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STATE-OF-THE-ART REVIEW

Skeletal Muscle-Cardiac Muscle Aging

Shared Mechanisms and Multimodal Interventions

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ABSTRACT

The progressive age-related deterioration of skeletal and cardiac muscle represents a critical determinant of morbidity and mortality in older adults. This state-of-the-art review examines the interconnected molecular mechanisms underlying muscle aging, including mitochondrial dysfunction, immunosenescence, oxidative stress, hormonal dysregulation, and anabolic resistance. These shared pathways manifest as sarcopenia in skeletal muscle and remodeling in cardiac tissue, creating a complex relationship that accelerates functional decline. Chronic diseases, including heart failure, diabetes, and hypertension, amplify these degenerative processes through metabolic dysregulation and systemic inflammation. Evidence-based interventions combining multicomponent exercise programs (resistance, aerobic, and balance training), optimized protein intake (1.0-1.5 g/kg/day), and emerging pharmacological agents have demonstrated efficacy in preserving muscle mass and function. Digital health technologies offer novel monitoring and intervention delivery platforms. Future directions include expounding on muscle-heart crosstalk mechanisms, developing predictive biomarkers, and implementing integrated care models to address the growing burden of age-related physical decline. (JACC Adv. 2025;4:102347) © 2025 Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Progressive changes in skeletal and cardiac muscles associated with disability disproportionately affect older patients, with far-reaching implications for functional independence and quality of life (QoL). Sarcopenia is a geriatric syndrome that involves age-related changes in skeletal muscle mass composition, quality, and function that affect older patients at higher rates than younger and more active individuals.[1] Cardiac muscle also undergoes characteristic structural, functional, and molecular changes with aging. These changes include loss of cardiomyocytes and compensatory hypertrophy, fibrosis, extracellular matrix (ECM) remodeling, mitochondrial dysfunction, and impaired calcium handling.[2] In turn, these result in left ventricle (LV) hypertrophy, altered LV diastolic function, diminished LV systolic reverse capacity, myocardial fibrosis, altered endothelial function, and reduced contractile function.[3] The changes in both skeletal and cardiac muscles associated with age are influenced by genetic, epigenetic, and environmental factors.[4]

Skeletal and cardiac muscle aging may be biologically intertwined in multiple ways. Chronic low

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ABBREVIATIONS AND ACRONYMS

6MWD = 6-minute walk distance

CAD = coronary artery disease

CVD = cardiovascular disease

ECM = extracellular matrix

eGFR = estimated glomerular filtration rate

GH = growth hormone

HF = heart failure

HMB = beta-hydroxy-beta-methylbutyrate

IGF = insulin-like growth factor

IL = interleukin

LV = left ventricle

mtDNA = mitochondrial DNA

QoL = quality of life

RCT = randomized controlled trial

ROS = reactive oxygen species

SPPB = short physical performance battery

TNF = tumor necrosis factor

levels of inflammation associated with the "aging process," also called inflammaging, are linked to impaired immunologic function (ie, immunosenescence) and directly affect skeletal myofibers and cardiomyocytes.[5,6] Changes in the endocrine system, including imbalances in sex steroids and growth hormones (GHs), lead to a catabolic state, fibrosis, and disrupted calcium handling.[7] Phenotypically, these changes contribute to the development of sarcopenia alongside ventricular remodeling and heart failure (HF) with preserved ejection fraction, conditions associated with increased mortality risk. The link between muscle health and functional resilience extends beyond physical performance, encompassing metabolic health, resilience to new exposures, and cardiovascular capacity.[8,9] As such, preserving muscle integrity represents a potential therapeutic target for promoting health span and addressing the burden of age-related diseases. In this state-of-the-art review, we examine the current evidence on the mechanisms underlying skeletal and cardiac muscle aging, examine shared pathophysiological pathways, and discuss the impact of nutrition and chronic disease on muscle health and function (Central Illustration).

HIGHLIGHTS

- Age-related cardiac and skeletal muscle deterioration share fundamental molecular pathways that synergistically accelerate functional decline.
- Chronic inflammation, mitochondrial dysfunction, and anabolic resistance represent key therapeutic targets for preserving muscle integrity and function.
- Combined exercise, optimized nutrition, and targeted pharmacological approaches offer the most promising strategy for muscle preservation.
- Future interventions must address muscle-heart crosstalk mechanisms and deploy integrated care models with personalized, multimodal approaches.

AGING AND MUSCLE HEALTH: BASIC MECHANISMS

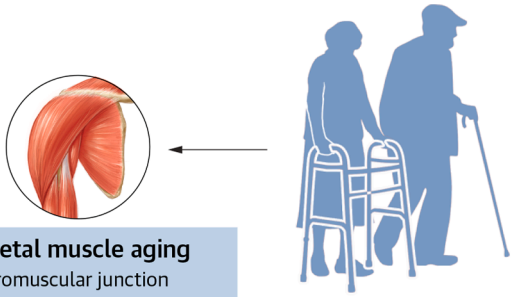
SKELETAL MUSCLE AGING. Mechanisms of sarcopenia. Sarcopenia manifests through several interconnected systemic mechanisms that collectively result in reduced muscle mass, altered muscle composition, and impaired contractile function.[1,10] The progressive loss of skeletal muscle mass begins between 40 and 50 years of age, with an approximate decline of 1% to 2% per year after age 50 years, accelerating to 3% annually after age 60 years.[11] This process involves both quantitative and qualitative changes in muscle tissue.

Neuromuscular junction dysfunction. Age-related deterioration of the neuromuscular junction contributes substantially to sarcopenia through interconnected structural, molecular, and functional alterations. Age-related thinning of motor axons, fragmentation of acetylcholine receptor clusters, and degenerating junctional folds are directly associated with declining contractile force.[12] The denervation of muscle fibers occurs through the retraction of motor neurons from the neuromuscular junction, leading to denervated muscle fibers that eventually undergo atrophy and apoptosis.[13] Motor unit remodeling follows, characterized by the denervation of fast-twitch type II fibers and reinnervation by slow-twitch motor neurons, resulting in fiber-type grouping and a reduction in the overall number of motor units. This process alters muscle contractile properties and reduces power generation capacity.[14]

Protein turnover imbalance. The maintenance of skeletal muscle mass depends on the balance between protein synthesis and degradation. Aging is associated with anabolic resistance, defined as a reduced ability of skeletal muscle to synthesize proteins in response to anabolic stimuli, including resistance exercise, amino acids, and insulin.[15] This phenomenon is associated with impaired mechanistic target of rapamycin complex 1 signaling, reduced amino acid transport, decreased insulin sensitivity, and diminished satellite cell activation.[7] Concurrently, protein degradation pathways, including the ubiquitin-proteasome system, the autophagy-lysosomal pathway, and the calpain system, may exhibit dysregulation with age, thereby contributing to enhanced protein catabolism.[16]

Mitochondrial dysfunction. Mitochondrial dysfunction represents another central feature of skeletal muscle aging. Aging muscle exhibits reduced mitochondrial content, impaired oxidative capacity, increased production of reactive oxygen species (ROS), and accumulation of mitochondrial DNA (mtDNA) mutations.[17] These alterations stem from decreased mitochondrial biogenesis, mediated by reduced activity of peroxisome proliferator-activated

CENTRAL ILLUSTRATION **Skeletal-Cardiac Muscle Aging: Shared mechanisms and Multimodal Interventions**



