The Journal of Nutrition, Health & Aging©
Volume 13, Number 8, 2009

JNHA: SARCOPENIA

PHYSIOPATHOLOGICAL MECHANISM OF SARCOPENIA

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Abstract: The aetiology of sarcopenia is multifactorial but still poorly understood while the sequelae of this phenomenon, i.e. loss of independence and metabolic complications, represent a major public health. The most evident metabolic explanation for muscle decline in elderly people is an imbalance between protein synthesis abd breakdown rates but other causes like neurodegenerative processes, reduction in anabolic hormone productions or sensitivity such as insulin, growth and sex hormones, dysregulation of cytokine secretions, modification in the response to inflammatory events, inadequate nutritional intakes and sedentarity lifestyle are involved. Consequently, the age-related loss of muscle mass could be counteracted by adequate metabolic interventions including nutritional intakes or exercise training. Recent observations clearly show that changes in quantitative as well as qualitative intakes of dietary protein are able to counteract some pathophysiological processes related to muscle loss progression. Other strategies including changes in daily protein pattern, the speed of protein digestion or specific amino acids supplementation may be beneficial to improve short term muscle anabolic response in elderly people. The beneficial impact of resistance or endurance training on muscle mass and function is highlighted in many studies suggesting that the potential anabolic response to exercise still remains despite a lesser metabolic response to nutrients. Thus a multimodal approach combining nutrition, exercise, hormones, specific anabolic drugs may an innovative treatment for limiting the development of sarcopenia with aging.

Introduction

Muscle erosion, which begins after the age of 55 years, is one of the most important factors of disability in elderly people. The cumulative decline in muscle mass reaches 40% from 20 to 80 years. The magnitude of this phenomenon, also termed sarcopenia, as a public health problem is not well established as there are few epidemiological and longitudinal studies focusing on the decrements of strength and muscle mass with advancing age. However, it is estimated that the direct healthcare cost attributable to sarcopenia in the United States in 2000 was $18.5 billion, which represented about 1.5% of total healthcare expenditures for that year (1). The reduction in muscle mass and strength provokes an impaired mobility and increased risk for falls and fall-related fractures. In addition, muscle loss is associated with a decrease in overall physical activity levels with subsequent metabolic alterations such as obesity, insulin resistance and a reduction in bone density in the elderly. As the elderly population increases around the world, the involuntary loss of muscle mass with aging may become a major health problem in the years to come. Sedentary individuals, subjects with poor protein intakes and those suffering from debilitating diseases are also at greater risks of sarcopenia.

Sarcopenia is believed to be due predominantly to atrophy and loss of skeletal muscle fibers, mainly type II fibers. This results in a relative elevation in type I fiber density related to a supposed preservation of muscle endurance and a reduction in muscle strength. Biochemically, muscle size, function and composition are closely regulated by muscle protein turnover. Consequently, the age-related loss of muscle proteins results from an imbalance between protein synthesis and degradation rates. Until now, most reports have indicated that muscle protein synthesis declines with age. The studies have demonstrated that synthesis rates of various muscle fractions, such as myofibrillar and mitochondrial fractions, decline in elderly or even by middle age. Reduced protein turnover adversely affects muscle function by inducing protein loss and damaged protein accumulation. Data also suggest that sarcopenia is due to failure of muscle protein synthesis in the postabsorptive as well as in the fed state. Other factors such as neurodegenerative processes with loss of alpha motor neurons in the spinal column, dysregulation of anabolic hormone (insulin, growth and sex hormones) and cytokine productions, modification in the response to inflammatory events, inadequate nutritional intakes and sedentarity may also participate in muscle loss during aging. So the determinants of sarcopenia include genetic and environmental factors, with a complex series of poorly understood interactions. In fact, it is still unknown whether muscle loss of aged people is an inevitable condition of aging per se, or if illnesses, inappropriate nutrition, sedentarity and other lifestyle habits are the major causes of sarcopenia. Currently, as the pathophysiology of sarcopenia is poorly understood, nutritional interventions to either prevent or at least to limit this condition are extremely limited (2).

