Sarcopenia: Twenty Open Questions for a Research Agenda

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Abstract

The term "sarcopenia" is used to indicate the progressive reduction in muscle mass and muscle strength that affect older persons and cause a large percentage of late-life disability. Searching for potential targets for intervention, many studies are currently focusing on the pathophysiologic mechanisms that may explain the development of sarcopenia, and in particular on the signaling pathways involved in this process. Other mechanisms being studied include physical inactivity, oxidative stress, chronic inflammation and general changes in body composition. Exercise is the only intervention that can prevent and, to a certain extent, reduce sarcopenia in older individuals. However, the relationship between physical activity and the intrinsic process of sarcopenia remain unclear. Current efforts are aimed at understanding whether some genetic characteristics exist that increase the risk of sarcopenia. In this review, we provide a list of 20 research questions that are likely to find answers in the near future.

Key words: aging, exercise, muscles, sarcopenia.

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Sarcopenia, a reduction in muscle mass and muscle strength, is considered one of the hallmarks of the aging process. Current views consider sarcopenia as the consequence of multiple medical, behavioural and environmental factors that are characteristic of older persons. Geriatricians have a strong interest in the study of sarcopenia because of its detrimental effect of physical function that is probably the single, most frequent cause of disability in the latter stages of human life [28]. However, it is important to recognize that the reduction in lean body mass has an effect on health that is completely independent of its functional consequences. A number of physiological functions that take place within muscle tissues have a critical effect on human metabolism: muscles are an important reserve of body proteins and energy that can be used in extreme conditions of stress or malnutrition; amino-acids can be mobilized during acute infections and used as building blocks for antibodies; hormones are produced and catabolized within muscle tissue. Thus, it should not be surprising that the reduction in muscle mass has a negative impact on metabolic adaptation and immunological response to disease, therefore reducing the ability of our body to resist environmental challenges. Indeed, low muscle strength is a strong predictor of mortality independent of any other known risk factors and disease and many diagnostic criteria for the "frailty syndrome" include poor muscle strength. Very little research work has been done in this direction (research question n. 1, RQ1).

Sarcopenia is the main focus of many research projects that are currently ongoing in the fields of epidemiology, physical medicine, molecular biology, and genetics. In spite of this, even simple issues such as establishing standard criteria for the clinical definition, or deciding whether values of muscle strength and mass should be adjusted for body size in clinical uses are matter of passionate argumentation (RQ2). In this paper, we touch on several aspects of sarcopenia, especially on issues that are only partially understood and, therefore are emerging research questions likely to be addressed in future studies.

Diagnosis

Baumgartner et al. [2] developed a standard definition of sarcopenia in the context of the New Mexico Aging Process Study (NMAPS). These authors performed a total body DEXA scan in a random sample of the general population and defined sarcopenia as a value of lean body mass two standard deviations below the average value calculated in healthy, young men and women. This strategy is analogous to that used to define osteoporosis, which is based on T-score values below a specific cut-off. The method also has the advantage of being easy to apply and immediately understandable by most clinicians. However, a definition of sarcopenia based on T-scores

also has several disadvantages: 1) It assumes as corollary that muscle mass is the most important clinical parameter to be assessed. On the contrary, a large body of preclinical and clinical data demonstrate that the force generated per unit of muscle mass is largely variable between individuals and tends to decline steadily with aging [8, 22]. Working with single, intact muscle fibers from rats, Gonzalez et al. [14] demonstrated that the force developed by both fast and slow-twitch fibers declines with aging. Data from the Baltimore Longitudinal Study of Aging Metter et al. [26] showed that the ratio of force to mass declines during the aging process, although the rate of decline is somewhat different depending on the method used to estimate muscle mass. These findings indicate that the decline in muscle strength with aging is in excess of what is expected by the decline in muscle mass and suggests that a direct measure of force is preferable for clinical practice (RQ3). It is still unclear what factors affect the magnitude of the force generated by muscle tissue, but preliminary data suggest that behavioral and environmental factors are more important than genetic predisposition [33] (RQ4). 2) The threshold in bone mineral density used for the definition of osteoporosis was originally selected based on observed risk of hip fracture in longitudinal studies [20]. Analogously, the threshold for the definition of sarcopenia should be based on functional consequences, for example, the risk of developing ADL disability. Unfortunately, this approach has not been pursued by appropriately designed longitudinal studies conducted in representative populations (RQ5).

