Nutrition in the spotlight in cachexia, sarcopenia and muscle: avoiding the wildfire

Carla M. Prado1*, Stefan D. Anker2,3,4, Andrew J.S. Coats5,6, Alessandro Laviano7 & Stephan von Haehling8,9

1Human Nutrition Research Unit, Department of Agricultural, Food and Nutritional Science, University of Alberta, Edmonton, AB, Canada, 2BKH Centre for Regenerative Therapies, Charité Universitätsmedizin Berlin, Berlin, Germany, 3Department of Cardiology (Campus Virchow-Klinikum), Charité Universitätsmedizin Berlin, Berlin, Germany, 4German Centre for Cardiovascular Research (DZHK), partner site Berlin, Berlin, Germany, 5Monash University, Melbourne, Australia, 6University of Warwick (UK), Warwick, UK, 7Department of Translational and Precision Medicine, Sapienza University, Rome, Italy, 8Department of Cardiology and Pneumology, University Medicine Goettingen, Goettingen, Germany, 9German Centre for Cardiovascular Research (DZHK), partner site Göttingen, Göttingen, Germany

Keywords Nutrition; Sarcopenia; Cachexia; Muscle; Muscle loss; Nutrition intervention; Supplements

*Correspondence to: Professor Carla Prado, 2-021 Li Ka Shing Centre for Health Research Innovation, University of Alberta, Edmonton, AB, Canada T6G 2E1. Tel: 780.492.9734, Fax: 780.492.9555. Email: Carla.prado@ualberta.ca

The pathophysiology of muscle loss alone or in the context of malnutrition, sarcopenia, or cachexia is multifactorial: hormonal, neurological, inflammatory, functional/mobility, age-related, disease-specific, treatment-related, and others. Nutrition is a key factor because both quality and quantity of nutrients are essential to support muscle anabolism, lessen catabolism, and improve prognosis. This is true even in the context of cachexia. Nutrition alone cannot reverse cachexia but can prevent or minimize further loss, alleviate symptoms, and improve quality of life and outcomes in general.

It is surprising that we know little about the specific nutrient needs of people with cachexia, sarcopenia, or other diseases of muscle loss. Nutrition-related guidelines in several such diseases are based mostly on expert consensus, rarely on clinical trial evidence. There is a fundamental need to understand the optimal macronutrient and micronutrient ‘mix’ that is advised for or offered to people with these conditions.

Likewise, we know little about the synergistic or additive roles of ‘muscle-building nutrients’ (Figure 1) to sustain muscle mass in muscle loss diseases. The same is true in the more neglected scenario of paediatric nutrition, where low muscle mass is emerging as an important problem with little past or ongoing research to inform clinical practice. This lack of targeted nutrient recommendations may also impact the optimal use of nutrition strategies within multimodal interventions, which are recognised as ideal for multifactorial conditions.

Nutrition research related to muscle loss, sarcopenia, and cachexia has been chronically underfunded, leaving many gaps and opportunities (Figure 2). We urge funding agencies and industry to support research to bridge and fill these gaps. We also urge researchers to include measures of nutritional status as an essential variable to be accounted for and optimised in their studies. For example, pharmacological trials should assess, control, and ideally optimize nutritional status to maximize each participant’s anabolic potential. The same is true for exercise intervention studies, where nutritional requirements will likely be impacted by changes in body weight and composition. Ultimately, anabolic treatments and interventions may fail if nutrition remains inadequate.

Avoiding the wildfire

A key to nutrition intervention is early and continuing intervention. Muscle loss is a defining feature of sarcopenia and cachexia, and muscle is lost rapidly in chronic and acute conditions, especially in cachexia. Conversely, muscle takes much longer to rebuild. The situation is similar to a wildfire followed by reforestation (Figure 3). Early intervention is essential, because preserving is better than rebuilding. From the nutritional perspective, interventions can use food, oral nutritional supplements, —enteral or parenteral nutrition as appropriate. Nutrition can also be maximised in multimodal interventions. Importantly, continuing intervention must address the changing metabolic needs of each person.