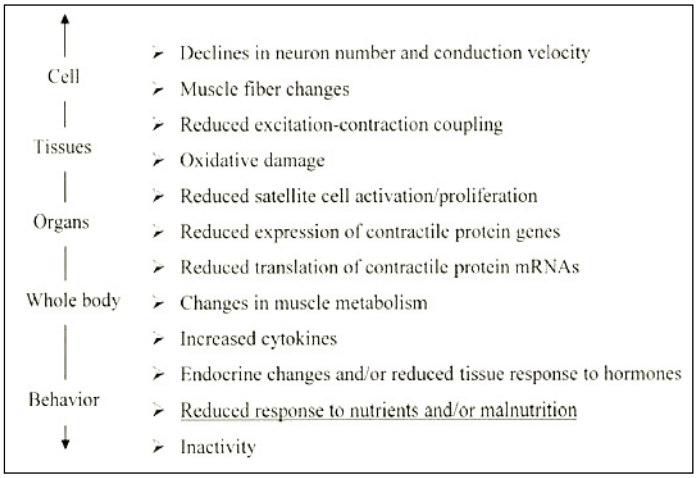
Mechanisms of sarcopenia

Many explanations for muscle decline in elderly people have been proposed such as neurodegenerative processes, reduction in anabolic hormone productions or sensitivity, dysregulation of cytokine secretions, modification in the inflammatory states (see Figure 1). All of these mechanisms can not be completely described in this review so that those which are eventually

Received May 18, 2009
Accepted for publication June 2, 2009

preventable or modified will be discussed with a special emphasis in the nutritional aspects.

Figure 1
Mechanisms of sarcopenia (from ref 69)



Age-related changes in hormones levels and sensitivity

Aging is associated with modifications of hormones production and sensitivity especially with regard to GH/IGF1, cortisosteroids, androgens, estrogens, insulin. These hormones may influence the anabolic as well as the catabolic state for an optimal muscle protein metabolism. A decrease in GH/IGF1 levels is frequently demonstrated in elderly people (3) and this is paralleled by changes in body composition, i.e, increased visceral fat and decreased lean body mass and bone mineral density. Thus it was tempting to treat patients suffering from muscle loss by GH injections but no evidence of increased muscle strenght was reported even if an increased muscle mass may occur (4, 5).

Similar changes in body composition are seen in the state of hypercortisolism so that cortisol-GH ratio has been proposed as an important factor for changes in body composition (6). Increasing age can be associated with elevated evening cortisol levels in men but changes in the sensitivity of the HPA axis also occurs with increasing age, resulting in an age-related decline in the resilience of the HPA axis. This might lead to an increased exposure of several tissues to glucocorticoids with aging,

Aging is associated with low testosterone which may lead to decreased muscle mass and bone strength, and thereby to more fractures and complications. Some intervention studies are ongoing to counteract muscle loss related to chronic diseases with some promising results.

Finally, the impact of insulin resistance on age-related muscle loss has been recently proposed since it is well known that increased in intramyocellular fat mass is associated with an increased risk of insulin resistance with aging. As shown below, a decreased response to insulin was demonstrated as the result of an impaired insulin signalling or an impaired insulin-mediated increased in muscle blood flow (7).

Inflammation and sarcopenia

Proinflammatory cytokines (TNF , IL1 and IL6) promote muscle wasting directly by increasing myofibrillar protein degradation (8) and by decreasing protein synthesis (9). Enhancement of proteolysis is accomplished by activation of the ubiquitin-dependent proteolytic system (10) since TNF activates several serine/threonine kinases and intracellular factors, including the inhibitor of the NF B (I B). IL6 is also involved in the regulation of muscle protein turnover and is considered as a catabolic cytokine (11). This activation contributes to trigger NF- B which is implicated in the upregulation of myofibrillar proteolysis by the proteasome system and in the suppression of myofibrillar protein synthesis. TNF impairs skeletal muscle protein synthesis by decreasing translational efficiency and initiation associated with alteration in the eukaryotic initiation factor-4E (eIF-4E). An indirect effect of TNF on muscle protein metabolism may also be its capacity to inhibit insulin action since this hormone has been showed to increase muscle protein synthesis and to decrease proteolysis (12, 13). It is now clear that many other inflammatory factors exhibit the same impact on muscle. Concerning protein metabolism, administration of leptin may result in a decreased rate of myofibrillar protein synthesis in skeletal muscle (14). IL6 and resistin are other well-characterized examples of compounds produced in adipose tissue that may participate in the regulation of muscle metabolism. Interestingly, the depletion of muscle mass with age does not necessarily result in weight loss, suggesting that a corresponding accumulation of body fat occurs. So, abdominal fat accumulation with aging is another candidate for a low grade inflammation process that may affect muscle protein metabolis and function. Indded, aging is associated with increased levels of circulating inflammatory components in blood including elevated concentrations of TNF , interleukin-6 (IL6), IL1 receptor antagonist (IL1Ra), soluble TNF receptor (sTNFR1), acute phase proteins such as C-reactive protein (CRP), and high neutrophil counts (15). This chronic low grade inflammation is associated with a variety of pathological phenomena that may affect the elderly, including sarcopenia, osteoporosis, atherosclerosis, reduced immune function and insulin resistance.

