REVIEW ARTICLE

Sarcopenia and cachexia in chronic diseases: from mechanisms to treatment

Alessia Lena[1,2,3], Sara Hadzibegovic[1,2,4], Stephan von Haehling[5,6], Jochen Springer[1,2], Andrew J. Stewart Coats[7], Markus S. Anker[1,2,4]

1 Berlin Institute of Health Center for Regenerative Therapies (BCRT), Berlin, Germany
2 German Center for Cardiovascular Research (DZHK), Partner Site Berlin, Berlin, Germany
3 Division of Cardiology and Metabolism, Department of Cardiology, Charité Universitätsmedizin Berlin, Campus Virchow Klinikum, Berlin, Germany
4 Department of Cardiology (CBF), Charité Universitätsmedizin Berlin, Berlin, Germany
5 Department of Cardiology and Pneumology, University Medical Center, Göttingen, Germany
6 German Center for Cardiovascular Research (DZHK), Partner Site Göttingen, Göttingen, Germany
7 University of Warwick, Coventry, United Kingdom

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ABSTRACT

Two main manifestations of wasting disorders in chronic disease are cachexia and sarcopenia. Due to shared pathological features, including impairments in systemic inflammatory responses, neurohormonal activity, and metabolic systems, the 2 disorders can present with similar symptoms (tissue depletion, dyspnea, anorexia, asthenia, fatigue, and impaired physical performance). Wasting disorders are associated with reduced quality of life and increased mortality. Cachexia is characterized by systemic tissue depletion with weight loss, and sarcopenia, by skeletal muscle loss accompanied by diminished muscular strength and physical performance. Wasting syndromes can be identified based on clinical criteria as well as with the use of multiple imaging and diagnostic techniques. Additionally, blood biomarkers can be used for diagnosing wasting disorders. In the past decade, intensive research has focused on new therapeutic strategies within a multimodal approach, which embraces nutritional support, physical activity, and targeted pharmacological therapy. Despite some initial promising therapeutic results for selected novel agents, guideline-recommended pharmacotherapy is not yet available for cachexia or sarcopenia. More research is needed to better understand these wasting disorders and learn how to treat them.

Correspondence to:
Markus S. Anker, MD, Department of Cardiology (CBF), Charité Universitätsmedizin Berlin, Hindenburgdamm 30, 12200 Berlin, Germany, phone: +4930450553092, email: markus.anker@charite.de
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Introduction In clinical practice, wasting disorders are often underdiagnosed due to uncertainties about the diagnostic approach to cachexia / sarcopenia.[1] Currently, there are several different definitions of sarcopenia[2,3] and cachexia.[4,5] Since there is no agreement upon a standard definition for either disorder, it is difficult to make comparisons between studies. Sarcopenia and cachexia can complicate many different chronic diseases including cancer,[6] heart failure (HF),[7,8] chronic kidney disease (CKD),[9,10] thyroid disease,[11] chronic obstructive pulmonary disease (COPD),[12] and chronic liver failure.[13] Once wasting disorders occur, they can aggravate the clinical condition of patients, impair their quality of life, cause prolonged or repeated hospitalizations, and potentially worsen patient prognosis.[14] Sarcopenia and cachexia share some pathophysiological pathways, for example, abnormalities in protein metabolism and increased inflammation.[15] Still, they need to be considered separately since the therapeutic approach in the 2 conditions is different. Therefore, the purposes of this review are: 1) to clarify the definitions of sarcopenia and cachexia and their clinical involvement in chronic diseases; 2) to elucidate the common and different underlying mechanisms; 3) to present the diagnostic possibilities; and 4) to give an insight into the current therapeutic strategies for these 2 syndromes.

From definition to pathophysiology In 2016, the European Working Group on Sarcopenia in Older People[16] defined sarcopenia as a progressive degeneration of the skeletal muscle system, characterized by a decline in muscle mass, strength, and

function. According to this definition, a sarcopenic phenotype can be identified in 10% to 40% of the elderly population, as an age-dependent muscle degeneration.[17] Sarcopenia is also observed in patients with chronic diseases, irrespective of age. For instance, the prevalence of sarcopenia among 200 chronic HF patients in the SICA-HF study (Studies Investigating Co-Morbidities Aggravating Heart Failure) was 20%.[18] A recent meta-analysis in 2565 patients with COPD differentiated between population-based, clinical-based, and nursing home–based studies and found a prevalence of sarcopenia of 8%, 21%, and 63%, respectively.[19] Sepulveda-Loyola et al[12] in a meta-analysis of 9637 COPD patients found that individuals with more severe COPD also showed a higher prevalence of sarcopenia compared with patients with less severe COPD (38% vs 19%). Likewise, in cancer patients, sarcopenia has been reported in up to 60% of cases, depending on cancer type and stage.[20] Therefore, sarcopenia cannot be considered a rare pathological condition among old, chronically ill patients and requires more clinical attention.

