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Muscle contractile and metabolic dysfunction is a common feature of sarcopenia of aging and chronic diseases: From sarcopenic obesity to cachexia☆

Gianni Biolo [a,d,f], Tommy Cederholm [b,e], Maurizio Muscaritoli [c,*,d,f]

[a] Department of Medical, Surgical and Health Sciences, Clinica Medica, AOUTS, University of Trieste, Italy
[b] Clinical Nutrition and Metabolism, Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden
[c] Department of Clinical Medicine, Sapienza – University of Rome, Italy

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SUMMARY

Skeletal muscle is the most abundant body tissue accounting for many physiological functions. However, muscle mass and functions are not routinely assessed. Sarcopenia is defined as skeletal muscle loss and dysfunction in aging and chronic diseases. Inactivity, inflammation, age-related factors, anorexia and unbalanced nutrition affect changes in skeletal muscle. Mechanisms are difficult to distinguish in individual subjects due to the multifactorial character of the condition. Sarcopenia includes both muscle loss and dysfunction which induce contractile impairment and metabolic and endocrine abnormalities, affecting whole-body metabolism and immune/inflammatory response. There are different metabolic trajectories for muscle loss versus fat changes in aging and chronic diseases. Appetite regulation and physical activity affect energy balance and changes in body fat mass. Appetite regulation by inflammatory mediators is poorly understood. In some patients, inflammation induces anorexia and fat loss in combination with sarcopenia. In others, appetite is maintained, despite activation of systemic inflammation, leading to sarcopenia with normal or increased BMI. Inactivity contributes to sarcopenia and increased fat tissue in aging and diseases. At the end of the metabolic trajectories, cachexia and sarcopenic obesity are paradigms of the two patient categories. Pre-cachexia and cachexia are observed in patients with cancer, chronic heart failure or liver cirrhosis. Sarcopenic obesity and sarcopenia with normal/increased BMI are observed in rheumatoid arthritis, breast cancer patients with adjuvant chemotherapy and in most of patients with COPD or chronic kidney disease. In these conditions, sarcopenia is a powerful prognostic factor for morbidity and mortality, independent of BMI.

1. Introduction

A great achievement of modern medicine is the ability to stabilize chronic diseases, leading to extended life expectancy of populations. The chronically ill patient journey, however, is often associated with metabolic abnormalities and alterations in body composition (i.e., muscle loss with changes in adipose tissue mass) which affect disease outcome and increase health care burden and cost. A physiological decline of skeletal muscle tissue is also an important feature of the aging process. There are strict relationships between muscle loss associated with aging and that due to chronic diseases. In addition, decreased physical activity and muscle unloading are key variables affecting skeletal muscle mass and body composition in aging and chronic disease.

The term sarcopenia was originally introduced to define age-related skeletal muscle decline, however it is now used to indicate any loss of muscle tissue and function due to aging, chronic diseases (including cancer), low protein-energy intake and physical inactivity.[1,2] Other definitions may be used to describe decreases in muscle mass and function. The term wasting describes disease- and cancer-related muscle loss.[3] Dynapenia defines decreased contractility and loss of strength.[4] Muscle loss secondary to inactivity and unloading is often referred to as disuse atrophy.[5] More

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* Corresponding author. Department of Clinical Medicine, Sapienza – University of Rome, Viale dell'Università, 37 00185 Rome, Italy.
E-mail address: maurizio.muscaritoli@uniroma1.it (M. Muscaritoli).

[d] ESPEN-SIG "Cachexia-Anorexia in Chronic Wasting Diseases".
[e] ESPEN-SIG "Nutrition in Geriatrics".
[f] These authors equally contributed to conception and writing of the paper.

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recently, Fearon et al. proposed the term of "myopenia" to indicate a clinically relevant degree of muscle loss that is also associated with impaired contractile function.[6] In 2010 the Special Interest Groups (SIG) "Cachexia-Anorexia in Chronic Wasting Diseases" and "Nutrition in Geriatrics" of the European Society of Clinical Nutrition and Metabolism (ESPEN) defined sarcopenia as any loss of skeletal muscle mass and strength secondary to aging and chronic diseases including cancer.[1] Subsequently, it was agreed to continue the common efforts aimed at improving the knowledge about sarcopenia, cachexia, pre-cachexia, sarcopenic obesity in aging and chronic diseases among the scientific community. The process for the production of the present document was started in September 2012 in Barcelona, during the joint meeting of the two ESPEN SIGs. The draft of the paper was elaborated during the first semester of 2013. The manuscript draft was then circulated among the participants to the two SIGs (listed in the acknowledgments section in this paper) and progressively improved and integrated based on the indications of the participants. The endorsement of the document by the two SIGs was obtained in September 2013 in Leipzig, during the annual joint meeting of the 2 SIGs. In agreement with our previous definition,[1] in the present paper we will use the term sarcopenia to define any clinically relevant skeletal muscle loss and dysfunction associated with aging, chronic diseases, cancer, low protein-energy intake and physical inactivity. This definition is also in agreement with the European Working Group on Sarcopenia in Older People (EWGSOP) that in 2010 developed a consensus document on sarcopenia endorsed by the following organizations: European Geriatric Medicine Society (EUGMS), the European Society for Clinical Nutrition and Metabolism (ESPEN), the International Association of Gerontology and Geriatrics—European Region (IAGG-ER) and the International Academy of Nutrition and Aging (IANA).[2] The EWGSOP made a distinction between aging-associated sarcopenia (primary sarcopenia) and disease-associated sarcopenia (secondary sarcopenia).[2] However, it is difficult to distinguish primary from secondary sarcopenia because 90–95% of older adults have at least one chronic disease, and 70–75% have two or more comorbidities.[7] Evidence indicates that chronic diseases prevalence is increasing over the last decades.[7]