Impaired response of protein metabolism to nutrition

Impaired anabolic response of skeletal muscle to nutrition

Muscle loss in elderly subjects possibly depends upon both inadequate nutritional intake and impaired adaptation of skeletal muscle to nutrients, e.g. essential amino acids (16). By using femoral arterio-venous catheterization and quadriceps muscle biopsies, Volpi et al. have reported that a peripheral

infusion of an amino acid mixture was able to increase amino acid delivery to the leg, amino acid transport, and muscle protein synthesis irrespective of the age (17). Despite no change in protein breakdown during amino acid infusion, a positive net balance of amino acids across the muscle was achieved. The authors concluded that, although muscle mass is decreased in the elderly, muscle protein anabolism can nonetheless be stimulated by a high amino acid availability (17). The same observation was described with an oral administration of a large dose of amino acid mixture but a higher first-pass splanchnic extraction of leucine as well as phenylalanine was demonstrated (18, 19). Amino acid transport into muscle, muscle protein synthesis, and net balance increased similarly in both the young and the elderly suggesting that muscle protein anabolism can be stimulated by oral amino acids in elderly as well as in young subjects. Similarly, muscle protein synthesis increased to the same extent after an oral intake of either balanced amino acids or essential amino acids in healthy elderly (20). Therefore, it could be concluded that even if non-essential amino acids seems not to be required to stimulate muscle protein anabolism in older adults, muscle response to nutrients especially amino acid intake is preserved in elderly subjects in comparison with younger ones. However, the amount, the quality of dietary proteins and the energy added to protein intake are more important to consider. Indeed, when glucose was associated with an oral administration of a mixture of amino acids (21), an increased amino acid delivery and transport into the muscle together with a decreased muscle protein breakdown was achieved in both groups. However, the stimulation of muscle protein synthesis in the young no more exists in the elderly subjects leading to a lower protein balance in the leg skeletal muscles. So the anabolic response of muscle protein to hyperaminoacidemia and to higher levels of endogenous insulin seems to be impaired in healthy elderly as a result of a blunted response of protein synthesis, implying that the route and the non-protein substrates added to amino acids on net muscle protein anabolism in young and elderly subjects has to be taken into account (18, 21). These studies lead us to open the question of muscle sensitivity to hormones like insulin and the impact of normal or low protein intakes during aging. Indeed, previous study (22) have demonstrated in old rats that the anabolic response of muscle protein metabolism to a complete meal is blunted compared to young adults animals. This lack of muscle anabolic response to meal intake may contribute to the long term development of sarcopenia in the elderly.

Protein intakes and quality of dietary proteins

Quantitative aspects

The mean dietary requirement for adult men and women of all ages, as set by the 1985 joint FAO/WHO/UNU expert consultation, was estimated to be 0.6 g protein/kg/d, with a suggested safe level of intake set at 0.75 g protein/kg/d (23). However, since body composition and protein metabolism changes occur with age, especially related to muscle, it has been suggested that the utilization of dietary proteins and amino acids may differ between the young and old adults. Consequently, using various methodologies, i.e. nitrogen balance and tracer procedures, protein requirement with advancing age was discussed. Taken together, studies based on nitrogen balance using the same formula, showed that protein requirement increases in elderly people. When the recalculated data from all studies were combined by weighted mean averages, a mean protein requirement of 0.89 g protein/kg/d was estimated (24, 25). Nevertheless, recent works based on tracer methodology reported that the rate of whole body protein turnover, a commonly assumed determinant of protein requirement, exhibited non significant change with age when expressed per kg of fat free mass (26, 27). However, because of modification in body composition and physiological functions, protein requirement might be increased in healthy elderly people. Nonetheless in hospitalized patients, calculations from spontaneous nitrogen intakes and loss indicated a safe protein intake of at least 1.3 g protein/kg/d (28). As nitrogen balance and tracer studies are still controversial, recommendations for protein intake in this population are still debated.

