The Role of Exercise on Sarcopenia

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Abstract

The skeletal muscle is a highly adaptable tissue and orchestrates many responses related to a healthy status. Sarcopenia, the age-related decline in muscle mass, muscle strength, and physical performance, has shown to affect up to 36.5% of adults aged ≥60 years. Currently, muscle strength has been considered as the primary indicator of sarcopenia. In this context, resistance training and its modalities have shown to improve the parameters of sarcopenia with positive impact on reducing the incidence of falls and fractures. The outcomes of resistance training are mediated primarily by an inversely proportional relationship between intensity and volume. Muscle strength gains seem to be more pronounced with higher intensity, whereas volume may be more effective in promoting muscle mass accrual. However, muscle strength improvement must increase physical performance to reflect significant clinical outcomes and adding exercise related to activities of daily living and aerobic training can be important tools in this process. In addition, resistance training associated with nutrition interventions can have additional effect on muscle mass accrual. In conclusion, adherence and safety of exercise training are important to the success of an exercise training program and depends on instruction by qualified professionals such as personal trainers and exercise physiologists.

Keywords: Aerobic training; Muscle strength; Physical performance; Resistance training; Sarcopenia

Abbreviations

1 RM	One repetition maximum
ACSM	American College of Sports and Medicine
Akt	Protein kinase B
ALM	Appendicular lean mass
ASM	Appendicular skeletal muscle mass
BIA	Bioelectrical impedance analysis
BMI	Body mass index
CRP	C-reactive protein
CSA	Cross-sectional area
CT	Computed tomography
DHEA-S	Dehydroepiandrosterone sulfate
DXA	Dual energy X-ray absorptiometry
EWGSOP	European Working Group on Sarcopenia in Older People
GS	Grip strength
IGF-1	Insulin-like growth factor 1
IL-6	Interleukin 6
MRI	Magnetic resonance imaging
mTOR	Mammalian target of rapamycin
NFκ-B	Nuclear factor kappa-light-chain-enhancer of activated B-cells
SD	Standard deviation
SMI	Skeletal muscle mass index
TNF	Tumor necrosis factor
VO_{2max}	Maximal oxygen consumption

1. Introduction

The skeletal muscle is the most abundant and malleable tissue of the human body. It comprises nearly 40% of the body weight, accommodating between 50-75% of the entire body proteins [1]. Despite its unique role on movement and locomotion, skeletal muscle, through contraction, orchestrates a variety of responses to maintain a healthy status, which includes the release of myokines with anti-inflammatory properties, glucose homeostasis control, production of heat to maintain body temperature, vascular plasticity, intrathoracic pressure during breathing, and gastrointestinal motility [2-4].

During the last three decades, since 1989 when Irwin Rosenberg coined the term sarcopenia referring to the loss of skeletal muscle mass [5], the importance of skeletal muscle to bodily functions has been receiving increased attention. The term derived from the Greek, which *Sarx* means "flesh" and *penia* means "loss". Initially, sarcopenia referred only to the progressive reduction in skeletal muscle mass due to the "healthy" ageing process and did not include function parameters as part of the syndrome. Along the subsequent years, definitions were primarily based on muscle mass alone to identify sarcopenia [6,7]. In fact, the term dynapenia has also been introduced to differentiate reduced muscle strength from changes in muscle mass, which both seem to occur in a different rate [8,9]. In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP) proposed a series of performance criteria (muscle strength and physical performance) to be added to the reduction of muscle mass to diagnose sarcopenia [10]. Then, the relevance of each criterion in the syndrome spectrum was edited in 2019, ascribing muscle strength as the main factor [11].

In essence, sarcopenia can be acknowledged as an organ failure representing a muscle insufficiency to maintain contractibility properties in the absence of contractile component (muscle mass) and/or adequate contraction efficiency (muscle strength/endurance). As the mean age of the population continues to rise, sarcopenia has become a public health issue worldwide.

Sarcopenia has been associated with physical disability [7], increased risk of falls and fractures [12], poor quality of life, increased hospital length of stay [13], and higher all-cause and cardiovascular mortality [14]. In a multi-continent study, it was estimated to affect from 12.6% (Poland) to 17.5% (India) of the general population [15], whereas, in a population-base study from the USA, the prevalence of sarcopenia reached up to 36.5% in adults aged 60 years or older [14]. The discrepancy between studies may be related to the different methods applied to measure muscle mass and criteria to define sarcopenia. Moreover, these numbers can vary even more in subpopulations with chronic disease, such as chronic heart failure [16], chronic obstructive pulmonary disease [17], chronic kidney disease [18], and cancer [19].

