

## Sarcopenia in the elderly: from clinical aspects to therapeutic options

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### Abstract

Sarcopenia is a major contributor to the risk of physical frailty, functional decline, poor health-related quality of life and premature death in older people. Sarcopenia can be considered a geriatric syndrome. The term *sarcopenia* indicates the loss of muscle mass that accompanies aging. Muscle mass declines with aging process with differences between subjects in relation to the presence of chronic diseases, to lifestyles habits (mainly diet and physical activity), to cognitive status. Sarcopenia in the elderly is associated with poor health outcomes, such as falls, disability, loss of independence, and mortality; however, it is potentially treatable if recognized and intervened early. The prevalence of sarcopenia rates between 5% and 13% in community-dwelling older people aged 65 years and over, and is higher in those 80 years and older (20-25%). The cause of sarcopenia is generally thought to be multifactorial, with environmental causes, disease triggers, inflammatory pathway activation, and a large number of cellular and biochemical abnormalities. Resistance training and amino acid supplementation are a recommended practice for the prevention of sarcopenia. The essential elements for the management of the sarcopenic patient are the recognition of a condition of frailty, an accurate multidimensional geriatric assessment, with attention to cognitive problems, mood, functional problems, living conditions, using standardized instruments. Combining exercise with some pharmacological compounds such as  $\beta$ -Hydroxy- $\beta$ -methylbutyrate (HMB) and dietary supplements (including proteins, aminoacids and vitamin D) may exert a beneficial effect on older adults thus influencing the progress to sarcopenia. The recommended daily amount of protein is greater for older people. Vitamin D and leucine enrichment seems mandatory in

order to improve muscle mass and lower-extremity function among sarcopenic older adults. There are some evidences that collagen peptides in this setting might be even superior to whey protein in promoting muscle growth and increasing the mobility.

### Introduction

Sarcopenia, the syndrome of progressive and generalized loss of muscle mass and strength, is a major contributor to the risk of physical frailty, functional decline, poor health-related quality of life and premature death in older people.<sup>1</sup>

The purpose of this article is to review the definition of sarcopenia, its potential role in the arising of frailty and disability, and the potential for intervention, particularly in elderly populations.

Over the last two decades, new insights into the etiology of skeletal muscle wasting/atrophy under diverse clinical settings have been reported in the literature.

Three factors can initiate the loss of skeletal muscle mass and they are cachexia, related to chronic diseases (*i.e.* diabetes or COPD), atrophic conditions (*i.e.* immobilization) and aging. These factors gradually lead to changes in the skeletal muscle by accelerating protein degradation.<sup>2</sup>

Sarcopenia can be considered a geriatric syndrome; with human aging we may recognize a progressive decline in skeletal muscle mass that may lead to decreased strength and functionality.<sup>3</sup>

This is a complex phenomenon and it involves different types of triggers and pathways including myostatin, pro-inflammatory cytokines (*i.e.* TNF, IL-1, IL-6), IFN gamma and TNF-like weak inducer of apoptosis (TWEAK). The final step is the activation of the NF $\kappa$ B, a common transcription factor in most of the protein catabolic pathways leading to proteolysis in skeletal muscles.<sup>2</sup>

### Definitions of sarcopenia and diagnosis

The term *sarcopenia* was coined by Rosenberg to indicate the loss of muscle mass that accompanies aging.<sup>4</sup>

Muscle mass declines with aging process with differences between subjects in relation to the presence of chronic diseases, to lifestyles habits (mainly diet and physical activity), to cognitive status.<sup>5</sup>

Muscle mass is lost at a rate of approximately 8% per decade from the age of 50 years until the age of 70 years, after which

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Key words: Sarcopenia; frail elderly; geriatric syndromes;  $\beta$ -Hydroxy- $\beta$ -methylbutyrate; dietary supplement.

Contributions: the authors contributed equally to the preparation of the paper.

Conflict of interests: the authors declare no potential conflict of interests.

Received for publication: 15 January 2019.  
Revision received: 17 March 2019.  
Accepted for publication: 29 March 2019.

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Geriatric Care 2019; 5:8033  
doi:10.4081/gc.2019.8033

weight loss is coupled with an accelerated loss of muscle mass, reaching a rate of 15% per decade.<sup>6</sup>

Sarcopenia in the elderly is associated with poor health outcomes, such as falls, disability, loss of independence, and mortality; however, it is potentially treatable if recognized and intervened early.<sup>7</sup>

The European Working Group on Sarcopenia in Older People (EWGSOP) recommended that measures of low muscle mass and low muscle strength or performance be utilized in any clinical definition.<sup>3</sup>

Ongoing debate continues in relation to the optimal cutoff values for diagnosing sarcopenia and, more practically, the most appropriate clinical tool to use for screening.<sup>8</sup>

### Epidemiology and risk factors

Sarcopenia is common, and its prevalence rise with aging. The prevalence of sarcopenia varies widely in different clinical settings, reflecting divergence in the approaches used for definition and diagnosis tools; it rates between 5% and 13% in community-dwelling older people aged 65 years and over, and is higher in those 80 years and older (20-25%) and in elderly resident in nursing homes or in hospital setting.<sup>9</sup>

In selected populations the prevalence of sarcopenia is higher and reflects the rela-

tionship between chronic condition and sarcopenia. For example, in cancer patients the proportion of sarcopenia may exceed the 70% of cases and in patients with chronic kidney disease in pre-dialytic stage it ranges between 12 and 30%.<sup>10</sup> In patients with hip fractures the prevalence of sarcopenia is near to 40% and is associated with older age and comorbidities.<sup>11</sup>

The cause of sarcopenia is generally thought to be multifactorial, with environmental causes, disease triggers, inflammatory pathway activation, and a large number of cellular and biochemical abnormalities (the most relevant are: mitochondrial abnormalities, loss of neuromuscular junctions, hormonal changes) (Figure 1).