Cachexia manifests with an unintentional weight loss of at least 5% to 10% in the previous 12 months.[5] It is characterized by an imbalance in energy and protein metabolism, with a predominance of energy dissipation over energy intake. Typical clinical and biochemical findings in this condition are anorexia, lower body mass index, anemia, and hypoalbuminemia[5] as well as increased inflammation with elevated levels of inflammatory biomarkers (eg, C-reactive protein, tumor necrosis factor α [TNF-α], and interleukin [IL] 6).[5] The frequency with which patients develop cachexia also greatly depends on the underlying disease. Frequencies of cachexia range from 5% to 15% in patients with end-stage HF, 20% to 30% in those with stroke, and 50% to 80% in those with advanced cancer.[21]

Both sarcopenia and cachexia clinically manifest with dyspnea, weakness, loss of appetite, and fatigue caused by the underlying metabolic dysregulation and impairment of the muscle system.[22] The skeletal muscle system is not only important for mobility and strength but also acts as a regulator of metabolic processes and stores macronutrients.[23] In patients with chronic diseases, factors such as immobility, malnourishment, hormonal abnormalities, poor blood flow to the muscle, endothelial dysfunction, and chemotherapy can compromise muscular homeostasis.[24] Consequently, proteolytic processes and systemic inflammation can cause extensive skeletal muscle depletion. Sarcopenia can occur as a single pathological condition or be a prestage of cachexia in chronic illnesses.[25] In cachectic tumor-bearing rats, upregulation of autophagic processes in the muscles through TP53INP2 overexpression was observed and was important for the switch from a sarcopenic to a cachectic phenotype.[26] Aberrations in protein metabolism, particularly in the activin type II receptor pathway that involves activin A, myostatin, and growth and differentiation factor 11, have been identified in both sarcopenic and cachectic phenotypes.[27] Myostatin, mainly released by the skeletal muscle but also by the heart and adipose tissue, negatively regulates muscle growth.[28] Serum concentrations of myostatin are increased in patients with HF[29] and CKD[30] and are correlated with reduced skeletal muscle strength in these individuals.

Anabolic disturbances are often observed in chronically ill patients. A study in individuals with prostate cancer receiving selective androgen deprivation therapy found that low levels of testosterone were associated with deficits in muscle mass and function of the lower limbs.[31] Additionally, it has been shown that downregulated androgen production in patients with HF[32] and end-stage liver disease[33] negatively influences their prognosis.

The adipose tissue also plays an important role in cachexia since fat tissue can release a wide range of adipokines such as IL-1β, IL-6, IL-10, TNF-α, adiponectin, and leptin.[34] Leptin, secreted entirely by adipocytes, reduces food intake by acting on the hypothalamus. There is evidence that leptin secretion is increased in cachectic patients.[35,36] In experimental models of hepatocellular carcinoma, it has been shown that leptin can induce skeletal muscle depletion.[37] Elevated levels of serum adiponectin have been found in chronic HF patients with cachexia.[38,39] Increased levels of natriuretic peptides can cause adiponectin release in patients with chronic HF.[39] Higher levels of adiponectin were associated with low muscle performance in elderly, noncachectic patients with chronic HF, suggesting a key role of this adipokine in muscle metabolism.[40]

It is important to underline that despite some common pathophysiological mechanisms, the 2 wasting conditions are histologically different. Abnormalities in the number and structure of myofibers type II (fast-twitch type) have predominantly been found in sarcopenia, while a reduced number of myofibers type I (slow-twitch type), associated with myofibrillary edema, have been reported mainly in cachexia.[41]

Cardiac wasting and malignant arrhythmias have been found in cancer patients,[42-44] providing more evidence that catabolic processes in cachexia are generalized.[45,46] In cancer patients, myocardial metabolism is hampered by multiple factors, such as tumor-dependent inflammatory cytokines, oxidative stress, and chemotherapeutic--dependent metabolic alterations.[15] As a consequence, cardiac wasting can occur and could be associated with further functional impairment.[47] Thus, maintaining myocardial homeostasis is important and requires careful therapeutic decision making, especially when dealing with cardiotoxic agents.[48] In experimental models in mice, cerebrovascular events have also been linked to myocardial impairments and abnormalities in cardiomyocytes.[49]

