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HUMAN SARCOPENIA FROM THE PLURALITY OF OUTCOMES TO THE UNDEFINED TITLES AND DIAGNOSIS CRITERIA

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Abstract: Besides one of the world's biggest risk factor for chronic diseases, Sarcopenia remains undernoticed. From the initial 'age-related loss in skeletal muscle', sarcopenia subsequently evolved to current operative definitions simultaneously capturing both quantitative (mass) and qualitative (strength function) declines. Further, the proposed term dynapenia (ergopenia) was to refer to the functional compromise of the entire neuromuscular apparatus. Additionally, due to the interactions of muscle with tendons, bone and neurons, the clinically relevant muscle wasting due to any illness and at any age has been named myopenia. Besides these names, sarcopenia is still a broadly clinically relevant degree of muscle wasting that is associated either with impaired functional capacity and/or with increased risk of morbidity or mortality. Sarcopenia may lead to frailty and so, it has been considered a "geriatric syndrome" termed "muscle-wasting", assembling sarcopenia, frailty, and cachexia. The Sarcopenia of cachexia syndrome connects muscle properties of generator of strength and muscle metabolic organ for protein storage, energy and glucose regulation, hormone production and other cellular mechanisms. The importance of muscle mass, strength, and metabolic function in the performance of exercise, as well as the activities of daily living, has never been questioned. Additionally, it is known that reduced muscle mass impairs the body's ability to respond to stress and chronic illness and a 10.5% reduction of the prevalence of sarcopenia could lead to a reduction of US-healthcare costs by 1.1 billion US dollars/year. This led to multidisciplinary efforts to identify, understand, prevent, and treat sarcopenia. For so, several consensus have been proposed but, despite progress, there is not yet a universally accepted clinical definition and, an unique International Classification of Diseases (10th Revision-ICD10), code for sarcopenia was assigned only in 2016. Yet, there is still much work to come to clear out remaining points in this important subject.
Keywords: Sarcopenia, concepts, definitions, diagnosis.

INTRODUCTION

Chronic diseases are the foremost cause of death globally and this prevalence continues to rise for both men and women, every ethnicity, and all age groups (ANDERSON & DURSTINE, 2019). Cardiovascular disease (CVD), type 2 diabetes (T2D), chronic lung disease, allergy, some forms of cancer, cognitive decline, osteoporosis, sarcopenia are the world's biggest killers. Based on current trends, non-communicable disease (NCDs) are expected to account for 70% of deaths worldwide (WORLD HEALTH ORGANIZATION, 2020).

The name sarcopenia is derived from Greek sarx (flesh) and penia (loss), literally meaning poverty of flesh (MORLEY, 1993). Involutional changes of the musculature were described as early as 1931 by Mac- Donald Critchley, then junior neurologist at King's College Hospital in London (CRITCHLEY, 1931) but it was at a meeting in Albuquerque, New Mexico, in 1988, that Irwin Rosenberg suggested to use the term sarcopenia (ROSENBERG, 1997). The Rosenberg's purpose of giving it a title was to strengthen the concept of loss of skeletal muscle with old age, independent of disease process, as an entity, and to stimulate scientific and clinical interest in the area (ROSENBERG, 1997).

Sarcopenia has been recognized as a key driver of limitations in physical function and mobility. In fact, from a mechanical point of view, the main function of skeletal muscle is to convert chemical energy into mechanical energy to generate force and power, maintain posture, and produce movement that influences activity, allows for participation in

social and occupational settings, maintains or enhances health, and contributes to functional independence. Therefore, skeletal muscle contributes significantly to multiple bodily functions. Skeletal muscle is vital to life as it provides the mechanical power for locomotion, posture and breathing. Mobility is required for survival and represents one of the most essential and necessary forms of physical function across all species. Maximum skeletal muscle force generating capacity, strength, is a product of the cross-sectional area of the muscle and the capacity of the nervous system to fully activate the corresponding motor neurons (AVERSA *et al.*, 2019).

