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Sarcopenia and Cardiovascular Diseases

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ABSTRACT: Sarcopenia is the loss of muscle strength, mass, and function, which is often exacerbated by chronic comorbidities including cardiovascular diseases, chronic kidney disease, and cancer. Sarcopenia is associated with faster progression of cardiovascular diseases and higher risk of mortality, falls, and reduced quality of life, particularly among older adults. Although the pathophysiologic mechanisms are complex, the broad underlying cause of sarcopenia includes an imbalance between anabolic and catabolic muscle homeostasis with or without neuronal degeneration. The intrinsic molecular mechanisms of aging, chronic illness, malnutrition, and immobility are associated with the development of sarcopenia. Screening and testing for sarcopenia may be particularly important among those with chronic disease states. Early recognition of sarcopenia is important because it can provide an opportunity for interventions to reverse or delay the progression of muscle disorder, which may ultimately impact cardiovascular outcomes. Relying on body mass index is not useful for screening because many patients will have sarcopenic obesity, a particularly important phenotype among older cardiac patients. In this review, we aimed to: (1) provide a definition of sarcopenia within the context of muscle wasting disorders; (2) summarize the associations between sarcopenia and different cardiovascular diseases; (3) highlight an approach for a diagnostic evaluation; (4) discuss management strategies for sarcopenia; and (5) outline key gaps in knowledge with implications for the future of the field.

Key Words: body mass index ■ cardiovascular diseases ■ older adults ■ sarcopenia

In the United States, the improvement in life expectancy has resulted in a rapid expansion of the older adult population.[1] It is projected that 1 in 5 Americans will be >65 years of age by 2030, and those >85 years will account for >20% of the older adult population.[1] Older adults are prone to cardiovascular disease (CVD) because the biologic underpinning of aging, including hormonal changes, immunosenescence, impaired autophagy, oxidative stress, and mitochondrial dysfunction, predispose to development of CVD. In addition, management of CVD is complicated by the presence of geriatric syndromes.[2,3] A particularly important geriatric syndrome that disproportionally affects older patients with CVD is sarcopenia.[2,3] Sarcopenia is the progressive loss of muscle strength, mass, and function, and is associated with increased risk of death, falls, disability, hospitalization, and loss of independence.[4]

There is a bidirectional association between sarcopenia and CVD.[5] Sarcopenia can lead to increased adiposity, insulin resistance, and chronic inflammation, and thus, predispose adults to developing cardiovascular events,[6] and the chronic inflammatory state, malnutrition, and decreased physical activity observed in cardiac patients are precursors to a catabolic state, leading to accelerated muscle loss and development of sarcopenia.[7] In this review, we aimed to: (1) provide a definition of sarcopenia within the context of muscle wasting disorders; (2) highlight an approach for a diagnostic evaluation; (3) summarize the associations between sarcopenia and different CVDs; (4) discuss management strategies for sarcopenia; and (5) outline key gaps in knowledge with implications for the future of the field.

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Nonstandard Abbreviations and Acronyms

ACE-I	angiotensin-converting enzyme inhibitor
AWGS	Asian Working Group for Sarcopenia
BMI	body mass index
CAD	coronary artery disease
CR	cardiac rehabilitation
CT	computed tomography
CVD	cardiovascular disease
D3-Cr	D3-creatine
DXA	dual-energy x-ray absorptiometry
EWGSOP	European Working Group on Sarcopenia in Older People
HF	heart failure
MRI	magnetic resonance imaging
PAD	peripheral arterial disease

SARCOPENIA AND THE WASTING CONTINUUM

Definitions

Sarcopenia, Greek for "flesh poverty," was originally proposed in recognition of a clinical condition of a substantial loss of muscle mass and function observed with aging and results in loss of independence among older adults (Supplemental Material).[8] The first operational definition only included low lean mass as a surrogate measure of muscle mass to define sarcopenia.[9] Subsequent evidence showed that muscle weakness and impaired mobility are better predictors of mortality and disability than low lean mass alone.[10,11]

Sarcopenia is a pathologic condition of "muscle failure," defined as "a progressive loss of muscle strength (dynapenia), mass (quantity), and function (quality), leading to a decline in physical functioning and increasing the risk of disability, fall, and mortality."[12] Although multiple sets of diagnostic criteria for sarcopenia exist, low muscle strength and function are universally agreed upon as key components. The EWGSOP2 (European Working Group on Sarcopenia in Older People 2) and the AWGS (Asian Working Group for Sarcopenia) diagnostic algorithms are the most widely used in clinical practice (Table 1).[14,20]

The EWGSOP2 defines sarcopenia as the coexistence of low muscle strength with either low muscle mass or quality; the presence of low physical performance indicates severe sarcopenia, and low muscle strength alone (without low muscle mass or quality) indicates "pre-sarcopenia." The SDOC (Sarcopenia Definitions and Outcomes Consortium), a collaboration funded by the National Institute on Aging and the Foundation for the National Institutes of Health, defines sarcopenia as "low muscle strength assessed by grip strength and slow gait speed (ie, slowness)."[21,24] Sarcopenia is distinct from malnutrition and cachexia, although each exhibits interrelated pathophysiology leading to different magnitudes of "wasting" and susceptibility to cardiovascular events (Table 2; Table S1).[25]

In this article, we adopted the EWGSOP2 definition of sarcopenia that combines impairments in strength (dynapenia), mass (quantity/structure), and function (quality); thus, we refer to sarcopenia as impairment in mass and function or strength. To indicate a diagnosis of sarcopenia, there must be impairment in any of the following domains, measured as 2 SDs below the mean normal reference value (or low gait speed <0.8 m/s), as follows (Table 1):

1. Low muscle mass is present (with criterion 2 or 3);
2. Low muscle strength; or
3. Low physical performance.

Sarcopenic obesity is a particularly important phenotype of sarcopenia[14] because the prevalence of obesity has increased substantially in recent years, now approaching 43% in the general population.[26] Sarcopenic obesity is defined as obesity (increased visceral adipose tissue) that concurrently presents with sarcopenia (decline in muscle mass/function).[23] Due to lack of consensus on diagnostic criteria, there is substantial variation in the reported prevalence and associated outcomes of sarcopenic obesity.[27] Regardless of definition, participants with sarcopenic obesity had the highest incidence of cardiovascular events compared with other forms of muscle disorders.[28] The ESPEN (European Society for Clinical Nutrition and Metabolism) and the EASO (European Association for the Study of Obesity) have established an initiative to standardize the diagnostic workup for sarcopenic obesity.[23] Sarcopenic obesity may be diagnosed on the basis of independent measures of obesity and sarcopenia.

