REVIEW ARTICLE

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Interrelationship of Sarcopenia and Cardiovascular Diseases: A Review of Potential Mechanisms and Management

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Abstract

Sarcopenia refers to an age-related reduction of lean body mass. It showed a reciprocal relationship with cardiovascular diseases. Thus, it is imperative to explore pathophysiological mechanisms explaining the relationship between sarcopenia and cardiovascular diseases, along with the clinical assessment, and associated management. In this review, we discuss how processes such as inflammation, oxidative stress, endothelial dysfunction, neural and hormonal modifications, as well as other metabolic disturbances influence sarcopenia as well as its association with cardiovascular diseases. Moreover, this review provides an overview of both non-pharmacological and pharmacological management for patients with sarcopenia and cardiovascular diseases, with a focus on the potential role of cardiovascular drugs to mitigate sarcopenia.

Key words: sarcopenia, cardiovascular diseases, aging, inflammation

INTRODUCTION

The term sarcopenia originates from the Greek word *"sarx,"* meaning muscle, and *"-penia,"* meaning deficiency. Collectively, sarcopenia means muscle deficiency or the age-related decline in lean body mass.[1] This disease is associated with other outcomes, e.g. increased risks for falls, functional decline, frailty, and mortality. The European Working Group on Sarcopenia in Older People (EWGSOP) clinically defines sarcopenia as the presence of low muscle strength and mass or muscle quality.[2] It is important to note that the definition of sarcopenia is not limited to muscle wasting, but also includes the functional impairment associated with it, thus shifting toward a function-centered model of approaching sarcopenia. This definition has also been acknowledged and espoused by the Asian Working Group for Sarcopenia (AWGS) with the inclusion of certain cut-off values for measuring muscle mass and strength in Asians.[3]

Sarcopenia is a prevalent disease; however, the exact numbers are difficult to determine due to varying diagnostic criteria. The prevalence of sarcopenia in people in their 50s, 60s-70s, and 80s are around 1–33%, 5-13%, and 50%,[4] respectively. This follows the trend that skeletal muscle mass is said to decline at 40 years old at approximately 8% per year and accelerates with age. Other studies reveal that the prevalence of sarcopenia in individuals aged 65 years and older ranges from 12.6% to 17.5% with an average of 15.2% in Europe[5] and 30.3% for males and 29.3% for females in Korea.[6] Aside from age, other factors that may contribute to the rate of sarcopenia are ethnicity, lifestyle, and physical activity.[7]

Sarcopenia is also associated with other disease entities such as cardiovascular disease (CVD), renal insufficiency, metabolic syndrome, and nonalcoholic fatty liver disease, among others.[7-9] In particular, sarcopenia was associated with a higher risk of carotid atherosclerosis, myocardial infarction, and atrial fibrillation.[8] Another study conducted on Korean adults older than 65 years old revealed that there was a higher likelihood of CVD in those with sarcopenia.[6] Conversely, some studies show that there was an increased chance of being diagnosed with sarcopenia in adults with CVD. In one study, results show that the prevalence of sarcopenia in patients with CVD was as high as 16.9%.[9]

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The objective of this paper is to further discuss the pathophysiologic mechanisms linking sarcopenia and cardiovascular diseases. Although sarcopenia is an established disease entity, management options for it are relatively sparse. Therefore, this paper also aims to provide an overview of the potential role of cardiovascular drugs in the management of sarcopenia.

PATHOPHYSIOLOGIC MECHANISMS UNDERLYING THE INTERRELATIONSHIP BETWEEN SARCOPENIA AND CARDIOVASCULAR DISEASES

Cardiovascular diseases associated with sarcopenia

Atherosclerosis is a persistent inflammatory process of thickening, hardening, and loss of elasticity of arteries in various organs such as the heart, brain, and even skeletal muscle due to the development of lipid-laden lesions.[10] Sarcopenia has been associated with atherosclerosis with inflammation and oxidative stress as possible underlying mechanisms linking the two.[11] Likewise, there is an association between frailty, arterial stiffness, vascular endothelial dysfunction, and hypertension in the elderly.[12-14]

The association between coronary artery disease and sarcopenia has been demonstrated by the increased prevalence of sarcopenia in patients who have coronary artery disease and the prognostic value of sarcopenia in the course of coronary artery diseases. In a study done in China, 78 (22.6%) out of the 345 enrolled participants who were hospitalized for coronary heart disease were found to have sarcopenia.[15] Similarly, results in another study showed that sarcopenia was linked to a greater prevalence of myocardial infarction in people who were overweight or obese compared to those who had normal weight (10.0% vs 4.3%, P = 0.020).[16] Even higher prevalence rates were observed in Brazil where 64.6% and 35.4% of the 99 elderly patients with myocardial infarction presented with sarcopenia and sarcopenic obesity, respectively.[17]

