Muscle Tissue Changes with Aging

Alterações do Tecido Muscular com o Envelhecimento

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ABSTRACT

Sarcopenia is characterized by a progressive generalized decrease of skeletal muscle mass, strength and function with aging. Recently, the genetic determination has been associated with muscle mass and muscle strength in elderly. These two phenotypes of risk are the most commonly recognized and studied for sarcopenia, with heritability ranging from 30 to 85% for muscle strength and 45-90% for muscle mass. It is well known that the development and maintenance of muscle mass in early adulthood reduces the risk of developing sarcopenia and leads to a healthy aging. For that reason it seems important to identify which genetic factors interact with aging and in particular with the musculoskeletal response to exercise in such individuals.

This review is designed to summarize the most important and representative studies about the possible association between certain genetic polymorphisms and muscle phenotypes in older populations. Also we will focuses on nutrition and some concerns associated with aging, including the role that exercise can have on reducing the negative effects of this phenomenon. Some results are inconsistent between studies and more replication studies underlying sarcopenia are needed, with larger samples and with different life cycles, particularly in the type and level of physical activity throughout life. In future we believe that further progress in understanding the genetic etiology and the metabolic pathways will provide valuable information on important biological mechanisms underlying the muscle physiology. This will enable better recognition of individuals at higher risk and the ability to more adequately address this debilitating condition.

Keywords: Aging; Exercise; Muscle, Skeletal; Nutritional Requirements; Sarcopenia.

RESUMO

Sarcopenia é caracterizada por uma diminuição generalizada e progressiva da força, massa e função muscular com o envelhecimento. Recentemente, a determinação genética tem sido associada com a massa muscular e força muscular em idosos. Estes dois fenótipos de risco são os mais comumente reconhecidos e estudados em relação à sarcopenia, com hereditariedade variando de 30 a 85% para a força muscular e 45-90% para a massa muscular. É bem conhecido que o desenvolvimento e manutenção da massa muscular na idade adulta reduz o risco de desenvolver sarcopenia e conduz a um envelhecimento saudável. Por isso, é importante identificar quais os fatores genéticos que interagem com o envelhecimento e, em particular, com a resposta músculo-esquelética ao exercício.

Esta revisão destina-se a resumir os estudos mais importantes e representativos sobre a possível associação entre determinados polimorfismos genéticos e fenótipos musculares nas populações mais velhas. Os aspetos nutricionais serão discutidos, incluindo o papel que o exercício pode ter sobre a redução dos efeitos negativos deste fenômeno. Alguns resultados são inconsistentes e desta forma é necessária uma maior replicação subjacente à sarcopenia, com amostras maiores e em diferentes ciclos da vida, especialmente no tipo e nível de atividade física. No futuro, acreditamos que mais progressos na compreensão da etiologia genética e as vias metabólicas vai fornecer informações valiosas sobre importantes mecanismos biológicos envolvidos na fisiologia muscular. Isto irá permitir um melhor reconhecimento dos indivíduos com maior risco e uma maior capacidade de enfrentar adequadamente essa condição debilitante.

Palavras-chave: Envelhecimento; Exercício; Nutrição; Sarcopenia.

INTRODUCTION

Sarcopenia is characterized by a decline in muscle mass and strength with increasing age. Currently, this is a problem in elderly people because it contributes to reduce the capacity for independent living. Hospitalization and falls often results in further disease atrophy and a decline in physical performance that results in a loss of autonomy.[1] Complications resulting from falls constitute the sixth cause of death in older people.[2] As a part of normal aging, muscle mass is reduced by approximately one-third between the ages of 50 and 80 years. Although it is possible to increase muscle mass and bone density after the fifth decade. However, prevention should be the main concern because is difficult to regain muscle tissue after several quantities are lost. For that reason, the increase and maintenance of muscle mass in early adulthood reduces the risk of developing sarcopenia and leads to a healthy aging.[2]