Patient education is also fundamental. An important barrier to behavioural change is that patients often do not recognize nutrition as a therapy. Animated videos,
Figure 1  Selected nutritional approaches under consideration for treating muscle loss. AA, amino acids; HMB, β-hydroxy-β-methylbutyrate; EPA, eicosapentaenoic acid. Adapted from Prado et al.6 Concepts to be adapted to the clinical needs of patients.

Figure 2  Checklist of selected gaps and opportunities around the role of nutrition in catabolic conditions.
educational materials such as infographics, and other patient-oriented resources (e.g. Figure 3) can be instrumental in educating patients about nutrition-based therapies.\textsuperscript{23,24} Selected examples can be watched online (at https://www.youtube.com/watch?v=pDSX_jaDCDM and https://www.youtube.com/watch?v=CAC2g03_-2Y).

**Figure 3** Graphic illustration of the need for early and continuing nutrition interventions for prevention and treatment of muscle loss to be used in knowledge translation and patient education materials. Muscle loss is a defining feature of sarcopenia and cachexia. (A) Muscle is lost rapidly, like a wildfire. Rebuilding muscle takes much longer than losing muscle, like reforestation. Summarised in (B): Long-term interventions are needed to support the anabolic period (post wildfire). *Months in calendar are random.*
Taking a stand: *Journal of Cachexia, Sarcopenia and Muscle* nutrition publications

We conducted a manual search of published Journal of Cachexia, Sarcopenia and Muscle (JCSM) issues from 2018, 2019, and 2020 (including ‘early view’ up to 12 December 2020) to identify human or animal studies on nutrition in sarcopenia or cachexia. We selected articles investigating nutrition interventions, macronutrient intake below recommended, and micronutrient deficiency. We found 26 articles: 10 clinical trials, three cross-sectional studies, three experimental animal studies (one of which also included a human cross-sectional analysis), three narrative reviews, two retrospective studies, two systematic reviews or meta-analyses, and one questionnaire survey. Within the 320 original and review articles published in 2018, 2019, and 2020 in JCSM, the 26 articles on nutrition that we found comprise approximately 8%.

Of the nutrition studies that we found, one explored the role of protein, three explored the role of vitamin D, two explored the role of several nutrients, and one explored the role of natural product (astaxanthin) supplements. Seven studies investigated the effects of multimodal interventions (defined as two or more approaches) on muscle mass. Articles also explored the associations of protein intake, iron deficiency, micronutrients, calorie restriction, nitrate dietary intake, retrospective evaluation of early dietary supplementation, and overall dietary intake and patterns with several clinical outcomes and/or biomarkers of sarcopenia or cachexia. Two studies evaluated the perceptions of oncology patients regarding disease-related nutritional issues and barriers to effective nutritional interventions. One narrative review discussed potential nutrition interventions to augment muscle mass.

Call for papers

Acknowledging the role of nutrition to counter cachexia, sarcopenia, and other muscle loss diseases, and the small number of publications in the topic, JCSM is launching a call for papers on the role of nutrition in preventing and treating cachexia, sarcopenia, or other muscle loss diseases. We welcome high-quality papers of all types, but particularly original articles that explore the role of nutrition in preventing and treating these conditions.

Acknowledgements

The authors of this manuscript certify that they comply with the ethical guidelines for editorship and publishing in the *Journal of Cachexia, Sarcopenia and Muscle*. We thank Camila Orso for her assistance.

Conflict of interest

C.M.P. reports receiving honoraria and/or paid consultancy from Abbott Nutrition, Nutricia, Nestle Health Science, Fresenius Kabi, Pfizer, and Helsinn.

S.D.A. reports grants from Vifor Int and Abbott and personal fees from Vifor, Bayer, Boehringer Ingelheim, Novartis, Servier, Abbott, Actimed, Cardiac Dimensions, and Impulse Dynamics, all outside the submitted work.