The Causes of Sarcopenia

The underlying biological mechanisms that account for the development of age-associated sarcopenia are probably complex and not exhaustively identified. To some extent, even masters athletes develop sarcopenia and, therefore, biological mechanisms, which are intrinsic to aging and independent of behavior and environment, should be hypothesized. Perhaps the most important is the damage caused by reactive oxygen species (ROS), which are produced within muscle mitochondria where large quantities of ATP are created by the electron transport chain. There is no direct evidence that the production of ROS and the rate of oxidative stress increase with aging [19]. However, there are convincing data suggesting that both the serum and tissue concentrations of antioxidant scavengers, especially superoxido-dismutase (SOD), increase with age. This phenomenon is thought to be reactive to increments in oxidative stress, although recent studies fail to confirm this hypothesis and propose alternative explanations [19]. In normal physiologic conditions, a small amount of ROS is "positive" because it serves the purpose of stimulating the production of antioxidants, activates the metabolic turnover, and continuously stimulates the renovation and substitution of damaged fibers. When the production of ROS is excessive, young organisms can make available adequate quantities of antioxidants while older organisms seem to progressively lose this compensatory ability. Thus, although in older adults the antioxidant activity tends to be higher in absolute terms, such activity may be inadequate to protect muscles from ROS (RQ6). Interestingly, the increment in antioxidant activities of molecules such as SOD is not associated with a parallel increment in the mRNA for SOD, suggesting that the increment in antioxidant activity is not caused by enhanced gene expression, and some still unknown post-translational mechanisms should be hypothesized.

Another possible mechanism that may account for sarcopenia is the catabolic effect of chronic inflammation. The catabolic effect of pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6 on muscle fibers has been suggested by studies *in vitro* and *in vivo* [27, 35, 36]. Epidemiological studies have found that muscle strength, and to a lesser extent, muscle mass, are cross-sectionally associated with circulating levels IL-6 and TNF-α [6]. Recently, Ferrucci et al. [10] demonstrated that the predictive effect of IL-6 serum level on accelerated decline of physical function in frail older women was accounted for by the detrimental effect of IL-6 on muscle strength [9, 11]. Altogether, these findings suggest that inflammation is an important cause of sarcopenia. Indeed, production of IL-6 and IL-1 is an essential mechanism in the muscle cell turnover in response to micro-damage following exercise. It remains to be demonstrated that high levels of pro-inflammatory cytokines predict accelerated decline of muscle mass in primates [9] (RQ7). This is important because the confirmation of this hypothesis can open new treatment perspectives. Incidentally, recent data show that high levels of physical activity are associated with low circulating levels of inflammatory markers [13]. This is in contrast with the fact that after a burst of acute exercise, serum levels of pro-inflammatory cytokines are extremely elevated [32]. However, it has been demonstrated that the peak levels of cytokines following exercise progressively decline in people who exercise regularly over time [23], and the level of these same cytokines at rest is diminished [16, 23]. This may be a mechanism contributing to the beneficial effect of exercise for the prevention of sarcopenia (RQ8).

Several recent lines of research have approached the problem of sarcopenia in the context of overall changes in body composition occurring over the aging process. It is well known that lean body mass declines and fat mass increases with aging. The mechanism by which this "tissue substitution" occurs is unclear. At least two mechanisms may be hypothesized. First, muscle atrophy leaves an "empty space" which is filled by adipocytes. Second, the expansion of adipose tissue facilitates muscle atrophy. Recently, an alternative mechanism has been proposed where increased numbers of adipocytes produces elevated levels of circulating leptin, which in turn facilitates the development of sarcopenia through the inhibition of growth hormone [31]. This is a fasci-

nating hypothesis that opens new perspectives to interventions aimed at prevention of sarcopenia (RQ9).

The Role of Exercise and Physical Activity

During the growing period, muscle development allows progressively better mobility and freedom of movement in the environment. The growth curve for muscle mass reaches a plateau around age 25. Then, after remaining stable for approximately one decade, muscle mass begins to decline. The rate of such a decline is determined by many factors but principally by level of physical activity. As far as we know, exercise is the most powerful tool that we can use to protect the integrity and functionality of our muscles while aging. This evidence should not be interpreted, by any means, as direct proof that exercise inhibits, slows down or stops the specific mechanism that causes sarcopenia over the aging process. In fact, the hypothesis that the biological processes leading to age-associated sarcopenia and the variability in muscle strength/mass attributable to exercise are mutually independent is compatible with the data provided by many epidemiological studies. The hypothetical mechanism is illustrated in Figure 1. The dashed line represents the trajectory of muscle mass/force during the aging process for an individual who is normally involved in daily life activities but does not exercise. If the process leading to sarcopenia is accelerated, the slope of the trajectory would be steeper and, reciprocally, if the process is slowed down, the trajectory tends to be flatter. Exercise in different periods of life will shift the curve up or down. The combination of speed of the intrinsic mechanism leading to sarcopenia and muscle mass an strength gained or lost because, respectively, of exercise or inactivity creates around the "normal" trajectory of muscle strength/mass over the life span an area of infinite number of possible values and trajectories. As previously mentioned, recent data suggest that exercise may have a direct, positive effect on the inflammatory pathway to sarcopenia [13] but these preliminary data should be confirmed in a longitudinal perspective (RQ10).

