HHS Public Access

Author manuscript

J Nutr Health Aging. Author manuscript; available in PMC 2015 April 03.

Published in final edited form as:

J Nutr Health Aging. 2008 ; 12(7): 470–478.

TARGET POPULATION FOR CLINICAL TRIALS ON SARCOPENIA

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Abstract

The term “sarcopenia” describes the progressive decline of muscle mass, strength and function occurring with aging. It is not considered a disease, but the direct consequence of the aging process on the skeletal muscle. Multiple demographic (e.g. gender, race), biological (e.g. inflammatory status) and clinical (e.g. diabetes, metabolic syndrome, congestive heart failure, medications) factors are able to influence (positively or negatively) the skeletal muscle quality and quantity. The extreme paucity of clinical trials on sarcopenia in literature is mainly due to difficulties in designing studies able to isolate the aging process from its multiple and interconnected consequences. In the present review, we present the major factors to consider as potential sources of biased results when evaluating potential candidates for clinical trials on sarcopenia. The development of clinical trials exploring the nature of the sarcopenia process is urgent, but several controversial issues on this hallmark of aging still need clarification.

INTRODUCTION

Sarcopenia (from Greek *sarx* for flesh, and *penia* for loss) describes one of the most noticeable changes occurring with aging, that is the progressive decline of muscle mass, strength and function(1–3). Sarcopenia is generally considered as a normal part of the aging process. It is not a disease, and does not require the presence of diseases.

Sarcopenia is often accompanied by poor endurance, physical inactivity, slow gait speed, and decreased mobility, all factors representing common features of the frailty syndrome(4;5). The age-related muscle mass loss has been associated with a higher risk of falls, as well as with lower thermoregulation capacity and insulin sensitivity(6–9). Moreover, the impaired muscle strength is highly predictive of incident disability and all-cause mortality in the elderly(10;11). Besides of these burdensome clinical consequences, sarcopenia has an extremely severe economic impact on the health care system. It has been estimated that the health care costs due to sarcopenia in the United States in 2000 were about $18.5 billion(12), and this expenditure is likely to significantly increase in the future given the progressive aging of the population. Therefore, the understanding of the

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mechanisms responsible for this phenomenon represents a public health priority. Unfortunately, sarcopenia is still limited to a “matter for researchers”, finding hard time to become an issue of clinical relevance. The reason for the scarce interest that sarcopenia has among clinicians resides in the many uncertainties still existing, and the extremely limited evidence about this phenomenon. Among the several uncovered issues on this condition, a major limiting point in the design of clinical trials on sarcopenia is the difficulty in identifying a target population.

In the present review, we discuss the main characteristics that potential candidates to clinical trials on sarcopenia should present. In particular, we will evaluate those factors potentially influencing the sarcopenia process that need to be considered in the design of intervention studies on the age-related muscle mass and strength loss. Excluded by this review are those conditions which are not related to sarcopenia, but may influence the successful completion of a clinical trial. For example, we will not discuss the exclusion of subjects with dementia or severe cognitive impairment from a trial on sarcopenia because this exclusion is mainly due to the difficulties in the subjects’ retention, adherence, and compliance to the study protocol. This is not an exclusion due to a direct effect of the disease on the age-related muscle decline. Similarly, those life-threatening conditions or diagnoses excluding subjects from a clinical trial for safety issues (e.g. high blood pressure, abnormal laboratory values) will not be considered in the present work.

AN AGE-RELATED PHENOMENON

Critical issues in designing clinical trials on sarcopenia reside in the long term and progressive nature of this process over time. In fact, muscle strength and mass reach their peaks in the teens and twenties, and begin to fall in the thirties. A 10–15% rate of decline in muscle strength has been estimated per decade of life after age of 50 years. This decline becomes even faster after 75 years of age(13). Moreover, by definition, sarcopenia is a continuous process strongly connected with age, so that everyone experiences the loss of muscle mass and strength. Interestingly, the age-related loss of muscle mass and strength has been reported in animal as well as human models, so that it is considered a universal phenomenon occurring in every living being. For example, progressive loss of muscle mass and function have even been reported in *Caernorhabditis elegans*, a short-lived nematode, extensively studied to explore the aging process(14).

