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REVIEW

Oxidative stress, exercise and Down syndrome

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KEY WORDS:
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Abstract
An imbalance between free radical production and antioxidant defence leads to an oxidative stress state that can potentially result in a change in the intracellular redox balance towards a more oxidizing environment, with the possibility of causing ill-health and disease. Down's syndrome (DS) is the first clinically defined chromosomal syndrome, and is caused by the presence of three copies of chromosome 21. It is one of the most significant human congenital defects, with an incidence of 1 in every 700-1000 births. Regular physical activity is known as an important factor for health. However, exhaustive and/or intense physical activity increases free radical and reactive oxygen/nitrogen species (RONS) production. A minimal amount of RONS is necessary for muscular contraction. Nevertheless, oxidative stress, which results in muscle-increased RONS concentration, is associated with muscular fatigue during contraction and in post-exercise muscular damage suffering. The mitochondrial respiratory chain, the ischemia reperfusion phenomenon and the inflammatory reaction have been identified as the main sources of RONS during and after exercise. However, results reported in literature seem to show a beneficial effect of exercise on DS subjects, although the effect of exercise on oxidative stress parameters has been poorly studied in this condition.

PALABRAS CLAVE:
Antioxidantes;
Síndrome de Down;
Ejercicio;
Estrés oxidativo

Estrés oxidativo, ejercicio y síndrome de Down

Resumen
Un desequilibrio entre la producción de radicales libres y defensas antioxidantes puede conducir a un estado de estrés oxidativo que podría causar un cambio en el equilibrio redox intracelular generando un entorno más oxidante, con la posibilidad de causar

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enfermedad. El síndrome de Down (SD) es el primer síndrome cromosómico clínicamente definido y está causado por la presencia de tres copias del cromosoma 21. Es uno de los defectos congénitos humanos más importantes, con una incidencia de 1 de cada 700-1000 nacimientos. Se sabe que la actividad física, si se practica regularmente, es un factor importante para la salud; sin embargo, practicada de forma exhaustiva e intensa incrementa la formación de radicales libres y de especies reactivas de oxígeno y nitrógeno (ERON). Para la contracción muscular es necesaria una cantidad mínima de ERON. Por otra parte, el estrés oxidativo que resulta de la concentración de ERON en músculo está asociado con fatiga muscular durante la contracción y daño muscular después del ejercicio. Las principales fuentes de ERON durante y después del ejercicio son: cadena respiratoria mitocondrial, isquemia reperfusión y reacción inflamatoria. Sin embargo, los resultados recogidos en la bibliografía muestran efectos beneficiosos del ejercicio en el SD, aunque los efectos del ejercicio en parámetros de estrés oxidativo han sido muy poco estudiados en el SD.

Introduction

Regular physical activity, associated with a balanced diet, is known as an important factor for health[1]. However, strenuous physical exercise is associated with a dramatic increase in oxygen uptake both by the whole body and particularly by the skeletal muscle. The production of reactive oxygen/nitrogen species (RONS) is believed to be the underlying mechanism for a series of biochemical and physiological changes that occur during exercise and are indicative of oxidative stress. In general, the body has adequate antioxidant reserves to cope with the production of reactive oxygen species ROS under physiological conditions. The system consists of antioxidant enzymes, antioxidant vitamins, glutathione and thiols. These antioxidant defence systems preserve homeostasis for normal cell functions at rest and perhaps during mild exercise. However, when ROS production is excessive, such as during prolonged aerobic exercise, or when antioxidant defence is severely hampered by nutritional deficiencies and pharmacological intervention, an inadequate defence may be overwhelmed by the RONS, leading to extensive cell and tissue damage[2]. Antioxidant enzymes are endogenous; however their production can be modulated by certain factors.

Exercise and training are well known to be potential factors for the increase of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) as shown by numerous studies[3].

The aim of this article is to critically review the scientific literature concerning the link between oxidative stress and exercise in Down syndrome (DS). We review the extent of information available in scientific literature regarding oxidative stress and exercise in DS, providing evidence against and in favour of increased oxidative stress in this condition.

Down syndrome

Down syndrome is one of the most prevalent genetic disorders; it occurs at frequency of one in 700-1000 live births[4] and results as a consequence of either a total or partial trisomy of chromosome 21[5]. The syndrome is characterized by chronicity and severity of abnormalities including intellectual disability, dysmorphic features, as well as immunological, hematological and endocrine defects[6]. The phenotypic expression of human trisomy 21 is presumed to result from the overexpression of certain genes residing on chromosome 21 at the segment 21q22-the Down locus[7,8].