Diagnostic assessment **Imaging** Since wasting disorders have a high impact on the clinical and prognostic course of the primary disease, it is important that they are detected early and patients at a high risk of developing such disorders are identified quickly.[14] Several diagnostic methods are available to assess the body composition and examine the presence of tissue depletion. On computed tomography imaging, the skeletal muscle index (SMI; derived from normalization to height squared of the total muscle area) and the psoas muscle index (PMI) can be calculated based on images taken at the level of the third lumbar vertebra. Both parameters are used as markers for muscular depletion and may help in predicting preoperative complications and mortality in cancer patients.[50,51] Cutoff points for both parameters have been previously investigated in patients with cirrhosis: low muscular mass was defined as an SMI below 50 cm^2/m^2 in men and below 39 cm^2/m^2 in women,[52] while low PMI was defined as a score below 5.1 cm^2/m^2 in men and below 4.3 cm^2/m^2 in women. In another study involving 365 patients with chronic liver disease it was found that SMI was more robust in the detection of muscle wasting and prediction of mortality.[53] However, SMI and PMI measurements are rarely used in routine clinical practice—they are costly and often require additional software tools, extra time for image analysis, and experienced radiologists. Additionally, the operational procedures are complex and there are no standard thresholds for sarcopenia.[54]

Bioelectrical impedance analysis (BIA)[55] and dual-energy X-ray absorptiometry scans (DEXA) represent further potential objective methods to define body composition and nutritional status in chronically ill patients.[56] These 2 techniques were recently compared in 120 HF patients[57] and they were highly comparable in the detection of fat and lean mass ($r = 0.95$; $P < 0.001$ and $r = 0.96$; $P < 0.001$, respectively); however, BIA in comparison with DEXA underestimated the fat mass (mean difference, –5.1 kg; 95% CI, –11.7 to 1.5) while overestimating the muscular mass (mean difference, 5.5 kg; 95% CI, –1.3 to 12.3). In another study, BIA was reported to be a valid screening tool in detecting fluid retention in HF patients,[58] but fluid retention proved to be a relevant determinant of the phase angle,[59] representing a potential bias. Because of the high oscillations of extracellular water compartment, and high population- and instrument-based variabilities,[60] BIA should be used with caution in clinical decision making when wasting syndromes are detected. Therefore, DEXA still remains the best diagnostic method to evaluate the body composition in the clinical setting. However, the high cost of this tool and its common use in the assessment of bone mineral density make it less available for the evaluation of nutritional and wasting statuses.

Biomarkers Biomarkers play an important role in the early detection of tissue depletion.[61] Interestingly, neurohormonal markers of cachexia show a positive correlation with the progress of the primary disease in HF,[62] suggesting a possible pathophysiological connection between the severity of wasting disorders and the underlying chronic disease. Increased levels of serological markers for skeletal muscle degradation can confirm the presence of abnormal proteolysis in wasting disorders. A wide range of biomarkers such as myostatin,[63] transforming growth factor β,[64] and activin A[65] as well as proinflammatory cytokines such as TNF, IL-1, and IL-6[66] have been investigated so far. Specifically in cachectic patients, biochemical proof of lipid loss reflected by free-fatty acids[67] and zinc-α-glycoprotein,[68] as well as imbalanced levels of ghrelin[69] and leptin[70] may be useful to investigate the nutritional status and progressive tissue degradation. However, due to the complex interaction between wasting mechanisms, chronic inflammation, and neurohormonal dysregulations present in chronic diseases, none of the abovementioned biomarkers has been specifically implemented so far in clinical practice as a screening tool for wasting syndromes.[61] Therefore, a multifactorial biomarker approach has been suggested as the best strategy for diagnosing wasting disorders,[63,71] together with clinical signs and symptoms.

Treatment Today, there is still no standard approved pharmacological or nonpharmacological treatment strategy for sarcopenia or cachexia at the disposal of clinicians.[72] Because of the overlapping nature of these disorders, a multitargeted approach aiming at increasing appetite and food intake, attenuating chronic inflammatory state, and improving exercise capacity and quality of life remains the most promising therapeutic strategy for both conditions.[72]