Skeletal muscle aging
- Neuromuscular junction deterioration
- Protein turnover imbalance
- Satellite cell dysfunction
- Anabolic resistance

Shared mechanisms: 12-hallmarks of aging

Cardiac muscle aging
- Myocardial fibrosis and stiffening
- LV remodeling
- Impaired Ca2+ handling
- T-tubule disorganization
- ↓ ß-adrenergic reserve

Skeletal muscle mass:
↓ 1-2%/year after 50
↓~3%/year after 60

Cardiomyocyte mitochondria:
Volume density: ↓~20% with age
HFpEF: ~50% in older HF patients

Amplifiers of decline

Multimorbidity
- Type 2 diabetes
- Obesity
- COPD
- Heart failure
- Hypertension
- Coronary artery disease

Geriatric syndromes
- Frailty
- Multimorbidity
- Polypharmacy
- Inactivity
- Inflammation
- Social isolation

Multimodal interventions

Exercise and rehabilitation
- Multicomponent: resistance + aerobic + balance
- Hospital: early mobilization
- Ambulatory: home-based PT

Nutrition
- Protein: 1.0 - 1.2 g/kg (healthy), 1.2-1.5 g/kg (disease), eGFR-guided
- Key supplements: Leucine, whey, HMB (consider)
- Emphasize whole-food patterns

Pharmacology (selected)
- Vitamin D: if deficient
- Testosterone: for hypogonadism (men)
- No FDA-approved sarcopenia drugs

Digital health
- Wearables: gait, activity
  Exercise: prescription apps
- Tele-rehab
- Remote nutrition

Assessment and risk stratification

Screening tools
- Grip strength
- Gait speed
- Chair rise test
- SPPB
- DXA scan

Risk stratification
- Low risk: 1 abnormal test
- Moderate: 2 abnormal tests
- High: ≥3 abnormal tests OR hospitalization
- Very high: Sarcopenia + CVD + falls

Integrated care model

Team: Geriatrics, Cardiology, Dietary, PT, and Pharmacy

Important to align interventions with patient-centered goals

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Continued on the next page

receptor-gamma coactivator 1-alpha and diminished expression of nuclear respiratory factors.[14] Additionally, mitophagy, the selective autophagic removal of damaged mitochondria, becomes less efficient with age. The resulting accumulation of dysfunctional mitochondria further propagates oxidative damage and cellular senescence. Electron transport chain deficiencies and proton leaks across the inner mitochondrial membrane reduce adenosine triphosphate production efficiency, compromising energy-dependent cellular functions and leading to age-related muscle atrophy and functional decline.[14]

Satellite cell dysfunction. Satellite cells, the resident stem cells of skeletal muscle, exhibit numerical decline and functional impairment with aging. These changes limit the regenerative capacity of aged muscle following injury or damage. The satellite cell microenvironment (niche) undergoes age-related alterations that affect satellite cell quiescence, activation, self-renewal, and differentiation potential.[18] Fibrosis within the muscle microenvironment, mediated by increased transforming growth factor-beta signaling, restricts satellite cell migration and impedes muscle repair. Furthermore, age-related changes in signaling pathways disrupt the balance between satellite cell self-renewal and differentiation, resulting in the progressive depletion of the satellite cell pool.[19]

Inflammation and oxidative stress. Chronic low-grade inflammation, termed "inflammaging," is likely to interact bidirectionally with sarcopenia. Skeletal muscles are a source of mediators supportive of T cell homeostasis. For instance, interleukin (IL)-2,[20] IL-7,[21] and IL-15[22] are the homeostatic cytokines responsible for T cell replication, and each has some degree of skeletal muscle expression. On the other hand, innate immune activation can exacerbate muscle atrophy via direct and indirect effects.[23-26] Pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and IL-1 beta (IL-1β), are present at increased systemic and local concentrations in aging muscle.[27] These inflammatory mediators activate nuclear factor kappa B and stimulate protein degradation while inhibiting anabolic signaling pathways, causing muscle atrophy.[14] Additionally, the activated protein kinase pathway further leads to inflammation, cell cycle arrest, apoptosis, and denervation-induced atrophy of skeletal muscle.[7] IL-6 is produced by skeletal muscle and has complicated local and systemic effects.[28]

Oxidative stress, resulting from an imbalance between ROS production and antioxidant defense mechanisms, causes cumulative damage to cellular proteins, lipids, and nucleic acids.[14] The activation of certain proteolytic pathways exacerbates oxidative stress and leads to additional immunologic changes in the aging muscle microenvironment. Age-related decline in antioxidant enzymes, including superoxide dismutase, catalase, and glutathione peroxidase, alongside increased mitochondrial ROS generation, accelerates the oxidative modification of contractile proteins and signaling molecules.[29]

An additional effect of inflammation in inducing muscle atrophy is via activation of the hypothalamic-pituitary-adrenal axis.[23] Certain cytokines (IL-1, IL-6) increase adrenocorticotropic hormone secretion (leading to glucocorticoid release) and also dysregulate the negative feedback loop of the hypothalamic-pituitary-adrenal axis (further increasing steroid production). Glucocorticoids play a significant role in the proteolysis pathways (ubiquitin-proteasome system and autophagy-lysosomal pathway) and catabolic processes while also inducing insulin resistance, which leads to the inhibition of protein synthesis and muscle atrophy. Another regulatory effect of inflammatory cytokines is through the control of fat metabolism, wherein factors such as IL-1β, TNF-α, and IL-6 are increasingly produced in cachectic individuals, leading to the degradation and utilization of muscle proteins as an energy source.

CARDIAC MUSCLE AGING.

Cardiac muscle aging is characterized by structural, functional, and molecular alterations that reduce cardiac reserve capacity and increase vulnerability to stress. There is a progressive loss of myocytes, decreased vascular

CENTRAL ILLUSTRATION Continued

Aging complexities, including frailty, multimorbidity, physical inactivity, systemic inflammation, and social isolation, amplify functional decline in older adults. Skeletal muscle aging and cardiac muscle aging share bidirectional pathophysiological mechanisms, including mitochondrial dysfunction, inflammaging, and hormonal dysregulation, leading to progressive muscle loss. Multimodal interventions encompass exercise and rehabilitation, pharmacological approaches (vitamin D, testosterone, investigational agents), and digital health technologies, with assessment tools for risk stratification using screening tests and biomarkers. CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; FDA = Food and Drug Administration; LV = left ventricle; SPPB = short physical performance battery; other abbreviations as in Figures 1 and 2.

compliance, and altered afterload, all of which lead to distinct adaptive and maladaptive remodeling patterns that increase vulnerability to stress and reduce functional reserve capacity.[2] Pressure overload is also known to trigger TNF secretion by cardiomyocytes.[30,31] This is unlike skeletal muscle, which undergoes atrophy with age.