It is also important to determine the genetic factors that interact with aging and thus modulate the functional capacity and muscle phenotypes in older adults.[3] It is clinically relevant, the identification of “unfavorable” genotypes associated with sarcopenia.[4] Special emphasis has been placed on two polymorphisms that have been most ex-

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tensively studied, i.e., the angiotensin converting enzyme gene (ACE) I/D and the alpha-actinin-3 (ACTN3) R577X.[5] Although the published studies indicate that hereditability is an important genetic contribution to individual variability in muscle phenotypes among elderly people, but the published data on specific gene variants are controversial.[5-7]

Furthermore, with increasing age it seems essential the participation in regular resistance exercise programs focused on strength and power exercises, benefiting muscle anabolism, an effect that can be enhanced if the exercise is followed by a nutrition rich in proteins.[8] To achieve maximum benefit, preventative strategies for sarcopenia should ideally begin before the fourth decade of life and continue long-term.[9] This review article describes some of these preventative strategies.

Etiology of Sarcopenia

The etiology of sarcopenia is not clearly understood, however several mechanisms have been proposed. Ageing is associated with quantity and quality of muscle tissue reductions.[2] Usually sarcopenia is defined by determining cut-off measures of skeletal muscle mass below in which there is evidence of functional decline or characterized by values two or more standard deviations below the young adult mean. Janssen, et al.[10] characterized values of cut-off measures of skeletal muscle mass by 5,76 - 6,75 kg/m^2 and 8,51 - 10,75 kg/m^2 for women and men, respectively. These values correspond to the risk of disabilities of muscle function during everyday activities. Social and financial costs associated with such disability have been increasing in the past decades; therefore strategies for preventing sarcopenia are of considerable importance. However, prevention requires an understanding of how it develops.

A group of mechanisms are involved in sarcopenia, namely the reduction in the number and size of type I and II fibers, decrease in the number of motor units, accumulation of oxidative products, reduced activation of satellite cells and also reduced excitation–contraction coupling.[11] Furthermore the reduction of anabolic hormones (testosterone, estrogen, growth hormone and insulin like growth factor-1), increasing inflammatory activity and inadequate nutrition and inactivity also contribute substantially to the development of age-related sarcopenia.

Muscle Tissue

The structure of muscle changes in older people have been well-described.[12] One of the effects of aging is the involuntary loss of muscle mass, strength and function.[13] Nevertheless, aging is also characterized by a gradual loss of motor neurons, due to apoptosis, high levels of circulating cytokines (TNF-α and TNF-β) and reduced signaling growth factors. Autopsies in the *vastus lateralis* muscle have shown that up to 90 years, there is a reduction by 50% in type I and II fibers per decade, when compared to young individuals. Histochemical studies conclude that the reduction and atrophy occurs mainly in type II muscle fibers with age.[14] This reduces the excitation–contraction coupling, affecting muscle function with increasing age.[15] Indeed, in an attempt to minimize fiber loss, collaterals from the type I motor neurons expand to some of the denervated type II fibers.[16] Therefore, the muscle tissue tends to lose its configuration, affecting the muscular system (disorders of myofilaments and Z-lines) and mechanisms (reduced satellite cell activation/proliferation and changes to mitochondrial function of muscle cells), which decreases muscle performance (reduction of maximum muscle strength and power). This will increase the disabilities and functional capacity for everyday tasks will also be affected reducing the quality of life and decreasing longevity.

