

Blood Zinc Levels and Oxidative Stress Parameters in Children and Adolescents with Down Syndrome

Keywords: Down syndrome; Oxidative stress; Zinc

Abstract

Down Syndrome (DS), or trisomy 21, occurs in one out of 700-1000 live births. It is commonly observed that DS patients present obesity and zinc deficiency. Zinc deficiency could be related to overactivity of the enzyme Cu/Zn Superoxide Dismutase (SOD) in these individuals. As a result of this overactivity, individuals with DS are in a state of continuous Oxidative Stress (OS). The aim of this study was to evaluate the nutritional status of individuals with DS, and to measure dietary zinc intake and blood zinc levels, as well OS markers, especially SOD. There were twenty-five children in the DS group aged between 2 and 19. In the control group, there were thirty-two individuals with the same age profile. There was an increased percentage of obesity and overweight in the DS group patients. There was no inadequate consumption or blood zinc deficiency in either group. We observed a reduction in the antioxidant enzymes SOD and Catalase (CAT) in the DS group as well as an increase in thiobarbituric acid-reactive substances (TBARS). This suggests a state of OS in the DS group. Unlike other studies, this study found no zinc deficiency or SOD overactivity in individuals with DS compared to the control group. There was OS in these patients as evidenced by higher levels of TBARS. However, unexpectedly, this elevation was related to a reduction of SOD and CAT activity. It is suggested that more studies should be conducted in this area to clarify the issue.

Abbreviations

DS: Down Syndrome; Zn: Zinc; OS: Oxidative Stress; SOD: Superoxide Dismutase Enzyme; CAT: Catalase Enzyme; TBARS: Thiobarbituric Acid Reactive Substances

Introduction

Down syndrome (DS) is a genetic disorder mostly associated with trisomy 21 [1]. It occurs in one out of 700-1000 live births. Clinical symptoms were described first and the association with an extra copy of chromosome 21 was later reported [2,3]. Complete trisomy 21 is now established as the major cause of DS, accounting for 90-95 per cent of cases. The remaining 5-10 per cent is caused by other genetic abnormalities including translocations (2 to 6%) and mosaicisms (2 to 4%) [4,5].

Characteristic facial features present in DS patients facilitate clinical diagnosis. Up-slanting palpable fissures, typically flat face, short neck, and hypotonia are examples of dysmorphic features. There is increased risk for respiratory infections, leukemia, heart problems, mental retardation and gastrointestinal tract obstruction. In adolescence DS patients commonly present hypothyroidism, and in older adulthood they often develop Alzheimer's disease. Many findings suggest overweight and obesity in DS children, which may be related to poor eating habits and inactivity, along with a basal



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metabolic rate less than that of the healthy population [6,7].

Another issue involving the nutrition of patients with DS is zinc deficiency. Several studies have shown changes in tissue distribution of zinc in individuals with DS, contributing to the clinical manifestations of this syndrome [8-14]. Zinc has catalytic, structural and regulatory functions. It participates in the processes of growth and development, reproduction, immunity, antioxidant protection, stabilization of cell membranes and genetic expression. In addition, zinc is critical for energy metabolism as a catalytic component of more than 300 metalloenzymes involved in the metabolism of proteins, lipids, carbohydrates and nucleic acids [15].

It is important to highlight the relationship of zinc with the antioxidant enzyme Cu/Zn-superoxide dismutase (SOD), which may have impaired function in the context of zinc deficiency. The gene encoding this enzyme is located on the human chromosome 21. Therefore, by definition, DS individuals are trisomic for this SOD isoform. In this sense, SOD is over expressed in about 50 per cent of these individuals [16].

SOD catalyzes the conversion of superoxide anion (O₂^{•-}) into hydrogen peroxide (H₂O₂). Both reactive oxygen species (ROS) are continuously generated in the mitochondria through the aerobic respiration. Subsequently, CAT and glutathione peroxidase (GPx) convert hydrogen peroxide to water and molecular oxygen. Hydrogen peroxide produced in excess is a result of increased SOD activity without the concomitant increase of other antioxidant enzymes mentioned above. Finally, the accumulation of hydrogen peroxide, which is highly diffusible and relatively stable, is thereafter able to generate other deleterious ROS, damaging important cellular components, oxidizing biomolecules including amino acid residues, proteins, lipids and DNA [17,18].

In view of the above, it is important to investigate the correlation between zinc levels in these patients and the levels of oxidative stress (OS). Such an investigation may be relevant to improvements in the quality of life for these patients.