Myocardial fibrosis and ventricular stiffening. Age-associated myocardial fibrosis stems from ECM remodeling characterized by increased collagen deposition, cross-linking, and reduced ECM turnover.[32] Advanced glycation end products accumulate with age, forming irreversible cross-links between collagen fibers that further augment myocardial stiffness. Ventricular stiffening results in impaired diastolic relaxation, elevated filling pressures, and reduced end-diastolic volume.[2] These alterations manifest clinically as exercise intolerance and HF with preserved ejection fraction, which account for approximately 50% of HF cases in older adults.[33]

Changes in cardiomyocyte structure, function, and contractility. Aging cardiomyocytes exhibit structural changes, including cellular hypertrophy, altered nuclear morphology, and reorganization of contractile elements, leading to contractile dysfunction.[34] Age-associated cardiomyocyte death leads to an increase in the production of fibroblasts, which in turn leads to hypertrophy of the remaining cardiomyocytes.[2] Myofibrillar density decreases, accompanied by disorganization of the sarcomere structure and an increase in interstitial space. The transverse tubule system, critical for excitation-contraction coupling, undergoes progressive disorganization with age.[2,32]

Functional alterations in aged cardiomyocytes include prolonged action potential duration, calcium handling abnormalities, and contractile dysfunction.[35] There is age-dependent dysfunction in adrenergic signaling leading to autonomic modulation, causing chronotropic incompetence and decreased inotropic reserve of the LV.[36] Sarcoplasmic reticulum calcium ATPase expression and activity decline with age, while its phospholamban inhibition increases, resulting in reduced calcium sequestration and prolonged calcium transients.[36] The ryanodine receptor exhibits increased oxidation and phosphorylation in aged cardiomyocytes, promoting diastolic calcium leak and arrhythmogenesis.[37]

Role of mitochondrial dysfunction and oxidative stress in cardiomyocytes. Cardiomyocytes contain an abundance of mitochondria, reflecting the high energy demands of cardiac function. Age-related mitochondrial changes in the heart resemble those in skeletal muscle but with tissue-specific implications. Mitochondrial volume density decreases by approximately 20% between youth and senescence, while mtDNA damage accumulates, disrupting the assembly and function of the electron transport chain complex.[2,38,39] Cardiac mitochondria exhibit increased ROS production with age, particularly from complexes I and III of the electron transport chain. The resultant oxidative damage affects mitochondrial membrane integrity and mtDNA, creating a vicious cycle of increasing dysfunction.[40] Mitochondrial quality control mechanisms, including mitophagy, fission, and fusion, demonstrate reduced efficiency in aged cardiomyocytes, allowing the accumulation of damaged mitochondria.[40] Additionally, metabolic substrate utilization shifts with cardiac aging from a predominant reliance on fatty acid oxidation toward increased glucose utilization.[41] This metabolic remodeling reflects a reduced mitochondrial capacity for fatty acid transport and oxidation, which affects the efficiency and flexibility of energy production. Pro-inflammatory cytokines, such as TNF-α and IL-1, also adversely affect the myocardium, inducing systolic and diastolic dysfunction and promoting remodeling.[42-45] Inflammation of the myocardial endothelium leads to an increase in adhesion molecules, which attract leukocytes, thus facilitating the formation of myofibroblasts and deposition of collagen in the interstitium.[46]

COMMON PATHWAYS BETWEEN SKELETAL AND CARDIAC MUSCLE AGING

MITOCHONDRIAL DYSFUNCTION, INFLAMMATION, AND METABOLIC DYSREGULATION. As discussed above, both skeletal and cardiac muscle demonstrate age-related mitochondrial impairments that contribute to cellular dysfunction. Mitochondrial biogenesis factors show reduced expression and activity in both tissues.[2] Decreased nicotinamide adenine dinucleotide levels with age limit sirtuin activity, which regulates mitochondrial function and antioxidant defense in both muscle types.[47] Inflammaging affects both muscle systems through similar mechanisms involving nuclear factor kappa B activation, cytokine production, and the activation of catabolic pathways.[5,48,49] Senescence-associated secretory phenotype components from senescent cells in muscle and adjacent tissues promote local and systemic inflammation that impairs regeneration and function in both muscle types.

Metabolic dysregulation manifests in both tissues through reduced insulin sensitivity, impaired glucose handling, and altered substrate utilization.

The mammalian target of the rapamycin signaling pathway, which integrates nutrient availability, energy status, and growth factor signals to regulate protein synthesis, exhibits age-related alterations in both skeletal and cardiac muscle, contributing to anabolic resistance and impaired autophagy.[3,50,51]

HORMONAL DYSREGULATION. Endocrine changes with aging significantly impact both muscle systems. Insulin resistance develops with advancing age, affecting glucose uptake, protein synthesis, and cell survival signaling in both skeletal and cardiac muscle. Skeletal muscle, as the primary site of insulin-stimulated glucose disposal, experiences marked consequences from insulin resistance, while cardiac insulin resistance promotes coronary microvascular dysfunction and diastolic dysfunction.[52] There is a bidirectional relationship between sarcopenia and insulin sensitivity, and hence, an accelerated aging process ensues.[53] Age-related decline in GH and insulin-like growth factor-1 (IGF-1) levels contributes to reduced protein synthesis and impaired tissue repair in both skeletal and cardiac muscle types. The GH/IGF-1 axis modulates satellite cell activation, myocyte hypertrophy, and cardiomyocyte survival.[3,54] However, the role of IGF-1 overexpression in altering both cardiovascular and skeletal muscle aging is still unclear, as studies have shown both agonist and antagonist effects.[3] Sex hormone reductions, particularly testosterone in men and estrogen in women, affect both skeletal and cardiac muscle.[55] Testosterone possesses anabolic effects on skeletal muscle and cardioprotective properties, while estrogen modulates inflammatory responses, oxidative stress, and substrate metabolism in both tissues.[54,55] The clinical application of these hormones remains to be established.

ROLE OF TELOMERE SHORTENING AND CELLULAR SENESCENCE. Telomere attrition occurs with repeated cell divisions due to the end-replication problem and oxidative damage. While postmitotic cardiomyocytes and skeletal muscle fibers experience limited replication, satellite cells, cardiac progenitor cells, and supporting cell populations (fibroblasts, endothelial cells) in both tissues undergo telomere shortening with age.[56] Telomere shortening is associated with vascular senescence, aortic valve stenosis, increased cardiovascular risk factors, and a higher risk of thromboembolic events.[36,52] Senescent cells accumulate in aging skeletal and cardiac muscle, secreting inflammatory factors, proteases, and growth factors that compromise tissue homeostasis. Interestingly, exercise training attenuates telomere shortening and cellular senescence in both muscle types by enhancing telomerase activity, reducing oxidative stress, and improving DNA repair mechanisms.[57]

SKELETAL MUSCLE AND CHRONIC DISEASE

MUSCLE WASTING AND ATROPHY IN CHRONIC CARDIOVASCULAR DISEASES. Various mechanisms can explain the association of type 2 diabetes and muscle atrophy.[23] First, diabetic patients have high levels of pro-inflammatory cytokines (such as IL-6 and TNF-α), which induce proteolysis. Second, protein synthesis is impaired due to reduced sensitivity of the mammalian target of rapamycin complex 1 to insulin, which results in the blockage of the IGF-1 pathway. Third, loss of myonuclei has been observed in patients with diabetes, causing dysfunction of the muscle satellite cells. Along similar lines, obesity promotes muscle atrophy through the development of diabetes, insulin resistance, the release of pro-inflammatory cytokines (such as IL-1β and TNF-α), and oxidative stress.

Chronic obstructive pulmonary disease is characterized by chronic hypoxia, increased level of IL-6, and myostatin expression, leading to muscle mass loss and inhibition of myoblast proliferation. Around 20% to 40% of HF patients have skeletal muscle atrophy, which is an independent predictor of mortality.[58] Furthermore, HF is associated with reduced fiber cross-sectional area and a shift from type I fibers (small, high vascular supply/mitochondrial content) to type IIX fibers (larger, more fatigable). A pro-inflammatory state (causing the release of cytokines), mitochondrial dysfunction, and increased production of ROS contribute to HF-induced muscle atrophy.