ACE and ACTN3 genes and their association with muscle phenotypes

A wide range of human phenotypes (e.g., muscle strength and bone structure) influence muscle function and result in a complex interaction between different systems: anatomic, biochemical and physiological. About 20 000 genes defines each of us as human beings.[4] However, there is substantial variation among individuals and that can be seen from *replicating* of gene sequences, or changes in base pairs (individual mutations if frequency < 1% and polymorphisms if single nucleotide > 1% frequency). Some polymorphisms can significantly affect muscle structure, the functional performance and even the response to exercise training. One potential candidate gene is the Angiotensin Converting Enzyme (ACE) gene. ACE gene is located at C17 (17q23.3) and has 25 exons resulting in an mRNA with 4022 nucleotides and a protein with 1306 amino acids (ENSG00000159640) (http://www.ncbi.nlm.nih.gov/SNP//snp_ref.cgi?locusId=1636). Multiple alternatively spliced transcript variants encoding different isoforms have been identified.[17] ACE has a key role on the endocrine rennin-angiotensin system and is responsible for catalyzing the conversion of angiotensin I into angiotensin II. Research has centered on an insertion–deletion (I/D-allele) polymorphism in intron 16, which is characterized by the presence (I-allele) or absence (D-allele) of a 287 bp *Alu* repeat sequence with 535 SNPs. This result in three genotypes: II, DD and ID. In Caucasians, the genotype frequency is approximately 25%, 25% and 50%, respectively.[18] However, there is some evidence of a different distribution in other racial groups.[19]

In cross-sectional studies, the D allele has been associated with subjects with higher values of muscle mass, volume and strength,[20,21] while other studies found no association.[22] The possibility that the DD genotype may be associated with a greater proportion of fast twitch fibers could explain the possible influence of the ACE D allele upon strength/ power, particularly at high velocities tasks.[21] Besides, the II genotype confers some disadvantage in functional tasks and, therefore, may correspond to a lower muscle performance.

Another candidate gene, ACTN3, is located at C_{11} (11q13.1) and has 21 exons resulting in an mRNA with 3084 nucleotides and a protein with 944 amino acids (ENSG00000248746) (http://www.ncbi.nlm.nih.gov/SNP//

snp_ref.cgi?locusId=89). This gene expression is limited to skeletal muscle and is localized to the Z-disc, where it helps to anchor the myofibrillar actin filaments.[23] Variations in ACTN3 gene can explain individual variability in muscle phenotypes by a substitution of arginine at amino acid residue 577 (R-allele) with a premature stop codon (X-allele). Judson, et al.[24] showed that functional ACTN3 R577X genotype represents a genetic risk factor in older women and reported a strong association between R577X genotype with increased risk of falling (10% - 61%). Clarkson, et al.[25] and Walsh, et al.[26] also found that women with the XX genotype had lower strength in the elbow flexors and knee extensors compared with individuals with genotype RR. Thus alpha-actinin-3 577X may induces muscle weakness and some influence in responses to muscle damaging exercise. However, it is necessary to develop and reproduce more studies in the elderly people to strengthen these sentences. Future studies should consider the association between muscle phenotypes in this population and complex gene-gene and gene-environment interactions.

PREVENTION OF SARCOPENIA

Nutrition

A variety of hormonal changes that contribute to the loss of muscle mass is observed during the aging process. The body weight and consequently the body mass index (BMI) tend to decline after ages of 50 - 60 years.[27] The weight guidelines for body mass index in older people is in the range of 27 – 30 kg/m^2 and for younger individuals is between 18,5 - 25 kg/m^2 and when is considered ideal weight for older subjects this may already be at malnutrition and sarcopenia risk.[10] Besides, the decline in food intake in older persons has been termed “anorexia of ageing”.[27] In older obese, weight loss should be achieved in a way that preserves lean tissue. Older subjects also reduce their nutrition and meals by quantity in food intake, especially dietary protein.[28] However, the quantities of protein intake in recommended daily allowance may be inadequate for exercising subjects.[8] However, the effect of the protein supplement is not always statistically significant for all exercises.[8,28] Comparatively, creatine supplementation may enhance the increase in lean mass but this also has been shown only in some exercises[8]. Thus, the inclusion of an exercise program for older people that includes strength and aerobic exercises may include simultaneous ingestion of protein, calcium and vitamin D. Nutritional interventions, as obtaining nutrients from natural food (soybeans, lentils, beef, peanuts, salami and salmon) are also potential means for the prevention and treatment of sarcopenia.[29]