Zinc is a mineral that can aid in the treatment of DS because it is a potent antioxidant and is an important cofactor for Cu-Zn SOD. The aim of this study was to evaluate the nutritional status of individuals with DS, the dietary zinc intake and blood zinc levels, as well as OS markers, particularly SOD.

Material and Methods

Study design

A cross-sectional study was conducted in children and adolescents diagnosed with DS (DS Group) (n=25) aged 2 to 19 years (mean age 11.8 ± 5.72) of both sexes, that were recruited from special schools (denominated APAEs in Brazil) in micro-region municipalities in Capanema, Paraná, Brazil. The control group (C Group) (n=32) consisted of healthy children aged 2 to 19 years (mean age 14.7 ± 4.8) of both sexes who were recruited from schools in the same districts.

All patients received information regarding the study and their parents signed an informed consent form.

This clinical research was approved by the ethics committee on human research at the Federal University of 'Fronteira Sul', under the protocol number 36031814.3.0000.5564.

Anthropometric measurements

Height and weight were measured using a portable stadiometer and a digital scale with a capacity of 150 kg, respectively. Both parameters were measured with children wearing light clothing and no shoes. The body mass index (BMI) was calculated and data were expressed weight, eutrophic, overweight or obese. For evaluation of nutritional status in the DS group, we used growth curves from Cronk et al. which were adapted curves for DS patients by age [19]. For participants in the control group, we used growth curves proposed by the World Health Organization [20, 21].

Review of clinical manifestations and health conditions

We evaluated the presence of clinical manifestations of DS in participants, including hypotonia, protuberant language, height, weight, flat nose, epicanthal folds, small ears, small ear lobes, neck and short fingers, and large space between the first and the second toe. We also investigated the occurrence of the disturbances related to DS, including complications related to the nervous system, thyroid gland, eye, liver, bone marrow, lung, aortic arch, heart, pancreas, kidneys, adrenals, small intestine, gall bladder, intestine, and the knee and hip joints.

We ran a questionnaire to analyze the health status of individuals, addressing issues of pathological disorders in general, lifestyle habits and medication use.

Dietary intake of zinc

The analysis of dietary intake of zinc was estimated using a food frequency questionnaire (FFQ) containing source foods nutrient and a 24-hour dietary recall (24 form). Subsequently, we calculated the

food intake of zinc by Ava nutri 9.0.

Sample blood collection

Blood samples were collected from all participants (C and DS groups) and were placed in tubes containing EDTA. First, a small aliquot of whole blood was separated in order to determine zinc levels. Subsequently, the rest of the whole blood sample was centrifuged at 3400 rpm for 15 min to separate plasma and erythrocytes fractions for further analysis. These were, cooled and transported to the Analytical Chemistry and Biochemistry Laboratories of the Federal University of Santa Maria-UFSM, Rio Grande do Sul, Brazil, where the analysis was conducted. The plasma samples were utilized to quantify lipid peroxidation (TBARS) and vitamin C levels, while erythrocytes samples were utilized to quantify SOD and CAT activities. The methodology used for each measure is described below.

Determination of blood zinc levels

The determination of blood zinc levels was carried out using an inductively coupled plasma optical emission spectrometer with axial view configuration (SpectroCiros CCD, Spectro Analytical Instruments, Germany) equipped with a cross-flow nebulizer coupled to a Scott double pass-type nebulization chamber. The wavelength used was 213.856 nm, the plasma power was set at 1400 W, and the argon flow-rate was 14 L min^{-1} (plasma), 1 L min^{-1} (nebulizer) and 1 L min^{-1} (auxiliary). A stock solution of 1000 mg L^{-1} of Zn (Titrisol, Merck, Germany) was used to prepare standard solutions. Samples were analyzed after previous digestion of about 500 mg of blood with 6 mL of double distilled nitric acid (Merck) in open vessels, using conventional heating. The heating program was (i) $80 \text{ }^\circ\text{C}$ for 10 min; and, (ii) $140 \text{ }^\circ\text{C}$ for 120 min. After cooling, the digests were diluted with ultrapure water up to 50 mL in a polypropylene vessel.

Thiobarbituric acid reactive substances

The thiobarbituric acid reactive substances (TBARS) assay measures peroxidative damage to lipids that occurs by excessive ROS generation. Lipid peroxidation was estimated in plasma according to the method of Lappena D et al. using 1% phosphoric acid and 0.6% thiobarbituric acid (TBA) [22]. The pink chromogen produced by reaction of TBA with malondialdehyde (MDA) and other minor aldehydes was measured spectrophotometrically at 532 nm. The results were expressed as nmol TBARS/mL plasma, using MDA as standard [22].