ROLE OF PHYSICAL INACTIVITY AND SYSTEMIC INFLAMMATION. Regular physical activity and exercise reduce chronic inflammation via upregulation of IL-6 receptor expression in the muscles and increased removal of IL-6 by hepatosplanchnic viscera; higher capacity of skeletal muscles to utilize fatty acids; reduction in IL-1 beta levels by down-regulation of toll-like receptor 4 and nucleotide oligomerization domain-like receptor P3 inflammasome expression; and increase in the levels of anti-inflammatory cytokines such as IL-10 and IL-1R antagonist.[59,60] In contrast, inadequate physical activity is associated with increased pro-inflammatory cytokines and adipokines (including TNF, plasminogen activator inhibitor-1, and chemokine C-C motif ligand 2). Thus, a sedentary lifestyle and accompanying obesity promote chronic inflammation, leading to muscle wasting, fatigue, and reduced

cardiovascular performance, which in turn impair the exercise capability, resulting in a vicious cycle.[61,62] Translational studies have shown endurance exercise has been shown to have metabolic benefits (eg, increased insulin sensitivity and decreased inflammation) and muscle hypertrophy, in part through activating 5′ adenosine monophosphate-activated protein kinase and a transcriptional coactivator, peroxisome proliferator-activated receptor gamma coactivator 1α (PPARGC1A, also called PGC1α), which promotes mitochondrial function and biogenesis.[63,64]

CARDIAC MUSCLE AND CHRONIC DISEASE

HYPERTENSION, ATHEROSCLEROSIS, AND EFFECTS ON CARDIAC REMODELING. Long-standing and poorly controlled hypertension is a well-known risk factor for myocardial remodeling, which involves cardiomyocyte hypertrophy, interstitial inflammation, arteriolar wall thickening, cardiomyocyte death, interstitial fibrosis, and reduced capillarization.[65-67] This leads to LV hypertrophy, LV dysfunction, HF, and arrhythmias. Additionally, hypertension also contributes to coronary artery disease (CAD) (obstructive and nonobstructive) and increased risk of myocardial infarction, which can induce cardiac remodeling similar to that seen in patients with conventional atherosclerosis.[68-70]

LEFT VENTRICULAR HYPERTROPHY AND DIASTOLIC DYSFUNCTION IN CHRONIC DISEASES. Around 15% to 20% of the general population is found to have left ventricular hypertrophy (LVH), with the highest prevalence in untreated hypertensives (19% to 48%) and those with high-risk hypertension (58% to 77%).[71] Aging, obesity, and chronic kidney disease also increase the risk of developing LVH.[72-74] The underlying pathogenesis of LVH includes the activation of cytokines, the renin-angiotensin-aldosterone system, sodium-potassium pumps, heterotrimeric G proteins, endothelin, and calcium-mediated modulation. The initial compensatory mechanism of increased muscle mass progresses toward increased stiffness and myocardial fibrosis, which manifests into diastolic dysfunction and, subsequently, systolic dysfunction.

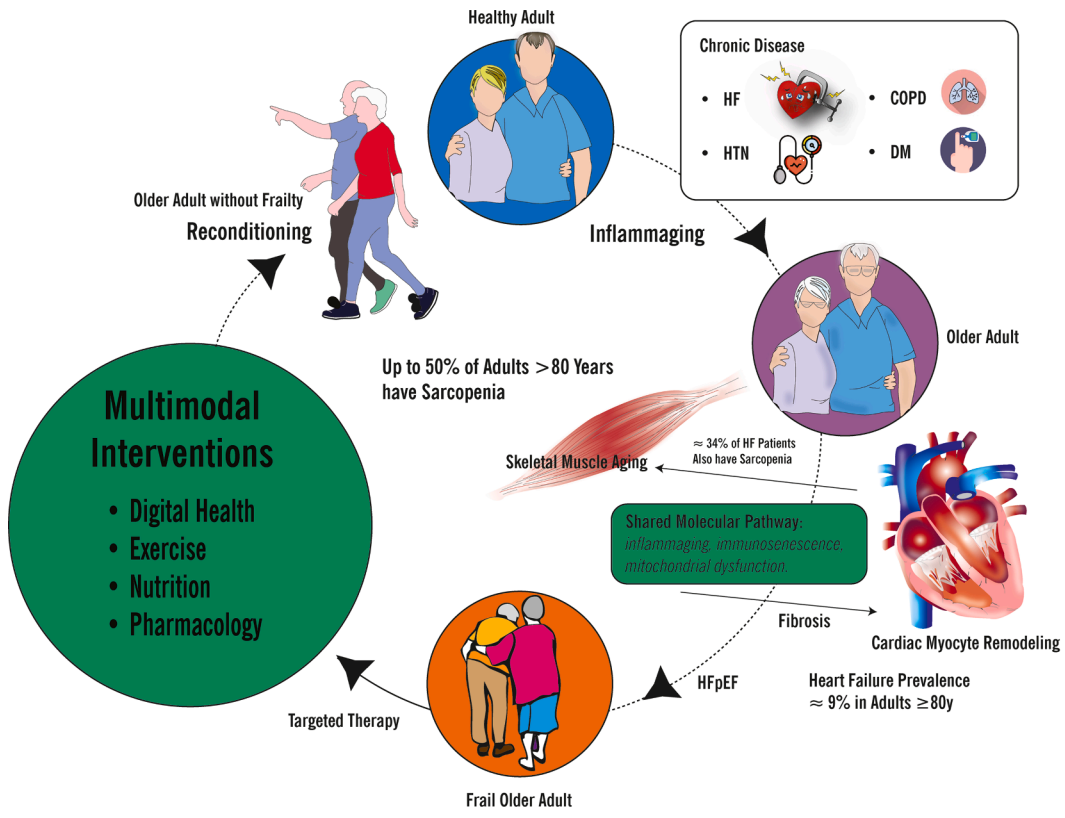
CARDIOMETABOLIC SYNDROME: A DUAL THREAT. Cardiometabolic syndrome encompasses key contributing factors, such as environmental influences, genetic predisposition, behavioral patterns, hyperglycemia, and dyslipidemia, as well as adverse cardiovascular outcomes including HF, CAD, and atrial fibrillation.[75,76] Chronic diseases (obesity, diabetes, hypertension, etc) are characterized by chronic low-grade inflammation, which induces cardiac remodeling, impaired skeletal muscle regeneration, and microvascular dysfunction.[27,77-79] A recent study demonstrated that a cardiometabolic disease staging system has strong predictive value for identifying the risk of major adverse cardiovascular events in patients without a prior history of myocardial infarction or stroke.[80] Thus, it becomes imperative to focus on early lifestyle interventions, prevention modalities, pharmacotherapy, and bariatric procedures.[75]

INTERACTION BETWEEN SKELETAL AND CARDIAC MUSCLE IN CHRONIC DISEASE. Patients with HF (reduced or preserved ejection fraction) demonstrate significant changes (structural and functional) in the skeletal muscle, such as a reduction in the number of type I fibers, oxidative capacity, and mitochondrial density, along with increased glycolysis, resulting in muscle atrophy and exercise intolerance.[81] Similarly, skeletal muscle inflammation leads to the release of myokines, such as IL-6, which contribute to cardiac remodeling. Therefore, a bidirectional relationship is formed between cardiac and skeletal muscles, resulting in a vicious cycle of dysfunction and atrophy (**Figure 1**).

