are important mediators of adverse effects (insulin resistance) so that the normalization of their levels has been reported as a therapeutic target in subjects at high cardiovascular risks [21,22].

Contradictory data have been reported about the effect of statins on adiponectin plasma levels. In this respect, atorvastatin (10-80 mg/day) increased adiponectin plasma levels in subjects at high cardiovascular risk. Further, adiponectin concentrations were positively correlated with high-density lipoprotein-cholesterol both before and after atorvastatin treatment [23]. Similar results were found using simvastatin (40mg/day) suggesting a novel anti-inflammatory effect of this drug [24].

Fortunately several studies have reported both endurance and resistance training programs at low/moderate intensity may reduce proinflammatory adipokines both at early life stages and elderly in obese people without intellectual disability [25]. However, to the best of our knowledge, there is a lack of information in people, especially women, with intellectual disabilities. Accordingly additional studies based on specific training programs that are adaptable to the needs of individuals with intellectual disability are strongly required [26].

In addition, it would be of interest to reduce the length of training programs previously published. In fact, it is expected shorter training programs may facilitate their follow-up, reducing drop-out rates.

#### *Regular exercise in Down Syndrome*

The benefits of physical activity are universal for general population, including those with disabilities [14, 27].

In fact, the participation of people with disabilities in sports and recreational activities promotes social inclusion, minimizes deconditioning, optimizes physical functioning, and enhances overall welfare [14,28]. Further sports participation enhances the psychological well-being of people with disabilities through the provision of opportunities to form friendships, express creativity, increase self-esteem, develop a self-identity, and foster meaning and purpose in life [29].

Physical consequences of inactivity for persons with disabilities include among others: reduced cardiovascular fitness, osteoporosis and impaired circulation. In addition, the psychosocial implications of inactivity include decreased self-esteem, decreased social acceptance, and ultimately, greater dependence on others for daily living [14].

Despite the benefits associated to regular exercise, subjects with disabilities are still, to a large extent, more restricted in their participation than their peers without disabilities. They may experience negative societal stereotypes and low performance expectations, rendering them with limited opportunities for participation in physical activities [30].

In this regard, people with Down syndrome are especially at risk because of physical and health impairments, as well as perceived and real barriers to participation in exercise [31].

In a more detailed way, it is accepted that persons with Down syndrome exhibit low peak aerobic capacities and maximal heart rates when compared with healthy non-disabled peers. These findings may be explained by a lower walking economy that is mainly related to their inability to adapt efficiently to positive variations in walking speed [32]. Furthermore, they present a different catecholamine response to exercise [33]. Accordingly, intervention programs based on regular exercise should be designed by taking into account their chronotropic incompetence. On the contrary, sessions theoretically designed at moderate intensity for the general population become exhausting for participants with Down syndrome, leading to undesired results and increased withdrawal rates.

However, it is important to note that environmental and family factors seem to be more significant determinants of participation than characteristics of the subjects themselves. In fact, families who engage in physical activities themselves tend to promote similar participation for their relatives with disabilities. Conversely, inactive role models, competing demands and time pressures, unsafe environments, lack of adequate facilities, insufficient funds, and inadequate access to quality daily physical education seem to be more prevalent among populations with special needs. The establishment of short-term goals, emphasizing variety and enjoyment, and positive reinforcement through documented progress toward goals can help spark and sustain the motivation for participation [14, 27,34].

In summary, misconceptions and attitudinal barriers at the level of the individual, the family, and the community need to be addressed to integrate people with disabilities into recreational and sports activities [14].

Another point of interest is that physical activity comes with an inherent risk for injury. For people with intellectual disability, previous studies have reported their injury risk may be complicated by preexisting disability [26]. Accordingly it is important for caregivers, educators and others to identify strategies to minimize risks of illness and injury related to participation through activity adaptations and safety precautions.

Fortunately, little or no sport-related injuries are reported in the literature during intervention programs based on regular exercise [32,35,36]. It may be explained, at least in part, due to the preparticipation physical examination (PPPE) and the design of specific training programs that are adaptable to the needs of individuals with intellectual disability. This is of particular interest since injuries and discomfort may lead to participants to interrupt their training program, increasing withdrawal rates and sedentary lifestyle [37].

