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REVIEW

Muscle wasting and sarcopenia in heart failure and beyond: update 2017

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Abstract

Sarcopenia (loss of muscle mass and muscle function) is a strong predictor of frailty, disability and mortality in older persons and may also occur in obese subjects. The prevalence of sarcopenia is increased in patients suffering from chronic heart failure. However, there are currently few therapy options. The main intervention is resistance exercise, either alone or in combination with nutritional support, which seems to enhance the beneficial effects of training. Also, testosterone has been shown to increased muscle power and function; however, a possible limitation is the side effects of testosterone. Other investigational drugs include selective androgen receptor modulators, growth hormone, IGF-1, compounds targeting myostatin signaling, which have their own set of side effects. There are abundant prospective targets for improving muscle function in the elderly with or without chronic heart failure, and the continuing development of new treatment strategies and compounds for sarcopenia and cardiac cachexia makes this field an exciting one.

Keywords Muscle wasting; Sarcopenia; Cardiac cachexia

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Introduction

Cardiovascular disease is a highly prevalent group of disorders including chronic heart failure (CHF) in the elderly population with numbers affected reaching approximately 2% of the population.[1,2] CHF prevalence increases strongly with age and its rates double approximately every 10 years in male and every 7 years in female patients after 55 years of age; hence, the majority of CHF patients are elderly to very old and the numbers of affected people are expected to rise with the increased overall life expectancy, particularly in Asia.[3–6] Overall, CHF leads to a significant morbidity, institutionalization and mortality, as well as to an enormous socio-economic burden[6] and studies focusing on the care and needs of the patients are desirable.[7] The most common form of CHF is heart failure with preserved ejection fraction.[2] Interestingly, heart failure with preserved ejection fraction patients demonstrate a high prevalence of sarcopenic obesity.[8–10] In advanced stages of CHF, a loss of skeletal muscle mass (sarcopenia) is commonly observed which contributes to reduced exercise capacity and frailty,[11–13] which may represent a risk marker for adverse outcomes in CHF.[14] Sarcopenia itself is a common occurrence in the aged population[15,16] and is associated with increased mortality independently of age or other clinical and functional variables.[17,18,19,20] A retrospective study involving more than 18 000 subjects aged >/=65 years showed that the prevalence of sarcopenia in the general population ranged from 12.6% (Poland) to 17.5% (India) and that of sarcopenic obesity ranged from 1.3% (India) to 11.0% (Spain).[21] Interestingly, sarcopenia itself may be a risk factor for cardiovascular disease in non-obese men[22] and may predict adverse outcome in CHF.[14] However, using a combined lean mass and gait speed approach, sarcopenia was found in 36.5% subjects in a cohort of approximately 4400 with a mean age of 70 years, which was associated with an increased risk of cardiovascular-specific death for women, but not men.[19] A gender-specific effect was also seen in a rat model of ageing with males being more prone to muscle loss, particularly when fed a high fat diet.[23] Sarcopenia is also associated with standard R-CHOP chemotherapy intolerance in patients with malignancies[24] and

worse survival of patients with ovarian cancer receiving neo-adjuvant chemotherapy.[25]

Sarcopenia in heart failure

Sarcopenia is considered to be a primarily age-dependent syndrome and was initially defined as the age-related loss of skeletal muscle of the limbs 2 SD below the mean of a healthy young reference group, and has been associated with a range of adverse outcomes.[26–28] In contrast to cachexia, sarcopenia and muscle wasting cannot be diagnosed by simply weighing the patients longitudinally to detect unintentional weight loss.[29]

Sarcopenia affects 5–13% of elderly persons aged 60–70 years and up to 50% of all octogenarians.[30] In Asia, the prevalence of sarcopenia is thought to range from 4.1% and 11.5% of the general older population.[31] Sarcopenia is not only limited to the loss of muscle mass but is also associated with muscle dysfunction and impaired physical performance, which may be exacerbated by chronic diseases.[32] However, the major problem with the development of sarcopenia therapies is its lack of definition and hence its detection.[10,33] Unfortunately, despite large research efforts both by academic and industry, decisive and validated biomarkers are still lacking making the detection of sarcopenia difficult.[34–37] As a result, the definition of sarcopenia has been adapted to include measurements of impaired physical function, such as slow walking speed and/or low grip strength,[29,38] and a sarcopenia-specific questionnaire on Quality of Life has recently been described.[39] Unfortunately, there are several definitions of sarcopenia using different cut-off values,[40,41] which were all confirmed to be independent factors of adverse outcomes.[42]