Elderly persons frequently decline physical activity and reduce nutritional intake, with inadequate protein and caloric intake; consequently, an accelerated loss of muscle mass and function is observed.<sup>12</sup> These environmental influences are superimposed on a multifactorial, age-related change in biology that determines the observed declines in skeletal muscle mass and strength.

## Sarcopenia as a geriatric syndrome

The term *geriatric syndromes* defines some clinical conditions in the elderly that cannot be clearly described with the classic diagnostic categories.<sup>13</sup> A Geriatric syndrome may be considered the *final common pathway* of several conditions and is the result of interaction between age-related changes, co-morbidities, social stress factors and individual resilience. Geriatric syndromes include many common conditions such as delirium, falls, frailty, dizziness, syncope, sarcopenia and urinary incontinence that are the reasons why elderly patients contact the physician.<sup>14</sup>

Sarcopenia and frailty may be considered as part of the same phenomena, even is difficult to realize if frailty is due to sarcopenia, or if sarcopenia is a manifestation of frailty. The term frailty is used to indicate a geriatric syndrome characterized by reduced homeostatic reserves, which exposes the individual at an increased risk of negative health-related events (including falls, hospitalizations, worsening disability, institutionalization, and mortality).<sup>15</sup>

Frailty is defined as a clinically recognizable state of higher vulnerability, resulting from aging-associated decline in reserve and function across multiple physiologic systems such that the ability to cope with daily or acute stressors is compromised.<sup>16</sup> In the absence of a gold standard, frailty has

been operationally defined by Fried *et al.* as meeting three out of five phenotypic criteria indicating compromised energetics: low grip strength, low energy, slowed waking speed, low physical activity, and unintentional weight loss.<sup>17</sup> On the other hand, Rockwood *et al.* describe frailty using a multidimensional framework including psychological and social components, multimorbidity, and disability in addition to the physical impairments (Table 1).<sup>18</sup>

Sarcopenia is a frequent cause of physical frailty and both frailty models have an overlap in the physical component, in the role of nutrition and physical activity, and in biological mechanisms (Figure 2).

Sarcopenia definition includes low physical performance, which means that sarcopenia is an essential component of physical frailty. Frailty and sarcopenia show a significant overlap and sarcopenia may be considered a component of the multidimensional phenotype of frailty.<sup>19</sup>

Cognitive decline is an important predictor of disability and part of the frailty syndrome. Therefore, is not surprising that sarcopenia is related to cognitive decline and, in more general terms, to psychogeriatric syndromes.<sup>20</sup> In cross sectional studies sarcopenia is more frequent in Alzheimer disease, then in mild cognitive impairment and in controls (respectively 23.3%, 12.5%, 8.6%);<sup>21</sup> and in severe dementia about 70%

of patients have sarcopenia.<sup>22</sup> In cross sectional studies sarcopenia is associated with depressive symptoms (OR 2.2) and cognitive impairment (OR 3);<sup>23</sup> and about 60% of sarcopenic subjects present disability and cognitive impairment.<sup>24</sup>

Sarcopenia is found to be a strong predictor of cognitive decline and loss of weight, motoric dysfunction, and modification of eating behavior may be considered as early sign of cognitive impairment.<sup>25</sup>

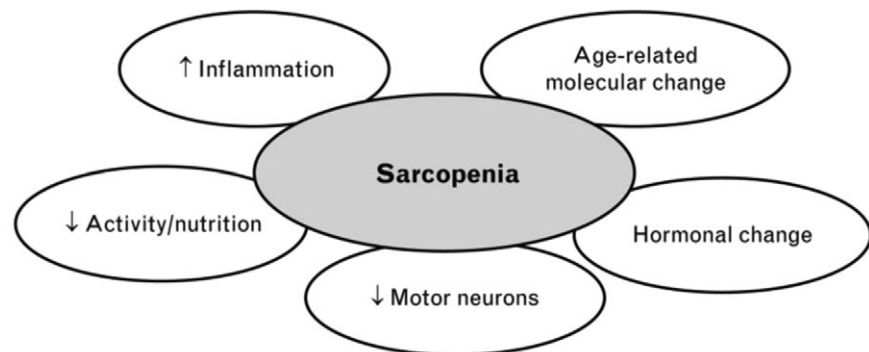
Recognizing a sarcopenic state in elderly patients could be very useful in order to generally assess the condition of frailty, as well as the evaluation of cognition and mood; the main aim should be identifying patients with high risk of disability so to early start all the necessary actions to improve clinical outcomes, mainly lifestyle changes (nutrition and exercise) and treatments of chronic conditions.<sup>26</sup>

## Geriatric assessment for sarcopenic patients in clinical practice

The evaluation of the presence of sarcopenia might be a part of the more general multidimensional assessment of an elderly subject; this approach allows to define the

**Table 1. The measures of frailty.**

Physical phenotype	Multidimensional frailty index
Unintentional weight loss	Physical impairment
Muscle weakness	Sensory limitation
Slow physical activity	Mood
Low physical activity	Cognition
Exhaustion	Social environment
	Comorbidity
	Disability



**Figure 1. Multifactorial causes of sarcopenia in the elderly.**

presence of geriatric syndromes, the level of disability, the presence of conditions of frailty that are correlated with the risk of developing sarcopenia.

