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Publication trends in cachexia and sarcopenia in elderly heart failure patients

Jochen Springer · Stefan D. Anker

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Summary The loss of skeletal mass – sarcopenia and cachexia – is considered to be a major contributor to morbidity and mortality in chronic heart failure (CHF). Unfortunately, sarcopenia is generally considered to be a geriatric syndrome, but not necessarily seen as a comorbidity in CHF, even though it has a wide range of adverse health outcomes. While there were 15,574 publication with the title word "heart failure" in PubMed in the 5-year period from 1 June 2011 to 31 May 2016, only 22 or 71 publications were found with the search combination "sarcopenia" or "cachexia" (title word) and "heart failure" (all fields), respectively. This shows very clearly that loss of muscle quality and function due to heart failure is still an underappreciated problem in the medical field.

Keywords Chronic heart failure · Sarcopenia · Cachexia · Muscle · Geriatrics

Introduction

Cardiovascular illness, such as acute [1, 2] or chronic heart failure (CHF) is a highly prevalent condition among the elderly affecting approximately 2% of the population in the developed world [3–5]. The prevalence of CHF doubles approximately every 7 years in females and every 10 years in males beyond the age of 55 years. This sharp increase with age results in elderly people being 80% of all patients with CHF. Particularly in Asia a rise in numbers of patients with heart failure is expected [6–10]. Distinct differences in prevalence and clinical features may occur between regions in the world. As an example, Egyptian patients presented at a much younger age, women were less represented, and obesity was more prevalent in the hospitalized cohort. The majority of the patients had HF with reduced ejection fraction [11]. Overall, CHF leads to a considerable morbidity, institutionalization and mortality [12–15] and studies to obtain a better understanding of the care needs of CHF patients are needed [16]. Muscle atrophy, particularly of the lower limbs, is a common comorbidity in advanced stages of CHF and associated with reduced exercise capacity [17, 18] and frailty [19, 20] and the latter may be a risk marker for adverse outcomes in CHF [21]. Sarcopenia is a common comorbidity in the elderly population [22, 23] and has also been shown to be associated with increased mortality independent of age and other clinical and functional variables [24–26]. In a large retrospective study with 18,363 people aged ≥65 years who participated in the Collaborative Research on Ageing in Europe survey conducted in Finland, Poland, and Spain, as well as the World Health Organization (WHO) study on global AGEing conducted in China, Ghana, India, Mexico, Russia, and South Africa, between 2007 and 2012, the prevalence of sarcopenia ranged from 12.6% (Poland) to 17.5% (India), and that of sarcopenic obesity ranged from 1.3% (India) to 11.0% (Spain) [27]. Human data show that an approximately 30% reduction in muscle cross-sectional area and an approximately 40% decline in muscle strength are observed at 70 years [28]. Moreover, sarcopenia may be a risk factor for cardiovascular disease in non-obese men [29].

The most common form of heart failure in older adults is heart failure with preserved ejection fraction (HFpEF), [30], which shows a high prevalence of sarcopenic obesity [31–33] and can also be recapitulated in the Dahl salt sensitive rat model of heart failure [34]. In the SICA-HF study 19.5% of the patients

PD Dr. J. Springer (✉) · S. D. Anker
Institute of Innovative Clinical Trials, Department of Cardiology and Pneumology, University Medical Centre Göttingen, Robert-Koch-Str. 40, 37075 Göttingen, Germany
Jochen.springer@med.uni-goettingen.de

showed muscle wasting associated with a reduced exercise capacity [35]. This may be due to an abnormal energy metabolism, mitochondrial dysfunction, and a transition of myofibers from type I to type II. These skeletal muscle abnormalities can be classified as either low endurance due to mitochondrial dysfunction or reduced muscle mass or strength due to an imbalance of protein synthesis and degradation [36–38]. Interestingly, CHF has been shown to induce divergent antioxidative and metabolic but similar catabolic responses between the diaphragm and quadriceps muscles [39]. The enhanced catabolic status seen in CHF patients leads to exercise intolerance, ventilatory inefficiency, and chronotropic incompetence, as well as insulin resistance suggesting a significant contributing mechanism to the limited functional status. [40, 41].