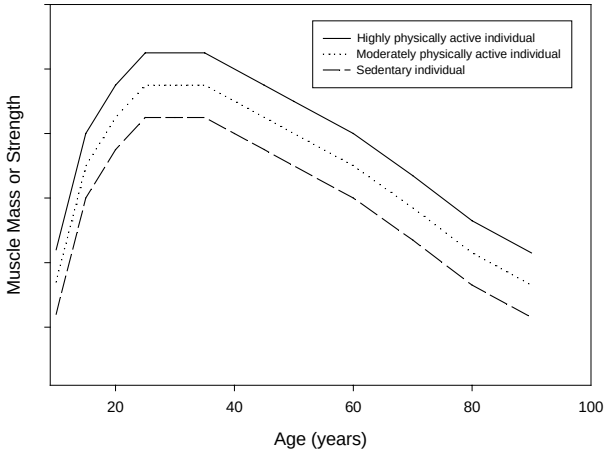

Figure 1. Hypothetical tragectories of age-associated losses in muscle mass and strength.

The effectiveness of exercise in increasing muscle mass and muscle function has been clearly demonstrated in frail, extremely old individuals [12], and has been subsequently confirmed in a number of clinical trials. It is not clear whether different types of exercise yield different results. For example, in the FAST trial, aerobic exercise and strength resistance training were associated with similar beneficial effects on physical function [24]. However, it is well known that strength resistance training is the only type of exercise that substantially improves muscle mass. Also, some recent lines of research suggest that some individuals are genetically predisposed to hypertrophy more than others [17]. Thus, the identification of the approach to exercise that is most appropriate for specific individuals remains an important research question (RQ11). Consideration of body composition may offer some hints. It has been suggested that intentional weight loss in older obese adults may potentially be harmful because it tends to disproportionately reduce muscle mass compared to fat mass. Thus, coupling a resistance exercise program to weight loss intervention may have synergistic benefits. These hypotheses should be adequately assessed in specifically designed clinical trials (RQ12).

The Genetics of Sarcopenia

The contribution of physical inactivity to various pathophysiologic conditions including sarcopenia has recently been viewed from an evolutionary biology perspective. Booth et al. [5] contend that the portion of the current human genome that determines the basic anatomy and physiology of humans evolved between 10,000 and 50,000 years ago, when the selection pressures in the hunter-gatherer societies was much higher than in modern industrialized societies. The selective advantage conferred by larger skeletal muscle masses in the late Paleolithic period may be the basis for the increased mortality rates of sarcopenic individuals that has been observed in many modern epidemiological studies. The mismatch between our "ancient" genome and our relatively sedentary life-style may be creating inappropriate low levels of gene expression of certain genes (e.g., the α-actinin gene) contributing to the progressive reduction of muscle mass. Although difficult to verify directly, this interesting hypothesis pertaining to differential gene expression may provide valuable insight into the molecular basis of sarcopenia (RQ13).

The study of such gene expression patterns that relate to sarcopenia is becoming more feasible with the availability of new technology. Contemporary research can start exploring and dissecting the effects of age and resistance exercise training on the activation profile of numerous genes [30]. The application of the microarray technique to large-scale cross-sectional and longitudinal studies will provide greater details about gene expression patterns characteristic of normal aging and various levels of physical activity. By comparing the gene ex-

pression patterns detected in sarcopenic individuals and those found in normal controls, researchers may achieve a more accurate understanding on the effective strategies for prevention and treatment of sarcopenia (RQ14).

Catabolism vs. Anabolism

Because an individual's skeletal muscle mass is determined by the balance between muscle protein synthesis and degradation, recent studies have focused on the signaling pathways that are involved in muscle hypertrophy and atrophy. Specifically, these studies have focused on the identification of potential targets for pharmacological treatments. The study of signaling pathways affecting muscle mass was first mostly conducted in patients affected by AIDS and cancer, but lately most investigators have concentrated their attention on aging and sarcopenia [18].