PATHOPHYSIOLOGIC MECHANISMS OF SARCOPENIA

The underlying pathophysiologic mechanism of sarcopenia is complex and involves interactions of multiple physiologic systems (Figure 1).[29–35]

Structural Changes of Skeletal Muscle

Human skeletal muscle consists of 2 main fiber types (slow and fast) and is classified into 3 subtypes of myofibers: type I (slow-oxidative and fatigue-resistant in low-intensity prolonged activity), type IIa (fast-oxidative and relatively fatigue-resistant), and type IIb or IIx (fast-glycolytic, functional in rapid and high-intensity movements, and are fatigue-susceptible).[36,37] Myofibers are organized in motor units, and each motor unit consists of a myofiber and its alpha motoneuron innervation.[38] Satellite cells are the skeletal muscle somatic stem cells responsible for muscle repair and regeneration (myogenesis).[39] The disturbances

Table 1. Clinical Definitions of Sarcopenia and Sarcopenic Obesity

Society	Consensus definition	Diagnostic criteria
EWGSP (2010)[13]	Sarcopenia was recognized as a geriatric syndrome and defined as "a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life, and death."	• Screen older adults >65 y by measuring gait speed • Diagnose sarcopenia if: 1. Low muscle mass is present with either (2) or (3) 2. Low muscle strength 3. Low physical performance (Recommended cut-off points were defined as 2 SD below the mean of normal reference value and low gait speed <0.8 m/s).
EWGSOP2 (2019)[14]	Updated consensus. Sarcopenia is defined as "a progressive and generalized skeletal muscle disorder that is associated with increased likelihood of adverse outcomes including falls, fractures, physical disability, and mortality." EWGSOP2 recognizes sarcopenia as muscle disease, "muscle failure," and could be acute (<6 mo) or chronic. In addition, EWGSOP2 promoted low muscle strength as the primary indicator for sarcopenia as opposed to muscle mass.	F-A-C-S Algorithm: • Find: case finding by clinical symptoms of functional decline or SARC-F questionnaire, • Assess: measure muscle strength by handgrip or chair rise test, • Confirm: measure muscle quantity or quality by DXA, BIA, or muscle cross-sectional area by MRI or CT, • Severity: measure physical performance by gait speed, SPPB, TUG, or 400-m walk. 1. Low muscle strength (sarcopenia is probable) 2. Low muscle quantity or quality (sarcopenia is confirmed) 3. Low physical performance (sarcopenia is severe) Low muscle strength: - Handgrip strength: <27 kg for men <16 kg for women - Chair rise test: >15 s for 5 rises Low muscle mass "quantity": ASM/height^2 Men ≤7 kg/m^2 Women ≤5.5 kg/m^2 Low physical performance: - Gait speed: ≤0.8 m/s - SPPB: score ≤8 points - TUG: ≥20 s - 400 m walk test: noncompletion or ≥6 min for completion
SIG (2010)[15]	"Sarcopenia is a condition characterized by loss of muscle mass and muscle strength. Muscle mass decrease is directly responsible for functional impairment with loss of strength, increased likelihood of falls, and loss of autonomy. Although sarcopenia is primarily a disease of the elderly, its development may be associated with conditions that are not exclusively seen in older persons, like disuse, malnutrition, and cachexia."	Diagnose sarcopenia in the presence of 2 criteria: 1. Low muscle mass (muscle mass 2 SD below the mean of young adults) 2. Low gait speed (walking speed <0.8 m/s in the 4-m walk test)
IWGS (2011)[16]	"Sarcopenia is the age-associated loss of skeletal muscle mass and function. Sarcopenia is a complex syndrome that is associated with muscle mass loss alone or in conjunction with increased fat mass. The causes of sarcopenia are multifactorial and can include disuse, changing endocrine function, chronic diseases, inflammation, insulin resistance, and nutritional deficiencies. While cachexia may be a component of sarcopenia, the two conditions are not the same."	• Consider sarcopenia in all older adults with a decline in physical functioning, strength, or health status • Diagnose sarcopenia if gait speed <1 m/s and low muscle mass is present Low muscle mass: ASM/height^2 Men ≤7.23 kg/m^2 Women ≤5.67 kg/m^2
SCWD (2011)[17]	"Reduced muscle mass with limited mobility. The limitation in mobility should not clearly be a result of otherwise defined specific diseases of muscle, peripheral arterial disease with intermittent claudication, central and peripheral nervous system disorders, or cachexia."	• Screen older adults >60 y with a functional decline or recent hospitalization/prolonged bed rest. • Diagnose sarcopenia if 1. Gait speed ≤1 m/s or walk <400 m in 6-min walk test and 2. Lean appendicular mass/hieght^2 <2 SD below the mean of young adults of the same ethnicity
FNIH (2014)[18]	"True medical condition related to low lean mass, beyond that found in usual aging. The medical condition cannot be defined based on lean mass alone but should be related to loss of strength and function, and perhaps to increased health care utilization and mortality. This condition should be both prevented and treated." FNIH highlighted the superiority of muscle weakness and mobility impairment in predicting future disability and adverse outcomes. "Low muscle mass should be determined based on the risk of muscle weakness."	▪ Screen older adults for low physical performance (mobility) by gait speed (<0.8 m/s) or SPPB. ▪ Assess muscle weakness in all Individuals with reduced physical performance. ▪ Assess muscle mass to identify individuals whose weakness is caused by low muscle mass to guide intervention. Low muscle strength: handgrip strength Men <26 kg Women <16 kg Low muscle mass: ASM adjusted for BMI Men <0.789 Women <0.512

(*Continued*)

Table 1. Continued

Society	Consensus definition	Diagnostic criteria
AWGS (2014)[19]	AWGS adopted a similar definition as the EWGS of an age-related geriatric syndrome characterized by loss of muscle mass with low muscle function. Distinctively, AWGS required both low strength and physical performance for the diagnosis. In addition, different cut-off points were proposed based on the Asian population anthropometrics.	▪ Screen all community-dwelling older adults aged ≥60 or 65 y and older adults with certain medical conditions* in health care settings by measuring handgrip strength and gait speed ▪ Diagnose sarcopenia if: 1. Low gait speed and handgrip strength is present and 2. Low muscle mass Low muscle strength: Handgrip strength: Men <22.4 kg Women <14.3 kg Low muscle mass: ASM/height^2: By DXA Men <7.0 kg/m^2 for Women <5.4 kg/m^2 By BIA Men <7.0 kg/m^2 Women <5.7 kg/m^2 Low physical performance: Gait speed <8 m/s
AWGS (2019)[20]	Updated consensus. AWGS 2019 retains the previous definition of sarcopenia, "age-related loss of muscle mass, plus low muscle strength, and/or low physical performance," but proposed an updated diagnostic algorithm and cut-off points. In addition, AWGS 2019 recommended different algorithms for community and hospital settings and introduced the term "possible sarcopenia" to promote early interventions in the community setting.	▪ Screen older adults by measuring either calf circumference (men <34 cm, women <33 cm), SARC-F (≥4), or both SARC-CalF (≥11). ▪ Possible sarcopenia: low muscle strength (handgrip strength) or low physical performance (chair rise test) ▪ Diagnose sarcopenia by: 1. low muscle strength or physical performance and 2. low muscle mass ▪ Severe sarcopenia: 1. Low muscle strength, 2. Low physical performance and 3. Low muscle mass. Low muscle strength: Handgrip strength Men <28 kg Women <18 kg Low muscle mass: ASM/height^2 By DXA Men <7.0 kg/m^2 for Women <5.4 kg/m^2 By BIA Men <7.0 kg/m^2 Women <5.7 kg/m^2 Low physical performance: - Gait speed <1.0 m/s - Chair rise test ≥12 s - SPPB ≤9
SDOC (2020)[21,22]	SDOC defines sarcopenia for community-dwelling adults as weakness defined by low grip strength and slowness defined by low gait speed. Distinctive from all other consensus definitions, SDOC does not recommend ASM by DXA given its poor predictivity for adverse health-related outcomes.	1. Low muscle strength (weakness): Handgrip strength Men <35.5 kg Women <20 kg 2. Slowness: Gait speed <0.8 m/s
ESPEN/EASO (2022)[23]	"Sarcopenic obesity is the co-existence of obesity (high body fat %) and sarcopenia (low muscle mass and function)."	▪ Screen for sarcopenic obesity by measuring BMI or WC and sarcopenia validated questionnaires (eg, SARC-F) or surrogate measures*† If elevated BMI or WC and positive screen for sarcopenia, proceed to diagnosis. ▪ Diagnosis is done in 2 steps: 1. Assess muscle function by measuring strength (BMI-adjusted handgrip or knee extensor strength, or chair rise test). If low muscle function is detected, then 2. assess body composition (fat mass % and muscle mass) by either DXA or BIA. CT is preferred when possible (being done for other diagnostic purposes) Sarcopenic obesity diagnosis is established in the presence of altered muscle function and body composition. ▪ Stages of sarcopenic obesity: Stage I: no complication related to altered muscle function and body composition Stage II: at least 1 complication is present (functional disabilities, metabolic disease, CVD or respiratory disorders)