These issues are severely limiting the design of trials following the development of sarcopenia. In fact, they may render necessary extremely long follow-up (and consequent high costs) to obtain statistically significant differences between the study intervention and the control arms in the body composition changes. In fact, it is noteworthy that any possible control group will experience the development of the sarcopenia process. Consequently, it will be required the enrollment of a large sample population to obtain the adequate statistical power detecting significant differences. Translational studies on animal models may partly solve these issues by providing preliminary data (to be later verified in humans) in shorter time and a relatively less expensive way.

In literature, there is extreme scarcity of clinical trials considering the sarcopenia phenomenon as primary outcome. Moreover, large part of the available evidence is primarily focused on muscle function modifications, rather than considering the combined body composition changes. Although this choice might be legitimate because considering the muscle mass loss through a surrogate (i.e. decline in strength and function), it is still limited to a monothematic (and, therefore, partial) evaluation of the two-dimension sarcopenia phenomenon. The importance of a combined evaluation of the two components of sarcopenia (i.e. loss of muscle mass and loss of muscle strength) needs to be underlined, especially in the light of recent studies 1) limiting the prognostic value of skeletal muscle mass for health-related events(15;16), and 2) enhancing the role played by low muscle strength in the physical decline(16). Moreover, it is important to take into account how the functional surrogates of sarcopenia (i.e. physical function measures) may go beyond mere measures of muscle strength, but represent markers of well-being. Therefore, an intervention improving muscle strength (and, consequently, increasing muscle mass) may not necessarily be beneficial through a direct effect on the skeletal muscle. Its benefits may find a broader and indirect explanation in the improvement of the overall health status.

Several studies investigating the sarcopenia process in humans were based on the comparison between results obtained from a sample of healthy older subjects and a control group of young individuals. This approach implicitly accepts that the absence of clinical diagnoses might 1) render similar (and comparable) a young individual in his/her twenties to a subject aged 60 years and older, and 2) isolate the mechanisms at the basis of the aging process. Again, the approach is legitimate and possibly the best way to study the long-term phenomenon of aging (ideally starting with our birth). But then, the limitations of it (which are also the hinges of the evidence-based medicine controversy) cannot be ignored. In fact, the cultural (and consequent lifestyle) differences, as well as the number of subclinical conditions (even possibly due to limitations of diagnostic procedures) cannot be considered when using this approach.

INFLUENCES ON THE SARCOPENIA PROCESS

An important issue to be taken into account when designing a clinical trial on sarcopenia resides in the multiple potential confounders influencing the skeletal muscle quantity and quality (Table 1). In fact, a wide spectrum of behavioral, biological, and clinical factors is able to (positively or negatively) modify the sarcopenia process. If the clinical trial is indeed focused on the study of a mere marker of aging (as sarcopenia is), all these potential confounders need to be reduced to the minimum when recruiting the study sample population.

Since, as stated above, sarcopenia cannot be considered a disease (or the consequence of diseases), the identification of this physiologic condition is (at least partly) limited by the difficulties in isolating this phenomenon to the only context of aging. For these reasons, multiple sociodemographic, behavioral, clinical, therapeutic, and biological factors need to be ascertained for the selection of the ideal candidates in clinical trials, especially when recruiting older subjects.

