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REVIEWS

Redox homeostasis and physical activity

Simona Tache[1,2], Camelia-Manuela Mîrza[1,3], Nicolae Horaţiu Pop[4], Nikolaos Mavritsakis[5]
[1] *Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania*
[2] *Dept. of Functional Sciences, Physiology, Cluj-Napoca, Romania*
[3] *Dept. of Functional Sciences, Pathophysiology, Cluj-Napoca, Romania*
[4] *Babeş-Bolyai University, Faculty of Physical Education and Sport, Cluj-Napoca, Romania*
[5] *1 Decembrie 1918 University, Dept. of Physical Education and Sports, Alba-Iulia, Romania*

Abstract

Physical activity/exercise is a non-pharmacological treatment with a sanogenetic, antiaging and therapeutic role, depending on exercise intensity, duration, frequency and type.

Physical activity/exercise determines biochemical changes in the redox homeostasis of the O/AO balance: either generation of OS in acute exhausting exercise, high intensity and endurance exercise, and overtraining syndrome, or decreased OS and AOC generation in appropriate exercise during moderate training.

Controlling the oxidant/antioxidant balance during physical exercise through proper training and nutritional and non-nutritional supplementation of antioxidants can help reduce oxidative stress and increase performance.

Keywords: oxynitrosative stress, redox homeostasis, physical activity.

Physical inactivity

Physical inactivity is considered sedentariness, while sedentary people are those who have difficulties to leave their home, who do not exercise outside, whose professional activities are static and who perform minimal physical activity in general.

Physical inactivity has negative consequences, even anti-sanogenetic effects of causing or aggravating certain conditions (Lee et al., 2012; Cai et al., 2019; Moreira et al., 2014; Alberti et al., 2009; Lessiani et al., 2016):

- cardiovascular diseases (hypertension, coronary diseases, varices of the lower limbs, arteriosclerosis)
- respiratory diseases (chronic pulmonary diseases, infections of the airways)
- various digestive diseases, hemorrhoids, irritable bowel syndrome, colorectal cancer
- osteomuscular diseases, static disorders of the spine, arthroses, sarcopenia
- obesity, type 2 diabetes, metabolic syndrome
- psychic diseases (depression, anxiety)
- increase in the population risk of morbidity and mortality

Physical activity / Physical exercise

Automation, mechanization and robotisation of the contemporary society have led to a gradual decrease in physical activity, alongside the professional stress of underload and overload. In industrialized countries, more than 60% of the population do not engage in sufficient physical exercise.

WHO recommends 150 minutes of moderate intensity physical exercise a week.

Physical exercise represents a complex strain of the body from a physiological (neuromuscular, cardiorespiratory, endocrine metabolic), immunological, psycho-emotional and biochemical point of view. Correctly carried out, moderate intensity physical effort, either continuous or intermittent, has beneficial effects on the body: preventive sanogenetic role, curative and recovery role, pro-longevity role and active longevity role, as well as therapeutic role.

a) The sanogenetic role, of maintaining the health of the body, is achieved through (Joseph et al., 2016; Simioni at al., 2018; Sallam & Laher, 2016; Rezende Freitas et al., 2017; Daimiel et al., 2020; Dumitru, 1997):

- cardiovascular mechanisms, reducing the risk of cardiac diseases (ischemic cardiopathy), cerebrovascular accident, hypertension, increase of the good cholesterol (HDL)
- endocrine mechanisms of reducing increased hormone release (growth hormone, glucagon, testosterone, adrenaline)

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Address for correspondence: Iuliu Haţieganu University of Medicine and Pharmacy, Faculty of Medicine, Dept. of Functional Sciences, Physiology, Cluj-Napoca, Romania, 1 Clinicilor Street, 400006, Cluj-Napoca, Romania
E-mail: camelia.mirza@umfcluj.ro
Corresponding author: Camelia Manuela Mîrza; e-mail: camelia.mirza@umfcluj.ro
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- digestive mechanisms (appetite control, improving digestion)
- respiratory mechanisms (reducing the decline of pulmonary activity, improving tissue oxygenation)
- maintaining the health of the myo-arthro-kinetic system (muscle mass and strength, joint mobility, right posture, minimizing the risk of osteoporosis and fractures)
- protection effect against breast cancer or colorectal cancer
- body weight control, through reducing the overall fat mass and obesity prevention
- reducing the occurence of infections and improving immunity
- maintaining and improving cognitive psychic functions (memory, attention, creativity, intellectual performance)
- metabolic mechanisms (reducing the glycemia level and increasing glucose use, prevention of diabetes, increasing lipid use and prevention of arteriosclerosis).