In general terms multidimensional geriatric assessment (often called comprehensive geriatric assessment) may be considered not only a diagnostic process, but even a man-

agement approach, aimed to determine an older person's medical, psychosocial, functional and environmental resources, and problems and to develop an overall plan for treatment and long-term follow-up.<sup>27</sup>

The evaluation of physical performance, general conditions, included muscle mass and strength, essential for the diagno-

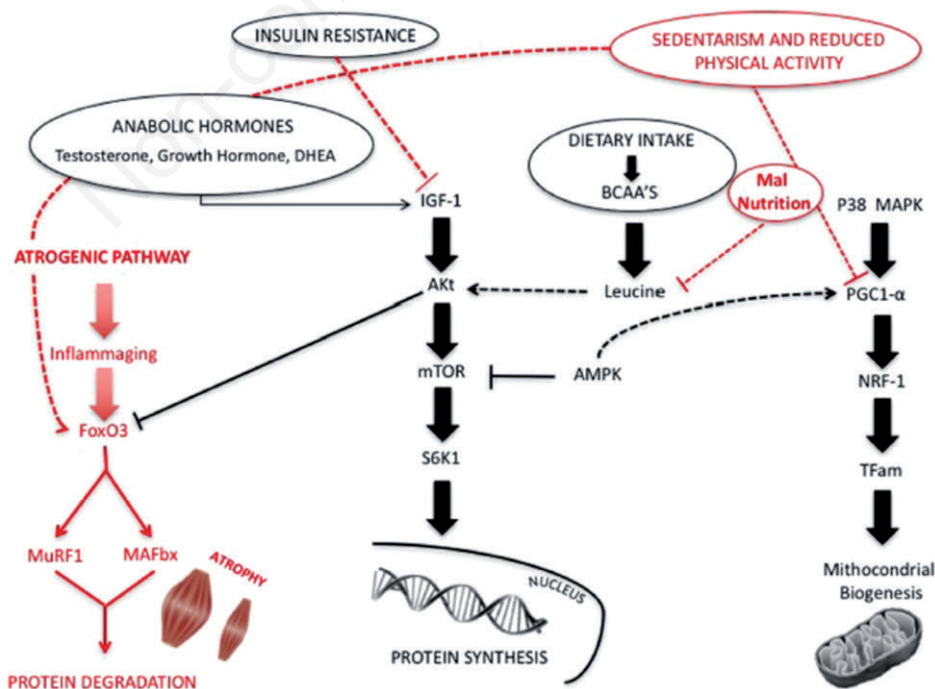
sis of sarcopenia, may be considered part of the geriatric assessment.

Despite a relatively large number of tools being available to measure muscle mass, muscle strength and physical performance, some of them are likely to be of greater validity and utility for the assessment of sarcopenia in clinical practice (Table 2).<sup>28</sup>

**Table 2. Tools for the assessment of muscle mass, muscle strength and physical performance in research and clinical settings.**

	Applicable in research settings	Applicable in specialist clinical settings	Applicable in primary care settings
<b>Assessment of muscle mass</b>			
DXA	+++	+++	+
<b>Anthropometric measurements</b>			
CT-scan	+++	++	+
MRI	+++	++	+
BIA	++	++	+
US	++	++	+
<b>Assessment of muscle strength</b>			
Handgrip strength	+++	+++	+++
Lower limb muscle strength	+++	++	+
Repeated chair stands test	+	+	++
<b>Assessment of physical performance</b>			
Gait speed	+++	+++	+++
Timed Up and Go test	++	+	+
Balance test	+	+	+
6-min walk test	++	+	+
400 m walk test	++	+	+
Stair climb test	++	+	+
SPPB test	+++	++	+

SPPB Short Physical Performance Battery. The classification +++ (best recommended tool) or ++ (best alternative tool) or + (less recommended tool) is based on the availability and the costs, the required time for the examination and the availability of robust cut-off points. *Modified from Beaudart et al., 2016*<sup>28</sup>



**Figure 2. Similar mechanism of frailty and sarcopenia.**

Muscle mass may be assessed using magnetic resonance imaging (MRI) and computed tomography (CT) scan for the non-invasive assessment, but this approach is limited in primary care settings by difficulties in access, costs and the lack of specialized centres and used primarily for research purposes. Dual-energy x-ray absorptiometry (DXA) is a well-established, low-radiation technique used to assess body composition and provides reproducible estimates of appendicular skeletal lean mass; DXA is still considered as the procedure of choice for routine clinical assessment. An alternative, low expensive, method to estimate the volume of fat and lean body mass is bioimpedance analysis (BIA). The method is relatively easy to use in clinical practice, both on ambulatory subjects or on hospitalized patients, with reference values defined for older individuals; however, the results may be altered by fluid retention.<sup>29</sup>

