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The evaluation of superoxide dismutase 1 gene insertion/deletion variant in athletes

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SUMMARY

OBJECTIVE: Regular exercise benefits health by increasing the body's antioxidant defenses. However, excessive exercise can produce excessive reactive oxygen species, which can lead to oxidative stress. Superoxide dismutase is the primary enzyme involved in the elimination of reactive oxygen species. This study aimed to determine the relationship between the *SOD1* gene insertion/deletion variant and elite athletes.

METHODS: A total of 305 subjects, including 165 elite athletes from different branches and 140 sedentary individuals, participated in this study. The *SOD1* insertion/deletion variant was genotyped using polymerase chain reaction. The results were evaluated statistically.

RESULTS: There was no statistical significance between the athletes and control groups in terms of *SOD1* insertion/deletion genotype distribution and allele frequency. Then, we evaluated the groups as females and males. There were no female athletes carrying the D/D genotype. The *SOD1* I/I genotype and the I allele were more prevalent in female athletes than in the control group. There was a significant difference in terms of *SOD1* I/I: I/D+D/D in females (p=0.028). *SOD1* genotype and allele distribution did not differ between male athletes and male controls.

CONCLUSION: As far as we know, this is the first study to evaluate the *SOD1* insertion/deletion variant in athletes in Turkey. Our results showed that the *SOD1* I allele was more common in female athletes, but not in male athletes.

KEYWORDS: Sport. Performance. Superoxide dismutase. Variant. PCR.

INTRODUCTION

Physical inactivity is a known risk factor for the development of several diseases, such as obesity, diabetes, and cardiovascular disease. The beneficial effects of regular moderate-intensity exercise are indisputable[1]. Regular physical exercise also improves mental health by positively changing symptoms of depression[2]. In addition, physical exercise facilitates social interaction with positive results for quality of life[2]. Cells constantly produce free radicals and reactive oxygen species (ROS) through metabolic processes. Oxidative stress (OS) results from an imbalance between the production and accumulation of ROS in cells and tissues and the body's ability to detoxify these reactive products. Physical activity increases the formation of free radicals in various ways. Notably, 2–5% of the oxygen used in the mitochondria forms free radicals. As oxidative phosphorylation increases in response to exercise, there will be a concomitant increase in free radicals[3]. Oxidants produced in skeletal muscles are derived from two main molecules: superoxide and nitric oxide.

Superoxide dismutases (SODs) are the most important enzymes that perform antioxidant enzyme defense against ROS and superoxide anion radicals[4]. SOD1 (CuZn-SOD), which is one of the SOD isoenzymes, carries Cu and Zn in their catalytic centers. The other is SOD3 (EC-SOD), which is localized in extracellular elements. SOD1 is found in the cytoplasm, nuclear compartments, and lysosomes of mammalian cells[5]. The *SOD1* gene, which is located on chromosome 21 (region 21q22) in humans, contains four introns and five exons. It is hypothesized that *SOD1* gene mutations may impair antioxidant enzyme activity, resulting in the accumulation of toxic superoxide anions[6]. Numerous genetic polymorphisms in the *SOD1* gene affect regulatory regions, including the promoter region, UTRs, and introns. Several studies have linked *SOD1* variants to an increased risk of diabetes, cardiovascular disease, heroin addiction, breast cancer, and type 1 bipolar disorder[7]. A functional variant called the 50-bp insertion/deletion (I/D) polymorphism (rs 36232792) (1684 bp upstream of the ATG start codon) has been identified in the promoter region of the *SOD1* gene. *SOD1* I/D variant deletion (D) allele changes gene

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expression and results in lower levels of SOD1 mRNA[8]. Based on this information, we aimed to evaluate the *SOD1* I/D variant in elite athletes in this study.

METHODS

Study population

Our research group consisted of 165 athletes who regularly trained at least four times a week (44 females and 121 males, mean age: 22.02±2.87 years) from different sports branches representing the Faculty of Sport Sciences, Samsun. The control group consisted of 140 age- and gender-matched voluntary sedentary individuals (46 females and 94 males, mean age: 22.42±2.91 years) studying at Samsun. The age of all subjects was higher than 18 years, and they were from the Turkish population in the Northern Black Sea region. The demographic data of participants such as age, height, weight, body mass index (BMI), number of daily cigarettes, monthly alcohol consumption, sports branch, family history, disease status, and how many years they have been involved in sports were collected. All subjects submitted informed written consent before enrollment in the study, based on the ethical guidelines of the Declaration of Helsinki, and the Samsun Ethical Committee approved the investigation.