NUTRITION AND MUSCLE HEALTH IN AGING AND CHRONIC DISEASE

NUTRITION IN PREVENTING AND TREATING SARCOPENIA. Protein-calorie malnutrition increases the risk of sarcopenia in older adults.[82] The Food and Nutrition Board of the National Academy of Sciences of the United States recommends 0.8 g/kg/day protein for all adults to prevent muscle mass loss.[83] Bauer et al recommend protein consumption of 1.0 to 1.2 g/kg body weight/day for healthy older adults, 1.2 to 1.5 g/kg body weight/day for those with acute or chronic disease, and 2 g/kg body weight/day for those with frailty, severe illness, or malnutrition.[84] This is in keeping with recommendations by the European Society for Clinical Nutrition and Metabolism, which also recommends coupling a high-protein diet with physical activity (aerobic and resistance exercise) for older adults.[85] Current evidence suggests that higher protein intake (1-1.2 gm/kg) in older adults may actually be protective for kidney function rather than harmful. The OmniHeart (Optimal Macronutrient Intake Trial to Prevent Heart Disease) trial demonstrated that a diet with 25% of calories derived from protein (compared to 15%) increased estimated glomerular filtration rate (eGFR) by approximately 4 mL/min/1.73 m^2 when measured using cystatin C, a more reliable marker than creatinine for assessing kidney function in the context of dietary protein

FIGURE 1 Interplay of Skeletal and Cardiac Muscle Aging and Points for Interventions



COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HTN = hypertension.

changes.[86] Similarly, longitudinal data from the Cardiovascular Health Study found no adverse association between protein intake and kidney function decline in older adults, with protein intake showing no significant effect on eGFR changes over 6.4 years of follow-up.[87] Furthermore, a multicohort study of over 8,500 older adults found that higher protein intake (1.2-1.4 g/kg/day) was associated with lower mortality in those with mild-to-moderate chronic kidney disease, suggesting potential protective effects.[88] Several studies suggest the use of protein and amino acid supplementation (whey, L-carnitine, leucine, beta-hydroxy-beta-methylbutyrate [HMB]) in improving muscle strength and mass, as well as physical performance and frailty scores, compared with controls or no intervention, although data are limited.[89-91] However, in older adults with chronic kidney disease, where the eGFR is below 30 mL/min/1.73 m^2, protein restriction to 0.6 to 0.8 g/kg/day may be necessary to prevent uremic complications.[92] Lower protein intake has been shown to slow the progression of chronic kidney disease (CKD) in individuals with stages 4 and 5 CKD who are not on dialysis.[93,94] It is therefore essential to involve a multidisciplinary team in caring for older adults with multimorbidity and sarcopenia.

In 2 Asian studies, a high protein intake and low percentage of energy from fat ("mushrooms-fruits-milk" pattern) was found to be protective against sarcopenia.[95] These findings suggest that, in addition to increased protein intake, reducing fat intake may also be considered for the prevention and management of sarcopenia. In a cross-sectional study that assessed the association between dietary patterns and sarcopenia, a higher "snacks-drinks-milk product" and "vegetables-fruits" dietary pattern score was associated with lower odds of developing sarcopenia in older Chinese men.[96] The same effect was, however, not observed in women. It is essential to note that dietary habits vary significantly from

country to country. Currently, the available literature does not support a specific nutritional pattern for sarcopenia prevention. The general recommendation is for balanced diets comprising $^1/_4$ protein, $^1/_4$ wholegrains, and $^1/_2$ fruit and vegetables.

There is some evidence linking pro-inflammatory diets to an increased risk of sarcopenia.[95] Conversely, antioxidant-rich diets appear to have protective effects. In a cross-sectional study by Wang et al, consumption of antioxidant-rich food (chili and sweet pepper, which are rich in capsaicin and capsiates) was significantly associated with a lower risk of sarcopenia. A community-based study by Huang et al also found an association between a higher level of serum betaine and a higher lean body mass percentage.[97] Conversely, a diet rich in red or processed meat has been associated with a high pro-inflammatory index, making it imperative to consider the source of protein for muscle building.[98] In a systematic review and meta-analysis by Lim et al,[99] animal and plant proteins were compared in terms of their lean muscle mass building effects. The protein source did not significantly affect changes in lean muscle mass or muscle strength, but animal protein favored the percentage of lean mass in younger adults (<50 years). A recent meta-analysis found insufficient evidence to support the benefit of vitamin D supplementation for improved muscle mass or function.[100]

CHALLENGES IN NUTRITION FOR OLDER ADULTS

The challenges in nutrition for older adults encompass complex physiological, social, and pharmacological factors that limit the effectiveness of interventions. Physiological barriers include anorexia of aging, age-related anabolic resistance reducing muscle protein synthesis response by 25% to 30%, and gastrointestinal changes impairing protein absorption.[82,101-103] Gastrointestinal changes, including reduced gastric acid secretion and slower gastric emptying, affect protein digestion and amino acid absorption.[104] Social determinants of health compound these challenges: low socioeconomic status limits access to quality protein sources.[105] Older adults tend to make simpler food choices when eating alone, with social isolation affecting approximately 24% of community-dwelling older adults. Medication interactions and comorbidities add complexity to the nutritional management process. Polypharmacy, with the average older adult taking 5 to 8 medications daily, significantly affects nutrient absorption and metabolism. Additionally, comorbidities may have conflicting therapy; chronic kidney disease requiring protein restriction directly opposes sarcopenia guidelines, while high-dose vitamin D supplementation may paradoxically increase fall risk through hypercalcemia.[92]

These limitations highlight the need for personalized nutritional protocols that account for phenotypic heterogeneity, medication interactions, socioeconomic constraints, and cultural preferences rather than universal supplementation approaches.

INTERVENTIONS TO ADDRESS FUNCTIONAL AND PHYSICAL DECLINE

Pathologic aging and chronic disease adversely affect nutrition and skeletal muscle health, leading to progressive physical decline and reduced resilience. Management of functional impairment in older adults should, therefore, begin with comprehensive assessment and risk stratification (**Table 1**, **Figure 2**). Optimizing the underlying cardiac condition, whether it is valvular disease, cardiomyopathy, or ischemic heart disease, and then implementing targeted interventions preserves muscle mass, strength, and cardiovascular endurance. A multidisciplinary team comprising a geriatrician, cardiologist, primary care provider, nutritionist, and rehabilitation specialist, working through integrated care pathways, can coordinate exercise-based rehabilitation, pharmacotherapies, nutritional strategies, and digital health technologies (such as wearables, remote monitoring, and pressure sensors) for early detection, personalized intervention planning, and sustained engagement.

PHYSICAL ACTIVITY AND REHABILITATION. Multicomponent programs that combine resistance, aerobic, and balance exercises yield the most significant preservation of lean mass and improvements in functional performance[106] and promote cellular adaptations such as mitochondrial biogenesis, reduced inflammation, increased muscle protein synthesis, and enhanced oxidative phosphorylation.[107,108] Among the exercise interventions, progressive resistance training (adjusting load, volume, and intensity) constitutes the cornerstone of sarcopenia management and preserving functional capacity. Exercise interventions can occur in various environments, as seen below.