In alternative, when instrumental methods are not available, clinicians may use anthropometric measurements to assess muscle mass; anthropometric data are currently the most widely used methods in clinical practice (57.5% of clinicians who measure muscle mass in their practice use anthropometric data) followed by DXA (45.9%).<sup>30</sup> Several anthropometric measurements exist (*i.e.* body mass index, calf circumference, mid-upper arm circumference and skinfold thickness). Moreover, mid-arm muscle and calf circumferences have been shown to correlate with appendicular muscle mass and reflect both health and nutritional status and predict performance, health and survival in older people.<sup>31</sup> Anthropometric measurements adjusted for age, sex or BMI are highly correlated with DXA-measured lean mass.<sup>32</sup> The limitation of anthropometric measure is the need of well-defined cut-off points in very elderly subjects, so, if a patient is identified as at risk of having sarcopenia by anthropometric measurements, an additional measurement of muscle mass would still be recommended.<sup>33</sup>

Recently, ultrasounds method has been used for muscle mass estimation in clinical and research settings; this is a promising technique, because is safe, noninvasive, repeatable and portable, and it allows simplicity of measurements in body composition assessment, though it needs an experienced operator.<sup>34</sup>

In recent years numerous mediators linked to systemic inflammation, hormonal status, and redox homeostasis have been associated with the presence of muscle atrophy and muscle dysfunction. However, they are not specific to muscle and their levels may, therefore, be altered in a vari-

ety of conditions unrelated to sarcopenia, so their usefulness in clinical and research setting is limited.

Some of these, in particular plasma concentrations of procollagen type III N-terminal peptide (P3NP), the circulating C-terminal agrin fragment (CAF), the circulating skeletal muscle-specific troponin T (sTnT), have been proposed as biomarkers of muscle mass and are actually under evaluation.<sup>35</sup>

A variety of tools are used in clinical practice for the assessment of physical performance. The measurement of gait speed is widely used in clinical settings and do not require special equipment. The EWGSOP recommended the 4-m gait speed test for the assessment of sarcopenia. In this test men and women with a gait speed <0.8 m/s are described as having a poor physical performance.

Gait speed can be performed alone or as part of a test battery, such as the the Short Physical Performance Battery (SPPB), a test scored to a maximum of 12 points, comprising an assessment of gait speed (over 3–4 m), a balance test and a repeated chair stand test. Subjects presenting a score ≤8 points have been described as having a poor physical performance.<sup>36</sup>

Other tests can be performed to assess the physical performance, such the Timed Up and Go (TUG) test, in which individuals are asked to rise from a standard armchair, walk to a marker 3 m away, turn, walk back and sit down again.<sup>37</sup>

For the assessment of muscle strength handgrip strength is the most widely used method, and is considered a reliable measure, not expensive and easy to assess muscle strength.<sup>38</sup> A variety of grip strength thresholds have been proposed to characterize low muscle strength, ranging from 16 to 20 kg for women and 26–30 kg for men.<sup>28</sup>

In the clinical settings it is important to promptly and easily detect the clinical signs that can indicate the presence of sarcopenia and then activate detailed evaluations.

The patient can be asked about symptoms such as loss of weight, loss of muscle strength, loss of energy, falls, loss of appetite. An assessment of nutrition habits should also be performed to check, for example, if the subject has adequate protein intake. Specific questionnaire, such the Mini-Nutritional Assessment, might be used for the assessment of the risk of malnutrition.<sup>39</sup> The next step is the assessment of physical activity. Indeed, physical inactivity or high levels of sedentary behaviour may be considered a red flag. In presence of symptoms or signs of sarcopenia from preliminary examinations, more sophisticated assessment procedures of sarcopenia can be implemented.

Early identification of sarcopenia in primary care may make easier by the use of screening tests. One of the most used screening test is the SARC-F questionnaire.<sup>40</sup> The test consists in 5 questions addressing strength, assistance in walking, rising from a chair, stair climbing and falls. A score ≥4 points is reported to be predictive of sarcopenia and poor outcomes and could be a trigger for a more detailed assessment of sarcopenia.

## The treatment of sarcopenia

Therefore, the treatment of skeletal muscle wasting remains an unresolved challenge to this day.

Among the possible compounds theoretically useful for these patients a role might be played by CoX2 inhibitors (by a reduction of pro-inflammatory cytokines and improved protein anabolism), Omega 3 PUFA, mainly EPA (by reducing the expression level of many pro-inflammatory molecules including NFκB, and increasing the level of PPARγ thus correcting the metabolic abnormalities, improving myogenesis and modulating the immune function) and progestinic hormones (*i.e.* megestrol acetate, which down-regulates several inflammation mediated molecules and up-regulates the neuropeptide Y levels, leading to increased appetite and body mass, mainly in cancer or AIDS cachexia).<sup>41–43</sup>

Finally, since the mammalian target of rapamycin (mTOR) plays a central regulatory role in many cellular processes and it is thought that it largely governs the accretion of protein in the growing myofiber, it may be considered a possible pharmaceutical target, though at present it is still unclear if and how therapeutic effects could be obtained with pharmacological activators of this protein-kinase.<sup>44</sup>

mTOR forms two structurally and functionally distinct complexes: mTOR Complex 1 (mTORC1), which governs anabolic processes such as protein synthesis in response to nutrients or Resistance Exercise (RE), and mTOR Complex 2 (mTORC2), which controls many cellular processes and has been shown to regulate muscle glucose uptake during Endurance Exercise (EE).<sup>44</sup>

