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Resistance circuit training reduced inflammatory cytokines in a cohort of male adults with Down syndrome

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Background: It is widely accepted that muscle strength plays a key role on functional tasks of daily living and employability in individuals with Down syndrome (DS). Recent studies have also reported resistance training may improve chronic inflammation in other clinical situations. This is the first study conducted to determine the effect of resistance circuit training on low-grade systemic inflammation in adults with DS.





Material/Methods: A total of 40 young male adults with DS were recruited for the trial through different community support groups for people with intellectual disabilities and their families. They had medical approval for physical activity participation. Twenty-four were randomly assigned to perform resistance circuit training with 6 stations, 3 days per week for 12 weeks. Exercise intensity was based on function of the 8RM assessments. The control group included 16 age-, sex-, and BMI-matched adults with Down syndrome. Plasma levels of leptin, adiponectin, and TNF- α were assessed by commercial ELISA kits. C-reactive protein (CRP) was assessed by nephelometry. Body composition was also determined, measuring fat-free mass percentage and waist circumference (WC). This protocol was approved by our Institutional Ethics Committee.

Results: Plasma levels of leptin, TNF- α , and IL-6 were significantly decreased after the completion of the training program, as were fat-free mass and WC. No sports-related injuries or withdrawals from the program were reported during the entire study period. No changes were observed in the control group.

Conclusions: Resistance circuit training improved low-grade systemic inflammation in male sedentary adults with DS.

Key words: **Down syndrome • resistance training • systemic inflammation • leptin • tumor necrosis factor-alpha**

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Background

Given the significant increase in the life expectancy of people with intellectual disability (ID) observed during the last 2 generations, there is greater need for understanding the nature, timing, and impact of associated comorbidities [1].

In this respect, recent studies have reported that obese and overweight individuals with ID have low-grade systemic inflammation, which has been proposed as a pathogenic mechanism of several disorders such as metabolic syndrome and insulin resistance [2,3].

The adipocytokines, primarily released from abdominal fat mass, are important mediators of these adverse effects, thus the normalization of their levels has been reported as a therapeutic target [4].

Promising results regarding the anti-inflammatory effect of exercise have been found in experimental [5] and human studies in healthy individuals [6] as well as in other clinical situations [7,8]. Furthermore, a 12-week aerobic training program reduced proinflammatory cytokines in obese female adults with Down syndrome (DS) [9]. However, there is a lack of evidence in the literature documenting whether resistance training can improve systemic inflammation in DS. In addition, this finding would be of great interest given the positive effects of muscle strength on functional tasks of daily living and employability in young adults with DS [10].

Accordingly, this was the first study conducted to determine the influence of resistance circuit training on low-grade systemic inflammation in sedentary male adults with DS.

Material and Methods

To achieve this goal, 40 male adults with DS (23.7±3.1 years; 26.2±2.8 Kg/m²) were recruited for the trial through different community support groups for people with ID and their

families. They had an intelligence quotient (IQ) range of 60–69, determined by Stanford-Binet Scale, being diagnosed as having mild ID. The exclusion criteria were as follows: 1) atlantoaxial instability; 2) congenital heart disease; 3) thyroid disease 4) orthopedic conditions limiting the range of motion of the knee; 5) consumption of antioxidant supplements; 6) toxic habits (smoking or alcohol); 7) participation in a training program in the 6 months prior to their participation in the trial; and 8) not completing at least 90% of the training sessions.

Furthermore, all of them had medical approval for physical activity participation. Twenty-four were randomly assigned to perform 12-week resistance circuit training, 3 days per week (Table 1). This training was circularly performed in 6 stations: arm curl, leg extension, seated row, leg curl, triceps extension, and leg press. Each training session started and finished with a warming-up and cooling-down period of 5–10 minutes during which muscle stretching exercises were performed [11]. Furthermore, training sessions were in small groups (6 participants) and were supervised by experienced physical therapists to ensure that participants used the correct technique and intensity (ratio 1 monitor/2 participants).

It should be pointed out that before starting training program, participants included in the intervention group underwent a pre-training session to become familiar with resistance exercises as well as to perform the 8-repetition-maximum (8RM) test per each exercise [12]. In fact, exercise intensity (load) was based on function of the 8RM assessments.

The control group included 16 age-, sex-, and BMI-matched adults with DS who did not take part in any training program. The potential confounding effect of diet should be discarded, because parents were carefully informed to avoid quantitative or qualitative differences. The present research was conducted in full accordance with ethical principles, including the World Medical Association Declaration of Helsinki (version 2002). In this respect, written informed consent was obtained from all their parents or legal representatives. Further, our protocol was approved by our Institutional Ethics Committee.

Table 1. Resistance circuit training, comprised of 6 stations, performed by participants in the intervention group.

