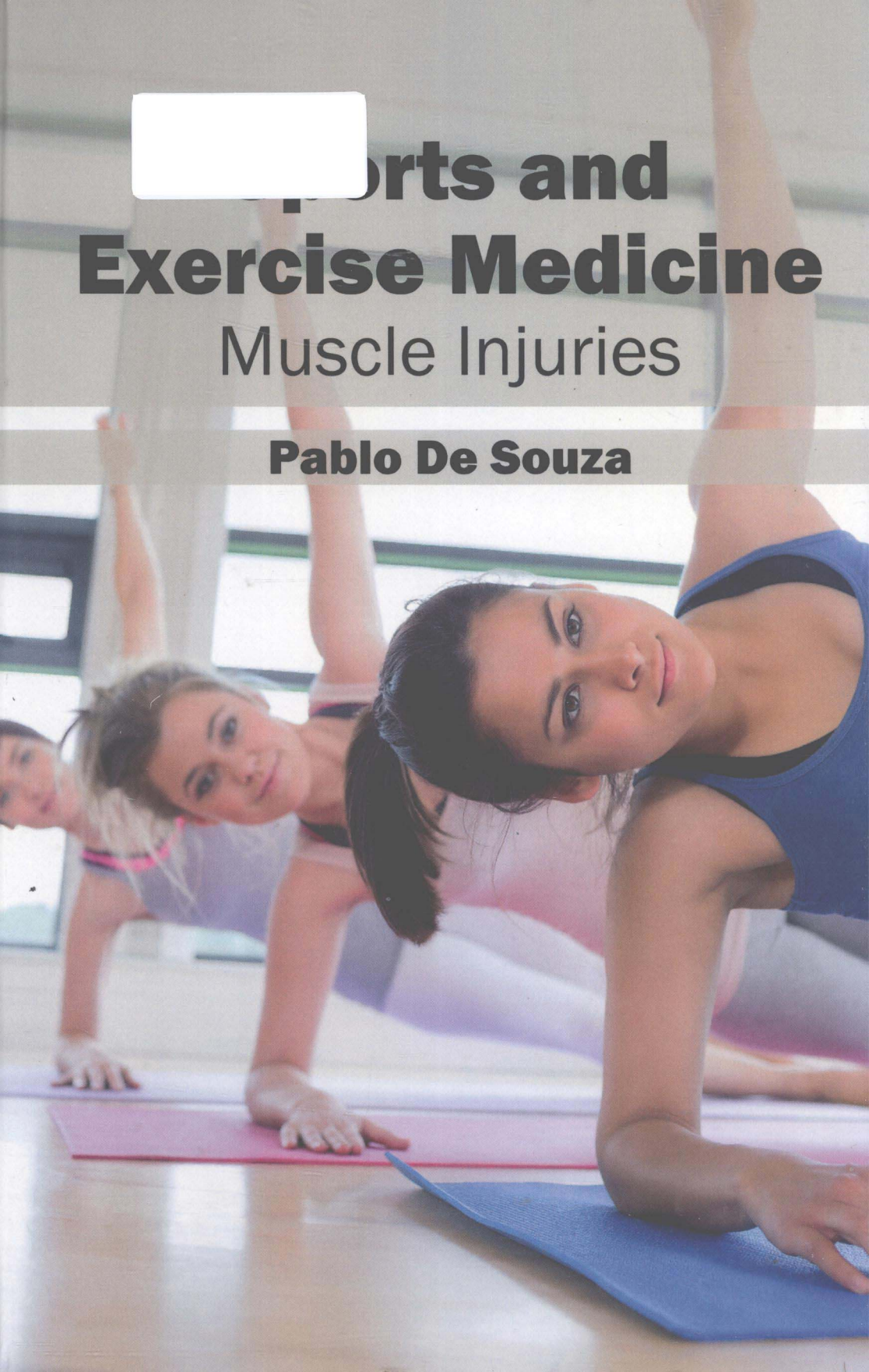
Sports and Exercise Medicine

Muscle Injuries

Pablo De Souza



Sports and Exercise Medicine: Muscle Injuries

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Preface

This insightful book on common injuries in the domain of sports medicine provides updated information to readers. A very common pathology in sports and a leading cause of sport activity suspension is muscle tear. This book is aimed at presenting a review on the current knowledge available on muscle tears in athletes, specifically regarding the biology of muscle healing, both traditional and modern surgical treatments as well as preventive measures. This book will be a valuable resource for sports medicine practitioners including physicians, physiotherapists and fitness coaches.