Very few experiments were designed to study the effect of increased or high protein intake in the elderly population. Whole body protein turnover was enhanced in elderly men and women when the protein amount in the diet increased from 12% to 21% of total energy (29). Of note, Walrand et al. recently showed (30) that a high protein diet ingestion, i.e. 3 g/kg fat free mass/d for 10 days, was inefficient to enhance protein synthesis at whole body as well as skeletal muscle levels. Interestingly in this study, although a high protein diet enhanced glomerular filtration rate in young adults, it reduced renal function in the aged group, suggesting that very high protein diet may be deleterious in healthy subjects.

Inversely, following a low protein intake (50% of usual intake), no modification of whole body protein synthesis and breakdown was noticed in a group of aged women (31). However, whole body protein oxidation, nitrogen balance, muscle mass, muscle function and immune response were significantly affected in the group fed a low protein diet (32). Collectively, these observations highlight the importance of maintaining adequate protein intakes in elderly people to counteract the negative effect of aging on protein metabolism. The recently published Health ABC study clearly indicates that during a 3 y. follow up, elderly subjects consuming a higher amount of daily protein have the lesser reduction in appendicular lean body mass (33)

Qualitative impact of dietary proteins during aging

According to the different types of dietary protein, it is possible that their impact on protein metabolism is not the same. The consumption of three different protein sources and its effect on protein metabolism was analyzed in elderly women

(34). A first diet was composed half of animal proteins and half of vegetable proteins, whereas one-third of the proteins consumed in the second diet were from vegetable and two-third from animals, and inversely in the third diet. Nitrogen balance was not modified in this study but whole body protein breakdown was not inhibited to the same extent by the meal when the protein source was from vegetables in comparison with meat (34). This study showed that intake of high quality proteins may be an important issue in elderly people.

Another important consideration regarding the quality of dietary protein is the speed of protein absorption from the gut. By analogy with carbohydrates, protein can be digested at different rates, i.e. concept of "fast" and "slow" proteins (35). For example, the two main milk proteins, i.e. casein and whey protein, have different behaviors in the intestinal tract. Whey protein, a soluble protein, is considered as a fast protein: after digestion and absorption, plasma appearance of amino acids derived from this protein is high, fast but transient. On the contrary, casein clots in the stomach, which delays its gastric emptying and therefore results in a slower, lower but prolonged release and absorption of amino acids. This new concept was recently applied to the modification of protein metabolism during aging (36). In this population, the duration and magnitude of elevated plasma amino acids are key factors to counteract the decrease in muscle sensitivity to amino acids. Accordingly, postprandial protein gain was higher after a meal containing fast protein, i.e. whey protein, than slow protein, i.e. casein, in elderly, when considering either isonitrogenous or isoleucine (as leucine is a well-known anabolic factor) meals. In addition, post-prandial protein utilization by the body was significantly higher with the fast protein than with the slow one (36). A recent report (37) also showed that whey proteins are able to stimulate muscle protein synthesis rate in a group of healthy elderly individuals. These data clearly suggest that a protein mixture that can be quickly digested and absorbed might be more efficient to limit protein loss during aging than a mixture yielding slower kinetics.