ASM indicates appendicular skeletal muscle mass; AWGS, Asian Working Group for Sarcopenia; BIA, bioelectrical impedance analysis; BMI, body mass index; CT, computed tomography; DXA, dual-energy x-ray absorptiometry; ESPE/EASO, European Society for Clinical Nutrition and Metabolism/European Association for the Study of Obesity; EWGSOP, European Working Group on Sarcopenia in Older People; FNIH, Foundation for the National Institutes of Health; IWGS, International Working Group on Sarcopenia; MRI, magnetic resonance imaging; SARC-F, Strength, Assistance Walking, Rise From a Chair, Climb Stairs, and Falls; SCWD, Society of Sarcopenia, Cachexia and Wasting Disorders; SDOC, Sarcopenia Definitions and Outcomes Consortium; SIG, Special Interest Group; SPPB, Short Physical Performance Battery; TUG, Timed Up and Go; and WC, waist circumference.

*Recent functional decline, unintentional weight loss >5% in a month, depressive mood or cognitive impairment, repeated falls, undernutrition, and chronic illnesses.

†Age >70 y, recent rapid weight gain, corticoid treatment.

Table 2. Differences Among Sarcopenia, Cachexia, and Malnutrition

	Sarcopenia	Cachexia	Malnutrition
Clinical features	Loss of muscle strength and muscle mass	Weight loss with loss of muscle mass	Weight loss
Functional impairment	Indicate severity	+++	-
Mechanism	Age-related, pathologic	Pathologic	Inadequate caloric intake, malabsorption
Illness(es)	+/-	+++	+/-
Inflammation	+/-	+++	-
Anorexia	+/-	++	+/-
Fat mass	+/-	Decreased	Decreased
Protein degradation	+/-	+++	+
Resting energy expenditure	Decreased	Increased	Decreased

Adapted with permission from Ali et al.[25a]

in muscle homeostasis and neuronal degeneration with aging lead to senescence of satellite cells, preferential loss of type II fibers (hypoplasia), and the loss of functional motor units, collectively associated with muscle atrophy and decreased contractile force capacity, leading to muscle weakness and slowness.[35,38,40]

Myosteatosis

Fat infiltration of skeletal muscles, or myosteatosis, refers to ectopic fat deposition in skeletal muscles that is frequently seen in patients with cardiometabolic disease. The process of fatty infiltration of skeletal muscle is thought to be an independent process from loss of muscle mass and function. Fatty infiltration can take the form of different types of adipose depots within the skeletal muscle structure: (1) intermuscular adipose tissue; (2) intramuscular adipose tissue; and (3) intramyocellular lipids.[41] Myosteatosis is associated with frailty and deterioration in muscle mobility and function.[42] Excessive adipokines with visceral adiposity accelerates muscle loss because of proinflammatory activity that counters anabolic myokines. Collectively, this leads to a state of chronic inflammation, increasing insulin resistance and muscle breakdown.[29,34] It is interesting that fatty infiltration and muscle fibrosis can impair muscle quality without atrophy; in these situations, muscle mass may not actually change.

The muscle–fat imbalance that specifically leads to sarcopenic obesity is, in part, a result of chronic proinflammatory state and metabolic dysregulation from insulin resistance and glucose intolerance. The increased body fat deposition accounts for most gain in body weight, but the total lean muscle mass progressively declines and results in further reductions in basal metabolic rate. With aging, body composition of muscle, bone, and fat changes, with a progressive decline in muscle and bone mass and an increase in total body fat, visceral adiposity, and fatty infiltration of skeletal muscle, liver, and bone marrow.[43] These changes make older adults susceptible to myosteatosis and the development of sarcopenic obesity.

Muscle Homeostasis and Anabolic Resistance

Muscle homeostasis is maintained through a balance between the anabolic and catabolic molecular signaling. The anabolic pathway is stimulated by the upregulation of serine/threonine kinase Akt/mTOR (mammalian target of rapamycin) cascade, and the catabolic pathway is regulated by Fox-O (Forkhead O), NF (nuclear factor)-κB/

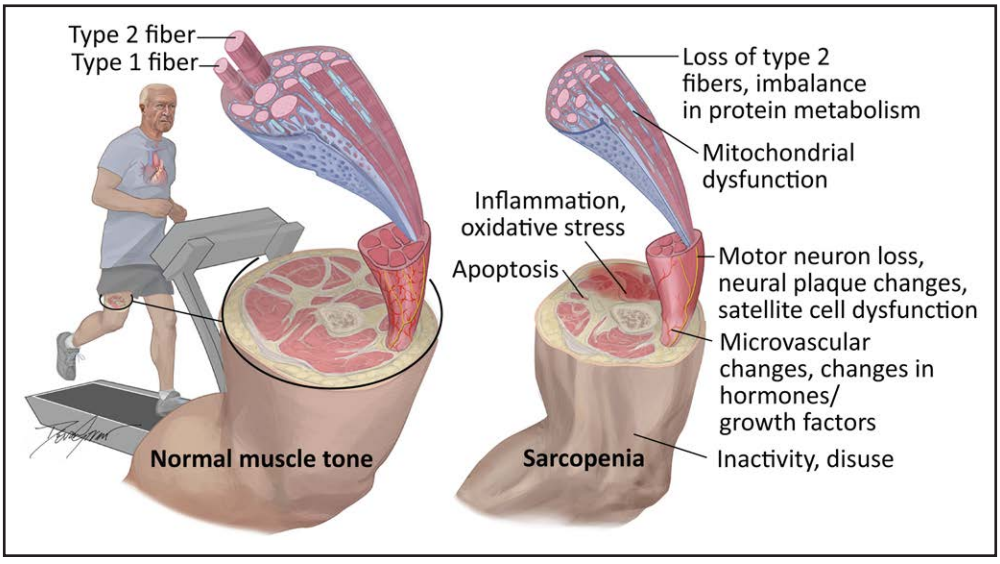

Figure 1. Pathophysiologic mechanisms for development of sarcopenia in patients with cardiovascular disease.