It has been proposed that the factors that lead to the development of coronary artery disease such as atherosclerosis, hypertension, diabetes mellitus, and obesity may have a more direct association with sarcopenia. Results of a few studies have shown that diabetes mellitus is significantly associated with sarcopenia.[18,19] It has been postulated that the muscle dysfunction observed in diabetic patients is due to hyperglycemia, insulin resistance, and inflammation.[20] In particular, chronic hyperglycemia leads to the accumulation of advanced glycation end products that build up in skeletal muscle and cartilage, making them less flexible.[21]

Sarcopenia has also been observed to influence the progression of coronary artery disease. In a prospective study by Kim et al.,[18] 1928 patients with coronary artery disease who underwent percutaneous coronary intervention were followed up to assess the clinical significance of sarcopenia in the course of CAD. Serum biomarkers, specifically the ratio of serum creatinine to serum cystatin C (Scr/Scys) and the ratio of estimated glomerular filtration rate by Scys to Scr (eGFRcys/eGFRcr), were used to estimate muscle mass. Results of the study show that low muscle mass, as indicated by the decreased values of the surrogate markers, is significantly associated with increased 3-year mortality risk.

Lastly, sarcopenia and heart failure have been shown to be interrelated, each one influencing the development and progression of the other. In the studies investigating the impact of muscle wasting in patients with chronic heart failure, muscle wasting was found to be higher among patients with chronic heart failure (19.5%)[22] compared to otherwise healthy older individuals.[5,6] Additionally, in the same study by Fulster et al.,[22] results indicate that muscle wasting is more prevalent in males and older patients.

Pathophysiological mechanisms for sarcopenia and cardiovascular diseases

Common pathophysiologic pathways link cardiovascular diseases with sarcopenia. The main disease processes involved in the development of sarcopenia and CVD are inflammation, oxidative stress, endothelial dysfunction, neural and hormonal modification, malnutrition, and physical inactivity. Figure 1 shows these overlapping pathophysiological mechanisms and the interaction between cardiovascular diseases and sarcopenia.

Inflammation

Various cytokines and inflammatory markers that induce atherosclerosis and heart failure are associated with sarcopenia. Some of those cytokines are interleukin (IL)-6, IL-1, tumor necrosis factor-α (TNF-α), galectin 3, TNF receptor 1, and TNF receptor 2.[23] Inflammatory cytokines may act on muscle receptors, increasing muscle breakdown or impairing their reproduction by upregulating the catabolic pathways while downregulating anabolic proteins such as growth hormone.[24]

IL-6 has both pro- and anti-inflammatory properties; however, its pro-inflammatory properties dominate and are associated with cardiovascular diseases, with higher levels leading to higher morbidity.[25] IL-6 is found in abundance in atherosclerotic plaques as it is synthesized by arterial wall cells, namely macrophages, vascular smooth muscle cells, and endothelial cells.[25] This inflammatory state may increase arterial wall stiffness by decreasing elastin which may then further release inflammatory mediators.[26] Additionally, IL-6 can be proatherogenic by stimulating the proliferation of vascular smooth muscle cells and platelets as well as endothelium activation. Vascular smooth muscle proliferation is due to the effects of monocyte chemoattractant protein-1 which recruits monocytes and smooth muscles to atheromas. Endothelial activation leads to increased expression of cell adhesion molecules such as ICAM-1, VCAM-1, and E-selectin. These adhesion

