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EFFECT OF SUPERVISED PHYSICAL EXERCISE ON OXIDATIVE STRESS IN CHILDREN WITH AUTISM

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[A] Study Design; [B] Data Collection; [C] Statistical Analysis; [D] Manuscript Preparation

Abstract Background: The etiology of autism spectrum disorders is not well known but oxidative stress has been suggested to play a pathological role. Purpose: The present study aimed to investigate the effects of supervised physical exercise on oxidative stress in children with autism. Methods: Thirty boys with autism (7 to 9 years old) voluntarily participated in this study. They were randomly divided into experimental and control groups. The experimental group performed a physical curriculum known as sports, play and active recreation for kids (SPARK) for 12 weeks (3 sessions of 45 minutes per week), while the control group was exempted to participate in the program. As the clinical parameters, the level of brain-derived neurotrophic factor (BDNF) and malondialdehyde (MDA) were measured before and after the intervention. Results: The results indicated that BDNF levels significantly increased (85.7 %) and MDA concentration significantly decreased (29.2%) in the experimental group ($p < 0.05$). Conclusions: In conclusion, the supervised physical exercise may result in less oxidative stress in children with autism.

Key words: exercise training, oxidative stress, BDNF, malondialdehyde, autism

Introduction

Autism is one of the most complex childhood psychiatric disorders whose effects usually continue through the life (Mirzavandi et al., 2023). Recently, Centers for Disease Control and Prevention (*Morbidity and Mortality Weekly Report)* reported that one in 36 (2.8%) 8-year-old children have been identified with autism spectrum disorders (ASD) (*Autism Prevalence Higher, According to Data from 11 ADDM Communities*, 2023).

ASD's etiology is complex, and it may be due to the interaction of genetic and environmental factors (Zhang et al., 2021). Clinical evidence suggests that immunological dysregulation, inflammation, oxidative stress, mitochondrial dysfunction, and excitotoxicity are key components in ASD pathogenesis (Liu et al., 2022; Shen et al., 2020). Many markers of oxidative stress, such as malondialdehyde (MDA) are elevated in children with ASD (Chauhan et al., 2004). MDA is an indicator of lipid peroxidation as it increases following liver damage. Besides, the expression of Brain Derived Neurotrophic Factor (BDNF) which has a crucial role in survival and differentiation of neuronal populations during development is usually changed in children with ASD. The increased oxidative stress markers have been observed to be correlated with ASD severity (Ghezzo et al., 2013).

A curriculum known as sports, play and active recreation for kids (SPARK) is a physical program for living better along with enjoyment. This program has been designed in a way that it includes guidelines from the National Association of Physical Education and Sports, a program which is flexible enough and increases the cooperation of participants (McKenzie et al., 2016). This motor program may be welcomed by children with autism because of its liveliness, freshness and variety of games. By our knowledge, no previous study has investigated the effects of SPARK program on oxidative stress in ASD. Therefore, this study aimed to investigate the effects of a supervised physical exercise program on oxidative stress in children with autism.

Methods

This research was carried out according to the ethical principles of the World Medical Association (Declaration of Helsinki, 1993) and was approved by the ethics committee of the Islamic Azad University, Tehran's Science and Research Branch (project identification code: 920000427, 4.11.1395).

Subjects

Thirty boys with autism ranging from 7–9 years old from Imam Hassan Mojtaba institute in Shiraz (the capital of Fars province of Iran) voluntarily took part in the present study. Participants were randomly divided into experimental (n = 15) and control (n = 15) groups. The criteria for entering the study included: lack of heart, respiratory or orthopedic infectious and epilepsy diseases, not being prohibited to do physical activities, not using any certain medications that may have positive or negative effects on the results of blood samples, and finally having parent or legal guardian's consent form to participate in the research protocol. A subject was excluded from the study if he was absent in 3 consecutive or 4 nonconsecutive training sessions. To prevent participants from being excluded, however, the program was set to be conducted between class times and a make-up session was considered if necessary.

Study design

The present study was a semi-quasi study with pre-test, post-test, and control group during which the effectiveness of SPARK program on oxidative stress in children with autism has been investigated. To perform the study, first the method of doing study and considered objectives were explained shortly to the parents through a letter and they were asked to sign the consent form if they are satisfied with their children's participation in the study. Then, all participants had pre-test blood sample. After that, the experimental group participated in the SPARK program for 12 weeks (3 sessions of 45 minutes each week). This program included 10 minutes of body warm up, 10 minutes of physical activities, 20 minutes of recreational and fun games followed by 5 minutes of cooldown activities. The control group didn't participate in such intervention and they had their normal life and daily routine activities.