ubiquitin proteasome, caspases cascade, and myostatin pathway.[44] Myostatin is a skeletal muscle myokine; it downregulates Akt/mTOR and decreases the number of satellite cells, inhibiting muscle formation and repair.[44,45] Dysregulation in muscle homeostasis leads to muscle atrophy or hypertrophy, depending on which pathway predominates. Anabolic stimuli of skeletal muscle, such as muscle contraction (exercise), essential amino acids (eg, leucine), and anabolic hormones, such as testosterone, insulin, and IGF-1 (insulin-like growth factor-1), work by upregulating the Akt/mTOR pathway, inhibiting myostatin and downregulating Fox-O, stimulating muscle protein synthesis, and inhibiting protein breakdown. Muscle atrophy is likely to develop when muscle protein breakdown exceeds muscle protein synthesis capacity, resulting in a net negative protein balance.[45]

The response of skeletal muscle to anabolic stimuli, particularly to essential amino acids, is blunted with aging, a phenomenon called "anabolic resistance."[46] The attenuated effect of dietary essential amino acids in stimulating muscle protein synthesis is likely a result of a diminished expression of Akt/mTOR signaling.[46,47] Anabolic resistance is proposed to be related to age-associated vascular changes, which diminish muscular perfusion, subsequently impairing nutrients and oxygen delivery.[48] Cross-sectional studies have shown that low lean muscle mass and sarcopenia are associated with arterial stiffness and arteriolosclerosis.[49–51] Although the exact causal mechanism of the association between arterial dysfunction and the decline in muscle mass and function remains to be further elucidated, many theories have been suggested.[51,52] Chronic inflammation, oxidative stress, insulin resistance, and impaired blood flow, from both endothelial dysfunction and calcification of skeletal muscle vasculature, have all been highlighted as possibly contributory.[52] Insulin is well known for its anabolic action by promoting skeletal muscle protein uptake[53]; however, insulin also has a pivotal role in redistributing blood flow from nonnutritive to nutritive capillaries and activates endothelial nitric oxide in precapillary muscle arterioles, increasing the capillary surface area for nutrient exchange.[48] With older age, muscle and vasculature become less sensitive to insulin, leading to diminished insulin-mediated microvascular blood flow, thus decreasing the delivery of amino acids.[54]

Inflammation and Mitochondrial Dysfunction

Together, immunosenescence, the accumulation of senescent cells, and increased visceral adiposity induce a state of low-grade chronic systemic inflammation characterized by increased levels of proinflammatory cytokines in the absence of infection ("inflammaging").[55,56] Proinflammatory cytokines such as CRP (C-reactive protein), IL-1 (interleukin 1), IL-6 (interleukin 6), and TNF-α (tumor necrosis factor-alpha) are key factors in inducing cell degradation by mechanism of skeletal muscle mitochondrial dysfunction, leading to increased production of reactive oxygen species that causes activation of the ubiquitin proteosome cascade and increasing muscle proteolysis.[34,56] In addition, IL-6 induces insulin resistance, which hinders the activation of the Akt/mTOR pathway and impedes muscle protein synthesis.[55] Individuals with low appendicular skeletal muscle were found to have significantly higher levels of IL-6 and CRP.[57] "Inflammaging" is associated with increased risk for multiple chronic conditions, including heart failure (HF), atherosclerotic CVD, frailty, and poor health outcomes.[58]

The role of inflammation is most enhanced among patients with HF. In these patients, sarcopenia often begins early, with the activation of gastrometabolic, musculoskeletal, inflammatory, neurohormonal, sympathetic, and oxidative factors.[59] These known HF factors interact in a complex manner to induce sarcopenia through the upregulation of muscle atrophy via the ubiquitin-proteasome system and the autophagy-lysosome system.[60] In addition, proinflammatory factors such as TNF-α, IL-6, and IL-1 are elevated in patients with chronic HF.[61] Skeletal muscle wasting is also thought to be heightened secondary to mitochondrial dysfunction from reactive oxygen species[62] and significant upregulation of myostatin released from both peripheral myocytes and cardiomyocytes.[63] In adults with HF, there is also a decline in anabolic hormones that exacerbates the naturally reduced levels observed with aging,[64] including testosterone,[65] ghrelin,[66] IGF-1, and growth hormone.[67] These cellular processes, when coupled with interstitial edema of the gut that cause early satiety, anorexia, and malabsorption, are associated not only with an enhanced catabolic state, but also with an independent decrease in muscle synthesis and mass.[68]

Neuronal Pathway

The age-related degenerative changes of the nervous system are believed to be a contributor to the development of sarcopenia. Muscle strength and power are determined by contractile force and velocity. Impairment in the integrity of the neuromuscular system plays a significant role in the decline of muscle strength and power, with consequent muscle weakness (dynapenia).[31,32,69] The mechanism by which the nervous system specifically causes sarcopenia is not fully understood,[32] but axonal degeneration, neuronal hypoexitability, and loss of α-motoneurons (particularly large motor-neuron innervating fast-twitch motor units) lead to dysregulation in the denervation–reinnervation cycle of motor neurons. In turn, "sick motoneurons" are associated with impairments in contractile velocity, muscle synergy, and, subsequently, muscle weakness.[31,32,38,39] In healthy adults, muscle mass and strength (and relatedly, performance) peak by the

third decade of life.[70] As individuals approach their fourth decade, muscle mass and strength decline, with reductions in muscle strength by an average of ≈8% to 10% per decade. By 80 years of age, most adults have lost nearly 30% of their peak muscle mass and 50% of their peak muscle strength.[71–73] Naturally, the rate of decline is influenced by comorbid conditions as well as genetic, behavioral, and environmental factors.[35,47,74] Taken together, these lead to impaired muscle quality, diminished muscle remodeling, muscle atrophy, and loss of muscle fibers or motor neuronal units, which, in turn, translate into the development and progression of sarcopenia.[45,55,75,76]

CLINICAL CONTRIBUTORS TO SARCOPENIA

Sarcopenia is conceptualized as an age-related, multifaceted condition involving biological, environmental, socioeconomic, and genetic factors that collectively contribute to the loss of muscle mass and function. The interaction of multiple domains at the individual level can either counteract or hasten the effect of aging on muscle loss.[74] Multiple factors such as malnutrition, prolonged immobility, and chronic systemic inflammatory state caused by malignancy, chronic diseases such as HF, coronary disease, diabetes, and end-organ failure have been recognized to influence the rate of age-related muscle decline.

The degree of muscle loss is exacerbated by a sedentary lifestyle, prolonged bed rest, smoking and alcohol intake, malnutrition, and anorexia of aging. Midlife obesity has been found to be associated with an increased incidence of sarcopenia later in life.[77] Lutski et al found that among 337 men who were followed for 19.9 years, more than half of the participants (54.3%) who were obese (body mass index [BMI], ≥30.0 kg/m^2) at baseline developed sarcopenia later in life (adjusted odds ratio, 5.31 [95% CI, 2.50–11.27]) compared with 24.8% of participants who had normal weight (BMI, 18.5 to 24.9 kg/m^2).[77] In another cohort of older men with a mean age of 68.7 ± 5.5 years and a mean follow-up of ≈11 years, sarcopenic obesity (obesity measured by waist circumference and sarcopenia by mid-upper-arm circumference) had the highest rate of all-cause mortality, even after adjusting for lifestyle and inflammatory markers.[78] This may indicate that lifestyle factors partly explain the increased cardiovascular risk, and also indicate that behavioral interventions that target lifestyle could modify cardiometabolic risks among adults with sarcopenic obesity.

