Sarcopenia and Approaches

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Contributor: Erika Cione

Sarcopenia, an age-related decline in skeletal muscle mass and function, dramatically affects the quality of life. Although there is a consensus that sarcopenia is a multifactorial syndrome, the etiology and underlying mechanisms are not yet delineated. Moreover, research about nutritional interventions to prevent the development of sarcopenia is mainly focused on the amount and quality of protein intake. The impact of several nutrition strategies that consider timing of food intake, anti-inflammatory nutrients, metabolic control, and the role of mitochondrial function on the progression of sarcopenia is not fully understood. This narrative review summarizes the metabolic background of this phenomenon and proposes an integral nutritional approach (including dietary supplements such as creatine monohydrate) to target potential molecular pathways that may affect reduce or ameliorate the adverse effects of sarcopenia. Lastly, miRNAs, in particular those produced by skeletal muscle (MyomiR), might represent a valid tool to evaluate sarcopenia progression as a potential rapid and early biomarker for diagnosis and characterization.

Keywords: mitochondria ; aging ; protein ; muscle

1. Introduction

According to the World Health8 Organization (WHO), life expectancy has increased by 5 years since 2000 in developed countries [1]. This increase in life expectancy leads to aging and, in turn, to physical and cognitive decline. Current research shows that physical exercise can be a decisive protective factor for both functional decline and negative body composition changes during aging [2][3]. Resistance and endurance exercise have been shown to contribute to the improvement of cognition [4], as well as related psychological and social factors [5]. However, nutrition and eating strategies also play an essential role in preventing and treating functional limitations in the elderly population. For example, muscle mass declines by approximately 3–8% for each decade after 30 years, and this percentage increases significantly in people older than 60 years [6].

Sarcopenia is a condition characterized by a progressive and generalized loss of skeletal muscle mass and function with an increased risk of adverse outcomes such as disability, metabolic dysfunction, poor quality of life, and death [7]. Even though sarcopenia is mainly associated with the aging process seen in the elderly, there are several other populations at risk due to lifestyle decisions or pathological states. These include sedentary, immobilization, malnutrition, diabetes, obesity, and other acute or chronic inflammatory diseases that could promote the loss of muscle mass [8]. Moreover, the loss of muscle mass could also negatively affect the outcomes of those conditions [9][10]. In the last decade, three different consensus papers were published, giving both a definition of sarcopenia and diagnostic criteria. According to the European Working Group on Sarcopenia in Older People (EWGSOP), the presence of low skeletal muscle mass (e.g., DXA, Anthropometry) and either low muscle strength (e.g., handgrip, isokinetic) or low muscle performance (e.g., walking speed, muscle power), which is often related to the most advanced stages of sarcopenia, are the criteria for the diagnosis of sarcopenia [9]. For both the European Society for Clinical Nutrition and Metabolism Special Interest Groups (ESPEN-SIG) and the International Working Group on Sarcopenia (IWGS), only the loss of muscle concomitant with a loss of muscle strength (which could also be assessed by walking speed) represents the recommended parameters. The IWGS also highlights that the loss of muscle mass could be alone or in conjunction with an increase in fat mass [10][11].

Thus, the diagnosis of sarcopenia can then be carried out by assessing the following parameters in the elderly (>65 years): (i) if walking speed is below 0.8 m/s at the 4 m walking test, and there is a low amount of muscle mass (i.e., a percentage of muscle mass divided by height squared is below two standard deviations of the normal young mean (<7.23 kg/m^2 in men and <5.67 kg/m^2 in women) as defined using dual-energy X-ray absorptiometry [12], or (ii) if the walking speed at the 4 m walking test is higher than 0.8 m/s, the hand-grip strength should be tested. If this last value is lower than 20 kg in women and 30 kg in men, the muscle mass must be analyzed [12].

While sarcopenia is mainly observed in the elderly, it can also develop in young adults [10]. A clear cause of sarcopenia cannot always be identified. Thus, the category of primary and secondary sarcopenia may be useful for choosing the best

strategy to delay the progression. Primary sarcopenia is considered when there is no other evident cause rather than the aging process itself, while sarcopenia can be considered secondary when one or more of the following causes are evident [10]: (i) activity-related causes (bed rest, sedentary lifestyle, reconditioning, or even zero-gravity conditions seen in astronauts); (ii) nutrition-related causes, as a result of an inadequate dietary intake either energy or protein, malabsorption of nutrients or gastrointestinal disorders, and anorexigenic medication; (iii) disease-related causes, where there is a cross-talk between muscle mass and other organs that could lead to sarcopenia, such as inflammation, endocrine diseases, advanced organ failure, and malignancy. In this sense, sarcopenia is linked to the prognostic state of some pathologies, e.g., in those that affect the intestinal function and, as aforementioned, the absorption of nutrients as reported in abdominal hernias [13] and inflammatory bowel disease (IBD) [14]. Furthermore, sarcopenia has been recently related to the prognosis of various tumors [15][16][17][18], which leads to a monitoring status at the initial stage, as well as during and after chemotherapy.