In this multimodal approach, nutritional support is a crucial intervention that needs to be applied as early as possible to avoid wasting, especially in old (>65 years), chronically ill patients.[72] It is generally recommended to increase protein intake up to 1.2–1.5 g/kg of body weight/day to prevent the development of sarcopenia (except in patients with advanced CKD and estimated glomerular filtration rate <30 ml/min/1.73 m^2 or patients on hemodialysis).[73] In a study by Rozentryt et al,[74] recruiting chronic HF patients with cachexia, a diet with high protein content (20 g) led to weight gain and a significant improvement in the inflammatory profile and clinical outcome after 18 weeks ($P < 0.05$ for both). An improvement in whole body protein synthesis was observed in non–small-cell lung cancer[75] and COPD[76] patients who received essential amino-acid supplementation. To decrease systemic tissue depletion, omega-3 fatty acids have also been investigated[77]: several studies have shown positive results with regards to weight gain, reduced skeletal muscle loss, and improvement in quality of life.[78,79] However, there are currently no validated recommendations for preventing

or counteracting wasting in chronically ill patients. There has been a limited number of studies focusing specifically on nutritional interventions against wasting syndromes and those that have been done were carried out in the context of different chronic disorders and at different stages. Therefore, it is difficult to find a consensus in this approach.[80]

Targeting altered muscle metabolism by increasing anabolic activity through physical training has been explored as a therapeutic method in sarcopenic patients. Aerobic and resistance exercise have also demonstrated beneficial effects on inflammation and as a defense against oxidative stress.[81] In 2011, the Heart Failure Association and the European Association for Cardiovascular Prevention and Rehabilitation recommended regular and customized physical activity for the prevention of muscle atrophy in patients with HF.[82] Nevertheless, physical activity or neuromuscular electrical stimulation cannot be applied to all chronically ill patients.[83] Whilst physical training proves to be effective as a preventive strategy in sarcopenic patients, this therapeutic approach is limited in cachectic individuals by different factors such as fatigue, exertional dyspnea, and pain[84] that characterize advanced chronic disease. Beneficial effects against cachexia that may be induced by physical training can also be reduced by noncompliance of the patient. For example, an experience involving a multimodal approach with free fatty acids, exercise, and an anti-inflammatory drug (celecoxib) showed a modest compliance (60%) towards physical activity in a small group of cachectic cancer patients.[85] In contrast, pharmacological therapy had a compliance of 76%, while nutritional approach, of only 48%.

Concerning pharmacological therapy against wasting disorders, anabolic compounds have been investigated as possible agents to reverse hypercatabolic processes. Recent findings were obtained in a small group of patients (n = 22) with cervical or head and neck cancer. In this randomized trial,[86] testosterone treatment showed a slight increase in lean body mass after 7 weeks compared with placebo (+3.2%; 95% CI, 0%–7% vs –3.3%; 95% CI, –7% to 1%, respectively; $P = 0.015$). This result was also correlated with improved quality of life and preserved physical activity. The groups (testosterone vs placebo) did not differ in terms of fat mass loss, suggesting testosterone as ineffective in reducing fat depletion in these patients. The use of testosterone supplementation was also combined with growth hormone replacement therapy in a restricted group (n = 5) of chronic HF patients.[87] This pilot study reported a significant increase in the cardiopulmonary function (left ventricular ejection fraction +5.4%; $P < 0.01$ and peak oxygen consumption +19.3%; $P < 0.01$) after 1 year of growth hormone monotherapy, and a significant improvement in muscular strength (+17.5%; $P < 0.01$) after an additional year of combined therapy. Moreover, testosterone showed positive results in a randomized double-blind placebo-controlled trial involving 101 men with end-stage liver disease and low levels of serum testosterone: after 12 months of follow-up there was a significant increase in lean mass, bone mass, and bone density, assessed by DEXA, and a significant decrease in fat mass in the study group compared with the placebo group.[88] Despite these promising results, researchers and clinicians must also consider the adverse events of testosterone-based supplementation therapy, such as an increased risk of cardiovascular events.[89] For this reason, testosterone has not been implemented in the regular management of wasting disorders in chronically ill patients so far.[72]

Selective androgen receptor modulators (SARMs) may constitute a valid alternative to unselective anabolic steroids, particularly testosterone, in treating wasting syndromes. Most data come from investigations on cancer-related cachexia. The selective anabolic effects of SARM-2f against wasting processes were explored in castrated mice with cancer-induced cachexia[90]: this compound, resulting in an increase in body weight, lean mass, and the mass of individual muscles, did not influence fat mass, demonstrating selective modulation of anabolic metabolism in the skeletal muscle system. Castrated male mice have been used for testing MK-4541, an androgen receptor agonist with a 5α-reductase inhibitor function.[91] Similar to SARM-2f, this modified SARM exhibited anabolic effects and improved muscle function. A double-blind, placebo-controlled trial enrolling 159 cancer patients was designed to investigate another SARM agent, enobosarm, and its potential muscle-protective role in cachexia.[92] Over 4 months, both treatment arms of cancer patients exhibited a significant increase in total lean body mass (enobosarm 1 mg/d: median, 1.5 kg; range, 2.1–12.6 kg; $P = 0.0012$; enobosarm 3 mg/d: median, 1.0 kg; range, –4.8 to 11.5 kg; $P = 0.046$), while no significant changes were observed in the placebo group (median, 0.02 kg; range, –5.8 to 6.7 kg; $P = 0.88$). However, the compound did not influence muscle strength or physical performance in these patients, resulting in a suboptimal therapeutic effect for improvement of clinical outcomes.

