



Major clinical outcomes of metabolism and sports physiology: a systematic review

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Abstract

Introduction: In the sports medicine setting, many of the established positive health benefits of exercise have been documented by historic discoveries in the field of exercise physiology. Mitochondrial function is critical in regulating all three of the classic physiological factors that limit endurance performance. **Objective:** It was to carry out a systematic review to present the main information on exercise physiology in the light of mitochondrial redox activities in sports performance, as well as the guidelines of sports medicine in this regard.

Methods: The systematic review rules of the PRISMA Platform were followed. The search was carried out from August to September 2023 in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases, using articles dated from 2008 to 2023. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 200 articles were found, and of the 77 articles were evaluated in full and 32 were included and developed in this systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 37 studies with a high risk of bias and 78 studies that did not meet GRADE. It was concluded that sports physicians may seek to use an increasing number of non-invasive techniques to study muscle metabolic functioning, answering how mitochondrial networks interact with O₂ kinetics, how to remodel mitochondrial

networks to increase performance, and how training affects the interaction between glycogen/lipid storage site and mitochondrial networks. Physiological and psychological demands during training and competition generate fatigue and reduce an athlete's sport-specific performance capacity. The magnitude of this decrease depends on several characteristics of the exercise stimulus, such as type, duration, and intensity, as well as on individual characteristics, such as physical conditioning, profile, and fatigue resistance. Recent evidence suggests that exercise-induced reactive species are essential upstream signals for the activation of redox-sensitive transcription factors and the induction of exercise-associated gene expression. Free radicals and oxidative stress are increasingly included in major reviews of exercise physiology as regulators of responses and adaptations.

Keywords: Sports medicine. Metabolism. Exercise physiology. Sports performance. Mitochondria. Oxidation-reduction.

Introduction

In the sports medicine setting, many of the established positive health benefits of exercise have been documented by historic discoveries in the field of exercise physiology. These investigations generally evaluate performance limits or exercise-induced health benefits [1,2]. Thus, several important findings have

been informed by the study of highly trained athletes. Recent progress has been made regarding skeletal muscle metabolism and personalized exercise regimens [2,3].

In this context, regenerative sports medicine aims to address conditions related to sport and aging in the locomotor system, using techniques that induce tissue regeneration [4]. It also involves the treatment of meniscal and ligament injuries in the knee, Achilles tendon tears, rotator cuff tears, and cartilage and bone defects in various joints, as well as the regeneration of tendon-bone and cartilage-bone interfaces [5]. There has been considerable progress in this field in recent years, resulting in promising steps towards the development of improved treatments, as well as the identification of enigmas that require further targeted research [6].

Moreover, regular physical training has broad health benefits by acting positively on almost all of the body's organic systems [7]. The mysteries of human physiology and the adaptive response to acute and chronic physical training have been largely elucidated through exercise science. Thus, exercise physiologists have studied the physiological response to physical activity and sports. Clinical exercise physiologists prescribe exercise in the prevention and rehabilitation of acute and chronic illnesses. Physical training is a clinically proven practice that is a cost-effective primary intervention that can delay and prevent the health burdens associated with metabolic disorders [8].

In this sense, physical training is defined as planned exercises of physical activity that occur repeatedly over a period lasting from weeks to years. There is aerobic training, which consists of weight-bearing and non-weight-bearing activities, and weight training, which consists of weight-bearing activities that work against an external load. Both types of training can be developed as progressive programs, which are defined as a planned increase in duration, frequency, and/or intensity of activity throughout the training period [8].

Despite the value of being able to fractionate training intensity more accurately, there has not yet been a general strategy that links training frequency \times intensity \times time to performance changes in any type of quantitative model. Starting in the mid-1970s, Eric Banister and his colleagues developed the concept of "Training Impulse" or TRIMP [9]. This concept recognized that measuring training intensity as a function of the percentage of Heart Rate Reserve (% HRR) multiplied by a non-linear factor (conceptually equivalent to the intensity vs. blood lactate relationship) multiplied by the duration produced a number (TRIMP) that represented both the gain in physical conditioning

and the gain in fatigue, contributed by this training session. Thus, if this number is added over a convenient period (one week), it is possible to obtain an appreciation of the product in training volume and intensity [1,3,4,9].