Although the mechanisms involved in the development of sarcopenia are still inconclusive, increased pro-inflammatory cytokines [20], reduced anabolic hormone concentrations [21], mitochondrial dysfunction [22], inadequate nutrition/digestive disorders [23], physical inactivity [24], and loss of motor neurons [25] may be key drivers of the syndrome. In addition, the proposed treatment of sarcopenia has been based on resistance exercise usually associated with aerobic exercise and nutrition intervention with a higher caloric or protein intake [26]. Several pharmacological agents that act in many aspects of the muscle wasting spectrum have also been studied, but none of them is currently approved by regulatory agencies, showing limited effect on clinical outcomes like muscle strength and physical function [27].

Therefore, considering the low cost and effectiveness of exercise training and the positive effect with low

adverse events in elderly subjects with sarcopenia, the aim of this review is to outline the specific role of exercise training on sarcopenia and discuss strategies to enhance muscle strength and muscle mass.

2. Definition of sarcopenia

Sarcopenia is a syndrome defined by a global and progressive reduction in skeletal muscle mass associated with changes in muscle strength and physical performance. The muscle wasting and decreased function have a great impact on adverse outcomes, such as falls, fractures, physical disability and mortality, with a significant socioeconomic burden [11]. Sarcopenia has also been recognized as a disease entity and received ICD-10 code in 2016 (M62.84) [28], which may lead to an increased awareness of the condition by physicians and interest of pharmaceutical companies in investing on new compounds for prevention and treatment. However, a consensus about sarcopenia that encompasses research and clinical practice has not been reached yet.

In 1998, Baumgartner *et al.* proposed the first definition of sarcopenia using dual energy X-ray absorptiometry (DXA), which was based on the sum of lean mass in both arms and legs, termed appendicular skeletal muscle mass (ASM), divided by height squared. The cutoff values for sarcopenia were ASM/height^2 ≤ 7.26 kg/m^2 for men and ASM/height^2 $\leq 5.45\%$ kg/m^2 for women [6]. These values represented two standard deviations (SD) below the mean value of a sex-specific population between 18-40 years of age. Indeed, it was a very similar approach applied to body mass index (BMI) to classify individuals according to body composition categories.

In 2002, Janssen *et al.* introduced another definition, dividing total skeletal muscle mass by total body mass, and designed the term skeletal muscle mass index (SMI). Based on a sex-specific mean of SMI in a young population aged 18-39 years, this new definition intended to categorize sarcopenia into: normal SMI (within one SD), Class I (between one and two SD) and Class II (below two SD) [7]. This type of approach has also been used to classify bone mineral density into normal, osteopenia, and osteoporosis [29].

It is worthy mention that Baumgartner's definition used DXA, while Janssen measured muscle mass by bioelectrical impedance analysis (BIA). Although other methods to measure muscle mass, such as magnetic resonance imaging (MRI) and computed tomography (CT), have been considered gold standard tests in the assessment of muscle mass with a great reliability compared to cadaver skeletal muscle measurement [30], the high cost, the need of highly skilled personnel, and the lack of cut-off points to define sarcopenia have been limiting the application of these methods in clinical setting [31].

Moreover, the equation proposed by Baumgartner *et al.* underestimates body fat percentage, limiting its applicability in patients who presented sarcopenia associated with higher amount of fat mass (sarcopenic obesity) [6]. In this perspective, Newman *et al.* proposed an index based on the residual of a linear regression that included appendicular lean mass (ALM; initially termed ASM by Baumgartner *et al.*) as the dependent variable and height and total fat mass as the independent variables [32]. Thus, a negative residual indicated a sarcopenic individual, while a positive residual indicated a muscular individual. In fact, this method was able to identify patients with

sarcopenia, especially those with BMI $\geq 25 \text{kg/m}^2$, showing a strong correlation with Baumgartner's definition (r=0.88 for men; r=0.71 for women).