Exercise Training

The best way of preventing sarcopenia appears to be by maintaining a regular exercise program.[9] Strength exercise has been suggested as the preferred strategy to attenuate and reverse the age-related loss of muscle mass and function.[16] Multiple studies have demonstrated that acute resistance exercise increases myofibrillar muscle protein synthesis in older adults.[16,30] Recent studies have shown that the increase in muscle mass and myonuclear content in response to strength exercise is accompanied by an increase in number and activation of satellite cells.[31] It has also been associated with improvements in aerobic capacity (VO_2max), improved performance on daily tasks, such as climbing stairs, rising from a chair and even walking.[32]

As the area of strength-training investigation progresses, some scientists are trying to identify the best exercise programs for this population, while others continue their research in determining what exercise prescription will confer the most benefits for older adults. Currently, it seems generally agreed that the benefits of strength training can be achieved with low intensities of 50% of one repetition maximum (1RM) and not only in greater intensities (to 80% of 1RM). Indeed, a markedly lower capacity for concentric contractions may result in decline in performance, particularly in tasks where rapid movements are essential (counteracting a forward fall, climbing steps or crossing the road).[15] Nevertheless, early studies evaluating whether resistance training interventions could increase especially lower extremity muscle in older people.[15,33] Thus, recent randomized trials in both men and women, have been designed to maximize muscle performance generally and have demonstrated that high velocity power training is well tolerated and effectively.[15] (Table 1) However, the efficacy and feasibility of high-velocity power training in older adults with chronic conditions (osteoarthritis and/or osteoporosis), remains uncertain. Aerobic exercise also helps to delay age-related decline. Although, depending on its type and intensity, aerobic exercise seems to have quite minor beneficial effects to prevent the aging effects in muscle system.[34]

CONCLUSION

There is a need to develop strategies to prevent sarcopenia in both men and women in order to prevent loss of muscle mass and functionality with aging. Further the progress to understanding the genetic etiology of sarcopenia will provide valuable mechanisms that will improve the ability to recognize individuals at risk. Current research has suggested that the optimal intervention program should include predominantly resistance exercises (strength training), complemented with some aerobic stimuli. Besides, an adequate nutrition is essential to obtain all benefits from resistance training.

CONFLICT OF INTERESTS

The authors have no conflicts of interest that are directly relevant to the content of this article.

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Table 1: Studies of high-velocity resistance training interventions on physical functioning in older people.

Study	Subjects	Training Intervention	Intervention Frequency and Duration	Muscle Performance Increase	Significant Improvement in Muscle Function
Henwood et al.[35]	19 male and female (71 yr.)	6 upper and lower body exercises (40%–75% 1RM)	3 sets × 8 reps. 2 × wk: 24 wk	Leg extension: 62% Leg press: 58%	Stair time: 6,5% 6-m fast walk: 15% 5-chair stand: 13% Reach test: 9%
Bottaro et al.[36]	11 healthy male subjects (67 yr.)	6 upper and lower body exercises (40%–60% 1RM).	3 sets × 8–10 reps. 2 × wk, 10 wk	Leg press: 31% Chest press: 37%	8-ft GUG: 15% 30-s chair stand: 43% Arm curl: 50%
Orr et al.[37]	112 healthy male and female subjects (69 yr.)	5 upper and lower body exercises at 3 intensities 20% (low) 50% (med), 80% (high) of 1RM.	3 sets × 8 reps. 2 × wk, 8–12 wk	Leg press and leg extension: Low: 9%, 14% Med: 14%, 18% High: 12%, 14%	Balance: Low: 10,8% Med: 2,1% High: 3,0%
Earles et al.[38]	21 healthy male and female subjects (77 yr.)	Hip and knee extensor, plantar, and hip flexor exercises (50%-70% 1RM)	3 sets × 10 reps. Plus 45 min of walking, step-ups and chair rises 3 × wk,12 wk	Leg press: 22%	6-min walk distance: 20 m SPPB score: 0,7 unit

Legend: reps = repetitions; 1RM = 1 repetition maximum; GUG = timed up and go; SPPB = Short Physical Performance Battery Test

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