An Acad Bras Cienc (2024) 96(3): e20231132 DOI 10.1590/0001-3765202420231132
Anais da Academia Brasileira de Ciências | *Annals of the Brazilian Academy of Sciences*
Printed ISSN 0001-3765 I Online ISSN 1678-2690
www.scielo.br/aabc | www.fb.com/aabcjournal

HEALTH SCIENCES

The relationship of cognitive functions with brain damage markers, myokines and neurotrophic factors in amateur soccer players

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Abstract: Concussive and subconcussive head impatcs in sports have drawn more attention in recent years. Thus, the cognitive ability of soccer players and its relationship with circulating levels of irisin, brain-derived neurotrophic factor (BDNF), and neuron-specific enolase (NSE) were studied in this study. Fifteen amateur soccer players and 15 sedentary men volunteered to participate in this study. After evaluating the aerobic and anaerobic capacities of the participants, their cognitive performances were measured. Blood samples were obtained at rest, and the ELISA method was used to measure the concentrations of serum NSE, plasma BDNF, and irisin. There were no differences between groups in terms of cognitive abilities or serum NSE levels ($P > 0.05$). Plasma irisin ($P = 0.019$) and BDNF ($P < 0.001$) levels were higher in the soccer players than the sedentary subjects. There was a positive correlation between irisin and NSE ($r = 0.461$, $P = 0.010$) and BDNF ($r = 0.405$, $P = 0.007$) concentrations. General cognitive performance is maintained in amateur soccer players. This is accompanied by the unchanged NSE. However, elevated irisin and BDNF levels appear to be independent of cognitive performance.

Key words: BDNF, Cognitive performance, irisin, NSE; soccer, subconcussion.

INTRODUCTION

Soccer is in many ways one of the most popular sports in the world (Kunz 2007). Although soccer players are not in the high-risk group, they may suffer a concussion due to contact with the ball, other players, the ground or goal posts during match or training (Hanlon & Bir 2012), and 5.8-22% of all football injuries are due to these reasons (Levy et al. 2012, Hubertus et al. 2019). Most of the time, these blows to the head are referred to as subconcussive head blows (Díaz-Rodríguez & Salvatore 2019), and it has been documented that both former and current football players may experience anatomical, functional, and behavioral changes in their brains as a result of repeated exposure to these impacts (Ling et al. 2017, Tarnutzer et al. 2017). Although there are studies investigating cognitive functions in soccer players, their results are inconsistent. While some studies suggested a relationship between repeated heading and cognitive impairment (Tysvaer & Løchen 1991, Matser et al. 1998, 2001, Downs & Abwender 2002, Webbe & Ochs 2003, Rutherford et al. 2005, Lipton et al. 2013, Koerte et al. 2017, Stewart et al. 2018), others found no evidence of a relationship (Janda et al. 2002, Straume-Naesheim et al. 2005, Vann Jones et al. 2014, Kemp et al. 2016, Rodrigues et al. 2019).

In recent years, several neurochemical markers such as S100β, neuron specific enolase (NSE), and brain-derived neurotropic factor (BDNF) have been focused on to provide diagnostic and prognostic information in

concussion research. In this framework, the relationship of concussion and subconcussion caused by repetitive head blows in soccer players with these biomarkers was investigated by evaluating them in blood and cerebrospinal fluid (CSF) (Maher et al. 2014, Kawata et al. 2016). NSE is an enzyme involved in glycolysis in neurons and released into the circulation after neuronal damage (Pelinka et al. 2005, Papa 2016). NSE level is affected by ischemia, and neurodegenerative conditions (Cao et al. 2008, Polcyn et al. 2017). There is a correlation between the neuronal loss and increased NSE concentrations in blood and CSF (Kawata et al. 2016). Stålnacke et al. (2004, 2006) found that serum NSE level was increased after the soccer match and was not related to the number of headings.