Recent studies have determined the mechanism of a decreased skeletal muscle sensitivity to amino acids in elderly people (38). A defect in branched chain amino acid (BCAA) activation pathway may be responsible for this alteration. Consequently, the alteration of muscle protein synthesis response to anabolic signals may be counteracted by nutritional strategies aiming at improving BCAA availability. Within the dietary proteins, essential amino acids are very important for muscle anabolism. For example, in vitro or in vivo high leucine administration is able to stimulate muscle protein synthesis rate in aged rodents (39-41). In these models, leucine acts as an actual mediator able to modulate specific intracellular pathway linked with the stimulation of protein translation (42). Interestingly, when given to old rats for 10 days, the beneficial effect of leucine supplementation persisted, indicating that a long-term utilization of leucine-enriched diets may limit muscle wasting in aged individuals (43). In addition, these data suggest that nutritional manipulations increasing the availability of leucine into skeletal muscle, such as the utilization of the leucine-rich fast protein, i.e. whey protein, could be beneficial to improve postprandial protein retention during aging. The beneficial effect of such a diet on muscle protein synthesis in aged humans is currently under study.

Daily protein feeding pattern

The impact of daily protein distribution might be crucial for a better protein anabolism. Studies by Arnal et al. (44-45) clearly demonstrated that a protein feeding pattern that combines meals rich and low in proteins during the day may improve protein retention in elderly persons. A "spread" diet composed of four meals, spreading daily protein intake over 12 hours was compared to a pulse diet providing 80% of daily protein intake concentrated at midday. The pulse protein pattern was more efficient at improving nitrogen balances and whole body protein retention in aged people. The pulse protein diet possesses a couple of advantages: i) the midday protein pulse meal may stimulate whole body synthesis by highly increasing amino acid concentration and ii) high carbohydrate and low protein meals are known to limit protein loss by reducing protein breakdown rate via postprandial hyperinsulinemia. Interestingly, the beneficial effect of the pulse protein pattern on protein accretion still persisted several days after the end of the diet (45). The pulse protein diet also restored a significant anabolic response of skeletal muscle protein synthesis to feeding without affecting protein breakdown in old rats (46). These studies suggest that the use of a pulse protein pattern increases body protein retention, in particular in skeletal muscle. This concept would represent a more attractive and safe approach than simply increased protein intake in the elderly population.

Anabolic response to physical exercise in elderly

Data from muscles in elderly men who have trained as swimmers, runners or strength-trainers continuously for 12-17 years (47) suggest that long-term regular strength training in senescence can maintain the function and morphology of human skeletal muscles. Further study of both young and elderly strength-trained men will help establishing whether strength training started in early adulthood would result in further changes in skeletal muscle contractile properties (48).

Many studies (for review see (49)) demonstrated that elderly people could significantly improve muscle strength and performance after a short period of high-intensity resistance training. These observations indicate that the capacity of muscle to adapt to resistance physical activity is preserved in old age even after a short period of training (50). In addition, an interesting study (51) reported that the protein synthetic machinery adapts rapidly to increased contractile activity even in frail elders.

The anabolic effect of resistance exercise occurs via enhanced muscle protein synthesis. Yarasheski et al. (52)

determined the rate of vastus lateralis muscle protein synthesis by using the in vivo incorporation of intravenously infused 13C-leucine into mixed muscle protein in both young and elderly men before and at the end of 2 weeks of resistance exercise training. Although the muscle fractional synthesis rate was lower in the elderly before training, it increased to reach a comparable rate irrespective of the age of the subjects after two weeks of exercise. In contrast to these results, Welle et al. (53) found no improvement in myofibrillar protein synthesis rate in either young or old men who completed 12 weeks of resistance training. The discrepancy of these observations could be explained by the different experimental designs used in these studies. The training stimulus may not have been powerful enough to affect protein turnover in the investigation by Welle et al. (53). In addition, the timings of the measurements relative to the last bout of exercise were also different in these investigations. Finally, the protein fraction, i.e. myofibrillar fraction, used by Welle was different from those used by Yarasheski, i.e. mixed muscle proteins. Other measurements of synthesis rate of individual muscle proteins showed that a 2-week weight-lifting program increased MHC synthesis rate in 23-32 and 78-84 year-old subjects (54). However, in this work the protein synthesis rate of actin was increased after exercise only in the younger group, showing that the anabolic effect of resistance exercise in elderly subjects is protein-dependent. Another work including young, middle-aged and old people (55) demonstrated that age-related lowering of the transcript levels of MHC IIa and IIx is not reversed by 3 months of resistance exercise training, whereas exercise resulted in a higher synthesis rate of MHC in association with an increase in MHC I isoform transcript levels (56). Other results (57) showed that the stimulation of MHC synthesis rate by resistance exercise is mediated by more efficient translation of mRNA. Furthermore, the effect of 16 weeks of endurance exercise on MHC isoform protein composition and mRNA abundance was tested in a recent study (58). The regulation of MHC isoform transcripts remained robust in older muscle after endurance exercise, but this did not result in corresponding changes in MHC protein expression.