Skeletal muscle's unique capacity to generate force and power is perhaps one of its most important functions. Studies that assessed changes in mass and strength in the same sample report a loss of strength 2–5 times faster than loss of mass. Loss of strength is a more consistent risk for disability and death than is loss of muscle mass (VON HAEHLING *et al.*, 2012). Then, whilst originally referred just to the loss of lean mass, it has also been used to refer to the loss of both strength and size. The United States National Institutes of Health sooner recognized this broader definition (NATIONAL INSTITUTES OF HEALTH, 2004). Therefore, from the initial definition of 'age-related loss in skeletal muscle', sarcopenia subsequently evolved to current operative definitions simultaneously capturing both quantitative (i.e., muscle mass) and qualitative (i.e., muscle strength and function) declines. For this, the term dynapenia (or ergopenia) has been proposed to refer to the functional compromise of the entire neuromuscular apparatus (CLARK & MANINI, 2008). Further on, due to the interactions of muscle with tendons, bone and neurons, the presence of clinically relevant muscle wasting due to any illness and at any age received the name of myopenia. Therefore, differently from the original gerontological approach of muscle loss of mass and function, presently, myopenia is a broadly clinically relevant degree of muscle wasting that is associated either with impaired functional capacity and/or with increased risk of morbidity or mortality.

In fact, sarcopenia may lead to frailty and, it has been suggested that sarcopenia should be considered a "geriatric syndrome" (CRUZ-JENTOFT *et al.*, 2010) under a suggested term of "muscle wasting". This would bring together the concepts of muscle wasting, sarcopenia, frailty, and cachexia (ANKER *et al.*, 2014; KIM & CHOI, 2013). Sarcopenia is one of the four main reasons for loss of muscle mass, the others being anorexia, dehydration, and cachexia. Cachexia is a well-defined nosocomial pattern known in advanced cancer, cardiac and other chronic-inflammatory diseases. However, the term sarcopenia is still prevalent, yet largely unknown among clinicians and researchers.

The cachexia syndrome involves anorexia, anemia, myofibrillar waste, decreased wound healing and hypoalbuminemia. It has pro-inflammatory cytokines and oxidative stress on its pathophysiological background. The sarcopenia found in cachexia syndrome, is an example showing that besides a generator of strength, muscle tissue is also an important organ performing protein storage, glucose regulation, hormone production and other cellular mechanisms (BUFORD *et al.*, 2010).

THE METABOLIC IMPORTANCE OF MUSCLE MASS

In humans, skeletal muscle comprises approximately 40% of total body weight and though is a robust metabolic organ, which can store, utilize, and provide vast amounts of energy. The roles of skeletal muscle include a contribution to basal energy metabolism, serving as storage for important substrates such as amino acids and carbohydrates, the production of heat for the maintenance of

core temperature, and the consumption of the majority of oxygen and fuel used during physical activity and exercise (AVERSA *et al.*, 2019). Skeletal muscle is the primary site of insulin mediated glucose disposal (~80%) and therefore it is the largest reservoir of glycogen in the human body (DEFRONZO *et al.*, 1981)total glucose metabolism rose to 6.63 ± 0.38 mg/kg · min. Basal splanchnic (hepatic venous catheter technique. Skeletal muscle contains 50–75 % of all body proteins and therefore plays a central role in whole-body protein metabolism by serving as the principal reservoir for amino acids to maintain protein synthesis in vital tissues and organs in the absence of amino acid absorption from the gut and by providing hepatic gluconeogenic precursors (WOLFE, 2006). Proteins produced by skeletal muscle that are not released into the circulation, can work via autocrine or paracrine mechanisms, exerting their effects on signaling pathways (myokines) within the muscle itself (PEDERSEN & FEBBRAIO, 2012).

IMPORTANCE OF MUSCLE MASS REDUCTION

The importance of muscle mass, strength, and metabolic function in the performance of exercise, as well as the activities of daily living (ADL), has never been questioned. Altered muscle metabolism plays a key role in the genesis, and therefore the prevention, of many common pathologic conditions and chronic disease. Skeletal muscle is a highly plastic tissue that remarkably adapts to diverse stimuli including exercise, injury and disuse. Of relevance to disease prevention and health maintenance, a reduced muscle mass impairs the body's ability to respond to stress and chronic illness (FRONTERA & OCHALA, 2015).