In 2014, Studenski *et al.* proposed another index to identify sarcopenia that corrected ALM by BMI and also included grip strength (GS) [33]. The cut-off values for sarcopenia were ALM/BMI <0.789 + GS <26 kg for men and ALM/BMI <0.512 + GS <16 kg for women. Recently, our group showed that, by applying different definitions to detect sarcopenia in patients with heart failure, the prevalence of sarcopenia was similar across all patients regardless of BMI values (normal vs. overweight/obese categories) [16]. In other words, when appropriate definitions are used, obese patients can be as affected by sarcopenia as lean patients.

More recently, the EWGSOP revised the criteria proposed in 2010 to diagnose sarcopenia, which at the time included reduced muscle mass assessed by DXA or BIA associated with either impaired muscle strength (GS <30 kg for men and GS <20 kg for women or GS according to BMI categories and sex) or decreased physical performance (Short Physical Performance Battery ≤8 or gait speed <0.8 m/s) [10]. The new revised definition draws attention to the low muscle strength as the primary indicator of sarcopenia (GS <27 kg for men and GS <16 kg for women) because low muscle strength may have a good sensitivity to detect sarcopenia in the early stage of the syndrome, before the occurrence of reduced muscle mass [11]. This paradigm shift occurred because muscle strength has shown to be better than muscle mass at predicting adverse outcomes [34-37]. However, future studies applying these criteria are necessary to validate this new definition.

3. Relationship between the loss of muscle mass and muscle strength

Several studies have intended to quantify the decline in muscle mass across the lifespan. The relationship between age and skeletal muscle mass seems to be inversely related throughout the years, but many factors may influence the magnitude of these changes [8]. Although muscle mass has been widely quoted to decrease about 1-2% per year after the fifth decade of life [38,39], this loss may not be as linear as it has been thought, with still conflicting data. Studies have shown that skeletal muscle mass can reach its peak in the third [40] and even fourth decade of life [41] followed by a plateau or a slowly progressive decline until the sixth decade [42,43], which then a steep decline takes place [44].

One of the major factors that impact the loss of skeletal muscle mass is sex with men showing a greater absolute and relative decline when compared with women, independent of changes in body weight and height [40,41,44,45]. However, women may be more affected by the reduction in skeletal muscle mass due to a lower reached peak muscle, an earlier decline in muscle mass and a greater longevity [42,46]. Additionally, the sex difference with age may also vary according to the ethnicity group. African American men and women have shown to have the highest values of muscle mass followed by White, Hispanic and Asian [40], although the drop in muscle mass may arise in a slightly different rate for these groups. In women, after the third decade of life, there was a decline in muscle mass of 1.11 kg/decade for African Americans, 0.69 kg/decade for Asians, 0.65 kg/decade for Whites, and 0.48 kg/decade for Hispanics. In men, Hispanics showed a decline of 2.03

kg/decade, followed by African Americans (1.81 kg/decade) and Whites (1.26 kg/decade) [40]. Interestingly, a higher prevalence of sarcopenia has been found in elderly Hispanics than in non-Hispanic [6].

Moreover, the loss of muscle mass may also differ from body compartments, since lower limbs have shown to contribute to a greater extent to the wasting process in comparison to the upper limbs in both sexes [41].

Nevertheless, the loss of muscle strength seems to occur in a more rapidly fashion than the loss of muscle mass, with the peak in muscle strength appearing between the second and third decade of life followed by a significant decline after the fifth decade (12-15%/decade) [47]. In a study involving 3075 participants followed for 3 years, men have shown to lose muscle strength twice as much as women and the loss of muscle strength was 3-fold greater than the loss of leg lean mass independent of sex and race [9]. Moreover, a reduction of 6-7% in muscle mass, 30% in physical performance and 60% in muscle strength have been reported in men and women over the age of 75 years compared to a younger group aged 18-19 years [48]. Supporting this data, a longer longitudinal study that followed men and women (≥75 years old) for 5 years showed a reduction of 20 and 15% in muscle strength, whereas muscle mass assessed by BIA diminished only 3.6 and 2.1%, respectively [49].

Interestingly, quadriceps muscle strength and handgrip strength, but not muscle mass, have shown to be a predictor of mortality in a cohort of elderly men and women [35], while maintaining or improving muscle mass does not seem to delay the decline in muscle

strength [9]. Thus, the changes in muscle mass have shown to explain only in part the decline in muscle strength [38].