Demographic factors

Sarcopenia and gender—Besides of age, several other demographic factors are able to influence the progression of the skeletal muscle decline. The initial amount of muscle mass represents the first and crucial factor determining the clinically-evident condition of sarcopenia. In fact, the level of initial muscle mass (as well as its function) plays an important role in the reaching of an hypothetical threshold distinguishing the normal from an abnormal muscle decline(17). In other words, the greater the starting reserve capacity, the longer it will be before the threshold of clinically-evident sarcopenia is crossed. Consequently, the greater total muscle mass and strength that men show compared to women at all ages may (at least partly) explain the gender differences found in the prevalence of sarcopenia(2;18) and the related incidence of negative outcomes(19). Several studies have also shown that the decline of skeletal muscle does not follow a similar pattern across gender. In fact, it has been suggested that the age-related decline in skeletal muscle might be steeper in men compared to women(20;21). Moreover, body composition may differently affect muscle function in men and women. Low muscle mass is more strongly related to poor muscle strength in men than in women. In these latter, adipose tissue may play a more relevant role to impair the function(22). It is likely that age-related muscle function differences can only be partly explained by body composition modifications *per se*. It is possible that the muscle decline is the result of the combined action of a wider number of gender-specific confounders (e.g. different patterns of physical activity(23), hormonal differences(24;25)…). Therefore, clinical trials should never combine genders when investigating sarcopenia and muscle strength in older persons.

Sarcopenia and race/ethnicity—Race and ethnicity differences have also been reported when examining the prevalence of sarcopenia(2). In fact, it has been suggested that African-Americans present more muscle mass than Caucasian, Asian or Hispanic subjects(26;27). Moreover, significant racial differences also exists in adipose tissue, for what concern both the amount(28) and the distribution(29;30). This is particularly important given the close mechanic and biological interactions existing between lean and fat tissues(31;32). Therefore, it is possible that genetically-based ethnic differences may play an important role in the determination of the age-related skeletal muscle decline. Consequently, race and ethnicity differences are needed to be taken into account when exploring sarcopenia and body composition in clinical trials. Assuming similarities across race/ethnic groups in this field might lead to biased results.

Behavioral factors

Skeletal muscle is a dynamic tissue. A constant turn-over of proteins into amino acids guarantees its maintenance, but an adequate amount of amino acids still needs to be supplied through the diet. Therefore, inadequate protein and caloric intakes may contribute to the development of sarcopenia and cause visceral protein depletion. In fact, a prolonged low protein intake leads to dramatic reductions in cell mass, muscle mass, and nitrogen balance(33). Malnutrition is an extremely frequent issue in older persons. Approximately 25% of older women do not reach the recommended daily allowance for protein (i.e. 0.8 grams per kilogram). With aging, food intake tends to decrease because of several (and concurrent) reasons (e.g. early satiety, hormonal modifications, sensory reduction, increased

inflammatory status, depression, chronic clinical conditions, higher medications use, disability, social issues,…).

Current smoking and sedentary lifestyle have been indicated as reversible contributors to sarcopenia by several studies(34;35). Multiple explanations can be given to the negative effect of smoking on muscle mass. Long-term smoke exposure has been associated with significant systemic modifications(36), such as oxidant-antioxidant imbalance (due to the increase of lipid peroxidation(37;38) and reduction of plasma vitamin A and C(39)), evidence of higher inflammatory status(40), as well as coagulation and endothelial dysfunctions(41;42). It is noteworthy that the impairments of all these biological pathways are involved in the acceleration of the aging process, and potentially disruption of the skeletal muscle homeostasis. A recent study by Petersen and colleagues(43) has demonstrated that muscle protein synthesis is markedly reduced in smokers compared to subjects who had never smoked. Moreover, Authors documented the enhanced expression of myostatin and muscle atrophy F-box (MAFBx) genes, which control the inhibition of muscle growth and the muscle catabolism. The study was concluded by a statement underlining the importance to control for smoking status all the studies evaluating the muscle protein metabolism.