Sarcopenia is also particularly common in adults with kidney disease, especially among those with end-stage renal disease on hemodialysis. Several studies have documented that a loss of muscle mass and performance is a consistent feature in patients with chronic kidney disease, which is regarded as a model of "accelerated aging."[79] In one study that evaluated dialysis patients, quadriceps muscle weakness was observed in more than two-thirds of participants, and those with malnourishment exhibited slowing of muscle relaxation compared with healthy controls.[80] The primary mechanism for muscle weakness is thought to be muscle atrophy, which is present even after adjusting for age, sex, and physical activity.[81] Malnourished patients on dialysis had significantly smaller type IIb fiber areas compared with well-nourished patients.[80]

Sarcopenia is also frequently observed among older people with cancer. Decreased oral intake associated with chemotherapies, malnutrition, progressive protein catabolism, chronic inflammation, and increased metabolic demand, and physical inactivity are frequently observed in cancer patients. The presence of sarcopenia is a poor prognostic marker in different types of cancers and can influence the response to chemotherapy and radiation therapy, leading to higher adverse events and treatment interruption.[82,83]

IMPLICATION OF SARCOPENIA ON CVD

Sarcopenia and HF

Sarcopenia is common among patients with HF with reduced ejection fraction and HF with preserved ejection fraction. The prevalence of sarcopenia ranges from 34% to 66% (Table S2), and it is highest among those hospitalized for acute decompensated HF (≈66%).[84] Sarcopenia is an independent risk factor for prolonged and recurrent hospitalizations and increased risk for mortality.[85,86] As a result of muscle wasting and myopathy, there is a substantial decline in physical function, capability, and performance. Exercise intolerance is a hallmark of HF with reduced ejection fraction and HF with preserved ejection fraction resulting from congestion and low cardiac output[87]; sarcopenia and muscle apoptosis further exacerbate these impairments,[87] with contributions to symptoms such as shortness of breath and fatigue. Indeed, the SICA-HF trial (Studies Investigating Co-morbidities Aggravating Heart Failure) aimed to compare the effect of changes in body composition (sarcopenia and cachexia) in symptomatic patients with HF with reduced ejection fraction or patients with HF with preserved ejection fraction and a left atrial diameter >50%. There was a lower peak VO_2 (maximal oxygen consumption, VO_2 max) in patients with HF and sarcopenia compared with those without sarcopenia.[88] Sarcopenia also contributes to the risk of falls among adults with HF, which can be significant as a result of pharmacological therapy for HF such as loop diuretics, osteoporosis secondary to decreased calcium reuptake, and poor vitamin D synthesis from being functionally homebound.[88] Table S2 summarizes the studies that have examined the diagnosis, prognosis, pathophysiology, and treatment of sarcopenia in patients with HF.

Sarcopenia and Atherosclerotic CVD

Sarcopenia and coronary artery disease (CAD) share similar underlying biological mechanisms, namely, low-grade chronic systemic inflammation. Accordingly, sarcopenia is common among adults with CAD; many studies have shown that sarcopenia (defined by AWGS) affects 1 out of 8 community-dwelling adults with CAD, and 1 out of 4 hospitalized patients with CAD (Table S3).[89] This is important because low skeletal muscle mass in older patients with CAD is associated with increased cardiovascular mortality, major adverse cardiovascular events, myocardial infarction, and low exercise capacity.[90,91] Sarcopenia may also be a risk factor for CAD; previous work has shown that low skeletal muscle mass among asymptomatic community-dwelling older adults is associated with subclinical atherosclerosis, increased coronary artery calcium score, arterial stiffness, and carotid arterial wall thickening.[92–94]

Sarcopenia and Peripheral Arterial Disease

Patients with peripheral arterial disease (PAD) are at an increased risk for muscle mass disorders such as sarcopenia, particularly those with chronic limb ischemia. Among those with lower extremity vascular disease, sarcopenia is observed in up to 35% of the patients.[95] The typical age-related pathophysiologic changes to muscle occur prematurely in patients with PAD; this includes oxidative stress, inflammation, mitochondrial dysfunction, impaired signaling pathways, and ischemia-reperfusion injury.[96] As a result, reductions in the number and size of type II muscle fibers that occur in PAD patients lead to muscle weakness, functional impairment, and abnormal muscle histology. Sarcopenia is also a poor prognostic marker in patients with PAD. Prospective evaluations found a strong association between skeletal muscle weakness with long-term mortality, major adverse cardiovascular events, and limb events in patients with PAD.[97,98]

Sarcopenia and Transcatheter Aortic Valve Replacement

The prevalence of sarcopenia in patients undergoing aortic valve replacement ranges between 21% and 70.2%, depending on the instrument used, degree of impairment, and type of valve replacement.[99–102] Pre–transcatheter aortic valve replacement sarcopenia is associated with longer hospital lengths of stay,[101,103,104] higher resource use,[105] in-hospital adverse outcomes,[105,106] disability,[107] discharge to a skilled nursing facility,[107] readmission,[108] and higher 30/90-day and long-term mortality[109] (Table S4). The transcatheter aortic valve replacement procedure has substantially improved survival for severe aortic stenosis, but 50% of survivors have sarcopenia, and many of these participants report poor HR-QOL (health-related quality of life) and a decline in their overall functional status during follow-up. A study of 13 351 older adults found that 39% either died or had a poor or declining quality of life 1 year after transcatheter aortic valve replacement.[110] The authors attributed the decline in quality of life and poor outcomes to sarcopenia, frailty, disability, unintentional weight loss, and inability to perform activities of daily living.[110] Sarcopenia and these geriatric syndromes are intimately connected to prognosis, and there is an unmet need to address these age-associated risks among older patients.

Sarcopenia and Cardiac Surgery

An increasing number of older adults are undergoing cardiac surgery for various cardiovascular conditions. Frailty, malnutrition, and sarcopenia are common in older patients undergoing cardiac surgery.[111] Similar to other conditions, sarcopenia is associated with postoperative adverse events and long-term mortality in patients undergoing cardiac surgery.[106,112,113] Age, comorbidities, and malnutrition in association with underlying cardiovascular disorders cause muscle wasting, immobility, and decline in physical function before, during, and after hospitalizations (Table S5).[111] During the period before surgery, reduced mobilization leads to reduced muscle strength, function, and reduced respiratory muscle performance.[114] This loss of muscle mass and strength is further exacerbated by prolonged bed rest, greater length of intensive care unit stay, and inadequate nutrition, and causes significant functional limitations that may persist for years after discharge.[111] Rehabilitation interventions to maintain or recover function are traditionally performed during the hospitalization postoperatively and after discharge. Preoperative rehabilitation interventions, also termed prehabilitation, have garnered interest. Prehabilitation encompasses nutrition, exercise, respiratory and cardiocirculatory training, psychological interventions, and optimization of drug therapies. Prehabilitation is safe in most patients and may be associated with a reduction in length of stay and postoperative complications after a major surgery.[111,114]

APPROACH TO DIAGNOSIS

Screening

Screening for early signs and stages of sarcopenia is important because therapeutic interventions are likely to be most effective before sarcopenia has reached advanced stages. There are myriad clinical screening tools that can be used to identify low muscle function and surrogate measures for low muscle mass (Figure 2). There is no current consensus on the best screening tool for clinical practice. The strengths and limitations of each screening tool are listed in Table 3. Of note, the SARC-F (Strength, Assistance Walking, Rise from a Chair, Climb Stairs, and