Other synthetic agents modulating appetite have lately emerged in the treatment of cachexia. Ghrelin, an endogenous ligand for the growth hormone secretagogue receptor, secreted by the stomach and pancreas, promotes appetite and, consequently, food intake. In addition, it plays a key role in the modulation of cellular energy metabolism.[93] Acylated ghrelin was intravenously administered for 3 weeks in a restricted number of HF patients (n = 10). Positive results such as improvement of muscle strength and increased lean body mass were observed in this study.[94] Anamorelin, a ghrelin receptor agonist, was tested in tumor-bearing mice and showed positive results in preventing, but not reversing,

reduced food intake and weight loss when administered in early stages of cancer.[95] Promising results regarding oral administration of anamorelin in cancer patients with cachexia come from Japan—in a phase II randomized trial,[96] 181 non–small-cell lung cancer patients were divided into 3 groups: one receiving 50 mg of anamorelin daily, the second, 100 mg of anamorelin daily, and the third one receiving placebo. Lean mass change, muscle strength, body weight, performance status, and quality of life were examined after 12 weeks. After the follow-up period, the group treated with 100 mg of anamorelin exhibited an improvement in all these variables except muscle strength. Interestingly, the agent was approved in Japan in December 2020 for the treatment of cancer cachexia in 4 types of carcinoma (gastric cancer, non–small-cell lung cancer, colorectal cancer, and pancreatic cancer), but not by the United States Food and Drug Administration and European Medicines Agency, which requested a further phase III study that is currently underway.[97] This is the first step towards a promising frontier of cachexia management. However, the potential use of these novel agents to treat wasting syndromes is limited by multiple factors: study groups are heterogeneous in terms of cancer entity and cancer stage. Moreover, the majority of clinical trials investigate cancer patients: data on patients with other chronic diseases and cachexia are scarce or come from small studies.[98]

β-Blockers have shown muscle-protective properties. Patients with HF (with left ventricular ejection fraction <25% and dyspnea at rest or with minimal exertion; n = 2289) were recruited in the COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival) trial[99] and randomized to treatment with carvedilol (n = 1156) or placebo (n = 1133). It was reported that the group receiving carvedilol preserved the body weight in comparison with the placebo group during 24 months of follow-up. In addition, carvedilol prevented cachexia in this study population: 10% of patients in the carvedilol group in comparison with 14% in the placebo group developed cachexia during the follow-up period (P = 0.005).

β-Blockers have been also adopted in the treatment of cancer cachexia. Through β and central 5-HT1α receptors, espindolol exerts proanabolic (by stimulating β2 receptors) and anticatabolic (by blocking β1 receptors) effects. This drug was studied in a randomized placebo-controlled trial (ACT-ONE) involving 87 patients with non–small-cell lung cancer or colorectal cancer who developed cachexia.[100] A weight gain of 2.83 kg (95% CI, 1.00–3.68) was observed in the treatment group compared with a weight loss of 0.99 kg (95% CI, –3.97 to 1.52) in the placebo group. The group receiving espindolol showed an increased lean body mass in comparison with the placebo group (1.76 kg; 95% CI, 1.43–3.18 vs 0.57 kg; 95% CI, –0.01 to 1.71; P = 0.012), and improved muscle strength measured through the handgrip strength test (P = 0.013). Despite initial promising results, larger studies are needed to validate the effects of β-blockers on cachectic patients.

Conclusions Sarcopenia and cachexia are frequent comorbidities in chronically ill patients, they aggravate the underlying disease and negatively influence the clinical outcome. As such, more research is needed to better understand the underlying mechanisms, which is essential for the development of customized diagnostic and therapeutic targets for both conditions. Furthermore, worldwide accepted definitions are required for sarcopenia and cachexia in order to facilitate earlier diagnosis and enable clinicians to make better treatment decisions. Additionally, future directions should explore effective preventive strategies against wasting syndromes. An increase in the number and scale of clinical trials is also warranted to confirm the safety and effectiveness of therapeutic agents in patients with chronic diseases.

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