	1°–2°-wk	3°–4°-wk	5°–6°-wk	7°–8°-wk	9°–10°-wk	11°–12°-wk
Load	40%	45%	50%	55%	60%	65%
Series	2	2	2	2	2	2
Rep.	10	10	8	8	6	6
Rest	90	90	90	90	90	90

Load – expressed as percentage of 8 repetition-maximum (8RM) test; Rep – number of repetitions; Rest – resting periods between stations expressed in seconds.

Table 2. Effects of a 12-week resistance circuit training on low-grade systemic inflammation in sedentary adults with Down syndrome.

	Exercising group		Control group		Cohen's d
	Pre-test	Post-test	Baseline	Final	
Leptin (ng/ml)	50.6±6.4	45.1±6.2***	49.8±6.3	50.1±6.2	0.80
Adiponectin (ng/ml)	38.8±5.7	40.4±5.8	39.1±5.7	39.3±5.8	0.18
TNF-α (pg/ml)	10.6±1.5	9.0±1.6***	10.4±1.5	10.5±1.5	1.00
IL-6 (pg/ml)	7.1±1.2	5.8±1.0***	6.9±1.2	7.0±1.1	1.21

TNF-α – tumor necrosis factor; IL-6 – interleukin-6. Results are expressed as mean ±SD. * p<0.05 vs. pre-test; ** p<0.05 vs. control group (final).

Blood samples were obtained from antecubital vein puncture and collected in heparinized tubes. The whole blood was centrifuged at 3000 rpm for 10 minutes in a clinical centrifuge. Plasmatic levels of leptin, adiponectin, TNF-α, and IL-6 were assessed by commercial ELISA kits (Immunotech, MA, USA).

Regarding anthropometric assessment, fat-free mass percentage was assessed by bioelectrical impedance analysis BIA (Tanita TBF521). Participants were requested to not participate in moderate or vigorous exercise for 24 hours prior to testing as well as to abstain from eating or drinking for 2 hours before testing. Moreover, they were asked to urinate immediately prior to data collection.

Waist circumference (WC) was measured with an anthropometric tape (Holtain, Ltd) halfway between the costal edge and the crista. These parameters were assessed according to the International Society for the Advancement of Kinanthropometry (ISAK) guidelines by an experienced investigator who was blind to group allocation and was not involved in any other aspect of the trial.

Finally, the timed get-up-and-go (TGUG) test was performed to assess functional tasks. Participants were instructed to sit in a chair with their back against the chair and their arms on the armrest. To standardize their sitting posture prior to testing, their feet were placed into 2 lines separated 30cm in front of the chairs' legs. A third line was drawn 3 meters in front of the chairs. At the word "go" they were required to stand upright and to walk to the 3-m line, turn around and walk back again to the chair and sit down. A manual stopwatch was started on the word "go" and stopped when the subject returned to the sitting position [13]. All participants underwent a preliminary session to become familiar with the correct use of the test. All tests were performed and supervised by the same experienced occupational therapist who was blind to group allocation and was not involved in any other aspect of the trial.

All outcomes at the individual level were assessed firstly at baseline and secondly 72 h after the end of the intervention. The results are expressed as means (SD). The Kolmogorov-Smirnov test was used to assess whether data were normally distributed. To compare the mean values, a one-way analysis of variance (ANOVA) with post-hoc Bonferroni correction to account for multiple tests was used. Pearson's correlation coefficient (r) was used to determine potential associations among tested parameters. For all tests, statistical significance was set at an alpha level of 0.05. Finally, Cohen's d statistics were used for determining mean effect sizes as follows: small d ≥0.2 and <0.5; medium d ≥0.5 and <0.8; large d ≥0.8.

Results

When compared to baseline results, the intervention group demonstrated significantly improved performance in the TGUG test (8.7±1.4 vs. 7.5±1.3s; p=0.362). Furthermore, fat-free mass (69.9±3.2 vs. 71.3±3.0%; p=0.011) and waist circumference (93.8±2.7 vs. 92.7±2.5 cm; p=0.0416) were significantly changed after the completion of the training program.

As hypothesized, resistance training significantly reduced plasma levels of leptin, TNF-α, and IL-6. Conversely, no significant changes were found in plasma adiponectin in the intervention group. These results are summarized in Table 2. Significant correlations were found between plasma levels of adipocytokines and anthropometric parameters. The strongest correlations were found between leptin and WC (r=0.50; p=0.0282), IL-6, and WC (r=0.44; p=0.0341), as well as TNF-α and WC (r=0.38; p=0.0413). Finally, a negative but significant correlation was observed between plasma adiponectin and WC (r=-0.35; p=0.477). No changes were found in any assessed outcome in the control group.

Finally, no sports-related injuries or withdrawals from the program were reported during the entire study period in the intervention group.

