

Understanding sarcopenia as a geriatric syndrome

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Purpose of review

Highly prevalent in the population older than 65 years and leading to poor outcomes (functional decline and its related consequences), sarcopenia does not benefit yet either of a clear understanding of its pathophysiology or of precise clinical or biological markers allowing its identification.

Recent findings

The new scientific definition of 'geriatric syndromes' challenges the authors to review the current sarcopenia literature, allowing them to affirm that sarcopenia cannot be considered as an age-related disease but as a true 'geriatric syndrome'. More than 50% of the population older than 80 years suffer from this medical condition, which is linked to multiple causations: the ageing process itself, genetic susceptibility, certain life habits, changes in living conditions and a number of chronic diseases. Moreover, sarcopenia favours poor outcomes such as mobility disorders, disability, poor quality of life and death.

Summary

Considering sarcopenia as a geriatric syndrome allows us to request its recognition and assess its multiple risk factors, to implement a clinical and public health approach to the management of sarcopenic patients and population at risk and to disentangle the links among sarcopenia, frailty, disability and mortality.

Keywords

ageing, geriatric syndrome, nutrition, poor health outcomes, sarcopenia

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Introduction

More than 600 skeletal muscles of the human body constitute 45–55% of the total body mass, being muscular mass mostly located in the lower limbs, and change significantly in size and function with ageing. These changes may lead to decreased physical performance, decline of strength, mobility impairment, falls and disability [1]. Apart from these serious and important clinical consequences, sarcopenia has a severe economic impact on the healthcare system.

In 1989, Irwin Rosenberg [2] stated that 'there is probably no decline in structure and function more dramatic than the decline in lean body mass or muscle mass over the decades of life' and proposed the use of the Greek term 'sarcopenia' (meaning 'sarx' for flesh and 'penia' for loss) to describe the loss of muscle mass among older people. Two decades after its first recognition as a distinct clinical condition, the definition of sarcopenia is still elusive and actively discussed, and the word 'sarcopenia' itself, as well as the clinical relevance of the concept have been challenged [3,4**].

Currently, open questions about sarcopenia concern its nosology, understanding and clinical identification: is sarcopenia a normal part of the ageing process? When does it become a disease state [2]? Is it only a morphologic or functional abnormality, or is it an age-related disease? Can sarcopenia be understood as a classical syndrome or does it better fit with current concepts about geriatric syndromes? By systematically answering these questions, we will argue that including sarcopenia within the current concept of a 'geriatric syndrome' category seems to be the most realistic approach at present. Should this be accepted, the next step would be to define the most appropriate approach for diagnosis and management of sarcopenia syndrome. The better understanding of the mechanisms involved in this geriatric syndrome represents a public health priority.

Evolution of the definition of sarcopenia

Rosenberg's [2] second definition suggested that sarcopenia is an 'involuntary loss of skeletal muscle mass that occurs with advancing age', a concept that was later clarified as an 'ageing-associated normal muscle wasting'

which may not be accompanied with significant weight loss, considering that the loss of muscle mass is counter-balanced by gains in fatty tissue [5]. Later, the age-associated loss of muscle mass was linked to a loss of muscle quality [6] and muscle strength [7]. Physiopathological explanations of these phenomena followed: loss of individual myofibrils, mainly fast-twitch type II fibres [8], diminished synthesis of muscle proteins and altered mitochondrial functions [9]. But it was only recently that both nonrelated factors – such as a sedentary lifestyle [10] and a less than optimal diet [11•] – and the functional impact of sarcopenia (poor endurance, slow gait speed, decreased mobility, falls and disability) were addressed in the proposed definitions [12].

In our view, sarcopenia represents a complex medical condition characterized by a progressive loss of mass, quality and function of skeletal muscles associated with ageing. It carries multiple contributing and risk factors that, through a common and complex path [13,14], increase frailty [10,15•] and predict mobility disability, leading in turn to loss of independence, reduced quality of life, increased healthcare costs and ultimately to death [16–19].

It should be stressed that none of the currently used definitions of sarcopenia is fully accepted, and that sarcopenia is not yet included in common classifications of diseases (i.e. International Classification of Diseases), although some recent initiatives are trying to move in this direction.

