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Review Article

Analyzing Superoxide Dismutase as A Molecular Signal Transducer that is Beneficial for Health during Physical Exercise: A Systematic Review

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ABSTRACT

Physical activity has been considered as one factor that increases oxidative stress. However, the body's natural reaction to exercise might provide more contribution to increase the levels of endogenous antioxidants, including superoxide dismutase. This study aimed to determine how exercise affects the increase in superoxide dismutase enzyme. To reach the objective, the study traced a number of journal databases, including Embase, Pub med, Web of Science, Science Direct, and Scopus. The study considered a number of factors, especially studies that investigated antioxidants, physical activity, and superoxide dismutase. In addition, the studies must have been published within the last five years. Only articles published in non-reputable journals were excluded from our study. A total of 1,026 papers were located using Embase, Web of Science, Pub med, Science Direct, and Scopus databases. About ten carefully selected and peer-reviewed papers addressed the need for this systemic change. Systematic Preferred Reporting and Meta-analysis (PRISMA) items were used in the creation of the standard operating procedures of the investigation. The findings of the systemic analysis showed that exercise has been shown to increase superoxide dismutase levels. The presence of ROS during exercise is what causes the increase. Superoxide dismutase functions as an endogenous antioxidant to reduce free radical production. It is highly recommended to exercise to increase endogenous antioxidant levels which will improve health status. The limitation in this review is only discussing the effect of exercise on increasing SOD. For the next review, the effect of exercise on other endogenous antioxidants such as glutathione peroxidase and catalase can be studied in depth.

Introduction

The scientific advances achieved in the social and medical fields in the 20th century have had a significant impact on increasing life expectancy in modern times, leading to an increase in life expectancy globally (1). This clinical condition is characterized by a number of body systems that are increasingly compromised and highly susceptible to stress, causing a number of physiological systems to become dysregulated (2). This includes various conditions and dynamics that affect the circulatory system and skeletal muscles to be disrupted (3). The process of oxidative stress is triggered by an imbalance between oxidant and antioxidant activity, which can cause oxidative damage at the molecular and cellular levels (4). One of the main causes of the negative impact of oxidative stress is the increase in reactive oxygen species (ROS) (5).

Damage to lipids, proteins, and deoxyribonucleic acid (DNA) in cells caused by oxidative stress can lead to carcinogenesis, aging, neurological disorders, cardiovascular disorders, and autoimmune diseases (6). When the body is in a state of oxidative stress, genes encoding defense enzymes are activated in an effort to counter the effects of reactive oxygen species (ROS) and attempt to restore redox balance (7). On the other hand, ROS are also very important because of their role as signaling molecules to initiate the defense system and the impact of ROS also results in excessive oxidative damage if there is no regulation in order to neutralize it (5). The origin of the formation of ROS during exercise is then discussed in a study, and whether the formation of ROS during exercise is good for health or not is still a debate (8).

Regular exercise being the only health habit associated with reduced human mortality, it therefore seems strange that physical training could increase the formation of ROS that are detrimental to health (9). The knowledge that oxidative stress is closely associated with several chronic diseases, including cancer, cardiovascular disease, hypertension, Alzheimer's disease, and Parkinson's disease, has sparked scientific interest in the debate over whether exercise-induced ROS generation is beneficial or detrimental (10). Exercise has been shown to induce intracellular acidosis, increase O_2 release from erythrocytes, and improve metabolic conditions of glycolysis through glucose and lactate (11). Although erythrocytes are known to have antioxidant capacity that protects them from extreme oxidative stress, it is not known exactly how eccentric exercise affects this capacity (12). Eccentric and concentric exercise can also have an effect on increasing antioxidant levels so that they can counteract oxidative stress disorders caused by physical activity (13).

It is still unclear how physical activity affects cellular antioxidant defense mechanisms and oxidative damage to macromolecules, although there is a marked increase in free radicals and reactive oxygen species (ROS) (11). Free radical biology studies are much influenced by the identification of superoxide dismutase (SOD). Similarly, the subject of muscle redox biology provides important knowledge that skeletal muscle contraction can produce reactive oxygen species (ROS) (14). Empirical evidence shows that endurance training can increase the activity of certain antioxidant enzymes in skeletal muscle, such as superoxide dismutase 1 (SOD1) (14). These results suggest further research to examine how endurance training may affect the levels of three important antioxidant enzymes such as catalase, glutathione peroxidase, and superoxide dismutase (15).