Another behavioral (and reversible) risk factor for sarcopenia that has to be carefully investigated in the design of clinical trials is physical activity. Levels of physical activity fall with increasing age. The reduction of physical activity causes a critical decrease of the most important trophic factor acting on the skeletal muscle. At the same time, sedentary lifestyle predisposes people to the positive energy balance responsible for weight gain, which is largely due to an increment of fat mass. Significant improvements from physical exercise in muscle strength have been documented even among very frail older persons(44). These physical exercise-associated gains in muscle strength are parallel to the improvement of muscle quality. In fact, physical exercise is able to increase in skeletal muscle fiber size (both type I and II)(45), capillary density(46), and the number of myonuclei per fiber and myonuclei per unit length of muscle fiber(47). Physical activity also stimulates the muscle protein synthesis, independently of age(48–51). In particular, this increase in muscle protein synthesis seems to occur in specific muscle proteins (i.e. myosin heavy chain) that are crucial for the fiber contraction(49;52). Moreover, physical activity plays an important role in limiting the free radical production and oxidative damage. Even if exercise is associated with an abnormal production of free radicals, the elderly who are physically active benefit from exercise-induced adaptations in the cellular antioxidant defense systems(53). Both *in vitro* and *in vivo* studies have demonstrated the beneficial effects of physical exercise on inflammation(54). A change in muscle innervation and activation patterns has been included among the physical exercise-related benefits(55). Physical exercise reduces the need of dietary protein intake through an improved efficiency of protein absorption(56;57). It is also important to consider the wide range of clinical and subclinical conditions (many of those potentially enhancing the age-related muscle decline) which may beneficiate from physical exercise(58–60).

Finally, among the behavioral factors potentially influencing the skeletal muscle status (and modify the progression of sarcopenia), weight loss is one of the most studied. Weight loss

programs have shown to improve physical performance and function in older adults(61). A recent paper by Miller and colleagues(62) showed that intensive weight loss program in obese older persons significantly improves the inflammatory status. Confirming the close interaction existing among body composition, inflammation and physical function, Authors reported that the inflammatory markers modifications due to the 6-month weight loss intervention were predictive of changes in 6-minute walk distance. If intentional and controlled reductions of body weight in obese subjects are capable to significantly (and positively) modify the body composition, the unintentional weight loss is clearly indicated as a major feature of frailty(63) (and associated with worse body composition profile).

Biological factors

A wide range of anabolic and catabolic signals is able to affect skeletal muscle. Cytokines are intercellular messengers regulating the inflammatory cascade. The increase of pro-inflammatory cytokines (e.g. tumor necrosis factor [TNF]-α, interleukin [IL]-6) has been indicated as a potential explanation for several age-related phenotypic changes, including sarcopenia(64). At the same time, anabolic cytokines (e.g. IL-15, insulin-like growth factor [IGF]-1, and muscle growth factor) also exist, and counteract the negative effects of pro-inflammatory ones. Increased levels of inflammation have shown to be detrimental for skeletal muscle both in human(65) and animal models(66–68). In fact, inflammation may negatively affect the skeletal muscle through direct catabolic effects or through indirect mechanisms (i.e. induction of anorexia, decrease of growth hormone and IGF-1 concentrations)(69). Consistently with this hypothesis, several studies have demonstrated the existence of an inverse relationship of inflammatory status with muscle mass and muscle strength(70;71).

Among the inflammatory markers showing to be more strongly associated with muscle mass and quality, TNF-α needs special attention. In fact, levels of TNF-α tend to increase with age in several tissues, including skeletal muscle(72;73). TNF-α is a central mediator of cellular inflammatory and apoptotic signaling pathways, and plays a major role in the aging process(72;74). TNF-α stimulates a cellular kinase complex (i.e. I Kappa B Kinase [IKK]), which activates nuclear factor (NF)-κβ, a transcription factor regulating the production of proinflammatory cytokines (including IL-6)(75).

Although the screening of potential participants for clinical trials on sarcopenia cannot be based on the routine evaluation of expensive biomarkers of inflammation, exclusion criteria should still include an evaluation of the inflammatory status. In fact, it is important to distinguish sarcopenia from cachexia(76).

Age-related hormonal changes (in particular, testosterone and GH modifications) have also been indicated as important biological contributors to the skeletal muscle decline. A direct association between testosterone levels and appendicular muscle mass has been reported(77). Moreover, testosterone induces muscle fiber hypertrophy by regulating muscle protein synthesis and breakdown(78;79), and promoting pluripotent stem cell commitment differentiation(80). Levels of GH (and its major messenger IGF-1) also decline with aging, providing a further hormonal pathway potentially involved in the development of sarcopenia. In fact, GH and IGF-1 are crucial for the growth and development of immature

organisms, and the maintenance of lean body and bone mass(81). GH also has an important lipolytic effect which tends to decline with aging due to a higher resistance to the stimulus(82). The exclusion of participants with inflammatory diseases and/or hormonal abonrmalities is a must to avoid the biasing of study results.