It is well known that EE and RE significantly ameliorate the symptoms of various chronic pathologies, *e.g.* by reducing inflammation and insulin resistance, and positively influencing cognitive function. Many of these systemic effects are mediated by signaling molecules that are produced and secreted by skeletal muscle in response to exercise. Generally speaking, EE training leads to increased mitochondrial content

and thus oxidative capacity, while RE leads to an increased myofiber size and elicits changes in contractile properties of muscle fibers.<sup>44</sup>

As previously stated, older adults are frequently frail with an increased risk of falls, incident disability and hospitalization and frailty and sarcopenia overlap.<sup>45</sup>

Therefore, in sarcopenic elderly peoples with progressive loss of muscle mass, strength and/or performance with age, exercise remains one of the most important choices, since it is capable to modulate mitochondrial function. However, there is a growing evidence that combining exercise with some pharmacological compounds such as  $\beta$ -Hydroxy- $\beta$ -methylbutyrate (HMB) and dietary supplements (including proteins, aminoacids, collagen peptides and vitamin D) may exert a beneficial effect on older adults thus influencing the progress to sarcopenia.<sup>46</sup>

### $\beta$ -hydroxy- $\beta$ -methylbutyrate

$\beta$ -hydroxy- $\beta$ -methylbutyrate (HMB) is a metabolite of leucine, one of the three essential aminoacids with valine and isoleucine, and its ketoacid alpha-ketoisocaproate (KIC).<sup>47</sup> HMB has the potential to increase lean body mass, muscular strength and size, reduce skeletal muscle damage, and enhance speed of recovery post-exercise. The prevalent mechanisms involved in these favorable

effects are mainly the inhibition of both the ubiquitin-proteasome and the autophagy-caspase systems and the stimulation of protein synthesis via mTOR pathway (with a higher efficacy than leucine).<sup>47-50</sup>

HMB may also stimulate protein synthesis through the growth hormone/IGF-1 axis.<sup>51</sup> Recent studies have demonstrated that HMB supplementation increases mitochondrial biogenesis and fat oxidation, while experimental animal models suggest that HMB improves excitation-contraction coupling in muscle cells (Figure 3).<sup>52,53</sup>

Numerous human studies on the use of HMB reported benefits with positive effects on muscle hypertrophy, strength and reduction of damage. In particular, in studies in which the duration of the training was at least 3 weeks, HMB supplementation increased lean mass and strength. Nevertheless, several studies, specifically conducted in strength-trained athletes, failed to demonstrate beneficial effects, thus suggesting that HMB might be more effective in untrained individuals who are exposed to strenuous exercise.<sup>47,54,55</sup>

In elderly people HMB supplementation can prevent the loss of lean body mass without causing a significant change in fat mass.<sup>56</sup> Stout *et al.* in a randomized, double-blind pilot trial in men and women over 65y of age, demonstrated that a 24 week supplementation of CaHMB improved strength and muscular quality when compared with placebo even without RE. These Authors also confirmed that in this setting RE is an effective

intervention for improving all measures of body composition and functionality.<sup>57</sup>

Moreover, it has recently reported that in rats HMB plasma levels tend to diminish with age while lower KIC dioxygenase levels are present in the livers of old rats.<sup>58</sup>

Finally, the observation that HMB almost reduced the effects of ageing in the pyramidal neurons and improved the cognitive functions in old-age rats supports the possibility of more beneficial effects in old people. Studies are also needed to examine whether HMB in elderly subjects may also improve the anabolic response of muscle to a meal.<sup>47,59,60</sup>

Commercially, HMB is available as the calcium salt. A dose of 3 g of HMB per day is routinely recommended to maintain or improve muscle mass and function. Usually the supplementation with HMB is well tolerated and has no toxic effects.<sup>47,61</sup>

However, the stimulation of protein synthesis and the suppression of proteolysis exerted by HMB may reduce the release from muscles of various amino acids and particularly glutamine, as observed in experimental studies and its deficiency can decrease protein synthesis in skeletal muscle.<sup>62</sup>

### Nutritional supplementation

Nutrition can have a positive impact on protein anabolism. The increase in quantity and quality of dietary protein (*i.e.*,