HOSPITALIZED SETTINGS. Early mobilization in acute care preserves functional capacity. In a single-blind randomized controlled trial (RCT) of 370

TABLE 1 Comprehensive Sarcopenia Assessment and Risk Stratification Protocol

Assessment Component	Screening Tools	Risk Stratification	Clinical Action
Muscle strength	Grip strength: <27 kg (men), <16 kg (women)	Low risk: 1 abnormal test	Refer to community exercise program
	Chair rise test: >15 s for 5 rises	Moderate risk: 2 abnormal tests	Supervised exercise 2×/week + nutrition consult
Muscle mass	DXA scan: ALM/height^2 <7.0 (men), <5.5 (women)	High risk: 3+ abnormal tests OR hospitalization	Multidisciplinary team + intensive intervention
Physical performance	Gait speed: <0.8 m/s	Very high risk: sarcopenia + CVD + falls	Consider pharmacological adjuncts + daily PT
	SPPB: <8 points		
Nutritional status	MNA-SF: <12 points	Low-high risk based on nutritional status	Nutritional counseling and interventions
Medication review	Polypharmacy assessment	Review for high-risk drugs	Close medication review for high-risk medications

ALM = appendicular lean mass; CVD = cardiovascular disease; DXA = dual-energy x-ray absorptiometry; MNA-SF = mini nutritional assessment-short form; SPPB = short physical performance battery; PT = physical therapy.

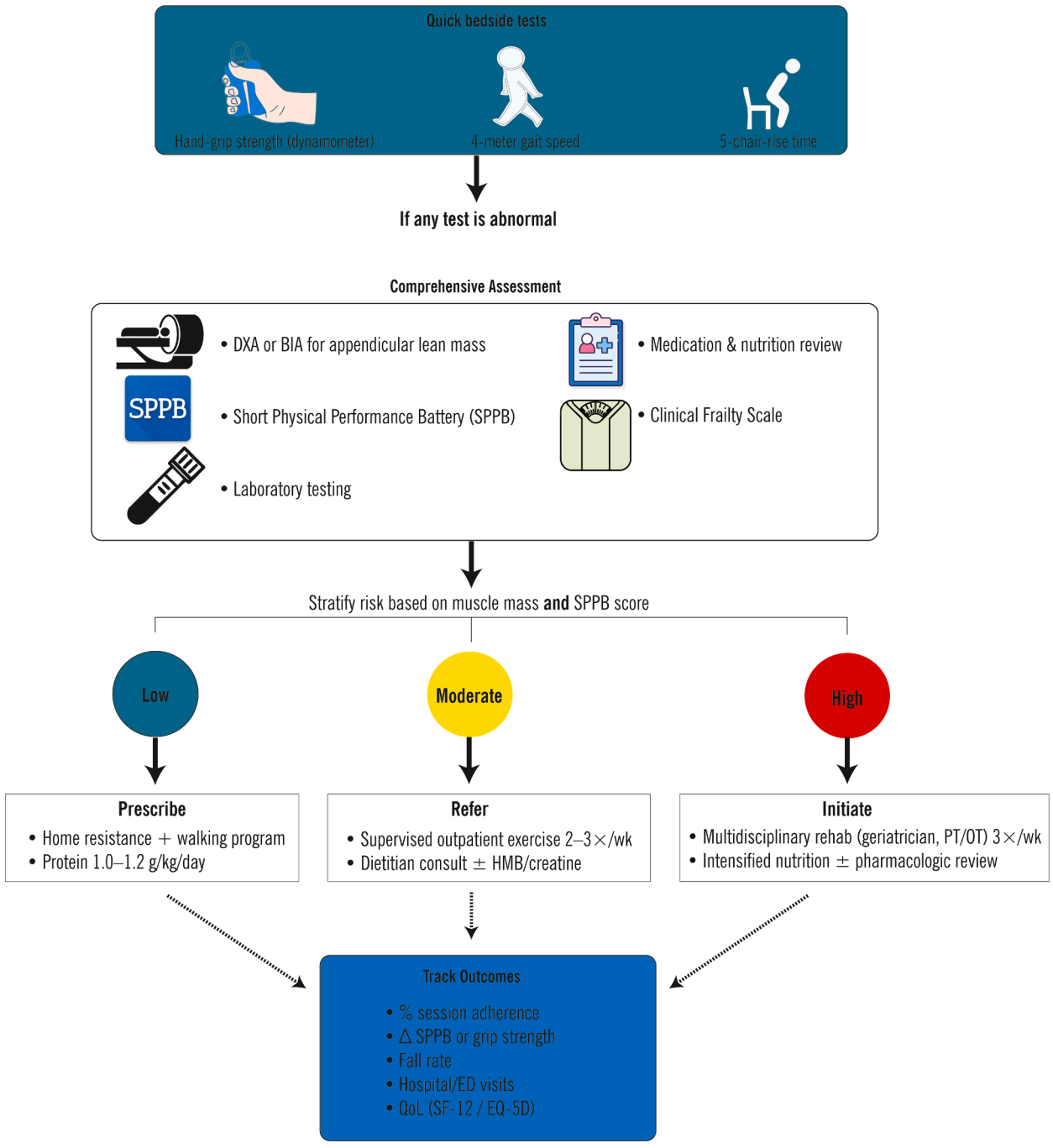
hospitalized older adults (mean age 87.3 years), twice-daily 20-minute resistance, balance, and walking sessions initiated within 48 hours of admission for 5 to 7 days produced greater gains in Short Physical Performance Battery (SPPB) and Barthel Index scores, better hand-grip strength, and more preserved cognition vs usual care.[109] A Vivifrail-adapted program (resistance/power, balance, flexibility, and cardiovascular endurance) across 3 geriatric departments (n = 200; >75 years) similarly improved SPPB and functional capacity.[110] Even among critical-care survivors (n = 53), a protocol integrating breathing techniques, mobilization, resistance, and aerobic exercises, and neuromuscular stimulation for 2 hours daily shortened the length of stay.[111] Several other studies noted that goal-directed mobilization, including power training, balance, and walking, enhanced muscle strength/power at discharge, preserved functional status, and is cost-effective compared to usual care.[112-118]

AMBULATORY SETTINGS. A brief, twice-daily "exercise-snacking" regimen for 28 days improved SPPB, Timed Up-and-Go, and sit-to-stand in prefrail patients.[119] Short interventions (as brief as 4 weeks) can also yield functional gains.[120] A 6-month program (physical therapy that focused primarily on improving underlying impairments in physical abilities, including balance, muscle strength, ability to transfer from one position to another, and mobility) in 188 moderately frail adults (≥75 years) reduced functional loss compared with education alone.[121] Another systematic review of 21 RCTs found that home-based resistance training improved lower-limb strength, muscle power, and balance but did not affect hand-grip strength, gait speed, QoL, or fall rates.[122] Even among frail adults, resistance training (at least twice weekly) alone improved sit-to-stand time and increased SPPB compared to standard of care.[123] In a multicenter RCT of 111 frail older adults (≥75 years), a 6-month Otago exercise program (72 sessions performed over a 6-month intervention encompassing balance, strength, and aerobic exercises, supplemented with walking periods) vs a supervised group-based multicomponent exercise with oral supplementation enhanced mobility, balance, and hand-grip strength vs controls.[124] Other forms of exercise, such as mind-body exercises and Tai chi, do improve some components of skeletal muscle function, including chair-stand performance and Timed Up-and-Go, but do not impact muscle mass or SPPB.[125] Exercise prescription in ambulatory cardiac rehabilitation should follow progressive protocols, with initial sessions at 40% to 80% of exercise capacity, as determined through graded testing, and advancing to 150 minutes per week of moderate-intensity exercise.[126]

