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GENERAL INFORMATION

Sarcopenia: biological bases

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Abstract
The ageing process is associated with a loss of muscle mass, decrease of strength and a decline in physical ability. The term sarcopenia has been defined primarily as the reduction of muscle mass associated with age, but this definition does not extend to addressing the underlying condition of cellular processes involved in the loss of skeletal muscle and its clinical manifestations. The typical level changes in sarcopenia are diminishing muscle anabolism and increase of the expression of pro-inflammatory factors that contribute to the catabolism of aged cells. There is also a gradual loss of spinal motor neurons due to apoptosis and high amounts of cytokines as well as increased cellular oxidative stress. The age-related loss of the spinal motor neurons leads to a decrease in the number and size of muscle fibres resulting in altered mechanical muscle performance such as declined functional capacity to perform daily activities (walking, climbing stairs, getting up from a chair, among others). Specifically, decreased muscle mass can be considered the end point of sarcopenia as there is a substantial reorganisation of the neuromuscular system and of the central nervous system during ageing, which contributes to function loss in geriatric patients. The pathogenesis of sarcopenia is multifactorial and attributed to oxidative stress, pro-inflammatory response and endocrine changes. Many of the aetiological factors in sarcopenia cannot be found as a single symptom and several of their causal pathways interact or overlap.

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PALABRAS CLAVE
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Respuesta proinflamatoria

Sarcopenia: bases biológicas

Resumen
El envejecimiento se asocia a la pérdida de masa y fuerza muscular y a la disminución de la capacidad física. El término sarcopenia se define básicamente como la disminución de masa muscular relacionada con la edad, pero su definición a menudo se amplía, para incluir procesos celulares subyacentes involucrados en la pérdida del músculo esquelético y sus manifestaciones clínicas. Los cambios a nivel celular propios de la sarcopenia hacen que disminuya el anabolismo muscular y aumente la expresión de factores proinflamatorios que contribuyen al catabolismo de las células envejecidas. También existe pérdida gradual de neuronas motoras espinales, por la apoptosis, cantidad elevada de citosinas y aumento del estrés oxidante. La pérdida de neuronas motoras espinales, relacionada con la edad, conduce a la disminución del número y tamaño de las fibras musculares, que resulta en el rendimiento muscular mecánico alterado, que se traduce en la capacidad funcional disminuida para realizar actividades cotidianas (caminar, subir escaleras, levantarse de una silla, etc.). Específicamente, la disminución del músculo esquelético se puede considerar como el punto final de la sarcopenia, ya que durante el envejecimiento se presenta una reorganización sustancial del sistema neuromuscular y del sistema nervioso central, lo que contribuye a la pérdida de la funcionalidad en los pacientes geriátricos. La patogénesis de la sarcopenia es multifactorial y se atribuye al estrés oxidante, a la respuesta proinflamatoria y a los cambios endocrinos. Muchos de los factores etiológicos de la sarcopenia no actúan de manera aislada, y varias de sus vías causales interactúan o se superponen.

Background

Sarcopenia is defined as the loss of mass, strength and function of the skeletal muscle; it is a clinical condition associated with the ageing process[1]. The word sarcopenia etymologically comes from the Greek root *Sarco*, meaning flesh, muscle, and *penia*, meaning deficiency/decrease[2]. It has been reported that one of the most damageing effects of ageing is the loss of skeletal muscle, which affects ambulation, mobility, functionality and causes loss of independence among the ageing population[3,4]. At 50 years of age, the slow decline of mass and muscle strength being produced throughout life and peaking at between 20 and 30 years old accelerates significantly, particularly among sedentary people. Muscle loss, particularly of type II fibres, follows a different pattern for men and women: for men it occurs gradually, for women it occurs more abruptly, especially when they reach menopause[5]. After approximately the fifth decade of life there is a progressive decrease in muscle mass at a rate of 1-2% per year. Similarly, but with a different rate of decline, muscle strength also decreases by 3% per year after the age of 60[6].