This dissociation between muscle mass and muscle strength must be interpreted with caution because most of these studies have been conducted in "healthy" ageing subjects, so that muscle mass alterations can become more evident in subjects with chronic disease and associated comorbidities. In addition, the relevance of muscle function over muscle mass alone might also explain why the EWGSOP decided to place muscle strength as the first step in the algorithm to start screening for sarcopenia, even before submitting individuals to an assessment of muscle mass (DXA, BIA, MRI, CT) [11].

The mechanisms behind this interwoven relationship between muscle mass and muscle strength have not been completely elucidated, but it has been speculated that muscle weakness may lead to a decrease in physical activity and limited mobility, which consequently cause disuse of the muscular apparatus culminating in atrophy. A vicious cycle, therefore, is developed in which reduced muscle mass is thought to be the result and cause of the decline in muscle strength.

4. Mechanisms of sarcopenia

The etiology of sarcopenia is multifactorial and the maintenance of muscle mass depends on a fine balance between muscle protein synthesis and breakdown. Catabolic pathways prevail over anabolic metabolism in sarcopenic patients, and a blunted post-prandial muscle protein synthesis, known as anabolic resistance, has also been shown to affect older adults [50].

The age-related increase in intramuscular adipose tissue deposition has been associated with metabolic abnormalities (*i.e.*, insulin resistance) and also caused alterations in performance and muscle strength [51]. The ectopic accumulation of fat within muscle, referred as muscle lipotoxicity, is believed to occur due to a reduced uptake of fat acids from adipose tissue and, as a result, skeletal muscle, a highly active tissue, captures and stores these fat acids (myosteatosis) for its own metabolic requirements [52]. This redistribution in body composition may lead to mitochondrial dysfunction reducing capability of muscle cells to oxidize free fat acids [53]. In addition, increased fat mass, especially visceral fat, can also trigger the release of pro-inflammatory cytokines, including interleukin 6 (IL-6) and tumor necrosis factor (TNF) (Figure 1) [54].

Inflammation is an acute physiological response of the immune system mediated by macrophages in the presence of infection or tissue injury, with the purpose of destroying the pathogen, repairing the damage, and restoring homeostasis again. Persistently increased levels of IL-6 and TNF even in the absence of acute infection/injury, the so-called chronic low-grade inflammation, has been negatively associated with muscle mass and muscle strength (Figure 1) [55, 56]. These inflammatory markers can act through different mechanisms. First, TNF, via the nuclear factor kappa-light-chain-enhancer of activated B-cells (NFκ-B) pathway, has shown to cause directly protein degradation in skeletal muscle myotubes [57]. Secondly, IL-6 has been reported to inhibit the mammalian target of rapamycin (mTOR) signaling pathway, resulting in reduced protein synthesis [58].

However, the sensitivity and specificity of these cytokines used as biomarkers of sarcopenia have shown to be limited, whereas C-reactive protein (CRP), another pro-inflammatory cytokine, seems to be more related to sarcopenia [59]. Longitudinal studies are necessary to determine the influence of inflammation on the development of sarcopenia and a multivariate approach, including more than one inflammatory marker, should be consider to encompass the complex pathophysiology of muscle wasting [60].

Sarcopenia can also be a result of reduced blood flow to the skeletal muscle that impairs oxygen delivery and nutrients to muscle cells (Figure 1) [61]. Interestingly, endothelial dysfunction has been linked to sarcopenia and reduced exercise capacity in patients with heart failure [62].

In addition, an age-related impairment in sex steroid hormones has been linked to sarcopenia [63]. Dehydroepiandrosterone sulfate (DHEA-S), a precursor of testosterone, is associated with muscle mass and muscle strength [64] and an imbalance between increased activity of catabolic hormones (*i.e.*, cortisol) and impaired action of anabolic hormones (*i.e.*, DHEA-S) has also been independently associated with sarcopenia [65]. Moreover, insulin-like growth factor 1 (IGF-1), circulating or released by muscle contraction, also plays an important role on this anabolic cascade that sustain the turnover of muscle protein synthesis via protein kinase B/mTOR (Akt/mTOR) [66] and a decline in growth hormone and IGF-1 may lead to reduced muscle mass [67].