Various studies have approached the subject by analyzing it with a single perspective, but the present book provides diverse methodologies and techniques to address this field. This book contains theories and applications needed for understanding the subject from different perspectives. The aim is to keep the readers informed about the progress in the field; therefore, the contributions were carefully examined to compile novel researches by specialists from across the globe.

Indeed, the job of the editor is the most crucial and challenging in compiling all chapters into a single book. In the end, I would extend my sincere thanks to the chapter authors for their profound work. I am also thankful for the support provided by my family and colleagues during the compilation of this book.

Editor

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General Aspect

Nutritional Interventions as Potential Strategy to Minimize Exercise-Induced Muscle Injuries in Sports

Giuseppe D'Antona

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1. Introduction

Muscle injury has been related to resistance exercise and prolonged endurance exercise paradigms both leading to significant local mechanical constraints followed by focal disorders such as sarcolemmal damage and leakage of intracellular proteins, oedema, myofibrillar disorganization and microtrauma-triggered inflammation. These unfavorable events lead to variable soreness, swelling, loss in muscle strength and function with reduced range of motion.

To date strategies finalized to minimize exercise-induced muscle injury are scarce and often not adequately supported by research studies.

Based on the notion that dietary supplementations may exert a variety of beneficial effects on the skeletal muscle, in the last 20 years there has been a great deal of interest in nutritional strategies aiming to attenuate signs and symptoms of exercise induced muscle injuries. Anyhow a large number of variables influences the muscular outcome of nutritional supplements, strongly depending on nutrient type, genotype, age, and regulation of nutrient sensing pathways.

Overall there is a paucity of studies on the topic, partly related to the high number of supplements to be considered and their combined use. In general nutrients as vitamins (as vitamin C), N-acetyl-cysteine, L-carnitine, creatine, and branched chain amino acids (BCAA) may exert a potential beneficial role but the underlying cellular mechanism, the optimal dosage and the duration of the pretreatment/treatment period are currently unknown.

This chapter addresses the current knowledge on the potential use of nutritional supplements in preventing and/or minimizing muscle injuries due to resistance or endurance exercise training.

"If the soreness then, be caused by the same conditions which produce fatigue, namely the presence of diffusible waste products of activity we should expect to find, as we do find, that it takes the course described above, passing away within few hours of the work itself" [1]

In 1900 Theodore Hugh first described that exercise induced muscle injury is not a fatigue phenomenon but the consequence of mechanical overload followed by structural and functional muscular changes [1].

Cycles of repetitive eccentric and concentric contractions represent a fundamental source of mechanical stress for active skeletal muscle and vulnerability of skeletal muscle fibers appears to be particularly evident in unaccustomed individuals. In fact conditioning of the muscle through prior similar activity may minimize damage appearance (so called "repeated bout effect") [2]. Overall the process appears as a fundamental step for the arising of exercise-induced plastic response as it is followed by muscle remodeling and adaptation [3]. However muscle damage may delay muscle recovery from exercise and performance thus reducing the athletes compliance to exercise programmes.

The direct consequence of mechanical stress on active skeletal muscle fibers is the appearance of soreness (delayed onset muscle soreness, DOMS), stiffness and reduced force production. This is particularly the case as a consequence of strenuous physical work involving heavy resistance exercise including eccentric (i.e. lengthening) actions [4-6]. In these conditions force loss appears immediately post-exercise whereas soreness becomes evident within 24-48 hours after and, as the force impairment, may last several days depending of the extent of damage [7]. At the microscopic and submicroscopic level fibers damage, which preferentially involves fast twitch fibers [8], is already evident within minutes from the mechanical insult [9] displays throughout individual fibers (i.e. focal injury), and includes plasma membrane disruption accompanied by the loss of muscle proteins in the serum (i.e. creatine kinase (CK), myoglobin, lactate dehydrogenase (LDH), aldolase, troponin), myofibrillar disorders as streaming and broadening of the Z-lines, loss of sarcomeres register, the appearance of regions of overextended sarcomeres, regional disorganization of the myofilaments, subsarcolemmal lipofuscin granules accumulation, alterations of the proteoglycan components, increased interstitial space, and capillary damage [10-15]. Interestingly dramatic changes in the organization of the membrane systems involved in excitation-contraction coupling have been also found following eccentric contractions [16]. The most commonly identified alterations include disorders of the T tubule, changes in the direction and spatial orientation of the triads, and the appearance of caveolar clusters, pentads and heptads (close apposition of two or three T tubule elements with three or four elements with three or four elements of terminal cisternae of sarcoplasmic reticulum).

