NUTROLOGY AND DIETS
FOR DETOXIFICATION IN SPORTS

MAJOR CONSIDERATIONS AND CLINICAL OUTCOMES

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Preface

Dear Reader

Cellular redox balance is essential for maintaining cellular homeostasis. Under normal physiological conditions, ROS act as signaling molecules and are essential for metabolic and metabolomic function. Exposure to heavy metals is inevitable due to our social and economic structure; understanding the molecular mechanisms of heavy metal toxicities would have an impact on exploring their therapeutic potential. Studying oxidative stress induced by heavy metals or xenobiotics and their interaction with signal transduction is crucial for a better understanding of toxicity in athletes. Aspects of mitochondrial crosstalk that signal dysfunction and the extent to which heteroplasmy influences mitochondrial function and disease remain unclear. Regarding epigenetic modifications, studies investigating the role of mtDNA methylation in gene expression and disease outcomes should consider mtDNA copy number. Therefore, the detoxification diet (DETOX) has become a strategy for physical activity practitioners to promote toxin removal and weight loss, enabling improved health and quality of life. An adequate intake of vitamins and minerals through a varied and balanced diet remains the best approach to maintaining optimal antioxidant status. Therefore, this book explored the main clinical studies on toxic exposure and detoxification in physical activity practitioners through nutrients and a detoxifying diet.

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SUMMARY

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INTRODUCTION

In the sports arena, heavy metal-induced cellular and organ toxicity has become a major health problem [1]. The indiscriminate use of heavy metals in various sectors, such as industrial, agricultural, healthcare, cosmetics, and household goods, has contaminated environmental matrices and poses a serious health concern for athletes [2]. The xenobiotic-mediated effect enables harmful cellular responses. Oxidative stress is one of these primary cellular responses, resulting from an imbalance in the redox system [3].

Furthermore, oxidative stress is associated with macromolecular damage and the activation of various cell survival and death pathways [4]. Epidemiological and laboratory data suggest that the cellular response induced by oxidative stress after heavy metal exposure is associated with an increased risk of neoplasia, neurological disorders, diabetes, infertility, developmental disorders, renal failure, and cardiovascular disease [5]. The connection between heavy metal-induced oxidative stress and various signaling pathways is complex. Further studies are needed to decipher the interaction between exposure to heavy metals/metalloids (arsenic, chromium, cadmium, and lead), oxidative stress, and signal transduction, which are essential for mounting the cellular and organismal response. The main signaling pathways involved in this interaction include NF-κB, NRF2, JAK-STAT, JNK, FOXO, and HIF [5].

To better understand and improve the detoxification processes of the human body, it is important to always focus on oxidative stress, which is a phenomenon caused by an imbalance between the production and accumulation of reactive oxygen species (ROS) in cells and tissues and the ability of a biological system to detoxify these reactive products. ROS can play various physiological roles (i.e., cell signaling) and are typically generated as byproducts of oxygen metabolism [6].

Despite this, environmental stressors—such as UV, ionizing radiation, pollutants,

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heavy metals, and xenobiotics (antiblastic drugs) - significantly increase ROS production, thus causing an imbalance that leads to cellular and tissue damage (oxidative stress). Several antioxidants, such as vitamin E, flavonoids, and polyphenols, have been explored in recent years for their actual or perceived beneficial effects against oxidative stress. Although the literature describes oxidative stress as harmful to the human body, it is also explored as a therapeutic approach to treat clinical conditions such as cancer, with some clinical success [6].

In this sense, maintaining the mitochondrial genome is essential for proper cellular function. To this end, mitochondrial DNA (mtDNA) must be faithfully replicated, transcribed, translated, and repaired in the face of constant attack from endogenous and environmental agents [7]. Although only 13 polypeptides are encoded in mtDNA, the mitochondrial proteome comprises over 1,500 proteins that are encoded by nuclear genes and translocated to mitochondria to maintain mitochondrial function. The regulation of mtDNA and mitochondrial proteins by epigenetic changes (heavy metals and xenobiotics) and post-translational modifications facilitates crosstalk between the nucleus and mitochondria and ultimately leads to the maintenance of cellular health and homeostasis [7].

In this context, DNA methyltransferase enzymes have been identified in mitochondria, implying that methylation occurs within this organelle; however, the extent to which mtDNA is methylated has been debated for many years. The mechanisms of demethylation within this organelle have also been postulated, but the exact mechanisms and their outcomes remain an active area of research. Mitochondrial dysfunction, characterized by altered gene expression and impaired ATP production resulting from epigenetic changes, can lead to various conditions, including aging-related neurodegenerative diseases, metabolic disorders, alterations in the circadian rhythm, and

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cancer [6,7].