Although the etiology of sarcopenia has been long focused on morphological changes in muscle mass, a neurogenic origin of sarcopenia based on motor neuron alterations has been proposed [68]. Indeed, reduction in the number of motor units has been reported in sarcopenic patients when compared to non-sarcopenic [25]. Interestingly, there may be prototypic disease models to study the endocrinological and neurological cause of sarcopenia (Figure 1) as suggested by Stangl *et al.*, comprising patients suffering from diabetes, Cushing syndrome, chronic kidney disease, Klinefelter syndrome, and amyotrophic lateral sclerosis [69].

Physical inactivity, not only related to sedentary behavior, but also including prolonged bed rest and limb immobilization, has shown to contribute to the loss of muscle mass as well (Figure 1) [70-72]. Kortebein *et al.* showed that 10 days of bed rest caused a decrease of 1 kg in leg lean mass, a decline of 16% in knee extensor strength, and protein synthesis impairment [73]. In addition, reduced skeletal muscle mass, considered the main organ responsible for maintaining glucose homeostasis, may also lead to worsen insulin sensitivity in older subjects during bed rest, impairing anabolic responses [74].

5. Characteristics of resistance and aerobic training: intensity and volume

Regular exercise, composed mainly by resistance and aerobic training (*e.g.*, walking, running, cycling, and swimming), is associated with numerous physical health benefits [75] and reduced risk of developing comorbidities related to sarcopenia [76]. Every program of resistance training is developed with a unique goal to improve muscle strength and muscle mass that eventually contributes to improved physical performance and quality of life, while aerobic training enhances cardiorespiratory fitness. For such purposes,

a vast range of training variables can be manipulated considering that each variable can elicit a specific response in these modes of exercise.

The intensity of resistance training is the amount of weight lifted in a single exercise determined by one repetition maximum test (1 RM) of the respective movement. The volume of resistance training is characterized by the amount of time that a muscle is exposed to a certain stimulus (number of sets and repetitions). Although intensity and volume are the main variables manipulated during progressive resistance training to improve muscle strength and muscle mass, other variables, such as frequency, interval between sets, lifting cadency, type of contraction, time under tension, range of motion, and exercise grouping, have a direct impact on muscle strength and muscle mass [77].

For any mode of exercise, the relation between intensity and volume is inversely proportional so that when intensity is increased volume must be decreased, and vice-versa. In aerobic exercises, intensity is represented by a percentage of maximal oxygen consumption (VO_{2max}), while volume consists of the exercise duration [75].

6. Resistance training, muscle strength, and physical performance

Progressive resistance training has proven to be well tolerated and safe in elderly subjects. Adequate prescription of this exercise modality can improve mobility, physical performance, muscle mass, and muscle strength, with positive results in reducing the incidence of falls, fractures, and injuries [78]. Several forms of resistance training, including weight stack, pneumatic machines, free weights, elastic bands, and

body weight, have shown beneficial effects on these parameters [79,80].

Sarcopenia is thought to affect predominantly type II fibers and resistance training has shown to promote higher adaptation in this type of fibers in elderly subjects [81]. Muscle hypertrophy is one of the main benefits of resistance training mediated by satellite cells activation. In response to muscle damage, satellite cells, initially in a quiescent state, are activated and undergo proliferation and differentiation adding myonuclei to preexisting muscle cells, which in turn leads to muscle repair and regeneration [82]. Although a reduced content of satellite cells, assessed by muscle biopsy, has been found in the vastus lateralis muscle of older subjects and resistance training was able to effectively reverse this loss [83], the role of satellite cells in sarcopenia is still controversial [84].

Resistance exercise program associating flexibility, balance, and weight-lifting exercises (3 sets of 8-12 repetitions at ≥85% 1 RM) in frail elderly women and men with multiple co-morbidities showed improvement in fat-free mass as well as muscle strength in leg extension/flexion, leg press, and seated row [85]. Interestingly, as the decline in muscle mass and muscle strength throughout ageing occurs in a distinct rate, so does the improvement of these parameters due to resistance training. In a study with older subjects (≥85 years) performing progressive resistance training (3 sets of 8 repetitions at 50 to 80% 1 RM) for 12 weeks, the increment of cross-sectional area (CSA) in quadriceps muscle represents only 9.8%, whereas isokinetic knee strength improved up to 47% [81].