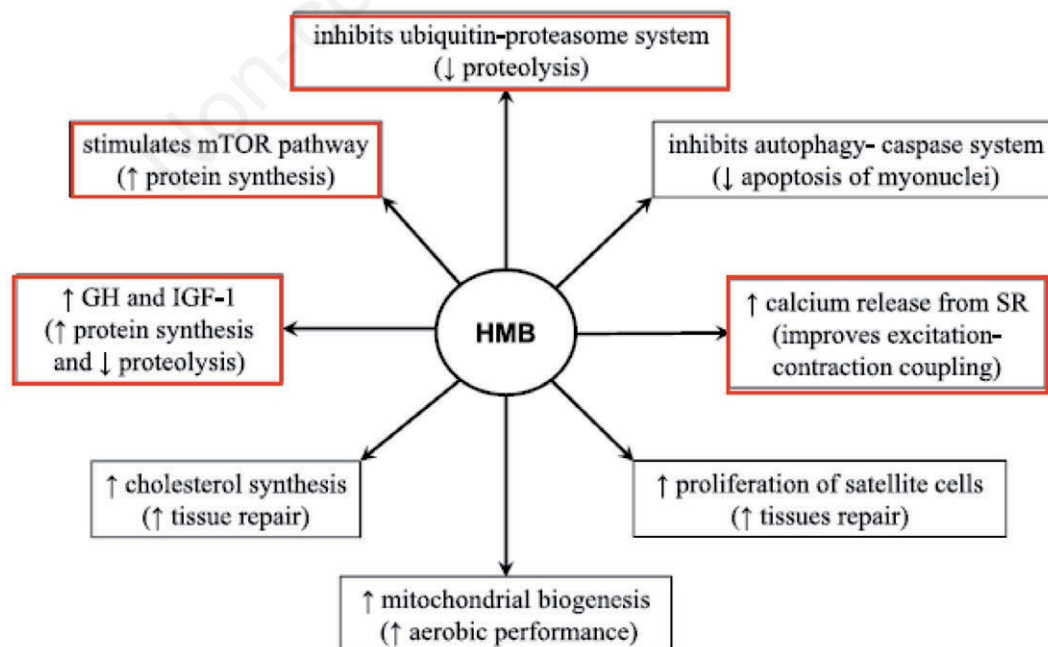


Figure 3. HMB: Mechanisms for favourable effects on skeletal muscle. Modified from Holeček, 2017.<sup>47</sup>

leucine) stimulates muscle protein synthesis in the elderly.<sup>63,64</sup> Increased intake of vitamin D stimulates muscle protein synthesis and enhances strength and balance.<sup>65</sup> It also reduces the inflammation that is associated with decreased muscle strength in the elderly.<sup>66,67</sup>

### Vitamin D

Vitamin D has been traditionally considered a key regulator of bone metabolism and calcium and phosphorus homeostasis.

The prevalence of low vitamin D concentrations in subjects older than 65 years of age has been estimated at approximately 50%, but this figure is highly variable because it is influenced by living factors. Similarly, there is a reduced concentration of vitamin D with aging and there is an age-dependent reduction in vitamin D receptor expression in skeletal muscle.<sup>46,68</sup>

Prolonged vitamin D deficiency has been associated with severe muscle weakness, which improves with vitamin D supplementation.<sup>69</sup>

Low vitamin D concentrations represent an independent risk factor for falls in the elderly and supplementation increases muscle strength and performance, thus reducing the risk of falling.<sup>69,70</sup>

### Proteins and derivatives

A significant number of elderly women and men aged 50 or older consume less than the suggested daily amount of proteins.<sup>71</sup> Epidemiological studies have demonstrated that protein intake is positively associated with the preservation of the muscle mass. Many reviews indicate that certain nutritional interventions such as a high protein intake or an increased intake of essential amino acids and particularly the essential amino acid leucine along with resistance training may help to attenuate fiber atrophy in sarcopenic muscle by the modulation of both anabolic and catabolic pathways.<sup>71-73</sup>

In particular, leucine as itself and via HMB (see above), plays an important role in muscle metabolism regulation, which include the translational control of protein synthesis, glucose homeostasis and nitrogen donation for the synthesis of muscle alanine and glutamine.<sup>47-50,63,64,69,74</sup>

Considering these findings, the use of leucine as an anti-atrophic agent is biologically justified and an oral post-exercise amino acid supplementation has a synergistic effect on the muscle protein synthesis following acute RE through an mTOR-mediated mechanism.<sup>44,46,75,76</sup>

Treatment with amino acids has been shown to induce additive hypertrophy in response to continuous resistance training. Moreover, the administration of essential

amino acids would have a positive effect on the muscle mass and protein synthesis both under normal conditions and with resistance training.<sup>69,73,77,78</sup>

Nutritional supplementation is effective in the treatment of sarcopenia in old age, and its positive effects increase when associated with physical exercise. The main limitation of this treatment is lack of long-term adherence.<sup>79</sup>

### The management of a sarcopenic patient: clinical pharmacological considerations

Even sarcopenia and frailty may not be considered as a single entity, the essential elements for the management of the sarcopenic patient recall those underlying the management of the frail elderly. The first step is the recognition of a condition of frailty; this is important because earlier detection allows for programs implementation focused on prevention and management to reduce the risk of future hospitalization, improve outcomes, and enhance vitality and quality of life.

As previously mentioned, the first step is an accurate multidimensional geriatric assessment, with attention to cognitive problems, mood, functional problems, living conditions, using standardized instruments.<sup>80</sup>

The identification of comorbidities is an important part of the geriatric assessment and sarcopenia is frequently found in association with chronic diseases (*i.e.*, osteoporosis, type II diabetes mellitus, neoplasm, chronic cardiac or pulmonary failure). Sarcopenia in such cases may be considered a consequence of the co-existing disease and, at the same time, a condition that aggravates the diseases.

