EDITORIAL

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Treatment of sarcopenia: the road to the future

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This year, two new consensus conferences on the diagnosis and management of sarcopenia have been published.[1,2] Both confirm the need to screen for sarcopenia in older persons. Suggested screening approaches are the SARC-F,[3,4] the Ishii screening test,[5,6] or grip strength. It should be recognized that grip strength was suggested for screening by one consensus group[1] and as part of the diagnosis by the other.[2] Measuring mid-calf muscle circumference improves the sensitivity and specificity of the SARC-F when it is compared with the consensus definitions.[7–9]

A number of consensus definitions for sarcopenia have been developed.[2,11–13] All require either functional impairment (slow walking speed) or grip strength together with a low muscle mass. While the persons diagnosed by any of these definitions overlap, they all have different sensitivity and specificity when compared with one another or functional outcomes due to the different cut-off points.[14,15] The Asian Group made it clear that cut-offs are very different for persons with Asian ethnicity compared with Europeans.[13] [These definitions have led to the International Classification of Disease (10th edition) to recognize sarcopenia as an independent condition (M62.84)].[16,17]

There are a number of different methods available to measure lean body mass including air displacement plethysmography, bioelectrical impedance analyses, dual-energy X-ray absorptiometry, and ultrasound.[18–21] Each of these methods has been demonstrated to have problems in accurately determining muscle mass.[22] Recently, D_3-creatine dilution has been demonstrated to be more accurate in measuring muscle mass[23] and more strongly related to physical performance.[22]

While age-related sarcopenia is considered to be primary sarcopenia, a number of disease states, for example, diabetes mellitus,[24,25] male hypogonadism,[26,27] and chronic obstructive pulmonary disease[28] can produce secondary sarcopenia. Cachexia is a complex metabolism disorder leading to anorexia, muscle wasting, and loss of fat.[29] The Glasgow Prognostic Score (low serum albumin and elevated C-reactive protein) can be used to distinguish secondary sarcopenia from cachexia.[30]

The advent of patient-centred (P4) care has increased attention to the fact that different molecular changes can result in the need to have different therapeutic approaches to similar conditions such as sarcopenia[31,32] (Table 1). In this issue of the journal, Riuzzi *et al.*[33] highlight that sarcopenia can result from a variety of molecular changes resulting in changes in myofibre metabolism and alterations in satellite cell properties. Abnormalities in these pathways can be due to insulin growth factor-1/insulin receptors, activin (myostatin) receptors, tropomysin receptor, kinase C receptors (neurotrophin and G-protein receptors), a variety of cytokines, and testosterone through activation of β-catenin.[34–38] Thus, in the long run, the ideal treatment of sarcopenia will involve identification of the aberrant molecular pathway and the possible hormone causing this imbalance.

At present, the treatment of sarcopenia is focused on resistance exercise.[1] The use of leucine essential amino acids and/or β-hydroxybutyrate has not been clearly established but would seem a reasonable adjunct in persons with low protein intake.[39–45] Drugs that have potential to treat sarcopenia include testosterone and anabolic steroids,[46–48] myostatin antibodies,[49,50] activin receptor antibodies,[51] and the ghrelin agonist, anamorelin.[52] There is also interest in the role of beta-blockade,[53] some angiotensin-converting enzyme inhibitors,[54] and sarconeos, which activates the MAS (angiotensin-1) receptor.[55] A recent study suggested that metformin may improve mobility in persons with diabetes mellitus.[56] Still highly experimental but likely to play a role in the future management of sarcopenia are CRISPR techniques[57] and possibly stem cell therapy.[58]