Other effects of physical exercise include:
- improvement of sleep
- body detoxification through sweating
- reducing the risk of premature birth and death by cardiovascular diseases
- prevention of sedentary behavior
- harmonious physical development.

b) The pro-longevity and active longevity role consists of:
- prolonging life expectancy and increasing survival through performing physical exercise and maintenance sports (30-40 minutes of jogging per day can delay aging by up to 9 years)
- reduction of the mortality rate.

c) The therapeutic role of physical activity consists of:
- increase in immunity
- normalization of glycemia
- stimulation of antioxidant defense mechanisms
- post-traumatic physical therapy and physical therapy of locomotor diseases
- treatment of cardiovascular diseases, coronary diseases and hypertension, as well as respiratory diseases by physical therapy
- treatment of psychic diseases (depression, schizophrenia, anxiety)
- improving psychosocial behavior

Oxidative stress

Oxygen (O_2) consumption in aerobic organisms leads to the formation of reactive O_2 species (ROS) or O_2 metabolites or catabolites, which according to Halliwel (2007) can be:
- radical species:
  - inorganic: superoxide (hyperoxide) – $O_2^{\bullet -}$; hydroxyl – $OH^{\bullet}$; hydroxyl radical – $RO^{\bullet}$;
  - organic: alkoxyl – RO; hydroperoxyl – $HO_2^{\bullet}$;
- non-radical species: perhydrol or oxygenated water – H_2O_2; hypochlorous acid – HOCl; singlet oxygen or molecular oxygen in activated state – $1O_2\Delta g$; ozone – O_3; dioxygen O_2.

ROS formation is tightly connected to the formation of reactive nitrogen species (RNS), while either antagonistic or synergistic relationships occur between them. RNS can be:
- radical species: nitrogen monoxide or nitric oxide – NO; nitrogen dioxide – NO_2; nitronium ion – NO_2^-;
- non-radical species: nitrous acid – HNO_2; peroxynitrous acid – ONOOH or HNO_3; dinitrogen trioxide – N_2O_3; dinitrogen tetraoxide – N_2O_4; nitronium ion – NO_2^+; alkyl-peroxynitrate – ROONO; nitroxyl – HNO; nitrite anions - NO_2^- and nitrate NO_3^-.

The interaction of oxygen-dependent processes with ROS and RNS is involved in:
- acute inflammatory response and phagocytosis
- anticoagulant, antifibrinolytic action
- procoagulant, antifibrinolytic, prothrombotic proaction.

At cellular level, as well as at the level of the entire organism, ROS determines a series of paradoxical effects, which can be either harmful or beneficial.

a) Harmful effects of ROS occur in the case of production of large quantities and lead to the destruction/ deterioration of cellular structures, to malignant transformation, abnormal cell proliferation, cytotoxic cell aging, cell death (apoptosis). Major harmful prooxidant effects of ROS with OS production are due to the oxidative attack on nucleic acids, proteins, lipids and carbohydrates:
- DNA lesions, referring to thymine, cytosine, adenine, guanine and deoxyribose, followed by cellular injuries and mutations
- modifications of proteins and glycoproteins
- alterations of membrane proteins and transport disturbances through the membrane
- modification of enzyme activity and lipid metabolism
- lipid peroxidation, modifications of the structure and function of membranes
- carbohydrate damage, effects which can lead to apoptosis and necrosis (Evans et al., 2004; Bullone & Lavoie, 2017).

Oxidative stress (OS) was described as the total oxidative lesions caused by O&NS or, in terms of accumulation, modification and depletion:
- accumulation – refers to lipofuscin, lipoprotein pigments from the brain and myocardium
- modification – refers to nucleic acids, glycoproteins, proteins and lipids
- depletion – refers to the loss or reduction of the enzyme activity (Beckman & Ames, 1998).