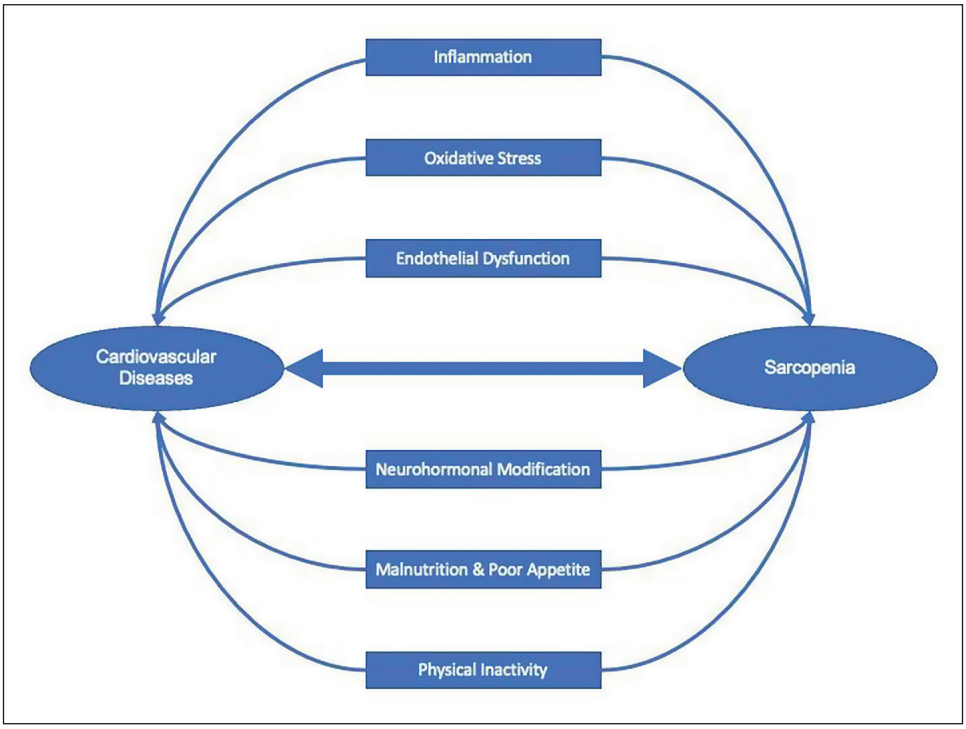

Figure 1. Pathophysiology of Sarcopenia and CVD and their interaction.

molecules then recruit monocytes that transmigrate into the subendothelium becoming macrophages and subsequently foam cells which produce atheromas.[25]

Furthermore, IL-6 levels can be increased by aging via several mechanisms. One mechanism is that aging increases bone marrow adiposity which stimulates the production of IL-6 and, subsequently, induces myeloid cell differentiation. The increased number of myeloid cells then recruits monocytes that are *TET*2-mutants that have a higher tendency for hematopoietic proliferation, thus leading to atheroma formation. Another mechanism is that aging enhances the production of IL-6 in vascular smooth muscle cells and decreases mitochondrial function. A decreased mitochondrial function affects mitophagy, or the removal of damaged mitochondria, which then increases IL-6.[27]

IL-6 is also a catabolic factor that promotes protein breakdown and muscle atrophy and inhibits muscle synthesis. Sarcopenia may be caused by IL-6 as this cytokine activates the ubiquitin-proteasome system which accelerates skeletal muscle breakdown.[28,29] In the study by Fulster et al.[22] in which serum cytokine levels of 200 patients with stable chronic heart failure were measured, those who presented with muscle wasting had significantly higher levels of IL-6 compared to those who did not have muscle wasting, furthermore implicating the role of inflammation in the pathogenesis of sarcopenia in the context of CVD. Indeed, it has been established that heart failure is a state of chronic low-grade inflammation.[23]

Another cytokine that links sarcopenia and CVD is TNF-α which is a key regulator in inflammation as it controls leukocyte activation, cytokine release, and production of free radicals.[30] Like IL-6, TNF activates endothelial cells to increase the expression of adhesion molecules which then recruit leukocytes. Moreover, TNF-α may promote endothelial cell injury and endothelial cell apoptosis, as well as decrease endothelial repair mechanisms, thus, leading to endothelial dysfunction. Endothelial cells may then recruit and activate leukocytes, induce apoptosis, and suppress endothelial cell progenitors, ultimately leading to atherosclerosis. Additionally, TNF-α may alter adipocyte metabolism which may result in atherosclerosis.[30]

One mechanism showing the association of TNF-α with sarcopenia is its potential to induce cell apoptosis via cysteine proteases called calpains, which are responsible for the proteolysis of proteins needed for cellular integrity, enzymes, and transcription factors.[31] Type II muscle fibers are said to be more susceptible to TNF-α-induced apoptosis. This apoptosis may be via the mitochondria-dependent internal pathway in which elevation in reactive oxygen species (ROS) and calcium (Ca^{2+}) levels in the cytosol affects mitochondrial homeostasis and increases cell permeability. Another pathway is the external pathway wherein TNF-α recruits adapter proteins on the cell surface which then activates a caspase cascade that leads to apoptosis, thus resulting in decreased muscle mass.[31]