Table 1 Patient-centred approach to management of sarcopenia

Early identification	Primary prevention	Secondary prevention	Tertiary prevention
SARC-F or ISHII screening test	Exercise	Resistance exercise	Physical therapy
	Adequate protein diet	Low-protein diet: leucine-enriched essential amino acids or methyl hydroxy butyrate supplementation	Occupational therapy
	In ALL hospitalized: aggressive resistance exercise (include intensive care unit)	Male hypogonadism: testosterone	If dysphagia: speech therapy
		If falling: use CDC STEADI or F3ALLS approach	Provide adequate protein intake
		If low 25(OH) vitamin D—1000 IU vitamin D	Optimal treatment of COPD; CHF and diabetes mellitus Exclude cachexia: elevated CRP + low protein Exclude protein energy malnutrition (anorexia or malabsorption) -Look for treatable causes -Caloric supplement -Future: anamorelin Future: antibodies to myostatin

Sarcopenia is a major cause of physical frailty[59–61] and falls[62,63] in older persons. As at present, there is a simple therapy—aggressive resistance exercise—when sarcopenia is detected early, it seems reasonable to screen older persons and those with diabetes for sarcopenia and frailty using the Rapid Geriatric Assessment tool[64–67] and begin secondary prevention as early as possible. The SarQOL can be utilized to measure an improvement of health-related quality of life in these persons.[68] A recent study demonstrated that an intense level of physical exercise in hospital patients can prevent the muscle and functional loss that occurs in hospitalized patients.[69]

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Conflict of interest

None declared.

References

1. Dent E, Morley JE, Cruz-Jentoft AJ, et al. International clinical practice guidelines for sarcopenia (ICFSR): screening, diagnosis and management. *J Nutr Health Aging* 2018; Epub ahead of print.
2. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing* 2018. Oct 12; https://doi.org/10.1093/ageing/afy169 [Epub ahead of print].
3. Malmstrom TK, Miller DK, Simonsick EM, et al. SARC-F: a symptom score to predict persons with sarcopenia at risk for poor functional outcomes. *J Cachexia Sarcopenia Muscle* 2016;**7**:28–36.
4. Tanaka S, Kamiya K, Hamazaki N, et al. Utility of SARC-F for assessing physical function in elderly patients with cardiovascular disease. *J Am Med Dir Assoc* 2017; **18**:176–181.
5. Locquet M, Beaudart C, Reginster JY, et al. Comparison of the performance of five screening methods for sarcopenia. *Clin Epidemiol* 2017;**10**:71–82.
6. Ishii S, Tanaka T, Shibasaki K, et al. Development of a simple screening test for sarcopenia in older adults. *Geriatr Gerontol Int* 2014;**14**(Suppl:93–101.
7. Yang M, Hu X, Xie L, et al. Screening sarcopenia in community-dwelling older adults: SARC-F vs SARC-F combined with calf circumference (SARC-CalF). *J Am Med Dir Assoc* 2018;**19**:277.e1–277.e8.
8. Barbosa-Silva TG, Menezes AM, Bielemann RM, et al. Enhancing SARC-F: improving sarcopenia screening in the clinical practice. *J Am Med Dir Assoc* 2016;**17**:1136–1141.
9. Bahat G, Oren MM, Yilmaz O, et al. Comparing SARC-F with SARC-CalF to screen sarcopenia in community living older adults. *J Nutr Health Aging* 2018;**22**: 1034–1038.
10. Morley JE, Abbatecola AM, Argiles JM, et al. Sarcopenia with limited mobility: an international consensus. *J Am Med Dir Assoc* 2011;**12**:403–409.
11. Fielding RA, Vellas B, Evans WJ, *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;**12**: 249–256.
12. Dam TT, Peters KW, Fragala M, et al. An evidence-based comparison of operational criteria for the presence of sarcopenia. *J Gerontol A Biol Sci Med Sci* 2014;**69**: 584–590.
13. Chen LK, Liu LK, Woo J, et al. Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. *J Am Med Dir Assoc* 2014;**15**:95–101.
14. Woo J, Leung J, Morley JE. Validating the SARC-F: a suitable community screening tool for sarcopenia? *J Am Med Dir Assoc* 2014;**15**:630–634.