Major intracellular sources of OS are: the mitochondrial transport chain, polymorphonuclears and xanthine oxidases (Sessa et al., 2020).

b) Beneficial effects of ROS occur in the case of production of small quantities:
- anti-infective defense through bactericidal activity in the course of phagocytosis and stimulation of the activation of lymphocytes
- control of normal vascular tone
- modification of the hydrosolubility of certain substances
- stimulation of cell growth, proliferation and transformation
- cellular signaling and regulation of gene expression
- stimulation of erythropoietin secretion

- learning and memory (Janssen et al., 1993; Ivanov et al., 2016; Faienza et al., 2020).

Normal aerobic life is constantly subject to an attack from ROS-RNS, which take part in oxidative and nitrosative stress (O&NS). The sources of ROS-RNS can be:

- endogenous, intracellular – mitochondria, microsomes, endoplasmic reticulum in neutrophils, eosinophils, monocytes, endothelial cells, myocytes
- exogenous – redox substances, UVR/IR radiation, pollution, lifestyle (for example physical activity and diet), alcohol and smoking (Riga & Riga, 2007; Rytz et al., 2020).

Antioxidant capacity of the body (AOC)

Aerobic life is characterized by the balance between ROS and the capacity of the antioxidant systems (AOS), both at cell level and at the entire body level, to counterattack ROS actions. AOS comprise all antioxidants (AO) that operate within the intracellular and extracellular compartment.

The body developed its own AOS, which can be classified according to different criteria as follows (Olinescu, 1994; Halliwell, 1990; Bonorden & Pariza, 1994):

- according to the moment of intervention:
  - primary, preventive, classical or true AO, which operate from the initiation stage of ROS, forming: thiols, sulfides, catalase, peroxidase, transferase, diaphorase, SOD, urate, ascorbate, isomers of the linoleic acid, chelating agents (peptides)
  - secondary AO, which fragment the oxidation chain: α-tocopherol, β-carotene
- according to the place where they operate:
  - intracellular AO in the membrane, cytoplasm and nucleus: vitamin E, β-carotene, vitamin C, GSH, CuZnSOD, GSH-Px, GSH-S-T, ferritin, metallothionein, carnosine, anserine, CAT
  - extracellular AO: CuZnSOD, transferrin, lactoferrin, haptoglobin, hemopexin, ceruloplasmin, albumin, vitamin C, uric acid, bilirubin, vitamin E
- according to the operating mechanism:
  - enzymatic AO: the SOD family (CuZnSOD, CuSOD), CAT, the glutathione redox cycle (GSH-Px, GSH-S-T, GSH-r, G-6-PDH)
  - non-enzymatic AO: GSH, vitamin E, vitamin C, carotenes and vitamin A, Se, uric acid, bilirubin, albumin, estrogens, metallothionein, polyamines, saturated fatty acids, quinones
- according to solubility:
  - hydrosoluble AO: vitamin C, uric acid, glucose, cysteine, GSH, Se, histidine, taurine, metal chelating proteins, heme fixation proteins
  - liposoluble AO: vitamin E, β-carotene, bilirubin, estrone, estradiol.

The antioxidant systems of the body comprise all AO and they control physiological processes, as well as prooxidant pathological systems.

The research of Olinescu et al. (1994) pointed out that the total AO status of the body shows variations according to gender, age and blood type. Cellular redox homeostasis is maintained and OS is prevented through:

- genetic control of the AO: CAT, SOD, NOS
- vitamin control through vitamins C and E
- myokine intervention.

Genetic control is achieved by nuclear factor-kappa B (NF-kappa B) and mitogen-activated protein kinase (MAPK), which are the signal transduction pathways in ONS, activating the genetic expression of a number of enzymes in O/AO homeostasis: MnSOD, NOSi and NOSe (Ji, 2008).

Vitamin C (ascorbic acid) is a hydrosoluble AO, present in intra- and extracellular fluids (plasma, synovial fluid, CSF), with multiple AO properties: direct scrubber for $^1O_2$, $O_2^{\bullet -}$, $OH^{\bullet}$; neutralizes the oxidants set free by neutrophils; helps regenerate vitamin E, a liposoluble AO; reduces the α-tocopheroxyl radical to α-tocopherol, has a synergistic action compared to vitamin E (α-tocopherol); reduces nitroxide radicals. When in excess it can have a prooxidant effect by Fe^{3+} in Fe^{2+}.