In CHF, the prevalence of patients with sarcopenia is higher at 20% compared to healthy subjects of the same age.[43] A recent study suggests an even higher prevalence of 47% in young patients (<55 years of age) suffering from dilated cardiomyopathy.[44] This may be caused by an abnormal energy metabolism coupled with mitochondrial dysfunction, as well as a transition of myofibers from type I to type II.[45–47] In CHF, divergent anti-oxidative and metabolic but similar catabolic responses, i.e. wasting of myofibrillar proteins, of the diaphragm and quadriceps muscles have been observed.[48] The increased catabolic stress in the skeletal muscle of CHF patients results in exercise intolerance, ventilatory inefficiency and chronotropic incompetence, as well as insulin resistance suggesting a significant contribution of the catabolic status mechanism to the patients limited functional status.[49,50] Another contributing factor to sarcopenia is a variable degree of malnutrition that may be caused by inflammatory cytokines,[51–53] which have been known to contribute to anorexia.[54,55] Malnutrition and sarcopenia are also common features of rehabilitation patients in whom the prevalence of malnutrition was 49–67% and that of sarcopenia 40–46.5%.[56] However, in 518 middle-aged and elderly men, low levels of testosterone or vitamin D were not predictive for muscle mass and function, while low IGF-1 was found to predict changes in gait speed in men aged >/=70 years.[57] Moreover, among older adults with normal body mass index physical activity was associated with lower risk of heart failure and death, regardless of healthy eating.[58] In contrast, a high vitamin D deficiency in the elderly was described, which was strongly associated with an increased risk of heart failure.[59]

So far, there are only limited treatment options for sarcopenic patients, which include (resistance) exercise,[60–63] nutritional strategies to increase intake of proteins and micronutrients[64–66] and finally, drug treatment, including compounds like testosterone,[67,68] growth hormone and IGF-1.[69]

Resistance exercise is often used in combination with nutrition support, which increases muscle mass and muscle strength more than exercise alone.[41,70–72] Supplementation of a low dose creatine in combination with resistance training improved lean mass in elderly over a period of 12 weeks.[73] In a patient-centered exercise approach in frail elderly and older adults with mobility limitations, physical activity was considered to improve effective quality of life and reduce frailty, while also being cost-effective.[74] An accelerometer-determined physical activity showed an independent, dose-response relationship with lean mass percentage and lower limb strength.[75] In many cardiovascular diseases including CHF, exercise training has been recognized as an evidence-based therapeutic strategy with prognostic benefits improving risk factor such as hyperlipidemia, hypertension and coronary endothelial function.[76] It has been shown that exercise training not only has cardio-protective effects and slows down the transition from cardiac dysfunction to (chronic) heart failure but also induces anti-catabolic signaling in skeletal muscle, possibly by induction of PGC1α.[77] The beneficial effect of resistance exercise training was also observed on sarcopenia and dynapenia in breast cancer patients receiving adjuvant chemotherapy.[78] However, in a meta-analysis review on the effectiveness of exercise rehabilitation after intensive care unit discharge on functional exercise capacity and health-related quality of life was unable to find an overall effect on these parameters.[79] A novel interesting therapy option is the use of neuromuscular electrical stimulation in HF patients. It seems to be safe and to improve functional capacity, muscle strength and quality of life when compared with conventional aerobic exercise.[80]

As testosterone levels decline at the rate of 1% per year from 30 years of age, which is associated with a reduction in muscle mass and strength,[81] the decline in testosterone has been observed to selectively decrease lower-limb muscle function.[82] Therefore, testosterone seems a perfect

choice to treat sarcopenia. However, there is a fear that it will produce excessive side effects, particularly an increased risk of prostate malignancies and cardiovascular events.[69] Interestingly, the administration route of testosterone seems to influence the cardiovascular risk. In a meta-analysis of 35 randomized controlled trials, oral testosterone induced a significant risk of cardiovascular events, while no significant negative effects were seen when testosterone was given transdermally or by i.m. injections.[83] Therefore, more studies focused on the application route of testosterone are needed, particularly in patients with CHF. The possible severe side effects of testosterone have driven the development of selective androgen receptor modulators like enobosarm, which display the anabolic effects of testosterone, but are thought to have less severe side effects.[84,85] However, MK0773, a 4-aza steroidal drug that has androgen gene selectivity, has shown to improve IGF-1 levels and muscle function in females, but due to increased cardiovascular risk, the trial was terminated.[86]

An alternative therapy option to testosterone and selective androgen receptor modulators may the use of growth hormone and IGF-1, which induces muscle mass and strength. However, a meta-analysis of 31 articles describing 18 independent study populations showed that subjects treated with growth hormone were significantly more likely to experience soft tissue edema, arthralgias, carpal tunnel syndrome and gynecomastia.[87] Up-stream from the growth hormone/IGF-1 axis are several growth hormone secretagogues, of which ghrelin that is mainly produced in the fundus of the stomach has been studied extensively for the treatment of disease-related anorexia and conditions of muscle loss like sarcopenia and cachexia. Ghrelin has been shown to increase food intake in patients with cancer cachexia,[88,89] and anamorelin also improved muscle mass, but unfortunately not muscle strength.[90] Moreover, ghrelin prevented tumour-induced and cisplatin-induced muscle wasting in a mouse model of cancer cachexia.[91] A similar effect was reported in a rat model of cisplatin-induced cachexia, where the growth hormone secretagogues hexarelin and JMV2894 attenuate dysregulation of calcium homeostasis in skeletal muscle.[92]