Nitric oxide (NO) precursors are also known to reduce inflammation. Thus, a decrease in motor function due to chronic inflammation can be attributed to decreased NO signaling. Subsequently, sodium nitrite, a precursor of NO, was determined to attenuate the decline of motor function in mice by decreasing inflammation.[13]

Oxidative stress

Oxidative stress is known to create ROS that induces damage on various tissues.[7] Oxidized LDL-cholesterol (ox-LDL) is said to cause and induce atherosclerosis especially in the elderly due to the proinflammatory state seen in this age group. Oxidative stress may also lead to endothelial dysfunction which may increase the expression of endothelin-1 that promotes endothelium constriction, resulting in hypertension and atherosclerosis.[32] Furthermore, oxidative stress has not only been shown to be involved in cardiac remodeling in heart failure but also plays a role in the development of sarcopenia in these patients. The decreased cardiac output, endothelial dysfunction, and reductions in oxygen transport to the skeletal muscle that are implicated in the decline of muscle function in heart failure patients can all be linked to the generation of ROS.

Aging is associated with increased generation of ROS and decreased antioxidant production. Skeletal muscle is said to generate a large amount of ROS which induces post-transcriptional modifications. ROS also increases proteolysis and decreases protein synthesis leading to a decrease in muscle mass.[32] Additionally, increased production of ROS affects neuromuscular junctions (NMJ) by disrupting the homeostasis of Cu/Zn superoxide dismutase knockout mice motor neurons which also leads to disruption of skeletal muscle mitochondrial function. This increased ROS in skeletal muscle triggers a feedback mechanism that further affects the NMJ.[7] ROS also decreases acetylcholine release at the synaptic cleft, thus, leading to the failure of generation of an action potential. Furthermore, oxidative stress may influence NMJ physiology leading to a decrease in its innervation and muscle fibers, affecting the excitation-coupling mechanism, and altering the actin and myosin structures of muscle fibers – all of which may subsequently lead to sarcopenia.[32] Another proposed mechanism for the role of ROS in skeletal muscle dysfunction is ROS-induced insulin resistance which ultimately leads to decreased exercise tolerance.[33]

Aging cells have altered peroxisome proliferator-activated receptor-γ coactivator 1 α pathway which leads to an increased production of ROS which may, in turn, induce mitochondrial damage., and decrease the proliferation of skeletal muscle. The antioxidant sestrin has also been associated with sarcopenia and endothelial dysfunction with low levels correlating with low muscle mass.

Endothelial dysfunction and peripheral perfusion abnormalities

The pathogenesis of heart failure and hypertension may also involve endothelial dysfunction. Oxidative stress plays a role in endothelial dysfunction through the negative effects of reactive oxygen species on the availability of nitric oxide (NO), a powerful vasodilatory molecule, resulting in exaggerated vasoconstriction and decreased peripheral perfusion.[34] Since NO is responsible for blood redistribution during exercise through vasodilation of skeletal muscle arteries, its reduced availability in heart failure is associated with decreased exercise tolerance.[34] In a study evaluating sarcopenia and endothelial function in patients with chronic heart failure, results show that peak flow was significantly correlated with exercise capability in the forearm and leg.[35] Compared to patients without sarcopenia or controls, those with sarcopenia had reduced baseline forearm and leg blood flow. The observed exercise intolerance could be explained by the lack of oxygen delivery secondary to impaired blood flow. This is further illustrated by a decrease in the density of skeletal muscle capillaries and the ratio of slow, oxidative type I fibers to fast, glycolytic type II fibers.[29,36]

As aforementioned, NO is said to be an important cytokine in the dilation of blood vessels. Asymmetric dimethylarginine (ADMA) is a substance that inhibits endothelial NO synthase, an enzyme important in the generation of NO and vascular endothelial function, thus, leading to the inhibition of the NO signaling pathway and altering the homeostasis of vascular tone and arterial stiffness. A decrease in NO leads to an increase in vascular stiffness, which subsequently may lead to elevated blood pressure. Likewise, an increase in ADMA has been associated with an increase in cardiovascular mortality and is associated with frailty.[13]