Apart mechanical stress, other mechanisms may contribute to muscle damage. In particular a metabolic impairment has been proposed as a result of ischemia or hypoxia during prolonged and intense resistance exercise. This insult leads to changes in ion concentration, accumulation of metabolic wastes, and adenosine triphosphate (ATP) deficiency which contribute to soreness and impaired function.

Importantly the early mechanical and metabolic mechanisms can promote biochemical changes within the affected area, leading to the generation of a secondary muscle damage including disruption of intracellular calcium homeostasis, local accumulation of inflammatory cytokines such as tumor necrosis factor-a, interleukin (IL)-1b, IL-6, and IL-1 receptor antagonist (IL-1ra) [17], *de facto* mimicking the sequential release of cytokines after trauma [18], and reactive oxygen species (ROS) that may further degrade muscle proteins and increase the local expression of cytokines [19, 20]. This condition may contribute to persistence of signs and symptoms of injury.

Although it is widely accepted that high intensity eccentric exercise is the fundamental exercise paradigm resulting in muscle damage and subsequent adaptation, structural and functional damage may also arise following long lasting endurance exercise paradigms as demonstrated by the appearance of ultrastructural alterations, as fibers necrosis, sarcolemmal disruption, Z discs streaming, contracture knots, and inflammatory infiltration in endurance athletes even before a race [21]. Anyhow even though the extent and location of damage may greatly vary according to the exercise paradigm and the previous conditioning of the muscoloskeletal system, the extent of damage observed with low intensity and long duration endurance exercise is often less pronounced than with higher intensities. This is the main reason of why most of works finalized to the identification of the physiological mechanisms that regulate the response to exercise-induced stress in skeletal muscle and the possible countermeasures, including the approach based on nutrient supplementation, have been focused on strength training exercise.

2. Nutritional intervention to minimize exercise-induced muscle injury

For decades, dietary supplementation has been proposed in various physiological or pathological conditions. Based on the recent progress in our understanding of the cell signaling and *in vivo* metabolism of nutrients and on accumulating experimental results, the concept that dietary supplementation might have effects in prevention or treatment of several disorders is experiencing a new revival. To date several investigations have been focused on accumulating experimental evidence aiming to extend the use of specific nutritional supplements in the prevention and/or treatment of exercise induced muscle injuries. Anyhow available outcomes on potentially efficacious supplements are mixed and often conflicting and confident conclusions cannot be drawn. Several variables may concur to contradictory results including the wide number of supplements to be considered, their combined use, their dose and timing of administration. Furthermore the choice of the proper indexes to be analyzed is certainly a major bias for several published studies on the topic as a misinterpretation of results may follow the analysis of indirect instead of direct signs of muscle injury. Thus, although many nutrients are potentially able to impact on the mechanisms underlying the appearance of muscle damage following exercise, the final efficacy and safety of their supplementation deserves future rigorous investigation.

The present chapter discusses the potential role of antioxidants, creatine, carnitine and branched chain amino acids on exercise induced muscle damage.

3. Antioxidant/vitamines

Nutritional antioxidants are non enzymatic compounds including the lipid-soluble vitamin E, β-carotene, co-enzyme Q10 (CoQ), and the water-soluble vitamin C, glutathione, and uric acid. These antioxidants either scavenge ROS into less reactive molecules or prevent their transformation into more highly reactive forms, having intracellular and extracellular sites of action [22].