Genotyping

DNA was extracted from all peripheral blood samples using a commercial isolation kit (Zymo Research Kit). The *SOD1* variant was genotyped using a polymerase chain reaction (PCR) method. A total volume of 50 µL was used for the PCR, which included 25 L of Master Mix OneTaq and 1 L of forward primer (10 µM) F:5'-AATTCCTTACCCCTGTTCTA-3', 1 µL reverse primer (10 µM) R:5'-GGCAGATTTCAGTTCATTGT-3', and 2 µL PCR grade dH2O[9]. The PCR program was performed as follows: initial denaturation at 94°C for 5 min, denaturation at 94°C for 20 s, binding of the primer at 54°C for 30 s, elongation at 68°C for 40 s, and final elongation at 68°C for 5 min. The amplified PCR product was separated on a 2% agarose gel at 100 V for 25 min. Genotypes were detected as 247 base pairs (bp) of the D/D genotype, 297 bp of the I/I genotype, and 247 and 297 bp of the I/D genotype, consisting of two bands. To check the results, 10% of the randomly selected samples were reworked, and a 100% match was found.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (IBM SPSS Statistics, version 21) and the OpenEpi Info software package version (www.openepi.com). The relationship between the demographic and clinical characteristics of the patients was analyzed using the χ^2 test or analysis of variance statistics. Differences in *SOD1* I/D genotype and allele distribution between patient and control groups were evaluated with the chi-square test, and Fisher's exact test was used when needed. OR and 95%CI were also calculated. $p<0.05$ were considered significant.

RESULTS

A total of 305 subjects were evaluated in this study. The mean age of 165 athletes aged between 18 and 30 years was 22.02±2.87. BMD was analyzed as a continuous variable. The baseline clinical and demographic characteristics of patients and controls are reported in Table 1.

Table 1. Demographic characteristics of the subjects.

Characteristics	Athletes (n=165) (%)	Controls (n=140) (%)
Gender		
Female/male, n (%)	44/121 (26.7/73.3)	46/94 (32.9/67.1)
Age (years)		
mean±SD	22.02±2.87	22.42±2.91
min–max	18–30	18–30
Weight (kg)		
40–49	1 (0.6)	0
50–59	23 (13.9)	15 (10.7)
60–69	45 (27.3)	40 (28.6)
70–79	53 (32.1)	40 (28.6)
80–89	23 (13.9)	25 (17.9)
90–99	16 (9.7)	18 (12.9)
100–109	4 (2.4)	2 (1.4)
Height (cm)		
150–159	6 (3.6)	4 (2.9)
160–169	25 (15.2)	19 (13.6)
170–179	75 (45.5)	72 (51.4)
180–189	33 (20)	33 (23.6)
190–200	26 (15.8)	12 (8.6)
BMI		
Lower than 18.5	1 (0.6)	1 (0.7)
18.5 up to 25	133 (80.6)	106 (75.7)
25 up to 30	28 (17)	31 (22.1)
30 and above	3 (1.8)	2 (1.4)

Continue...

Table 1. Continuation.

Characteristics	Athletes (n=165) (%)	Controls (n=140) (%)
Smoking (day)		
0	136 (82.4)	98 (70)
5–9	8 (4.8)	8 (5.7)
10–15	21 (12.7)	34 (24.3)
Number of alcohol drinks per month		
0	147 (89.1)	115 (82.1)
1–4	1 (0.6)	0
5–9	5 (3)	6 (4.3)
10–14	6 (3.6)	13 (9.3)
15–20	6 (3.6)	6 (4.3)
Sports branch		
Football	38 (23.0)	–
Basketball	36 (21.8)	
Volleyball	62 (37.6)	
Wrestle	29 (17.6)	
Training (week)		
2	1 (0.6)	–
3	53 (32.1)	
4	66 (40)	
5	45 (27.3)	
Family history		
Football	102 (61.8)	128 (91.4)
Basketball	15 (9.1)	8 (5.7)
Volleyball	5 (3)	4 (2.9)
Wrestle	8 (4.8)	0
Judo	28 (17)	0
Athleticism	5 (3)	0
Swimming	1 (0.6)	0
Disease		
No chronic disease	146 (88.5)	127 (90.7)
Chronic disease	19 (11.5)	13 (9.3)
Sports time (years)		
1–5	21 (12.7)	–
6–10	99 (60)	
11–20	45 (27.3)	

BMI: body mass index.