2. The Importance of MicroRNAs

Low-grade inflammation is defined as an inflammatory state that cannot be determined by classical standards such as CRP or where an increase in IL-6 and TNFα is sometimes noted. It is established in sarcopenia [19], as well as in various pathological states such as obesity [20], cancer [21], polycystic ovary syndrome [22], and osteoarthritis [23]. In addition to the afflicted tissue, the latent and chronic inflammation state makes the whole organism less efficient by triggering chain reactions through crosstalk between tissues. For instance, Wang et al. [24] proposed that, during insulin resistance (associated with obesity), there is a phenomenon of latent inflammation that aggravates the extent and progression of sarcopenia. It is reasonable to think that an inflammatory state is also present in sarcopenia; therefore, if it is a secondary state or there are chronic comorbidities, there will be a further contribution to the inflammatory state. Hence, mitigating inflammation could be beneficial in the management of sarcopenia. Kwang Byun et al. [25] correlated systemic inflammation present in chronic obstructive pulmonary disease (COPD) with sarcopenia. Similarly, Dalle et al. [26] demonstrated that three apparently different pathological states (i.e., type II diabetes, osteoarthritis, and COPD) are associated with an inflammatory state and lead to sarcopenia. Interestingly, a latent inflammatory state such as IBD also correlates to a greater onset of sarcopenia [14][27]. This status of low-grade inflammation has been a constant focus of research in order to identify new potential biomarkers.

MicroRNAs (miRNAs) are a unique class of short endogenous nucleotides sequences (around 15–30 bases). They are single-stranded noncoding RNAs capable of modulating gene expression by binding to the complementary regions of the 3′UTR sequence of specific mRNA targets, resulting in the inhibition of protein synthesis (translation) and/or mRNA degradation. This peculiar regulatory capability makes them crucial for normal development in all living beings [28][29]. miRNAs are present in all tissues and body fluids [30][31]. One important characteristic of the skeletal muscle is a group of miRNAs, identified as myomiRs [32][33][34], which seem to have a central role in the regulation of skeletal muscle plasticity by coordinating changes in fiber type and muscle mass in response to different contractile activity. Like every tissue, skeletal muscle also expresses miRNAs. In particular, the pool of these molecules is defined as myomiRs and is related to the differentiation of satellite cells, the maintenance of physiological trophism, the switch between fibers, and the development and conservation of muscle mass in response to physical exercise [32]. For example, Soares and colleagues [33] demonstrated an important regulatory action of a group of miRNAs on the progression of muscle atrophy. Brown et al. [35] showed that a pool of miRNAs (miR-23a, miR-182, miR-486, miR-206, miR-21, miR-27, and miR-128) are strong regulators of muscle size via the FOXO1 pathway, PTEN genes and translational regulation, and myostatin signaling. MyomiRs are secreted via exosomal vesicles, circulate in the bloodstream, and serve as regulators/communicators in proximal muscle tissue and even fat cells [33][34].

As aforementioned, sarcopenia is certainly the result of several factors, and its etiopathogenesis is still not well identified. For this reason, the identification of miRNAs might contribute to better understand this phenomenon, although the description of the myomiR profile is in its infancy. This group of miRNAs is potentially involved in the regulation of the satellite cell differentiation, the general proteostasis, the structure and type of muscle fibers, mitochondria and oxidative stress metabolism, the neurodegeneration process, and the infiltration of adipocytes into skeletal muscle tissue [34][36].

2.1. Satellite Cell Regulation

The differentiation of satellite cells is a fundamental process for the maintenance of muscle trophism. In this sense, certain miRNAs (miR-1, miR-206, and miR-486) have been identified to regulate cell survival and proliferation [37][38]. miRNAs have been sown to downregulate the MyoD and paired-box transcription factor (e.g., Pax3) pathways, which result in an inhibition of apoptosis, thereby increasing or maintaining muscle mass. These results have been seen in preclinical research; hence, it is highly plausible they have similar action mechanisms in humans (considering well-conserved

metabolic signatures) [39]. It is noteworthy that both endurance and resistance training impact myomiRs, particularly those involved in skeletal muscle allostasis. For example, certain miRNAs regulate the expression of growth factors (miR-29, miR-422-5p, and miR-143-3p), cell-cycle regulation (Let-7b and Let-7e), and myocyte differentiation (miR-139, miR-155, miR-501-3p, and miR-29) [40].