A.J.C. has received personal fees from Astra Zeneca, Bayer, Boehringer Ingelheim, Menarini, Novartis, Nutricia, Servier, Vifor, Abbott, Actimed, Arena, Cardiac Dimensions, Corvia, CVRx, Enopace, ESN Cleer, Faraday, W.L Gore, Impulse Dynamics, and Respiscardia, all outside the submitted work.

A.L. reports receiving consulting fees for honoraria for lectures at industry-sponsored events; consulting fees from Abbott, Baxter, BBraun, Fresenius Kabi, NestleHealth Science, Nutricia, and Smartfish; and research grant from Fresenius Kabi.

S.v.H. has been a paid consultant for and/or received honoraria payments from AstraZeneca, Bayer, Boehringer Ingelheim, BRAHMS, Chugai, Grünenthal, Helsinn, Hexal, Novartis, Respiscardia, Roche, Sorin, and Vifor. S.v.H. reports research support from Amgen, AstraZeneca, Boehringer Ingelheim, IMI, and the German Center for Cardiovascular Research (DZHK).

References

1. Bauer J, Morley JE, Schols AMWJ, Ferrucci L, Cruz-Jentoft AJ, Dent E, et al. Sarcopenia: a time for action. An SCWD Position Paper J Cach Sarc Muscle 2019;10:956–961.
2. Peixoto da Silva S, Santos JMO, Costa ESMP, Gil da Costa RM, Medeiros R. Cancer cachexia and its pathophysiology: links with sarcopenia, anorexia and asthenia. J Cach Sarc Muscle 2020;11:619–635.
3. Calder PC, Laviano A, Lonnqvist F, Muscarioli M, Öhlander M, Schols A. Targeted medical nutrition for cachexia in chronic obstructive pulmonary disease: a randomized, controlled trial. J Cachexia, Sarc and Mu 2018;9:28–40.
4. Cereda E, Turri A, Klersy C, Cappello S, Ferrari A, Filippi AR, et al. Whey protein isolate supplementation improves body composition, muscle strength, and treatment tolerance in malnourished...
advanced cancer patients undergoing chemotherapy. *Cancer Med* 2019;8:6923-32:6923–6932.
5. Deutz NEP, Ashurst I, Ballesteros MD, Bear DE, Cruz-Jentoft AJ, Genton L, et al. The underappreciated role of low muscle mass in the management of malnutrition. *J Am Med Dir Assoc* 2019;20:22–27.
6. Prado CM, Purcell SA, Laviano A. Nutrition interventions to treat low muscle mass in cancer. *J Cachexia Sarcopenia Muscle* 2020;11:366–380.
7. Rassavas P, Monteiro-Grillo I, Vidal PM, Camilo ME. Dietary counseling improves outcomes: a prospective, randomized, controlled trial in colorectal cancer patients undergoing radiotherapy. *J Clin Oncol Off J Am Soc Clin Oncol* 2005;23:1431–B:1431–1438.
8. Schols AM, Ferreira IM, Franssen FM, Gokser HR, Janssens W, Muscaritoli M, et al. Nutritional assessment and therapy in COPD: a European Respiratory Society perspective. *Eur Respir J* 2014;44:1504-20:1504–1520.
9. Tan S, Meng G, Jiang Y, Zhuang Q, Xi Q, Xu J, et al. Nutritional interventions in post-discharge patients at nutritional risk following colorectal surgery: a randomised clinical trial. *Clin Nutr* 2020; https://doi.org/10.1016/j.clinu.2020.05.038.
10. Ukovic B, Porter J. Nutrition interventions to improve the appetite of adults undergoing cancer treatment: a systematic review. *Support Care Cancer* 2020;28:4575-83:4575–4583.
11. Fearon K, Strasser F, Anker SD, Bosaueis I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol* 2011;12:489–495.
12. Roeland EJ, Bohlke K, Baracos VE, Bruera E, Fabbro ED, Dixon S, et al. Management of cancer cachexia: ASCO guideline. *J Clin Oncol* 2020;38:2438-53:2438–2453.
13. Oei PH, Thompson-Hodggets S, Pritchard-Jones K, Blauwhoff-Buskermolen S, Versteeg KS, van der Valk B, et al. Low muscle mass, fat-free body mass, and prognosis in patients with chronic obstructive pulmonary disease from a random population sample: findings from the Copenhagen City Heart Study. *Am J Respir Crit Care Med* 2006;173:79–83.
14. Parry SM, Puthucheary ZA. The impact of extended bed rest on the musculoskeletal system in the critical care environment. *Ext Phys Med* 2015;14:16:416.
15. Dirks ML, Wall BT, van de Valk B, Holloway TM, Holloway GP, Chabowski A, et al. One week of bed rest leads to substantial muscle atrophy and induces whole-body insulin resistance in the absence of skeletal muscle lipid accumulation. *Diabetes* 2016;65:2862-75:2862–2875.