During exercise and exercise-induced damage whole body oxygen consumption increases up to 20 fold and ROS are generated in excess [23]. The primary sources of ROS are endogenous sites within the skeletal muscle, whereas the secondary sites of production are exogenous [24]. Within the muscle the main font of ROS is reputedly through electron leakage in the mitochondria during mitochondrial phosphorylation and via xanthine oxidase metabolism in the capillary endothelium [25, 26] whereas the main secondary source of ROS is generated during the inflammation mainly by neutrophils.

Considering that increased ROS production could challenge the natural antioxidant defense system and that ROS play a major role in the initiation and progression of exercise-induced skeletal muscle injury [27, 28], it has been hypothesized that antioxidants supplementation may minimize its extent and this topic has been faced by a plethora of studies. However, to date, strong evidence to support significant reductions in structural or functional impairment due to antioxidants is missing. Inconsistencies of findings may relate to ununiformities in the experimental designs in terms of type, dose, time of administration and chosen indexes to evaluate and quantify muscle injury. In fact the majority of investigations have been focused on the effects of vitamin C and E and looked at changes in plasma concentrations in CK and LDH and oxidative stress markers. Much less studies have analyzed direct indexes of muscle damage as loss in muscle strength, soreness and structural/ultrastructural changes of the fibers [26, 29]. Indeed a not univocal strategy in the timing of supplementation (pre exercise, during exercise, post exercise) has been adopted demonstrating *de facto* a lack of a univocal and definite and generally accepted mechanism underlying the correlation between exercise, muscle damage, and antioxidant activity. As a matter of facts several studies have examined the effects of antioxidants on indices of ROS-induced muscle damage in exercise and suggested that antioxidant supplementation may exert some protection particularly in relation to bouts of resistance exercise in untrained or physically active individuals [30-35] as demonstrated by a reduced inflammation [35-39], force loss [30, 40, 41], and fatigue appearance [42, 43] and no evidence for any beneficial effect on performance [44]. On the contrary no significant effects of antioxidant supplements have been found by other authors on indices of inflammation [45-49], cell damage [45, 48, 50-53], oxidative stress [53], and muscle soreness [54-57]. The lack of effects appears to be particularly evident in highly trained individuals whose adaptation to increased exposure to oxidation is normally able to promote a secondary increase of the endogenous antioxidant defenses that reduce the risk of oxidative damage [58, 59] Therefore even following extreme exercise paradigms, unlike short periods of modest exercise [60], indications of oxidative damage may lack in well trained athletes [61]. Importantly in these conditions exposure to antioxidants may hinder the beneficial cell adaptations to exercise

thereby promoting muscle damage instead of recovering from it [55, 62-64]. In fact there are concerns about possible adverse effects of megadose supplementation, as several of these nutrients have been shown to increase markers of exercise-induced oxidative stress thus serving as prooxidants instead of antioxidant nutrients. For example after intense exercise, supplementation with vitamin C, vitamin E, N-acetylcysteine and coenzyme Q10 was associated with oxidative stress, increased serum CK and, in some cases, reduced performance [63-67]. In another study prolonged (2 months) vitamin E supplementation increased lipid peroxidation and inflammation [68] whilst no effects on resting levels of oxidative stress were observed by others following vitamin C and E supplementation in ultraendurance athletes [69].

Vitamin C. To date there is no evidence to support the hypothesis that acute and prolonged supplementation with ascorbic acid before and/or after exercise may prevent/attenuate exercise induced muscle damage.

Although a long lasting supplementation with vitamin C before exercise bouts has met with conflicting results, some of them reporting a beneficial effect on lipid peroxidation and inflammation [70] probably due to an increase of the baseline response of antioxidant enzymes [71], nowhere a clear effect on muscle damage has been reported. Similar results have been obtained following acute supplementation prior to exercise. In particular an early study by Ashton and colleagues [72] demonstrated a protective effect of an acute dose of ascorbic acid against ROS production following exhaustive exercise. In this study no indices of muscle damage were measured. Later the effects of an identical dose of ascorbic acid 2 hours before 90 minutes of intermittent shuttle running were investigated by others [52]. Supplementation did not affect the increases in serum CK, serum aspartate aminotransferase, and delayed onset muscle soreness [52]. Importantly the same negative results were obtained when supplementation was performed after training. In particular vitamin C supplementation for 3 days after an intermittent shuttle running showed no effects on indexes of muscle damage, lipid peroxidation and inflammatory response [56]. In another study combination of vitamin C with n-acetylcysteine for 7 days after an eccentric bout of exercise exerted a prooxidant effect. Furthermore equivocal results emerged when supplementation was given before and after exercise bouts, as the smoothening effects on DOMS observed by some authors [34, 73] have been not confirmed by others [54, 55].