A variable degree of malnutrition is often superimposed on poor nutrient intake due to inflammatory cytokines [42], which are also associated with anorexia in sarcopenia [43]. Malnutrition and sarcopenia often occur in patients undergoing rehabilitation. The prevalence of malnutrition and sarcopenia in older patients undergoing rehabilitation was found to be 49–67% and 40–46.5%, respectively [44]. A major problem associated with sarcopenia is its definition and detection [45–48]. Conclusive biomarkers are lacking, even though a lot of research effort has been focused on the development of such biomarkers [49–52]. Recently, neuromuscular junction fragmentation was suggested to contribute to sarcopenia in CHF [53]. Sarcopenia in CHF may ultimately lead to cardiac cachexia, [54, 55], which is associated with a poor prognosis [56, 57]. The prevalence of cardiac cachexia has been estimated to be 10% in the current heart failure population, a drop from earlier numbers of up to 40% due to an improved treatment of heart failure [58]; however, other studies estimated a prevalence of 5–15% in CHF and the mortality rates of patients with cachexia ranged from 10–15% per year in chronic obstructive pulmonary disease (COPD) through 20–30% per year in CHF and chronic kidney disease [59]. Cardiac cachexia has a dramatic prognostic impact in CHF patients, with an 18-month mortality rate of up to 50% [60].

Heart failure trials

There have been a significant number of new trials in the cardiovascular field over the last few years. Drug trials [61–67] as well as surgical [68, 69] and pathophysiological studies [7, 70–75] have increased our knowledge in the field. While the results of a study focused on continuous positive airway pressure (CPAP) for cardiovascular protection were neutral [76], other device-based therapies showed more promising results, e. g. cardiac resynchronization therapy in stage 3 chronic kidney disease [77]; however, no benefits of primary implantable cardioverter defibrillator (ICD) therapy were seen in pivotal trials in patients aged 66 years or over who received ICDs during a hospital admission for exacerbation of heart failure or other acute comorbidities [78]. The ixCELL-DCM multicellular therapy study using cells produced from a patient's own bone marrow and involving 126 patients with CHF due to ischemic dilated cardiomyopathy, New York Heart Association (NYHA) class III or IV, resulted in a significant reduction in adjudicated clinical cardiac events [64]. This method would eliminate the ethical conundrum of using embryonic stem cells as cardiac progenitor cells, which may also be safe to use [79].

All these aforementioned trials and studies have one thing in common: they all focus on the heart itself and have not assessed the metabolic changes or the quality and function of the skeletal muscle that is often impaired in HF. In contrast, critically ill patients in intensive care units (ICU) including HF patients are recognized to develop not only ventilator-induced diaphragmatic dysfunction (VIDD) and associated atrophy of the diaphragm but also wasting of skeletal muscles that cannot be explained by disuse atrophy alone, which was termed intensive care unit-acquired weakness (ICUAW) [80, 81]. This may lead to increased dependence on caregivers in surviving patients with one study reporting the number to be 57% of survivors after a 1-year follow-up period [82]. Although ICUAW has received more attention as a clinical entity, identifying high-risk patients and understanding the role of ICUAW in long-term outcomes after critical illness requires more attention [83].

Number of publications in the field

In the 5-year period from 1 June 2011 to 31 May 2016, there have been 54,343 publications including the search term "heart failure" (all fields) even with the limitation of "heart failure" (title word) 15,574 publications were found and of the latter 11,665 publications included humans of which 2442 were reviews. Using the title word "sarcopenia" only 972 hits were found on PubMed and 626 involved human subjects of which 163 were reviews. The title word "cachexia" was found in 675 publications, 364 including humans of which 155 were reviews. The search combination of the title word "sarcopenia" with "heart failure" (all fields) resulted in a mere 22 hits over the 5-year period. Of these, 14 involved humans and of these 5 were reviews (Fig. 1). The combination of "cachexia" (title word) and "heart failure" (all fields) delivered 71 publications with 41 including humans of which 23 were reviews (Fig. 2). This shows very clearly that loss of muscle quality and function due to heart failure is an underappreciated problem in the medical field.