2.2. Proteostasis

At the moment, there are not many studies in humans. For example, Connors et al. [41] reported an increase in miR-424-5p during a decrease in protein synthesis at the skeletal muscle level with a consequent loss of muscle mass. It is well known that the control of protein metabolism is mediated by several miRNAs: miR-199, miR-125b, and miR-195 regulate hormones such as insulin and IGF-1; miR-432, miR-675-3p, miR-26a, miR-29, and miR-199-3p regulate signal transduction within the muscle cell; miR-27 and miR-128 serve as myostatin regulators; miR-129c, miR-23c, miR-27a, and miR-35 regulate protein catabolism [36].

2.3. Size and Type of Muscle Fiber

Some miRNAs seem to play a decisive role in the structure of muscle fibers. In particular, miR-23a and miR-182 regulate what are called iatrogenic genes (i.e., those who oversee the muscle atrophy program), as they appear to be able to restore drug-induced atrophy. Similarly, miR-21 and miR-206 are capable of acting on the regulation of atrophy. On the other hand, miR-27a seems to downregulate myostatin, thus favoring muscle turnover in a positive balance [34][42][43].

3. Counteracting Strategies

3.1. Physical Exercise with Emphasis on Resistance Training

The fundamental role of physical exercise in countering the progression of sarcopenia, associated or not with obesity, is now evident. Clinical research has confirmed the effectiveness of physical exercise, both cardiovascular and resistance training [44]. As we described before, myomiRs are closely related to an optimal condition of muscle tissue and show an important role as signaling molecules that mediate physiological adaptations to exercise training. Furthermore, these miRNAs change differently in response to cardiovascular, resistance, or combined exercise (e.g., miR-1, miR-133a/b, miR-206, miR-499a-5p, and miR-486), but with no apparent difference in response between young and old men [45]. There is strong evidence that strength training is one of, if not the most, effective interventional strategy to enhance muscle mass and strength in the elderly; thus, it can be used for treating, slowing, and/or preventing sarcopenia and dynapenia [46]. Resistance training enhances physiological adaptations of the neuromuscular system, which positively affects the muscle strength. Maximal motor unit discharge rates increased 49% in older adults that followed only 6 weeks of a high-intensity progressive strength training program [47]. Moreover, muscular factors independent of muscle mass, such as fascicle length and tendon stiffness, have also been observed to improve (10% and 64%, respectively) following resistance training in older adults [48]. Moreover, resistance training is also a powerful stimulus for muscle protein synthesis, which leads to an increase in muscle mass. In this sense, an increase in the cross-sectional area of the thigh muscle (+4.6%) has been reported in mobility-limited older adults after 24 weeks of a resistance training program in conjunction with protein supplementation [49]. Thus, there is a strong consensus in this regard. A review of 121 trials including over 6700 participants concluded that '*progressive resistance training is an effective intervention for improving physical functioning in older people, including improving strength and the performance of some simple and complex activities*' [50]. The authors reported a large positive effect on muscle mass, strength, and functionality. Additionally, high-intensity resistance training is associated with greater benefits in muscle strength with an average improvement of 5.3% after each incremental in exercise intensity from low intensity (<60% 1-RM), to low/moderate intensity (60–69% 1-RM), moderate/high intensity (70–79% 1-RM), and high intensity (≥80% 1-RM) [47]. High-intensity resistance training has been reported to be well tolerated in older adults, particularly when a proper progression is applied [51][52], although intensities between 65% and 75% 1-RM can be sufficient to promote significant adaptations [53]. Higher resistance training volumes are associated with greater improvements in lean body mass after controlling for a variety of confounders (e.g., age, study duration, sex, and training intensity and frequency) [54]. With regard to strength training frequency, 2–4 days per week are commonly recommended with training typically being performed on alternating days (e.g., Monday, Wednesday, and Friday) [53]. A well-prescribed resistance training program should also include exercises targeting all major muscle groups, but emphasis on lower limbs is recommended. Significant improvements in muscle strength and size have been reported in training programs that include 1–3 sets per exercise [55] with an adjustment of the numbers of repetitions that considers the maximum number that can be performed with a given intensity (max effort) [56]. Even in delicate conditions such as osteoarthritis or spondylarthritis, strength training can give excellent results [57][58]. Lastly, in order to continually reach improvements in mass, strength, and functional capacity, it is key to consistently incorporate progression and variation

into the program. Every training variable can be adjusted over time considering the training experience of the subject and the adaptation rate on a case-by-case basis [53][59]. It is worth mentioning that it is not always possible to practice physical exercise, particularly strength training, for bedridden subjects and/or long-term patients due to chronic diseases such as cirrhosis, COPD, or severe renal insufficiency up to dialysis.

