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Research paper

Sarcopenia and frailty: From theoretical approach into clinical practice

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ABSTRACT

Physical function decreases with aging leading to a wide spectrum of negative outcomes, such as mobility disability, falls, social isolation, reduced quality of life, dependency and institutionalization. The age-related loss of physical performance typically results from multiple clinical and subclinical conditions. The clinical picture of frailty (especially when assessed using instruments focused on the physical function domain) shows remarkable overlap with that of sarcopenia (“a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death”). In this paper, the conceptualisation of sarcopenia as the biological substrate of physical frailty is illustrated. It is also elaborated that sarcopenia may be envisioned as the pathophysiologic pathway through which the negative health-related outcomes of physical frailty develop.

1. Introduction

The demographic transition experienced by Europe over the last decades poses unprecedented challenges for managing the care of older persons. The existing healthcare systems, built around the traditional medical paradigm of patients suffering from a single acute illness, are largely unprepared to face the medical needs of older persons with (often chronic) multimorbidities, geriatric syndromes, and polypharmacy [1]. It follows that a large and growing segment of the older European population currently presents substantial unmet clinical needs and/or is potentially exposed to the risk of medical malpractice.

Although the prolongation of life remains an important public health goal, the preservation of the capacities to live independently is of even greater significance. Indeed, disabling conditions are extremely burdensome for the individual as well as for the sustainability of healthcare systems [2].

In this scenario, the geriatric syndrome of frailty and possible interventions targeting this condition have gained special relevance. In recent years, there has been growing interest around the “frailty” condition affecting older people. Several operational definitions and assessment tools have been proposed [3]. However, despite the efforts of many researchers, there still are not a universally agreed definition and standardised evaluation methodology.

Sarcopenia is similarly a major phenomenon of the aging process and one of the most discussed topics in the geriatric literature [4]. Unfortunately, as occurring for frailty, the scientific community has not yet reached a final consensus about the operational definition of sarcopenia. Not only the definition of sarcopenia is discussed, but even the underlying theoretical and methodological framework (e.g., is sarcopenia only low muscle mass? Which is the role of muscle strength and/or physical performance?) is still under debate.

The long-lasting discussion over which came first in a sort of “the chicken or the egg dilemma” comes to mind. Does frailty lead to sarcopenia or is it the opposite? Certainly, sarcopenia and frailty have much in common, such that they may be envisioned as the two sides of the same coin [3,5].

If we focus the discussion on physical frailty (i.e., reduced functional reserve linked to the capacity of movement), it might be easier to find a framework and theoretical organisation for the condition, moving from a purely speculative response to an answer that can be effectively translated into clinical practice. Only in this case can we reach a consensus based on what it is necessary to evaluate and how to assess it. Such process is essential for obtaining the endorsement of regulatory agencies, so that

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sarcopenia and physical frailty become clinically recognised conditions and relevant targets for interventions [6].

Taking advantage of existing clinical models [e.g., congestive heart failure (CHF) and chronic obstructive pulmonary disease (COPD)], it is possible to attempt a linear, practical and convincing response. These conditions are:

- pathophysiologically related to a specific organ dysfunction (i.e., heart and respiratory tract);
- characterised by signs and symptoms suggesting the presence of disease (e.g., dyspnoea, peripheral oedema, cough);
- staged through the use of functional performance tests.

By translating these examples to physical frailty and sarcopenia, it can be noted that the muscle may indeed represent at the same time the anatomic site of sarcopenia and the biological and clinical substrate of physical frailty.

2. Sarcopenia: from biological modifications to clinical manifestations

One of the most serious consequences of human aging is the development of sarcopenia, which consists in a progressive decline in skeletal muscle mass and strength [7]. Such decline accelerates after the age of 60 and in most cases leads to functional impairment (e.g., poor endurance, slow gait speed and decreased mobility). Sarcopenia is highly predictive of incident disability, poor quality of life and all-cause mortality in older adults [8–10]. This, combined with the relevance of lack of strength (or *dynapenia*) as an important determinant of an older person's, may induce to the operationalisation of a muscle quality definition based on the strength production capacity per unit of muscle mass. Consequently, an understanding of the influence of aging on the skeletal muscle requires attention to changes in both muscle size and muscle quality. This is particularly important when considering the potential effects of treatments, in terms of improvements not only in muscle mass but also in function and physical performance [11].