16. Beelen J, Vanse E, Ziyalan C, Janssen N, de Roos NM, de Groot LCPGM. Undernutrition: who cares? Perspectives of dietitians and older adults on undernutrition. *BMC Nutrition* 2017;3:24:3:24.
17. Craven DL, Lovell GP, Pelly FE, Isenring E. Community-living older adults’ perceptions of body weight, signs and sources of information: a descriptive analysis of survey data. *J Nutr Health Aging* 2018;22:393–399.
18. Gyan E, Raynard B, Durand JP, Lacau Saint, Debray J, et al. Low muscle mass, fat-free body mass, and prognosis in patients with type 2 diabetes mellitus. *J Cachexia Sarcopenia Muscle* 2019;10:721–733.
19. Dirks ML, Wall BT, van de Valk B, Holloway TM, Holloway GP, Chabowski A, et al. One week of bed rest leads to substantial muscle atrophy and induces whole-body insulin resistance in the absence of skeletal muscle lipid accumulation. *Diabetes* 2016;65:2862-75:2862–2875.
20. Beelen J, Vanse E, Ziyalan C, Janssen N, de Roos NM, de Groot LCPGM. Undernutrition: who cares? Perspectives of dietitians and older adults on undernutrition. *BMC Nutrition* 2017;3:24:3:24.
21. Craven DL, Lovell GP, Pelly FE, Isenring E. Community-living older adults’ perceptions of body weight, signs and sources of information: a descriptive analysis of survey data. *J Nutr Health Aging* 2018;22:393–399.
22. Gyan E, Raynard B, Durand JP, Lacau Saint, Debray J, et al. Low muscle mass, fat-free body mass, and prognosis in patients with type 2 diabetes mellitus. *J Cachexia Sarcopenia Muscle* 2019;10:721–733.
23. ten Haaf DSM, Eijssengels TMH, Bongers CCWG, Horstman AMH, Timmers S, de Groot LCPGM, et al. Protein supplementation improves lean body mass in physically active older adults: a randomized placebo-controlled trial. *J Cachexia Sarcopenia Muscle* 2019;10:298–310.
24. van den Holder J, Mehra S, van Dronkelaar C, ter Riet G, Tieland M, Visser B, et al. Blended home-based exercise and dietary protein in community-dwelling older adults: a cluster randomized controlled trial. *Journal of Cachexia, Sarcopenia and Muscle*. n/a;doi:https://doi.org/10.1002/jcsm.12634.
25. Watanabe Y, Yamada Y, Yoshida T, Yokoyama K, Miyake M, Yamagata E, et al. Comprehensive geriatric intervention in community-dwelling older adults: a cluster randomized controlled trial. *J Cachexia Sarcopenia Muscle* 2020;11:26–37.
26. Abete I, Konieczna J, Zulet MA, Galmés-Parades AM, Ibero-Baraibar I, Babio N, et al. Association of lifestyle factors and inflammation with sarcopenic obesity: data from the PREDIMED-Plus trial. *J Cachexia Sarcopenia Muscle* 2019;10:974–984.
27. Kochlik B, Stuetz W, Péres K, Pilleron S, Féart C, Garcia Garcia FJ, et al. Associations of fat-soluble micronutrients and redox biomarkers with frailty status in the FANCLOMIC initiative. *J Cachexia Sarcopenia Muscle* 2019;10:1339–1346.
28. Sim M, Lewis JR, Blekkenhorst LC, Bondonno CP, Devine A, Zhu K, et al. Dietary nitrate intake is associated with muscle function in older women. *J Cachexia Sarcopenia Muscle* 2019;10:601–610.
29. Tkaczyzyn M, Drozd M, Węgrzynowska-Teodorczyk K, Flinta I, Kobak K, Banasiak W, et al. Depleted iron stores are associated with inspiratory muscle weakness independently of skeletal muscle mass in men with systolic chronic heart failure. *J Cachexia Sarcopenia Muscle* 2018;9:547–556.
30. Yang A, Lv Q, Chen F, Wang Y, Liu Y, Shi W, et al. The effect of vitamin D on sarcopenia depends on the level of physical activity in older adults. *J Cachexia Sarcopenia Muscle* 2018;9:679–689.
31. Cheung WW, Hao S, Wang Z, Ding W, Zheng R, Gonzalez A, et al. Vitamin D repletion ameliorates adipose tissue browning and muscle wasting in infantile nephropathic cystinosis-associated cachexia. *J Cachexia, Sarcopenia and Muscle* 2021;12:3–8. DOI: 10.1002/jcsm.12673
40. Nishida Y, Nawaz A, Kado T, Takikawa A, Igarashi Y, Onogi Y, et al. Astaxanthin stimulates mitochondrial biogenesis in insulin resistant muscle via activation of AMPK pathway. J Cachexia Sarcopenia Muscle 2020;11:241–258.