Neurohormonal modification

Neurohormonal modification is also said to be involved in the pathogenesis of heart failure, myocardial infarction, and atherosclerosis. The enhanced activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS) in heart failure appears to be associated with increased catabolism of muscles.[36] The renin-angiotensin-aldosterone system may also be associated with sarcopenia and hypertension as sarcopenic patients were noted to have higher rates of urinary angiotensinogen excretion.[26] Angiotensin II is said to bind to angiotensin II type 1 receptor which then activates the PKC and/or Src pathway which subsequently leads to the activation of NADPH oxidase II which increases the production of reactive oxygen species. This may cause oxidative damage to muscle and increase protein catabolism and decrease protein synthesis. Elevated angiotensin II levels may also contribute to inflammation by increasing circulating glucocorticoids, IL-6, and serum amyloid A.[37] Furthermore, the role of RAAS in heart failure-related sarcopenia has been elucidated through the observed positive effects of angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin-II receptor blockers (ARB) on exercise and functional capacity.[36] However, there is sparse research on the benefits of mineralocorticoid antagonists such as spironolactone on the physical function of patients with heart failure.[36]

It was shown in rat models, that although the sympathetic nervous system has anabolic effects on skeletal muscle through B2-adrenoreceptors, chronic sympathetic stimulation could result in the downregulation of these receptors and, eventually, muscle wasting and atrophy.[38] To illustrate,

in a study assessing the role of autonomic modulation in 116 male patients with stable chronic heart failure, those with sarcopenia had higher muscle sympathetic nerve activity when compared to patients without sarcopenia.[39] The effects of sympathetic hyperactivity are further supported by the apparent efficacy of beta-blockers in slowing down catabolism while increasing the anabolism of skeletal muscles.[36] Furthermore, there are a few anabolic hormones that have been observed to be decreased in heart failure, namely growth hormone, testosterone, and ghrelin.[40] In another study, however, growth hormone levels are increased whereas insulin-like growth factor-1 (IGF-1) levels are notably lower in patients with sarcopenia and heart failure, implying that some form of resistance may be in play, resulting in less muscle formation.[41]

Patients with heart failure frequently have low testosterone levels which appear to be involved in the development of cardiac dysfunction.[40] Similarly, decreased testosterone levels have been shown to be linked to loss of muscle mass and function.[28] This is because testosterone may increase type 1 and 2 muscle fibers through increased insulin-like growth factor-1 (IGF-1).

Insulin resistance may also lead to arterial stiffness as insulin has anabolic effects on the skeletal muscle that increase endothelial-derived NO production leading to vasodilation.[26]

Additionally, levels of ghrelin, a hormone produced in the stomach that functions to increase appetite and food intake as well as promote growth hormone release, appear to be reduced in elderly patients with heart failure.[29] As nutrition and growth hormones have both been established to influence protein synthesis, it can be inferred that low ghrelin levels are associated with the development of sarcopenia in heart failure.

Myostatin, a protein belonging to the TGF-β family, is a strong inhibitor of the growth of skeletal muscles.[42] Enhanced expression of this protein from the heart is observed during pathological cardiac conditions such as myocardial infarction[43,44] and heart failure.[42] In a study where wild-type mice were compared with mice whose cardiomyocyte-specific myostatin (MSTN-CKO) was genetically deleted, skeletal muscle atrophy was associated with elevated serum myostatin levels in wild-type mice.[42] While myostatin serves as a compensatory mechanism by preventing further ventricular hypertrophy in heart failure, it also contributes to heart failure-induced muscle mass loss and, therefore, sarcopenia.

Malnutrition and poor appetite

Malnutrition is a frequent complication in patients with heart failure due to several factors such as poor appetite leading to decreased food intake, increased loss of nutrients from frequent diuresis, and elevated levels of inflammatory cytokines resulting in metabolic disturbances.[45] Commonly prescribed cardiovascular drugs, including digoxin, angiotensin-converting enzyme (ACE) inhibitors, β-blockers, and diuretics, have also been shown to cause nausea and dysgeusia, thereby negatively affecting appetite.[29] Heart failure could also be complicated by gastroenteropathy from intestinal edema which further promotes anorexia and malabsorption. Ultimately, these factors result in an imbalance between energy requirement and expenditure, favoring a catabolic state and loss of muscle mass.

Physical inactivity

In the elderly, decreased physical activity and exercise tolerance often lead to loss of muscle mass and, subsequently, increases the risk for obesity.[46,47] As obesity is linked to the increased production of pro-inflammatory markers such as adipokines and cytokines, infiltration of fat into muscle, and insulin resistance; the presence of obesity further exacerbates the development of sarcopenia, decreases physical performance, and increases the risk of mortality.[10,48,49] This vicious cycle between loss of muscle mass and gain of fat mass ultimately results in sarcopenia and sarcopenic obesity.