Sarcopenia is a multidimensional clinical entity of ageing that represents a significant risk factor of adverse events occurring in the health of the elderly population. The association between sarcopenia and alterations in physical functioning, fragility, functional dependence and increased risk of falls has been documented[7]. It has also been reported that decreased muscle strength is a highly predictive indicator of disability and mortality in the elderly[8]. The prevalence of sarcopenia varies widely not only because of the characteristics of the study group, but also because of the differences in diagnostic criteria and the method used in each study for its operational definition such as the reference population, technique to measure or estimate skeletal muscle mass, cut-off points, etc.[9,10].

Aetiology

The aetiology of sarcopenia is multifactorial and its progression is attributed generally to age-related changes in skeletal muscle and the multiple risk factors that trigger them (Fig. 1). The dynamic balance between the anabolic and catabolic states of the human skeletal muscle also relates

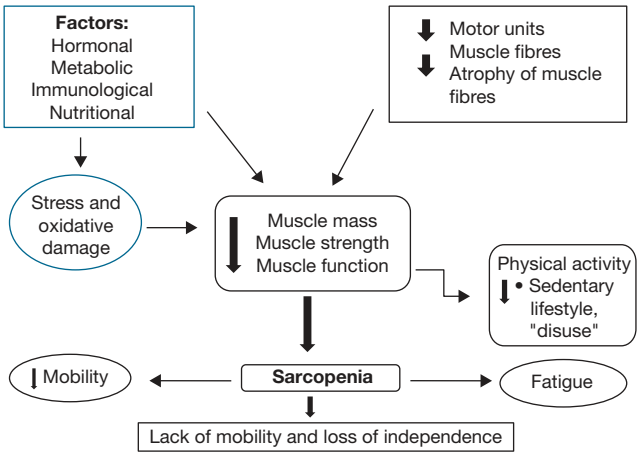

Figure 1 Elements that contribute to the development of sarcopenia.

to mechanical and nervous stimuli, hormonal changes, as well as nutritional intake (specific nutrients: protein, amino acids such as leucine and vitamin D), which interact to determine both tropism and muscular vitality[11].

Diagnosis

The European Working Group on Sarcopenia in Older People (EWGSOP)[12,13] proposed a diagnostic strategy for application in the clinic, thereby recommending identifying the presence of reduced mass and muscle strength and function (performance). The EWGSOP also defined the conceptual stages as "pre-sarcopenia", "sarcopenia" and "severe sarcopenia." It also classified sarcopenia according to its primary or secondary cause, the latter related to various diseases and nutrition (Table 1). Finally, the EWGSOP proposed an algorithm for detecting sarcopenia in people >65 years (Fig. 2).

The prevalence of sarcopenia varies considerably between different groups of elderly people and this variation depends on the selection method used to make the diagnosis of sarcopenia. However, the importance of operationally defining sarcopenia as a two-dimensional musculoskeletal entity, based on "quantitative" assessment of muscle mass and "qualitative" strength and muscle function points, has been highlighted.

Clinical consequences of sarcopenia

The consequences of sarcopenia in elderly men and women focus on three key areas: functional status, falls and mortality[14]. The mechanism by which these consequences appear is associated with decreased muscle strength, which favours a decrease in physical performance and, in turn, makes carrying out basic activities of daily living difficult, which fosters disability and dependence[15.] People with sarcopenia are between two and five times more likely to have disabilities than those without sarcopenia. Sarcopenia has also been associated with decreased muscle strength and endurance; however, few longitudinal studies have demonstrated the association between sarcopenia and disabilities[16].

Table 2 summarises the main adverse consequences that come from sarcopenia, as well as the clinical consequences, representing a major impact on the public health of the country because of its increase in the elderly population who are more prone to an association between low physical performance and disabilities[17].