BDNF, a member of the neurotrophin family, is a protein molecule primarily synthesized in neurons. BDNF has various neuroprotective effects such as neurogenesis, axonal growth, inhibition of neurodegeneration, and hippocampal neuroplasticity (Pedersen 2019). In addition to its known roles in brain and cognitive functions, it may be a reliable marker of brain damage and microtrauma (Rodrigues et al. 2016). In support of this hypothesis, it has been reported that repeated heading increases circulating BDNF levels and this may be related to the recovery of possible trauma-related damage to the central nervous system (CNS) (Rodrigues et al. 2016, Bamaç et al. 2011).

Irisin, cleaved version of fibronectin type III domain-containing protein 5 (FNDC5), is defined as a myokine which secreted after muscle contraction (Boström et al. 2012). Irisin is also expressed in the brain, particularly in the hippocampus (Qi et al. 2022, Tanhaei et al. 2018). It has been reported that irisin exerts neuroprotective effects by stimulating neurogenesis, cell proliferation and neural synaptic plasticity, both in physiological and neurodegenerative conditions (Islam et al. 2021, Lourenco et al. 2022, Kam et al. 2022). Moreover, FNDC5/irisin promotes BDNF expression in the hippocampal region (Wrann et al. 2013, Belviranlı & Okudan 2018). Also, it has been asserted that irisin protects against traumatic brain injury and may be able to enhance cognitive performance following acute brain injury (Guo et al. 2021, Tu et al. 2020).

Here, we conducted a cross-sectional study design to examine the cumulative effects of the concussive and subconcussive head impacts in the soccer players. Therefore, this study was aimed to determine whether there are differences in cognitive functions and levels of various biochemical markers such as NSE, BDNF, and irisin between soccer players and sedentary subjects. This study also explores the possible interaction between the measured parameters.

MATERIALS AND METHODS

Subjects

Fifteen male amateur soccer players competing at the regional amateur league and 15 sedentary controls almost similar age, anthropometric characteristics, and education level volunteered to participate in this study. Body fat percentage of the soccer players was lower than that of the sedentary controls. Subjects' characteristics are shown in Table I.

The soccer players have been involved in regular training for 9.0 ± 3.2 years on average. They have been trained at least 3 days per week and performing 1.5-2 h/day of training on average.

All participants had to be between 20 and 25 years old, and soccer players needed to have played the soccer for at least five years in order to be included. A history of a head injury, neurological condition, or a clinical diagnosis

Table I. Characteristics and aerobic and anaerobic performances of participants (mean ± standard deviation).

	Sedentary	Soccer players	P
n	**15**	**15**	
Age (years)[a]	23.00 ± 1.20	22.40 ± 1.60	0.174
Weight (kg)	74.78 ± 12.55	71.11 ± 7.94	0.346
Height (cm)	174.47 ± 4.78	178.07 ± 4.10	**0.035**
BMI (kg/m^2)	24.50 ± 3.27	22.41 ± 2.28	0.053
Body fat (%)	17.37 ± 3.64	14.07 ± 3.36	**0.015**
VO_{2max} (ml/kg/min)	28.17 ± 3.63	42.76 ± 5.80	**0.000**
Peak power (W)	1050.22 ± 209.65	1039.93 ± 149.58	0.878
Mean power (W)	509.51 ± 82.90	564.63 ± 47.78	**0.034**
Fatigue index (%)	80.78 ± 5.91	74.76 ± 4.90	**0.005**

[a]**Mann-Whitney U test, BMI: body mass index, VO_{2max}: Maximal oxygen consumption.**

of a learning disability during the previous 12 months were also exclusion factors. Also, none of the subjects used hormone therapy, alcohol, or antioxidant supplements.

Selcuk University Medical Faculty Institutional Review Board approved the study (2018/4), and all procedures were carried out in compliance with the Helsinki Declaration. All participants received signed informed permission after being informed about the study.