Among adults with cardiovascular disease (CVD), such as HF, targeted rehabilitation improves functional capacity. The phase-2 REHAB-HF (Rehabilitation Therapy in Older Acute Heart Failure Patients) trial showed no reduction in readmissions or mortality but demonstrated significant improvements in SPPB, gait speed, and 6-minute walk distance (6MWD) at 3 months.[127] Resistance training similarly enhanced upper and lower extremity strength, oxygen consumption peak (VO_2), and 6MWD in this population.[128]

In summary, as reflected in a systematic review and network meta-analysis of 69 trials, physical activity, primarily resistance training, followed by mind-body exercise and aerobic training, was

FIGURE 2 **Muscle Health Management Pathway for Older Adults: Screening, Risk Stratification, Targeted Intervention, and Outcome Tracking**



A simple bedside algorithm screening test (grip strength, gait speed, or chair rise) triggers more extensive diagnostic work for sarcopenia to stratify patients into low-, moderate-, or high-risk pathways. Outcomes monitored include cardiac rehabilitation program completion, change in short physical performance battery, falls, and fall-related hospitalizations. BIA = bioelectrical impedance analysis; DXA = dual-energy x-ray absorptiometry; ED = emergency department; EQ-5D = EuroQol 5-Dimension questionnaire; HMB = β-hydroxy β-methylbutyrate; OT = occupational therapy; PT = physical therapy; QoL = quality of life; SF-12 = 12-Item Short Form Health Survey.

associated with reducing frailty compared to a control group, with physical activity being the most effective type of intervention.[129] Supervised, multicomponent programs, initiated early during hospitalization, transitioned to home-based maintenance, and supplemented by nutritional support appear optimal for mitigating sarcopenia. Tailored regimens (eg, supervised strength training 2-3 times a week with balance exercises) benefit even very old or frail patients, with higher levels of total and moderate-to-vigorous physical activity inversely correlating with sarcopenia risk.[130-133] Lastly, patient education, in addition to multidisciplinary engagement (including physiotherapists, geriatricians, and exercise practitioners), remains key to sustained participation. The integration of cardiovascular-specific parameters with skeletal muscle rehabilitation represents a critical advancement in contemporary practice. Progressive rehabilitation protocols must synchronize central cardiac physiology with peripheral vascular and skeletal muscle function, utilizing structured approaches that account for hemodynamic variability, arrhythmia risk, and fluctuating cardiac output.[134]

PHARMACOLOGICAL INTERVENTIONS. Pharmacological interventions have shown promise in early-phase and preclinical studies; however, their clinical efficacy remains unestablished. Pharmacological interventions include anabolic agents, inhibitors of the myostatin/activin receptor II pathway, hormonal therapies (testosterone replacement, selective androgen receptor modulators), ghrelin agonists, and GHs.

Enobosarm, a nonsteroidal selective androgen receptor modulator, produced dose-dependent gains in lean mass and function over 12 weeks in healthy older men and postmenopausal women.[135] Myostatin-pathway inhibitors, a protein that naturally inhibits muscle growth, increased lean body mass but yielded variable strength outcomes.[136] Testosterone, a primary anabolic hormone, stimulates muscle protein synthesis and growth. In a meta-analysis, testosterone therapy in stable chronic HF improved the 6MWD, shuttle walk test, and peak VO_2 without cardiovascular adverse events.[137] Additionally, testosterone leads to an increase in lean body mass, handgrip strength, and the prevention of muscle wasting and functional loss. Nonetheless, the recommendation to initiate testosterone therapy is for those with low serum testosterone levels.[138] Vitamin D_3 has also been shown to improve lower-limb strength substantially. However, the evidence remains questionable, as the 3-year DO-HEALTH (Vitamin D3-Omega-3-Home Exercise-Healthy Aging and Longevity) trial found that replete populations showed no benefit in SPPB or fracture outcomes. The benefit is mainly seen in individuals with specific vitamin D deficiency.[139] Protein-energy supplementation, particularly branched-chain amino acids or whey protein formulations, improves muscle mass, hand-grip strength, and functional outcomes. Guidelines recommend 1.0 to 1.5 g/kg/day of high-quality, leucine-rich protein.[140,141] In malnourished HF patients (EFFORT [Effect of Early Nutritional Support on Frailty, Functional Outcomes, and Recovery of Malnourished Medical Inpatients] trial, n = 645), individualized nutritional support reduced mortality and cardiovascular events.[142] HMB, a leucine metabolite, has shown some functional benefits.[143,144] In the NOURISH [Nutrition Effect on Unplanned Readmissions and Survival in Hospitalized Patients] trial, high-protein, HMB-enriched supplements at discharge improved nutritional status and reduced 90-day mortality among older adults with malnourishment and any of the conditions (congestive HF, acute myocardial infarction, pneumonia, or chronic obstructive pulmonary disease).[145]

The translation of promising preclinical findings to clinical practice faces substantial barriers as the heterogeneity of sarcopenia populations confounds clinical trials. The disconnect between surrogate endpoints (lean mass gain) and functional outcomes challenges regulatory approval pathways, as seen with myostatin inhibitors. Furthermore, the optimal timing for pharmacological intervention remains undefined, that is, whether to initiate treatment when sarcopenia is first diagnosed, during acute hospitalization, or preventively in presarcopenic states. Long-term safety data extending beyond 12 to 24 months are absent for most investigational agents, given the chronic nature of sarcopenia requiring potentially lifelong treatment. These limitations necessitate a paradigm shift toward identifying biomarkers for treatment response, developing combination therapies that target multiple pathways simultaneously, and establishing pragmatic trial designs that include real-world populations with multimorbidity, rather than highly selected cohorts that poorly represent clinical practice.

In summary, no pharmacological treatments have been explicitly approved for sarcopenia or frailty. The combination of exercise and nutritional interventions remains the mainstay, with protein supplementation, vitamin D repletion, and testosterone for those with hypogonadism.[146] We discuss the current evidence in nutrition interventions in **Table 2**.

TABLE 2 Integrated Nutritional and Pharmacological Interventions for Muscle Health

Intervention	Target Population	Dosing/Protocol	Evidence Level	Expected Outcomes
Protein supplementation				
Healthy older adults	Age >65 y, independent	1.0-1.2 g/kg/day	Strong	Maintain muscle mass
Acute/chronic disease	Hospitalized/CVD	1.2-1.5 g/kg/day	Strong	Prevent muscle loss
Frailty/sarcopenia	SPPB <8, low muscle mass	2.0 g/kg/day	Moderate	Improve strength
Specific nutrients				
Leucine	All sarcopenic patients	2.5-3g per meal	Moderate	Enhance MPS
HMB	Postdischarge malnutrition	3 g/day	Moderate	Reduce mortality
Vitamin D	Deficiency (<20 ng/mL)	800-2,000 IU/day	Strong	Improve strength
Pharmacological				
Testosterone	Hypogonadal men	Per clinical guidelines	Moderate	↑ Muscle mass, strength
ACE inhibitors	HF with sarcopenia	Standard HF dosing	Emerging	Improve muscle perfusion
SARMs (investigational)	Clinical trials only	Variable	Investigational	↑ Lean mass

ACE = angiotensin-converting enzyme; HF = heart failure; HMB = β-hydroxy β-methylbutyrate; IU = international units; MPS = muscle protein synthesis; SARMs = selective androgen receptor modulators; other abbreviations as in Table 1.