Clinical factors

The number of clinical conditions significantly increases with aging. Theoretically, any disease should be considered as a departure from the normal aging process, consequently affecting the study of the "pure" age-related muscle decline. However, the line separating "aging" from "disease" is often extremely thin. This distinction is mainly limited by 1) the accuracy of current diagnostic procedures, and 2) the adoption of clinical-friendly definitions which not necessarily capture the *continuum* of physio-pathological processes. Therefore, too rigid clinical criteria to select participants for clinical trials on sarcopenia might be not easily applicable because of 1) the adopted definitions potentially arguable in the research setting, and 2) the relative difficulty in finding older subjects with no clinical conditions. A more practical approach might be required. It could be based on the careful evaluation of those chronic diseases that more than others are able to affect body composition and skeletal muscle function. Investigators need to do any effort to limit to the minimum the potential biases due to clinical conditions.

Sarcopenia has severe metabolic effects (e.g. reduced metabolic rate due to lower muscle mass and/or physical activity) which are responsible for increased insulin-resistance, diabetes, dyslipidemia, and hypertension(83). Diabetes is not only associated with higher inflammation (which represents a potent contributor to skeletal muscle loss)(84), but also to physical decline(85). It is also important to remind how body composition parameters are largely modified by the presence of diabetes. For example, Azuma and colleagues(86) recently demonstrated that diabetic subjects present lower appendicular lean mass, but higher truncal and hepatic fat mass than non-diabetic individuals.

Another clinical condition to closely evaluate for potentially influencing the results of clinical trials on sarcopenia is congestive heart failure. Not only this disease is associated with a wide range of biological modifications affecting the skeletal muscle quality and quantity (e.g. inflammation(87), oxidative stress(88), hypoxia(89)…), but the liquid retention may significantly influence results of imaging techniques estimating body composition. Certainly, as happening with congestive heart failure, all those diseases which have been associated with cachexia (e.g. cancer, chronic renal failure, chronic obstructive pulmonary disease, rheumatoid arthritis, AIDS)(90), and thus are characterized by inflammatory, hormonal, and metabolic abnormalities, had to be considered as critical exclusion criteria for studies exploring the sarcopenia phenomenon.

Unintentional weight loss is a common feature of Parkinson's patients. It has been reported that Parkinson's patients have significant lower amount of fat-free mass, possibly due to decreased physical activity and deconditioning(91). More widely, all the clinical conditions affecting central and peripheral nervous system (e.g. stroke, spinal root compressions, or motor neuron diseases) should be considered as promoters of accelerated decline of muscle mass or function. Neurons innervating skeletal muscles have their nuclei originating within

the spinal cord. The reduction or interruption of the neurothrophic signalling of motor neurons leads to significant impairment of function and reduction of muscle mass. The consequent skeletal muscle decline predisposes to the activation of the vicious cycle determining reduced physical activity, unfavorable body composition modifications, and further decline of function.

Severe arthritis should also be considered in the evaluation of potential candidates to clinical trials on sarcopenia. In fact, pain and antalgic positions may limit the muscle functioning, leading to an accelerated decline of it. Moreover, inflammatory markers tend to be higher in arthritis patients, especially in active phases of the diseases, potentially affecting the skeletal muscle quality and quantity(92).