Collectively, the consequences of skeletal muscle loss pose substantial socioeconomic burden. Hence, strategies to promote muscle health in life promise to have beneficial effects on physical function, metabolism, and resilience, and subsequently, the independence and quality of life of individuals (AVERSA *et al.*, 2019).

Skeletal muscle is one of the most dynamic and plastic tissues of the human body. In general, muscle mass depends on the balance between protein synthesis and degradation and both processes are sensitive to factors such as nutritional status, hormonal balance, physical activity/exercise, and injury or disease, among others (MANDA & BURINI, 2010).

Skeletal muscle appears to bestow resilience to physical challenges, and the loss of muscle increases vulnerability to adverse outcomes following medical and surgical interventions. Collectively, the clinical consequences of skeletal muscle waste profoundly impact the health, independence, and quality of life of subjects and pose a significant burden on healthcare resources and health expenditures (AVERSA *et al.*, 2019).

The maintenance of adequate muscle mass, strength, and metabolic function has rarely, if ever, been targeted as a relevant endpoint of recommendations for dietary intake (WOLFE, 2006). Today, sarcopenia is a matter of immense public concern for aging prevention. Age-related sarcopenia is common and has huge personal and financial costs. It is estimated that a 10.5% reduction of the prevalence of sarcopenia could lead to a reduction of healthcare costs by 1.1 billion US dollars per year in the United States (JANSSEN *et al.*, 2004).

OPERATIONAL DEFINITIONS OF SARCOPENIA BASED ON METHODS

The most commonly used, low cost and accessible methods to assess SMI include dual energy X-ray absorptiometry (DXA),

anthropometry and bioelectrical impedance analysis (BIA). Magnetic resonance imaging (MRI), computerized tomography (CT) and creatinine excretion are the most specific standards for assessing muscle mass or cross-sectional muscle area (BURINI & MAESTÁ, 2012; ORMSBEE *et al.*, 2014).

DXA uses low-radiation X-rays of two different photon energy levels that pass through the body and are identified by a photon detector that measures the amount of energy absorbed by soft tissue and bone at each pixel. This method measures both bone and soft tissue. Soft tissue is further subdivided into fat and lean, also called lean body mass (LBM) (ILICH *et al.*, 2016).

Based on studies showing that amount of appendicular SMI (ASM) could be estimated by using the bone-free and fat-free mass of the arms and legs assessed by DXA (HEYMSFIELD *et al.*, 1990; WANG *et al.*, 1996), ASM was the first approach to develop a definition of sarcopenia with DXA (BAUMGARTNER *et al.*, 1998). Analogous to the body mass index (BMI), the ASM was divided by height squared (ASM/height2) to adjust for the strong association between body height and ASM. According to this definition, individuals presenting an ASM/height2 ratio between −1 and −2 standard deviations (SD) of the gender-specific mean value of young adults are categorized as having class I sarcopenia. Individuals with an ASM/height^2 ratio below −2 SD are categorized as having class II sarcopenia.

A second definition of Sarcopenia was developed by Janssen and colleagues (JANSSEN *et al.*, 2002) by measuring SMI (%; total SMI (kg)/weight (kg)×100) through BIA. Analogous to the osteoporosis definition, an index less than two SD from the sex-specific mean value of a young reference group was considered to indicate class II sarcopenia. An index within one to two SD from the young reference group was considered class I sarcopenia.

Although limited by the high cost and operational complexity the use of MRI and CT in clinical trials, are considered the most accurate imaging methods to assess muscle mass, muscle cross-sectional area (CSA), and muscle quality as determined by muscle density and intramuscular fat infiltration. A smaller mid-thigh muscle area measured by CT was associated with poorer lower extremity performance in well-functioning older men and women (VISSER *et al.*, 2002).

Since thigh muscle CSA showed a strong association with body weight than with body height, thigh muscle CSA was corrected by body weight (CSA/weight), as a sarcopenic index of body weight burden thigh muscle mass (OCHI *et al.*, 2010). Sarcopenia was then defined as thigh muscle CSA/ weight within 1 SD value of the CSA/weight distribution in a young reference group for both men and women (OCHI *et al.*, 2010).