EMERGING TECHNOLOGIES IN MONITORING MUSCLE AND CARDIAC HEALTH

Digital health solutions, including telemedicine, remote monitoring, and implantable sensors, enhance both cardiovascular and skeletal muscle care. These technologies offer viable solutions to barriers such as mobility limitations, transportation challenges, and resource disparities by delivering exercise prescriptions, nutrition counseling, and fall risk monitoring. For example, implantable hemodynamic monitors have significantly reduced both mortality and HF hospitalizations.[147-150] Technological advancements offer promising strategies for enhancing physical function and addressing sarcopenia in older adults. Wearable accelerometers, pedometers, and pressure-sensing insoles have enabled continuous gait and activity monitoring, which can estimate patients' functional status. Moreover, devices like exoPill capture electromyographic signals have diagnosed sarcopenia with >89% accuracy.[147,151,152] Furthermore, these devices can precisely target patients toward specific physical activity goals, such as achieving a number of daily steps. Smartphone applications can also enhance interventions by integrating components such as nutritional assessment, daily step monitoring, and exercise program engagement, in addition to reminders to walk and exercise. In parallel, novel mobile applications are being developed to assess sarcopenia through video analysis, which could evaluate patients' functional status.[153]

Early pilot studies demonstrate feasibility: a web-based Physical Function-Life program (lifestyle integrated functional exercise, customized exercise programs, and monitor participants' progress) improved hand-grip strength and chair-rise performance in frail older adults,[154] voice-activated exercise programs increased grip strength and chair-stand speed in older users;[155,156] tablet-delivered home strengthening (3 days/week using prescription app on tablet computer) achieved 95% adherence over 8 weeks with increased mean weekly walking time, moderate-vigorous physical activity time, in addition to Short Physical Performance Battery.[157]

For instance, a 4-week mobile app-based telerehabilitation program compared to traditional therapist-supervised rehabilitation significantly improved grip strength and functional measures (30-second Arm Curl Test, 30-second Sitting-to-Rising Test, quadriceps femoris extension peak torque, Berg Balance Scale, and Instrumental Activities of Daily Living scale) in older adults with sarcopenia.[158] In a systematic review and meta-analysis exploring the efficacy of managing malnutrition in community-dwelling older adults through telehealth, telephone consults were feasible, associated with improved QoL, increased protein intake by 0.13 g/kg, and cost-effectiveness.[159] Tele-nutrition interventions improved QoL and protein intake, and a 6-month telemedicine-supported exercise and nutrition program in CAD/diabetes patients modestly lowered hemoglobin A1c (glycated hemoglobin) and body weight.[160,161] However, future studies are needed to validate diagnostic criteria, correlate sensor outputs with clinical definitions of sarcopenia, and optimize artificial intelligence-driven behavior change.[155,156]

It is important to note that current evidence examining digital health modalities for sarcopenia management reveals inconsistent interpretability of

clinical efficacy outcomes. These studies typically have limited sample sizes (enrolling fewer than 100 participants), short observation periods, and lack clinical primary endpoints, including fall incidence, hospitalization rates, or mortality outcomes, and also lack rigorous intention-to-treat analytical frameworks.[158,159] The translational validity of wearable device technologies remains questionable, with validation studies demonstrating 20% to 40% degradation in diagnostic accuracy when algorithms developed under controlled laboratory conditions are applied to the real-world population.[162] This is further compounded by the absence of industry-wide standardization protocols across heterogeneous manufacturers. Additionally, the feasibility of implementation within the target older adult population encounters significant barriers, including digital literacy deficits, simultaneous physical limitations such as arthritic changes or essential tremor, and cognitive impairment, which substantially impede the capacity to execute multistep digital protocols.[163] These challenges associated with the human-technology interface, when considered alongside the paucity of robust clinical benefits, represent fundamental constraints to the scalability and real-world deployment of digital health interventions for sarcopenia management in older adults. Addressing these implementation barriers requires the development of standardized protocols and clinically validated devices specifically designed for older adults with CVD. There is an urgent need for strategic collaboration between cardiovascular aging investigators and medical technology companies committed to improving muscle mass and physical functioning in this vulnerable population.

INTEGRATED CARE MODELS

Optimal management of older adults with functional limitations begins with addressing underlying etiologies, particularly in the presence of underlying CVD, aiming for guideline-directed therapy optimization to enhance cardiac function and functional capacity. This includes prescribing guideline-directed therapies and deprescribing medications that may impair functional status, such as those causing orthostatic symptoms, to mitigate the risk of falls and deconditioning. Evidence demonstrates that programs initiated within 1 week of discharge achieve superior functional outcomes compared to typical 4-week delays, with many patients exceeding baseline functional capacity. This demonstrates the critical importance of seamless transitions from inpatient mobilization to outpatient rehabilitation programs.[134] Polypharmacy assessment is also essential, and an underutilized but critical component of comprehensive rehabilitation involves structured medication optimization protocols. Multidisciplinary care, integrating cardiologists, geriatricians, nutritionists, physiotherapists, occupational therapists, and social workers, is crucial for addressing physical, nutritional, and psychological needs.[164,165]

A proposed outpatient clinic model could operate through weekly team conferences, coordinated by a geriatrician who conducts comprehensive geriatric assessments, manages multimorbidity, and facilitates deprescribing.[166] The team would include: a cardiologist optimizing therapies while monitoring exercise hemodynamics; a dietitian developing personalized protein protocols that account for renal function and medication timing; a physical therapist designing progressive resistance programs based on SPPB scores; and a clinical pharmacist identifying potential drug-nutrient interactions.[134,166] Geriatricians also play a central role in balancing competing treatment priorities across multiple chronic conditions while aligning interventions with patient-centered functional goals.[134] Monthly reassessments using validated measures would guide modifications, with telehealth monitoring between visits. Such integrated care models represent the practical translation of the molecular and clinical evidence presented in this review.[134]

CONCLUSIONS

The intricate interrelationship between skeletal and cardiac muscle aging reveals shared molecular and cellular mechanisms, including mitochondrial dysfunction, chronic inflammation, oxidative stress, and anabolic resistance, that collectively drive functional decline. Neuromuscular junction deterioration and satellite cell dysfunction in skeletal muscle parallel myocardial fibrosis and calcium handling abnormalities in the aging heart, with both systems demonstrating heightened vulnerability to chronic disease states that amplify these degenerative processes. Nutritional factors significantly modulate these trajectories, with protein requirements increasing with age to overcome anabolic resistance. Meanwhile, specific nutrients, including leucine, vitamin D, and anti-inflammatory compounds, attenuate catabolic signaling and support muscle preservation.

Multimodal interventions that integrate structured exercise (particularly combining resistance and aerobic training), optimized nutrition, and targeted pharmacological approaches demonstrate the greatest efficacy for preserving muscle function and cardiovascular health throughout the lifespan. Future research should focus on elucidating the molecular mediators of muscle-heart crosstalk, developing predictive biomarker panels for personalized risk stratification, investigating senolytic agents and mitochondrial-targeted therapeutics, and establishing evidence-based protocols that can be implemented across diverse health care settings. By targeting the fundamental biological mechanisms underlying concurrent skeletal and cardiac muscle aging, we may develop more effective strategies for preserving functional independence and reducing the health care burden associated with age-related physical decline.

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