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Review

What effect does regular exercise have on oxidative stress in people with Down syndrome? A systematic review with meta-analyses

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ABSTRACT

Objective: What effect does regular exercise have on oxidative stress in people with Down syndrome?
Design: Systematic review with meta-analyses.
Methods: A systematic review with meta-analyses was conducted. Six databases were searched from inception until August 2017. Studies where included if participants with Down syndrome (any age) had completed an exercise program of at least 6 weeks duration and at least one biomarker measured the generation or removal of reactive oxidative species. Data were extracted using a customised form. Risk of bias was assessed using the Cochrane Collaboration's Risk of Bias assessment tool. Effect sizes were calculated and meta-analyses completed for clinically homogeneous data using a random effects model.
Results: Seven studies (11 articles) involving 144 inactive participants investigated the effect of moderate intensity aerobic exercise. No pattern emerged for how most biomarkers responded with non-significant pooled effect sizes and high levels of heterogeneity observed. The exception was catalase which increased significantly after exercise (standardised mean difference 0.39, 95%CI 0.04–0.75; I^2 15%). Available studies were at high risk of bias. Two of five studies that measured more than one biomarker reported a decrease in oxidative stress with increased antioxidant activity after exercise but the other three (including one small randomised controlled trial) reported increased oxidative stress with variable change in antioxidant activity.
Conclusions: There remains uncertainty about the effect of exercise on oxidative stress in people with Down syndrome.
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1. Introduction

Down syndrome (trisomy-21) is the most common known cause of intellectual disability.[1] It has whole-of-genome and epigenetic effects with consequences for the structure and function of every organ system. The intellectual disability is usually mild or moderate with variation in ability to manage daily living activities, and physical impairments include poor cardiovascular fitness.[1] Improvements in early cardiac care for children with Down syndrome have increased life expectancy[2] resulting in a growing adult

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population.[3] However, this population is not ageing well.[4] Half to three quarters of adolescents and adults with Down syndrome are overweight or obese.[5,6] Older adults with Down syndrome have high rates of age related morbidity and most experience early cognitive decline with a cumulative risk of dementia of 45% by 55 years and 80% by 65 years[7] compared to 20–35% by 75 years in the general population.

Oxidative stress is defined as the imbalance between the generation and removal of reactive oxygen species (ROS) in the body and is elevated from birth in people with Down syndrome.[8] It is caused by the overexpression of superoxide dismutase-1 (SOD1), encoded by the SOD1 gene located on chromosome 21.[8] SOD catalyses the dismutation of the superoxide anion to hydrogen peroxide which is then converted to water by glutathione peroxidase (GPX) and catalase (CAT). In Down syndrome, the ratio of SOD to GPX and CAT is increased,[9] producing more hydrogen peroxide than CAT and GPX can catabolise. The excess hydrogen peroxide and/or its conversion product (hydroxyl radical), can lead to cellular oxidative damage.[9]

The consequences of oxidative stress include neurodegeneration and intracellular accumulation of amyloid-beta (Aβ) deposits (that define Alzheimer disease),[10] which have a direct role in the cognitive decline in Down syndrome.[4,11,12] The brain is particularly susceptible to oxidative stress because of its high lipid content. In Down syndrome, increased ROS production renders neurons prone to apoptosis and more likely to degenerate.[10] Adults with Down syndrome have oxidative damage in the brain prior to the onset of Aβ deposits.[13] Further, the oxidative system is associated with cognitive functioning in adults with Down syndrome.[14] Increased lipid peroxidation[12] and poorer SOD functioning predicts poorer memory functioning in older adults with Down syndrome.[15]

