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REVIEW

Metabolic disorders in heart failure and cancer

Alessia Lena[1,2,3,4], Andrew J.S. Coats[5] and Markus S. Anker[1,2,3,4]*

[1]*Division of Cardiology and Metabolism, Department of Cardiology, Charité, Berlin, Germany;* [2]*Berlin-Brandenburg Center for Regenerative Therapies (BCRT), Berlin, Germany;* [3]*DZHK (German Centre for Cardiovascular Research), partner site, Berlin, Germany;* [4]*Department of Cardiology, Charité Campus Benjamin Franklin, Berlin, Germany;* [5]*IRCCS, San Raffaele, Pisana, Rome, Italy*

Abstract

In an aging population, the number of patients affected by heart failure and cancer is constantly increasing and together these two conditions account for more than 50% of all deaths worldwide. Both diseases share similar risk factors including smoking, obesity, and hypertension. Presenting symptoms may also be similar, with patients frequently complaining of dyspnea, fatigue, and anorexia. Many affected patients, especially those with more advanced heart failure or cancer, suffer also from metabolic disorders. These can lead eventually to muscle wasting, sarcopenia, and cachexia. These complications are associated with increased morbidity, a poorer quality of life, a worse prognosis and indeed they represent an independent risk factor for the advancement of the underlying disease itself. Very few therapeutic options have been established to treat these co-morbidities. For sarcopenia the only validated treatment is resistance training. Moreover, there is currently no guideline recommended therapy for the treatment of cachexia. New treatment strategies are urgently needed to prevent and treat muscle and wasting disorders in patients with chronic diseases such as cancer and chronic heart failure.

Keywords Cachexia; Sarcopenia; Heart failure; Cancer

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**Correspondence to: : Markus S. Anker, Department of Cardiology, Campus Benjamin Franklin (CBF), Charité University Medicine, Berlin, Germany.
Email: markus.anker@charite.de*

Introduction

World-wide more than 55 million patients suffer from either cancer or heart failure.[1,2] More than 5% of all medical expenditure in the western world is related to either cancer and heart failure treatment.[3–5] Both disease states can mimic each other and often present with similar symptoms such as weakness, dyspnoea, oedema, severe weight loss, anorexia, sleep problems, and depression.[6–10] They share similar risk factors including obesity, hypertension, and tobacco smoking.[11,12] It is also known that modern day anti-cancer treatments are commonly associated with cardiotoxicity which can aggravate or precipitate acute or chronic heart failure.[13] Newer research has shown that oncometabolites, secreted by tumours, can also cause cardiovascular dysfunction independent of cardiotoxic effects of anti-cancer treatments,[14,15] but much more research is needed is this area.[16,17] Once heart failure develops it is associated with high 5-year mortality rates of 50% or more.[18–20] Vice versa it is currently unclear whether heart failure itself can cause cancer.[21,22] Unfortunately major randomized controlled trials in both conditions usually list the other as an exclusion criterion, so that we have less trial evidence of the interaction between HF and cancer. To better understand the problems[23–25] and necessities[26–28] of both patient groups it is essential to include patients in large scale, multicentre, international registries.[29–32] They enable us to better understand how patients are being treated in a real world scenario[33–35] and how this effects outcomes such as quality of life, morbidity, and mortality.[36–39] Registries also allow us the unique possibility to examine the wide-range of co-morbidities of heart failure patients. So far, a lot of research has focused on anaemia,[40,41] iron deficiency,[42,43] kidney disease,[44,45] chronic obstructive pulmonary disease,[46,47] sleep apnoea,[48,49] liver dysfunction,[50,51] and sexual dysfunction.[52,53] Newer research in heart failure and cancer also focuses on the understanding and more importantly, on how to treat anorexia,[54,55] cachexia,[56,57] and sarcopenia.[58,59] These rather new areas of research are a common problem in chronic diseases, gaining growing attention from the scientific community.[60,61] Recent epidemiological data[62] show that patients affected by chronic heart failure (CHF) or cancer are at major risk of developing these conditions. The prevalence of cachexia in CHF ranges from 5–15%[63–65] and in advanced

cancer from 50–80%.[66,67] Likewise, muscle loss disorders frequently occur in 20% of older CHF patients[68] and 30–70% of metastatic cancer patients.[69]

Sarcopenia

Sarcopenia represents a wide-spread complication in patients with chronic diseases.[70–73] Fulster *et al*.[74] has shown in data from the SICA-HF trial that 20% of CHF patients are affected by muscle wasting. Even in the healthy elderly, aged 60–70 years, the prevalence of sarcopenia is reported to be at 5–13%, increasing to up to 50% in those over 80.[75] This important co-morbidity is not only associated with muscle mass depletion but also various impairments in muscular performance.[76] In particular, in younger patients with cardiomyopathy[77] muscle wasting contributes to cardiovascular decline and can lead to a worsening in their clinical condition and exercise capacity. In elderly patients, sarcopenia is related to more frequent hospitalization and increased mortality.[78]

Ongoing studies are currently investigating possible molecular and cellular pathways responsible for the development of sarcopenia in many chronic diseases.[79] Preclinical studies have shown that Cardiac Troponin T (cTnT) expression[80] in skeletal muscle is increased as a consequence of ageing processes. Recently, growth differentiation factor 15 has been found to be upregulated in patients with chronic obstructive pulmonary disease (COPD) and to be associated with loss of skeletal muscle mass.[81] In CHF, recent findings[82] postulate a correlation between adiponectin resistance and skeletal muscle impairments. Other preclinical studies are directed to a better understanding of anabolic signaling pathways. L-leucin active metabolite, β-hydroxy-β-methylbutyrate (HMB),[83] was discovered to stimulate protein synthesis in rats suffering from wasting disorders, suggesting that HMB may be considered a helpful supplement to decrease the catabolic processes. Furthermore, an overexpression of miRNA-675 and abnormalities in the acetylation of H19 gene has been described in a cohort of older men with COPD, compared to healthy controls.[84]

To identify patients that are at increased risk of developing sarcopenia a new symptom score has been introduced: SARC-F.[85] Such scores are important since muscle wasting can even occur in patients one would clinically not suspect to be at increased risk. Hence, it has been shown that sarcopenia also frequently occurs in overweight patients,[86] suggesting that not only a low body mass index (BMI) predicts muscular depletion, but also other factors, such as reduced physical activity. These factors have an incremental role in the development of catabolic processes in the elderly community.

