

Cachexia as a common characteristic in multiple chronic disease

Nadja Scherbakov^{1,2*} and Wolfram Doehner^{1,2,3,4}

¹Department of Cardiology (CVK), Charité—Universitätsmedizin Berlin, Berlin, Germany, ²Berlin-Brandenburg Center for Regenerative Therapies (BCRT), Berlin, Germany, ³German Centre for Cardiovascular Research (DZHK), partner site Berlin, Berlin, Germany, ⁴Berlin-Brandenburg Center for Regenerative Therapies (BCRT), Berlin, Germany

Keywords cachexia; cancer; chronic diseases; muscle wasting

*Correspondence to: Nadja Scherbakov, Center for Stroke Research Berlin (CSB), Charité—Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Germany, Email: nadja.scherbakov@charite.de

Cachexia, or body wasting,¹ is a serious complication and frequently occurs at advanced stage of the variety of chronic diseases, including cancer, multiple inflammatory organ-specific disease, and cardiovascular disease. Cachexia affects the life quality and survival of the patients.^{2,3} The prevalence of cachexia depends on the underlying disease and widely ranges between 15 and 90%.⁴ Patients with cancer are most commonly affected by cachexia that often occurs as a late-stage complication. In cancer, the prevalence of cachexia⁵ may vary between 50 and 90% depending on the type of cancer,⁶ where a clinical course of gastrointestinal or lung cancers is most frequently associated with the development of cachexia.^{7,8} The multifactorial pathogenesis of cachexia, including anorexia, inflammatory activation, and impaired metabolic turnover of both structural and energy metabolism, lead to a decrease of adipose and lean tissue mass and low muscle strength.⁹

The discussion is ongoing whether cachexia in various chronic diseases should be viewed as a common final metabolic pathway regardless of the underlying disease or if it is disease specific, and distinct pathophysiological mechanisms exist in different diseases. A recent retrospective clinical study described different phenotypes of cachexia in patients with advanced pancreatic ductal adenocarcinoma (PDAC) undergoing chemotherapy.¹⁰ The assessment of longitudinal changes of body composition by computed tomography (CT) revealed three phenotypes of body wasting in these patients: patients who lost skeletal muscle and fat tissue, patients who only lost fat tissue, and patients without wasting who had a significantly improved survival. Several other studies investigated patients with different types of gastrointestinal cancer and reported either a loss of muscle tissue^{11,12} or a loss of both skeletal muscle and adipose tissue

mass.¹³ In addition, loss of cardiac muscle tissue in cancer cachexia (CC) has been shown in clinical and experimental studies.^{14–16}

It is known that cachexia is characterized by body wasting that involves all compartments of body tissue (i.e. muscle, adipose, and bone tissues).^{9,17,18} From all of these compartments, the loss of muscle tissue is considered the key pathophysiological mechanism to explain reduced physical capacity, increased frailty, susceptibility to disease progression, increased hospitalization rate, and, consequently, increased mortality. A major hurdle for the research on loss of muscle tissue, or sarcopenia,^{19,20} is a lack of the reference standard for determination of skeletal muscle mass.^{21,22} A number of clinical diagnostic methods are available ranging from easy applicable, such as bioelectrical impedance analysis (BIA),^{23,24} to highly complex, challenging, and costly techniques, such as magnetic resonance imaging (MRI) or CT.^{25,26} The setting of the research question and specific study design define the appropriate method to be used for the given context. Importantly, apart from the assessment of muscle bulk, functional and metabolic characteristics of the skeletal muscle tissue might have a role in the determination of functional capacity and symptomatic severity of muscle wasting and hence may have an impact on clinical outcome.^{27–30}

As previously mentioned, cachexia is usually reported as a complication of chronic diseases, including chronic obstructive pulmonary disease (COPD),^{31,32} rheumatoid arthritis,^{33,34} chronic hepatitis and cirrhosis,^{35,36} diabetes mellitus,³⁷ chronic kidney disease (CKD),³⁸ and chronic heart failure (CHF).^{39–41} A hypothesis has been proposed that independent of the individual chronic disease, the wasting process follows a common final metabolic pattern. This metabolic pattern

usually relates to an advanced stage of the underlying disease and can best be summarized as an increased catabolic turnover and anabolic blunting.