Genotyping results

The prevalence of genotypes I/I, I/D, and D/D profiles for the *SOD1* I/D variant was 72.1, 26.1, and 1.8%, respectively, in athletes, and 65.7, 28.6, and 5.7%, respectively, in the control group. There was no statistical significance between the athletes and control groups in terms of *SOD1* I/D genotype distribution and allele frequency (p>0.05). Table 2 represents the *SOD1* I/D genotype distribution and allelic frequency in the groups.

Then, we evaluated the groups as males and females. *SOD1* I/D genotype and allele distribution in female and male groups are shown in Tables 3 and 4. There were no female athletes carrying the D/D genotype. *SOD1* I/I genotype and the I allele were higher in female athletes than in the control group (p=0.055 and p=0.019, respectively). There was a significant difference in terms of SOD1 I/I: I/D+D/D (p=0.028). *SOD1* genotype and allele distribution did not differ between male athletes and male controls (p>0.05).

DISCUSSION

Physical activity can be defined as any bodily movement produced by skeletal muscles that results in energy expenditure[10]. Physical effort and skills constitute the content of "sport," which is a human activity that can be competitive by nature and organization and has the ability to achieve a result that generally requires physical effort and/or physical skill. Oxidant and antioxidant systems are important in order to ensure the structural integrity of cells and tissues and fulfill their normal functions. Fats, proteins, and other cell parts oxidize if free radical levels exceed antioxidant capacity[11]. Free radicals are short-lived and extremely reactive molecules. These have a detrimental effect because of the necessity to create electronic stability[12]. ROS is constantly produced in small quantities in biological systems. However, there is an increase when they are exposed to environmental and physical stress factors[13]. Exercise is one such stressor. It is thought that the increase in oxygen consumption during exercise leads to changes in the oxidant/antioxidant balance[14]. Studies have shown that an increase in oxygen consumption during exercise promotes the massive leaching of free radicals in the mitochondria and subsequently leads to an antioxidant reaction. Moderate exercise can increase antioxidant levels, facilitating an optimal ROS level, while high-intensity exercise can induce ROS generation, providing maximum cellular adaptation[15]. However, there are data showing that regular long-term training induces an antioxidant response to OS. In a study investigating the relationship between OS and excessive exercise or overreach, it was shown to support the possibility of being useful. This physical exercise reduces OS and may be explained by increased antioxidant defense[16]. Studies in sports involving aerobic metabolism, such as running or swimming, have shown an increase in the activity of antioxidant enzymes, such as SOD or MDA, as well as an increase in free radical production[17].

The SOD enzyme activity encoded by the *SOD1* gene is affected by variants in this gene. Differences in gene sequences determine changes in gene expression, which contribute to disease occurrence[18]. Variants have been identified in the *SOD1* gene, mostly affecting the regulatory regions of the gene. The *SOD1* promoter region harbors binding sites for several transcription factors. Sequence differences in these cis-responsive elements affect the expression of various mRNAs[19]. *In vitro*

Table 2. Genotype distribution and allele frequencies of *SOD1* insertion/deletion variant in groups.

SOD1 I/D	Athletes (n=165) (%)	Controls (n=140) (%)	χ^2	OR (95%CI)	p
Genotypes					
I/I	119 (72.1)	92 (65.7)	0.50	1.20 (0.72–2.00)	0.476
I/D	43 (26.1)	40 (28.6)	2.34	2.83 (0.72–14.02)	0.126
D/D	3 (1.8)	8 (5.7)	3.58	3.43 (0.91–16.3)	0.58
I/I+I/D: D/D	162:3	132:8	3.30	3.26 (0.87–15.4)	0.68
I/I: I/D+D/D	119:46	92:48	1.45	1.34 (0.82–2.20)	0.227
Alleles					
I	281 (85.15)	224 (80)	2.821	1.43 (0.93–2.19)	0.093
D	49 (14.85)	56 (20)			

Table 3. *SOD1* insertion/deletion genotype and allele distribution in the female groups.