Other studies, applying resistance training, have shown slightly higher muscle hypertrophy [86], lower [87-89] or no changes at all [90,91], while the changes in muscle strength seem to be more pronounced and consistent across trials [86,87,92]. Even though there is a difference in absolute muscle strength between men and women at baseline and post exercise, women are still able to positively respond to resistance training [92]. In addition, sarcopenic patients may respond better to muscle strength acquisition when compared to healthy elderly subjects [93,94].

However, the increase in muscle strength is not totally dependent on the muscle mass accrual and neural adaptations play a major role in this process. Indeed, the adaptations of resistance training in older subjects seem to depend more on neural than hypertrophic adaptation [95]. The main neural adaptations of resistance training in elderly subjects may include augmented firing rate from neurons, increased motor unit recruitment, and improved agonist activation with reduced antagonist coactivation (Figure 2) [91].

The intensity of resistance training (*i.e.*, weight lifted) has shown to be determinant in acquiring muscle strength. Comparing high intensity (>75% 1RM) to moderate (55-75% 1RM) and low intensities (<55% 1RM), higher intensity showed to be more effective in increasing muscle strength, showing a dose-dependent relationship with muscle strength in elderly subjects (≥65 years) [96].

Nonetheless, these changes in strength must reflect an enhancement of physical performance to produce significant clinical outcomes. In a study comparing supervised high intensity (80% 1RM) to low intensity (40% 1RM) resistance training in frail elderly subjects

≥70 years, the improvement in functional outcomes, assessed by six-minute walking distance test, chair-rising time, and stair climbing, were related to changes in knee extensor strength [97]. However, other authors have shown that changes in muscle strength and stair climbing occur after resistance training in spite of intensity applied [90]. A reason for this difference may be the baseline strength of the participants, considering that institutionalized subjects [97] tend to show greater improvement in the assessed parameters than community-dwelling subjects [90].

Higher intensity may elicit better function results in elderly subjects, but recent meta-analysis demonstrated substantial increases in muscle strength with low-moderate intensity (~45% 1 RM) [98]. It is important to mention that blood pressure response to high intensity resistance training (80% 1 RM) in hypertensive patients, a critical point of concern, is lower than low intensity (40% 1 RM) [99]. However, in sarcopenic patients with associated cardiovascular disease, the exercise execution should be encouraged to stop 2-3 repetitions before reaching the maximal volitional fatigue to avoid valsalva maneuver. Additionally, adherence to exercise seems to increase when intensity is moderate, whereas adding more session to the exercise program per week increases volume of exercise and does not alter adherence [100].

Other studies suggest that improving muscle power (force multiplied by velocity) may lead to greater impact on functional tasks [101]. This type of resistance training is characterized by high-velocity contraction during the concentric phase of the movement, while the eccentric phase is slower. Comparing different intensities of explosive resistance training (20% vs. 50% vs. 80% 1 RM) with pneumatic

resistance machines, de Vos *et al.* demonstrated that muscle power was improved regardless of intensity in comparison to a non-trained control group, but there was a linear increase between intensity, muscle strength, and endurance changes [102].

Moreover, explosive resistance training based on specific exercises of mobility improved gait speed and chair rise compared to a control group that performed progressive resistance training with a consistent speed during the concentric and eccentric phase of the movement [103]. These findings indicate that the training principle of specificity, which states that a certain skill/task is performed better when it is trained, may also contribute to the improvement of strength and function observed in older subjects. Thus, adding into resistance training exercises that resemble gestures of the activities of daily living and aerobic exercises can optimize the transference of muscle strength into physical performance.

7. Resistance training and muscle mass

Resistance training has shown to be effective in producing an acute positive muscle protein balance, which can chronically leads to muscle mass accretion. Muscle hypertrophy seems to take place with an optimal combination between mechanical tension, metabolic stress, and muscle damage [77].

Intensity appears to be an important variable to promote muscle growth. Comparing sarcopenic male patients that performed high-intensity progressive resistance training to those who did not exercise, SMI improved from baseline [7.01 (6.85 to 7.16) *vs.* 6.89 (6.74 to 7.02) kg/m^2] to one year [0.25 (0.18 to 0.33) *vs.* -0.08 (-.01 to -.15) kg/m^2] [104]. Although the compliance with this type of exercise was very high

(95%), the authors report that the prescribed intensity had not been achieved in one third of the sessions.