An overview of the epigenetic regulation of mtDNA via methylation, long and short noncoding RNAs, and post-translational modifications of nucleoid proteins (such as mitochondria that lack histones) is needed, highlighting the influence of xenobiotics and heavy metals on mtDNA methylation [7].

Thus, the detoxification diet (DETOX) has become a strategy for physical activity practitioners to promote toxin removal and weight loss, enabling improved health and quality of life. However, these diets remain controversial among researchers, as some argue that there is a lack of scientific evidence for their health benefits, or that such diets may even be harmful [8-11]. Even so, food-based nutrients have been studied for their ability to modulate the metabolic pathways involved in detoxification processes. Several preliminary studies have demonstrated that food and nutrient extracts can regulate the transduction and eventual excretion of toxins [12-17].

DETOX diets are calorie-restricted diets consisting of a single fruit, vegetable, or beverage (tea, vinegar, lemon juice, salt water, or micronutrient-blended beverages) [18-27]. The lemon diet and the Mediterranean hypocaloric diet [28] are low-calorie (low-carb), allowing 500 to 1000 kcal per day and being effective in reducing body weight and fat. However, this dietary intervention is difficult to maintain and can lead to deficiencies in minerals, vitamins, and dietary fiber, as well as increased binge eating and stress [29,30].

While fasting or low-calorie diets may enable weight loss, they can also lead to various health problems, such as malnutrition, muscle weakness, nervousness, headaches, dizziness, fatigue, gastrointestinal disturbances, and reduced quality of life [31,32]. Several preclinical studies have reported the effects of detoxification diets [33-35], and some clinical studies have been published [12-16, 17-19, 24, 26-28].

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CHAPTER I

Heavy Metals – Benefits and Toxicity

In this context, metals and metalloids (heavy metals) are elements with high atomic mass, weight, and densities five times greater than water. Heavy metals are produced naturally through processes such as rock weathering, soil erosion, forest fires, and volcanic eruptions. Furthermore, residing in the Earth's crust, heavy metals are naturally present in bodies of water through runoff from streams. Volcanic eruptions and forest fires also add heavy metals to the air. Although heavy metals are added to the environment through natural processes, various anthropogenic activities increase the concentration of environmental heavy metals in large quantities [36].

In this regard, excessive increases in heavy metal concentrations in environmental compartments result in their contamination and, consequently, directly and indirectly affect the health of athletes. Industries such as metal processing, mining, smelting, foundries, coal burning, petroleum, nuclear power plants, textiles, microelectronics, plastics, wood processing, paper processing, and pharmaceuticals add heavy metals through waste disposal, discharge, and smoke. Agricultural applications such as fertilizers, pesticides, and manures primarily contaminate soil and groundwater, and household products through sewage and fuel combustion add heavy metals to air, soil, and water [37].

Although their accumulation causes health problems for athletes and the general public, heavy metals are also present in living organisms and play significant roles in a variety of biological processes when maintained in homeostatic quantities. For example, copper (Cu) is present in almost all tissues and is essential for various metabolic reactions; iron (Fe) plays a vital role in oxygen transport and nucleic acid synthesis; and zinc (Zn)

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has immune regulatory functions and is structurally important for genetic material [38]. Similarly, molybdenum (Mo) acts as a cofactor for sulfite oxidase, xanthine oxidase, and aldehyde oxidase, and is essential for body growth. Selenium (Se), cobalt (Co), and chromium (Cr) play a role in defense as antioxidants, vitamin B12 synthesis, and glucose metabolism, respectively [39].

With increased use and widespread distribution in the environment, however, heavy metals pose a threat to the body's health, causing cellular, tissue, and organ toxicity through metabolic defects, behavioral changes, reproductive abnormalities, and reduced lifespan [40-42].

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CHAPTER II

Heavy Metals and Reactive Oxygen Species - REDOX Homeostasis

In this context, during normal cellular metabolism, the formation of reactive oxygen species (ROS) is a common phenomenon, which is regulated by the cellular antioxidant system. The enzymes superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and non-enzymatic antioxidants (glutathione) are prominent in maintaining redox homeostasis. SOD is a metalloenzyme whose active site is occupied by Cu^{2+} and Zn^{2+}, sometimes manganese (Mn) or Fe, which catalyzes the dismutation of superoxide radicals into oxygen (O_2) and hydrogen peroxide (H_2O_2). CAT and GPx act on H_2O_2 to decompose it into water (H_2O) and O_2. An imbalance between antioxidants and ROS, favoring the overproduction of free radicals, leads to oxidative stress [43].