Myokines are cytokines produced in the scheletal muscles during physical effort, influencing the formation of ROS, RNS and AOC. The myokine family comprises: brain-derived neurotrophic factor (BDNF), cathepsin B, decorin, growth factors of the fibroblasts-2 and 21, follistatin and follistatin-like, growth factor insulin-like-1, interleukins 6, 7 and 15, irisin, leukemia inhibitory factor, meteorin-like, myonectin, musclin, myostatin and osteoglycin (Szabó et al., 2020; Ost et al., 2016).

Effort/exercise capacity

Exercise capacity is the ability of the active muscle system to release the energy required for mechanical work, in the highest possible amount and for as long as possible. Physical exercise is supported via two metabolic pathways: anaerobic and aerobic, the latter being 50 times more efficient than the former one. Predominantly aerobic exercises are characterized by:

- low, medium or submaximal intensity
- real or apparent balance between O_2 demand and intake
- duration of more than 3 minutes, up to a few hours (i.e. 2-3 hours), depending on intensity, maximum VO_2 used
- mechanical efficiency 23-26%
- energy source: 30% carbohydrates during endurance exercise; 70% lipids
- final catabolites from univalent reduction of O_2: ROS.

Aerobic training determines:

- central adaptive changes, which affect the cardiorespiratory activity (heart rate, beat volume, O_2 extraction and uptake, muscle blood flow and muscle metabolism)
- peripheral adaptive changes at the muscle level: number and size of mitochondria, capillary density, myoglobin content, oxidative enzyme activity (Tache & Staicu, 2010).

Skeletal muscles, which are the active organs of the locomotor system, are characterized by very large changes in O_2 metabolism at rest and in exertion, which can be

considered normal; no other tissue in the body has such characteristics. During physical exercise, blood flow was found to increase by about 10-20 times, with hyperemia limits between 10-50 times, depending on exercise intensity and the type of muscle fibers; the O_2 influx in sarcosomes increased by about 100-200 and the O_2 arteriovenous difference increased by 3-4 times.

The increased O_2 consumption is determined by: particularities of the practiced exercise such as intensity, strength, endurance; aerobic, anaerobic or mixed nature; duration and speed of exercise; active muscle mass; body position; active and/or static components. In addition to these factors, the environmental circumstances in which exercise is carried out, such as atmospheric pressure, hypoxia, temperature, humidity, noise and adaptive or non-adaptive processes (training, acclimatization, fatigue, overtraining, emotions, etc.), also contribute to stress in sports, in its forms of eustress or distress (Tache et al., 2009).

Redox homeostasis during physical exercise

ROS and RNS production in muscle takes place continuously at a low level and increases during muscle activity. ROSs and RNSs have multiple direct and indirect effects on contractility, excitability, metabolism and calcium homeostasis.

a) Endogenous sources of ROSs and RNSs

Endogenous sources generating reactive species in the body can be: electron transport chains in mitochondria and microsomes; autoxidation reactions (ferrous ions, adrenaline); oxidative enzymes (oxidases - xanthine oxidase, galactosidase, monoamine oxidase, nitric oxide synthase - NOS, NADPH oxidase; oxygenases - tryptophan dioxygenase, indolamine dioxygenase, cyclooxygenase, lipoxygenase); blood phagocytic cells (neutrophils, eosinophils, monocytes, macrophages) and vascular (endothelial) cells (Riga & Riga, 2007).

The intracellular sources of ROS generation in striated muscle fiber are:

- sarcolemma (membrane), with the help of the NADPH-oxidase enzyme
- sarcosomes (mitochondria) (2-5%), with the participation of phospholipase A_2 (PLA_2) and the electron transfer respiratory chain, especially in stage 4
- microsomes (sarcoplasmic reticulum) in the electron transport chain
- sarcoplasm, with the help of oxidative enzymes (oxidases and oxygenases)
- interconversion of RNSs to ROSs
- transsarcolemmal diffusion of extracellular ROSs.

The major intracellular source of ROSs and RNSs is considered to be sarcosomes. NO in turn modulates the production of ROSs in sarcosomes, and the effects are reversible in the presence of oxymyoglobin (Sarkela et al., 2001; Di Meo & Venditti, 2001).