The amount of studies reporting a number of dysfunctions associating oxidative stress with DS phenotype is increasing. Oxidative stress is part of the fundamental biology of DS. It has been suggested that the main source of ROS in DS patients is the excessive production of hydrogen peroxide (H_2O_2) through the action of Cu,Zn-superoxide dismutase (Cu,Zn-SOD)[9,10]. As a result of the overexpression of Cu,Zn-SOD in DS patients, an imbalance between Cu,Zn-SOD and other antioxidant enzymes occurs, such as CAT and GPx, inducing a systemic oxidative damage[9]. SOD1 promotes the production of H_2O_2, an important precursor of hydroxyl radical (•OH), the most reactive and deleterious ROS, therefore it is able to react with important cellular components, oxidizing biomolecules such as amino acid residues, proteins, lipids and DNA[11].

Oxidative stress

Free radicals are reactive compounds that are naturally produced in the human body. They can exert positive effects (e.g. on the immune system) or negative effects (e.g. lipids, protein or DNA oxidation). A free radical is a molecule with one or more unpaired electrons in its outer orbital. These highly unstable molecules tend to react rapidly with adjacent molecules, donating, subtracting, or even sharing their outer orbital electron and being the most important ones those derived from either oxygen and nitrogen. ROS are substances that are released during oxidative metabolism. ROS include the superoxide anion (O2•—), hydrogen peroxide (H_2O_2), and the hydroxyl radical (OH•)[12]. The reaction of ROS with macromolecules can lead to DNA mutations, changes in the structure and function of proteins, and peroxidative cell-membrane lipids. Both the radicals and the non-radical species generated via interaction with free radicals, are referred to as RONS[13].

To limit these harmful effects, an organism requires complex and protection —the antioxidant system. An antioxidant is a substance that, when present in low concentrations relative to oxidizable substrate, significantly delays or reduces oxidation of the substrate[14]. This system consists of

antioxidants enzymes (SOD, CAT, GPx, glutathione reductase [GR]) and non-enzymatic antioxidant (e.g. vitamins C, E, glutathione and uric acid [UA]). The antioxidant system efficiency depends on nutritional intakes (vitamins and micronutrients) and on endogenous antioxidant enzyme production, which can be modified by exercise, training nutrition and aging.

An imbalance between free radical production and antioxidant defence leads to an oxidative stress state that can potentially result in a change in the intracellular redox balance towards a more oxidizing environment, with the possibility to cause ill-health and disease. However, despite their excess leads to oxidative/nitrosative stress, free radical, and RONS are involved in several important biological processes, including cell signalling, redox regulation of gene transcription, cellular immunity and apoptosis, being essential for normal physiological function[13].

Exercise and oxidative stress

Regular physical activity, together with a balanced diet, is known as an important factor for health. However, exhaustive or intense physical activity is associated with a dramatic increase in oxygen uptake both by the whole body and particularly by the skeletal muscle. The production of ROS is believed to be the underlying mechanism for a series of biochemical and physiological changes that occur during exercise and are indicative of oxidative stress. In general, the body has adequate antioxidant reserves to cope with the production of ROS under physiological conditions. The system consists of antioxidant vitamins, glutathione and thiols, and antioxidant enzymes[15]. These antioxidant defence systems preserve homeostasis for normal cell functions at rest and perhaps during mild exercise. However, when ROS production is excessive, such as during prolonged aerobic exercise, or when antioxidant defence is severely hampered by nutritional deficiencies and pharmacological intervention, an inadequate defence may be overwhelmed by the ROS, leading to extensive cell and tissue damage.

Since Dillard et al.[16] first reported in 1978 that exercise increases lipid peroxidation, the link between exercise and oxidative stress has received considerable attention and the studies about this topic are increasing significantly in number. Thus, it is now well established that exercise of enough intensity and duration increases the formation of RONS which could result in increased oxidative stress[17], as indicated by an increase in oxidized molecules in a variety of tissues and body fluids. However, whether or not an increase in RONS resulting from acute exercise causes oxidative damage remains still unclear.

The effect of exercise on the levels of oxidative stress biomarkers has been extensively studied for both healthy and diseased subjects[18]. These studies have reported inconsistent results concerning the effect of exercise on the levels of specific oxidative stress biomarkers, a fact that, at least partially, may be attributable to differences in the training status, dietary intake, age and gender of subjects, type of exercise test (mode aerobic or anaerobic, duration and intensity), sampling time points, tissue sampled and the assays used among the studies.

Exercise and Down syndrome

The mitochondrial respiratory chain is believed to be the major cellular source of free radical generation during exercise[19,20]. Mitochondrial anomalies and dysfunctions are present in DS, which are directly related to the presence of oxidative stress[21]. Moreover, in addition to generation through mitochondrial electron transport, RONS can be produced through a number of alternative pathways during exercise. This is the case of the enzyme XO, whose activity has been found increased in DS[22] and it has been suggested that this enzyme may be more important than mitochondria as a source of exercise-induced free radicals[23]. Thus, mitochondrial dysfunction and the excess in XO activity found in DS lead to think that exercise may exacerbate oxidative stress and tissue damage in these subjects compared to patients without DS.