Superoxide dismutase (SOD) is one of the defensive enzymes that serves as the main antioxidant in reducing ROS and its impact on the body. There are three types of SOD: NiSOD, MnSOD/FeSOD, and Cu-ZnSOD (7). Because SOD is essential to protect the body, it can neutralize superoxide anion (O_2^-) into oxygen (O_2) and hydrogen peroxide (H_2O_2), which makes the compound less harmful to human health (7). Animals and humans have the largest skeletal muscles, about 50% of their total mass. This muscle is essential for overall health (16). The increase in cytoprotective proteins, such as SOD, catalase, and heat shock proteins, which prevent oxidative damage, is a beneficial impact of the adaptive response triggered by exercise (17). Although research has extensively investigated the effects of exercise on the body's antioxidant levels, how the cellular systems worksto neutralize ROS during exercise remains unclear. To provide an overview of the mechanisms involved in the increase of SOD in cells during exercise and how it contributes to the improvement of the overall health of the human body, a thorough examination of the phases involved in this process is still needed. Thus, the aim of this systematic review is to try to elucidate the mechanism by which exercise can increase SOD as an endogenous antioxidant in the body.

Subjects and Methods

Study Design

This study looked at and analyzed a number of journal databases, including Pub med, Embase, Web of Science, Science Direct, and Scopus, as part of a systematic review procedure.

Eligibility Criteria

Inclusion criteria for this study were obtained from studies on antioxidants, physical activity, and superoxide dismutase published within the last five years. Papers published in non-reputable journals were included as exclusion criteria among publications that were not included in our analysis.

Procedure

Full text, abstracts, and titles of verified and approved articles were posted to the Mendeley database. Using Embase, Web of Science, Pub med, Science Direct, Scopus, and Web of Science databases, 1,026 publications were placed in the first part of the study. In the second step, 758 entries were evaluated based on how closely the abstract and title adhered to the rules. The third stage consisted of verifying 87 items for further processing. We now filtered based on whether the issue was acceptable for the overall discussion. After careful consideration, ten papers that met the inclusion criteria were selected for this systematic review. Ten publications that met the inclusion criteria were carefully selected and examined for this systematic review. This study supports the assessment of standard operating procedures using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