Elevated oxidative stress is associated with damage to cellular macromolecules, destabilization of cellular events such as cell division, cell cycle, immune system response, and increased cell death [43-46]. Recent evidence indicates that increased oxidative stress is a major cause of the pathogenesis of several health adversities, such as cancer, diabetes, neurodegeneration, asthma, inflammation, developmental, and reproductive disorders [37,45,47].

In this sense, an imbalance in cellular redox homeostasis is one of the main outcomes of heavy metal exposure [46]. ROS can be an upstream activator or a downstream effector of cellular signaling, depending on the nature of the stress. However, the interaction between ROS and the signaling pathway is complicated and sometimes controversial due to the multifactorial eukaryotic system. In toxicology, signaling between ROS and cells is a determining factor in the xenobiotic response. Therefore,

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deciphering the cellular and organismal response induced by heavy metals due to the interaction between ROS and signal transduction is an important target [48].

The involvement of different signaling pathways in heavy metal-induced pathological processes has been documented. For example, the malignant transformation of human bronchial epithelial cells was due to hedgehog signaling after hexavalent (Cr^{6+}) exposure to these cells [49]. The motor deficit in the rat striatum after Cd exposure is associated with cAMP-dependent PKA/DARRP-32/PP1α and non-canonical β-arrestin/AKT/GSK-3β signaling [48]. Disruption of insulin signaling by arsenic (As) leads to diabetes mellitus [50].

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CHAPTER III

Major Clinical Studies – Supplements/Xenobiotics and Athletes

The optimal nutritional requirements of athletes are dictated by their sport-related energy demands and training regimen, as well as their own metabolic needs, and are governed by the optimal amounts of heavy metals and xenobiotics. Thus, maintaining optimal nutritional requirements for athletes improves performance and recovery from exercise and injury, while inadequate nutrition can compromise both [51].

In this context, optimal nutritional requirements vary across different sports, although the most notable finding when reviewing the literature is the scarcity of such data. Supplements are often used by athletes to compensate for nutritional deficiencies and boost nutritional intake, aiming to achieve optimal energy requirements. However, the effectiveness of supplements and their potential adverse effects remain questionable, mainly due to the presence or excess of xenobiotics. Information regarding supplement consumption by athletes is quite scarce and relies primarily on research [51,52].

In this regard, a study profiled supplement consumption in elite athletes, identifying xenobiotics in their serum collected from two anti-doping laboratories. Several xenobiotics varied significantly between the sporting groups, including some potentially originating from drugs, supplements, food products, and other chemical contaminants. Although the exact sources of these metabolites and their potential effect on athlete performance remain to be confirmed, this study provided information on xenobiotics present in different sporting groups [52].

Xenobiotics increased in competitive athletics and showed higher concentrations of two xenobiotics potentially originating from food products and/or supplements,

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namely eugenol sulfate and stachydrin. Eugenol is a potent antioxidant found in many plants, herbs, and spices, especially cloves, but is also contained in some supplements that claim to purify the blood and reduce the risk of gingivitis and heart disease [53].

Also, stachydrine, a biomarker of citrus fruit consumption [54], was also increased in athletes. It is also contained in some supplements, promoting calming and soothing effects and relieving anxiety. It may serve as an osmoprotective compound for the kidneys and has recently been shown to exert anti-inflammatory and antioxidant action against the effects of stress in animal models [55].

A correlation has been revealed between stachydrine and methyl-glucopyranoside (alpha/beta), also elevated in athletics, suggesting a similar source, perhaps orange juice [56]. Other compounds elevated in athletics included 2,3-dihydroxyisovalerate, a dihydroxyacid dehydratase substrate known to be sensitive to nitric oxide, and 4-hydroxypurate, a microbial end product derived from polyphenol metabolism by gut microflora [57].

Supplements are widely used among elite athletes to maintain health and enhance performance. Despite several studies investigating the use of dietary supplements by athletes, a comprehensive profile of serum supplement metabolites in elite athletes is still lacking. Thus, a study of 478 elite athletes from different sports (soccer, track and field, cycling, rugby, swimming, boxing, and rowing) was conducted using untargeted metabolomics-based mass spectroscopy combined with high-performance liquid chromatography. The study analyzed the presence of various xenobiotics in serum samples from elite athletes from different sports, with a focus on metabolites potentially originating from nutritional supplements. Of the 102 xenobiotics detected, 21 were significantly different between sport groups, including metabolites that potentially prolong exercise tolerance (caffeic acid), carry a nootropic effect (2-pyrrolidinone), exert

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a potent antioxidant effect (eugenol, ferulic acid 4-sulfate, thioproline, retinol), or originate from medications for various types of injuries (ectoin, quinate). This provided evidence that athletes from different sports exhibit a distinct xenobiotic profile that may reflect their drug/supplement use, diet, and exposure to various chemicals [52].