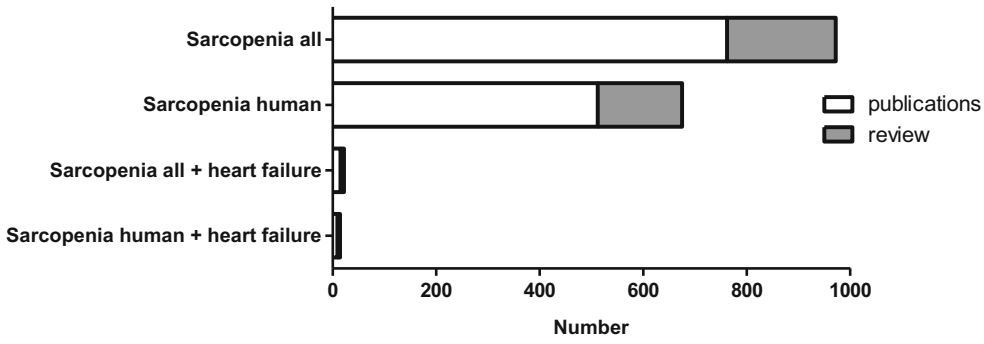

Fig. 1 The overall number of publications, including reviews (*grey*) with sarcopenia as a title word is shown for the 5-year period from 1 June 2011 to 31 May 2016. Unfortunately, there are only few publications concerning sarcopenia in CHF, as evidenced by the combination of sarcopenia (title word) and heart failure (all fields)

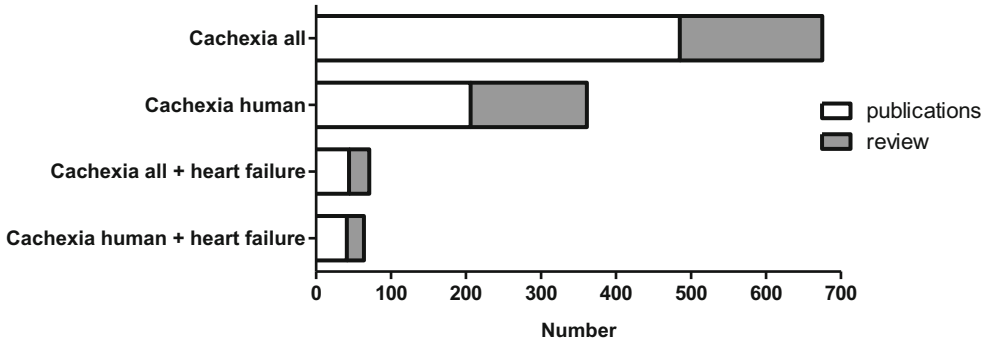

Fig. 2 The overall number of publications, including reviews (*grey*) for cachexia as a title word is shown for the 5-year period of 1 June 2011 to 31 May 2016. The number of publication with the combination of cachexia (title word) and heart failure (all fields) is very low

Sarcopenia and heart failure

Although sarcopenia is considered primarily to be a geriatric phenomenon, its progression is accelerated by the co-occurrence of various disease conditions, including CHF [84, 85]. Indeed, sarcopenia in older adults with CHF affects approximately 20% of the patients and thereby exceeds the prevalence observed in individuals of the same age without CHF resulting in a lower exercise capacity than in CHF patients with preserved muscle mass and function [35] In a group of 200 stable CHF patients muscle wasting was detected in 19.5% suggesting that skeletal muscle wasting is common in CHF patients and is associated with worse exercise capacity and reduced left ventricular ejection fraction [17]. Elderly male cardiac patients with sarcopenia had significantly lower physical activity levels compared to non-sarcopenia patients [86, 87]. Sarcopenia, defined as low fat-free mass index, is associated with an unfavorable prognosis in patients with CHF [32, 47] leading to increased mortality [56]. Using bioimpedance analysis to quantify skeletal muscle mass and gait speed to assess muscle function, a prevalence of sarcopenia of 36.5% was found in a cohort of 4425 elderly persons with a mean age of 70 years. In this study sarcopenia was associated with an increased risk of cardiovascular-specific mortality among females (HR 1.61, 95% CI 1.22–2.12, $p = 0.001$) but not among males (HR 1.07, 95% CI 0.81–1.40, $p = 0.643$); ($p = 0.079$) [26]. A recent review of the Asian Working Group for Sarcopenia estimates a prevalence of sarcopenia in Asia ranging between 4.1% and 11.5% of the general older population [9]. These dramatic differences in the prevalence of sarcopenia in study populations is probably due to the fact that there is still no worldwide accepted standard definition of sarcopenia and its diagnosis [22, 45, 48, 88]. In fact, seven clinical approaches to establish the diagnosis of sarcopenia in practice have been proposed since 1998 [45, 89–94]. For example, the European Working Group on Sarcopenia in Older People (EWGSOP) includes muscle mass, muscle function, muscle strength in the definition and has specified subgroups [90]. In contrast the International Working Group on Sarcopenia (IWGS) uses only muscle mass and function in thedefinition and has not identified subgroups [93]. The Foundation for the National Institutes of Health (FNIH) sarcopenia project defines muscle mass as low appendicular lean mass divided by body size, muscle strength as handgrip strength below 26 kg for men and below 16 kg for women, muscle function as a gait speed below 0.8 m/s and has identified two subgroups of sarcopenia [95]. This makes developing robust biomarkers for the loss of skeletal muscle mass imperative and ideally these biomarkers should be able to distinguish between sarcopenia, frailty and cachexia [18, 49–52]. Candidates, such as *N*-terminal peptide of procollagen type III (P3NP) and C-terminal agrin fragment (CAF) could possibly be used as circulating biomarkers of muscle mass [51].

