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## **Oxidative Stress, Sarcopenia, Antioxidant Strategies and Exercise**

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### **Abstract**

Sarcopenia is a geriatric syndrome characterized by the progressive loss of muscle mass that reduces strength and physical performance. On a cellular level, sarcopenia is associated with negative protein turnover, impaired mitochondrial function, and increased levels of apoptosis, which leads to reduced muscle regeneration capacity and atrophy. In this paper, we discuss how aging-associated reactive oxygen and nitrogen species (RONS) and oxidative stress may contribute to the pathogenesis of sarcopenia. The identification of cost-effective interventions that could help maintain muscle mass and physical functions in the elderly is an essential public health challenge. We also discuss the possibility that different types of antioxidant strategies might prevent or reduce symptoms of the disorder. Moreover, since exercise is the best current strategy to prevent sarcopenia, we also highlight the possibility that exercise acts as an antioxidant.

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Skeletal muscle is the most abundant tissue in the human body, representing ~40% of body weight and ~30% of basal energy expenditure. Skeletal muscle plays a central role in locomotion, enabling a person to perform activities of daily living and allowing for posture maintenance, balance, thermogenesis processes, energy supply (this tissue contains the most important glucose and amino acids stocks), and insulin resistance protection. In order to ensure these essential functions, skeletal muscle must have sufficient mass and quality [1].

Skeletal muscle is a very plastic tissue that can adapt itself to environmental constraints. Indeed, an increase in stimulation, exercise or nutrition can lead to muscle hypertrophy and improved endurance [2]. Conversely, a decrease in mechanical constraints will

lead to muscle deconditioning characterized by atrophied, weak and fatigable muscles [1].

Muscle deconditioning that occurs with aging is commonly called sarcopenia. The definition of sarcopenia is still under debate. However, by merging the different existing definitions, sarcopenia can be defined as a geriatric syndrome initially characterized by a decrease in muscle mass that will become worse, causing deterioration in strength and physical performance [1]. Numerous factors contribute to sarcopenia, including diet, chronic diseases, physical inactivity, and the aging process itself [1].

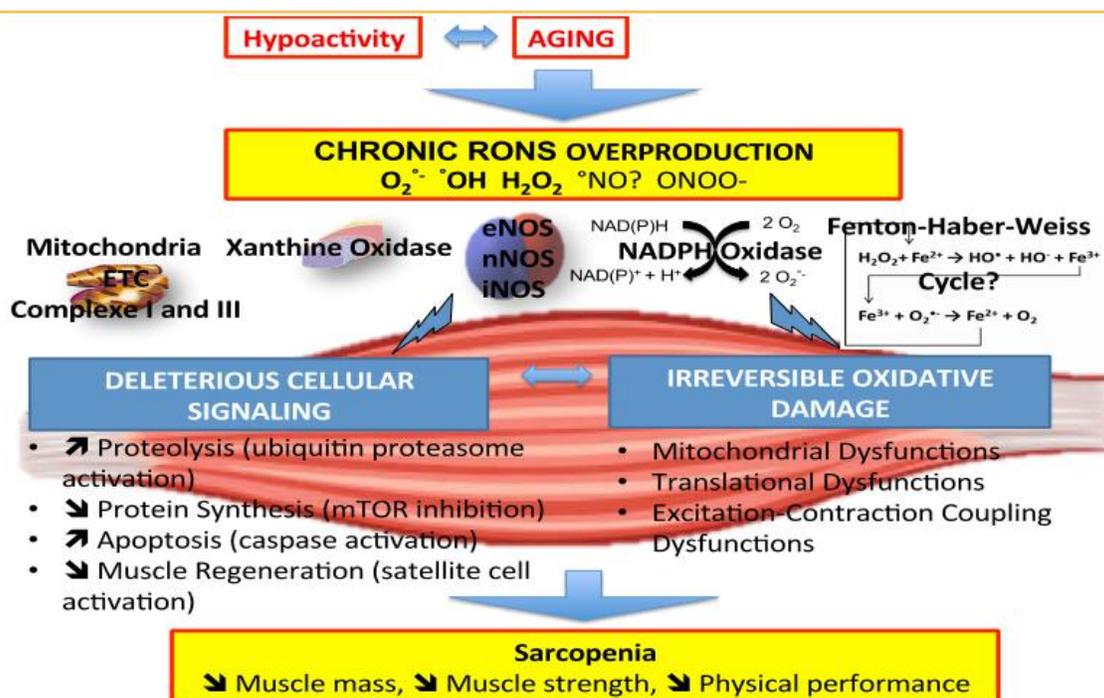
At the molecular level, muscle deconditioning during sarcopenia is due to higher proteolysis of contractile proteins by several proteolytic systems compared to their synthesis. Moreover, a higher rate of degradation of mitochondria compared to their