Nevertheless, cachexia has not been sufficiently investigated in many other pathological conditions, including stroke. Body weight loss after neurological stroke is frequently observed in clinical and experimental settings and associated with adverse clinical outcome.^{42,43} The consequences of ischaemic stroke on myocardium have been investigated in an experimental study by Veltkamp *et al.*,⁴⁴ which showed a transient myocardial dysfunction and atrophy of cardiomyocytes following the brain ischaemia. Further clinical studies investigating cachexia and muscle wasting in patients with stroke are warranted.

Despite intensified research in the field, no medical therapy has emerged for a wider clinical application to prevent or even reverse the development of cachexia and muscle wasting. The medical treatment of cachexia includes a dietary supplementation of proteins, vitamins, or minerals.^{45–48} Multiple attempts have been made to identify and validate treatment options to counteract the development of muscle wasting. The efficacy of physical exercise training has been confirmed in clinical and experimental studies, and it is regarded as the most promising treatment ap-

proach to delay or prevent progression of muscle wasting.^{49–53} However, there is an urgent need for the development of clinical practice guidelines for treatment patients with cachexia.⁵⁴ Additional clinical studies are highly warranted to explore further the mechanisms of tissue wasting in chronic illnesses and to discover novel drug therapies to prevent or reverse the development of cachexia regarded as a severe complication of a variety of end-stage chronic disease.

The authors certify that they comply with the ethical guidelines for publishing in the *Journal of Cachexia, Sarcopenia and Muscle: Update 2017*.⁵⁵

Acknowledgements

We acknowledge support from the German Research Foundation (DFG) and the Open Access Publication Fund of Charité – Universitätsmedizin Berlin.

Conflict of interest

None declared.