The current gold standard to diagnose sarcopenia is a dual energy X-ray (DXA) scan.[87] Another important, minimal risk and easy to use diagnostic tool to gather more evidence in patients with suspected sarcopenia is bioelectrical impedance spectroscopy.[88] This has been shown to be a good predictor of sarcopenia in normal- and underweight older patients affected by end-stage chronic kidney disease.[89] Lastly, muscle biopsies are also informative, although rarely used in clinical practice.[90] An important validated contribution to define the negative impact on quality of life due to a decline in muscular capacity in sarcopenic patients was recently introduced by the self-administered SarQoL questionnaire.[91]

Even though sarcopenia is recognized as a separate co-morbidity, treatment options remain limited. Evidence is gathering, that resistance training and treatment with aminoacids can prevent worsening of muscle wasting.[75,92,93] Various other drugs including testosterone, androgen receptor modulators, IGF-1, growth hormones, and drugs targeting the myostatin signalling pathway are currently being investigated for their potential to improve muscle wasting.[94] However, these treatments can also cause unwanted side effects. More effort is needed to discover and investigate new treatments with the aim of improving the burden of morbidity and quality of life occasioned by these muscle-related complications of the common chronic diseases.

Cachexia in heart failure

Cachexia is a multifactorial metabolic disorder[95] that is often seen in patients affected by chronic diseases such as CHF. It is primarily defined by weight loss of more than 5% and other coincident factors like decreased muscle strength, fatigue, anorexia, low fat-free mass index and abnormalities in blood biomarkers (elevated C-reactive protein and/or elevated interleukin (IL)-6, Hb <12 g/dL, or low serum albumin (<3.2 g/dL)).[96–98] Cachexia occurs when the physiological balance between anabolic and catabolic signalling is dysregulated.[99] This is accompanied by clinically evident malnourishment, systemic nutritional deficiencies, increased inflammation cytokines, immune system hyperactivity and neurohormonal alterations. Possible new biomarkers for the diagnosis of cachexia include pre-albumin, as a potential indicator of undernutrition and low-cholesterol levels, as an indicator of worse prognosis in CHF patients.[100]

Strategies to counteract and prevent the progress of wasting in CHF so far primarily include dietary supplements, while regular physical exercise plays a key role in maintaining the skeletal muscle status and prevent loss of lean mass.[65,101,102] Lately, an analysis of the COPERNICUS[103] trial has shown that carvedilol has the potential to stop and partially reverse wasting in cachectic patients with severe CHF (left ventricular ejection fraction $<25\%$ and dyspnoea at rest or during minimal work). The effects of other supplements including essential amino acids, omega-3 polyunsaturated fatty acids or pharmacological agents like immunomodulators,

anabolic hormones, appetite stimulants, and other new drugs are currently under investigation.[104]

Cachexia in cancer

Cachexia is a clinical phenomenon also observed in cancer patients. It is associated with worse clinical outcomes, quality of life and survival.[105,106] In end-stage cancer patients the overall metabolic rate is frequently significantlly increased, which is sometimes referred to as hypercatabolism.[103] Among the more recent findings, Iwata *et al*.[107] demonstrated that muscle wasting in cancer cachexia follows a different pathway of muscular damage from the one established in muscle dystrophies. In genomic studies, cachexia-related body mass index alterations in gastrointestinal cancer patients were found to be linked to the Cytokinesis 1 gene[108] and a transcriptome array study by Narasimhan *et al*. [109] identified specific abnormalities in alternative splicing of genes in patients with cancer cachexia.

Possible treatments that have been shown to be effective in preclinical studies include leucine[110] and megestrol acetate.[111] Furthermore, targeting muscle ring finger 1 (MuRF1) with small molecules also resulted in attenuation of catabolic effects on both skeletal and heart muscle.[112] So far, no validated strategies have been determined to correctly manage wasting disorders in cancer: dietary supplements have been suggested but their positive effects in improving the catabolic alterations are limited.[113] Since in cancer and heart failure dysregulation of the autonomic system is present,[114] the administration of the beta-blocker espindolol was tested in a randomized, placebo controlled, double blind phase II trial in end-stage non-small-cell lung and colorectal cancer patients.[115,116] The results obtained were promising since weight loss was reversed, and fat free mass and handgrip strength significantly increased.

Conclusions

Despite recent progress, more effort is needed to better understand metabolic disorders including muscle wasting and cachexia in heart failure and other chronic diseases in the quest to find specific therapies. More research is needed to prevent and treat these conditions in patients at risk. In clinical practice a multidisciplinary approach is required to optimize the treatment of patients with such co-morbidities. Several ongoing trials have the aim to enhance the knowledge on wasting disorders and prove the effectiveness of new treatment strategies.

Conflict of interest

A.L. reports no conflict of interest. M.S.A. reports receiving personal fees from Servier. A.J.S.C. reports receiving personal fees from Astra Zeneca, Impulse Dynamics, Menarini, Novartis, Actimed, Nutricia, Resmed, Faraday, Gore, Respicardia, Servier, Stealth Peptides, Verona, and Vifor.

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