synthesis is associated with the deregulations of mitochondrial fusion and fission. Finally, the imbalance between apoptosis and regeneration processes favors apoptosis, which participates in the aforementioned mechanisms. These mechanisms are fully involved in skeletal muscle atrophy, which contributes substantially to the loss of muscle strength during aging. However, others molecular mechanisms are also involved, such as posttranslational modifications of contractile proteins and decoupling of the excitation–contraction complex [2]. These mechanisms contribute to the onset of sarcopenia and are affected by numerous upstream factors such as decreased anabolic hormone release, increased pro-inflammatory cytokines production, and insulin resistance. The relationships and interactions between all these factors remain partly unknown; however, chronic oxidative stress that occurs during aging appears to be a serious candidate [2-5] (figure 1).

Aging (which is often associated with hypoactivity) leads to the chronic overproduction of reactive oxygen/nitrogen species (RONS) by mitochondria, xanthine oxidase, NO synthase and NADPH oxidase. The involvement of the Fenton-Haber-Weiss Cycle is still under debate, and more data are necessary to reach a conclusion [1-5]. RONS overproduction leads

to irreversible oxidative damage to cell lipids, proteins and nucleic acids. This damage can trigger mitochondrial, translational or excitation–contraction coupling dysfunctions. Moreover, RONS chronic overproduction and irreversible oxidative damage appear to disturb cellular and molecular signaling, which leads to an increase in proteolysis and apoptosis and a decrease in protein synthesis and muscle regenerative capacity[2-5].

For example, aging is associated with decoupling of the excitation–contraction complex, which is involved in the reduced muscle strength found in older people compared to younger people. This decoupling is due to a reduced release of calcium by the sarcoplasmic reticulum. Indeed, during aging, ryanodine receptor 1 is oxidized and nitrosylated by RONS, leading to less released calcium and ultimately leading to a decrease in muscle strength [6]. Moreover, in cell cultures, it has been demonstrated that RONS increase 4-hydroxynonenal levels, which inhibit calcium ATPase pumps (SERCA) [7]. Inhibition of SERCA would lead to higher intracellular calcium, which in turn would activate two calcium-dependent proteolytic pathways, calpains and caspase 3 proteases, known to degrade myofilaments. However, more studies are needed to confirm how these mechanisms contribute to sarcopenia in people.



**Figure 1:** Main events related to oxidative stress leading to sarcopenia

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During aging and cachexia, contractile proteins are known to be more degraded by the ubiquitin-proteasome system. RONS overproduction could lead to the activation of p38MAPK and I $\kappa$ - $\alpha$ , which would activate the translation of E3 ligase, especially MuRF-1 and MAFbx. These two E3 ligases will ubiquitinate muscle contractile proteins, which will be degraded by the proteasome. On the other hand, RONS overproduction increases the level of oxidized protein and increases myofilament release as previously stated, which will then also be degraded by the proteasome [2-5]. All these mechanisms need to be explored in the elderly. Autophagy occurs in 5 steps: induction, expansion, autophagosome completion, autophagosome and lysosome fusion, and protein and organelle degradation. Concerning oxidative stress, sarcopenia and autophagy exist in a paradoxical situation. In fact, RONS appear to induce autophagy induction while concurrently inhibiting autophagosome formation. Indeed, chronic RONS overproduction leads to increased ULK-1 activation by inhibiting mTOR, which is known to inhibit ULK1 [4]. Reduced autophagosome formation appears to be due to the inactivation of ATG4 (by H<sub>2</sub>O<sub>2</sub>), which is necessary for autophagosome formation [8]. Finally, aging RONS production would lead to impaired autophagy, causing an accumulation of protein aggregates and damaged mitochondria, which could then produce more RONS.