Catalase enzyme activity

Catalase (CAT) activity was measured by the method of Aebi H [23]. Packed erythrocytes were hemolyzed by adding 100 volumes of distilled water. Then 20 μL of the hemolyzed sample was added to a cuvette and the reaction was started by the addition of 100 μL of freshly prepared 300 mM H_2O_2 solution in phosphate buffer (50 mM, $\text{pH} 7.0$) to a final volume of 1 mL. The rate of H_2O_2 decomposition was measured spectrophotometrically at 240 nm for 120 s. CAT activity was expressed as $\mu\text{mol H}_2\text{O}_2/\text{mL erythrocytes/min}$ [23].

Superoxide dismutase enzyme activity

Superoxide dismutase (SOD) activity was measured according to the method of Misra HP et al. [24]. Briefly, epinephrine rapidly auto oxidizes at $\text{pH} 10.5$ producing adrenochrome, a pink colored

product that can be detected at 480 nm. The addition of samples containing SOD inhibits epinephrine auto-oxidation. The inhibition rate was monitored for 150 s at intervals of 10 s. The amount of enzyme required to produce 50% inhibition at 25 °C was defined as one unit of enzyme activity. SOD activity was expressed as USOD/mL erythrocytes [24].

Vitamin C

Plasma vitamin C (VIT C) levels were estimated as described by Galley HF et al. with some modifications by da Silva DL et al. (2001) [6,25]. Plasma was precipitated with 1 volume of a cold 5% trichloroacetic acid solution followed by centrifugation. An aliquot of 300 µL of the supernatants were mixed with 2,4-dinitrophenylhydrazine (4.5 mg/mL) and 13.3% trichloroacetic acid and incubated for 3 h at 37 °C. Then, 1 mL 65% sulfuric acid was added to the medium and the orange red compound was measured at 520 nm.

Statistical analysis

Data were evaluated by student’s t-test for independent samples when required. The multiple linear regression test was applied to verify the correlation between serum zinc levels and nutritional assessment, food consumption and manifestations of DS. Data were analyzed using Statistica software, version 11.0. Significance was defined as p<0.05. The figures were drawn using GraphPad Prism®, version 5.0.

Results

Anthropometric measurements

Anthropometric measurements are shown in Figure 1. There was a higher percentage of obesity and overweight in the DS group (33.3%) and in the C group (18.8%).

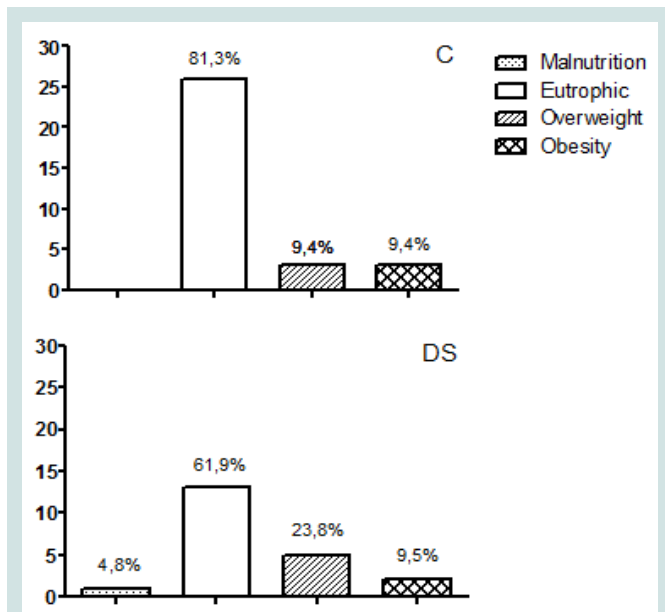


Figure 1: Results of anthropometric measurements carried out from the BMI calculation comparing C (n=32) and DS (n=21) groups. Group C - classification in WHO [20,21]. Group DS-classification in Cronk C et al. [19].

Table 1: Percentage of pathologies observed in the DS group (n=25).

| Pathology in DS | n | % |
|------------------------------------|----|----|
| Respiratory dysfunction | 13 | 54 |
| Thyroid dysfunction | 8 | 33 |
| Cardiovascular diseases | 6 | 25 |
| Dermatitis | 6 | 25 |
| Gastrointestinal tract obstruction | 2 | 8 |
| Epilepsy | 1 | 4 |

Table 2: Percentage of clinical manifestations observed in the DS group (n=25).

| Clinical manifestations of the DS | n | % |
|--|----|----|
| Dysmorphicears | 19 | 79 |
| Slanting eyelids | 17 | 71 |
| Large, protruded and grooved tongue | 15 | 63 |
| Short, wide hands | 15 | 63 |
| Curved 5 th finger | 14 | 58 |
| Separation between the 1 st and the 2 nd toe | 14 | 58 |
| Flat profile | 12 | 50 |
| Lower nasal bridge | 11 | 46 |
| Palmar single fold | 7 | 29 |

Review of health conditions and clinical manifestations of DS

With respect to primary pathologies observed in the DS group, the most frequently observed were: respiratory problems (54%), followed by thyroid dysfunction (33%), heart disease (25%), dermatitis (25%), gastrointestinal problems (8%) and epilepsy (4%) (Table 1).