References

1. von Haehling S, Ebner N, Dos Santos MR, Springer J, Anker SD. Muscle wasting and cachexia in heart failure: mechanisms and therapies. *Nat Rev Cardiol* 2017;**14**:323–341.
2. Bye A, Sjøblom B, Wentzel-Larsen T, Grønberg BH, Baracos VE, Hjermstad MJ, et al. Muscle mass and association to quality of life in non-small cell lung cancer patients. *J Cachexia Sarcopenia Muscle* 2017;**8**:759–767.
3. Mochamat CH, Marinova M, Kaasa S, Stieber C, Conrad R, Radbruch L, et al. A systematic review on the role of vitamins, minerals, proteins, and other supplements for the treatment of cachexia in cancer: a European Palliative Care Research Centre cachexia project. *J Cachexia Sarcopenia Muscle* 2017;**8**:25–39.
4. von Haehling S, Anker MS, Anker SD. Prevalence and clinical impact of cachexia in chronic illness in Europe, USA, and Japan: facts and numbers update 2016. *J Cachexia Sarcopenia Muscle* 2016;**7**:507–509.
5. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol* 2011;**12**:489–495.
6. Muscaritoli M, Bossola M, Aversa Z, Bellantone R, Rossi FF. Prevention and treatment of cancer cachexia: new insights into an old problem. *Eur J Cancer* 2006;**42**:31–41.
7. Mueller TC, Burmeister MA, Bachmann J, Martignoni ME. Cachexia and pancreatic cancer: are there treatment options? *World J Gastroenterol* 2014;**20**:9361–9373.
8. Ockenga J, Valentini L. Review article: anorexia and cachexia in gastrointestinal cancer. *Aliment Pharmacol Ther* 2005;**22**:583–594.
9. Evans WJ, Morley JE, Argilés J, Bales C, Baracos V, Guttridge D, et al. Cachexia: a new definition. *Clin Nutr* 2008;**27**:793–799.
10. Kays JK, Shahda S, Stanley M, Bell TM, O'Neill BH, Kohli MD, et al. Three cachexia phenotypes and the impact of fat-only loss on survival in FOLFIRINOX therapy for pancreatic cancer. *J Cachexia Sarcopenia Muscle* 2018;**9**:673–684.
11. Dolan RD, Almasaudi AS, Dieu LB, Horgan PG, McSorley ST, McMillan DC. The relationship between computed tomography-derived body composition, systemic inflammatory response, and survival in patients undergoing surgery for colorectal cancer. *J Cachexia Sarcopenia Muscle* 2018; <https://doi.org/10.1002/jcsm.12357>.
12. Daly LE, Ní Bhuachalla ÉB, Power DG, Cushen SJ, James K, Ryan AM. Loss of skeletal muscle during systemic chemotherapy is prognostic of poor survival in patients with foregut cancer. *J Cachexia Sarcopenia Muscle* 2018;**9**:315–325.
13. van Dijk DPJ, Krill M, Farshidfar F, Li T, Rensen SS, Olde Damink SWM, et al. Host phenotype is associated with reduced survival independent of tumour biology in patients with colorectal liver metastases. *J Cachexia Sarcopenia Muscle* 2018; <https://doi.org/10.1002/jcsm.12358>.
14. Barkhudaryan A, Scherbakov N, Springer J, Doehner W. Cardiac muscle wasting in individuals with cancer cachexia. *ESC Heart Fail* 2017;**4**:458–467.
15. Musolino V, Palus S, Latouche C, Gliozzi M, Bosco F, Scarano F, et al. Cardiac expression of neutrophil gelatinase-associated lipocalin in a model of cancer cachexia-induced cardiomyopathy. *ESC Heart Fail* 2018; <https://doi.org/10.1002/ehf2.12372>.
16. Bowen TS, Adams V, Werner S, Fischer T, Vinke P, Brogger MN, et al. Small-molecule inhibition of MuRF1 attenuates skeletal muscle atrophy and dysfunction in cardiac cachexia. *J Cachexia Sarcopenia Muscle* 2017;**8**:939–953.
17. Ehardt HA, Degen S, Tadini V, Schilb A, Johns N, Greig CA, et al. Comprehensive proteome analysis of human skeletal muscle in cachexia and sarcopenia: a pilot study. *J Cachexia Sarcopenia Muscle* 2017;**8**:567–582.
18. Pin F, Barreto R, Kitase Y, Mitra S, Erne CE, Novinger LJ, et al. Growth of ovarian cancer xenografts causes loss of muscle and bone mass: a new model for the study of cancer cachexia. *J Cachexia Sarcopenia Muscle* 2018;**9**:685–700.
19. 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;**39**:412–423.
