Unraveling the Interplay of Oxidative Stress, Aging, and Skeletal Muscle: Insights and Interventions for Optimal Muscle Function in the Elderly

Abstract

Purpose: Aging is related to the onset of sarcopenia. Understand how its development occurs by immunological factors by oxidative stress. One of the main effects for a person is the reduction of muscle function. Aerobic and resistance physical exercise can reduce the progression of oxidative stress and, consequently, sarcopenia. **Materials and Methods**: Systematic review with a sample of six scientific papers published in academic journals. **Results and Conclusion**: Studies show that exercise then induces a prevention response to free radical damage. Furthermore, physical exercise induces effects on the concentration of superoxide dismutase enzyme (SOD), catalase, adenosine monophosphate (AMP), sirtuin 1 (SIRT-1) and peroxisome proliferator-activated receptor-gamma coactivator (PGC-1α), which are important for better skeletal muscle condition. Understanding how the elderly muscle responds to exercise is important, and it is necessary to understand the mechanisms of reactive oxygen species (ROS) and reactive nitrogen species (RNS) generation and the modulation of the proinflammatory cytokines and the antioxidant system in response to the exercise.

Key-words: Sarcopenia; Cachexia; Exercise; Atrophy.

Introduction

Aging is a natural process directly related to genetic and environmental factors that can slow down or accelerate an individual's development. Changes in muscle conformation, oxidative stress, inflammation, physical activity and nutrition are all independently balanced, interacting and maintaining factors affecting the body's ability to perform physical activity [1].

Sarcopenia is a disease associated with aging that causes an exponential reduction in skeletal muscle [2] The reduction of muscle directly affects the muscular function, reduction of the functional capacity and consequently of the physical fitness of the bearer. Thus, sarcopenia causes reduced quality of life, increased falls and consequently mortality [3].

Exercise and caloric restriction effects on antioxidant actions, muscle content and oxidative stress are important for understand in aging [4]. Different effects how increased antioxidant, anti-inflammatory action, mitochondria increase and muscle content after exercise and caloric restriction should observed. The effects of aging on muscle atrophy were attenuated with exercise and caloric restriction [4,5].

The elderly muscle presents conditions that contribute to the muscular atrophy development and consequent sarcopenia. The increase of proinflammatory cytokines and oxidative stress have significant roles. Exercise, even temporarily raising free radicals, these are counteracted by the system antioxidants, balancing the whole system. The exercise then induces a prevention response to the damages caused by free radicals. Thus, understanding how the elderly muscle responds to exercise is important, and it is necessary to understand the mechanisms of ROS and RNS generation and the modulation of antioxidant system in response to exercise.

In skeletal muscle, the action of SIRT 1, a protein that increases the amount of PGC-1a occurs. PGC-1a acts on the biogenesis and proliferation of mitochondria. There was a reduction for SIRT-1 and PGC-1α in elderly rats compared to young rats [6].

Skeletal muscle cells produce transient ROS flux in response to a variety of stimuli, such as intense contractile activity, thermal stress, disuse atrophy, acute hypoxia, and physical stress [7]. ROS and RNS are produced in several ways. Physical exercise contributes, in an acute way, to the increase of free radicals [7]. Physical exercise stimulates the production of free radicals, and as a response to this system, an increase of antioxidant enzymes occurs [8].

Aging is also associated with increased generation of ROS and RNS, which cause changes in proteins, lipids and DNA. Moreover, the elderly muscle presents in a state of chronic inflammation, due to the increase of inflammatory cytokines. The inflammatory response to injury may subject the elderly muscle to increased oxidative stress [3]. In this scene, the muscle has a greater risk of injuries and capacity of regeneration reduced.

Material and methods

A literature search through PubMed, ResearchGate and HOLLIS Harvard Library Online Catalog was performed from the date of inception until 10/06/2021. A combination of the following keywords was used: Sarcopenia; Oxidative stress; free radicals; physical exercise; atrophy; and antioxidants. Furthermore, studies that were cited in the selected articles were verified.