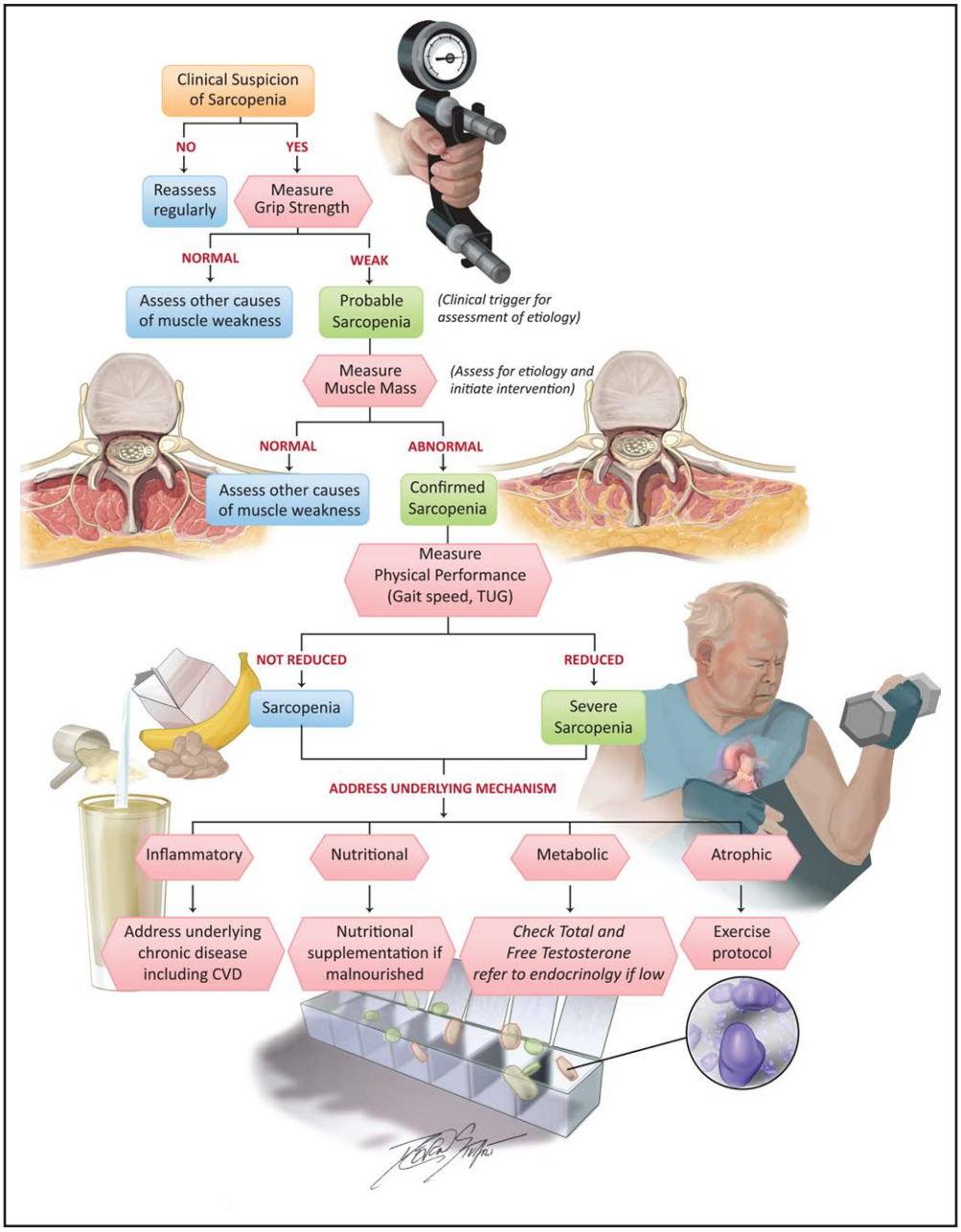

Figure 2. Algorithm providing a screening and diagnostic approach for sarcopenia and potential therapeutic interventions associated with improvement in patients with cardiovascular disease.
CVD indicates cardiovascular disease; and TUG, Timed Up and Go.

Falls) questionnaire and Ishii equation can be used as screening methods for sarcopenia in either the ambulatory or hospital setting.[115] If the screening tool suggests probable sarcopenia, a confirmatory test should follow (see section "Confirmatory Testing").

Symptoms that should trigger formal screening for sarcopenia include falls, subjective weakness, slow walking speed, difficulty rising from seated position, weight loss, and difficulties with activities of daily living. It may be reasonable to concurrently screen for malnutrition as well because malnutrition commonly coexists with sarcopenia.

It is important to note that BMI should not be used to screen for sarcopenia among older adults in whom sarcopenic obesity is common. Although BMI could be a good screening tool for younger individuals,[116] changes in body muscle and fat composition with aging are more complex, and patients with sarcopenia may appear well nourished on the basis of body habitus. Thus, BMI is less predictive.[117,118] Older adults could maintain the same BMI by increasing their body fat and visceral adiposity and decreasing muscle mass, important body composition changes that increase the risk of CVD and mortality. Tracking sarcopenia during

Table 3. Screening Tools for Sarcopenia

Name	Domains measured	Strengths	Limitations
SARC-F	Strength Ambulation Chair rise Stair climbing Fall history ▪ Score (0–10), positive when the score is ≥4	▪ Quick self-reported questionnaire ▪ Easy to perform in clinical and research setting ▪ Validated to be used as a proxy-reported in the acute care setting ▪ Highly specific, can rule out severe sarcopenia and identifies those at elevated risk of sarcopenia-related adverse outcome	Low-to-moderate sensitivity (28.9%–55.3%), thus limiting its utility to screen for those at risk of sarcopenia (presarcopenia)
SARC-F Calf	SARC-F plus calf circumference ▪ CC ≤33 cm for women and ≤34 cm is scored 10 SARC-F Calf is positive if score ≥11	▪ More sensitive than SARC-F (45.9%–57.2%)	
Ishii et al screening tool	Age Grip strength Calf circumference	▪ Uses a score chart to estimate the probability of sarcopenia with each score ▪ Has high sensitivity and specificity (84.9% and 88.2% for men and 75.5%, 92.0% for women, respectively) ▪ Can identify functional older adults at high risk of sarcopenia, allowing for early intervention	Validated in Japanese ethnic group
MSRA	Seven-item and five-item questionnaires (7-MSRA and 5-MSRA) that include age, physical activity, number of meals/d, consumption of dairy products and protein, number of hospitalizations, and weight loss in the last year	▪ Has high sensitivity, 80.4%	▪ Developed from Italian population, patients with heart failure (NYHA ≥2), renal failure, cognitive impairment, and cancer were excluded, thus limiting its generalizability ▪ Validated in Chinese and Polish languages only
SarSA-Mod	Age Weight Calf circumference	▪ Easily done in primary care setting ▪ Has high sensitivity, 84.3%	Tested in urban population of Middle Eastern origin only
Grip strength	Strength Cut-off points Male <27 kg Female <16 kg	▪ Easy to perform in clinic setting with simple, inexpensive tool dynamometer	Requires dynamometer
Chair rise	Strength Cut-off points >15 s for 5 chair rises	▪ Easy to perform in clinic setting, requires no specialized tools	

ASM_{PE} indicates anthropometric prediction equation for appendicular skeletal muscle mass; BMI, body mass index; CC, calf circumference; MRSA, Mini Sarcopenia Risk Assessment Questionnaire; NYHA, New York Heart Association; SARC-F, Strength, Assistance Walking, Rise From a Chair, Climb Stairs, and Falls; and SarSA-Mod, Sarcopenia Scoring Assessment Models.

weight gain or weight loss is accordingly complex. For example, with successful intended weight loss from treatment of cardiometabolic disease, there is a natural loss of muscle quantity, but it can be difficult to assess whether the degree of muscle loss is appropriate or inappropriate (ie, signs of worsening sarcopenia). For those in whom sarcopenic obesity is present, it may be worthwhile to evaluate waist circumference and waist-to-hip ratio, which are well-known surrogate markers for visceral adiposity and can potentially predict CVD events[119] and risk of death across all BMI categories.[120]

Confirmatory Testing

Multiple instruments can be used to confirm the presence of sarcopenia, although diagnostic criteria vary in terms of cut points (summarized in Table 1).[14,20,21,24] Confirmatory testing instruments can be classified as: (1) imaging and body composition assessment tools[121]; (2) physical performance; and (3) laboratory tests.