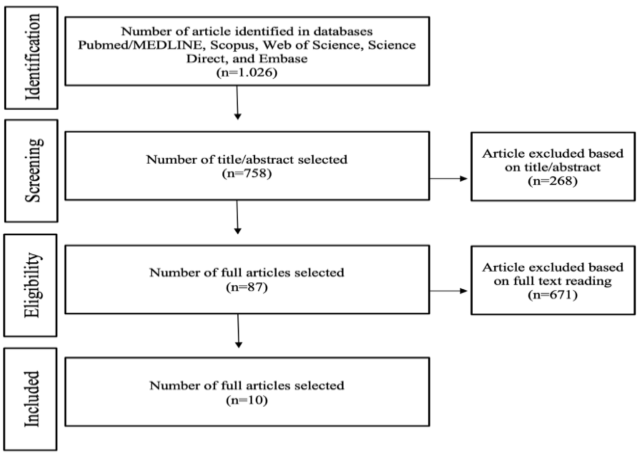

Figure 1: PRISMA flowchart of the article selection process

Results

Author	Sample Characteristics	Study Design	Intervention	Results
(Marsal Rispandi et al., 2022) (18)	The study involved two groups of young people aged 20 to 22 who were not overweight, and had not taken any other supplements or antioxidants within two weeks before and during the study. The sample was divided into two groups: group A with physical therapy intervention but no antioxidants, and group B with physical therapy and antioxidants.	Experimental	Exercise is defined as physical activity that involves running on a treadmill at 70-75% of maximal heart rate. Duration of half an hour, 4 weeks, and 3x/week, regular exercise was performed. The treadmill was built in the physical laboratory of Medan State University. For four weeks, 500 mg of vitamin C was given daily at bedtime.	There was an increase in SOD levels in both the antioxidant and non-antioxidant groups.
(Plasay & Muslimin, 2024) (19)	Five groups of research rats were then formed as follows: a healthy control group, a negative control group, and an antioxidant intervention group that received honey 2.0, 2.5, and 3.0 g/kg BW (grams per kilogram of body weight) twice a week for eight weeks.	Experimental	For eight weeks, five days a week, one hour a day of high-intensity swimming training.	The highest increase in SOD levels occurred in the group given 3.0 g honey/kg body weight.
(Griadhi et al., 2019) (20)	For this study, seven sedentary male subjects with an average age of 17 years were engaged and participated in the study.	Experimental	For three consecutive weeks, 30 minutes of moderate aerobic exercise by running will be given on Monday, Wednesday, and Friday.	After exercise, there is a significant increase in SOD levels.
(Wahyuni et al., 2021) (21)	Thirty-seven participants were randomly divided into two groups: a control group (n=19) and a yoga group (n=18).	Experimental	For eight weeks, there was yoga instruction twice a week. During the study, the control group received no physical exercise.	SOD levels increased in the yoga group.
(Ceci et al., 2020) (22)	In this study, 51 people in good health were divided into four groups: resistance training, endurance training, NMES neuromuscular electrical stimulation, and control.	Experimental	For 12 weeks, there were three physical training sessions per week given to the endurance and resistance training groups.	The resistance training group experienced the greatest increase in SOD levels.
(Kalvandi et al., 2022) (23)	In this study, forty healthy men who had not experienced RT in the year before the trial started gave informed consent and contributed to the study. They were randomly divided into four groups: vitamin D (VD; n=10), EBT-placebo (EP; n=10), vitamin D3 (ED; n=10), and control (Con; n=10).	Experimental	For eight weeks, three times a week on non-consecutive days, seven EBT elastic band resistance training exercises were performed. Every two weeks, the VD, EP and ED groups received 50,000 IU of vitamin D, D3 or placebo.	SOD levels increased overall for all treatment groups. However, the ED group treated with vitamin D3 experienced the greatest increase in SOD.
(Bargujar et al., 2022) (24)	Twenty healthy horses were selected and divided equally between groups I and II.	Experimental	The horse was trained to run 30 kilometers in one two-hour episode.	After receiving the physical activity intervention, group 1 experienced a significant increase in SOD levels.
(Lopes et al., 2021) (25)	In this study, 53 hypertensive patients were divided into two therapy groups: an exercise group (n=26) and a control group (n=27).	Experimental	Aerobic exercise program for 12 weeks; control: normal care.	SOD levels were significantly increased in the group receiving the exercise intervention.
(Hakgüder et al., 2021) (26)	For this investigation, five groups of male Sprague-Dawley rats were used: control (C), elderly (A), elderly with calorie restriction (ACR), elderly who exercised (AE), and elderly who exercised with calorie restriction (ACRE).	Experimental	Rats in the 15-month-old AE group that have undergone six weeks of swimming training. Rats in the 15-month-old ACRE group that had undergone six weeks of calorie restriction training. One way to implement calorie restriction is to feed 40% less than the usual amount. For six weeks, the rats were trained by floating for thirty minutes, three days a week, in a warm pool.	SOD levels increased in the exercising group.
(Lubkowska et al., 2019) (27)	64 albino, male and female. Three groups of 15-month-old Wistar rats were randomly selected. The initial group (long-term control) consisted of eight male and eight female rats. Twelve male and twelve female rats swam in cold water in the second group. Rats in thermonetral water (36 ± 2 ◦C; 12 male and 12 female rats) constituted the third group.	Experimental	For eight weeks, the exercise-trained group swam in a cage for four minutes per day, five days a week. Swimming was done as part of the training in glass tanks with tap water kept at 5 and 36 degrees Celsius. All rats were put to sleep 48 hours after the last session, which marked the completion of treatment.	SOD levels increased significantly in the physical activity group.