Is sarcopenia an age-related disease, a syndrome or a geriatric syndrome?

Sarcopenia is definitely age-related [7]. However, can it be considered a true disease (as diabetes or Alzheimer's disease), a syndrome in its classic concept (as Cushing's or Marfan's syndrome) or a geriatric syndrome (as falls or delirium) [20•]?

Can sarcopenia be considered as an age-related disease?

Interindividual variability in muscle mass and strength increases with age, and many individuals may not reach the point at which sarcopenia has clinically significant consequences [21•]. A broad spectrum of behavioural (lifestyle and living conditions habits), biological (inflammation and hormonal modifications) and clinical factors (diseases) is able to modify the sarcopenia process [22••]. Therefore, although sarcopenia is certainly an age-related phenomenon, it cannot be considered as a mere consequence of ageing.

A disease is a clinical entity that can be unequivocally defined by its aetiology and pathogenesis, and presents as

a single clinical symptom or sign or a well known combination of them [20•]. Sarcopenia does not seem to fit well into the single disease definition, as a disease should have a single and clear pathophysiological and clinical picture, which is not the case [4••]. Thus, sarcopenia is not an age-related disease.

Can sarcopenia be considered as a classical syndrome?

First used in English by Galien in 1541, the word syndrome ('running together') means a concurrence of constant patterns of abnormal symptoms and signs that occur together and constitute a picture of a disease with a single underlying cause that may not yet be known [20•]. The Cochrane library lists a large number of classical syndromes: acute chest pain, acute coronary, Behçet, burning mouth, carpal tunnel, Cushing, restless leg and so on. In each of these cases, the cause and/or the pathogenesis are not always well known, but in every case, the clinical symptoms or set of signs are well defined. Moreover, a specific morbid process causes multiple phenomenologies, which are more or less expressed but always present. For example, cortisol excess leads to moon face, Buffalo neck, truncal obesity, proximal muscle weakness, skin thinning/bruisability and osteoporosis. In any case, the reduction of the cortisol excess will cure or reduce the symptoms and signs of the classical syndrome, even when the origin of this excess cannot be tackled [23,24]. Therefore, sarcopenia cannot be considered as a classical syndrome: it has no unique pathogenesis, there is no direct relationship between muscle mass and strength and no single intervention can completely restore muscle quality (both mass and function).

Can sarcopenia be considered as a true geriatric syndrome?

The term 'geriatric syndrome' was used to define complex clinical conditions that are common in older persons and do not fit into discrete disease or syndrome categories. Typical 'geriatric syndromes' are delirium, dementia, depression, dizziness, failure to thrive, malnutrition, falls, functional dependence and gait disorders. The concept of 'geriatric syndrome' is well understood by any professional working in geriatric medicine, and most geriatric textbooks include a series of chapters on their diagnosis and management. However, the scientific definition of the concept of geriatric syndromes has recently been reconsidered and updated [25••], with the support of 20 years of basic, experimental and clinical research.

Geriatric syndromes manifest by phenotypic characteristics at the physical, morphologic and biochemical levels of an individual as determined by the genotype and the environment [26]. Moreover, the term 'geriatric syndrome' is now used to capture clinical conditions in older persons that do not fit into traditional 'disease categories' but are highly prevalent, multifactorial and associated

with multiple comorbidities and poor outcomes such as increased disabilities and decreased quality of life [25**].

The conceptual understanding of a geriatric problem as a geriatric syndrome has been shown to be feasible and useful [27]. Does sarcopenia fit in with this current definition of a geriatric syndrome?

- (1) Sarcopenia is highly prevalent: 30% in the population over the age of 65 years and more than 50% in the population over the age of 80 years [28–31].
- (2) Sarcopenia is a unified manifestation of multiple causations [20*,23]. The major risk factors and related mechanisms potentially influencing the skeletal muscle decline are the ageing process itself, genetic susceptibility, behavioural factors, changes in living conditions and many different chronic health conditions [32–34] (Table 1).
- (3) In most of the cases, sarcopenia is associated with poor endurance, physical inactivity, slow gait speed and decreased mobility. Furthermore, it is highly predictive of incident disability, poor quality of life and all-cause mortality (Fig. 1).
- (4) Moreover, the avoidance or the cure of any of the multiple risk factors/causes does not modify the clinical phenotype/consequences of sarcopenia.