Imaging Modalities and Body Composition Measurement Tools

Both computed tomography (CT) and magnetic resonance imaging are considered the "gold standard" instruments to quantify muscle mass because they can provide direct visualization of cross-sectional area or volume, which can then be converted into mathematical estimates of overall body muscle mass.[122] In a study that compared estimates of muscle mass from cadaveric sections with CT and MRI, both modalities provided accurate assessment of adipose tissue–free skeletal mass, interstitial adipose tissue, and subcutaneous adipose tissue. CT can also provide a measure of muscle density (the radiodensity of the muscle in Hounsfield units); low muscle density is thought to be a measure of poor muscle quality and is related to declines in function and mortality in older adults.[123] CT imaging at the third lumbar vertebra has been used as a surrogate measure for whole-body muscle mass, which correlates with prognosis in multiple cardiovascular populations. The measurement at the level of the third lumbar is also useful to detect patients with sarcopenic obesity. The quantifica-

tion of skeletal muscle at the third lumbar can be done by MRI as well, but midthigh measurement is also a good predictor of whole-body skeletal mass. Use of these modalities in the clinical setting is limited by their cost and feasibility. In addition, diagnostic cut-off points for sarcopenia in the clinical setting have not been uniformly established.[14]

Muscle ultrasound has been used in clinical research, and it holds promise as a tool to assess for sarcopenia, especially given that it can be conducted at the bedside with low cost.[124] Muscle ultrasound provides measures for muscle mass and muscle quality and correlates well with CT, MRI, and dual-energy x-ray absorptiometry (DXA).[14,125] To date, its use in the clinical setting is limited because it requires trained personnel and a standardized protocol.

The DXA scan provides measures of body composition but not muscle quality. It is the most commonly used instrument in research and clinical setting to measure appendicular skeletal muscle and appendicular muscle mass index/height^2. Although DXA scan is relatively inexpensive and fast, and the diagnostic cut-off points are validated, it has drawbacks. First, it only measures lean mass, which is only one component of muscle mass.[121] Second, hydration status can influence the diagnostic accuracy of the test because it has a poor ability to distinguish extracellular fluid from muscle mass; this can lead to overestimation of muscle mass/quantity among individuals with excess fluid such as those with HF. Finally, DXA is only weakly associated with measures of performance and function.[126] For that reason, DXA may not be the best measure to assess function decline in older patients.[127]

The bioelectrical impedance analysis estimates lean mass based on whole-body electrical conductivity. Bioelectrical impedance analysis is an inexpensive instrument that can be performed at bedside or in the office. Similar to DXA, hydration status can influence its accuracy.[128]

Laboratory Biomarkers

Cardiovascular clinicians are familiar with measuring cardiac biomarkers to diagnose cardiovascular conditions (eg, natriuretic peptides for HF and cardiac specific troponins for acute myocardial infarction).[129] Unfortunately, to date, there is no single circulating biomarker that is diagnostic of sarcopenia, although there is some promise for the future.

For the assessment of muscle mass, the D_3-creatine (D_3-Cr) dilution method is a promising strategy with high accuracy. The assay measures the quantity of deuterated creatinine from a single spot urine analysis performed 48 to 96 hours after administering a D_3-Cr tracer orally. The D_3-Cr obtains a steady state in skeletal muscle ≈48 hours after ingestion. There is a fairly constant creatine skeletal muscle turnover each day so that the amount of D_3-Cr in the urine is proportional to total body muscle mass.[130,131] D_3-Cr correlates well to MRI-determined whole body muscle mass (r=0.87) and is potentially more accurate than DXA.[132,133]

A simpler alternative to D_3-Cr for circulating markers of muscle mass assessment has been proposed, called the sarcopenia index, which is represented by (serum creatinine/serum cystatin C) × 100. Initially proposed by Kim et al, the index was found in ambulatory adults to associate strongly with DXA and also correlated with muscle mass in critically ill patients estimated by abdominal CT.[133,134] The sarcopenia index was shown to be prognostic of intermediate-term death in previously hospitalized older adults and major adverse cardiovascular event in older adults with coronary disease.[135,136] The sarcopenia index leverages the concept that creatine is nearly exclusively produced by muscle, but cystatin C is produced by all nucleated cells. A caveat is that although cystatin C production is thought to be steady-state, factors such as hyperthyroidism, malignancy, and some forms of inflammation can alter cystatin C levels.[137]

Table 4. Physical Performance Testing to Assess for Severity of Sarcopenia

Name	Description	Cut-off points
Gait speed	Measure speed doing 10-m walk	≤0.8 m/s
SPPB	Group of measures combing gait speed, chair stand, and balance test*	≤8 points
TUG	Measure speed going from seated position and walking 3 m, then back to chair	≥20 s
400-m walk test	Measure speed walking 400 m	≥6 min

SPPB indicates Short Physical Performance Battery; and TUG, Timed Up and Go.

*Other values as cut-offs were also proposed (eg, 9 or even 4), depending on the study population.

Physical Performance Tests

Physical performance testing has been used for assessing the severity of sarcopenia and for its prognostication (Figure 2). The EWGSOP recommends using physical performance/function to assess the severity of sarcopenia, and the SDOC recommends using physical performance/function to predict clinical outcomes. Table 4 summarizes instruments that can be used for physical performance tests, although performance of these tests is likely influenced by myriad factors, including concurrent comorbid conditions and other geriatric syndromes such as frailty.

TREATMENT

Sarcopenia is a modifiable condition that could revert to a normal state with early intervention (Figure 2). Such interventions may be similarly important for those with presarcopenia, which is also modifiable; for example, in a study, participants with probable sarcopenia were found to have equal likelihood of either reverting to normal or progressing into sarcopenia

at 5-year follow-up (10.7% versus 10.3%).[138] There are also several management strategies currently under investigation, including resistance exercise, nutritional supplements, and hormonal or pharmacotherapies (Table S6).

Treatment of Comorbid Conditions

The first step to treating sarcopenia is to identify and address underlying contributing factors. For example, treating and optimizing metabolic health and addressing obesity through exercise and caloric intake may reduce myosteatosis.[139] Treating co-occurring CVD that contributes to inflammation is similarly important. For example, treating HF with guideline-directed medical therapy can forestall disease progression and potentially suppress the inflammatory processes known to contribute to adverse changes in muscle pathophysiology that drives sarcopenia.