The clinical manifestations of DS observed in DS group are shown in Table 2. The clinical manifestations most often observed were: dysmorphic ears (79%), upward slanting eyelid (71%), large, protruded and grooved tongue (63%), short wide hands (63%), curved 5th finger (58%), separation between the 1st and the 2nd toe (58%), flat profile (50%), lower nasal bridge (46%) and single palmar crease (29%).

Dietary intake of zinc

Dietary zinc intake was measured by analyzing the 24-hour recall and Food Frequency Questionnaire (FFQ) (Figure 2). No significant differences were observed between the groups, and consumption was adequate for both groups.

Determination of blood zinc levels

Regarding blood zinc levels, no significant differences were observed between the control and DS groups (Figure 3) and both groups had normal levels of this micronutrient.

Analysis of oxidative stress markers

The OS analysis is shown in Figure 4. There was lipid peroxidation in the DS group, demonstrated by significantly higher TBARS levels in the DS group in relation than in the C group. However, SOD and CAT activities in erythrocytes were significantly lower in the DS group than in the C group. Plasma VIT C levels showed no significant difference between groups.

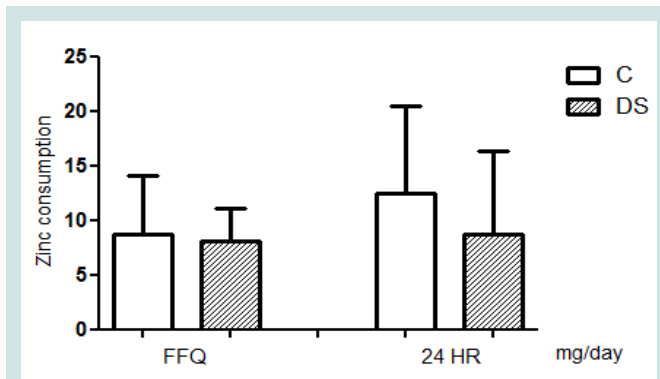


Figure 2: Comparison of dietary zinc intake between the C (n=32) and DS (n=25) groups, calculated from the 24-hour recall and food frequency questionnaire.

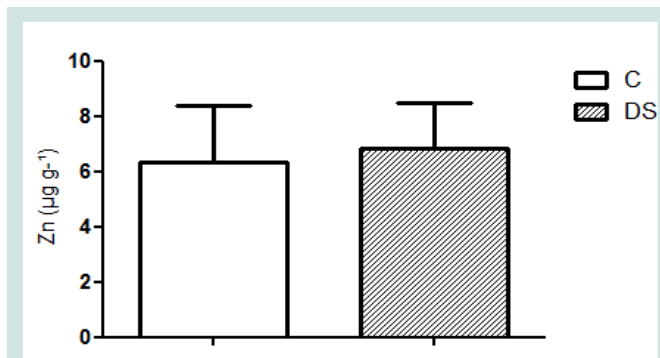


Figure 3: Comparison of blood zinc levels in groups C (n=31) and DS (n=22).

Discussion

We observed a higher percentage of obesity and overweight in children and adolescents with DS (33.3%) compared to children and adolescents without the syndrome (18.8%), fact that was also confirmed in the study by Brasil JS et al. where there was a higher percentage of obesity in the same age group [26]. According to Foerste T et al. obesity and overweight in children with trisomy 21 may be related to hyperphagia and physical inactivity [27]. Mazurek D et al. reported that overweight or obesity associated with slow metabolic rate, abnormal concentrations of leptin in the blood and low levels of physical activity [28].

The clinical manifestations found in children and adolescents with DS in this study are in agreement with dysmorphic features described for DS patients [29]. Dysmorphic features of DS affect whole body function and play a significant role in screening and diagnosis. They are mostly concerned with the face, eyes, ears, nose and limbs.

Regarding the pathologies observed in DS patients in this study, there was a higher percentage of a respiratory disease (54%). DS is associated with high morbidity because of underlying associated conditions, including congenital heart defects, respiratory diseases, gastrointestinal tract malformations, predisposition to infectious diseases and leukemia. It is important to analyze and monitor continuous health status of these patients in order to increase their life expectancy [30].