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CHAPTER IV

Regulators of Heavy Metal-Induced Oxidative Stress

Cells have mechanisms to cope with a variety of stress conditions. In response to stress, and depending on the nature of the stress, cells activate or deactivate various signaling pathways. Generally, the attempt is to repair stress-induced damage by inducing pro-survival pathways. However, when the extent of damage is high, cells activate cell death pathways (pro-apoptotic pathways) [58,59]. Under stress conditions, the decision process for activating pro-survival or pro-apoptotic pathways is collectively referred to as the cellular stress response.

In this sense, heavy metal toxicity corresponds to stress, and it has been well established that oxidative stress is a key factor in toxicant-induced health problems. Therefore, over the past few decades, researchers have focused primarily on elucidating toxicant-induced oxidative stress and its cellular regulators. As a result, several regulatory molecules have been reported to be activated in response to oxidative stress induced by heavy metal toxicants. Essential regulators are discussed below [60].

Non-coding RNAs (ncRNAs) are RNA molecules that cannot be translated into proteins [61]. The most common ncRNAs are tRNAs and rRNAs, which are essential for protein synthesis. Other ncRNAs, such as long and small ncRNAs, regulate gene expression through epigenetic mechanisms and can also act as signaling molecules to regulate essential cellular and biological processes [62,63]. NcRNAs involved in the epigenetic regulation of mitochondrial gene expression can be encoded by both the nuclear and mitochondrial genomes; however, it is unclear whether mtDNA-encoded ncRNAs are derived from mitochondrial genes integrated into the nuclear genome or are transcribed within mitochondria [64-69].

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CHAPTER V

Post-Translational Modifications of Mitochondrial Nucleoid Proteins

In the nucleus, epigenetic changes in the form of post-translational modifications of histone proteins alter gene transcription and maintain cell type-specific expression patterns. These modifications include methylation, phosphorylation, acetylation, ubiquitylation, sumoylation, and lysine paroxylation [70]. In mitochondria, where histone proteins are absent, epigenetic modifications of nucleoid proteins play an important role in regulating mtDNA gene expression.

In this context, it is estimated that approximately 63% of mitochondrial-localized proteins contain lysine acetylation sites, and in a 2011 study, 216 phosphopeptides were identified from mitochondrial preparations [69]. Mitochondrial proteins can be acetylated by enzymes or non-enzymes. Non-enzymatic acetylation is favored due to a high concentration of acetyl-CoA and alkaline pH in mitochondria. Enzymatic acetylation within mitochondria has recently been recognized with four types of acetyl transferases, ACAT1, MOF, GCN5L1, and PCAF, being responsible for regulating the acetylation levels of mitochondrial proteins [71-74].

Deacetylation is carried out predominantly by the NAD+-dependent sirtuin family of enzymes, specifically SIRT3, while two additional mitochondrial sirtuin enzymes, SIRT4 and SIRT5, remove longer acyl groups, including succinyl, malonyl, and lipoyl groups [75]. A number of kinases and protein phosphatases have also been identified in mitochondria and regulate protein phosphorylation and dephosphorylation [76]. In this scenario, mitochondrial transcription factor A is the major structural constituent of mitochondrial nucleoids and is an example of a mitochondrial protein that is post-translationally modified through acetylation, glycosylation, and phosphorylation [77].

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Two serine residues (S55 and S56) within the high-mobility group 1 (HMG1) domain are primary sites for phosphorylation, while four lysine residues (K62, K76, K111, and K118) also within HMG1 appear to be sites for acetylation. Phosphorylation and acetylation regulate aspects of mtDNA dynamics by altering the binding affinity of TFAM to DNA, where reduced TFAM binding to DNA causes increased protein diffusion on DNA and reduced mtDNA compaction. The extent to which mtDNA is compacted influences mtDNA replication and transcription. Acetylation and phosphorylation sites have also been identified in other mitochondrial nucleoid-associated proteins, including mtSSB and DNA Polγ [78].

Mitochondrial dysfunction caused by mtDNA alteration and damage is believed to be a key underlying mechanism in the development of diseases. Epigenetic modifications such as methylation play a role in mtDNA regulation; the effects of xenobiotic agents on mtDNA methylation levels, particularly 5mC and 5hmC, have also been explored. MtDNA methylation can be affected by exposure to various external factors, including air pollutants, metals, cigarette smoke, dietary oils, dietary supplements, and therapeutic drugs [5].