However, results reported in literature seem to show a beneficial effect of exercise on DS subjects, although the effect of exercise on oxidative stress parameters has been poorly studied in this condition. Monteiro et al.[24] found significant increases in plasma thiobarbituric acid reactive substance (TBARS) as well as in plasma and erythrocyte glutathione reduced (GSH) and glutathione oxidized (GSSG) in adults with DS after a 16-week training program. Besides, they also found that exercise did not significantly alter erythrocyte SOD1 activity, as it was also reported in a later study. Other antioxidant enzymes have been evaluated in DS subjects after an exercise program. Thus, increased activity of erythrocyte glucose-6-phosphate dehydrogenase (G6PDH), GPx[25] and GR[26] has been found in adolescents with DS, whereas not significant changes have been reported for erythrocyte CAT[26]. Lipid peroxidation was also evaluated by Ordoñez et al.[27] in adolescents with DS and, in contrast to Monteiro et al.[24], they found decreased levels of methylene dioxy amphetamine (MDA) after a very similar exercise program, so discrepancies in results could be due to methodological differences. Supporting the results of Ordoñez et al.[27], it has been reported that lipid hydroperoxides decreased in saliva samples of DS subjects after an exercise program of slight intensity[28]. Campos et al.[29] have found that the daily practice of physical exercise of moderate intensity reduces the urinary excretion of UA in DS individuals. On the other hand, it has been recently reported that exercise significantly reduced protein oxidation, measured as plasma protein carbonyl content, in adolescents with DS[30] and also plasma allantoin in the same population[31]. Since both plasma protein carbonyls and allantoin levels have been found increased in children with DS[32,33], exercise may improve health of this subjects.

The effect of exercise on total antioxidant capacity (TAC) has also been evaluated in DS and no significant effect was reported, in blood[34] or in saliva[28] samples. Moreover, levels of the ratio thiols/total proteins in plasma samples remained stable after exercise in DS, although these levels were lower over the entire physical activity test in DS compared with non-Down controls[34]. In contrast, blood TAC was higher in DS subjects than in non-Down controls after exercise[34]. Authors suggest that the greater TAC in DS participants during exercise might reflect a greater ability to mobilize blood-borne antioxidants due to chronic oxidative

stress. In our opinion, increased levels of UA during exercise could be another possible explanation for these results, even more when XO activity is increased in DS. In fact, it has been reported that high UA concentration increases serum antioxidant capacity and reduces exercise induced oxidative stress in healthy subjects[35]. Campos et al. 2013[29] have observed that physical exercise performed daily decreases urine UA levels in DS. However, Zambrano et al. [28] found that exercise had no effect on salivary UA of DS participants. Therefore, more studies are necessary to clarify these hypotheses.

Data pointed to a greater ability to mobilize bloodborne antioxidants or a significant increase of antioxidant enzymes activity (G6PDH, GPx and GR) by exercise in DS subjects as the possible causes of the decrease of oxidative stress by exercise. Thus, exercise does not alter CAT and SOD1 activities, but induces increased GPx activity in erythrocytes of these subjects. Since erythrocyte SOD1 activity seems to be increased in this disorder[42] and GPx is more efficient in scavenging H_2O_2 than CAT[43], exercise could compensate the imbalance of this enzymes protecting against oxidative stress in DS.

On the other hand, resistance exercise and endurance training cause adaptive responses of gene expression in nuclear and mitochondrial genomes in the skeletal muscle[44]. However, changes of gene expression induced by physical activities and its relation with the gene-dosage imbalance in DS have not yet been studied. Therefore, more well-conducted studies which examine long-term physical outcomes, adverse effects and psychosocial outcomes are needed to reach firm conclusions.

Conclusions

Down's syndrome individuals generally tend to be sedentary, however physical activity has the potential to improve their health when is practised regularly. Thus the strength of publishing works like ours, that show the advantages that performing physical exercise may bring, should help raise awareness that it is a tool that could improve their quality of life.

Search strategy and selection criteria

A literature search was performed using the electronic databases PubMed, Scopus, Google Scholar and SciFinder (1866 onwards). We focused on recently publications, but did not exclude commonly referenced and highly regarded older publications. Further PubMed searching was performed by using the "see all related citations" function by manual scanning of the reference lists of several review articles, as well as original investigations. Articles from all languages were included. The following search terms were included in multiple combinations: "Down syndrome", "trisomy", "oxidative stress", "oxidative damage", "nitrosative stress", "lipid peroxidation", "antioxidant "biomarker", "MDA", "TBARS", "4-hydroxy-2-nonenal", "carbonyls", dityrosine", "homocysteine", "glutathione peroxidase", "catalase", "glutathione reductase", "antioxidant enzyme", "glutathione", "uric acid", "vitamin", "thiol", "total antioxidant capacity", "allantoin", "xanthine oxidase", "xanthine oxidoreductase", "exercise", "physical activity". The search was conducted between September 2013 and March 2014.

Conflict of interests

Authors declare not to have any conflict of interests.

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