THE CONTEMPORARY DEFINITION OF SARCOPENIA SYNDROME

The recognition of sarcopenia as an important clinical syndrome has led to multidisciplinary efforts to identify, understand, prevent, and treat this condition (BUCKINX *et al.*, 2018; COOPER *et al.*, 2013; REGINSTER *et al.*, 2016). Several consensus-based definitions of sarcopenia have been proposed (CRUZ-JENTOFT *et al.*, 2010, 2019; FIELDING *et al.*, 2011; MORLEY *et al.*, 2011; MUSCARITOLI *et al.*, 2010). Despite progress, there is not yet a universally accepted clinical definition; however, a unique International Classification of Diseases, 10th Revision (ICD10), code for sarcopenia was assigned in 2016 (ANKER *et al.*, 2016; VELLAS *et al.*, 2017), A global consensus on the use of the term sarcopenia has not

yet been achieved (FEARON *et al.*, 2011). The more recent definition of sarcopenia accomplished its usual accompanied physical inactivity, decreased mobility, slow gait, and poor physical endurance (CRUZ-JENTOFT *et al.*, 2019).

The European Working Group on Sarcopenia in Older People (EWGSOP, the Sarcopenia Working Group) proposed the definition based on an algorithm based on the preliminary screening of low gait speed (threshold established at ≤ 0.8 ms^{-1}) and low handgrip strength (lowest quartile of sample distribution) (CRUZ-JENTOFT *et al.*, 2010).

THE PREVALENCE OF SARCOPENIA

The heterogeneity in sarcopenia definitions has made estimates of its prevalence in older adults vary widely, ranging from 0.5 to 13% (DAM *et al.*, 2014). The European Working Group on Sarcopenia in Older People document proposed a diagnosis of sarcopenia to require "low muscle strength" accompanied by either "low muscle quantity or quality" or "low physical performance." This group suggested that when low muscle strength is detected, probably indicate sarcopenia. The diagnosis is confirmed by the presence of low muscle quantity or quality. And it is considered severe when low muscle strength, low muscle quantity/quality and low physical performance are all detected. (CRUZ-JENTOFT *et al.*, 2019).

The precise cut-points to define myopenia may be different in various diseases. Myopenia could be diagnosed when a certain degree of muscle wasting over time has occurred (for instance, at least 5% in 6–12 months) or when muscle mass is below a certain threshold level (for instance, the <5th centile of healthy 30-year-olds or a fat- free mass index <16 kg/m2 for men and <15 kg/m2 for women) (MITCHELL *et al.*, 2012).

In conclusion, a clinically more relevant approach to define sarcopenia should be based on cutoff points of muscle mass or muscle quality levels determined by expert consensus according to the risk for future health-related events, such as mortality, physical disability, or metabolic disorders.

TREATING SARCOPENIA

The prevalence and measurable impact of sarcopenia depends crucially on how sarcopenia is defined. A proper definition is the necessary base for clinical diagnosis and development of tailored treatment (KIM & CHOI, 2013).

Therefore, the ultimate goal is to assess and measure sarcopenia, thereafter identify dietary and exercise strategies, lifestyle changes and treatments that can prevent or delay the onset of sarcopenia.

REFERENCES

Anderson E, Durstine JL. **Physical activity, exercise, and chronic diseases: A brief review.** Sport Med Heal Sci. 2019 Dec;1(1):3–10.

Anker SD, Coats AJS, Morley JE, Rosano G, Bernabei R, von Haehling S, et al. **Muscle wasting disease: a proposal for a new disease classification.** J Cachexia Sarcopenia Muscle. 2014 Mar;5(1):1–3.

Anker SD, Morley JE, Haehling S. **Welcome to the ICD-10 code for sarcopenia**. J Cachexia Sarcopenia Muscle. 2016 Dec 17;7(5):512–4.