In this regard, air pollution and cigarette smoke can cause several diseases, including birth defects, cardiovascular disease, respiratory diseases, neurological disorders, and cancer [79]. These particles can methylate the mitochondrial D-loop region and mitochondrial genes, leading to an increased risk of disease. For example, exposure of metalworkers to xenobiotics has been associated with hypermethylation of the MT-TF (phenylalanine tRNA) and MT-RNR1 (12S rRNA) genes in peripheral blood [80]. Similarly, prenatal exposure to air pollution has been correlated with increased placental mtDNA methylation in the D-loop and MT-RNR1 [81].

Environmental metal ions, such as chromium and arsenic, which accumulate due

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to occupational exposure or polluted drinking water, can alter mtDNA methylation patterns. Hypomethylation in the MT-TF and MT-RMR1 genes has been observed after chromium exposure [82]. Similarly, arsenic exposure has been associated with hypomethylation of the D-loop and MT-ND6 due to the presence of arsenic in drinking water. Furthermore, arsenic exposure also resulted in an increase in mtDNA copy number, upregulation in the expression of the nuclear-encoded TFAM gene, and increased expression of the mitochondrial proteins ND4 and ND6 [83].

Maternal diet can alter mtDNA methylation levels in newborns, modulating their mitochondrial capacity, which may have long-term consequences for energy homeostasis. For example, protein deficiency during pregnancy alters mtDNA methylation levels in a sex-specific manner, and betaine supplementation has been implicated in hypomethylation in the D-loop region and overexpression of mitochondrial-encoded OXPHOS genes [84].

Dietary lipid concentration can also affect mtDNA methylation, as observed in large yellow croaker fish, where a high-lipid diet increases D-loop methylation, but a low-lipid diet reduces methylation at MT-RMR1. Similarly, consumption of olive oil and perilla oil increases methylation at MT-ND4L and MT-TR (arginine tRNA). However, MT-RNR1 methylation decreased with perilla oil intake. Modulation of lipid metabolism in response to the high lipid content of these oils has been suggested to impair mitochondrial function [85].

Also, drugs can cause mitochondrial dysfunction by altering the expression of DNMT/TET enzymes and, consequently, causing changes in mtDNA methylation levels. Valproic acid (VPA), an anticonvulsant and mood stabilizer, is frequently used in the treatment of epilepsy and can cause liver toxicity due to mitochondrial dysfunction. In order to understand the underlying mechanism of hepatotoxicity, the effects of VPA on

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mtDNA methylation were tested using cultured mammalian cells. A reduction in 5hmC levels in mtDNA was observed after VPA treatment in mouse fibroblast cells and was associated with decreased TET1 mRNA and protein levels [86].

In a separate study using primary human hepatocytes, hypomethylation of seven mitochondrial genes was observed with VPA treatment, and within the same study, two nuclear genes crucial for DNA methylation, DNMT and MAT (methionine adenosyltransferase), were found to be hypermethylated, resulting in reduced levels of the enzymes DNMT and S-adenosyl methionine (SAM). This may impact downstream mtDNA methylation, suggesting crosstalk between the nucleus and mitochondria after VPA exposure [87].

In this context, downstream molecular events following VPA exposure have also been explored in human hepatocytes, where upregulation of DNMT caused transient hypermethylation in mtDNA and downregulation of mitochondrial proteins, resulting in impaired mitochondrial function. One study observed crosstalk between the nucleus and mitochondria, where the mitochondrial gene MT-CO2 initiates a complex cascade of interactions mediated by the nuclear genes FN1, MYC, and CPT1A. Most of these genes participate in various mitochondrial functions, such as electron transport, apoptosis, mitochondrial import, and fatty acid oxidation, whose impairment can lead to mitochondrial dysfunction [88].

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CHAPTER VI

Main Nutrients and Biotransformation

The general population is exposed to a variety of toxic substances. Some of these are from manufactured products and some from air and water pollution [89-94]. Toxins are also commonly found in many foods. A judicious choice of food will neutralize harmful agents. Therefore, diet can be an important factor in determining who does and who does not experience toxic symptoms after exposure [95-103]. For example, while humans can consume fish that have absorbed mercury from contaminated water, selenium can act as a natural antagonist to mercury poisoning. However, excess selenium can be harmful [104-116].

Some vegetables can accumulate cadmium in contaminated soil, and zinc in a variety of nuts is an antagonist to cadmium toxicity. Nitrites in preserved meats can be converted to nitroamines by saliva or stomach acid. Vitamin C, found in oranges and bell peppers, can inhibit this conversion. Furthermore, calcium antagonizes the toxicity of lead and aluminum. The second aspect concerns oxidants and antioxidants. Oxidative stress can cause some types of cancer, atherosclerosis, and adverse effects of aging. Antioxidants are the best protectors against damage caused by reactive oxygen species (ROS). The most effective antioxidants are found in highly colored fruits and vegetables, such as carrots, tomatoes, and berries, called carotenoids. Flavonoids (polyphenols) are another class of effective antioxidants that neutralize ROS [117].