In the present joint document elaborated by the ESPEN SIG "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics" we will try to highlight that:

(a) criteria for a clinical diagnosis of sarcopenia are required (see: Clinical diagnosis of sarcopenia);
(b) sarcopenia is a key feature of age- and disease-related malnutrition (see: Skeletal muscle as a marker of nutritional status);
(c) sarcopenia is a multifactorial disorder where specific mechanisms related to aging, chronic disease or inactivity are difficult to distinguish in individual subjects; in addition, sarcopenia includes both muscle loss and muscle dysfunction, the latter not only involves contractile impairment but also metabolic and endocrine abnormalities affecting whole-body metabolism, systemic inflammation and immune system regulation (see: Muscle dysfunction: impaired contractile, metabolic and endocrine functions);
(d) sarcopenia is a major determinant of disease outcome and longevity (see: Impact of sarcopenia on outcomes);
(e) there are different metabolic trajectories for muscle loss versus fat changes in aging and chronic diseases leading to the two different paradigms of sarcopenia, i.e., cachexia and sarcopenic obesity (see: Cachexia and sarcopenic obesity); and
(f) cost-effective control of chronic disease and optimal aging require sarcopenia prevention, diagnosis and treatment (see: Sarcopenia of aging and chronic diseases: towards a clinical definition and therapy).

2. Clinical diagnosis of sarcopenia

Currently proposed criteria for sarcopenia assessment in a clinical setting include determination of muscle mass, strength and physical performance (Table 1).[2,8–17] Muscle mass can be measured by anthropometry,[8] bioimpedance analysis (BIA),[2,9,13,15] dual energy X-ray absorptiometry (DXA),[11,12] computed tomography (CT) scan[10,11] and magnetic resonance imaging (MRI). BIA cannot reliably assess skeletal muscle mass in patients with body fluid abnormalities, as liver cirrhosis (LC), chronic kidney disease (CKD), chronic heart failure (CHF) or cancer.[13] Recently, a standardized method has been developed to accurately quantify lumbar skeletal muscle mass in patients using CT images acquired during routine care at the level of the 3rd lumbar vertebra.[10,11] This method can be used only if needed for the underlying disease. For measurement of muscle strength the handheld dynamometer is a reliable tool for measuring strength in upper extremities.[15] This method is widely used and has been validated in many physiological and pathological conditions. Several tests of physical performance are available such

Table 1
Clinical diagnosis of sarcopenia.

Muscle mass
Anthropometry
[a]Corrected arm muscle area (CAMA): ≤21.4 cm^2 for men and ≤21.6 cm^2 for women
Bioimpedence analysis (BIA)
[b]Fat-free mass index (FFMI): ≤17 kg/m^2 for men; ≤15 kg/m^2 for women.
[c]Skeletal muscle index (SMI): <8.87 kg/m^2 for men; <6.42 kg/m^2 for women.
Computed tomography scan
[d]Lumbar skeletal muscle index (3rd lumbar vertebra): <55 cm^2/m^2 for men, <39 cm^2/m^2 for women.
Dual energy X-ray absorptiometry (DXA)
[e]Appendicular skeletal muscle index: <7.26 kg/m^2 for men; <5.45 kg/m^2 for women.
Muscle strength
Handheld dynamometer
[f]Grip strength (GS, kg) [adjusted for body mass index (BMI, kg/m^2)]: Men: BMI ≤24: GS ≤29; BMI 24.1–28: GS ≤30; BMI >28: GS ≤32. Women: BMI ≤23: GS ≤17; BMI 23.1–26: GS ≤17.3; BMI 26.1–29: GS ≤18; BMI >29: GS ≤21.
Physical performance
[f]Gait speed (4-m walk test): speed <0.8 m/s
[g]Timed Up and Go (TUG) time that a person takes to rise from a chair, walk three meters, turn around, walk back to the chair, and sit down. >10 s
[g]Short Physical Performance Battery (SPPB) (standing balance, gait speed, and chair sit-to-stand)
EWGSOP criteria
[f]It is required the presence of low muscle mass combined with low strength or physical performance, i.e., low SMI by BIA plus low grip strength or low gait speed (see above).
Strength and performance questionnaires
[h]SARC-F screen for sarcopenia (0–10 score range) (see Table 1)

[a] CAMA is calculated from triceps skinfold thickness (TSF) and mid-upper arm circumference (MUAC) as follows: $MUAC - \pi \times (TSF/10)^2)/(4 \times \pi] - i$. Where $i = 10$ for men and 6.5 for women. See Ref. 8.
[b] See Ref. 9.
[c] Skeletal muscle mass (kg) = [(height^2/BIA resistance × 0.401) + (gender × 3.825) + (age × −0.071)] + 5.102. Where height is measured in centimeters; BIA resistance is measured in ohms; for gender, men = 1 and women = 0; age is measured in years. Absolute skeletal muscle mass (kg) is converted to skeletal muscle index standardizing by meters squared (kg/m^2). See European Working Group on Sarcopenia in Older People (EWGSOP) criteria Ref. 2.
[d] See Refs. 10,11. This method can be used only if needed for the underlying disease.
[e] See Refs. 11,12.
[f] See European Working Group on Sarcopenia in Older People (EWGSOP) criteria Ref. 2.
[g] See Ref. 15.
[h] See Refs. 16,17.

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