41. van Dijk M, Dijk FJ, Hartog A, van Norren K, Verlaan S, van Helvoort A, et al. Reduced dietary intake of micronutrients with antioxidant properties negatively impacts muscle health in aged mice. J Cachexia Sarcopenia Muscle 2018;9:146–159.

42. Dziegala M, Josiak K, Kasztura M, Kobak K, von Haehling S, Banasiak W, et al. Iron deficiency as energetic insult to skeletal muscle in chronic diseases. J Cachexia Sarcopenia Muscle 2018;9:802–815.

43. Mehrabani S, Bagherniya M, Askari G, Read MI, Sahebkar A. The effect of fasting or calorie restriction on mitophagy induction: a literature review. J Cachexia Sarcopenia Muscle n/a:https://doi.org/10.1002/jcsm.12611

44. Basile D, Parnoﬁel A, Vitale MG, Cortiula F, Gerratana L, Fanotto V, et al. The IM-PACT study: early loss of skeletal muscle mass in advanced pancreatic cancer patients. J Cachexia Sarcopenia Muscle 2019;10:368–377.

45. Nasrak R, van der Borch C, Kanbalian M, Jagoe RT. Deﬁning barriers to implementation of nutritional advice in patients with cachexia. J Cachexia Sarcopenia Muscle 2020;11:69–78.

46. Hengeveld LM, Boer JMA, Gaudreau P, Heymans MW, Jagger C, Mendonça N, et al. Prevalence of protein intake below recommended in community-dwelling older adults: a meta-analysis across cohorts from the PROMISS consortium. J Cachexia Sarcopenia Muscle 2020;11:1212–1222.

47. Rhee CM, Ahmadi S-F, Kovesdy CP, Kalantar-Zadeh K. Low-protein diet for conservative management of chronic kidney disease: a systematic review and meta-analysis of controlled trials. J Cachexia Sarcopenia Muscle 2018;9:235–245.

48. Muscaritoli M, Molfino A, Scala F, Christoforidi K, Manneh-Vangramberen I, De Lorenzo F. Nutritional and metabolic derangements in Mediterranean cancer patients and survivors: the ECPC 2016 survey. J Cachexia Sarcopenia Muscle 2019;10:517–525.