During the last decade, the negative regulator of muscle growth—myostatin (also termed growth differentiation factor-8)—and its main binding partner, the activin II B receptor, have received much attention in the context of muscle wasting, and several compounds are in clinical development.[29] Naturally occurring myostatin knock-outs in cattle, dogs and human all drastically display increased muscle mass, which was also seen in genetically modified mice.[93] In end-stage human heart failure, the myocardium produces myostatin and its signaling seems to have a gender difference.[94] Interestingly, myostatin released from the myocardium in a mouse model of CHF was shown to be crucially involved in the skeletal muscle atrophy.[95] However, neutralizing antibodies such as MYO-029, AMG 74, LY2495655 or soluble receptor decoys such as ACE-11, ACE-031 seem to have substantial effects on muscle mass and strength, but unfortunately also display a number of side effects including urticarial, aseptic meningitis, diarrhea, confusion, fatigue as well as involuntary muscle contractions.[69]

Other options to increase muscle mass include β_2-adrenergic agonists like salbutamol, clenbuterol and formoterol. These compounds have beneficial effects on muscle mass, most likely via an induction of protein synthesis in myocytes and increased blood flow.[96] Clenbuterol has been shown to increase lean mass and lean/fat ratio as well as a significant increase in maximal strength. However, endurance and exercise duration decreased after clenbuterol,[97] and patients with CHF were prone to develop detrimental ventricular arrhythmias when treated with salbutamol.[98] In contrast, in experimental cancer cachexia, formoterol has been shown to improve muscle mass, reduce progression of cachexia and improve survival, while also being cardio-protective.[99] Espindolol, the s-enantiomer of pindolol, may be the more interesting compound to use. It is a beta-1 receptor antagonist, a partial beta-2 receptor agonist and also has 5-HT1a receptor activities. In old rats, it has been shown to significantly increase muscle mass, while reducing fat mass without negative affecting cardiac function, making it an interesting compound to use in sarcopenic obesity.[100] Also, it has shown very promising results in Phase IIa cancer cachexia study leading to an increase in muscle mass and hand grip strength.[101]

Transition of sarcopenia in chronic heart failure to cardiac cachexia

Sarcopenia in CHF may ultimately progress to cardiac cachexia,[102,103] which is associated with an extremely poor prognosis.[104–106] The current prevalence of cardiac cachexia has been estimated to be 10% in the current heart failure population, a significant improvement from earlier numbers of up to 40%, which is thought to be due to an improved treatment of heart failure itself.[107] However, other studies estimate a prevalence of 5–15% in CHF, and the mortality rates of patients with cachexia range from 10–15% per year in COPD through 20–30% per year in CHF and chronic kidney disease.[5] Cardiac cachexia has a dramatic prognostic impact in CHF patients, with an 18-month mortality rate of up to 50%,[108] and it is particularly high in obese cachectic CHF patients,[109] i.e. obese subjects that lose more than 5% of their body weight and hence meet the clinical definition of cachexia. Subjects with cardiac cachexia show higher rates of atrial fibrillation,[110] possibly contributing to the higher mortality. In patients with severe CHF, the non-specific beta-blocker carvedilol has been shown to reduce the development and lead to a partial reversal of cachexia.[111] Overall, standard heart failure medication seems to reduce not only

cardiac cachexia but also has the potential to attenuate cachexia progression in cancer.[112] However, while the numbers of patients with cardiac cachexia have been lowered by heart failure medication, there is still a great medical need to find novel strategies for the sub-group of patients that seems to have no protection from developing cardiac cachexia by standard medication. Recently, several small molecule compounds directed at the E3-ligase muscle ring finger 1 have shown great potential for the treatment of experimental cardiac cachexia by attenuating muscle wasting and contractile dysfunction through an inhibition of apoptosis and ubiquitin-proteasome-dependent proteolysis.[113] Micro RNAs may also represent promising novel targets in cardiac cachexia for both intervention and as potential biomarkers.[114]

In conclusion, while there have been interesting and promising developments, there are several key points that still have to be addressed in muscle wasting, sarcopenia and cachexia in CHF: (i) the definition and discrimination of the different diseases states, (ii) robust biomarkers that help tailor the anti-wasting therapy and (iii) more research into exercise training in combination with existing drugs and/or investigational compounds.

Conflict of interest

None declared.

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