Measurements

To measure MDA and brain-derived neurotrophic factor (BDNF), the blood samples were taken from children's forearm vein. The blood samples were taken 24 hours before the start of intervention program (pre-test) and 48 hours after the end of week 12 (post-test), to make sure that the immediate effects of the intervention are removed. Then, the samples were transferred to the lab and were centrifuged at 3000 rpm for 10 minutes to separate the serum from plasma. After the separation serum from plasma, MDA and BDNF were measured by ELISA method using a special kit (Eastbiofarm, China) with the accuracy of 0.01 ng/ml.

Statistical Analysis

The skewness and kurtosis were used to examine the normal distribution of data. ANCOVA test was used to determine if significant ($P < 0.05$) differences existed among the groups for MDA variable between before and after exercise training. Post-test was the dependent variable; group was the fixed factor and pre-test was the covariate. Due to the skewed nature of the BDNF levels, Mann-Whitney U test was used to determine if significant ($P < 0.05$) differences existed among the groups for this variable between before and after training. The relationship between changes of MDA and BDNF was determined using Spearman correlation test. Data was analyzed using SPSS 22.0 statistical software. The level of significance in all statistical analyses was set at $P < 0.05$.

Results

Anthropometric measurements related to the experimental and control groups are presented in Table 1.

Table 1. Anthropometric parameters of the participants in each group (mean ±SD)

Variables	Experimental group	Control group
Height (cm)	140.5 ±8.0	140 ±8.0
Weight (kg)	33.1 ±5.8	31.1 ±4.9
Body mass index (kg/m^2)	16.6 ±1.2	15.7 ±1.4

The data on MDA concentration of the experimental and control group is presented on Figure 1. The results indicated that MDA concentration decreased after 12 weeks physical exercise compared to the control group (29.2%).

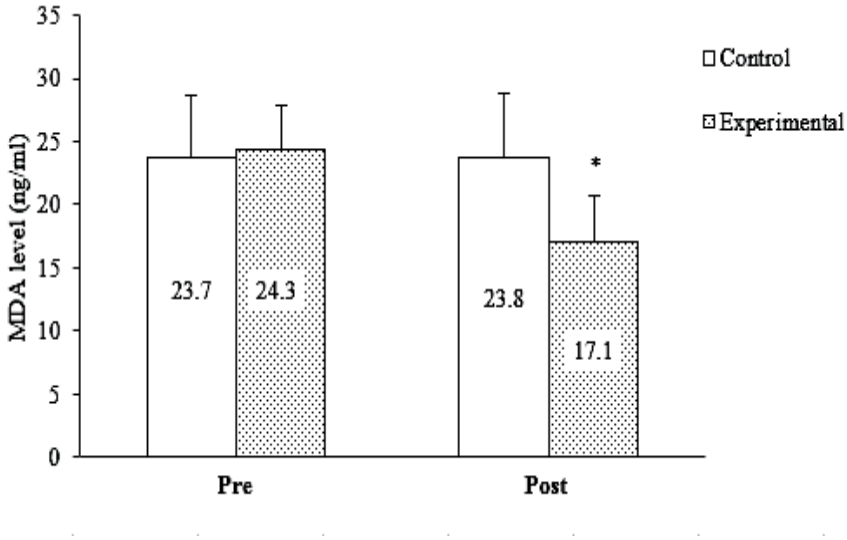

Figure 1. Changes of MDA in response to 12 weeks of supervised physical exercise. * Significant differences between group ($P < 0.05$)

The data on BDNF concentration of the experimental and control group is presented on Figure 2. The results on Mann-Whitney U test indicated that BDNF concentration increased in the experimental group compared to the control group ($Z = -3.5$; $p = 0.001$; 85.7%).