Older adults have shown evidence of anabolic resistance, where greater amounts of protein are required to stimulate muscle protein synthesis, and response is variable. Thus, the recommended daily amount of protein is greater for older people.<sup>81,82</sup>

The etiologies and mechanisms responsible for anabolic resistance are not fully understood. One possible involvement might be due to the gut microbiota either directly or indirectly. The gut microbiota changes with age and are influenced by dietary protein and there might be a role for the gut microbiome in skeletal muscle function.<sup>83</sup>

Therefore, although resistance training and amino acid supplementation are a recommended practice for the prevention of sarcopenia, in the literature there are conflicting results regarding the role of a nutritional supplement with exercise and the

critical aspects are represented by age, health and nutrition status of the patient's population as well as the design of the training program, the type of dietary protein intake and the time of protein supplementation.<sup>81,82,84</sup>

Regarding the type and amount of the nutritional supplement, a clear indication can be obtained from the PROVIDE study, a 13-week, multi-center, randomized, controlled, double blind, two parallel-group study in 380 sarcopenic primarily independent-living older adults.<sup>85</sup> This study demonstrated that the intervention of a vitamin D and leucine-enriched whey protein oral nutritional supplement resulted in improvements in muscle mass and lower-extremity function among sarcopenic older adults.<sup>85</sup> Similar results were obtained in different clinical studies conducted more recently: As an example, in 2016 Rondanelli *et al.* demonstrated that a nutritional supplementation containing whey protein (22 g), essential amino acids (10.9 g, including 4 g leucine), and vitamin D [2.5 mg (100 IU)], in combination with regular physical activity, was capable to increase fat-free mass, strength, physical function and quality of life of sarcopenic elderly patients.<sup>86</sup>

In 2017 Englund *et al.* conducted a randomized, double-blind, placebo-controlled trial (the VIVE2 study) on the effect of a 6 month - nutritional supplementation (20 g whey protein, 800 IU vitamin D) with physical activity in 149 mobility-limited older adults, concluding that the nutritional supplementation provides significantly additional benefits in these subjects to the effect of exercise training.<sup>87</sup>

Moreover, a post-hoc analysis of the PROVIDE study, published this year, concluded that sufficient baseline levels of vitamin D(25(OH)D >50nmol/L) and whey protein intake (>1g/kg/d) are required to increase muscle mass as a result of intervention with a vitamin D and whey protein supplement in sarcopenic older adults (Figure 4).<sup>88</sup>

These data suggest that the amount of vitamin D and protein intake might be a crucial point in nutrition strategies with the purpose of attenuating muscle loss in elderly subjects.<sup>82,88</sup>

However, there is a debate on a possible reverse J-shaped relation between the serum level of 25(OH)D and mortality and at present there is a need to better clarify the effects of 25(OH)D levels greater than 100 nmol/L, though low levels ( $\leq 0$  nmol/L) correlate with an increased risk of death.<sup>89,90</sup> On the other hand, a consensus on the measurement of 25(OH)D is still lacking.<sup>91</sup>

Thus, further evidence is required to draw firm conclusions or make explicit rec-

ommendations regarding combined exercise and vitamin D3 supplementation.<sup>92</sup>

The majority of the clinical studies on the use of a protein supplementation refers to whey protein. Whey is contained in dairy products such as milk, yogurt, and cheese and, as either casein or soy, it is recognized as a complete protein, since it contains all of the essential amino acids (EAAs). However whey has a higher proportion of the branched-chain AA (BCAA) leucine, which, as previously discussed, is very important in stimulating muscle protein synthesis via mTOR-mediated mechanism.<sup>44,46,75,76</sup> In addition, this protein, as well as soy but not casein, is also rapidly digested and leads to high aminoacid content in blood, which is thought to be critical for muscle protein synthesis.<sup>73</sup>

Collagen is an extracellular protein that accounts for 25-30% of the total protein content within the human body. The process of hydrolysis yields collagen peptides that are rapidly re-absorbed in the small intestine, which may be important for post-exercise recovery. These peptides are largely absorbed in intact form. Collagen is a fast-digested protein, though it is considered as having a relatively low biological value, mainly due to the low amount of BCAA and lysine. Nevertheless, since the N content is higher than in whey on per gram basis, the combination of amino acids has been shown to be superior in maintaining N balance and body weight during a low-protein diet.<sup>93</sup>

Moreover, this protein contains relatively high amounts of arginine and glycine, both known to be important substrates for the synthesis of creatine in the human body.<sup>94</sup>

Although hydrolyzed collagen is contained in sports drinks and bars aimed at improving regeneration and post-exercise muscle recovery to our knowledge there are few studies on the use of this protein for nutritional supplementation with resistance exercise in elderly people. Zdzieblik *et al.* recently published the results obtained in a double-blind placebo-controlled study on fifty-three male elderly subjects with sarcopenia (class I or II) undergoing guided resistance training program (three sessions per week) and supplemented with either collagen peptides (15 g/d) or silica as placebo. Patients supplemented with collagen peptides obtained a significantly higher effect on fat-free mass (FFM), bone mass (BM) and isokinetic quadriceps strength increment (IQS)<sup>95</sup> (Figure 5).

These Authors suggested that among the possible reasons for a so high beneficial effect we may consider the fact that collagen peptides positively influence microcirculation, thus promoting muscle growth compared with other protein sources.