Studies on association of sarcopenia, oxidative stress and physical exercise were included. Those excluded were: a) association between exercise and other pathologies only; b) association between exercise and young people's only; c) association between atrophy and neurodegeneration only; d) studies that utilized other isolated or concomitant supplementation.

From the researches made in the mentioned databases, there were 654 articles related to the key-words, from which, based on the titles scanning, 88 studies were separated in order to read the respective abstracts. After reading, 39 articles were selected to a complete reading and from these, 12 studies matched with the inclusion criteria and then were selected to this review.

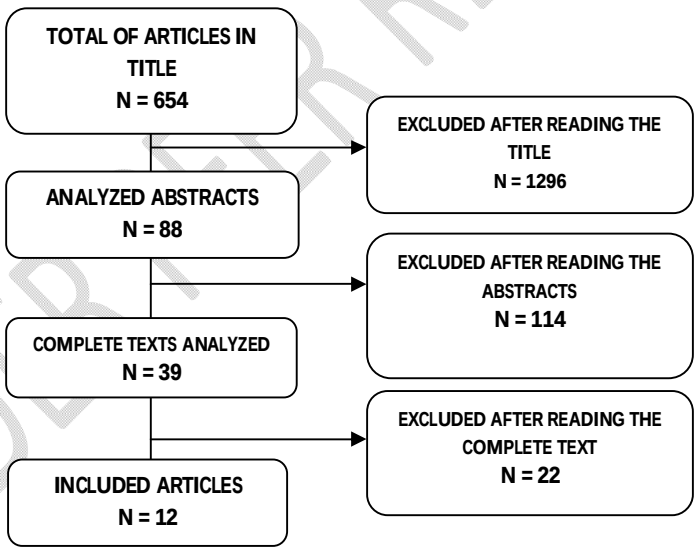

Figure 1. Organogram of the stages to sample delimitation

In table 1 there are six articles in which oxidative stress and exercise analysis in situation of metabolic and muscular assessment, with pre-clinical models (animals) and clinical ones (humans).

Results

The results of the systematic review are presented in table 1.

Table 1: Baseline characteristics of articles, which reported effects of oxidative stress and exercise analysis in situation of metabolic and muscular assessment.

Author/ Year	Design	Analyses	Results
Gianni et al., [10]	Humans 12 young people's 12 aged people's	8-OHdG Carbonyls Proteins mitDNA suppression SOD Catalase	Aged group ↑ Oxidative stress ↑Antioxidant action ↓ mitDNA
Morales-Alamo et al, [11]	Humans 9 young (Antioxidant and Control groups)	Carbonyls Proteins ACCβ AMPKα AMPKα_1e_2 AKT total	Antioxidant Group ↓ Proteolysis ↑Proteogenesis
Kujoth et al., [12]	Animals (Wild mouse) 3 at 30 months of age	Caspase-3 Quadriceps and gastrocnemius weight	Aged group (D257A) ↑Proteolysis ↓Peso muscular
Siu et al., [13]	Animals (Fischer 344 rats) 6 at 30 months of age	Gastrocnemius weight Protein content T-bars H_2O_2 Nitrotirosine SOD Catalase	Old Group and Suspension ↓Muscular weight ↑Oxidative stress ↑Antioxidant action ↓Antioxidant enzymes
Kim et al., [14]	Animals (Fischer-344 rats) 6 at 24 months of age	Plantar muscle weight Cross-sectional area (CSA) % Connective tissue Citrate Sintase H_2O_2 SOD IGF-1	Exercise group + Caloric Restriction (8%) ↑ Muscle Fibers ↑ IGF-1 ↑ Antioxidant ↓ Oxidative stress
Jackson et al., [15]	Animals (C57BL/6 mouse) 3, 18 and 28 months of age	SIRT-1 SOD H_2O_2 T-bars Carbonyls Proteins	Resveratrol Aged Group ↑ Sirt 1 ↑ Antioxidant action ↓ Oxidative stress

Discussion

The effects of exercise and caloric restriction on antioxidant actions, muscle content and oxidative stress were evaluated by the studies. Different effects were observed, but with increased antioxidant, anti-inflammatory action, mitochondria increase and muscle content after exercise and caloric restriction. The effects of aging on muscle atrophy were attenuated with exercise and caloric restriction.