Aversa Z, Zhang X, Fielding RA, Lanza I, LeBrasseur NK. **The clinical impact and biological mechanisms of skeletal muscle aging**. Bone. 2019 Oct;127:26–36.

Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR, et al. **Epidemiology of sarcopenia among the elderly in New Mexico**. Am J Epidemiol. 1998 Apr 15;147(8):755–63.

Buckinx F, Landi F, Cesari M, Fielding RA, Visser M, Engelke K, et al. **Pitfalls in the measurement of muscle mass: a need for a reference standard.** J Cachexia Sarcopenia Muscle. 2018 Apr;9(2):269–78.

Buford TW, Anton SD, Judge AR, Marzetti E, Wohlgemuth SE, Carter CS, et al. **Models of accelerated sarcopenia: Critical pieces for solving the puzzle of age-related muscle atrophy**. Ageing Res Rev. 2010 Oct;9(4):369–83.

Burini RC, Maestá N. **The meaning of muscle mass for health, disease, and strenght exercises**. In: Handbook of Anthropometry. 2012. p. 1747–59.

Clark BC, Manini TM. **Sarcopenia =/ Dynapenia**. Journals Gerontol Ser A Biol Sci Med Sci. 2008 Aug 1;63(8):829–34.

Cooper C, Fielding R, Visser M, van Loon LJ, Rolland Y, Orwoll E, et al. **Tools in the Assessment of Sarcopenia**. Calcif Tissue Int. 2013 Sep 11;93(3):201–10.

Critchley M. The neurology of old age. Lancet. 1931 Jun;217(5625):1331–7.

Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. **Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People.** Age Ageing. 2010 Jul;39(4):412–23.

Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. **Sarcopenia: revised European consensus on definition and diagnosis**. Age Ageing. 2019;48(1):16–31.

Dam T-T, Peters KW, Fragala M, Cawthon PM, Harris TB, McLean R, et al. **An Evidence-Based Comparison of Operational Criteria for the Presence of Sarcopenia**. Journals Gerontol Ser A Biol Sci Med Sci. 2014 May 1;69(5):584–90.

DeFronzo RA, Jacot E, Jequier E, Maeder E, Wahren J, Felber JP. **The Effect of Insulin on the Disposal of Intravenous Glucose: Results from Indirect Calorimetry and Hepatic and Femoral Venous Catheterization**. Diabetes. 1981 Dec 1;30(12):1000–7.

Fearon K, Evans WJ, Anker SD. **Myopenia-a new universal term for muscle wasting**. J Cachexia Sarcopenia Muscle. 2011 Mar;2(1):1–3.

Fielding RA, Vellas B, Evans WJ, Bhasin S, Morley JE, Newman AB, et al. **Sarcopenia: An Undiagnosed Condition in Older Adults. Current Consensus Definition: Prevalence, Etiology, and Consequences. International Working Group on Sarcopenia.** J Am Med Dir Assoc. 2011 May;12(4):249–56.

Frontera WR, Ochala J. Skeletal Muscle: **A Brief Review of Structure and Function**. Calcif Tissue Int. 2015 Mar 8;96(3):183–95.

Heymsfield SB, Smith R, Aulet M, Bensen B, Lichtman S, Wang J, et al. **Appendicular skeletal muscle mass: measurement by dual-photon absorptiometry**. Am J Clin Nutr. 1990 Aug 1;52(2):214–8.

Ilich JZ, Kelly OJ, Inglis JE. **Osteosarcopenic Obesity Syndrome: What Is It and How Can It Be Identified and Diagnosed?** Curr Gerontol Geriatr Res. 2016;2016:1–7.

Janssen I, Heymsfield SB, Ross R. **Low Relative Skeletal Muscle Mass (Sarcopenia) in Older Persons Is Associated with Functional Impairment and Physical Disability.** J Am Geriatr Soc. 2002 May;50(5):889–96.

Janssen I, Shepard DS, Katzmarzyk PT, Roubenoff R. **The Healthcare Costs of Sarcopenia in the United States.** J Am Geriatr Soc. 2004 Jan;52(1):80–5.

Kim TN, Choi KM. **Sarcopenia: Definition, Epidemiology, and Pathophysiology.** J Bone Metab. 2013;20(1):1.