In heart failure, age-related decline in skeletal muscle mass and decreased cardiorespiratory fitness contribute to physical inactivity and exercise intolerance, further aggravating sarcopenia in these individuals. The significance of physical inactivity in the development and progression of sarcopenia is demonstrated by the efficacy of aerobic and resistance training in attenuating lean body mass loss and improving muscle function and strength.[29,50]

CLINICAL ASSESSMENT

Various diagnostic methods have been used to objectively measure skeletal muscle mass. Computed tomography (CT) and magnetic resonance imaging (MRI) estimate skeletal muscle area, dual-energy X-ray absorptiometry, and bioelectrical impedance analysis (BIA) determine body composition including lean body mass, and handgrip dynamometer and isokinetic dynamometer measure muscle strength. Physical performance can be evaluated by measuring the distance achieved in a 6-minute corridor walk and obtaining the time spent to finish a 4-meter or 6-meter distance walk. Supplementary measurements of inflammatory cytokines, hormone levels, and surrogate biomarkers (e.g., serum creatinine and serum cystatin) are also recommended to assess the other factors that could impact the development of sarcopenia.

Screening tests for sarcopenia have also been developed. The SARC-F is a tool that assesses five items namely strength, assistance in walking, rising from a chair, climbing stairs, and falls.[51] A recent version called SARC-CalF is a test that evaluates the aforementioned five items with an additional item on calf circumference. In particular, a calf circumference of ≤34 cm for males and ≤33 cm for females points toward sarcopenia.[52] A total score of ≥4 in SARC-F and ≥11 in SARC-CalF is a positive result for sarcopenia.

The European Working Group on Sarcopenia in Older People (EWGSOP) suggests that sarcopenia be diagnosed using the following criteria: 1) low muscle mass with a skeletal index of ≤8.90 kg/m^2 for males and ≤6.37 kg/m^2 for females, 2) low muscle strength with a handgrip strength of <30 kg for males and <20 kg for females, 3) low physical performance with a gait speed of ≤0.8 m/s. Sarcopenia may be called if there is low muscle mass with low muscle strength or physical performance.[53] The Asian Working Group for Sarcopenia (AWGS) in 2019 has also proposed updated cutoff values for sarcopenia in Asians: 1) muscle mass measurements of <7.0 kg/m^2 for males and <5.4 kg/m^2 for females using dual X-ray absorptiometry or <7.0 kg/m^2 for males and <5.7 kg/m^2 for females through bioimpedance analysis, 2) muscle strength estimates of <28 kg for males and <18 kg for females by handgrip strength, and 3) physical performance of <1.0 m/s gait speed in a 6-m walk.[54]

MANAGEMENT

Pharmacologic management

Cardiovascular drugs

Renin-Angiotensin-Aldosterone System Drugs

As aforementioned, the RAAS plays an essential role in maintaining cardiovascular homeostasis and is also interlinked with the development of decreased muscle mass. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB) are frequently used medications for the treatment of cardiovascular diseases. Interestingly, a few studies have also demonstrated their muscle-protective properties through several mechanisms. Results of a study on mice by Marzetti et al., show that enalapril exerts its positive effects on muscles by reducing oxidative stress and inflammation.[55] ACE inhibitors are also shown to decrease loss in muscle strength in older adults without heart failure and increase muscle strength and exercise capacity, suggesting some potential in their use in sarcopenia.[56] In contrast, a recent systematic review and meta-analysis claim that the use of ACE inhibitors or angiotensin receptor blockers alone to enhance physical performance in the elderly is not supported by current research.[57] Additionally, a trial that aimed to determine the efficacy of leucine with or without perindopril compared to a placebo in improving physical function in adults of at least 70 years old with sarcopenia showed that neither enhanced physical performance.[58]

Similarly, another experiment illustrated that losartan protected against loss of muscle mass in rats by modulating the TGF-β signaling cascade and enhancing the insulin-like growth factor 1 (IGF-1)/Akt/mammalian target of rapamycin (mTOR) pathway.[59] The use of losartan in rat models also showed improved motility and reduced inflammation and oxidative stress.[56] Losartan intake and exercise in old mice also resulted to greater muscle mass and muscle fiber cross-sectional area which suggests that losartan may improve muscle mass and exercise capacity.[60] A longitudinal study conducted in aging populations showed that the use of ARBs was associated with greater frailty indices and increased calf circumference and composite muscle mass and strength.[61] A study also determined that elevated serum levels of losartan in pre-frail adults are associated with decreased frailty through a mechanism that is not dependent on the angiotensin II pathway which may suggest a role of losartan in maintaining physical function.[62] Furthermore, there has been a noted association in higher lean body mass in older females taking ACE inhibitors or ARBs which may suggest a protective function of these drugs for skeletal muscle mass.[63]