Study design

In this cross-sectional design, all participants visited the laboratory 4 times at least 24 hours apart. During their first visit, the 20-meter multistage shuttle test was performed and maximal oxygen consumptions (VO_{2max}) were calculated. At their second visit, anaerobic performances were measured with the Wingate Anaerobic test. At their third visit, cognitive capacities were assessed using the Mini-Mental State Examination (MMSE) and the Isaacs' Set Test (IST) of verbal fluency. At their fourth and final visit, after overnight fasting, venous blood samples were taken for analysis for NSE, BDNF and irisin levels. In order to avoid the acute effect, the soccer players were tested at least 48 hours after the last training or competition.

Measurement of aerobic and anaerobic fitness

Aerobic capacity of the participants was estimated using the 20-m multistage shuttle run test (Léger & Lambert 1982, Léger et al. 1988). During this test, subjects were asked to run continuously with a sound signal between two cones placed 20 m apart. The speed gradually increased at each stage. The test was terminated until the subject exhausted or failed to reach one of the cones a second time before the corresponding beep. The VO_{2max} values were determined using the equation proposed by Larsen et al. (2002).

Anaerobic capacity of the participants was measured using the Wingate Anaerobic test. The test was performed on the Monark 894Ea bicycle ergometer (Peak Bike, Monark Exercise, Sweden). Participants were informed about the exercise protocol before the test. The participants were seated on the bike, the seat and handlebar adjustments were made, and the feet were fixed on the pedal. After a warm-up period of 5 minutes without load, the test phase was started. A 75 g/kg body weight resistance

was used for the Wingate test. The participants were instructed to pedal as quickly as possible during the test, and when their pedal speed hit 100 rpm, the specified load was immediately placed to the flywheel and the 30-s test started. Participants were verbally motivated during the test.

Assessment of cognitive function

Two cognitive tests were performed in this study. The MMSE is an overall score that assesses various dimensions of cognition (Folstein et al. 1975). A higher score (which goes from 0 to 30) indicates stronger cognitive function. The IST is a test that evaluates verbal fluency abilities and verbal production speed (Isaacs & Kennie 1973). During testing, subjects must provide a list of words that belong to a particular semantic category (cities, colors, animals, and fruits) in a given time. Higher results on the IST scale, which goes from 0 to 40, indicate superior verbal fluency skills.

Blood sampling

After a 12-hour night fast, venous blood samples were collected from the subjects a day following the cognitive assessments in EDTA-coated, non-additive tubes. Blood samples taken into non-additive tubes were kept at room temperature for 30 minutes and then centrifuged at 3200 rpm for 30 minutes and serum samples were separated (NF1200R, Nüve, Ankara, Turkey). Blood samples taken into EDTA-coated tubes were immediately centrifuged at 3200 rpm for 10 minutes and plasma samples were separated. Samples were stored at -80°C until biochemical measurements were made.

Biochemical analysis

Serum NSE, plasma FNDC5/irisin, and BDNF concentrations were measured using commercially available kits (Cat. No: E-EL-H1047; E-EL-H2254; E-EL-H0010, respectively. Elabscience Biotechnology, Co., Ltd, Wuhan, China). These kits use the principle of sandwich enzyme-linked immunosorbent assay (ELISA). An ELISA spectrophotometer (Powerwave XS, Biotek, USA) was used to detect optical density at 450 nm. Intra- and inter-assay CV values was < 10%. BDNF concentration were expressed as pg/mL. Irisin and NSE levels were expressed as ng/mL.

Statistical analysis

Mean and standard deviation are used to present descriptive statistics. The Shapiro-Wilk test was used to determine the normality of each variable, and then Student's t-test for variables with normal distribution and Mann-Whitney U test for variables with non-normal distribution were used to compare mean values between groups. For analysis of bivariate correlation, Spearman correlation coefficient was used. The threshold for significance was set at 5% (P 0.05). With SPSS, all statistical evaluations were done (v.25.0, IBM Inc., USA).