Table 1: Results of The Effect Physical Exercise in Increasing Superoxide Dismutase

Discussion

The findings showed that those who exercised on a treadmill at 70-75% of their maximum pulse rate three times a week for four weeks were shown to increase superoxide dismutase (SOD) (18). Physical exercise has been shown to be therapeutic and preventive for several life-threatening diseases including cardiovascular disease, obesity, and cancer (28). The results of a study in men conducted for three consecutive weeks with aerobic exercise and a 30-minute rest period also showed an increase in SOD levels after physical exercise (20). During high-intensity physical exercise, excessive ROS generation suggests that unrelated systems generate significant levels of ROS during exercise and in response to noxious stimuli, as shown in muscle atrophy and immobility (29). However, ROS triggered by exercise will stimulate the regulation of several enzymatic and non-enzymatic antioxidant mechanisms in biological responses (30). Exercise can be a ROS optimizer in eliminating oxidants that also have a role as signaling molecules for muscle adaptation (31). In every aerobic organism, several SOD proteins are strategically arranged in different cellular and subcellular locations (32). One of the best things you can do to improve your health at any age is to exercise regularly. In fact, we think exercise is so proven to have amazing benefits that it qualifies as a medicine (33).

To fight MDA (malondialdehyde), a biomarker of oxidative stress, the body naturally produces antioxidants from the body (4). But if the body is unable to neutralize MDA at higher levels, the body will experience deadly adverse effects (34). A study involving thirteen endurance athletes who performed three different running training modalities, constant running, continuous running at 75% VO2max for twenty-five minutes, and randomized intermittent running also revealed a significant increase in MDA levels (35). In this study, the antioxidant defense enzyme (SOD) also increased after physical activity and decreased during intermittent running training, while oxidative stress damage increased after performing both types of exercise (35). As a physiological reaction to physical activity, an increase in MDA leads to an increase in endogenous antioxidants, one of which is SOD (4). Research from (Wahyuni et al., 2021) specifically doing yoga twice a week for eight weeks had the added benefit of increasing SOD levels after exercise (21). Based on the findings of previous research, those who received a 12-week physical activity intervention three times a week were also shown to have increased SOD levels (22). The balance between the body's oxidation and anti-oxidation systems is critical to human health. On the one hand, the body absorbs oxygen through aerobic metabolism, provides the energy the body needs, and produces oxygen-consuming waste at the same time every day. On the other hand, the kidneys reduce or eliminate the oxidative content of food through various biochemical reactions, and finally achieve a harmonious balance between the antioxidant system and the oxidation system (36).

The results of a study on twenty healthy horses selected and divided equally between groups I and II who were trained to run 30 kilometers in one episode for two hours proved that there was a significant increase in SOD levels (24). The results of another study, namely a 12-week aerobic exercise program in hypertensive patients, were shown to be able to significantly increase SOD levels (25). The results of a six-week study on rats trained by floating for thirty minutes, three times a week, in a warm pool also showed significantly increased SOD levels (26). Physical exercise is one perspective in the effort to remove byproducts of oxidation reactions 37. There are other perspectives why the body's SOD levels increase during exercise, one of which is also driven by supplementation from exogenous antioxidants that come from outside the body (38). As the results of a study that included the use of honey and a combination of high-intensity exercise lasting one hour each day and performed four times a week for a month, also showed a significant increase in SOD levels (19). Over the course of eight weeks, the group of rats trained in swimming exercise for four minutes per day five days a week proved to have significantly increased SOD levels (27). SOD enzymes play an important role in regulating cell growth and are recognized as a major defense mechanism against oxidative stress in aerobic cellular systems (32).