Thus, recognizing that there were distinct influence curves related to physical conditioning and fatigue, subsequent performance can be explained by the integration of the influence curves of physical conditioning and fatigue, making it necessary to monitor training, so that the details of the training could be expressed quantitatively and temporally linked to performance. The integration of elements already considered as part of the internal training load into single constructs appears to be of importance. It is known that the total training load, the distribution pattern of training intensity, and the variation in training load are independently related to performance [5,9].

Therefore, this study carried out a systematic review to present the main information on exercise physiology in light of mitochondrial oxidation-reduction activities in sports performance, as well as the directions of sports medicine in this aspect.

Methods

Study Design

The present study followed an international systematic review model, following the rules of PRISMA (preferred reporting items for systematic reviews and metaanalysis) [10]. The methodological quality standards of AMSTAR-2 (Assessing the methodological quality of systematic reviews) were also followed. Available at: <https://amstar.ca/>. Accessed on: 09/23/2023.

Data Sources and Research Strategy

The search strategies for this systematic review were based on the keywords (MeSH Terms): "Sports medicine. Metabolism. Exercise physiology. Sports performance. Mitochondria. Oxidation-reduction". The search was carried out from August to September 2023 in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases, using articles dated from 2008 to 2023. In addition, a combination of the keywords with the Booleans "OR", "AND" and the "NOT" operator was used to target scientific articles of interest.

Quality of Studies, Eligibility Criteria, and Risk of Bias

Studies were chosen that rigorously presented the results of the search process that presented scientific quality according to the GRADE classification [11], and that did not present a risk of significant bias, that is, that could compromise the safety of the results. According to

GRADE recommendations [11], the quality of scientific evidence in the studies covered was classified as high, moderate, low, or very low, according to the risk of evidence bias, sample size, clarity of comparisons, precision, and consistency in the effects of the analyses. High-quality evidence was assigned using four criteria: 1) Randomized or prospective controlled clinical trials; 2) Retrospective clinical trials or case series; 3) Sample size greater than 15 participants; 4) Studies with statistically well designed results; 5) Studies published in indexed journals and with a significant impact factor; 6) descriptive, interpretative, theoretical (credibility of methods) and pragmatic validity.

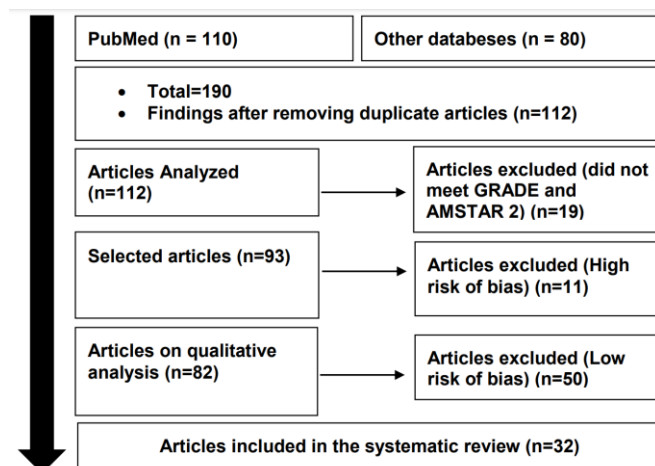
The Cochrane Instrument [12] was adopted to assess the risk of bias in the chosen studies using the Cohen Test to calculate the effect size (Effect Size) versus the Inverse of the Standard Error (precision or sample size) to determine the Risk of Bias studies using the Funnel Plot graph.

Results and Discussion

Summary of Literary Findings

A total of 190 articles were found. Initially, duplication of articles was excluded. After this process, the abstracts were evaluated and a new exclusion was carried out, removing articles that did not include the topic of this article, resulting in 112 articles. A total of 82 articles were evaluated in full and 32 were included and developed in the present systematic review study (Figure 1). Of the total of 35 articles, 3 articles are related to the PRISMA, GRADE, and COCHRANE standards, not being considered to compose the scientific writing, making a total of 32 final articles. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 11 studies with a high risk of bias and 19 studies that did not meet GRADE and AMSTAR-2.