15. Katlarczyk MP, Perera S, Nace DA, et al. Identifying sarcopenia in female long-term care residents: a comparison of current guidelines. *J Am Geriatr Soc* 2018;**66**: 316–320.
16. Cao L, Morley JE. Sarcopenia is recognized as an independent condition by an International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10-CM) Code. *J Am Med Dir Assoc* 2016;**17**:675–677.
17. Anker SD, Morley JE, von Haehling S. Welcome to the ICD-10 code for sarcopenia. *J Cachexia Sarcopenia Muscle* 2016;**7**:512–514.
18. Heymsfield SB, Adamek M, Gonzalez MC, et al. Assessing skeletal muscle mass: historical overview and state of the art. *J Cachexia Sarcopenia Muscle* 2014; **5**:9–18.
19. Scafoglieri A, Clarys JP. Dual energy X-ray absorptiometry: gold standard for muscle mass? *J Cachexia Sarcopenia Muscle* 2018;**9**:786–787.
20. Paris MT, Lafleur B, Dubin JA, Mourtzakis M. Development of a bedside viable ultrasound protocol to quantify appendicular lean tissue mass. *J Cachexia Sarcopenia Muscle* 2017;**8**:713–726.
21. Abe T, Thiebaud RS, Loenneke JP, et al. DXA-rectified appendicular lean mass: development of ultrasound prediction models in older adults. *J Nutr Health Aging* 2018;**22**:1080–1085.
22. Shankaran M, Czerwieniec G, Fessler C, et al. Dilution of oral D_3-creatine to measure creatine pool size and estimate skeletal muscle mass: development of a correction algorithm. *J Cachexia Sarcopenia Muscle* 2018 Jun;**9**:540–546.
23. Clark RV, Walker AC, O'Connor-Semmes RL, et al. Total body skeletal muscle mass: estimation by creatine (methyl-d_3) dilution in humans. *J Appl Physiol (1985)* 2014; **116**:1605–1613.
24. Morley JE, Malmstrom TK, Rodriguez-Mañas SAJ. Frailty, sarcopenia and diabetes. *J Am Med Dir Assoc* 2014;**15**:853–859.
25. Liccini A, Malmstrom TK. Frailty and sarcopenia as predictors of adverse health outcomes in persons with diabetes mellitus. *J Am Med Dir Assoc* 2016;**17**: 846–851.
26. Shin MJ, Jeon YK, Kim IJ. Testosterone and sarcopenia. *World J Mens Health* 2018; **36**:192–198.
27. Morley JE. Should frailty be treated with testosterone? *Aging Male* 2011;**14**:1–3.
28. Van de Bool C, Rutten EPA, van Helvoort A, et al. A randomized clinical trial investigating the efficacy of targeted nutrition as adjunct to exercise training in COPD. *J Cachexia Sarcopenia Muscle* 2017;**8**: 748–758.
29. Argiles JM, Anker SD, Evans WJ, et al. Consensus on cachexia definitions. *J Am Med Dir Assoc* 2010;**11**:229–230.
30. Douglas E, McMillan DC. Towards a simple objective framework for the investigation and treatment of cancer cachexia: the Glasgow Prognostic Score. *Cancer Treat Rev* 2014;**40**:685–691.
31. Morley JE, Anker SD. Myopenia and precision (P4) medicine. *J Cachexia Sarcopenia Muscle* 2017;**8**:857–863.
32. Morley JE, Bauer J. The future of sarcopenia. *Curr Opin Clin Nutr Metab Care* 2018; Nov 13; https://doi.org/10.1097/MCO.0000000000000531. [Epub ahead of print].
33. Ruizzi F, Sorci G, Arcuri C, et al. Cellular and molecular mechanisms of sarcopenia: the S100B perspective. *J Cachexia Sarcopenia Muscle* 2018; https://doi.org/10.1002/jcsm.12363 publ. online in Wiley online library (wileyonlinelibrary.com).
34. Haren MT, Siddiqui AM, Armbrecht HJ, et al. Testosterone modulates gene expression pathways regulating nutrient accumulation, glucose metabolism and protein turnover in mouse skeletal muscle. *Int J Androl* 2011;**34**:55–68.
35. Elkina Y, von Haehling S, Anker SD, Springer J. The role of myostatin in muscle wasting: an overview. *J Cachexia Sarcopenia Muscle* 2011;**2**:143–151.
36. McKee A, Morley JE, Matsumoto AM, Vinik A. Sarcopenia: an endocrine disorder? Endocr Pract 2017;**23**:1140–1149.
37. Morley JE. Hormones and sarcopenia. *Curr Pharm Des* 2017;**23**:4484–4492.
38. Ebhardt HA, Degen S, Tadini V, et al. Comprehensive proteome analysis of human skeletal muscle in cachexia and sarcopenia: a pilot study. *J Cachexia Sarcopenia Muscle* 2017;**8**:567–582.