Therefore, sarcopenia is certainly a multifactorial health condition that occurs when the accumulated effects of impairments in multiple systems render an older person vulnerable to situational challenges [26], and indeed,

sarcopenia fulfils the geriatric syndrome description in accordance with the current accepted definition [25**]. As expected, this geriatric syndrome is associated with other geriatric syndromes in the mood and cognition areas [34–36].

Describing sarcopenia as a geriatric syndrome

If sarcopenia is a geriatric syndrome, some elements of the definition of geriatric syndromes may help to better understand the concept of sarcopenia, including the need of a multiple risk factors assessment, and its relationship with function, frailty and other poor outcomes.

Risk factors of sarcopenia

The number of identified risk or causative factors of sarcopenia is high and seems to be increasing with recent research (Table 1) [4**,22**]. They can be grouped into different categories:

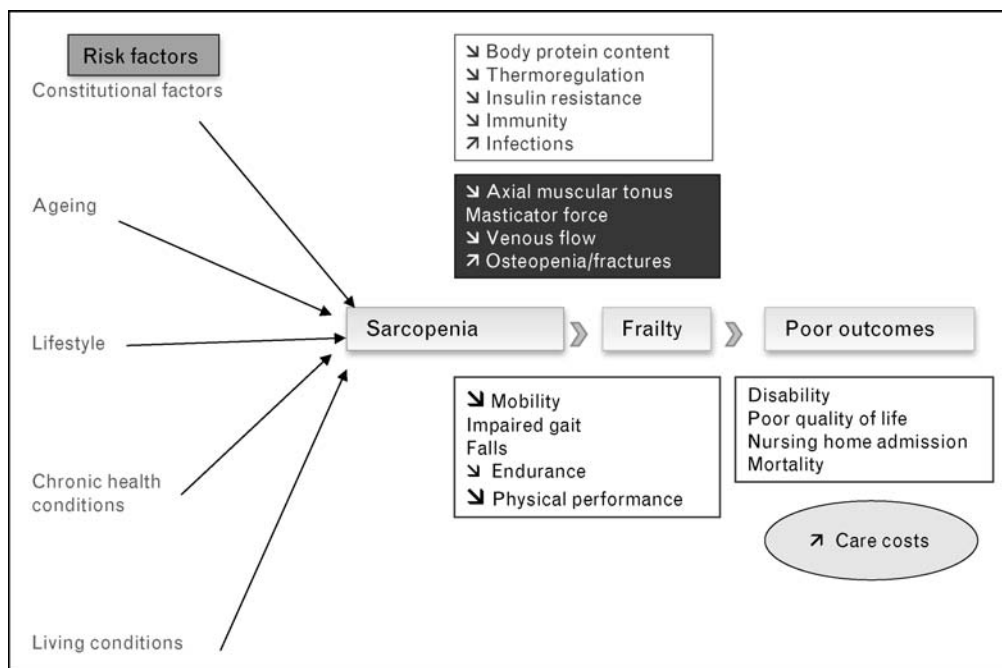
- (1) Constitutional factors. It is well recognized that age and sex modify the prevalence of sarcopenia [37*], low birth weight increases the risk of sarcopenia in later life and that many genetic aspects influence muscle metabolism and turnover along the lifespan [21*,38].
- (2) The ageing process itself modifies muscle turnover, with increased catabolic stimuli and decreased anabolic stimuli [39–41]. Subclinical inflammation can