Gianni et al [10] conducted a study that demonstrated the impact of mitochondrial aging theory on the elderly population, revealing an increase in reactive oxygen species (EROS) and a reduction in antioxidants. The findings of the study included elevated levels of carbonylated proteins and DNA degradation, a significant 37% reduction in mitochondrial DNA, as well as decreased activation of superoxide dismutase (SOD) and catalase. In another study by Morales-Alamo et al [11], the researchers investigated the effects of free radicals on the activation of AMP-activated protein kinase (AMPK) and Ca2+/calmodulin-dependent protein kinase II (CaMKII) during physical exercise. The study focused on young individuals who were supplemented with antioxidants. Interestingly, the results indicated that there was no notable difference in protein oxidation during exercise. However, the group supplemented with antioxidants exhibited higher AMPK activation and lower CaMKII activation compared to the control group. This suggests that antioxidants play a role in controlling free radicals during exercise, thereby preventing oxidative stress in the muscles.

Kujoth et al [12] conducted a study on genetically aged D257A mice to investigate the manifestation of sarcopenia at 9 and 30 months of age. The researchers analyzed the levels of Caspase-3, a marker of protein degradation, and the quantity of skeletal muscle in the animals. The results indicated a significant increase in Caspase-3 activity associated with age, suggesting an augmented protein degradation process. Furthermore, a progressive decline in skeletal muscle mass was observed with advancing age. In another study by Siu et al [13], aged and suspended rats were examined. These animals exhibited higher levels of reactive oxygen species (ROS) and reactive nitrogen species (RNS) compared to their younger counterparts and the control group. Surprisingly, the amount of antioxidant enzymes was excessively elevated in the aged and suspended rats. Additionally, these animals had lower skeletal muscle weight compared to the control group. Kim et al [14] demonstrated that a combination of caloric restriction and physical exercise can mitigate the effects of aging on skeletal muscle. Their study revealed that the joint implementation of calorie restriction and exercise led to an increase in the quantity of muscle fibers, elevated insulin-like growth factor 1 (IGF-1) levels, enhanced antioxidant enzyme activity, and reduced oxidative stress. Overall, these studies collectively highlight the impact of aging on skeletal muscle, including increased protein degradation, reduced muscle mass, elevated oxidative stress, and the potential for intervention through strategies such as caloric restriction, exercise, and antioxidant supplementation.

Several studies have shed light on the role of oxidative stress and the antioxidant system in aging and related conditions. Jackson et al [15] conducted a study focusing on resveratrol supplementation and its impact on oxidative stress and sarcopenia. The findings indicated that while resveratrol supplementation effectively reduced oxidative stress, it did not attenuate sarcopenia in elderly rats. Interestingly, the supplementation led to increased mitochondrial biogenesis and proliferation, as well as a reduction in inflammatory cytokines and free radicals. The integrity of the antioxidant system becomes particularly crucial during the aging process. It is widely recognized that aging is associated with an increased generation of free radicals, which subsequently results in the accumulation of oxidative damage. This oxidative damage has been implicated in the development of various diseases [3,16]. These studies collectively emphasize the importance of managing oxidative stress and maintaining the antioxidant system's functionality in aging. While interventions like resveratrol supplementation may show promise in reducing oxidative stress, further research is needed to explore their potential benefits in combating sarcopenia and age-related diseases effectively. The evaluation of physical exercise and antioxidant actions are interesting for the attenuation of aging actions on skeletal muscle. These effects may favor the reduction of the effects of sarcopenia on the individual and, consequently, increase in physical fitness, functional capacity and quality of life in the elderly.

In this way, as the muscle becomes more vulnerable by the antioxidant, structuring and gene changes, sarcopenia is favored to appear. Thus, muscle mass reduction is signaled by factors such as myostatin action and increased effects of the ubiquitin proteasome system [8]. The relationship between free radicals, oxidative stress, atrophy, sarcopenia, exercise and antioxidants can be observed in figure 1.