Table 1 Classification of sarcopenia by cause

Primary sarcopenia	Associated with the passage of ageing. Has no other obvious cause except ageing
Secondary sarcopenia	Associated with low physical activity. May result from prolonged bed rest, sedentary lifestyle and physical deconditioning
Disease-related sarcopenia	Associated with pathologies that are accompanied by muscle waste: cancer, AIDS, advanced organ failure (heart, lung, liver, kidney), diseases that have different inflammatory response
Nutrition-related sarcopenia	The result of inadequate intake of protein (essential amino acids: leucine) and other specific nutrients (vitamin D)

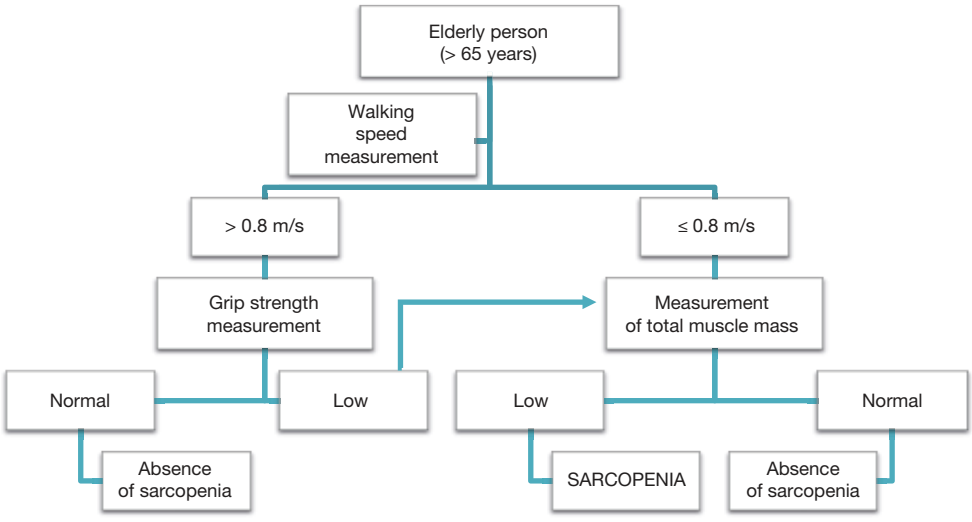

Figure 2 Algorithm for detecting sarcopenia in people aged >65 years.

Table 2 Adverse outcomes associated with sarcopenia

Results	Disability
Severe disability	Difficulty in performing basic daily living activities (need help to get out of bed or a chair, bathing or dressing), need for support to walk and the presence of a mobility disability (inability to walk in a room, climb stairs)
Physical disability	Positive response to two questions: *1)* do you need help from others to move about indoors because of a health problem or physical impairment problem? and *2)* do you need help from others to carry out your daily routine because of a health problem or physical impairment problem?
Physical performance	
Loss of independence	Limitations in performing basic daily living activities
Functional (or mobility) damage	Limitations in performing basic daily living activities
Physical functioning	Limitations in mobility performance (e.g., walking 0.400 m, climbing 10 stairs, lifting a 4.5 kg load or getting out of a chair)
	Decreased 6 or 7 m walk time
	More time taken to get out of a chair five times consecutively, without the help of the arms or unable to do so
	Difficulty performing the "get up and walk test"
Muscular strength	
Muscular strength	Decreased knee extension strength (maximum isokinetic strength) Decreased quadriceps strength
Muscle power	Decreased hand grip strength (measured with a dynamometer)
Muscle quality	Decreased force per time unit
	Decreased muscle strength per muscle mass unit

Biological bases

Skeletal muscle is mainly composed of two main types of fibres: *a)* type I myofibrils: which have a slow twitch and use oxidative pathways and resist fatigue, and *b)* type II myofibrils: which have a fast twitch, are based on glycolytic pathways and promote fatigue more easily. The loss of skeletal muscle mass associated with age is due to the decrease in the size and number of both types of myofibrils (fast and slow motion), although the loss of fast motion myofibrils tends to begin before age 70[18].