Due to its over-expression during compensatory hypertrophy, the role of insulin-like growth factor-I (IGF-I) has been investigated by many studies [7]. It has been suggested that the administration of IGF-I may be beneficial in the cure of sarcopenia because it may directly stimulate satellite cells and activate downstream signaling pathways that promote cell proliferation. Indeed, in animal studies the overexpression of the IGF-I gene causes substantial muscle hypertrophy. However, since the IGF-I receptor is expressed in many tissues throughout the body, there is concern about unintentionally affecting and harming tissues other than skeletal muscle. Interestingly, pre-clinical and epidemiological studies suggest that the biologic activity of IGF-I on muscle strength can be inhibited by IL-6 [1], suggesting that the detrimental effect of inflammation on muscle may be mediated by IGF-I (RQ15).

Another possible target for treatment is the ubiquitin-proteasome pathway that involves two genes integral to skeletal muscle atrophy. These genes, MuRF1 and MAFbx, are up-regulated during skeletal muscle atrophy and encode ubiquitin ligases [4]. These ligases bind and mediate ubiquitination of myofibrillar proteins for subsequent degradation during muscle atrophy. Incidentally, the ubiquitin pathway appears to be the critical target for the catabolic activities of many pro-inflammatory cytokines that belong to the IL-6 superfamily [21]. Such pathways hold significant promise as targets for pharmacologic treatment of sarcopenia, and continued research in this area may prove critical (RQ16).

Both medication and nutrition have the potential to affect – positively or negatively – the progression of sarcopenia. For example, Ibuprofen, a non-steroidal anti-inflammatory drug (NSAID) commonly used by elderly, may accelerate sarcopenia. Studies conducted in young, healthy men demonstrated that NSAIDs tend to blunt the protein synthesis response that naturally occurs after eccentric exercise via the inhibition of a prostaglandin signal [34]. It is still unclear whether similar effects are produced also in older individuals (RQ17).

The effect of nutrition on muscle metabolism is not well understood. Previous suggestions of a strong relationship between protein intake and muscle mass has never been confirmed. However, while some initial reports did not show significant effects on muscle mass and strength in the elderly [29], more recent data suggest that dietary supplementation in addition to exercise may prove helpful for delaying the progression of sarcopenia [15], and more controlled studies are needed. Particularly important is conducting these studies in settings that put older persons at high risk of immobility and malnutrition, such as nursing homes and hospitals (RQ18).

The Functional Consequences of Sarcopenia

A clearer picture of sarcopenia from molecular, biochemical, evolutionary and risk factor perspectives would be of little use if we could not put this information in the framework of sarcopenia's functional consequences. In fact, while our hopes for future treatment and prevention lay on the discovery of new pharmacologic intervention, exercise is currently our sole, solid resource. Thus, a better understanding of the applied physiology of muscle strength and power is necessary in order to prevent and/or reverse debilitating age-associated decrements that are associated with elevated rates of falls, morbidity and mortality. For example, while several authors have suggested that power (the amount of strength developed per time unit) is a better predictor of physical function than isometric or isokinetic strength [3] this statement has never been empirically confirmed in representative populations. Indeed, preliminary data indicate that muscle power plays a more vital role in determining functional capacity during dynamic activities [25]. As a result, future research should focus on the causes of muscle power loss and the exercise interventions that may reverse such detrimental age-associated trends (RQ19). Each of the above areas of research requires further longitudinal study in order to detect subtle yet potentially critical aging-related decrements within individuals.

Precise information on the relationship of strength levels of specific muscle groups to gait and other dynamic movements must be obtained through greater use of 3-dimensional kinetic modelling, force plates, and digitizing techniques. For example, if specific muscles are targeted for intervention of eccentric or concentric exercise, the effects of such interventions on gait and mobility should be carefully and safely studied in aging individuals (RQ20).

Conclusions

In conclusion, due to the highly multifactorial nature of sarcopenia, there is great need for focused yet integrated research in this area. Understanding the mechanisms that leads to age-associated sarcopenia can be key to develop effective interventions of prevention, cure and rehabilitation that can improve the quality of life of an increasing number of older persons who live in our society. In this paper, we attempted to briefly outline some of the most

important research question in the research agenda on sarcopenia. We are fully aware that this list is far from being exhaustive and fails to mention important research areas such as the effect of sex hormones, the relationship between bone and muscle and the relationship between poor strength and the "frailty syndrome". Ultimately, the most urgent research questions that need to be answered are those that become addressable from new advancements in technology and those that are posed by the creativity and inventiveness of curious investigators. However, we hope that this review may lay the basis for an active discussion on the research agenda on sarcopenia.

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