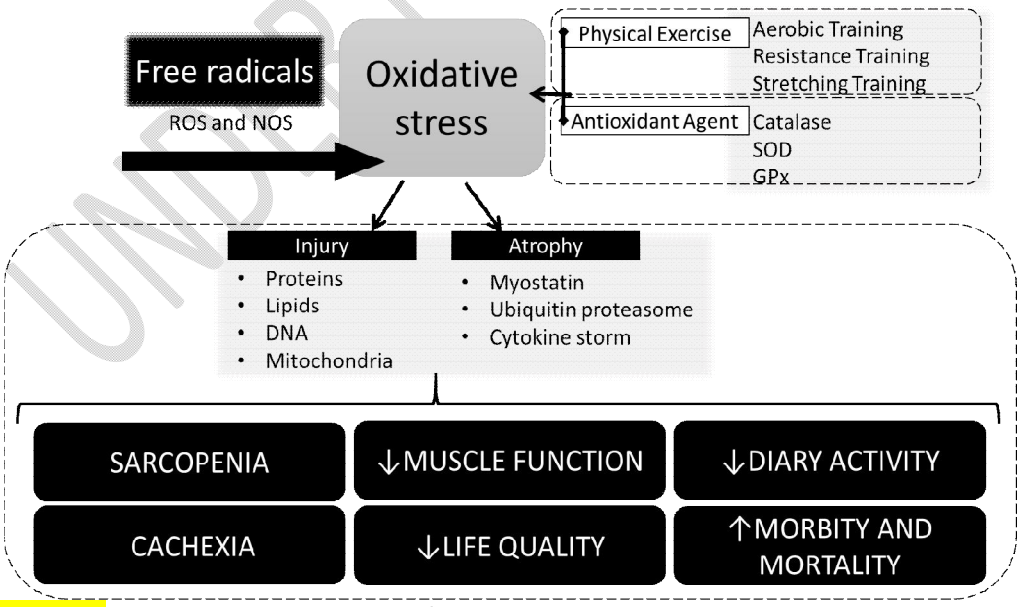

Figure 2. The relationship between free radicals, oxidative stress, atrophy, sarcopenia, exercise and antioxidants.

Conclusions

In conclusion, the studies discussed have provided valuable insights into the complex interplay between oxidative stress, aging, skeletal muscle health, and interventions to mitigate the effects of aging on muscle function. The impact of oxidative stress on mitochondrial function and the role of antioxidants in controlling free radicals during exercise. The detrimental effects of aging on skeletal muscle, including protein degradation, muscle mass decline, and elevated oxidative stress. However, showed promising results with the combination of caloric restriction and exercise, highlighting the potential for preserving muscle fibers, enhancing antioxidant enzyme activity, and reducing oxidative stress. While resveratrol supplementation, effectively reduced oxidative stress, its impact on sarcopenia attenuation was limited. Nevertheless, the overall findings underline the importance of managing oxidative stress and maintaining the integrity of the antioxidant system in aging. Further research is needed to explore comprehensive approaches that combine exercise and antioxidant strategies to combat the effects of aging on skeletal muscle effectively. By understanding the intricate relationships among free radicals, oxidative stress, atrophy, sarcopenia, exercise, and antioxidants, we can develop targeted interventions to improve muscle health and enhance the quality of life in the elderly.

References

1.Cohen S, Nathan JA, Goldberg AL. Muscle wasting in disease: molecular mechanisms and promising therapies. Nat Rev Drug Discov. 2015;14(1):58-74. doi: 10.1038/nrd4467.

2.Cruz-Jentoft AJ, Landi F, Topinkova E, Michel JP. Understanding sarcopenia as a geriatric syndrome. Curr Opin Clin Nutr Metab Care 2010;13:1e7.