Neuromuscular disorders during ageing

Among the causes that contribute to loss of muscle strength seen in sarcopenia, the changes that occur in the nervous system due to age and that cause loss of motor units are noteworthy. A motor unit consists of a single alpha motor neuron and all the muscle fibres connected to it. If an alpha motor neuron is lost, the denervated muscle fibres bond to connect to the surviving alpha motor neurons, which determine that a single alpha motor neuron must connect with more muscle fibres, forming larger motor units[19]. This results in loss of muscle efficiency, which could be causing the tremors and fatigue which are typically present in the elderly, as well as loss of precision and poor motor coordination, often observed with the passage of age[7]. These effects are secondary to changes in two essential proteins for the control of muscle contraction: *a)* the ryanodine receptor, and *b)* Ca-ATPase. A greater relaxation time can increase the time required for a new contraction. As mentioned above, type II fibres with high glycolytic potential, lower oxidative capacity and faster response compared to type I fibres, which are slow, are known as fatigue-resistant fibres due to their characteristics: they have a higher density of mitochondria and capillaries, more myoglobin content except for postural muscles, which consist of type I fibres. During slow, low-intensity activity, more force is generated from type I fibres, whereas in high-intensity exercise, resistance comes from both type I and type II fibres. With age, atrophy basically affects[20] type II fibres. Loss of myofibrillar innervation is a characteristic of ageing muscles subjected to changes that occur at different levels, from the central and peripheral nervous system and tissue cells to skeletal muscle. These changes include loss of motor neurons in the central nervous system, with decreased function of the remaining motor neurons, demyelination of axons and a decrease of the nerve connection terminals in the neuromuscular junctions[21]. Several studies on rodent models have been conducted, which describe the pathogenesis of aged skeletal muscle. In contrast to human muscles, which are composed predominantly of slow-moving myofibrils, mouse muscles are mainly fast moving; such differences among species should be considered when observations are translated from animal models to those of humans. In addition, humans have more time to develop a greater number of secondary consequences, which become more pronounced; gradually, disorders manifest over 20-30 years, whereas the duration (appearance and development of sarcopenia) is

much shorter in mice, >1 year (~ 18 to 30 months), with an average half-life of only 3 years or less. Innervation of the myofibrils is clearly necessary for the contraction of skeletal muscle in both mice and humans. Examination of aged mice (up to 29 months old) has revealed a marked denervation of hind limb muscles, without any change in the number or size of motor neuron cell bodies in the lumbar spinal cord, suggesting a primary problem at the muscular level per se[22]. In contrast, there have been changes in the function of motor neurons from electrophysiology studies during human ageing, supporting changes in the central nervous system, although it is difficult to determine whether they are secondary to previous changes to the neuromuscular junction[23,24]. Recent studies suggest that degeneration of motor neurons and subsequent denervation of myofibrils are a major cause of muscle mass loss[25]. In the elderly, muscle fibres undergo denervation and innervation cycles. During these cycles, some myofibrils are lost and others that were innervated by fast motor neurons (type II fibres) are reinnervated by slow motor neurons (type I fibres). This results in an increase of the percentage of type I fibres and the atrophy that characterises sarcopenia[26].

Oxidative stress

Oxidative stress is an imbalance between oxidant and antioxidant values[27]. It has been shown that ageing predisposes the skeletal muscle to increased levels of oxidative stress, both at rest and during atrophy because of disuse, suggesting that it plays a role in participating in induced disuse and sarcopenia-associated muscle loss. The state of oxidative stress accompanies the pathogenesis of chronic diseases involving muscle waste[28]. The increased levels of low impact chronic inflammation induced by oxidative stress has shown to be detrimental to skeletal muscle[29]. Under normal conditions there is a balance and a continuous degradation and re-synthesis of skeletal muscle proteins. However, during the ageing process, increased oxidative stress breaks that balance[30]. This imbalance is possibly the result of deterioration of the anabolic signalling and increased catabolic signalling. The pathogenesis of sarcopenia is multifactorial and attributed to oxidative stress, chronic inflammation and endocrine changes, among others. Many of these factors do not act in isolation and several of their causal pathways interact or overlap in regard to oxidative stress[31].