Apart from intensity, there are many variables that can also have a greater impact on muscle mass. In fact, low intensity resistance training (30-40% 1 RM) has proven to be as equally effective as high intensity (70-80% 1 RM) in promoting muscle protein synthesis when a volitional fatigue is reached [105]. Resistance training program with higher volume seems to elicit significant gains of lean body mass in adults $\geq$ 50 years (~1.1 kg) [106]. In clinical practice, the main strategies to increase volume in older populations include increased frequency of session per week and also number of sets per exercise.

However, several studies demonstrate that elderly subjects compared to young have a reduced ability to generate muscle hypertrophy [107-109] with training background, manipulation of training variables, and age itself explaining in part the impaired muscle regeneration in this population. Furthermore, though sarcopenic patients are able to increase muscle CSA with progressive resistance training (4 sets of 10 repetitions at 50 to 85% 1RM), it seems to occur to lesser degree than healthy elderly subjects, diverging from muscle strength that the adaptation is superior [93]. These findings raise attention to the importance of manipulating training variables precisely in order to optimize muscle mass gains in sarcopenia.

In elderly women with sarcopenia, resistance training with kettlebell (3 sets of 8-12 repetitions at 60-70% 1 RM) increased ALM and, consequently, ALM/height^2 [110]. In addition, a reduction of CRP in the resistance exercise group was also reported in this study, without differences for IL-6 and TNF in comparison to control

group (Figure 2). The impact of resistance training on reducing pro-inflammatory cytokines seems to be restricted to CRP, since studies with other populations have not demonstrated changes in IL-6 and TNF as well [111,112].

Moreover, Mero *et al.* showed that increased CSA of type I and II muscle fibers was more pronounced in young than in older subjects after progressive resistance training (40 to 80% 1 RM) for 21 weeks, but the authors reported a higher ingestion of protein, carbohydrates and fat per body mass in the young group, which may also explain the lower muscle hypertrophy in the older group due to a reduced caloric intake [107]. Indeed, not only total caloric intake, but the ingested amount of protein and essential amino acids in elderly may need to be higher in order to promote muscle protein synthesis [113,114], while resistance training associated with increased protein intake has shown to be more effective in increasing muscle mass than supplementation alone (Figure 2) [115]. Similar findings in patients with sarcopenia are still controversial, showing equal effect of exercise and exercise plus supplementation on ALM [116].

The impaired anabolic response in elderly subjects is thought to be related to a dysregulation of the Akt/mTOR signaling pathway [117], which is stimulated by circulating anabolic hormones. In this perspective, resistance training has shown to increase the release of testosterone associated with reduced catabolic hormones like cortisol, which leads to an improvement in muscle size and strength in older subjects (Figure 2) [118]. The differences in hormone response may also lie in types of exercise performed, considering that larger muscle groups can elicit a higher release of anabolic hormones [119]. However,

other authors, despite an acute spike in anabolic hormones after a single bout of exercise, demonstrated that this acute increase was not determinant in the process of muscle hypertrophy with chronic exposure to resistance training [120]. In this regard, studies assessing the effect of anabolic hormones on muscle mass in sarcopenic patients are still lacking.

8. Aerobic exercise and sarcopenia

The multifactorial nature of sarcopenia is a great barrier to determine only a specific treatment to counteract the loss of muscle strength, muscle mass, and physical performance. In contrast to resistance training, aerobic training, such as cycling, walking, and jogging, is characterized by an enhancement of metabolic capacity [75].

To maintain the energy and oxygen supply to active skeletal muscles, metabolic adaptations take place during aerobic training, including increases in capillarization, number and size of mitochondria, and expression of oxidative enzymes (Figure 2) [121]. Paradoxically, in initial states of aerobic training, particularly with cycling, and when a subject has a very limited baseline functional capacity, modest changes in muscle mass and muscle strength may be seen [122]. However, aerobic training is effective in improving maximum aerobic power (VO_{2max}) [123]. Despite the well-known cardiorespiratory fitness improvement documented with aerobic training, the association of aerobic and resistance training in elderly subjects showed to optimize cardiovascular benefits as well as muscle strength compared to each intervention alone [124].