Many foods naturally contain chemicals that are, in higher concentrations, quite toxic or carcinogenic. So-called "biotransformations" (detoxification mechanisms) involving type I and type II enzymes are known. Some foods modify these enzymes positively or negatively. Oranges, for example, contain a substance that inhibits a P450

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isoform, making some cardiac medications more toxic as substrates [117].

In this sense, detoxification is a vital cellular task that, when deficient, can lead to early morbidity and mortality. The detoxification process involves the mobilization, biotransformation, and elimination of toxins of exogenous and endogenous origin. The relationship between exercise and oxidative stress is extremely complex, depending on the mode, intensity, and duration of exercise. Regular moderate training appears beneficial for oxidative stress and health. Conversely, acute exercise leads to increased oxidative stress, although this same stimulus is necessary to enable upregulation of endogenous antioxidant defenses. Supporting endogenous defenses with additional oral antioxidant supplementation may represent a suitable non-invasive tool to prevent or reduce oxidative stress during training [118].

Excess exogenous antioxidants, however, can have detrimental effects on health and performance. Whole foods, rather than capsules, contain antioxidants in natural proportions and ratios, which can act synergistically to optimize the antioxidant effect. Thus, an adequate intake of vitamins and minerals through a varied and balanced diet remains the best approach to maintaining optimal antioxidant status. Antioxidant supplementation may be warranted under specific conditions, such as when athletes are exposed to high oxidative stress or do not meet their dietary antioxidant requirements. Furthermore, it is recommended that an individualized diet be adopted for each athlete practicing a given sport or during a given training period, under clinical supervision, including blood counts and physiological tests, as part of a comprehensive nutritional assessment [119].

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CHAPTER VII

Ketogenic Diet, Detoxification, and Exercise

The ketogenic diet (KD), a high-fat, low-carbohydrate, and adequate-protein diet that replaces glucose with ketone bodies, is effective against various diseases, from intractable epileptic seizures, metabolic disorders, tumors, autosomal dominant polycystic kidney disease, and neurodegeneration to skeletal muscle atrophy and peripheral neuropathy. Key mechanisms include increased mitochondrial efficiency, reduced oxidative stress, and regulated phospho-AMP-activated protein kinase, gamma-aminobutyric acid-glutamate, Na+/K+ pump, leptin and adiponectin levels, ghrelin levels, lipogenesis, ketogenesis, lipolysis, and gluconeogenesis [120].

In cancer cells, KD targets glucose metabolism, suppresses insulin-like growth factor-1 and the PI3K/AKT/mTOR pathways, and reduces cancer cachexia, muscle wasting, and fatigue. An associated increase in skeletal proliferator-activated receptor γ coactivator-1α activity alters systemic ketone body homeostasis, contributing to attenuated diabetic hyperketonemia. Antioxidant and anti-inflammatory properties allow KD to improve endurance and athletic performance, preventing exercise-induced muscle and organ weakness. KD also reduces allodynia associated with metabolic syndromes and promotes peripheral and sensory axonal regeneration [120].

Moderate exercise combined with adequate nutrition is considered protective against cardiovascular disease and musculoskeletal disorders. However, it is known that physical activity has more than just positive effects. Indeed, achieving good performance requires very high oxygen consumption, which leads to the formation of ROS, responsible for premature cellular aging and diseases such as heart failure and muscle damage [121].

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Antioxidants play a key role in this scenario, particularly natural antioxidants that can be ingested through the diet. Natural antioxidants are molecules capable of neutralizing oxygen-free radicals without causing cellular cytotoxicity. In recent years, several studies have been conducted to identify natural micronutrients to prevent or mitigate oxidative stress induced by physical activity, helping to support conventional drug therapies for heart failure and muscle damage. In particular, sulfur-containing compounds can protect the body from oxidative stress, including six natural and defined antioxidants as glutathione, taurine, lipoic acid, sulforaphane, garlic, and methylsulfonylmethane [121].