Manda RM, Burini RC. **Bases metabólicas da rabdomiólise e atrofia muscular.** Rev Bras Fisiol do Exerc. 2010 Jun 10;9(2):124.

Mitchell W, Atherton P, Williams J, Larvin M, Lund J, Narici M. **Sarcopenia, Dynapenia, and the Impact of Advancing Age on Human Skeletal Muscle Size and Strength: a Quantitative Review**. Front Physiol. 2012;3:260.

Morley JE, Abbatecola AM, Argiles JM, Baracos V, Bauer J, Bhasin S, et al. **Sarcopenia With Limited Mobility: An International Consensus**. J Am Med Dir Assoc. 2011 Jul;12(6):403–9.

Morley JE. **Aspects of the medical history unique to older persons**. JAMA. 1993;269(677):8.

Muscaritoli M, Anker SD, Argilés J, Aversa Z, Bauer JM, Biolo G, et al. **Consensus definition of sarcopenia, cachexia and pre-cachexia: Joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics"**. Clin Nutr. 2010 Apr;29(2):154–9.

National Institutes of Health. **Exercise: A Guide from the National Institute on Aging**. Bethesda: U.S. Department of Health and Human Services; 2004. 88 p.

Ochi M, Kohara K, Tabara Y, Kido T, Uetani E, Ochi N, et al. **Arterial stiffness is associated with low thigh muscle mass in middle-aged to elderly men**. Atherosclerosis. 2010 Sep;212(1):327–32.

Ochi M, Tabara Y, Kido T, Uetani E, Ochi N, Igase M, et al. **Quadriceps sarcopenia and visceral obesity are risk factors for postural instability in the middle-aged to elderly population**. Geriatr Gerontol Int. 2010 Feb 19;10(3):233–43.

Ormsbee MJ, Prado CM, Ilich JZ, Purcell S, Siervo M, Folsom A, et al. **Osteosarcopenic obesity: the role of bone, muscle, and fat on health**. J Cachexia Sarcopenia Muscle. 2014 Sep;5(3):183–92.

Pedersen BK, Febbraio MA. **Muscles, exercise and obesity: skeletal muscle as a secretory organ**. Nat Rev Endocrinol. 2012 Aug 3;8(8):457–65.

Reginster J-Y, Cooper C, Rizzoli R, Kanis JA, Appelboom G, Bautmans I, et al. **Recommendations for the conduct of clinical trials for drugs to treat or prevent sarcopenia**. Aging Clin Exp Res. 2016 Feb;28(1):47–58.

Rosenberg IH. **Sarcopenia: Origins and Clinical Relevance.** J Nutr. 1997 May 1;127(5):990S-991S.

Vellas B, Fielding RA, Bens C, Bernabei R, Cawthon PM, Cederholm T, et al. **Implications of ICD-10 for sarcopenia clinical practice and clinical trials: report by the international conference on frailty and sarcopenia research task force**. J Frailty Aging. 2017;1–7.

Visser M, Kritchevsky SB, Goodpaster BH, Newman AB, Nevitt M, Stamm E, et al. **Leg Muscle Mass and Composition in Relation to Lower Extremity Performance in Men and Women Aged 70 to 79: The Health, Aging and Body Composition Study**. J Am Geriatr Soc. 2002 May;50(5):897–904.

von Haehling S, Morley JE, Anker SD. **From muscle wasting to sarcopenia and myopenia: update 2012.** J Cachexia Sarcopenia Muscle. 2012 Dec;3(4):213–7.

Wang ZM, Visser M, Ma R, Baumgartner RN, Kotler D, Gallagher D, et al. **Skeletal muscle mass: evaluation of neutron activation and dual-energy X-ray absorptiometry methods**. J Appl Physiol. 1996 Mar 1;80(3):824–31.

Wolfe RR. **The underappreciated role of muscle in health and disease**. Am J Clin Nutr. 2006 Sep;84(3):475–82.

World Health Organization. **Noncommunicable diseases progress monitor 2020**. Geneva; 2020.