Generally, the therapeutic options for sarcopenia include nutritional support [96], exercise [97, 98] and drug treatment, such as testosterone [99]. A viable and relatively low-cost treatment is the combination of nutritional supplements and resistance training, which

in combination increases in muscle mass, strength further than exercise alone [44, 100, 101]. Interestingly, the beneficial effect of resistance exercise training was also observed in breast cancer patients receiving adjuvant chemotherapy and sarcopenia, [102] possibly by an increased insulin sensitivity; however, in 518 men aged 40–79 years low levels of testosterone or vitamin D did not predict the loss of muscle mass, gait speed, or grip strength in middle-aged and elderly men, while low insulin-like growth factor-1 (IGF-1) was found to be predictive for a change in change in gait speed in men aged ≥70 years [103]. Exercise training has been established as an evidence-based therapeutic strategy with prognostic benefits in many cardiovascular diseases, including HFrEF and the HFrEF form of CHF by improving risk factors, such as hyperlipidemia, hypertension and coronary endothelial function [104]. Aerobic exercise training not only attenuates the impairment of cardiac function in the transition from cardiac dysfunction to heart failure but also has protective effects on the skeletal muscle, possibly by an anticatabolic action of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α) [105]. Moreover, aerobic exercise training has been shown to reduce and counteract redox imbalance and ubiquitin-proteasome system (UPS) over-activation thus preventing muscle atrophy and exercise intolerance in sympathetic hyperactivity-induced heart failure in mice [106]. A similar effect was seen in a study of 37 patients with severe CHF, where a 12-week exercise regime reduced the expression of the E-3 ubiquitin ligase Rnf28, thus attenuating the catabolic drive and increasing muscle cross-sectional area [107]. A reduction in MuFR-1 expression in skeletal muscle of CHF patients though exercise has also been described [108]. This has also been observed in various animal models of muscle atrophy including CHF [109]. A down-regulation of MAFbx by administering the endogenous nitric oxide donor S-nitrosoglutathione was seen in a mouse model of CHF and also improved the expression of extracellular superoxide dismutase, which can also be increased by exercise [110]. Moreover, 12 weeks of exercise have been show to counteract the rise of myostatin levels, a negative regulator of muscle growth, in patients with late stage CHF (NYHA IIIb) [111] and to increase levels of the growth hormone secretagogue ghrelin [112]; however, the level of daily physical activity in most patients with CHF is low and a study planned to overcome this obstacle will rely on the use of a structured access to a Wii game computer [113]. Interestingly, an association of limited exercise capacity and limited heart rate rise during exercise – chronotropic incompetence (CI) – is commonly observed in CHF, which may have extensive consequences for pacemaker programming and the use of heart rate lowering agents [74].

In summary the prevalence of age-related loss of muscle mass is expected to increase sharply over the next decades. Particularly in patients with CHF, sarcopenia is a major factor of reduced quality of life, as well as in the progression to frailty and cardiac cachexia.