The extracellular sources of ROSs at the musculoskeletal level are the transsarcolemmal efflux of intracellularly formed ROSs and the extracellular interconversion of RNSs to ROSs. The extracellular sources of RNSs at the musculoskeletal level are: transsarcolemmal efflux of RNSs formed intracellularly with the help of eNOS, subsarcolemmal nNOS, and extracellular interconversion of ROSs to RNSs (Murrant & Reid, 2001).

Oxidative stress (OS) and nitrosative stress (NS) are generated by excess production of ROSs and RNSs. OS and NS are caused by divergent disruption: demands/resources, i.e. by the double imbalance between the increasing oxidizing aggression and the decreasing AO defense (Riga & Riga, 2007).

The term currently in use is oxynitrosative stress (ONS). The evaluation of ONS at the biological level, which is a process involved in the etiopathogenesis of over 100 human and animal diseases, is carried out in two opposite directions:

- measurement of aggressor factors (O_2 and N_2 catabolites or ROSs and RNSs) and their effects
- quantification of the body's AO defense and prooxidant enzyme activity.

ONS includes all oxidative chain damage caused by ROSs and RNSs in biological molecules of proteins, carbohydrates, DNA and lipids: oxidation, peroxidation, autoxidation, cooxidation. O_2 activation - a process which is considered to be fundamental and characteristic of the living world - generates mainly free radicals (FR) of O_2: singlet oxygen and free radicals - superoxide, perhydroxyl and hydroxyl. FRs are molecules or molecular fragments that contain an odd electron, have the property of being highly reactive and cause OS and NS (under conditions of imbalance with AO factors). They are themselves the main amplifying factor in the generation of "oxidative lesions": peroxides, hyperoxides, endoperoxides and epoxides, in addition to a new amplification resulting from balance disruption: excess of oxidants, doubled by AO deficiency (Riga & Riga, 2007).

ROS and RNS generation occurs in: muscle vascular endothelial cells (Mitchell & Tyml, 1996), vascular smooth muscle fibers (Charpie & Webb, 1993), inflamed joint cells, motor neurons, astrocytes, neutrophil leukocytes and lymphocytes (Suzuki & Machida, 1996), and red blood cells (Slater, 1987; Murell et al., 1990).

b) Effects of ROSs and RNSs

The direct effects of ROSs and RNSs on skeletal muscles involve the modulation of normal contractile processes, by alteration of the excitation-contraction coupling; decreased muscle metabolism and, indirectly, decreased contractility; influencing cellular redox status, which may frequently precede OS and NS (Kehrer & Lund, 1994; Li et al., 2003).

Other effects are: mediation of intercellular interactions, control of vascular tone and blood flow in large and small vessels of resistance ($NO^{\bullet}$ and $OH^{\bullet}$ - vasoconstriction/vasodilation and hyperemia) (Prior et al, 2003); neuromuscular transmission; fusion of myoblasts; satellite cell activation; invasion of neutrophils, depolarization of related nerve endings (Murrant & Reid, 2001).

NS is associated with OS and causes damage or destruction of lipids, proteins and nucleic acids; decreased physical performance, muscle fatigue, muscle injuries and overtraining (König et al., 2001).

c) AO defense during physical exercise

ROS generation has a dual effect: it causes OS and oxidative damage, and it stimulates adaptive responses for long-term AO protection and increased resistance to OS.

AO defense, effort-induced OS limitation and increased tolerance to effort-induced OS are the result of repeated moderate aerobic physical exercise, long low-intensity training, and detraining.

The AO defense mechanism at muscle level is supposed to be based on the hyperregulation of AO defense systems in muscle. Regular moderate physical exercise reduces OS. Moderate OS may produce a hormesis effect in non-muscular tissues, thus representing a beneficial mechanism of physical exercise by hyperregulating various AO mechanisms, including AO enzymes and degraded molecular repair enzymes (Goto et al., 2007; Radak et al., 2008).

ROSs play the role of signaling molecules that modulate both the contractile function in tired and non-tired skeletal muscles and the gene expression via redox-sensitive transcription pathways, which is an important mechanism in the adaptation to training and AO defense processes. In this context, the adaptation of endogenous AO systems to regular training reflects a potential mechanism for increasing the tolerance of skeletal muscles to exercise-induced OS (Niess & Simon, 2007).