Sarcopenia is also characterized by a decrease in muscle protein synthesis [1]. This decrease is due to an overproduction of RONS, particularly after lunch. When old rats were given antioxidants before lunch, increases in muscle protein synthesis occurred, reaching the same level as young rats [9]. Protein synthesis is mainly controlled by the mTOR pathways. It has been demonstrated in various cell cultures and animal models that the overproduction of RONS inhibits key molecules that control this pathway [4]. However, these mechanisms need to be studied in sarcopenic older adults.

Aging has often been described as being associated with hypoactivity [3]. It is currently well-established that both hypoactivity and the aging process itself lead to increased RONS production, resulting in muscle atrophy and sarcopenia [2, 3, 10]. During aging and/or periods of hypoactivity, RONS production increases before the onset of sarcopenia

and/or muscle atrophy, suggesting that RONS are a cause and not a consequence of sarcopenia and/or muscle atrophy [2, 3, 10]. In the future, it will be very important to determine the precise relationship between the aging process and its associated hypoactivity and the increased production of RONS.

RONS are involved in cellular and molecular functions and in signaling with an inverted U relationship. The best strategies against sarcopenia would allow for the maintenance of bodily functions in the optimal zone. Currently, however, we do not have sufficient knowledge to consistently provide a perfect dose of an ideal drug. Table 1 presents the main antioxidant strategies against sarcopenia. Globally, there are three classic antioxidant strategies:

- The first objective is to directly scavenge the RONS present in the organisms by supplementation with one antioxidant or a cocktail of various antioxidants such as vitamin C, vitamin E and carotenoids, or supplementation with natural compounds (which can be modified to increase their bioavailability) such as resveratrol
- The second objective involves directly targeting RONS sources with pharmaceutical products such as allopurinol, which is an inhibitor of xanthine oxidase.
- The last strategies involve providing supplementation with precursors of the synthesis of antioxidant molecules, such as precursors of GSH synthesis.

Based on studies measuring physical parameters or muscle mass, RONS scavengers appear to be ineffective in preventing sarcopenia [1]. In terms of RONS inhibitors, allopurinol and specific inhibitors of mitochondrial RONS showed very good results in the prevention of muscle wasting in hypoactivity and in diaphragm mechanical ventilation models [4, 5]. However, allopurinol causes side effects with prolonged treatment, and we do not have enough data for the specific inhibitors of mitochondrial RONS.

Supplementation with precursors of antioxidants could be a solution when physical exercise is not possible. A few years ago, [11] showed that a cocktail based on glutathione precursors over the course of six months prevented muscle mass decreases.

Glucose-6-Phosphate-Deshydrogenase (G6PDH) could be a target for combatting sarcopenia. Very recently, we showed that moderate G6PDH overexpression increased NADPH and GSH, which was associated with lower oxidative damage to DNA and lipids. These effects were associated with a longer median life expectancy in females and with better neuromuscular function in very old mice [12].

Antioxidants strategies	Examples	Efficiency
RONS Scavengers	Vitamin C, E, Carotenoids, Resveratrol	Poor efficiency
RONS sources inhibitors	Allopurinol, Oxypurinol, Inhibitors of mitochondrial RONS production	Lack of data in the elderly; very good results in muscle disuse models, need confirmation in elderlies
Precursor of antioxidants	Glutathione precursors	Very good results in rodents, need confirmation in elderlies
Potential Targets	G6PDH	Very good results in mice overexpressing G6PDH, need confirmation in elderlies
Physical Training	Endurance and/or Strength,	The best strategy. The only solution which can reverse sarcopenia