Oxidative damage has been proposed as one of the main factors causing the decrease in skeletal muscle that occurs during the passage of ageing[32]. The identification of free radicals as promoters of the ageing process may imply that by inhibiting them, limits are placed on the harmful changes they have on the body and in particular on skeletal muscle. In other words, if molecules with antioxidant capabilities can counteract oxidative damage, they may also play a key role in preventing the onset of age-related conditions including the disability process[33]. Currently, antioxidants have received special attention because of their potential as agents that delay ageing and thereby sarcopenia. Primarily, antioxidant enzymes (e.g., catalase, superoxide dismutase, glutathione peroxidase and glutathione reductase) help maintain the equilibrium, which favours the prevention of transformation of reactive oxygen species (ROS) to turn them into more stable molecules (such as water and molecular oxygen). Nonenzymatic endogenous elements with antioxidant properties also contribute to the maintenance of homoeostasis, mainly acting as cofactors for antioxidant enzymes.

In the elderly, the accumulation of transformation of ROS may lead to oxidative damage of biomolecules and contribute to the loss of muscle mass and strength. It is well documented that elevated oxidative stress is associated with various clinical situations of muscle wasting, but the precise nature of oxidative stress in different situations and their complex interactions in vivo are not yet well known[34]. Other forms of transformation of ROS can cause reversible oxidation of protein thiols, only to modulate the function of many other proteins (e.g., those involved in signalling the regulation of protein synthesis, degradation and muscle contraction); however, the contribution of thiol oxidation in the aetiology of sarcopenia is only beginning to be evaluated. Because there are different specific antioxidants for the transformation of ROS, it is essential to know exactly how the transformation of ROS emerges in sarcopenia in order to design an adequate pharmacological or nutritional intervention in the future.

Catabolic factors and inflammatory response

An increase of tumour necrosis factor alpha (TNFα), interleukin (IL) 6, IL-1 and C-reactive protein (CRP) in circulating levels has been observed in groups of elderly people[35]. These changes in immune function related to age are associated with a progressive increase in catecholamines and glucocorticoids as well as decreasing values of sex and growth hormones[36]. These changes are similar to those that occur in situations of chronic stress. Proinflammatory cytokines are directly associated with muscle loss and reduced strength in geriatric patients; in particular TNFα is a potent stimulant of proteolysis through the activation of the ubiquitin-proteasome pathway. A study of elderly men and women in the Netherlands found that each single standard deviation increase in the value of TNFα resulted in a reduction of 1.2 to 1.3 kg in grip strength of the hand. Also, each single standard deviation increase in IL-6 showed a reduction from 1.1 to 2.4 kg in the grip strength of the hand[37]. This suggests that inflammation may be a key factor in the genesis of sarcopenia.

A low level of chronic inflammation is highly prevalent in the elderly, as shown by the increased values of cytokines and acute phase proteins as well as in prolonged infectious or inflammatory diseases[38]. This phenomenon of chronic inflammation related to underlying age has been called *"inflamm-ageing"*[39]. Higher cortisol values were found in patients with sarcopenia than in healthy elderly people[40]. Ageing itself may be considered a form of stress and has been associated with an increase in circulating levels of cortisol and catecholamines and with a decrease of sex and growth hormone values, changes which in turn stimulate the release of IL-6 and TNFα. In ageing there is a simultaneous increase in various catabolic factors. This catabolism activates proinflammatory cytokines (IL-1, IL-6) and TNFα, which directly promotes muscle waste, increasing myofibrillar protein degradation and decreasing protein synthesis,

suppressing insulin action[41]. An increase in proteolysis favours the production of acute phase proteins such as CRP. This chronic inflammation process has been associated with several diseases affecting the elderly, such as sarcopenia. An increase in proinflammatory cytokines directly results in muscle waste as the myofibrillar protein catabolism increases and protein synthesis decreases. An increase in proteolysis favours the production of acute phase proteins such as CRP[42,43].

Conclusion

Sarcopenia is a clinical entity in which neuromuscular disorders, oxidative stress, catabolic factors and chronic low impact inflammatory response are significant aspects that try to explain the pathogenesis and clinical consequences, which ultimately affect the functionality and quality of life of the elderly. Additional studies will help us to better understand these mechanisms. The detection and proper diagnosis of sarcopenia at an early stage should be an important objective for geriatric preventive medicine to help older people stay independent and functional.

Conflict of interest

The authors declare no conflict of interest.

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