SOD1 I/D	Female athletes (n=44) (%)	Female controls (n=46) (%)	χ^2	OR (95%CI)	p
Genotypes					
I/I	36 (81.8)	28 (60.9)	3.66	2.54 (0.95–7.12)	**0.055**
I/D	5 (18.2)	16 (34.8)	0.96	–	0.326
D/D	0 (1.8)	2 (4.3)	2.47	–	0.115
I/I+I/D: D/D	44:0	44:2	1.95	–	0.162
I/I: I/D+D/D	36:8	28:18	4.80	2.85 (1.09–7.90)	**0.028**
Alleles					
I	80 (90.90)	72 (78.26)	5.47	2.76 (1.16–7.03)	**0.019**
D	8 (9.10)	20 (21.74)			

Bold indicates statistically significant values.

Table 4. *SOD1* insertion/deletion genotype and allele distribution in the male groups.

SOD1 I/D	Male athletes (n=121) (%)	Male controls (n=94) (%)	χ^2	OR (95%CI)	p
Genotypes					
I/I	83 (68.6)	64 (68.1)	0.14	0.88 (0.47–1.64)	0.707
I/D	35 (28.9)	24 (25.5)	2.13	2.87 (0.64–15.26)	0.143
D/D	3 (2.5)	6 (6.4)	1.83	2.57 (0.61–13.04)	0.175
II+ID: DD	118:3	88:6	2.01	2.67 (0.64–13.38)	0.156
II: ID+DD	83:38	64:30	0.006	1.02 (0.57–1.83)	0.936
Alleles					
I	201 (83.05)	152 (80.85)	0.35	1.16 (0.70–1.90)	0.553
D	41 (16.95)	36 (19.15)			

assays showed that the deletion of *SOD1* 50 bp has been associated with reduced promoter activity and lower mRNA levels due to the loss of two Sp1 binding sites in cells[20]. As ROS interacts highly with DNA, the Ins/Del genetic variant may play an important role in interindividual differences in maintaining genome integrity[21]. In various studies, antioxidant enzyme gene polymorphisms and antioxidant enzymes have become areas of interest as pharmacological targets to reduce ROS production. It provides a strategy to prevent or slow the progression of oxidative damage in these patients.

In this study, we investigated the *SOD1* I/D variant in athletes. As far as we know, there is no association study with the *SOD1* I/D variant in athletes. The results of the first report to analyze this relationship in athletes showed no significant difference between athletes and controls. However, when we evaluated the groups by gender, we found a significant difference between female athletes and female controls. No female athletes with the *SOD1* I/D variant homozygous D/D genotype were found. It is known that the D allele has a deficient activity effect on the SOD1 enzyme. This leads to insufficient cellular protective mechanisms and antioxidant defense capacity. The relationship between sex and OS is important because OS has played a role in many diseases that occur differently in men and women. In one study, OS was shown to be higher in male rats than in female rats[22]. Another study reported that in vivo biomarkers of OS were higher in young men than in women of the same age[23]. A study on athletes showed that women have higher resting antioxidant levels than men[24]. Also, it was observed that OS markers increased similarly in both genders after exercise of similar intensity and duration. In this study, we found that I/I genotypes and the I allele were more common in female athletes compared with sedentary female controls. This may be an indicator of higher SOD levels. Also, we found that there was a significant difference in terms of *SOD1* I/I: I/D+D/D in female groups. The genotype and allele distribution were similar in the male group.

Our study has some limitations. As our sample size was not very large, genotyping according to branches was not possible. In addition, the fact that the blood SOD level was not measured was a limitation.

CONCLUSION

Our results showed that the *SOD* I/D variant genotype and allele distribution were different in female and male athletes. In future studies, it will be necessary to genotype male and female athletes in larger sample groups according to branches.

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ETHICAL ASPECTS

Informed written consent was obtained from all subjects before enrollment in the study, according to the Declaration of Helsinki's ethical guidelines, and the investigation was approved by the Ondokuz Mayıs University Ethical Committee (2022/276).

AUTHORS' CONTRIBUTIONS

AFN: Conceptualization, Investigation, Methodology, Project administration, Resources, Validation, Writing – original draft. **ŞÜ:** Conceptualization, Data curation, Investigation, Methodology, Resources, Visualization, Writing – original draft. **SY:** Conceptualization, Formal Analysis, Methodology, Resources, Software, Visualization, Writing – original draft. **ÖMO:** Formal Analysis, Investigation, Resources, Software, Visualization, Writing – original draft. **TA:** Conceptualization, Formal Analysis, Investigation, Methodology, Resources, Supervision, Writing – review & editing.

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