Table 1 Risk factors of sarcopenia

Factors	Ageing process	Chronic health conditions
Constitutional		
Female sex	Increased muscle turnover	Cognitive impairment
Low birth weight	↑ Catabolic stimuli	Mood disturbances
Genetic susceptibility	↑ Protein degradation	Diabetes mellitus
	Low-grade inflammation	Heart failure
	↓ Anabolic stimuli	Liver failure
	↓ Protein synthesis	Renal failure
Lifestyle		Respiratory failure
Malnutrition	Reduced number of muscle cells	Osteoarthritis
Low protein intake	↑ Myostatin (↓ recruitment)	Chronic pain
Alcohol abuse	↑ Apoptosis	
Smoking		Obesity
Physical inactivity		
Living conditions	Hormonal deregulation	
Starvation	↓ Testosterone, DHEA production	Catabolic effects of drugs
Bed rest, immobility, deconditioning	↓ Oestrogen production	
Weightlessness	↓ 1–25 (OH) ₂ vitamin D	
	↑ Thyroid function	
	↓ Growth hormone, IGF-1	
	↑ Insulin resistance	
	Changes in neuromuscular system	
	↓ CNS input (loss of α-motor neurons)	
	Neuromuscular disjunction	Cancer?
	↓ Ciliary neurotrophic factor (CNTF)	Chronic inflammatory disease?
	↓ Motor unit firing rate	
	Mitochondrial dysfunction	
	↓ Peripheral vascular flow	

CNS, central nervous system; DHEA, dehydroepiandrosterone; IGF-1, insulin-like growth factor-1.

Figure 1 Sarcopenia is a geriatric syndrome



play a role in these changes [42[•],43,44]. Many hormonal dysregulations [in particular, testosterone and the growth hormone, insulin-like growth factor-1 (IGF-1) axis] have been described with ageing [45,46], as well as changes in neural input; together, they have been associated with the skeletal muscle mass decline [4^{••},7,47]. Moreover, mitochondrial dysfunction has also been related with muscle mass and ageing [48[•]].

- (3) Certain life habits, including a decrease of food intake and specifically protein intakes [49], together with disuse or poor physical exercise during life [50], and the use of alcohol and tobacco [51–54] have all been linked with a higher risk of sarcopenia.
- (4) Changes in living conditions, such as prolonged bed rest [55], immobility and deconditioning, have shown to increase sarcopenia, as weightlessness [56] has shown to rapidly lead to a loss in muscle mass.
- (5) A long list of chronic health conditions (including cognitive impairment, mood disturbances, diabetes and end-stage organ diseases) has also been linked with a loss of muscle mass and strength. Some are well known [57] and some have been the surprising topic of long-standing debates [15[•],58^{••}]. The main discussion linking these chronic conditions to sarcopenia is the potentially causative role of chronic inflammation in its own pathogenesis as well as in cachexia. However, cachexia is characterized by a higher inflammation degree as well as a severe wasting accompanying disease state such as cancer or immunodeficiency, leading to a reduction of both

fat and fat-free mass [42[•],59–61,62[•]], which is not the case in sarcopenia, as noticed above.

Consequences of sarcopenia

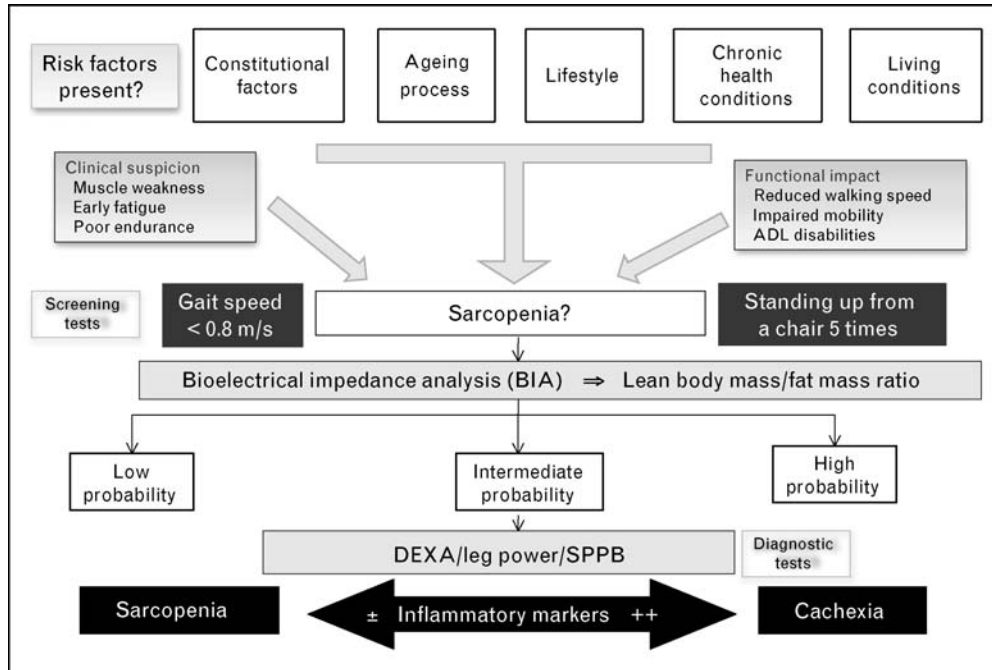
The consequences of sarcopenia have a perfect correspondence with those of the currently used definition of a geriatric syndrome [25^{••}] (Fig. 1). Included in a dynamic process, sarcopenia leads to a negative adaptation in the face of adversity or external stressors contributing to an increased vulnerability and poor outcomes [63]. As proposed by Fried *et al.* [64,65], sarcopenia plays a crucial etiological role in the frailty process itself, also being a key player of its latent phase and explaining many aspects of the frailty status [65]. Moreover, sarcopenia leads, through frailty, to dramatic consequences such as repeated falls, multiple and various trauma, functional decline, disability, multiple emergency room visits and hospital admissions, cross-infections, loss of independence, nursing home admission, poor quality of life and ultimately death [66].