Cachexia in heart failure

Advanced CHF has been associated with progressive weight loss and emaciation in approximately 10–15% of patient populations. Unfortunately, CHF is a common problem and afflicts over 10% of older persons [58, 114, 115]. The mortality rates of cardiac cachexia are estimated to be 20–30% per year [59]. Older patients with multiple comorbidities associated with muscle wasting are also likely to be at elevated risk of respiratory muscle atrophy and functional loss [116]. The mechanism of cardiac cachexia is similar to that of cancer cachexia and is thought to include increased resting energy expenditure, decreased nutrient absorption, decreased energy intake, increased inflammatory cytokines, neurohormonal activation, and impairment of skeletal muscle growth hormones [42, 98, 117–121]. This leads to an imbalanced metabolism resulting in a catabolic state and loss of muscle mass [122–125]. Additionally, iron deficiency has been observed to frequently complicate inflammatory-mediated chronic disorders, irrespective of anemia, particularly in patients with a low body mass index (BMI) [126, 127]. Moreover, adipokines such as adiponectin have been shown to be involved in the regulation of skeletal muscle metabolism and adiponectin levels increase with progressing disease severity in CHF patients, suggesting adiponectin resistance [128]. Unfortunately, cachexia also seems to change the pharmacokinetics of several compounds [129]. This shows that cardiac cachexia is a complex multifactorial syndrome, which has no approved drug therapy. Again, clinically relevant biomarkers would contribute for the diagnosis and management of cardiac cachexia as well as for the establishment of new therapeutic targets [52, 119, 130] and to differentially recognize sarcopenia from cachexia in CHF [55].

An induction of myostatin expression in the myocardium after cardiac insult has been shown to be causally involved with skeletal muscle wasting. This up-regulation occurs rapidly after cardiac ischemia and may be involved in peripheral protein degradation by activating atrogin1 and MuRF1 [131, 132]. In cachexia research, myostatin makes an attractive therapeutic target and several compounds are in development [133]. Interestingly, a significant reduction of myostatin by exercise training in skeletal muscle was seen in patients with advanced CHF (NYHA IIIb) [111]. Reduced levels of testosterone and its metabolite dehydroepiandrosterone contribute not only to loss of muscle mass in CHF but also to depression that increases with disease severity [134]. Testosterone therapy may be beneficial in CHF [135, 136], but there can be side effects seen in traditional testosterone supple-

mentation, particularly in female patients. The novel, orally active, ghrelin receptor agonist anamorelin is in clinical development for the treatment of (cancer) cachexia. It enhanced body weight, tended to improve handgrip strength, increased appetite and quality of life and decreased inflammatory markers [137]. The use of branched chain amino acids (BCAA) in a rat model heart failure model has been described to preserve the body weight and cardiac function and prolonged survival. The expression of genes involved in mitochondrial biogenesis and function in skeletal muscles was increased by BCAA [138]. Leucine supplementation alone modulated heart damage, cardiomyocyte proteolysis, and apoptosis driven by cancer cachexia. [139]. Interestingly, the beta blocker espindolol at 10 mg BID has been shown to significantly reverse weight loss, improve fat free mass, and maintain fat mass in advanced cancer cachexia. Espindolol was associated with a significant improvement in handgrip strength [140]. In healthy aged rats, espindolol use led to a reduction of fat mass while increasing fat free mass, without having any negative effects on cardiac function [117]. Additionally, beta-2 receptor agonists, such as formoterol may be an option to increase muscle mass, as they has been shown to also have positive effects on cardiac function in a rat model of cancer cachexia [141].

Taken together, all these studies show that cardiac cachexia is still a fairly common problem, which has a major impact on survival of CHF patients. Unfortunately, there are no clear treatment strategies, although exercise seems to be generally beneficial and drug candidates are being studied.

Conclusion

Although sarcopenia and cachexia have a major impact on outcome in CHF, only relatively few studies have been conducted with a focus on these complex multifactorial comorbidities/syndromes. Hence there is an urgent need to conduct more basic research as well as clinical trials; however, there are difficulties with clinical definitions of the syndromes, particularly for sarcopenia, which makes the design of clinical studies with a meaningful endpoint problematic at best.

Conflict of interest J. Springer and S.D. Anker declare that they have no competing interests.

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