Anemia is one of the major clinical problems in older persons, affecting about 12% of persons 60 years and older(93). Hemoglobin levels have been directly associated with muscle strength, muscle density and muscle mass(94). Anemia might affect physical performance through various pathways generally involving decreased oxygenation of tissues(95–98). One of the most common symptoms of anemia is fatigue, an important limitation to physical function and activity(99). Moreover, low levels of hemoglobin significantly reduce the oxygen delivery to skeletal muscle(100), negatively impacting muscular strength(101). Chronic hypoxia may also be responsible for several pathophysiological modifications (e.g. peripheral arterial vasodilatation, capillary angiogenesis, myocardial dysfunction, lower blood pressure, activation of the sympathetic and renin angiotensin aldosterone systems, salt and water retention), leading to the onset or worsening of disabling diseases(102;103).

In the presence of renal disease, multiple biological pathways are activated and capable to negatively influence the skeletal muscle. Inflammation, anorexia, increased metabolic rate, acidosis, and resistance to anabolic hormones (e.g. growth hormone [GH], IGF-1) may play pivotal role in the uremic skeletal muscle decline(104).

Serum albumin concentrations, which can be considered as a marker of well-being, decrease with age. It has been demonstrated that albumin levels are directly associated with muscle mass, independently of age, gender, protein intake, physical activity, and comorbidity(105). Therefore, since low concentrations of this serum protein may represent a marker of sarcopenia, it would be a useful additional biological measure to consider in the evaluation of clinical trial participants.

Acute clinical conditions should be considered as potential confounders of studies evaluating the skeletal muscle decline because of the multiple biological pathways they may activate. On the other hand, they may still be useful in the design of studies based on models of “accelerated aging”. Subjects experiencing the acute onset of a clinical condition (e.g. hip fracture patients, bed-ridden individuals due to acute illness or elective surgery procedures…) in the absence of other significant comorbidities are likely to develop a rapid decline of the skeletal muscle which may mimic some aspects of the sarcopenia process. Of course, the baseline acute condition may be responsible for some peculiarities in the pattern of the decline which may not be applicable to the aging phenomenon. However, the study of

this “provoked” skeletal muscle loss may still provide useful insights to understand the mechanisms underlying sarcopenia. In fact, it is noteworthy that clinical conditions share most of the biological pathways at the basis of the aging process (e.g. inflammation, oxidative damage, apoptosis, hormonal modifications,…), but at enhanced levels.

Therapeutic factors

Several medications are able to directly influence body composition and skeletal muscle. The decline in DHEA production occurring with aging has prompted the study of effects of DHEA administration in healthy older persons. It has been hypothesized that the supplementation of DHEA may provide the substratum to enhance the beneficial action of androgens on skeletal muscle, consequently improving its function. Even if the efficacy and safety of DHEA supplementation is still controversial(106), some reports demonstrated significant modifications in skeletal muscle mass and strength after this intervention(107;108).

The replacement of testosterone in hypogonadal men has shown to increase muscle mass, strength, and protein synthesis, independently of age(109–112). It has been estimated that 6-month of testosterone replacement therapy produces significant increase of lean mass and muscle protein synthesis, and decrease of fat mass(113). The effect of testosterone supplementation is not limited on skeletal muscle, but obviously modifies the functioning of all the systems which are influenced by the androgens action. For example, the progressive loss of motor neurons, innervation, and muscle stimulation are indicated as contributors to sarcopenia. In rats with spinal cord injury, testosterone treatment ameliorates the decrease in fiber cross-sectional area and the shift from slow to fast fibers type(114). Testosterone treatment also increases the number of motor neurons in the spinal nucleus of the pudendal nerve early in development of gerbils(115). Therefore, testosterone may slow down the sarcopenia process by acting at different levels, other than the only skeletal muscle.

Improvements in the well-being perception, body composition, lipid profile, and bone structure have been reported from GH replacement therapy(116). In normal older men, consistent results have been reported from GH supplementation showing increased lean body mass and decreased adipose tissue through improvements of IGF-1 concentrations(117;118). It has also been reported that the supplementation of recombinant GH or IGF-1 in older women leads to a 50% increase in muscle protein synthesis(119), potentially explaining the increase in muscle mass.