3.2. Nutrition and Supplementation

Maintenance of energy balance is crucial during a period of muscle disuse, but simply overfeeding does not further attenuate muscle atrophy since this merely increases adipose tissue. The key factor behind an accelerated loss of muscle tissue during a period of reduced food intake may not be the lower energy intake per se but more specifically the reduction in protein intake [60]. Barbera et al. [61] suggested some types of nutrients that would be able to influence the expression of myomiRs, regardless of the physical activity. Importantly, the intake of essential amino acids could positively impact miR-1, miR23a, miR208b, miR-499, and miR-27a, which have a positive effect on myocyte regeneration, proliferation, and differentiation [62]. In addition, resveratrol could regulate the differentiation of muscle cells and the activation of the PGC-1α through the positive modulation of miR-21 and miR27b and the downregulation of miR-133b, miR30b, and miR-149. Other nutrients have also been found to modulate these molecules such as albumin, palmitic acid, vitamin D, and fructose [63]. PGC-1α is a critical cofactor for mitochondrial biogenesis that it is mainly activated by the AMP-activated protein kinase (AMPK) pathway. AMPK is one of the main energy sensors (perturbations in ATP/ADP ratio) that regulate energy metabolism (e.g., protein synthesis, as an energy cost process) [64]. High levels of PGC-1α are associated with muscle mass sparing during sarcopenia, possibly by means of a reduction in the protein breakdown via FOXO inhibition (with no changes in protein synthesis) [65]. It has been shown that FOXO induces the expression of atrogin-1 and MuRF1 under conditions of energy stress in myofibers, but activation of PGC-1α could attenuate the negative regulation of proteostasis [65][66].

Starvation and aggressive hypocaloric diets have been reported as deleterious to the muscle mass and function, especially when the protein needs are not achieved [67][68]. This might be due to inhibition of the mTORC1 pathway, as demonstrated after some weeks of low-carbohydrate high-fat (LCHF) diets [69]. Even though extreme nutrient and energy deprivation induces autophagy, a mild carbohydrate restriction may result in a favorable impact on sarcopenia outcomes [65][70][71]. In fact, caloric restriction might confer lifespan and health benefits and, therefore, it is not surprising that intermittent and periodized caloric restrictions (e.g., alternate-day fasting or intermittent fasting) might be suitable as a counteracting strategy for sarcopenia [72][73]. Thus, certain biological elements might prevent the excessive activation of UPS via negative regulation of pro-atrophy transcription factors without modifying the translational process. From a nutritional standpoint, adequate protein intake and certain antioxidants (e.g., secondary metabolites) could modulate the muscle protein synthesis and breakdown. The subsections below summarize relevant findings in this regard.

3.2.1. High-Protein Diet

Older people have a diminished myofibrillar protein synthesis response to protein intake, which may have a strong influence on the progression of sarcopenia, and it is exacerbated in elderly population with obesity. This age-related muscle ‘anabolic resistance’ is more evident in response to low or moderate protein intake which is common in the diet of older individuals [74]. In addition, the current recommended dietary protein intake of 0.8 g/kg/day might not be sufficient for preserving muscle mass and quality on a long-term basis [75][76][77]. In a recent review and meta-analysis, carried out on older subjects with overweight and obesity, it was concluded that protein intakes ≥1.0 g/kg/day have a greater protective effect on the loss of lean tissue than lower intakes. It is worth mentioning that subjects were 50 years old, considering that, as age advances, the amount of protein intake may become more essential [78][79]. Moreover, feeding is a critical modulator of the inner biological clock; therefore, both the timing and the type of food can be important [80][81]. Erratic eating patterns can disrupt the temporal coordination of metabolism and physiology, which is associated with chronic diseases that are also characteristic of aging such as sarcopenia [82][83]. Therefore, timing is crucial to regulate autophagy and mitophagy in more metabolically sensitive populations such as older adults.

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