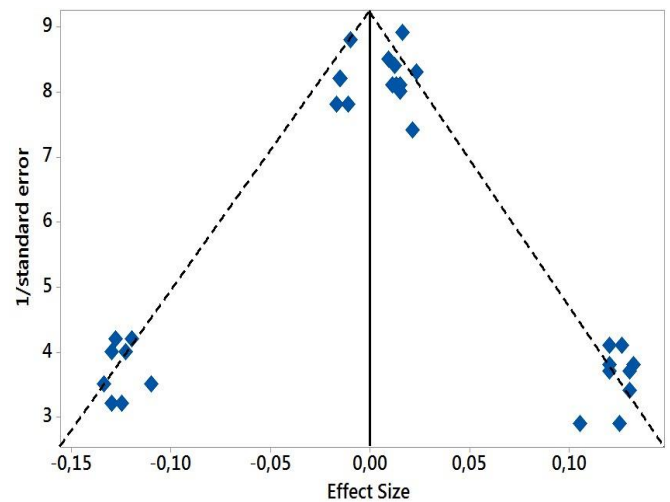
Figure 1. Article selection process.



Source: Own authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using the Cohen Test (d). The sample size was determined indirectly by the inverse of the standard error (1/Standard Error). This graph presented symmetrical behavior, not suggesting a significant risk of bias, both between studies with a small sample size (lower precision) that are shown at the base of the graph and in studies with a large sample size that are presented in the upper region.

Figure 2. The symmetric funnel plot suggests no risk of bias among the small sample size studies that are shown at the bottom of the plot. High confidence and high recommendation studies are shown above the graph (NTotal =32 clinical studies evaluated in full in the systematic review).



Source: Own Authorship.

Major Findings

Physical activity causes marked circulatory and metabolic adaptations and results in marked changes in, for example, skeletal muscle and connective tissue. Strengthening skeletal and cardiac muscles, better oxidative capacity and increased hormonal sensitivity improve the general functional level in athletes and contribute to the improvement of risk factors. However, physical exercise can lead to overuse injuries to connective tissue. A deeper understanding of the mechanisms underlying the development of overuse injuries is crucial to diagnostic and treatment regimens, not only in sports medicine but also more generally in disease prevention and treatment. In this sense, the effects of different types of resistance training on functional capacity, muscular strength, and power are observed [13].

In this regard, quadriceps weakness is common after anterior cruciate ligament (ACL) reconstruction,

resulting in prolonged disability and increased risk of reinjury and osteoarthritis. Functional resistance training (FRT) combines resistance training with task-specific training and can be beneficial in restoring quadriceps strength. Thus, one study looked at whether a walking-specific FRT program (e.g., resistance walking) improves knee strength in individuals after ACL reconstruction. A total of 30 participants were randomized into one of three groups, 1) FRT with a custom knee brace applied to the ACL leg, 2) FRT with an elastic band tied to the ankle of the ACL leg, or 3) a target match condition in which no resistance was applied externally. Participants in all groups received training while walking on a treadmill 2-3 times a week for 8 weeks. Isometric knee extension and flexion strength were measured before the start of the intervention, after the intervention (POST), and 8 weeks after the end of the intervention (POST-2). The brace group had greater knee extensor strength compared to the target match group in POST and POST-2 ($p < 0.05$). The brace group had greater knee flexor strength than the target match group in POST and POST-2 ($p < 0.05$) and the BAND group in POST ($p < 0.05$). Therefore, FRT applied through a custom knee brace results in improvements in knee extensor and flexor strength after ACL reconstruction. FRT is a beneficial adjunct to ACL rehabilitation and leads to improved strength compared to standard treatment [14].

In this context, both aerobic training and resistance exercise are beneficial for improving hyperglycemia associated with the metabolic disease Type 2 Diabetes. This beneficial blood glucose-lowering effect may be at least partially attributed to training-stimulated changes in glucose transport in muscle, skeletal and glucose metabolism. The effects of aerobic training are generally greater in magnitude than those elicited by resistance training [9].