Discussion

The vast majority of studies reporting the anti-inflammatory effect induced by exercise in different clinical situations were focused on aerobic training programs; however, the increase in muscle mass after resistance training may be a key mediator leading to better metabolic control and basal energy expenditure [14].

To the best of our knowledge, this is the first study to demonstrate resistance training reduced markers of low-grade systemic inflammation in adults with DS. Similar results were found in male adults without ID after the completion of 18-month progressive resistance training [15]. The present protocol lasted just 12 weeks, and thus may be considered to be feasible and practical for participants and also for guidance. In a previous study, alpha-linolenic acid supplementation and resistance training significantly reduced plasma levels of IL-6 in adults [16]. Our protocol achieved similar outcomes based only on exercise, so it may facilitate participant compliance with the intervention.

Conversely, a few studies have not found the same anti-inflammatory effect induced by exercise [17,18]. In a more detailed way, a single session of resistance exercise did not affect the serum concentrations of cell adhesion molecules in healthy young men [17], which can be explained given that the intervention program consisted of a single session of 30 min performing 3 sets of 10 resistance exercises with 10–12 repetitions at 70–75% of 1 repetition maximum in a circuit training.

Similarly, aerobic training induced no changes in messenger RNA levels of the TNF and IL-6 genes in subcutaneous abdominal adipose tissue (SCAAT) in obese pre-menopausal women [18]. These findings may be explained, at least in part, by the fact that visceral abdominal fat rather than subcutaneous abdominal fat has been associated to increased secretion of a plethora of proinflammatory cytokines, which underscores a state of chronic low-grade inflammation [19].

Accordingly, the anti-inflammatory effect induced by exercise may be explained, at least in part, by decreasing fat mass, especially abdominal fat mass. In this respect, we have also found significant correlations between proinflammatory cytokines and indices of body fat distribution, as previous studies focused on obese adults without ID [20].

Several studies have found aerobic training reduced fat mass in subjects with DS [9,21,22]. Results reported in adults with ID after the completion of a 20-week combined (aerobic + resistance) training program are also promising [23]. Resistance training, *per se*, has received less attention in this area, despite the fact that it also may increase fat-free mass. Furthermore,

improving muscle strength could potentially increase the amount of activity they undertake, which may give them the confidence to continue exercising after the trial finishes [24]. These findings are of particular interest because obesity is a major health problem for people with ID [25]. In this respect, obesity and its comorbid conditions may cause a significant increase in the cost of healthcare given the increase in the life expectancy of this population [26].

Increasing evidence highlights resistance training is an appropriate intervention for young adults with DS because they can master the repetitive skills required by this form of exercise [24]. Previous studies have found resistance training improved muscle strength in individuals with ID, expressed as increased maximal handgrip force, dynamic torque of knee flexors, and extensors [13,23,27,28]. However, whether this improvement transfers to improved functional tasks of daily living has received less attention [29,30]. The present resistance circuit training improved TGUG test, suggesting improved functional performance in the intervention group. Similar results were reported in elderly people with DS after the completion of a 6-month training program [31]. Lastly, improving muscle strength could potentially increase the amount of activity they undertake, which may give them the confidence to continue exercising after the trial finishes [24].

Major strengths of the current study included the large and uniform sample size, in contrast to previous studies that enrolled males and females with ID due to various causes [21,32]. Further, the presence of a control group consisting of siblings may reduce the recruitment bias of able-bodied controls. Lastly, the excellent adherence rate suggested the training program was effective, safe, and easy to follow.

This finding may be due, at least in part, to training sessions performed in small groups supervised by experienced physical therapists. Furthermore, the training program was adaptable to the needs of individuals with ID in order to achieve main objectives and hypothetically decrease the risk of injury. In this respect, the 8-repetition maximum test has been recommended as a method of prescribing intensity for resistance training in patients with various diagnoses [12]. In fact, erring on the conservative side of selected exercise duration and intensity is prudent and is even more important for persons training with a disability than those without [33].

The current study had some limitations. The use of weight lifting machines may limit the reproducibility of this study in case exercise equipment is not available. In this respect, future studies focused on circuits whose stations utilize body weight or free-weight exercises are also required to guarantee its reproducibility elsewhere. A lack of more accurate measures to evaluate body composition should be also considered.

However, the methods we performed (conventional anthropometry and BIA) are still used due to their low cost and simplicity, as well as their wide availability in any clinical setting. Another major weakness was the relatively short duration of the exercise intervention; there was no follow-up to determine whether these positive effects induced by aerobic training were maintained. Accordingly, there is a clear need for long-term, well-conducted studies to determine whether correction of low-grade systemic inflammation improves clinical outcomes of individuals with SCI.

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Conclusions

We found that resistance training improved low-grade systemic inflammation in sedentary adults with DS. Furthermore, it improved body composition and functional task performance in the intervention group.

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