RESULTS

Table I shows the aerobic and anaerobic performance indices of the groups. As expected, VO_{2max}, an indicator of aerobic capacity, and average power, an indicator of anaerobic power, were higher in the soccer players than the sedentary subjects ($P < 0.05$). Fatigue index was lower in the soccer players ($P < 0.05$). However, peak power was not different between groups ($P > 0.05$).

Cognitive test scores of groups are showed in Table II. The scores of the MSSE and IST tests were not different between the groups ($P > 0.05$).

Circulating NSE, irisin and BDNF levels of the two groups are shown in Table II. Plasma irisin and BDNF concentrations were higher in the

Table II. Cognitive test scores and measured biochemical parameters of the subjects (mean ± standard deviation).

	Sedentary	Soccer players	P
n	**15**	**15**	
Mini–Mental State Examination[a]	28.67 ± 1.80	28.67 ± 0.98	0.461
Isaacs' Set Test of Verbal Fluency	36.13 ± 2.72	36.07 ± 2.19	0.942
NSE (ng/mL)[a]	13.16 ± 5.49	18.84 ± 8.53	0.089
Irisin (ng/mL)[a]	5.85 ± 0.78	6.44 ± 0.88	**0.019**
BDNF (pg/mL)[a]	322.31 ± 173.61	613.48 ± 232.67	**0.000**

NSE: Neuron specific enolase; BDNF: Brain-derived neurotropic factor.
[a]Mann-Whitney U test.

soccer players. ($P < 0.05$). However, NSE levels were not different between the groups ($P > 0.05$).

Statistical analysis results of linear correlations between cognitive test scores and measured biochemical parameters are shown in Table III. No correlation was found between MMSE and IST scores and NSE, irisin and BDNF ($P > 0.05$; Table III). In addition, there was a positive correlation between irisin and NSE and BDNF ($P < 0.05$; Table III). However, there was no correlation between NSE and BDNF ($P > 0.05$; Table III).

DISCUSSION

The main consequences of our study are as follows: (1) there is no difference in MSSE and IST scores between soccer players and sedentary controls, (2) soccer players have higher irisin and BDNF concentrations than sedentary controls, (3) there is no difference in circulating NSE levels between soccer players and sedentary controls, and (4) irisin concentration is positively correlated with BDNF and NSE levels.

In the current study, there was no difference in MSSE and IST test scores between soccer players and sedentary subjects. In a limited number of studies conducted to date, the cognitive functions of the soccer players associated with concussion have been evaluated and it has been reported that cognitive functions are impaired (Matser et al. 1998, Downs & Abwender 2002) or unchanged (Straume-Naesheim et al. 2005, Rodrigues et al. 2019, Strauss et al. 2021). Interestingly, Stewart et al. (2018) showed that heading frequency rather than unintentional head impacts was associated with cognitive performance in amateur soccer players. In a systematic review published in recent years, it was emphasized that heading does not have a short-term effect on cognitive performance, and there is a lack of studies evaluating its long-term effect (McCunn et al. 2021). There was no correlation between head injury and neuropsychological performance in young soccer players, according to Janda et al. (2002) and Stephens et al. (2005). In terms of brain microstructural characteristics and cognitive ability, Strauss et al. (2021) did not discover a significant difference between amateur soccer players and inactive subjects. According to Prien et al. (2020), most neurocognitive test results were comparable, with the exception that retired elite female soccer players fared worse on verbal memory and fluency tests than non-contact sports controls. This may be due to the fact that the soccer players in our study, as in other studies, were relatively young (22.40 ± 1.60) and their sports ages were relatively low (9.0 ± 3.2). Additionally, differences in sample size, educational status, and methods of assessing cognitive functions in these studies may play a role here.

Table III. Spearman's correlation coefficients between cognitive test scores and measured biochemical parameters of groups.