As explained above, inflammatory cytokines are important contributors to the muscle wasting in chronic diseases, and several studies have investigated the effects of anti-cytokine antibodies as potential treatments. For example, thalidomide (an immunomodulatory drug) is able to inhibit TNF-α and selectively destabilize TNF-α mRNA(120). This drug also attenuates loss of muscle mass and improves physical function in cancer patients with advanced pancreatic cancer(121;122). A trial in patients with HIV/AIDS-related lymphoma showed reductions in fever and cachexia from anti-IL-6 therapy(123). In this context, the inclusion of participants with chronic anti-inflammatory (or immunosuppressive) therapy (especially if at high dosage) in clinical trials evaluating the age-related muscle decline should be discouraged.

SARCOPENIC OBESITY

Recently, several Authors have closely related the sarcopenia phenomenon to obesity. The age-related loss of skeletal muscle is not isolated, but strongly connected with a parallel increase in fat mass(31). This mechanism may potentially lead to a scenario represented by the concomitant presence of sarcopenia and obesity(31;124). Even if sarcopenia might be accelerated by several different underlying causes, it still represents the major contributor to fat gain, which in turn reinforces the muscle loss. The loss of metabolically active cell mass and the weakness due to the loss of skeletal muscle lead to a reduction in resting metabolic rate and physical activity. With higher fat mass and lower muscle mass, physical activity becomes progressively more difficult, and its habitual level declines further. The development of this vicious cycle potentially leads to sarcopenic obesity, a major risk factor for the onset of physical disability(19;124;125).

Interestingly, adipose tissue is not inert, but actively involved in a number of metabolic pathways. For example, adipocytes produce a wide spectrum of pro-inflammatory, which may directly affect body composition(126). The endocrine role played by adipose tissue may potentially explain the onset of health-related events associated with increased fat mass (e.g. cardiovascular diseases)(127;128).

Given the close relationship between skeletal muscle and adipose tissue, several studies have suggested that fat mass should be considered in conjunction with muscle mass when evaluating sarcopenia(124;129;130). The definition of obesity is usually based on the calculation of the body mass index (BMI) and the use of standardized cut-points (i.e. BMI 30–34.5 kg/m^2 to define obesity, BMI 35–39.9 kg/m^2 for clinical obesity, BMI ≥40 kg/m^2 for morbid obesity). Although this classification is widely accepted and adopted (especially in the clinical practice), they may still not be sufficiently accurate. In fact, misclassifications are possible due to 1) the increasing fatness occurring with aging even when BMI remains constant, 2) ethnic differences, and 3) subjects with different health status compared to counterparts with similar BMI. Moreover, BMI remains a measure of body mass (not adiposity), so that big and muscular individuals might be considered obese as well. In a recent study(28), Gallagher and colleagues defined obesity on the basis of age-, gender- and race-specific cut-points of total body fat percentage (assessed by dual energy X-ray absorptiometry [DEXA] scan). DEXA scan results also allow the estimate of appendicular lean mass, a commonly used marker of sarcopenia(129;130). Since DEXA is one of the most commonly used imaging techniques to investigate body composition, the adoption of this technique should be preferred, especially in clinical trials evaluating muscle mass in conjunction with adipose tissue.

PREVENTION OR TREATMENT OF SARCOPENIA?

The main objective of preventive strategies for sarcopenia is to reduce the rate of the age-related skeletal muscle decline. In fact, sarcopenia has to be considered an irreversible phenomenon (at least, to date). It is likely that specific interventions may slow down the process, but the blockage of it is not impossible. This characteristic is consistent with the theories of aging by Hayflick(131;132). Otherwise, the interventions preventing/treating

sarcopenia (as marker of skeletal muscle aging) might also be directed to other organs and systems, inhibiting the aging process, and potentially leading to the extreme longevity. Thus, interventions should be aimed at reducing the speed of the muscle mass decline.