Few data are currently available concerning the rate of muscle protein breakdown after exercise in elderly subjects. A 45 min of eccentric exercise produced a similar increase in whole body protein breakdown irrespective of the age of the volunteers (59). However, myofibrillar proteolysis, based on 3-methylhistidine (3-MH)/creatinine measurements, did not increase until 10 days post-exercise in the young group but remained high through the same period in the older men. Interestingly, a recent study (60) determined the influence of age and resistance exercise on human skeletal muscle proteolysis by using a microdialysis approach. A higher interstitial 3-MH concentration was detected in the aged subjects. This suggested an increased proteolysis of contractile proteins in the rested and failed states. By contrast, interstitial 3-MH was not different from pre-exercise at any time point within 24 hours following exercise in both the young and elderly subjects.

From this section, it may be concluded that ageing muscle still responds to resistance or endurance training. Therefore, as shown by convincing data, exercise would be beneficial to improve skeletal muscle strength and physical activity in elderly.

Combination of nutritional and training strategies

Most of the studies failed to show any beneficial effect of nutritional supplementations on muscle anabolic properties in exercising elderly subjects. For example, Welle et al. (61) reported that high protein meals (0.6-2.4 g protein/kg per day) did not enhance the myofibrillar protein synthesis rate in vastus lateralis muscle following three sessions of resistance exercise in 62-75-year-old men and women. In frail very old people (87 year-old), high-intensity resistance exercise training with or without concomitant multinutrient supplementation had the same efficiency on muscle weakness reversibility (62). Of note, reports showed that ingestion of oral pre or post-exercise amino acid supplements can improve net muscle protein balance in young volunteers (63, 64). The response to amino acid intake with concomitant exercise is dependent upon the composition and amount, as well as the pattern and timing of ingestion in relation to the performance of exercise (65). The response of net muscle protein synthesis to consumption of an essential amino acid-carbohydrate supplement solution immediately before resistance exercise is greater than when the solution is consumed after exercise, primarily because of an increase in muscle protein synthesis as a result of increased delivery of amino acids to the leg (66). Whether amino acid and carbohydrate intakes immediately before or after resistance exercise can enhance the anabolic effect of training in older individuals as shown in the younger group remains to be determined.

Concluding remarks and future direction

Sarcopenia, like many other geriatric phenomena, involves a number of underlying mechanisms including intrinsic changes in the muscle and central nervous system and humoral and lifestyle factors (67). Muscle intrinsic changes include a decrease in the proportion in type II fibers, a reduction in mitochondrial and myofibrillar protein synthesis rates and mitochondrial damages. Loss of alpha motor units from the spinal cord, alteration in hormone and cytokine productions also affect muscle mass and function in elderly. In addition, inadequate protein intakes and physical inactivity are described to accelerate sarcopenia. However, the interactions between intrinsic and environmental factors associated with sarcopenia are not currently established.

Previous data have demonstrated that nutritional means to counter sarcopenia certainly exist. These strategies may gather an improvement of quality and pattern of the daily protein intakes rather than simply increasing the amount of proteins which should be cautiously used in an aged population with a potentially reduced kidney function. Moreover, inactivity also

accelerates sarcopenia and resistance or endurance exercise reverse this phenomenon. Many studies have showed improvements in muscle function in response to strength training interventions in men and women of all ages, even frail elderly. New data showed that a combination of specific nutritional and physical activity programs may have a significant effect on muscle protein balance in young subjects. This strategy has to be tested in the long term in elderly people.

Furthermore, the possibility of any therapeutical approach to limit sarcopenia has been recently emphasized in studies aiming initially to care heart failure or hypertension. Therefore, when 78 years elderly subjects are treated with angiotensin-converting enzyme inhibitor, a remarkable prevention of strength and walking speed decline has been noticed in comparison with other antihypertensive agents (68). Thus a pharmacological approach being able to prevent age-related weakness might be combined to nutritional therapies.

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