39. Tieland M, Franssen R, Dullemeijer C, et al. The impact of dietary protein or amino acid supplementation on muscle mass and strength in elderly people: individual participant data and meta-analysis of RCT's. *J Nutr Health Aging* 2017;**21**: 994–1001.
40. Fielding RA, Travison TG, Kim DR, et al. Effect of structured physical activity and nutritional supplementation on physical function in mobility-limited older adults: results from the VIVE2 randomized trial. *J Nutr Health Aging* 2017;**21**:936–942.
41. Bauer JM, Verlaan S, Bautmans I, et al. Effects of a vitamin D and leucine-enriched whey protein nutritional supplement on measures of sarcopenia in older adults, the PROVIDE study: a randomized, double-blind, placebo-controlled trials. *J Am Med Dir Assoc* 2015; **16**:740–747.
42. Bauer J, Biolo G, Cederholm T, et al. Evidence-based recommendations for optimal dietary protein intake in older people: a position paper from the PROT-AGE Study Group. *J Am Med Dir Assoc* 2013;**14**:542–559.
43. Sanz-Paris C-RM, Lopez-Pedrosa JM, et al. Role of oral nutritional supplements enriched with β-hydroxy-β-methylbutyrate in maintaining muscle function and improving clinical outcomes in various clinical settings. *J Nutr Health Aging* 2018;**22**: 664–675.
44. Osuka Y, Fujita S, Kitano N, et al. Effects of aerobic and resistance training combined with fortified milk on muscle mass, muscle strength, and physical performance in older adults: a randomized controlled trial. *J Nutr Health Aging* 2017;**21**:1349–1357.
45. Cederholm T, Morley JE. Nutrient interface with biology and aging. *Curr Opin Clin Nutr Metab Care* 2016 Jan;**19**:1–4.
46. Rolland Y, Onder G, Morley JE, et al. Current and future pharmacologic treatment of sarcopenia. *Clin Geriatr Med* 2011; **27**:423–447.
47. Storer TW, Basaria S, Traustadottir T, et al. Effects of testosterone supplementation for 3 years on muscle performance and physical function in older men. *J Clin Endocrinol Metab* 2017;**102**:583–593.
48. Bassil N, Morley JE. Late-life onset hypogonadism: a review. *Clin Geriatr Med* 2010;**26**:197–222.
49. Becker C, Lord SR, Studenski SA, et al. STEADY GroupMyostatin antibody (LY2495655) in older weak fallers: a proof-of-concept, randomized, phase 2 trial. *Lancet Diabetes Endocrinol* 2015;**3**: 948–957.
50. Morley JE. Pharmacologic options for the treatment of sarcopenia. *Calcif Tissue Int* 2016;**98**:319–333.
51. Rooks DS, Laurent D, Praestgaard J, et al. Effect of bimagrumab on thigh muscle volume and composition in men with casting-induced atrophy. *J Cachexia Sarcopenia Muscle* 2017;**8**:727–734.
52. Anker SD, Coats AJ, Morley JE. Evidence for partial pharmaceutical reversal of the cancer anorexia–cachexia syndrome: the case of anamorelin. *J Cachexia Sarcopenia Muscle* 2015;**6**:275–277.
53. Clark AL, Coats AJS, Krum H, et al. Effect of beta-adrenergic blockade with carvedilol on cachexia in severe chronic heart failure: results from the COPERNICUS trial. *J Cachexia Sarcopenia Muscle* 2017; **8**:549–556.
54. Sumukadas D, Witham MD, Struthers AD, McMurdo ME. Effect of perindopril on physical function in elderly people with functional impairment: a randomized controlled trial. *CMAJ* 2007;**177**: 867–874.
55. Cabello-Verrugio C, Rivera JC, Garcia D. Skeletal muscle wasting: new role of non-classical renin–angiotensin system. *Curr Opin Clin Nutr Metab Care* 2017;**20**: 158–163.
56. Bassez G, Audureau E, Hogrel JY, et al. Improved mobility with metformin in patients with myotonic dystrophy type 1: a randomized controlled trial. *Brain* 2018;**141**: 2855–2865.
57. Wei Y, Chen Y, Qiu Y, et al. Prevention of muscle wasting by CRISPR/Cas9-mediated disruption of myostatin in vivo. *Mol Ther* 2016;**24**:1889–1891.
58. Tompkins BA, DiFede DL, Khan A, et al. Allogeneic mesenchymal stem cells ameliorate aging frailty: a phase II randomized, double-blind, placebo-controlled clinical trial. *J Gerontol A Biol Sci Med Sci* 2017; **72**:1513–1522.
59. Morley JE. Frailty and sarcopenia: the new geriatric giants. *Rev Invest Clin* 2016;**68**:59–67.