## 2. Body

### *Problem statement*

Accumulating evidence derived from both clinical and experimental studies highlight the association of visceral obesity with a proinflammatory status in general population [11,12]. Recent studies have also reported individuals with intellectual disability suffer from low-grade systemic inflammation that has been proposed as a pathogenic mechanism of several disorders [15]. The adipokines are important mediators of these adverse effects so that the normalization of their levels has been reported as a therapeutic target [21].

Fortunately several studies have reported both endurance and resistance training programs at low/moderate intensity may reduce proinflammatory adipokines both at early life stages and elderly in obese people without intellectual disability [25]. However, to the best of our knowledge, there is a lack of information in people, especially women, with intellectual disabilities.

Accordingly, this study was designed to assess the influence of a 10-week aerobic training program on plasmatic levels of adipokines in obese women with Down syndrome.

### *Application area*

Healthcare costs are continuously increasing because of the increasing life expectancy among people with disabilities [1]. This is a strong argument for strengthening the role of preventive strategies, such as exercise, with the aim to reduce future costs.

However, researchers suggest that people with an intellectual disability undertake less physical activity than the general population and many rely, to some extent, on others to help them to access activities [34,38].

Currently, a wide variety of sporting activities are accessible to people with disabilities, and guidelines are available to assist caregivers, volunteers, educators and healthcare-providers in recommending activities appropriate for those people with specific conditions. These training programs should be not only effective but safe since previous studies have reported their sport-related injury risk may be complicated by preexisting disability.

### *Research course & method used*

A 10-week aerobic training program was designed by a multidisciplinary team to reduce plasmatic adipokines in obese women with Down syndrome. In order to achieve this goal, twenty obese adult women with Down syndrome volunteered for the present interventional study. They had an intelligence quotient (IQ) range of 50–69, determined by Stanford-Binet Scale, being diagnosed as having mild intellectual disability. Eleven of them were randomly assigned to perform a 10-week aerobic training program, 3 sessions/week, consisting of warming-up followed by a main part in a treadmill (30–40 min [increasing 2 minutes and half each two weeks]) at a work intensity of 55–65% of peak heart rate (increasing a 2.5% each two weeks) and a cooling-down period. Control group included

9 age, sex and BMI matched women with Down syndrome. Fat mass percentage and fat distribution were measured.

Plasmatic levels of TNF- $\alpha$ , IL-6 and leptin were assessed by commercial ELISA kits (Immunotech, MA, USA). High-sensitive C-Reactive Protein (hs-CRP) in plasma was assessed by nephelometric methods on a BN-II analyzer (Dade-Behring Diagnostics, Marburg, Germany). Fat mass percentage was assessed by bioelectrical impedance analysis BIA (Tanita TBF521). To determine waist to hip ratio, waist and hip circumferences were measured with an anthropometric tape (Holtain Ltd). Furthermore, each participant underwent a maximal continuous treadmill graded exercised test. All outcomes at individual level were assessed firstly at baseline and secondly 72-h after the end of the intervention. Written informed consent was obtained from all their parents or legal representatives. Further this protocol was approved by an Institutional Ethics Committee.

The results were expressed as a mean (SD). The statistical analysis of the data was performed using Student's *t*-test for paired data. Pearson's correlation coefficient (*r*) was used to identify potential associations among tested parameters. The significance of the changes observed was ascertained to be  $p < 0.05$ .