In theory, the target populations for a preventive intervention are those at risk of developing a specific event. Similarly, participants in trials aimed at evaluating the treatment of a certain condition are those who already present that specific condition. In the context of sarcopenia, this is particularly difficult because 1) the definition of “high risk” relies on clinical standards that are currently lacking for this condition, and 2) every living being experience this phenomenon. Due to the continuous and prolonged nature of sarcopenia, a cut-point defining the presence or absence of sarcopenia does not currently exist. Moreover, the multiple methods to measure body composition parameters do not facilitate the identification of thresholds defining the “sarcopenic muscle”. The lack of this information does not allow a clear distinction between prevention and treatment.

The few available studies suggest that interventions aimed against physical function decline (e.g. physical exercise) are beneficial even among the oldest and frailest subjects(44;133). Therefore, it can be hypothesized that everyone can benefit from interventions aimed at improving the muscle quality/quantity. However, it cannot be ignored that (supporting the concept of irreversibility of sarcopenia) benefits are still likely to be only partial against the aging process. Otherwise, the constant age-related decline of skeletal muscle even experienced, for example, by master athletes could not be justified.

CONCLUSIONS

The study of the aging muscle is the study of a major hallmark of aging. Several still uncovered issues on the age-related skeletal muscle decline have to be clarified before sarcopenia can be specifically and adequately investigated in clinical trials. The recruitment of a sample population for clinical trials on sarcopenia needs to allow researchers to 1) capture the bidimensional nature of sarcopenia (i.e. decline of muscle mass and reduction of muscle strength), and 2) investigate the aging process on skeletal muscle, isolating it by the consenquences of the multiple age-related clinical and subclinical impairments. Therefore, as presented in the present review, several demographic, behavioral, clinical, biological and therapeutic factors have to carefully be evaluated to prevent the biasing of study results.

ACKNOWLEDGEMENTS

This work was supported by the University of Florida Institute on Aging and the Claude D. Pepper Older Americans Independence Center (NIH grant 1P30AG028740).

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Table 1

Major factors (and related mechanisms/pathways) potentially influencing the progression of age-related skeletal muscle decline.

	Mechanisms - Pathways
Demographic factors	
Age	-
Gender	Different body composition between men and women Men have higher levels of muscle mass at all ages compared to women Different patterns of muscle decline
Race/Ethnicity	Different body composition profile across races/ethnicities
Behavioral factors	
Physical inactivity	Muscle athrophy Body composition modifications Obesity due to positive energy balance Reduction of protein synthesis Increased inflammatory levels
Poor nutrition	Reduced proteins turn-over
Smoking	Major source of oxidative damage Reduction of antioxidant defenses Reduced muscle protein synthesis Increased inflammatory levels
Biological factors	
Inflammation	Direct and indirect detrimental effects on skeletal muscle quality and quantity
Hormonal modifications	Body composition modifications
Clinical factors	
Acquired immune deficiency syndrome (AIDS)	Presence of cachexia Body composition modifications due to antiretroviral therapy
Anemia	Decreased oxygenation of tissue due to chronic hypoxia Sedentay lifestyle due to easy fatiguability Comorbidities
Arthritis	Pain Increased inflammatory levels Physical impairment leading to reduced physical activity
Cancer	Increased inflammatory levels Presence of cachexia
Chronic obstructive pulmonary disease	Increased inflammatory levels Presence of cachexia Decreased oxygenation of tissue due to chronic hypoxia
Congestive heart failure	Increased inflammatory levels Presence of cachexia Oxidative damage Liquid retention
Diabetes	Body composition modifications Increased inflammatory levels Insulin-resistance Obesity (with consequent decreased physical activity level)
Kidney disease	Increased inflammatory levels Anorexia Resistance to anabolic hormones Presence of cachexia in end-stage renal disease
Metabolic syndrome	Body composition modifications Increased inflammatory levels Insulin-resistance Obesity (with consequent decreased physical activity level)
Neurological diseases (e.g. spinal compression, stroke,…)	Decreased neurotrophic effect on skeletal muscle

	Mechanisms - Pathways
	Impaired functioning leading to atrophy Sedentary lifestyle and body composition modifications due to physical limitations Increased inflammatory levels
Parkinson’s disease	Unintentional weight loss due to deconditioning and sedentariness