60. Dent E, Lien C, Lim WS, et al. The Asia-Pacific clinical practice guidelines for the management of frailty. *J Am Med Dir Assoc* 2017;**18**:564–575.
61. Morley JE, von Haehling S, Anker SD, Vellas B. From sarcopenia to frailty: a road less traveled. *J Cachexia Sarcopenia Muscle* 2014;**5**:5–8.
62. Morley JE. F3ALLS approach to preventing falls. *J Nutr Health Aging* 2018;**22**:748–750.
63. Balogun S, Winzenberg T, Wills K, et al. Prospective associations of low muscle mass and function with 10-year falls risk, incident fracture and mortality in community-dwelling older adults. *J Nutr Health Aging* 2017;**21**:843–848.
64. De Souza OF, Brochine Lanzotti R, Gomes Duarte J, et al. Translation, adaptation and validation of rapid geriatric assessment to the Brazilian context. *J Nutr Health Aging* 2018;**22**:1115–1121.
65. Morley JE, Little MO, Berg-Weger M. Rapid geriatric assessment: a tool for primary care physicians. *J Am Med Dir Assoc* 2017;**18**:195–199.
66. Morley JE, Adams EV. Rapid geriatric assessment. *J Am Med Dir Assoc* 2015; **16**:808–812.
67. Morley JE. Rapid geriatric assessment: secondary prevention to stop age-associated disability. *Clin Geriatr Med* 2017;**33**: 431–440.
68. Beaudart C, Biver E, Reginster JY, et al. Validation of the SarQoL®, a specific health-related quality of life questionnaire for sarcopenia. *J Cachexia Sarcopenia Muscle* 2017;**8**:238–244.
69. Martinez-Velilla N, Casas-Herrero A, Zambom-Ferraresi F, et al. Effect of exercise intervention on functional decline in very elderly patients during acute hospitalization: a randomized clinical trial. *JAMA Intern Med* 2018;Nov 12; https://doi.org/10.1001/jamainternmed.2018.4869. [Epub ahead of print].
70. von Haehling S, Morley JE, Coats AJS, Anker SD. Ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2017. *J Cachexia Sarcopenia Muscle* 2017;**8**: 1081–1083.