A few studies have shown the benefits of spironolactone, an aldosterone antagonist, in preventing skeletal myocyte apoptosis in rats and augmenting endothelial function and nitric oxide availability in patients with chronic heart failure.[64,65] However, recent studies have demonstrated that spironolactone, although effective as a treatment for cardiovascular diseases, did not significantly improve physical function and exercise capacity in patients with or without heart failure.[66,67]

Statins

Statins play a crucial role in preventing cardiovascular disease. It is an inhibitor of 3-hydroxy-methylglutaryl coenzyme A (HMG-CoA) reductase, an enzyme involved in the production of low-density lipoprotein cholesterol, thus effectively lowering it. Statins are known to reduce cardiovascular events and improve mortality in patients with coronary artery disease or those at high risk for CVDs.[68] However, statin use is also associated with myopathies as statins increase the vulnerability of skeletal myocytes and induce the destruction of muscle proteins.[69] This may suggest that statin use may exacerbate muscle loss in patients. However, a cross-sectional study examining skeletal muscle volume in older adults taking a combination of ARB and statin is associated with a significantly higher skeletal muscle index.[70] Additionally, a study involving 136 patients with heart failure show that statin use was inversely associated with sarcopenia.[71] These studies suggest that statins may still have a potential role in maintaining muscle mass and further studies on their role in sarcopenia may be warranted.

Beta-blockers

Beta-blockers, another common cardiovascular medication, are postulated to prevent the progression of sarcopenia by inhibiting excessive sympathetic activation. In the COPERNICUS trial consisting of 2289 randomly assigned patients with heart failure, those in the carvedilol group were 33% less likely to lose weight (>6%) (95% confidence interval: 14-48%, P = 0.002) and 37% more likely to gain weight (>5%) (95% confidence interval: 12–66%, P = 0.002) compared to those in the placebo group.[72] However, another study suggests that this observed weight gain from the use of beta-blockers is mostly due to the increase in total body fat mass and content instead of an improvement in lean body mass.[73]

Therefore, more extensive research is required to fully understand the benefits of these drugs with a possible focus on dose adjustments of currently known regimens or the development of novel medications to target sarcopenia along with cardiovascular diseases.

Hormone replacement

Several hormones were investigated to assess their value in treating sarcopenia, but most remain to have inconclusive benefits. The role of growth hormone and IGF-1 in improving skeletal muscle mass and function has been established.[74,75] Thus, supplementation is being investigated as an alternative treatment option for sarcopenia. Testosterone administration to patients with chronic heart failure resulted in significant improvement in muscle strength, exercise capacity, and insulin sensitivity compared to those only given placebo.[76] The same findings were previously observed in another study by Pugh et al. in which males with chronic heart failure who were administered testosterone exhibited enhanced physical function in comparison to those receiving placebo.[77] Nevertheless, the effects of testosterone on the cardiovascular system have yet to be fully described. Selective androgen receptor modulators (SARMs) are another class of drugs under investigation mainly for their potential to increase lean body mass. A few studies have demonstrated their anabolic effects in healthy elderly males and postmenopausal females, in patients with cancer, and adult mice deficient in androgen activity.[78,79] However, studies with larger, more representative samples are needed to confirm their muscle-protective properties. The benefits of ghrelin were also examined in a rodent post-myocardial infarction chronic heart failure model by Barazzoni et al.[80] Administration of acylated ghrelin showed positive effects on skeletal muscle mitochondrial function, inflammation, and insulin activity. Vitamin D supplementation has been shown to help enhance muscle strength in healthy elderly individuals but its efficacy in improving muscle function and exercise capacity in patients with cardiovascular disease and sarcopenia has not been fully explored.[81]