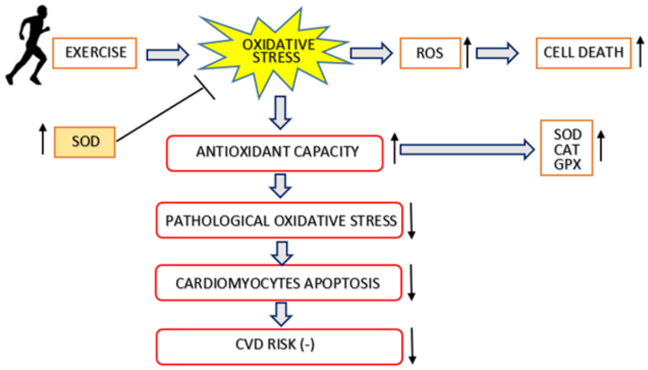

Figure 2: The Mechanisms of Physical Exercise in Increasing Superoxide Dismutase

Most people do sports to keep their weight balanced and achieve an ideal body, besides that, exercise can improve a person's health status and avoid various diseases (39). During functional and strength training, the body will increase oxygen consumption to meet energy production needs (40). During physical exercise, the performance of skeletal muscles has increased function in contracting (41). Mitochondria are considered the "energy powerhouse" of the cell due to their ability to regulate energy metabolism (42). These organelles also regulate important cellular processes, such as calcium homeostasis, and cell survival (42). AMPK activity also increases in response to exercise (43). This increase occurred in the muscles of mice running on a treadmill and in response to electrical stimulation (43). Analysis of mitochondria isolated from the livers of sedentary and exercise-trained mice showed that exercise can counteract the causes of mitochondrial damage by increasing antioxidant enzymes and anti-apoptotic protein expression, reducing ROS production, and the release of cytochrome c from mitochondria (43).

Free radicals are nasty molecules that damage cells (4). Harman, 1956 first discovered the active properties of free radicals and put forward the free radical theory of aging. It is widely believed that most age-related health problems, ranging from wrinkles, and including cardiovascular disease, cancer, and Alzheimer's disease, are related to the excessive accumulation of oxidative stress in the body (8). When the oxidative state increases, enzymatic and non-enzymatic antioxidant systems increase their activity to fight cellular stress (44). Key enzymes and antioxidants involved in the line of defense against oxidative stress include glutathione peroxidase (GSX/Px), superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), carotenoids, flavonoids, ascorbic acid and alpha tocopherol (44). The adverse effects of oxidative stress include damage to nucleic acids, proteins, and lipids (45). When the level of oxidative damage exceeds its repair capacity, cellular damage occurs (46). Disruption of redox balance is also associated with various diseases, aging and carcinogenesis (46). Antioxidants play a very important role in neutralizing ROS (47). SOD is one of the most important antioxidants in neutralizing ROS, located in the mitochondria, and the results of the study also prove that there is an increase in SOD levels after HIIT physical exercise (47). SOD is responsible for the conversion of O2- into H2O2. Although H2O2 is not radical, it is able to diffuse to form more reactive species (14). Therefore, it is important to remove H2O2 in order to eliminate ROS that adversely affect cell damage. There are several enzymes that also play a role in removing H2O2, such as glutathione peroxidase and catalase (14). CAT is an enzyme that plays a role in ROS neutralization. Increased CAT levels were previously reported to be one of the mechanisms responsible for ROS as an effort in the body's defense system (48). Superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX) act as the main antioxidant enzymes that scavenge reactive oxygen species in order to prevent the adverse effects caused by ROS (49).

In the end, every systematic review writing certainly has limitations on the discussion and the topics discussed. This review only discusses the role of physical exercise in increasing one of the endogenous antioxidants, namely superoxide dismutase. It is highly recommended that the next research writing should explore more deeply how the mechanism of physical exercise on increasing other endogenous antioxidants such as glutathione peroxidase and catalase. As well as how the correlation and stages in neutralizing ROS after physical exercise. It is also possible to discuss exogenous antioxidants and their role during physical exercise such as vitamin C and vitamin E or a combination of both.

Conclusion

Regular physical exercise is proven to increase endogenous antioxidants as an effort to ward off free radicals. This physiological response occurs because during exercise, ROS increases, stimulating the emergence of endogenous antioxidants, one of which is SOD, which plays a role in neutralizing oxidative stress so that ROS becomes unreactive. Regular exercise provides benefits for anyone who does it. This systematic review certainly still has limitations in research, which only examines related to the increase in endogenous antioxidant SOD during exercise. Of course, further research can be analyzed in depth how exercise affects other endogenous antioxidants such as catalase and glutathione peroxidase. Exercise makes an effort to improve health status and also as a medicine in preventing various diseases.

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Conflict of Interest

The authors declare no conflict of interest

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