The literature suggests that dietary antioxidants are capable of detoxifying peroxides produced during exercise, which could result in lipid peroxidation, and that they are capable of scavenging peroxyl radicals and, therefore, may prevent muscle damage. Endogenous antioxidant enzymes also play a protective role in the lipid peroxidation process. The reviewed studies (rodents and humans) showed significant increases in malondialdehyde (a product of lipid peroxidation) after exercise to exhaustion, as well as favorable changes in plasma antioxidant levels and antioxidant enzyme activity. In trained individuals and trained rats, antioxidant enzyme activity increases markedly. Thus, the increase in exercise-induced oxidative stress is offset by increased antioxidant activity, preventing lipid peroxidation. Human studies have shown that dietary supplementation with antioxidant vitamins has favorable effects on lipid peroxidation after exercise [122].

The reviewed human studies indicate that antioxidant vitamin supplementation may be recommended for individuals who perform regular heavy exercise. Furthermore, trained individuals have an advantage compared to untrained individuals, as training results in increased activity of several important antioxidant enzymes and overall

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antioxidant status. Furthermore, vitamin C supplementation attenuates oxidative stress (lipid peroxidation) and the inflammatory response (IL-6) to a single exercise session [123].

Regarding the biotransformation of human molecules and elimination systems, several clinical and in vivo studies have been conducted to evaluate the effects of foods and food-derived components on the activity of detoxification pathways, including phase I cytochrome P450 enzymes, phase II conjugation enzymes, Nrf2 signaling, and metallothionein [124].

To study the effect of specific dietary components on health and performance in athletes, several groups have used metabolomics. Vitamin E supplementation has been shown to influence phospholipid metabolism and induce lysoPC generation, a general pro-inflammatory response. A diet rich in flavonoids triggered changes in 63 plasma metabolites, with 70% belonging to lipids and xenobiotics [97,98].

Also, soy protein polyphenol complex supplementation was associated with increased phenolic signature and ketogenesis in runners during recovery from a 3-day hard effort [99]. Fruit consumption, such as bananas and pears, improved 75-km cycling performance, reduced fatty acid oxidation, and increased antioxidant capacity [100]. Furthermore, pistachio intake was also associated with improved 75-km cycling time and increased post-exercise plasma levels of raffinose, sucrose, and oxidative stress-related metabolites [101].

In addition, studies have adopted a predictive metabolomic approach, examining the effect of macronutrient composition consumed immediately after exercise on serum metabolic profiles in the early recovery phase. These studies have suggested that proanabolic processes were favored with a mixture of carbohydrates and proteins compared to water or carbohydrate consumption [102].

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Besides, the Wellnessup Diet (WD) was conceived as a healthy diet based on organic plant-based diets, including various vegetables, fruits, whole grains, nuts, and phytonutrients. Thus, a study evaluated the effects of a 4-week intake of WD on the detoxification of toxic trace elements, reduction of body fat, and safety parameters. Forty-five women with a body mass index (BMI) of 23.5-30 kg/m^2 were recruited. Thirty of them were assigned 1:1 to the test group (WD, 15 subjects) and the control group (calorie-restricted diet, CRD, 15 subjects) in a single-blind, randomized design, and the remaining 15 subjects were assigned to control group 2 (maintaining a regular diet, MRD). Hair levels of four toxic trace elements (nickel (Ni), rhodium (Rh), tin (Sn), and gallium (Ga)) decreased in the WD group after the diet compared to before the diet, compared to the CRD or MRD groups ($p < 0.05$). At the end of the trial, both the WD and CRD groups had lower BMI, waist circumference (WC), hip circumference (HC), and WHR compared to baseline ($p < 0.05$). Compared to the WD group, the CRD group had a greater mean change ($p < 0.05$) from baseline in weight loss and fat-free mass [125].

Detoxification through diet could be used to reduce and eliminate chromium toxins from the human body. Thus, a descriptive study with 10 workers analyzed the intake of glutathione-containing foods to enhance chromium detoxification and calculate the cost of dietary intake. Intake of foods containing glutathione (avocado, broccoli, carrots, tomatoes, and grapes) considerably increased chromium detoxification [126].

Finally, to investigate whether aquatic athletes follow an optimal diet, 58 athletes, all members of the Greek national swimming teams, were tested. Dietary intake was assessed at the nutrient, food, and food group levels using the 24-hour dietary recall method and a food frequency questionnaire. The mean energy intake for men and women was 14.3 and 8.5 MJ, respectively. The mean carbohydrate intake for male and female athletes was 4.5 g/kg and 3.8 g/kg of body weight, respectively. Fat intake was 153 g for

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men and 79 g for women. A significant number of athletes (71% of men, 93% of women) did not meet the Dietary Reference Intake for at least one of the antioxidant vitamins. The data suggest that athletes of both sexes consumed too much fat and too few carbohydrates. Therefore, insufficient fruit and vegetable intake was related to low antioxidant intake [127].