Furthermore, several important gaps in the current understanding of how aerobic and resistance training alter skeletal muscle transport and muscle glucose metabolism have been identified. Therefore, aerobic exercise training comes in a wide variety of forms, such as aerobics classes, cycling, dancing, jumping jacks, jumping rope, rowing, running, skating, skiing, swimming, and hiking. In aerobic training research, the most common forms of exercise used in humans are treadmill running and cycle ergometer training [2,3,9]. As for resistance physical training, there are also a variety of forms, such as biceps curls, bench presses, bench presses, barbell squats, bent-over rows, and sideband walks. The most common form of exercise used in humans is weight-bearing exercise [3-5].

Oxy-Reduction (redox) – Basis of Exercise

Physiology

Redox reactions control fundamental processes in human biology. Therefore, it is safe to assume that responses and adaptations to exercise are mediated by redox reactions [15]. Several scientific studies show that redox reactions are the basis of exercise physiology, describing the redox signaling pathways that regulate four characteristic acute responses induced by exercises, such as muscle contractile function, muscle contractile function, glucose uptake, blood flow, and bioenergetics and four chronic exercise-induced adaptations such as mitochondrial biogenesis, muscle hypertrophy, angiogenesis redox homeostasis [15,16].

In this sense, it is well established that exercise stimulates a set of local and systemic stressors that trigger integrated acute responses that, in the long term, result in phenotypic adaptations in all systems of the human body [16-18]. An interesting series of studies has been performed on intact mouse fibers (i.e., fibers together with their entire redox environment consisting of antioxidants and target molecules) [19]. Transient exposure (4 minutes) or low concentration (in the order of nM and pM) of hydrogen peroxide (H_2O_2) or tert-butylhydroperoxide (t-BOOH) increased submaximal muscle force production in fast-twitch muscle fibers, while the addition of the antioxidant dithiothreitol (DTT) resulted in a progressive decline in strength. On the other hand, prolonged exposure (8 minutes) or high concentration (in the order of mM) of H_2O_2 decreased the submaximal production of muscle force, an indication of the development of muscle fatigue, and this was reversed by the addition of DTT [19].

In this context, transient exposure of unrestrained intact muscle fibers to DTT decreased submaximal force production and this was reversed after treatment with the opposite redox stimulus, H_2O_2 [20]. Thus, an optimal cellular redox state appears to be the main determinant for normal muscle force production, while a more reduced (e.g., at rest) or oxidized (e.g., during fatigue protocols) state negatively regulates this process [21].

Similar studies using mechanically engineered skin muscle fiber preparations have shown that H_2O_2 , in concentrations up to 10 mM, does not necessarily exert an effect on force production [22]. However, in some cases, comparable or even higher levels of H_2O_2 have been found to negatively affect contractile function due to the oxidation of specific cysteine and methionine residues at the actin-myosin interface [23,24].

Furthermore, a study carried out by Murphy et al. (2008) [25] treated injured muscle fibers with myoglobin and glutathione, together with low concentrations of H_2O_2 (100-300 μM). They found that glutathione partially prevented the decline in muscle

force production induced by the $\text{H}_2\text{O}_2\text{-Fe}^{2+}$ /myoglobin reaction in slow-twitch muscle fibers, while in fast-twitch muscle fibers, glutathione increased Ca^{2+} sensitivity. This was later explained by the interaction of glutathione with oxidized cysteine residues in the fast isoform of troponin, which increased myofibrillar Ca^{2+} sensitivity. Therefore, H_2O_2 regulates the production of muscular force positively or negatively mainly by altering myofibrillar sensitivity to Ca^{2+} [22].

Still in this context, in addition to H_2O_2 , it was also demonstrated that the superoxide radical affects the production of muscular force, however, this was facilitated by a different mechanism, that is, a cross-linked sarcoplasmic alteration of Ca^{2+} , and not sensitivity to Ca^{2+} [26].

Regarding nitric oxide (NO) and its effects on force production, experiments with intact fast-twitch muscle fibers showed that NO affects contractile function by altering myofibrillar sensitivity to Ca^{2+} . Furthermore, a study using injured muscle fibers treated with S-nitroso-N-acetylpenicillamine and nitrosogluthione (nitric oxide donors) reported decreased Ca^{2+} sensitivity in fast-twitch fibers, but maximum strength was not affected [27].

