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Sarcopaenia complicating heart failure

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Sarcopaenia is defined as reduced skeletal muscle mass associated with either a decline in muscle strength or low physical performance. It has been shown to affect 17.5% of people worldwide, with a prevalence of 20% or higher in patients with heart failure (HF). Sarcopaenia has severe impact on mortality, physical capacity, and quality of life. Even though several mechanisms, such as autonomic imbalance, reduced muscle blood flow, increased inflammation, hormonal alterations, increased apoptosis, and autophagy have been proposed to fuel the pathogenesis of sarcopaenia, additional studies assessing the interaction of these conditions need to be conducted to elucidate how the presence of sarcopaenia can exacerbate the progression of HF and vice-versa. Resistance training combined with nutritional protein intake seems to be effective in the treatment of sarcopaenia, although current pharmacotherapies have not been extensively studied with this endpoint in mind. In conclusion, sarcopaenia is interwoven with HF and leads to worse exercise capacity in these patients. The mechanisms associated with this bilateral relationship between sarcopaenia and HF are still to be elucidated, leading to effective treatment, not only for the heart, but also for the skeletal muscle.

Introduction

The current definition of sarcopaenia is based on reductions in skeletal muscle mass associated with either a decline in muscle strength or low physical performance.[1] As ageing becomes a global issue, reduced skeletal muscle mass has been found to affect 5–13% of elderly people aged 60–70 years and reach a prevalence of up to 50% in octogenarians or people older than this.[2] Exercise capability, however, is not only provided by skeletal muscle mass but also by functional components including mitochondrial function[3–5] and iron supply[6,7] to the cells of the reticuloendothelial system.

In a multicontinent study, the prevalence of sarcopaenia in the general population has been shown to be between 12.6% and 17.5%.[8] In patients with heart failure (HF), prevalence values are much higher and reach values between 19.5% and 47.3%.[9] Moreover, among patients with diabetes mellitus and obesity, sarcopaenia has been described as a common metabolic comorbidity in patients with HF[10] with reduced or preserved ejection fraction, showing a prevalence of almost 20% in both conditions.[11,12] Sarcopaenia may be a strong predictor of mortality in patients with HF, but evidence on this is still limited.[13] In addition, these patients present lower peak oxygen consumption, reduced distance in 6-min walking test, frailty and poorer quality of life than their counterparts without sarcopenia.[14,15] Altogether, skeletal muscle dysfunction is a crucial component not only in HF, but also in patients with other cardiovascular disorders including stroke,[16] and even certain medications can have effects on exercise intolerance.[17–19]

The presence of one condition can probably exacerbate the progression of the other. Thus, HF, characterized by

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insufficient oxygen supply to the periphery and possibly decreased cardiac output, may reduce the oxygen and nutrient supply to skeletal muscle. On the other hand, skeletal muscle, a highly adaptable tissue, can change its morphology to adjust body resting energy expenditure in favour of other body functions and also present increased sympathetic afferent drive via ergoreflex activation, which contributes to cardiac damage.[20]

Therefore, the aim of this brief review is to present the main mechanisms involved with sarcopaenia in patients with HF and also give a clinical perspective about sarcopaenia in these patients.

Pathogenesis of sarcopaenia in heart failure

Patients with chronic HF have increased muscle loss due to an imbalance between anabolic and catabolic pathways.[14] Increased sympathetic drive and decreased parasympathetic activity is a hallmark in HF.[20,21] In a recent study, patients with sarcopaenia demonstrated a higher muscle sympathetic nerve activity (MSNA) and impaired heart rate recovery (HRR) compared to patients without sarcopaenia, and MSNA was negatively correlated with appendicular lean mass (ALM), whereas HRR at 1st and 2nd minutes after maximal exercise showed a positive correlation with ALM.[22]

Moreover, patients with sarcopaenia also present lower resting and peak forearm blood flow, correlated with a short distance covered in a 6-min walking test, suggesting an impairment in endothelial-dependent vasodilation.[23] In addition, another mechanism that can play a role in endothelial dysfunction and muscle damage is increased low-grade inflammation, a common feature in patients with sarcopaenia and HF, and rises in tumour necrosis factor-alpha, interleukin-6, and C-reactive protein levels have been associated with decline in muscle mass and strength.[24]

Furthermore, reactive oxygen species, also called free radicals, may lead to mitochondrial dysfunction and cause muscle degradation though the activation of ubiquitin protein system in patients with HF.[25] Increased apoptosis is another mechanism that has been described to cause damage in skeletal muscle myocytes.[26] Additionally, in a model of cancer cachexia-induced cardiomyopathy, muscle wasting was attenuated with megestrol acetate by down-regulation of autophagy in skeletal and heart muscle.[27] However, to elucidate the role of apoptosis and autophagy in the degradation of muscle mass in patients with HF and sarcopenia further studies need to be conducted.

Hormonal changes have been shown to occur in patients with HF, decreases in the levels of testosterone with insulin-like growth factor-1 and growth hormone resistance have been described in these patients, showing a strong association with reduced functional capacity.[28] Moreover, myostatin, a negative regulator of muscle cells growth and differentiation, has been shown to be increased in patients with HF and to be correlated with important circulating neurohormonal biomarkers related to HF progression.[29] To date, despite large trials assessing the pharmacological applicability of myostatin inhibitors, there is no data available to indicate the administration of such drugs in patients with sarcopaenia.[30]

Clinical management

The development of sarcopaenia is multifactorial and so is its management. Despite reported anorexia in patients with HF,[31] nutritional protein supplementation alone has been shown to produce significant improvement in body composition and inflammatory markers.[32] However, resistance training combined with nutritional protein intake seems to promote greater improvements in muscle mass and has recently been recommended in the treatment of sarcopenia.[33] Altogether, any form of exercise, rehabilitation programmes, or even dancing may have beneficial effects.[34–37] Although testosterone administration has shown positive impact on muscle mass and function, its application may lead to undesirable side effects and cardiovascular outcomes which are still being debated.[38]

In spite of optimal HF pharmacotherapy,[39] new pharmacological agents to treat sarcopenia have been extensively studied in the past two decades, including selective androgen receptor modulators, ghrelin receptor antagonists, myostatin inhibitors, growth hormone, and insulin-like growth factor-1.

Conclusion

In summary, sarcopaenia is interwoven with HF and leads to worse functional outcomes in these patients. Moreover, the mechanisms associated with this bilateral relationship between sarcopaenia and HF are still to be elucidated, leading to effective treatment, not only for the heart, but also for the skeletal muscle.

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