	MSSE score		IST score		NSE		Irisin	
	r	P	r	P	r	P	r	P
NSE	- 0.249	0.184	0.282	0.131	-	-	-	-
Irisin	- 0.180	0.341	- 0.158	0.405	0.461	**0.010**	-	-
BDNF	- 0.079	0.679	- 0.181	0.338	- 0.145	0.446	0.405	**0.027**

MMSE: Mini–Mental State Examination; IST: Isaacs' Set Test of verbal fluency; NSE: Neuron specific enolase; BDNF: Brain-derived neurotropic factor.

We demonstrated in this study that there was no difference in blood NSE levels between soccer players and sedentary controls, and there was also no correlation between serum NSE levels and cognitive test results. NSE controls axonal transport in the brain, and the expression of this protein varies according to the cell's need for energy. NSE expression is increased in axon damage. Therefore, NSE is accepted as a marker of neuronal damage (Kawata et al. 2016, Papa 2016). Studies in athletes to date have generally examined acute changes in the NSE after competition (Stålnacke et al. 2004, 2006). In this context, it has been shown that serum NSE levels increase after an actual soccer match compared to pre-match in both male (2004) and female (2006) players. Because both concussive and subconcussive hits are known to be hazardous, athletes who are repeatedly exposed to head impacts should be extremely concerned about permanent neurological impairment (Papa et al. 2015). Accordingly, biomarkers of the brain injury can remain elevated even after discontinuation from sports. Although there are a limited number of studies (Zetterberg et al. 2009) examining the cumulative changes that may occur as a result of repeated blows, there are no studies specifically in the soccer players. Zetterberg et al. (2009) reported that NSE levels in boxers were higher than controls even after 2 months of nonparticipation in boxing. The half-life of serum NSE is 24-48 hours and peak serum levels are reached within 6 hours after brain injury. These findings therefore suggest that NSE can be released into the peripheral circulation after recurrent brain injury, even in the absence of head trauma (Kawata et al. 2016). The fact that concussion and subconcussion in soccer players in this study was not evaluated with brain imaging methods such as diffusion tensor imaging, magnetic resonance spectroscopy, transcranial sonography and electroencephalography seems to be the most important limitation of the study. However, since NSE is considered one of the markers of brain damage (Papa 2016), changes in NSE level can provide information about the presence or degree of concussion and subconcussion.

In our study, mean serum NSE levels were 13.16 and 18.84 ng/mL in controls and football players, respectively. When NSE levels in humans were examined, Liu et al. (2019) reported that serum NSE levels in healthy adults aged 20-29 ranged between 13.7 and 15.8 ng/mL. Stålnacke et al. (2004, 2006) showed that the average serum NSE concentrations in male and female football players were 8.57 and 9.05 ng/mL, respectively, and increased to 10.29 and 10.14 ng/mL immediately after the football match. Stefanović et al. (2017) reported that serum NSE levels were 32.5 to 52.5 ng/mL immediately after traumatic brain injury in humans and gradually decreased in the following days. Therefore, it

can be said that the serum NSE levels measured in our study are within the expected ranges.