3.Morley JE, Anker SD, von Haehling S. Prevalence, incidence, and clinical impact of sarcopenia: facts, numbers, and epidemiology—update 2014. Journal of Cachexia, Sarcopenia and Muscle. 2014;5(4):253-259. doi:10.1007/s13539-014-0161-y.

4.Wu X, Lu Y, Zhou S, Chen L, Xu B. Impact of climate change on human infectious diseases: Empirical evidence and human adaptation. Environment International, 2016; 86:14-23.

5. Narici MV, Maganaris C, Reeves N. Myotendinous alterations and effects of resistive loading in old age. Scand J Med Sci Sports. 2005;15(6):392-401.

6. Sakellariou GK, Jackson MJ, Vasilaki A. Redefining the major contributors to superoxide production in contracting skeletal muscle. The role of NAD(P)H oxidases. Free Radic Res. 2014;48(1):12-29. doi: 10.3109/10715762.2013.830718.

7. Falowo AB., Fayemi PO., M Voster. Natural antioxidants against lipid–protein oxidative deterioration in meat and meat products: A review. Food Research International, 2014; 64:171-181.

8. Niedzielska E, Smaga I, Gawlik M, Moniczewski A, Stankowicz P1, Pera J, Filip M. Oxidative Stress in Neurodegenerative Diseases. Mol Neurobiol. 2016;53(6):4094-4125. doi: 10.1007/s12035-015-9337-5.

9. Nakka VP, Prakash-Babu P, Vemuganti R. Crosstalk Between Endoplasmic Reticulum Stress, Oxidative Stress, and Autophagy: Potential Therapeutic Targets for Acute CNS Injuries. Mol Neurobiol. 2016;53(1):532-544. doi: 10.1007/s12035-014-9029-6.

10. Gianni P, Jan KJ, Douglas MJ, Stuart PM, Tarnopolsky MA. Oxidative stress and the mitochondrial theory of aging in human skeletal muscle. Exp Gerontol. 2004;39(9):1391-400.

11. Morales-Alamo D, Ponce-González JG, Guadalupe-Grau A, Rodríguez-García L, Santana A, Cusso R, Guerrero M, Dorado C, Guerra B, Calbet JA. Critical role for free radicals on sprint exercise-induced CaMKII and AMPKα phosphorylation in human skeletal muscle. J Appl Physiol (1985). 2013;114(5):566-77. doi: 10.1152/japplphysiol.01246.2012

12. Kujoth GC, Hiona A, Pugh TD, Someya S, Panzer K, Wohlgemuth SE, Hofer T, Seo AY, Sullivan R, Jobling WA, Morrow JD, Van Remmen H, Sedivy JM, Yamasoba T, Tanokura M, Weindruch R, Leeuwenburgh C, Prolla TA. Mitochondrial DNA mutations, oxidative stress, and apoptosis in mammalian aging. Science. 2005;309(5733):481-4.

13. Siu PM, Pistilli EE, Alway SE. Age-dependent increase in oxidative stress in gastrocnemius muscle with unloading. J Appl Physiol. 2008;105(6):1695-705. doi: 10.1152/japplphysiol.90800.2008.

14. Kim SH, Kang KA, Zhang R, Piao MJ, Ko DO, Wang ZH, Chae SW, Kang SS, Lee KH, Kang HK, Kang HW, Hyun JW. Protective effect of esculetin against oxidative stress-induced cell damage via scavenging reactive oxygen species. Acta Pharmacol Sin. 2008;29(11):1319-26. doi: 10.1111/j.1745-7254.2008.00878.x.

15. Jackson JR1, Ryan MJ, Alway SE. Long-term supplementation with resveratrol alleviates oxidative stress but does not attenuate sarcopenia in aged mice. J Gerontol A Biol Sci Med Sci. 2011;66(7):751-64. doi: 10.1093/gerona/glr047

16. Sbardelotto ML, Pedroso GS, Pereira FT, et al. The Effects of Physical Training are Varied and Occur in an Exercise Type-Dependent Manner in Elderly Men. *Aging and Disease*. 2017;8(6):887-898. doi:10.14336/AD.2017.0209.