Muscles have, together with their crucial role in function, other roles in metabolic processes, especially in amino acid metabolism and insulin resistance [67–70]. The consequences of muscle ageing and sarcopenia in these processes are still poorly understood.

A diagnostic approach to sarcopenia

Understanding sarcopenia as a geriatric syndrome may help in the design of both a ‘multiple (shared) risk factor assessment’ and a multicomponent intervention for

Figure 2 A practical approach to sarcopenia



reducing the deleterious effects of the modifiable risk factors [71], an approach that has shown to be effective in other geriatric syndromes [72–74].

However, the practical diagnosis of sarcopenia remains yet an unsolved problem. Standardized measurements of sarcopenia need to be validated. This highlights the urgent need of an operational definition of sarcopenia, which would be based on the evaluation of muscle mass and function [22**], not forgetting the importance of the relationship between lean body and fat body mass and the role of biomarkers of inflammation.

Although numerous groups of specialists are working on this specific issue, and undoubtedly, new data may change this approach, we believe that it is possible to propose a practical approach to manage sarcopenia as a geriatric syndrome (Fig. 2). The clinical suspicion of sarcopenia based on the multiple risk factors' assessment is corroborated by muscle weakness, early fatigue and poor endurance, associated with reduced walking speed, impaired mobility, inabilities in activities of daily living or all. The two easiest clinical tests to start the investigation of suspected sarcopenia may be measurement of walking speed or five time-stands from a chair. If any of these tests is positive (walking speed <0.8 m/s, inability to stand-up from a chair), a bioelectrical impedance analysis (BIA) may be a cheap and easily available method to evaluate the probability of sarcopenia by measuring the ratio between lean body and fat body

mass. Very often, BIA may be sufficient to confirm or rule out the presence of sarcopenia. Only in doubtful cases or for research purposes, further investigations such as dual-energy X-ray absorptiometry (DEXA) may be needed [knowing that the gold standard measure of the ratio of lean/fat body mass is computed tomography (CT)/magnetic resonance imaging (MRI)].

Conclusion

The new scientific definition of 'geriatric syndromes' challenges the authors to review the current sarcopenia literature, allowing them to affirm that sarcopenia cannot be considered as an age-related disease but as a true 'geriatric syndrome'. More than 50% of the population above 80-years-old suffer from this medical condition, which is linked to multiple causations: the ageing process itself, genetic susceptibility, certain life habits, changes in living conditions and numerous chronic diseases. Moreover, sarcopenia favours poor outcomes such as mobility disorders, disability, poor quality of life and death.

Considering sarcopenia as a geriatric syndrome leads to the implementation of a specific multiple risk factor assessment and a new practical and managerial approach of sarcopenic patients or patients at risk of sarcopenia. This consideration also allows for reconsideration of the links among sarcopenia, frailty, mobility disorders, disability and mortality.

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There are no conflicts of interest.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 110–112).

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