### *Results*

When compared to baseline results, plasmatic levels of TNF- $\alpha$  ( $11.7 \pm 2.6$  vs.  $10.2 \pm 2.3$  pg/ml;  $p = 0.022$ ), IL-6 ( $8.0 \pm 1.7$  vs.  $6.6 \pm 1.4$  pg/ml;  $p = 0.014$ ) and leptin ( $54.2 \pm 6.7$  vs.  $45.7 \pm 6.1$  ng/ml;  $p = 0.026$ ) were significantly reduced in interventional group. Similarly, C-reactive protein level was significantly decreased after being exercised ( $0.62 \pm 0.11$  vs.  $0.53 \pm 0.09$  mg/dl;  $p = 0.009$ ). Regarding anthropometric measurements, both fat mass percentage ( $38.9 \pm 4.6$  vs.  $35.0 \pm 4.2\%$ ;  $p = 0.041$ ) and WHR ( $1.12 \pm 0.006$  vs.  $1.00 \pm 0.005$  cm;  $p = 0.038$ ) were also reduced. We also found significant associations between WHR and IL-6 ( $r = 0.51$ ;  $p < 0.001$ ).  $VO_2$ max was also increased in exercised at the end of the experience ( $20.2 \pm 5.8$  vs.  $23.7 \pm 6.3$  ml/kg/min;  $p = 0.0007$ ) suggesting an improvement of their physical fitness.

In contrast, control group showed no changes in any of the tested parameters.

### *Further research and Discussion*

The main finding of this study was that aerobic training reduced significantly plasmatic levels of adipokines (TNF- $\alpha$ , IL-6 and leptin) as well as C-reactive protein (CRP) in adult women with Down syndrome. Similar results regarding anti-inflammatory effect of a 16-week aerobic training program have been reported in young women without intellectual disability [39]. Furthermore, a 6-month aerobic training program (four times/week, 45-60 min/session) reduced plasmatic levels of TNF in adults with type 2 diabetes [40].

Another challenge of this study was to identify significant associations between plasmatic adipokines and indices of obesity in order to provide an easier, quicker, cheaper and non-invasive assessment of the outcomes. The strongest correlation was found between IL-6 and waist-to-hip ratio (WHR). Our findings not only confirmed adipokines correlated with indirect body fat mass measures in obese women without intellectual disability [41,42]. It also

provided the evidence that abdominal fat was significantly correlated to plasmatic levels of CRP.

To the best of our knowledge this is the first study conducted exclusively in premenopausal women with intellectual disability, in attempt to keep our sample homogeneous. To date, many studies focused on the influence of regular exercise in people with intellectual disability have recruited mixed (males and females) groups in order to increase their sample size to strengthen research designs and increase generalization of study findings [43,44,45]. A few studies have been conducted in males [35,36,46].

However, less attention has been paid to women in spite of the higher prevalence of obesity in the latter [4]. This finding may contribute to explain women with DS are observed to have a shorter life expectancy than men with DS [47]. A major strength of the present study was that we discarded gender mismatching, which itself influences total adiposity and fat distribution.

Further, it should be emphasized that our sample size was similar to the largest ones reported in previous exercise intervention research on persons with trisomy 21[35,36,43,44]. This is of particular interest since studying subjects with intellectual disabilities is associated with many challenges that restrict the number of participants investigated.

The present protocol lasted just 10 weeks, so that it may be considered more feasible and practical for participants and guidance. In order to promote sustainability of these healthy programs based on exercise, it is essential targeting not only participants but also their parents, caregivers, educators, etc. However the latter have received little attention so that future studies designed as cluster-randomized interventions are highly required [38].

As was hypothesized, peak VO<sub>2</sub>max was also significantly increased after being exercised for 10 weeks. These results are lower than that of male adults with Down syndrome.[46] In this respect, it is widely known that persons with Down syndrome exhibit low peak aerobic capacities and maximal heart rates when compared with healthy non-disabled 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.[32] Furthermore, they present a different catecholamine response to exercise.[33] Accordingly, intervention programs based on regular exercise should be designed by taking into account their chronotropic incompetence. On the contrary, sessions theoretically designed at moderate intensity for the general population become exhausting for participants with Down syndrome, leading to undesired results and increased withdrawal rates.

Finally, despite the high prevalence of obesity in people with Down syndrome, it should be pointed out it may be even more prevalent in several genetic syndromes such as Prader-Willy syndrome, Bardet-Biedl syndrome, Cohen syndrome etc. Accordingly further studies on these populations are also required [10].

### 3. Conclusion

In summary, it was concluded a 10-week aerobic training program reduced plasmatic levels of adipokines and acute phase proteins in adult obese 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.

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