20. 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;**29**:154–159.
 21. Scherbakov N, Doehner W. Do we need a reference standard for the muscle mass measurements? *ESC Heart Fail* 2018;**5**:741–744.
 22. 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;**9**:269–278.
 23. Gonzalez MC, Heymsfield SB. Bioelectrical impedance analysis for diagnosing sarcopenia and cachexia: what are we really estimating? *J Cachexia Sarcopenia Muscle* 2017;**8**:187–189.
 24. Blauwhoff-Buskermolen S, Langius JAE, Becker A, Verheul HMW, de van der Schueren MAE. The influence of different muscle mass measurements on the diagnosis of cancer cachexia. *J Cachexia Sarcopenia Muscle* 2017;**8**:615–622.
 25. Grimm A, Meyer H, Nickel MD, Nittka M, Raithele E, Chaudry O, et al. Repeatability of Dixon magnetic resonance imaging and magnetic resonance spectroscopy for quantitative muscle fat assessments in the thigh. *J Cachexia Sarcopenia Muscle* 2018;**9**:1093–1100.
 26. Brown JC, Caan BJ, Meyerhardt JA, Weltzien E, Xiao J, Cespedes Feliciano EM, et al. The deterioration of muscle mass and radiodensity is prognostic of poor survival in stage I–III colorectal cancer: a population-based cohort study (C-SCANS). *J Cachexia Sarcopenia Muscle* 2018;**9**:664–672.
 27. Newman AB, Kupelian V, Visser M, Simonsick EM, Goodpaster BH, Kritchevsky SB, et al. Strength, but not muscle mass, is associated with mortality in the health, aging and body composition study cohort. *J Gerontol A Biol Sci Med Sci* 2006;**61**:72–77.
 28. Bourgeois B, Fan B, Johannsen N, Gonzalez MC, Ng BK, Sommer MJ, et al. Improved strength prediction combining clinically available measures of skeletal muscle mass and quality. *J Cachexia Sarcopenia Muscle* 2018; <https://doi.org/10.1002/jcsm.12353>.
 29. Goodpaster BH, Park SW, Harris TB, Kritchevsky SB, Nevitt M, Schwartz AV, et al. The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and body composition study. *J Gerontol A Biol Sci Med Sci* 2006;**61**:1059–1064.
 30. Doehner W, Turhan G, Leyva F, Rauchhaus M, Sandek A, Jankowska EA, et al. Skeletal muscle weakness is related to insulin resistance in patients with chronic heart failure. *ESC Heart Fail* 2015;**2**:85–89.
 31. Calder PC, Laviano A, Lonnqvist F, Muscaritoli M, Öhlander M, Schols A. Targeted medical nutrition for cachexia in chronic obstructive pulmonary disease: a randomized, controlled trial. *J Cachexia Sarcopenia Muscle* 2018;**9**:28–40.
 32. McDonald MN, Won S, Mattheisen M, Castaldi PJ, Cho MH, Rutten E, et al. Body mass index change in gastrointestinal cancer and chronic obstructive pulmonary disease is associated with Dedicator of Cytokinesis 1. *J Cachexia Sarcopenia Muscle* 2017;**8**:428–436.
 33. Santo RCE, Fernandes KZ, Lora PS, Filippin LI, Xavier RM. Prevalence of rheumatoid cachexia in rheumatoid arthritis: a systematic review and meta-analysis. *J Cachexia Sarcopenia Muscle* 2018;**9**:816–825.
 34. Alabarse PVG, Lora PS, Silva JMS, Santo RCE, Freitas EC, de Oliveira MS, et al. Collagen-induced arthritis as an animal model of rheumatoid cachexia. *J Cachexia Sarcopenia Muscle* 2018;**9**:603–612.
 35. Bering T, Diniz KGD, Coelho MPP, Vieira DA, Soares MMS, Kakehasi AM, et al. Association between pre-sarcopenia, sarcopenia, and bone mineral density in patients with chronic hepatitis C. *J Cachexia Sarcopenia Muscle* 2018;**9**:255–268.
 36. Ebadi M, Wang CW, Lai JC, Dasarathy S, Kappus MR, Dunn MA, Carey EJ, Montano-Loza AJ; From the Fitness, Life Enhancement, and Exercise in Liver Transplantation (FLEXIT) Consortium. Poor performance of psoas muscle index for identification of patients with higher waitlist mortality risk in cirrhosis. *J Cachexia Sarcopenia Muscle* 2018;**9**:1053–1062.
 37. Zhang A, Li M, Wang B, Klein JD, Price SR, Wang XH. miRNA-23a/27a attenuates muscle atrophy and renal fibrosis through muscle–kidney crosstalk. *J Cachexia Sarcopenia Muscle* 2018;**9**:755–770.