Our research demonstrates that amateur soccer players' irisin levels were substantially higher than those of the sedentary controls. It can be concluded that this difference is the result of the soccer players' higher aerobic and anaerobic capacity given the similarity in age and anthropometric features between the two groups. Gaudio et al. (2021) demonstrated that soccer players have higher irisin levels than inactive individuals, which is consistent with our findings. In support of these findings, Kurdiova et al. (2014) showed that irisin levels typically correlated with the volume and intensity of physical activity. Irisin has neuroprotective effects in the brain, especially in the hippocampus, once it is released from the skeletal muscle and passes through the blood-brain barrier (Wrann 2015). Irisin has also been demonstrated to have protective benefits against neurodegenerative diseases including Alzheimer and Parkinson (Zhang et al. 2022) as well as traumatic brain injury (Guo et al. 2021). Furthermore, irisin has anxiolytic and antidepressant effects (Jodeiri Farshbaf & Alviña 2021). In our study, although irisin was not correlated with cognitive test scores, its positively correlated with NSE. Since NSE increases to maintain homeostasis after neuron damage (Pelinka et al. 2005), the correlation of irisin level with NSE supports its neuroprotective effect. Consistent with these findings, a prior study (Belviranlı et al. 2016) found that pentathletes and other endurance athletes had higher resting irisin concentrations than sedentary controls. We also demonstrated a favorable link between the results of cognitive function tests such the MSSE and IST. The fitness and exercise capacity of the study groups may be a factor in the variations in the outcomes. In addition, the participants' exposure to concussion and subconcussion may explain the difference in the studies.

In this study, one of our aims was to compare baseline BDNF levels with the soccer players and the sedentary controls and to reveal the possible relationship between cognitive test scores and other biochemical parameters. In this study, plasma BDNF concentrations were higher in the soccer players. Although it is commonly recognized that exercise is a useful tactic for raising BDNF levels, (Zoladz et al. 2008, Szuhany et al. 2015) there is a dearth of information on soccer. There are limited studies (Bamaç et al. 2011, Williams et al. 2020) investigating BDNF levels in soccer players, and some of these studies have focused on the change in BDNF levels after a soccer match or repetitive heading. Williams et al. (2020) reported that serum BDNF levels did not change in male adolescents after a 60-minute soccer match. Similarly, Bamaç et al. (2011) showed that serum BDNF levels increased after repetitive heading in male soccer players. In the light of these findings, it has been claimed that repetitive heading and/or microtrauma caused by the survival process of injured neurons may cause increased BDNF levels. However, contrary to these findings, Zetterberg et al. (2009) reported that there was no difference between boxers and sedentary controls in terms of basal serum BDNF levels. Based on these results, it is difficult to say whether the high BDNF levels observed in soccer players are the result of endurance training or repeated microtrauma. Additionally, in the present study, BDNF was not correlated with either cognitive test scores or NSE. Aerobic exercise training has been shown to directly regulate the PGC-1α/FNDC5/BDNF pathway in the hippocampus (Wrann et al. 2013, Belviranlı & Okudan 2018). Thus, exercise increases hippocampal FNDC5/irisin expression in a PGC-1-dependent way, which in turn causes an increase in hippocampal BDNF expression

(Schnyder & Handschin 2015). These results indicate a strong association between BDNF and irisin. We also examined the connection between BDNF and irisin in soccer players and found a positive association between them to support this theory. As a result, one of the molecular mediators of exercise-induced neurogenesis is FNDC5/irisin.

The following list of limitations applicable to this study. First, this study was cross-sectional; A long-term study should be conducted to confirm these findings. The second limitation is that players' total headings or blows during a training session or match are not evaluated. Therefore, it was assumed that all soccer players were hit with equal severity. The lack of a specific cognitive performance test is the third disadvantage. Another limitation of the study is that concussion and subconcussion status of the soccer players were not evaluated with brain imaging methods.

The current study shows that circulating BDNF and irisin concentrations of the amateur soccer players are higher than sedentary controls, but their cognitive test performance and NSE levels are not different. It has also been shown that there is a positive correlation between irisin and BDNF and NSE. However, more detailed research is needed to further delineate the effect of repetitive heading on brain function in the soccer players.

Acknowledgments

This work was supported by the Selçuk University Scientific Research and Project Coordinatorship (project number: 18202013).

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How to cite
IPEKTEN E, BELVIRANLI M & OKUDAN N. 2024. The relationship of cognitive functions with brain damage markers, myokines and neurotrophic factors in amateur soccer players. An Acad Bras Cienc 96: e20231132. DOI 10.1590/0001-3765202420231132.

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