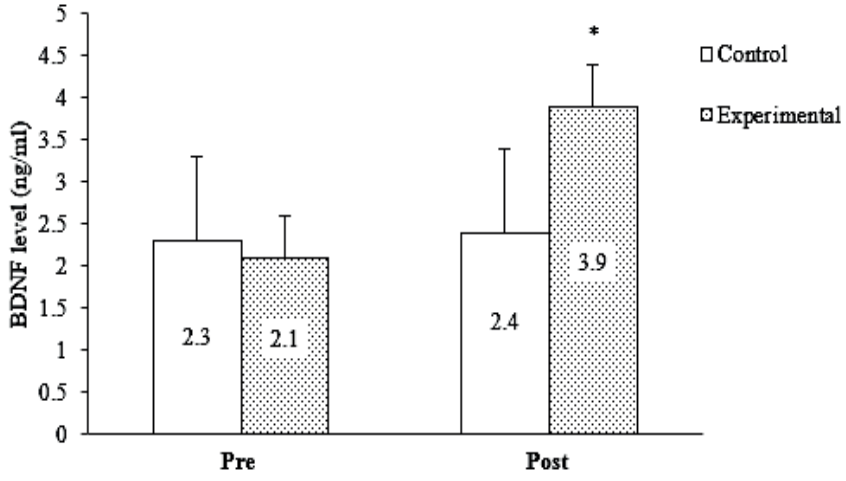

Figure 2. Changes of BDNF in response to 12 weeks of supervised physical exercise. * Significant differences between group ($P < 0.05$)

Spearman correlation demonstrated an inverse relationship between MDA levels and BDNF ($r = –0.73$, $P = 0.002$).

Discussion

The purpose of this study was to examine the effects of 12 weeks supervised physical exercise on oxidative stress in children with autism. The study results indicated that MDA concentration decreased after 12 weeks physical exercise compared to the control group. In line with the present study, recently, Mirzavandi et al. (2023) had been reported that moderate-intensity exercise training decreases MDA in rat model of autism (Mirzavandi et al., 2023). There is evidence that exercise training specifically promotes the upregulation of antioxidant defenses by elevating the activity of catalase (CAT) and total antioxidant capacity (TAC) (Sabet et al., 2022). Previous studies showed that regular exercise training decreased oxidative stress and promoted the upregulation of antioxidant factors by increasing the activity of superoxide dismutase (SOD), gluilktathione peroxidase (GPX) and CAT (Ennezat et al., 2001; Mirzavandi et al., 2023).

Autism is a neurodevelopmental disorder and BDNF plays an important role in neurodevelopment (Zaki et al., 2022). Recent studies have provided evidence to support the involvement of BDNF in autism through its neurotrophic effects on the developing brain (Han et al., 2022). Clinical studies indicated that BDNF levels are lower in the ASD cases than in the normal cases (Barbosa et al., 2020; Skogstrand et al., 2019). The BNDF concentration of plasma in normal people increases in the first few years after birth, and decreases slightly in adulthood. However, the opposite status is shown in ASD patients (Liu et al., 2020). Thus, it seems that due to their low expression in the early stages of development, ASD patients have a group of neurodevelopmental disorders.

The results of our research in confirmation of Al-Ayadhi's findings (Al-Ayadhi, 2012) showed that there is a direct relationship between BDNF and oxidative stress (MDA) in patients with autism. Thus, it seems that physical exercise training induced increase in BDNF concentration is responsible for MDA decreases in children with autism. In line with the present study, Zong et al. (2023) have reported that exercise training increases BDNF in ASD. Regulation of BDNF appears to be dependent on the calcium/calmodulin-dependent protein kinase II (CaMKII) signaling pathway and the cAMP response element-binding protein (CREB). Gomez-Pinilla et al. (2011) demonstrated that 3 months of exercise training increased BDNF gene expression within the hippocampus and researchers suggested that these observations were due to activation of CaMKII and CREB. On the other hand, cortisol inhibits hippocampal BDNF production and resting BDNF level has inverse relationship to the cortisol concentration (de Assis & Gasanov, 2019), thus exercise- induced changes on BDNF levels are related to blood cortisol levels.

Conclusions

In conclusion, according to the present study results, it can be suggested that supervised physical exercise (SPARK program) improves oxidative stress in boys with autism to some extent by increasing BDNF.

We had some limitations in this study. We did not measure antioxidant markers such as SOD and GPX and cortisol. If we could measure these items, we could explain the effects of physical exercise on MDA in children with autism with more precision. Therefore, future studies are highly recommended to measure more clinical factors if they intend to investigate the effects of physical exercise on MDA in children with autism. Moreover, Regulation of BDNF appears to be dependent on the calcium/calmodulin-dependent protein kinase II (CaMKII) signaling

pathway and the cAMP response element-binding protein (CREB). Thus, it would be worth checking the expression of molecules involved in the above signaling pathway before and after physical exercise.

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Data availability The data associated with the paper are not publicly accessible, and they can be available from the corresponding author on reasonable request (e-mail: mehrzad.moghadasi@gmail.com).

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