**Table 1:** Main antioxidant strategies against sarcopenia

Activation of G6DPH could lead to higher NADPH synthesis, leading to increased antioxidant defenses. In turn, this could lead to decreased levels of RONS and subsequently decreased apoptosis and proteolysis, thus restoring protein synthesis and regeneration processes [1]. However, currently, such effects have yet to be studied in skeletal muscle. Finally, physical training is currently the best strategy against sarcopenia because it can increase muscle mass, muscle strength and improve physical performance [2]. Moreover, exercise has numerous other beneficial effects and does not have any side

effects. Endurance training can restore a young redox status [2]. Endurance exercise activates PGC1- $\alpha$ , leading to higher antioxidant defenses [13]. Strength training is known to increase IGF-1 levels, which would activate the KEAP1/NRF2 pathway and result in higher antioxidant defenses. However, this hypothesis needs to be studied further. Although physical activity has many well-established health benefits, aging and strenuous exercise (especially exhaustive exercise) are associated with increased free radical generation [14]. Studies support the notion that heavy training may cause a deficit in muscle antioxidant reserve and protective margins [14-16]. Therefore, training programs in elderly people should be progressive and should avoid exhaustive exercise.

### Acknowledgements

Our studies are supported by the Centre National d'Etudes Spatiales (CNES). Special thanks to Professor Angèle Chopard and Assistant Professor Guillaume Py (Université de Montpellier), Professor Arlette Delamarche and Assistant Professor Sophie Lemoine (Laboratoire M2S), Professor José Viña and Assistant Professor MariCarmen Gomez-Cabrera (Universidad de Valencia) for trusting my job performance for many years.

### References

1. Brioché, T., et al., Muscle wasting and aging: experimental models, fatty infiltrations, and prevention. *Mol Aspects Med*, 2016.
2. Brioché, T. and S. Lemoine-Morel, Oxidative stress, Sarcopenia, Antioxidant strategies and Exercise: Molecular aspects. *Curr Pharm Des*, 2016.
3. Derbre, F., et al., Inactivity-induced oxidative stress: a central role in age-related sarcopenia? *Eur J Sport Sci*, 2014. 14 Suppl 1: p. S98-108.
4. Powers, S.K., et al., Redox control of skeletal muscle atrophy. *Free Radic Biol Med*, 2016. 98: p. 208-17.
5. Pierre, N., et al., From physical inactivity to immobilization: Dissecting the role of oxidative stress in skeletal muscle insulin resistance and atrophy. *Free Radic Biol Med*, 2016. 98: p. 197-207.

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6. Andersson, D.C., et al., Ryanodine receptor oxidation causes intracellular calcium leak and muscle weakness in aging. *Cell Metab*, 2011. 14(2): p. 196-207.
  7. Siems, W., et al., High sensitivity of plasma membrane ion transport ATPases from human neutrophils towards 4-hydroxy-2,3-trans-nonenal. *Life Sci*, 2003. 73(20): p. 2583-90.
  8. Scherz-Shouval, R., et al., Reactive oxygen species are essential for autophagy and specifically regulate the activity of Atg4. *EMBO J*, 2007. 26(7): p. 1749-60.
  9. Marzani, B., et al., Antioxidant supplementation restores defective leucine stimulation of protein synthesis in skeletal muscle from old rats. *J Nutr*, 2008. 138(11): p. 2205-11.
  10. Powers, S.K., A.J. Smuder, and A.R. Judge, Oxidative stress and disuse muscle atrophy: cause or consequence? *Curr Opin Clin Nutr Metab Care*, 2012. 15(3): p. 240-5.
  11. Sinha-Hikim, I., et al., Long-term supplementation with a cystine-based antioxidant delays loss of muscle mass in aging. *J Gerontol A Biol Sci Med Sci*, 2013. 68(7): p. 749-59.
  12. Nobrega-Pereira, S., et al., G6PD protects from oxidative damage and improves healthspan in mice. *Nat Commun*, 2016. 7: p. 10894.
  13. Mason, S.A., et al., Muscle redox signalling pathways in exercise. Role of antioxidants. *Free Radic Biol Med*, 2016. 98: p. 29-45.
  14. Ji, L.L., Exercise at old age: does it increase or alleviate oxidative stress? *Ann N Y Acad Sci*, 2001. 928: p. 236-47.
  15. Gohil, K., et al., Effect of exercise training on tissue vitamin E and ubiquinone content. *J Appl Physiol* (1985), 1987. 63(4): p. 1638-41.
  16. Starnes, J.W., et al., Skeletal muscle lipid peroxidation in exercised and food-restricted rats during aging. *J Appl Physiol* (1985), 1989. 67(1): p. 69-75.