Both the DS and C groups had sufficient zinc consumption, according to dietary reference intake (DRIS-2002), that suggested values of 8 to 11 mg/day of the mineral for children and healthy adolescents. We also observed that the main food sources of zinc consumed by children were milk, rice and black beans. Other studies had similar results to those found here [31-33].

We did not observe significant differences in whole blood levels of zinc between groups, a result similar to that observed in the study of Soler Marin S et al. [7]. We conclude that zinc consumption and absorption was adequate. Other previous studies analyzed zinc levels in other compartments and returned different results. Matin MA et al. and Martins MP analyzed plasma zinc and observed normal levels in the samples studied [34,35]. Licastro F et al. and Soto-Quintana M et al. found reduced levels of plasma zinc in DS patients [10,11]. Lima AS et al. and Marques RC et al. analyzed zinc in plasma, erythrocytes and urine and reported reduced levels of zinc in plasma and urine and increased levels in erythrocytes [12-14].

According to the literature, the decrease of plasma-free zinc and an increase in erythrocytes is related to increased SOD activity, which is expected in patients with Trisomy 21, since this enzyme is responsible for encoding the gene located on chromosome 21. Furthermore, zinc is a co-factor for SOD enzyme and is therefore essential important for its function.

Because SOD is located in erythrocytes and requires zinc to remain active, we expected to find more zinc in erythrocytes and less zinc in plasma and urine. In fact, we observed that zinc levels did not decrease. We might have expected SOD activity increase because SOD activity would require more zinc than normal in DS patients and would cause a total body deficiency of the mineral [8].

However, this study found low SOD activity in erythrocytes of patients with DS compared to the control group, the opposite of what we expected. We also observed significantly reduced levels of antioxidant enzyme CAT and increased TBARS levels in the DS group. This can be explained by the fact that SOD was significantly low, with free superoxide leftover and little hydrogen peroxide formation, thus reducing CAT activity. Because of this, excess of superoxide could

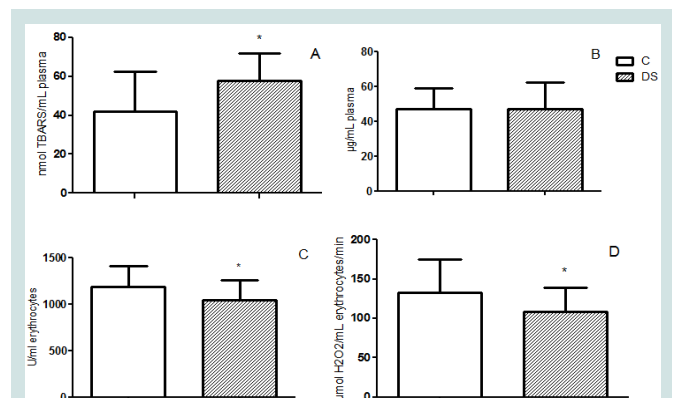


Figure 4: Oxidative stress (OS) markers analysis in C (n=25-27) and DS groups (n=15-17). (A) Plasma lipid peroxidation (TBARS levels). (B) Plasma vitamin C (VIT C) levels. (C) Erythrocyte superoxide dismutase (SOD) activity. (D) Erythrocyte catalase (CAT) activity. Asterisks (*) indicate significant difference from C group.

cause lipid peroxidation, as verified by the increase of TBARS.

Suggest the presence of an OS state in DS patients demonstrated by elevated plasma TBARS levels, suggesting lipid peroxidation, and decreased antioxidant enzymes SOD and CAT. SOD is the key enzyme required for the removal of O₂ by converting it to hydrogen peroxide (H₂O₂), which catalyzed by CAT and peroxidases. CAT helps neutralize the toxic effects of H₂O₂ by converting it to water and non-reactive oxygen species, thus preventing the generation of hydroxyl radicals and protecting cells from oxidative damage [36].

A study similar to ours showed different results, with levels of SOD and CAT significantly increasing with weight with DS and normal levels of TBARS compared to a healthy group [15]. Another study also observed 28% higher levels of SOD in DS patients compared to a control group [37]. Further studies are needed to verify the cause of these effects.

Conclusion

We observed that the zinc consumption and blood zinc levels were adequate. SOD activity was decreased, not using large amounts of zinc for its action. In addition to SOD, CAT also decreased, causing an excess of ROS that led to lipid peroxidation. All these associated events may indicate an increase in OS in these patients. More research should be conducted in this area to clarify these issues, with a larger number of participants and better monitoring.

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