Non-pharmacological management

Diet and nutritional intake

Several studies have demonstrated the importance of protein consumption for the maintenance and improvement of skeletal muscle mass and function. A few of these aimed to investigate the recommended amount of protein to be given per meal to optimize the dose-response relationship between dietary protein intake and myofibrillar protein synthesis.[82,83] According to Moore et al., compared to younger males, healthy elderly males require a relatively greater amount of protein per meal to maximize its potential anabolic effects.[84] Lancha et al.,[85] recommend 0.4 g protein/kg body weight per meal, equivalent to 1.2-1.6 g protein/kg body weight/day, for adequate protein synthesis in the elderly. This amount exceeds the daily recommended intake of 0.8 g protein/kg for younger individuals. Thus, the elderly must adhere to a dietary regimen that ensures increased healthy protein intake that will not compromise the status of existing comorbidities such as cardiovascular diseases. This increase in protein intake can be achieved by consuming whey and other dietary protein supplements that may provide bioavailable essential amino acids that may be used for protein synthesis. Furthermore, whey protein is noted to have high leucine content which has been shown to increase protein synthesis in animal models.[86]

Furthermore, supplementation of essential amino acids, specifically β-hydroxy-β-methylbutyrate (HMB), has been examined for its potential anabolic and anti-catabolic activity. Most studies about HMB claim that it is significantly more efficacious in reducing the risk of sarcopenia and in increasing muscle mass and strength when its supplementation is combined with exercise.[87-90] Still, its potential to mitigate muscle atrophy and improve muscle mass, albeit less prominent, is significant in the management of sarcopenia in bedridden and sedentary elderly individuals.[91]

Exercise

Aerobic exercise and resistance training have been demonstrated to improve muscle strength, exercise tolerance, and overall functional capacity in patients with cardiovascular diseases and have shown to be the only therapeutic strategy supported by adequate clinical data for treating muscle wasting in heart failure.[38] In a study by Pu et al.,[50] patients with chronic heart failure who underwent progressive resistance training exhibited significant improvements in skeletal muscle strength and endurance compared to those only performing low intensity stretching exercises. Several mechanisms behind these positive effects have been extensively researched which include enhancing IGF-I/Akt/mTOR signaling pathway, reducing levels of inflammatory cytokines specifically TNF-α, mitigating the catabolic effects of the ubiquitin-proteasome system, and decreasing the levels and activity of myostatin.[92-96]

CONCLUSION

Multiple studies support that a mutual relationship between sarcopenia and cardiovascular diseases exists. The pathophysiology behind this association is complex and

Table 1. Summary of key findings

- Sarcopenia is a pathologic loss of muscle mass and functional impairment associated with aging
- Sarcopenia is said to be associated with cardiovascular diseases (CVDs) such as atherosclerosis, hypertension, coronary artery disease, and heart failure
- Various mechanisms may link sarcopenia and CVDs but the two major underlying pathologic mechanisms are inflammation and oxidative stress. Other mechanisms that may contribute to sarcopenia may be decreased physical activity, neurohormonal modification, and malnutrition.
- There are several modalities that may mitigate the progression of sarcopenia and CVDs such as cardiovascular drugs, hormone replacement, modification of diet and nutritional intake, and exercise.

involves several systemic factors including inflammation, oxidative stress, endothelial dysfunction, neurohormonal signaling, and other metabolic disturbances. Sarcopenia in the elderly not only influences the development and progression of cardiovascular diseases but is also heavily affected by the presence and severity of these comorbidities. Thus, early screening and diagnosis of sarcopenia have relevant implications for the management of cardiovascular diseases and overall quality of life. There are several potential management options for sarcopenia. The pharmacologic approach includes utilizing angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, mineralocorticoid antagonists, statins, beta-blockers, and hormone replacement. However, further investigation is required to fully comprehend their potential to treat sarcopenia, especially in the context of cardiovascular diseases. Another approach that has been proven to be effective is to introduce lifestyle modifications which include increasing dietary protein intake and engaging in regular exercise, particularly aerobic and resistance training. Overall, more comprehensive research has to be done to gain a clearer understanding of the mechanisms involved in sarcopenia and their implications on future therapeutic approaches.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement

FR: Conceptualization, Methodology, Validation, Resources, Writing - review and editing, Supervision, Project administration, Funding acquisition; **BTE:** Formal Analysis, Investigation, Data Curation, Writing - original draft preparation, Writing - review and editing, Visualization; **FMN:** Formal Analysis, Investigation, Data Curation, Writing - original draft preparation, Writing - review and editing, Visualization; **SC:** Writing - review and editing, Supervision, Project administration; **GPC:** Writing - review and editing, Visualization, Supervision; **EL:** Conceptualization, Methodology, Validation, Resources, Writing - review and editing, Supervision, Project administration**; KV:** Writing - review and editing, Visualization, Supervision; **MGY:** Writing - review and editing, Visualization, Supervision

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