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FINAL CONSIDERATIONS

Cellular redox balance is essential for maintaining cellular homeostasis. Under normal physiological conditions, ROS act as signaling molecules and are essential for metabolic and metabolomic function. However, ROS imbalance, directly or indirectly due to the accumulation of heavy metals or xenobiotics, interacts with a range of signaling pathways, which can lead to a number of pathological conditions. Exposure to heavy metals is inevitable due to our social and economic structure; understanding the molecular mechanisms of heavy metal toxicities would have an impact on exploring therapeutic potential. The interaction between ROS and signal transduction is a central mechanism behind heavy metal-associated health consequences. This interaction can be between ROS and cell and nuclear membrane receptors/ROS transcription factors/ROS signaling proteins. The outcome of the ROS-heavy metal cell signaling interaction can vary under different experimental conditions, which should be considered when studying this axis. Furthermore, in the environment, heavy metals are present in a mixture, and humans are routinely exposed to heavy metal mixtures.

Studying oxidative stress induced by heavy metals or xenobiotics and their interaction with signal transduction is crucial for a better understanding of toxicity in athletes. Furthermore, the presence of numerous signaling pathways and their interactions also increases the complexity of understanding cell signaling and ROS, requiring a thorough elucidation. Mitochondria not only contain their DNA, which is inherited from the mother, but their endosymbiotic origin makes them evolutionarily unique. The double-membrane organelle, much like its prokaryotic ancestor, is capable of supporting processes such as replication, protein production to generate ATP, and possesses the machinery to drive its division. While only a small fraction of the proteins found within the organelle are encoded by mtDNA, the majority of the mitochondrial proteome is

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encoded within the nucleus, making crosstalk between the two organelles necessary and inevitable.

Depending on the cell type, many mitochondria exist within a single cell, and each mitochondrion has multiple copies of mtDNA, leading to heteroplasmy, where wild-type mtDNA molecules coexist with those that may have acquired mutations. The aspects of mitochondrial crosstalk that signal dysfunction and the extent to which heteroplasmy influences mitochondrial function and disease remain unclear. Regarding epigenetic modifications, studies investigating the role of mtDNA methylation in gene expression and disease outcomes must consider mtDNA copy number.

Gene expression within mitochondria is regulated by epigenetic mechanisms, but information remains lacking. Whether mtDNA methylation leads to a specific disease condition or occurs as a consequence of a disease still requires further study. Several diseases that have been associated with differential mtDNA methylation include age-related neurodegenerative disorders (Alzheimer's, Parkinson's, etc.), cancer, obesity, diabetes, and cardiovascular disease.

Thus, the detoxification diet (DETOX) has become a strategy for physical activity practitioners to promote toxin removal and weight loss, enabling improved health and quality of life. Typically, detox diets are calorie-restricted diets consisting of a single fruit, vegetable, or beverage (tea, vinegar, lemon juice, salt water, or micronutrient-infused beverages). Several preclinical studies have reported the effects of detox diets, and some clinical studies have been published.

Antioxidants are the best protectors against damage caused by reactive oxygen species (ROS). The most effective antioxidants are found in highly colored fruits and vegetables, such as carrots, tomatoes, and berries, and are called carotenoids. Flavonoids (polyphenols) are another class of effective antioxidants that neutralize ROS.

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An adequate intake of vitamins and minerals through a varied and balanced diet remains the best approach to maintaining optimal antioxidant status. The ketogenic diet, a diet high in fat, low in carbohydrates, and adequate protein, replacing glucose with ketone bodies, is effective against various diseases, from intractable epileptic seizures, metabolic disorders, tumors, autosomal dominant polycystic kidney disease, and neurodegeneration to skeletal muscle atrophy and peripheral neuropathy.

The antioxidant and anti-inflammatory properties allow ketogenic diet to improve endurance and athletic performance, preventing exercise-induced muscle and organ weakness. Furthermore, sulfur-containing compounds can protect the body from oxidative stress, including six naturally occurring antioxidants, namely glutathione, taurine, lipoic acid, sulforaphane, garlic, and methylsulfonylmethane.

Human studies have shown that dietary supplementation with antioxidant vitamins has favorable effects on lipid peroxidation after exercise. Furthermore, vitamin C supplementation attenuates oxidative stress (lipid peroxidation) and the inflammatory response (IL-6) to a single exercise session. A flavonoid-rich diet triggered changes in 63 plasma metabolites, with 70% belonging to lipids and xenobiotics. The Wellnessup Diet was designed as a healthy diet based on organic plant-based diets, including various vegetables, fruits, whole grains, nuts, and phytonutrients. Intake of foods containing glutathione (avocado, broccoli, carrots, tomatoes, and grapes) significantly increased chromium detoxification.

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Conflict of Interest

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