Overall, although conflicting results on the topic may result from ununiformities of supplementation strategies and inconsistencies in the experimental procedures adopted (for example the lack of crossover design or the missing measures of direct indexes of muscle damage), there is limited evidence of a protective effect of vitamin C on exercise induced muscle damage.

Vitamin E. Vitamin E, the most important lipid-soluble antioxidant vitamin, is known to stop the progression of the lipid peroxidation chain reaction and is an important scavenger of the superoxide, hydroxyl and lipid peroxyl radicals [74]. Vitamin E can be recycled from its radical form by vitamin C and less efficiently by other antioxidants (glutathione, CoQ, cysteine and a-lipoic acid). Importantly, this vitamin may also act as a prooxidant in the absence of these antioxidants [75]. Most of studies investigating the effects of vitamin E on exercise induced muscle damage have utilized a preexercise supplementation strategy starting from the assumption that vitamin E, contrarily to vitamin C, being lipid-soluble can be stored in tissues.

Anyhow direct indexes of muscle damage were not adequately measured in most cases and available results, albeit suggesting a minimal, unless absent [45], protection of vitamin E supplementation on oxidation, membrane damage [76, 77], and inflammation [76], do not provide enough evidence for a protective effect of vitamin E on exercise induced muscle damage.

In conclusion, there is little evidence to support the suggestion that supplementation with antioxidant nutrients can improve exercise performance, but there is a growing body of evidence to suggest that supplementation may reduce the extent of exercise induced oxidative damage. If this is indeed the case, it may be that the athlete undertaking a strenuous training programme may benefit in the long term by being able to sustain a higher training load (less fatigue). There is also evidence, however, that prolonged exposure to training increases the effectiveness of the endogenous antioxidant mechanisms, and it may be that supplementation is unnecessary or prooxidant and thus potentially unsafe.

4. Carnitine

Carnitine is the required carrier of fatty acids from the cytoplasm into mitochondria, where they undergo β-oxidation [78, 79]. In the cytoplasm carnitine combines with fatty acyl-coenzyme A (acyl-CoA) thus allowing that fatty acids may enter the mitochondrion. The first step of this process is catalysed by carnitine palmitoyl transferase 1 (CPT1) and the trans-membrane transport is facilitated by acylcarnitine transferase. Within the mitochondrion free carnitine is regenerated by the action of carnitine palmitoyl transferase 2 (CPT2) and the released fatty acyl-CoAs entry the β-oxidation pathway. Within the mitochondrion, carnitine also regulats the acetyl-CoA concentration and the concentration of free CoA. Considering that free CoA is involved in the pyruvate dehydrogenase reaction and in the process of β-oxidation it contributes to the coordinated integration of fat and carbohydrate metabolism. In fact when glucose oxidation increases, acetyl groups can be translocated from acyl-CoA within the mitochondrial matrix to the cytoplasm. The accumulation of cytosolic acetylcarnitine may result in a limitation of CPT-1 activity because of the decrease in availability of free carnitine. Consequently, there is fatty acid oxidation, since skeletal muscle predominantly expresses an isoform of CPT-1 with low affinity for L-carnitine [80].

In humans, 75% of carnitine is obtained from the diet. The primary dietary sources of carnitine are red meat and dairy products [81]. Dietary carnitine is absorbed from the intestinal lumen across the mucosal membrane by both passive and active transport mechanisms. Carnitine is also synthesized in the liver and in the kidneys (not in skeletal and cardiac muscle) [82] from the essential amino acids, lysine and methionine [83, 84] having ascorbic acid, ferrous iron, pyroxidine, and niacin as necessary cofactors [85]. More than 95% of the body's total carnitine store is within skeletal muscle tissue [86], and decreased plasma carnitine level has been related to low tissue concentrations [79, 87].

Considering the key roles of carnitine for normal skeletal muscle bioenergetics (long-chain fatty acid oxidation; removal of acyl groups from the mitochondria; detoxification), its