 38. Yu R, Chen JA, Xu J, Cao J, Wang Y, Thomas SS, et al. Suppression of muscle wasting by the plant-derived compound ursolic acid in a model of chronic kidney disease. *J Cachexia Sarcopenia Muscle* 2017;**8**:327–341.
 39. Clark AL, Coats AJS, Krum H, Katus HA, Mohacs P, Salekin D, 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.
 40. Springer J, Springer JI, Anker SD. Muscle wasting and sarcopenia in heart failure and beyond: update 2017. *ESC Heart Fail* 2017;**4**:492–498.
 41. Saitoh M, Dos Santos MR, Emami A, Ishida J, Ebner N, Valentova M, et al. Anorexia, functional capacity, and clinical outcome in patients with chronic heart failure: results from the Studies Investigating Comorbidities Aggravating Heart Failure (SICA-HF). *ESC Heart Fail* 2017;**4**:448–457.
 42. Jönsson AC, Lindgren I, Norrving B, Lindgren A. Weight loss after stroke: a population-based study from the Lund Stroke Register. *Stroke* 2008;**39**:918–923.
 43. Springer J, Schust S, Peske K, Tschirner A, Rex A, Engel O, et al. Catabolic signaling and muscle wasting after acute ischemic stroke in mice: indication for a stroke-specific sarcopenia. *Stroke* 2014;**45**:3675–3683.
 44. Veltkamp R, Uhlmann S, Marinescu M, Sticht C, Finke D, Gretz N, et al. Experimental ischaemic stroke induces transient cardiac atrophy and dysfunction. *J Cachexia Sarcopenia Muscle* 2018; <https://doi.org/10.1002/jcsm.12335>.
 45. Santarpia L, Contaldo F, Pisanis F. Dietary protein content for an optimal diet: a clinical view. *Cachexia Sarcopenia Muscle* 2017;**8**:345–348.
 46. Solheim TS, Laird BJA, Balstad TR, Stene GB, Bye A, Johns N, et al. A randomized phase II feasibility trial of a multimodal intervention for the management of cachexia in lung and pancreatic cancer. *J Cachexia Sarcopenia Muscle* 2017;**8**:778–788.
 47. Naito T, Mitsunaga S, Miura S, Tatematsu N, Inano T, Mouri T, et al. Feasibility of early multimodal interventions for elderly patients with advanced pancreatic and non-small-cell lung cancer. *J Cachexia Sarcopenia Muscle* 2018; <https://doi.org/10.1002/jcsm.12351>.
 48. Burden ST, Gibson DJ, Lal S, Hill J, Pilling M, Soop M, et al. Pre-operative oral nutritional supplementation with dietary advice versus dietary advice alone in weight-losing patients with colorectal cancer: single-blind randomized controlled trial. *J Cachexia Sarcopenia Muscle* 2017;**8**:437–446.
 49. Lans C, Cider Å, Nylander E, Brudin L. Peripheral muscle training with resistance exercise bands in patients with chronic heart failure. Long-term effects on walking distance and quality of life; a pilot study. *ESC Heart Fail* 2018;**5**:241–248.
 50. Sugie M, Harada K, Takahashi T, Nara M, Ishikawa J, Koyama T, et al. Relationship between skeletal muscle mass and cardiac function during exercise in community-dwelling older adults. *ESC Heart Fail* 2017;**4**:409–416.
 51. Tanaka Y, Takarada Y. The impact of aerobic exercise training with vascular occlusion in patients with chronic heart failure. *ESC Heart Fail* 2018;**5**:586–591.
 52. Ennis S, McGregor G, Shave R, McDonnell B, Thompson A, Banerjee P, et al. Low frequency electrical muscle stimulation and endothelial function in advanced heart failure patients. *ESC Heart Fail* 2018;**5**:727–731.
 53. Cattadori G, Securini C, Picozzi A, Padeletti L, Anzà C. Exercise and heart failure: an update. *ESC Heart Fail* 2018;**5**:222–232.
 54. Mochamat CH, Marinova M, Kaasa S, Stieber C, Conrad R, Radbruch L, et al. A systematic review on the role of vitamins, minerals, proteins, and other supplements for the treatment of cachexia in cancer: a European Palliative Care Research Centre cachexia project. *J Cachexia Sarcopenia Muscle* 2017;**8**:25–39.
 55. 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.