Unlike fast-twitch fibers, the same study showed that slow-twitch muscle fibers treated with the two nitric oxide donors did not exhibit altered myofibrillar Ca^{2+} sensitivity. Other studies have demonstrated that along with Ca^{2+} sensitivity, reactive nitrogen species can also affect muscle force production and this may result from S-nitrosylation of myosin heads by peroxynitrite, a highly reactive species produced by the reaction of superoxide radical with nitric oxide [27].

Finally, retroactive modifications, along with other redox reactions, of calcium release uptake proteins, such as the ryanodine receptor/ Ca^{2+} release channel (RyR1), have also been described. These structural changes also affect muscle contractile function, indicating that oxygen, nitrogen, and sulfur radicals regulate the production of muscle force and the development of fatigue by altering Ca^{2+} release [28-30].

Mitochondrial in Exercise Physiology

Mitochondrial function is critical in regulating all three classic physiological factors that limit endurance performance [31]. Mitochondria have been overlooked in the era of genomic research, but these organelles are experiencing a renaissance as their importance as signaling modulators, not just energy producers, becomes clear. Although exercise physiologists have consistently studied mitochondria concerning their ability to metabolize substrates [32], new data further elucidate the mechanism of energy generation and delivery within skeletal muscles [33].

Subsarcolemmal and intermyofibrillar mitochondria are heterogeneous subpopulations [34]. This heterogeneity may be partially due to subsarcolemmal mitochondria's need for regulation of sarcolemmal membrane function, while mitochondria are the main powerhouses of exercise due to their proximity to contracting sarcomeres [35]. However, the subsarcolemmal and intermyofibrillar changes are part of a mitochondrial reticulum that provides a conductive pathway for energy distribution. Within this mitochondrial reticulum, proteins associated with the proton-mitochondrial motif and force production are preferentially located at the cell periphery, and proteins that use the proton-motive force for the production of ATP inside the cell [33].

Given this recent advance in understanding the mechanism of mitochondrial energy creation and delivery, it is prudent to ask what else is opaque regarding skeletal muscle metabolism. Several key principles of skeletal muscle metabolism are the results of perceiving muscle as an integrated network of energy creation and delivery. This also applies when thinking about O_2 kinetics in the cell phone, peripheral fatigue from resistance exercise, and the economy of energy generation and locomotion [31].

The time needed to fully recover is proportional to the level of fatigue and the consequences of exercise-induced fatigue are multiple. Whatever the objective of the exercise session that follows, training or competition, it is crucial to understand the importance of optimizing the period between exercise sessions to accelerate regenerative processes and facilitate recovery or define the next stimulus at the right time. ideal [3-5]. Not respecting an athlete's recovery needs can lead to excessive fatigue accumulation and overreaching. There is still a lack of consideration of specific time frames for different physiological mechanisms of exercise-induced fatigue. Furthermore, recommendations regarding the timing and dosing of recovery based on these timings are limited [1,2].

In this regard, redox reactions are increasingly recognized as a fundamental element of the cellular signaling mechanism, along with other well-established types of biochemical reactions that fine-tune human metabolism, for example, phosphorylation and ubiquitination. There are many other examples of responses and adaptations linked to exercise metabolism that is controlled, at least in part, by redox reactions, such as neuroprotection and cognitive function, mechanotransduction, muscle regeneration, autophagy, insulin sensitivity and glycemic control, heat shock proteins metabolism and nerve-muscle interactions [1].

Conclusion

It was concluded that sports physicians may seek to use an increasing number of non-invasive techniques to study muscle metabolic functioning, answering how mitochondrial networks interact with O₂ kinetics, how to remodel mitochondrial networks to increase performance, and how training affects the interaction between glycogen/lipid storage site and mitochondrial networks. The physiological and psychological demands during training and competition generate fatigue and reduce an athlete's sport-specific performance capacity. The magnitude of this decrease depends on several characteristics of the exercise stimulus, such as type, duration, and intensity, as well as individual characteristics, such as physical conditioning, profile, and fatigue resistance. Recent evidence suggests that exercise-induced reactive species are essential upstream signals for the activation of redox-sensitive transcription factors and the induction of exercise-associated gene expression. Free radicals and oxidative stress are increasingly included in major reviews of exercise physiology as regulators of responses and adaptations.

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Informed consent

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Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

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