Sarcopenia is caused by the simultaneous reduction in the number of muscle fibres and atrophy of remaining myocytes, likely as a result of lower rate of myofibrillar protein synthesis and enhanced myonuclear elimination via an apoptosis-like mechanism [12,13]. These findings reflect a progressive withdrawal of anabolism and an increased catabolism, along with reduced muscle regeneration capacity. Histological sections of aging muscle also show increased infiltration of non-contractile tissue (i.e., collagen and fat) [14].

Many factors are responsible for skeletal muscle decline: the aging process itself, genetic susceptibility, behavioural factors (e.g., less-than-optimal diet, prolonged bed rest, sedentary lifestyle), chronic health conditions, and certain drugs [15]. Progressive muscle atrophy directly results in impaired mechanical muscle performance. Of particular importance, there is a non-linear loss of maximum muscle strength, and the ability to produce muscular power is reduced even more than muscular strength [16].

The age-related reorganisation of the neuromuscular system and the central nervous system is another factor responsible for the loss of motor performance in older adults. Indeed, alterations in neural function can be identified both at the peripheral level (i.e., axons, motor end plates) and at spinal and supra-spinal levels [17].

It has been demonstrated that the loss of spinal motor neurons (MNs) is (at least partially) due to apoptosis [17]. Other research has shown that there is a reduced number and decreased diameter size of myelinated MN axons in the ventral roots, which coincides with accelerated loss of large-diameter axons [17]. Many denervated muscle fibres are re-innervated through collateral sprouting of nearby surviving motor axons or motor end plates, which results in the formation of very large motor units. The alteration also affects neuromuscular function producing changes in maximal MN firing frequency, agonist muscle activation, antagonist muscle co-activation, force steadiness, and spinal inhibitory circuitry. All these factors account for the loss in muscle strength, but also for balance and coordination impairment. Therefore, the formation of these large motor units affects force steadiness and fine motor control [18].

Finally, considerable evidence has implicated age-related declines in the actions of insulin-like growth factor (IGF-1) at muscle level. IGF-1 promotes myoblast proliferation, differentiation, and protein accretion in muscle through multiple signalling mechanisms, including the PI3-kinase, MAP kinase and calcineurin pathways [19].

The atrophy of muscle and impairment of function lead to reduced functional capacity in everyday basic tasks (e.g., walking, stair walking, standing from a chair) [20]. This aspect of sarcopenia explains why it is an important independent predictor of disability.

3. Physical frailty

As physical function becomes impaired during aging, the elderly are exposed to a wide spectrum of negative outcomes, such as impaired mobility, falls, social isolation, reduced quality of life, dependency and institutionalisation. The age-related loss of physical performance often is the result of multiple clinical and subclinical conditions [21].

In recent years, special interest has been paid to the geriatric syndrome of frailty, in order to establish whether interventions can be designed to prevent or slow the disabling cascade in older persons [5,6].

Frailty has been defined as a "multidimensional syndrome characterized by decreased reserve and diminished resistance to stressors" in older persons [22]. Thus, if frailty is considered a pre-disability condition, it may well serve as a target for preventive interventions [23].

Unfortunately, while the theoretical concept of frailty is largely agreed upon, its translation into clinical practice still presents limitations due to the existence of multiple (and largely non-overlapping) operational definitions. Multiple instruments have been developed that aim to capture this condition and make it objectively measurable.

Fried et al. [24] hypothesised some core clinical presentations of frailty, which were then operationalised into an instrument (i.e., the 5-item frailty phenotype) validated in the Cardiovascular Health Study. Taking a different approach, Rockwood et al. [25] used the Canadian Study of Health and Aging to develop and validate the so-called frailty index. Over the past few years, several other instruments to measure frailty have been proposed, frequently building on those two prototypical models. Even though agreement among the existing instruments assessing frailty is relatively poor, each of them presents a strong predictive value for negative outcomes. In other words, each of them can be considered legitimate and appropriate in the identification of older persons at risk of negative outcomes, but consensus for a possible "gold standard" has yet to be achieved. Such a major methodological issue limits the clinical identification, and thus treatment, of high-risk older subjects with significant unmet needs [26].

The clinical picture of frailty, especially when assessed using instruments focused on the physical function domain, shows substantial overlap with that of sarcopenia ("a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death") [3,7]. Namely,