Changes in redox homeostasis during exercise depend on physical exercise frequency, duration, intensity, and type. Such changes consist of homeostasis alteration and homeostasis regulation. Some authors have recommended a practical investigation of the level of prooxidants-antioxidants and their ratio (PO/AO) or the Loverro coefficient in order to determine the OS risk (level of lipid peroxidation products/SOD, CAT and erythrocyte GSHPx) (Zembron-Lacny et al., 2008). The PO/AO ratio is influenced by factors + processes + mechanisms / resources + protection + defense (Riga & Riga, 2007).

Redox homeostasis alteration consists of the generation of ONS in acute exhausting exercise, endurance training and high intensity training, or overtraining syndrome (Kruk et al., 2019; Sessa et al., 2020; Navarro-Ibarra et al., 2019; Neves et al., 2018; Thirupathi & Pinho, 2018; Powers et al., 2020).

ONS caused by intense physical exercise induces an increase of oxidative indicators in serum and muscle (peroxidated lipids, expired ethane, MDA, F2-isoprostanes, conjugated dienes, 8-hydroxy-2 deoxyguanosine), which recommends AO supplementation (Urso & Clarkson, 2003).

Redox homeostasis regulation occurs in moderate, regular exercise, in long low-intensity training, in combined physical exercise (aerobic + strength training) and in fractional training (Tromm et al., 2016).

Adaptive changes consist of:

- lower ONS (limitation of ROS and RNS generation)
- increased AO defense capacity (Kruk et al., 2019; Alikhani & Sheikholeslami-Vatani, 2019; Lamarão-Vieira et al., 2019; Thirupathi et al., 2020; Radak et al., 2005; Lee et al., 2017; Mota et al., 2019; Rytz et al., 2020)
- lower prooxidant parameters (de Sousa et al., 2017)
- increased activity of AO enzymes (Tromm et al., 2016).

Training causes similar changes in young people and the elderly (Alikhani & Sheikholeslami-Vatani, 2019), and also gender-dependent changes (Rytz et al., 2020).

ROS generation in moderate exercise and low-intensity training plays a role in:

- induction of AO defense, DNA repair and antioxidant enzyme repair (Angulo et al., 2020) and adaptation to exercise (Elejade et al., 2021; Ismaeel et al., 2019; Angulo et al., 2020)
- redox intracellular signaling, acting as a signaling molecule (Ismaeel et al., 2019; Thirupathi & Pinho, 2018)
- hyperrelation of AO gene expression involved in redox homeostasis (Ji et al., 2007).

Muscular AO defense systems are hyper-regulated during exercise. Nuclear factor-kappaB (NF- kappaB) and mitogen-activated protein kinase (MAPK) are the signal transduction pathways in OS, which activate the gene expression of a number of enzymes and proteins that play an important role in maintaining intracellular O/AO homeostasis; this idea is supported by numerous recent studies (Ji, 2007; Ji, 2008). NF-KappaB and MAPK intervene in skeletal muscles in the changes occurring in gene expression hyperregulation of enzymes involved in O/AO homeostasis: MnSOD and iNOS and eNOS in mitochondria (Ji et al., 2007). MAPK and NF-kappaB are the two major regulators of gene transcription and metabolism in response to oxidative, energetic and mechanical stress in skeletal muscles. The activation of these factors is stimulated by exercise (Kramer & Goodyear, 2007).

Conclusions

1. Physical activity/exercise is a non-pharmacological treatment with a sanogenetic, antiaging and therapeutic role, depending on exercise intensity, duration, frequency and type.
2. Physical activity/exercise determines biochemical changes in the redox homeostasis of the O/AO balance: either generation of OS in acute exhausting exercise, high intensity and endurance exercise, and overtraining syndrome, or decreased OS and AOC generation in appropriate exercise during moderate training.
3. Controlling the oxidant/antioxidant balance during physical exercise through proper training and nutritional and non-nutritional supplementation of antioxidants can help reduce oxidative stress and increase performance.
4. Anti-stress measures taken during physical exercise aim to overcome the stress caused by physical exercise, reduce systemic physiological stress, reduce oxidative stress, overcome and reduce psycho-emotional stress. Controlling and overcoming the stress caused by physical exercise can contribute to athletic success.

Conflicts of interests

The authors declare no conflict of interest.

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