Taken into consideration the limited effect of resistance training on inflammation, aerobic training can be an aligned tool to produce an anti-inflammatory

state [125], as shown by reduce pro-inflammatory cytokines in rats with cachexia [126]. In fact, moderate intensity physical activity may lead to more significant reductions in CRP than those at low intensity (Figure 2) [127], suggesting that exercise intensity may also modulate inflammation.

9. Exercise prescription

The American College of Sports and Medicine (ACSM) suggests that participants engaged in resistance training should perform 1-4 sets of 8-15 repetitions at moderate (50-69% 1 RM) to vigorous intensity (70-84% 1 RM) with a rest interval of 2-3 minutes between sets [75]. The session can be comprised of 8-10 exercises for the major muscle groups and also involve balance, agility, and coordination exercises, performed with a frequency of 2-3 times per week with a 48-hour interval between sessions. It is important to mention that these variables must be manipulated according to the experience, goals, health status, and exercise response of each participant.

For aerobic training, the ACSM recommend continuous and rhythmic exercises, including walking, running, cycling, and swimming, performed either ≥5 times per week at moderate intensity (46-63% VO_{2max}), ≥3 times per week at vigorous intensity (64-90% VO_{2max}) or a combination of both ≥3-5 times per week [75].

In summary, the definition of sarcopenia has evolved from only considering the loss of muscle mass to including criteria of physical performance and muscle strength, with the latter being recently suggested as the primary indicator of the syndrome. In this scenario, resistance training, performed using a variety of modalities, rises as a great clinical tool to counteract the impairment of muscle mass and muscle strength. The intensity of resistance training (>70-80% 1 RM) seems to be more effective than volume in improving muscle strength, whilst reaching a maximal controllable volitional fatigue, despite the intensity (high vs. low), may be essential to promote muscle mass.

In addition, resistance training associated with nutrition interventions can have additional effect on muscle mass accrual. Transferring muscle strength into physical performance may produce better clinical outcomes, with aerobic training being an aligned therapy in this process. Finally, it is important to highlight that adherence and safety of exercise training are important to the success of an exercise training program and depends on instruction by qualified professionals such as personal trainers and exercise physiologists.

9. Conclusion
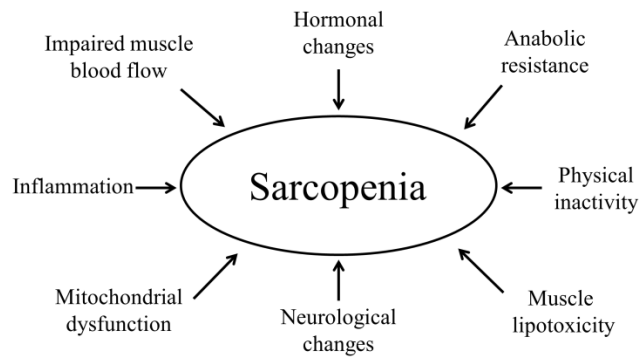
Figure 1: Scheme of the different mechanisms involved in sarcopenia
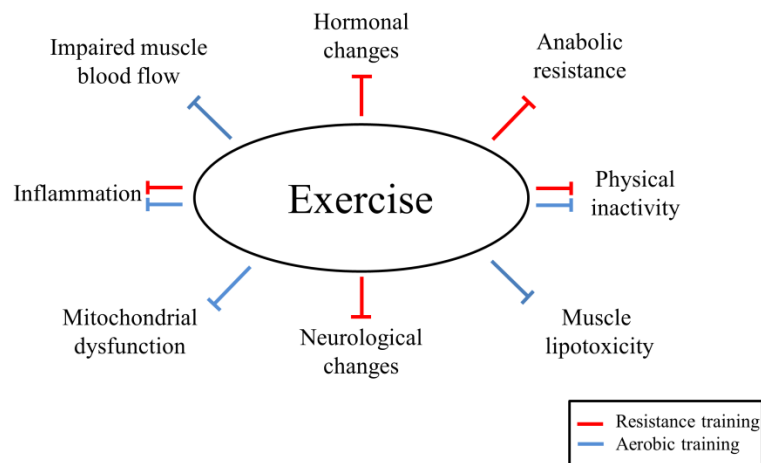
Figure 2: Scheme of the impact of resistance and aerobic training on the mechanisms of sarcopenia

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