Moreover, collagen peptides are capable to significantly reduce pain in osteoarthritis patients and in functional joint pain thus increasing mobility.<sup>96,97</sup> This aspect may favor the ability to perform the resistance

exercises with less pain, and having a better training gain. Collagen peptides can also be found associated with Vitamin D, leucine and HMB in one nutritional supplement known as Peptivis®

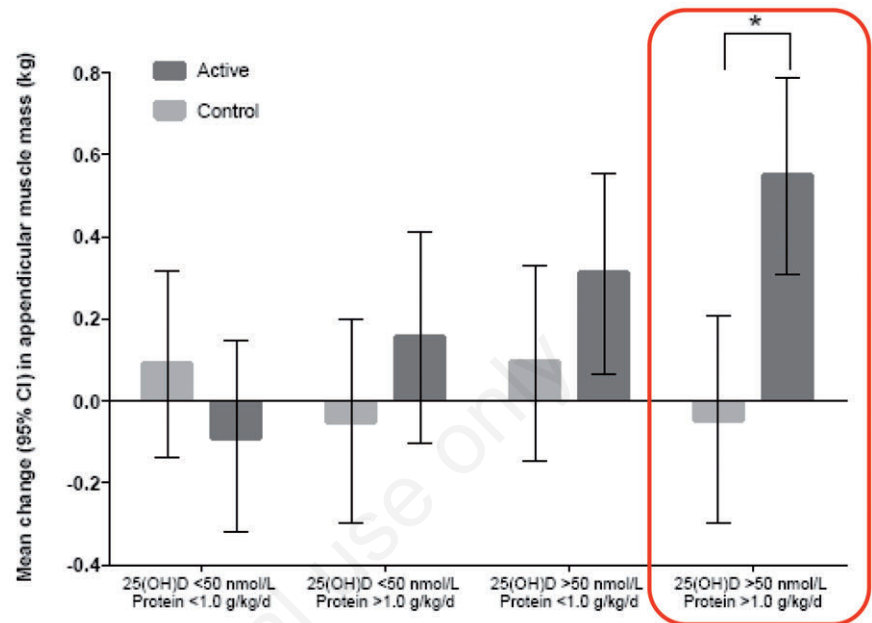


Figure 4. Effect of a Vit D and Leu-enriched whey protein supplement on appendicular muscle mass of sarcopenic older adults (The PROVIDE Study). Modified from Verlaan *et al.*, 2018.<sup>88</sup>

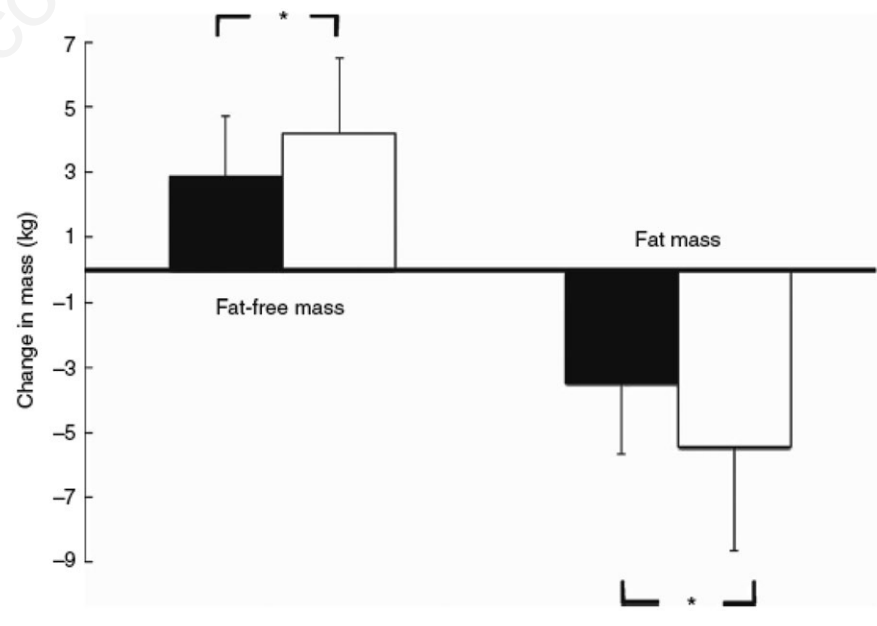


Figure 5. Collagen peptides supplement and resistance training in elderly men: change in fat-free mass and fat-mass after 12 weeks of training and supplementation. Values are expressed as means  $\pm$ SE. Modified from Zdzieblik *et al.*, 2015.<sup>95</sup>

## Conclusions

Resistance training and amino acid supplementation are a recommended practice for the prevention of sarcopenia. The recommended daily amount of protein is greater for older people, probably due to a direct and/or indirect effect of the gut microbiota. There is still a debate regarding the type of dietary protein intake and the time of protein supplementation as well as the design of the training program.

Vitamin D and leucine enrichment seems mandatory in order to improve muscle mass and lower-extremity function among sarcopenic older adults. There are some evidences that collagen peptides in this setting might be even superior to whey protein in promoting muscle growth and increasing the mobility. Nevertheless, for trying to draw a final statement on this topic, advanced analytical techniques are needed for a better understanding of the effects of these nutraceuticals with or without exercise in elderly people while increasing the number of well-designed clinical trials is mandatory to reduce bias related to age, health and nutrition status of the patient' population.

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