Regular exercise reduces oxidative stress and enhances antioxidant activity in the general population[16] including the elderly.[17,18] The effects in people with Down syndrome are unclear because their physiological responses to exercise differ from the general population.[19] The physiological responses to exercise of people with Down syndrome include diminished cardiac responses, blunted arterial stiffness responses, autonomic dysfunction and chronotropic incompetence, each contributing to reduced exercise capacity, limited work performance and poorer exercise economy compared to healthy controls.[19] Studies also show differences in response to *a single session of aerobic exercise* in oxidative stress and antioxidant activity[20,21] between people with and without Down syndrome. Oxidative stress decreased[21] or did not change[20] in young adults with Down syndrome, whereas in healthy controls, there was an increase in oxidative stress immediately after exercise followed by a decrease to resting values after 60 min of recovery.[20] There were also between group differences for antioxidant activity. Immediately after a single exercise session and during recovery total antioxidant capacity decreased in healthy controls, but did not change in young adults with Down syndrome.[20]

Given the different responses to a single session of exercise, we cannot assume people with Down syndrome will respond in terms of oxidative stress in the same way to regular exercise as the general population. Therefore, we completed a systematic review and conducted meta-analyses on clinically homogeneous measures to investigate the effect of regular exercise on oxidative stress in people with Down syndrome.

2. Method

This systematic review was reported with reference to the PRISMA guidelines[22] and was prospectively registered with PROSPERO (CRD42016048492). Six electronic databases (Medline, EMBASE, CINAHL, PubMed, AMED, SPORTDiscus) were searched from inception to August 2017. The search strategy covered three main concepts: Down syndrome, exercise and oxidative stress, along with synonyms of each (Supplemental file 1). The search yields were downloaded into Endnote bibliographic software (version X7) and duplicates were removed. A manual search of the reference lists of included studies was also performed and citation tracking of the included articles was completed using Google Scholar.

Studies were included in the review if (1) the participants had been diagnosed with Down syndrome (any age), (2) exercise training or physical activity (all types) was completed for at least 6 weeks, (3) at least one measure of oxidative stress was included, (4) written in English and (5) available in full text. The exercise or physical activity interventions could include but were not limited to aerobic training, strength training, walking, swimming or cycling. The setting for the intervention could be at home, in a laboratory or at a community venue. All quantitative study designs (e.g. pre-test/post-test intervention designs, controlled trials) that assessed any biomarker measuring outcomes related to the generation of reactive oxygen species (oxidative stress), its removal and products of reactions between reactive oxygen species and lipid or protein biomolecules over any time-points were included.

Studies were excluded if (1) data from participants with Down syndrome were included as part of a larger group of participants (e.g. people with intellectual disability) but their data could not be separated from the larger cohort; (2) the effect of a single session of exercise on oxidative stress was investigated; (3) they were qualitative studies or narrative reviews. Two reviewers (NS, NT) independently assessed the titles and abstracts of the search yield for eligible articles based on the criteria above. Full text versions of articles that could not be excluded based on title and abstract were obtained and the eligibility criteria reapplied. Reasons for exclusion were recorded. Any discrepancies were settled by discussion until consensus was reached.

Data were extracted on the following variables: study design, participant characteristics (age, sex, BMI, severity of intellectual disability, exercise participation), sample size (number of participants in each study arm), intervention (including mode of exercise, intervention duration, frequency per week, individual session duration, setting, supervision required, exercise intensity), outcomes measured, statistical analysis and adverse events. Data were extracted by one reviewer (NS) using a standardised data extraction form developed for the review and checked by a second reviewer (MK). Any disagreements were discussed until consensus was reached.

Risk of bias was assessed independently using the Cochrane Collaboration's Risk of Bias assessment tool[23] by two reviewers (JD, HL). Seven domains were assessed using this two-part tool: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and 'other issues'. The first part of the tool described what was reported to have happened in the study, in sufficient detail to support a judgment about the risk of bias. The second part of the tool assigned a judgment relating to the risk of bias for that domain. The judgment assigned by the reviewers for each domain for each study was either low risk of bias, high risk of bias, or unclear risk of bias. If insufficient detail was reported of what happened in the study, the judgment assigned was 'unclear risk' of bias. Disagreements were resolved through discussion until a consensus was reached.

Data on participant characteristics and the interventions implemented were synthesised descriptively. Effect sizes were calculated for all studies, where appropriate, using standardised mean differences of post intervention scores between experimental and control groups,[24] or pre and post intervention scores for pre-test/post-test studies estimated by $d = \frac{t}{\sqrt{N}}$, with associated 95%

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