Resistance Exercise Training

An important factor in the development of sarcopenia is the lack of physical activity followed by anabolic resistance. Therefore, the strongest evidence currently available for the treatment and prevention of sarcopenia is derived from studies on exercise intervention programs, such as resistance and aerobic training, that have been shown to increase muscle mass, strength, and physical performance. Progressive resistance training programs can be used as a successful intervention for the management of sarcopenia. In these programs, participants exercise their muscles against increasing external force for at least 2 to 3 times a week for a duration of 8 to 12 weeks. The amount of resistance and duration of the session increase gradually over time depending on each individual's capability and progress. In healthy older adults, improvement in muscle strength can be achieved with as few as one resistance exercise session per week.[140] Liang et al noted that among sarcopenic older adults 80 to 99 years of age, combined resistance and balance exercise twice weekly during 12 weeks accomplished a significant improvement in performance of activities of daily living, with a 10% absolute risk reduction in the number of falls compared with resistance exercise alone.[141]

Muscle hypertrophy occurs when protein synthesis in the muscle exceeds protein breakdown. Older patients performing resistance exercise show a characteristic increase in muscle protein synthesis without an increase in total body protein breakdown. Some evidence indicates a significant increase in the size of both type 1 and type 2 muscle fibers after both progressive resistance training and a prolonged exercise program consisting of resistance and high-intensity interval training, which could explain the improved muscle strength and performance.[142,143] Roth et al demonstrated that resistance strength training significantly increases the proportion of active satellite cells for both older adults, 65 to 75 years of age, and young individuals, 20 to 30 years of age. However, older women had the most augmented improvement.[144] Although increases in myofiber size explain some observed clinical strength gains with resistance training programs, most gains are derived from increased recruitment of motor units and other neural adaptations.

Aerobic exercise, such as swimming, walking, and jogging, has long been associated with improved cardiovascular fitness and physical performance. With aerobic exercise, the large muscle groups move in a rhythmic manner for a sustained period of time that increases the energy expenditure.[145] It has been shown to increase the muscle fiber cross-sectional area, but it is less likely to cause muscle hypertrophy.[146] After aerobic exercise alone, mitochondrial volume and enzyme activity increase, indicating that muscle quality improves regardless of age.[147] In patients with both HF and sarcopenia, aerobic activity is associated with reduced hospitalizations and mortality, which is thought to be a result of reductions in skeletal muscle inflammatory markers, isoform of nitric oxide synthase, and myostatin, and an increase in the skeletal muscle cross-sectional area.[148]

Cardiac Rehabilitation

Cardiac rehabilitation (CR) is a multidisciplinary secondary prevention program designed for patients after a cardiovascular event (eg, myocardial infarction, percutaneous or surgical revascularization, and other cardiac surgical procedures) to promote cardiovascular health through education, risk factors management, exercise training, and psychosocial health. Although CR has not been specifically studied as a therapeutic option for sarcopenia, it has the potential to target risk factors that contribute to the progression of muscle wasting disorders such as sedentariness, malnutrition, and polypharmacy.[149,150] The tailored exercise training that is part of CR programs improves muscle strength, performance, and nutritional assessment, and counseling can identify and address malnutrition. In a retrospective study of 322 Japanese older adults with CVD attending a comprehensive CR program that included exercise training (aerobic, resistance, and balance) and nutritional intervention, sarcopenia was present in 28% of participants, and those with sarcopenia tended to be female and of older age.[151] Participants both with and without sarcopenia observed a significant improvement in muscle strength and gait speed. Posttraining muscle strength of those with sarcopenia was similar to the pretraining muscle strength of those without sarcopenia.[151] This suggests that comprehensive CR programs have the potential to reverse or delay the progression of sarcopenia.

Nutritional Intervention

Protein and Amino Acids

Diet may be an important intervention to mitigate the negative effects of sarcopenia. The role of dietary interventions

such as protein, antioxidants, creatine, fatty acids, and vitamin D has been evaluated. In brief, protein supplementation and amino acids appear to be the most promising dietary supplementation (Figure 2). Incorporating protein concentrates (eg, whey) or branched-chain amino acids, such as leucine, into the diet can increase the rate of mixed skeletal muscle protein synthesis.[44] The Food and Nutrition Board of the National Academy of Sciences of the United States recommends 0.8 g/kg/d of protein for all adults to prevent muscle mass loss. Despite this recommendation, >38% of older men and 41% of older women do not meet this recommended daily allowance.[152] The European Society for Clinical Nutrition and Metabolism recommends that for healthy older people, the diet should provide at least 1.0 to 1.2 g protein/kg body weight per day.[153] For older people who are malnourished or at risk for malnourishment due to acute or chronic illnesses, the diet should provide at least 1.2 to 1.5 g protein/kg body weight per day, and even higher intake for those with severe chronic illnesses or injuries. The society also recommends coupling a high-protein diet with daily physical activity (resistance and aerobic exercise) for all older individuals.[153]

Combined Resistance Exercise Training and Protein Supplementation

The effects of combining a moderate- to high -rotein diet and resistance exercise remain an area of active investigation. An increase in muscle protein synthesis without concurrent change in muscle protein breakdown after amino acid ingestion can happen in both young and older individuals.[154] A diet that is inadequate in proteins or amino acids may further facilitate muscle protein loss in older adults by blunting protein synthesis and promoting subsequent protein catabolism.[155]

Consuming a diet that is higher in protein than the recommended daily allowance but within the Acceptable Macronutrient Distribution Range may have health benefits. Coupling a high-protein diet with resistance exercise can result in an increase in muscle strength and greater muscle mass preservation, mainly when consumed in a state of negative energy balance. Further, the beneficial effect on muscle protein synthetic response is greater if protein intake is distributed across meals in a balanced manner.[156] The type of protein can influence digestion and absorption. For instance, whey and soy, a milk protein, are frequently described as a "fast" protein because they rapidly release amino acids when digested, as opposed to casein, another milk protein, which is considered a "slow" protein. In a study by Tang et al, consumption of whey or soy protein in young men with resistance exercise resulted in greater muscle protein synthesis compared with casein.[157]

Iglay et al[158] conducted a study in which 36 men and women >50 years of age participated in 12 weeks of resistance training in conjunction with a lower protein (0.9 g protein.kg^{-1}.d^{-1}) or higher protein (1.2 g protein.kg^{-1}.d^{-1}) intake. Although all outcome measures showed overall improvement (eg, increased total-body protein mass, increased strength, and decreased fat mass), no differences were observed between the low-protein and high-protein groups. Furthermore, Andrews et al[159] proposed that daily protein consumption (1.35 versus 0.72 protein.kg^{-1}.d^{-1}) has no additional effect on lean mass gains associated with resistance training. Variability in protein consumption was not associated with variability in muscle hypertrophy among both groups. Further studies to investigate which protein supplement type is most effective in a clinically meaningful improvement in muscle function are needed.

Testosterone Replacement

The level of testosterone gradually declines with aging. At 60 years of age, nearly 20% of men have testosterone levels in the hypogonadal range, and by 80 years of age, >50% of men have low testosterone.[160] Although higher testosterone is linked to increased muscle mass and decreased percentage of total body fat in older men, studies on testosterone treatment in older men are controversial, and outcomes have varied by the dosage, subject, and method of administering testosterone (Table S6).[161] Several studies have found that oral testosterone supplementation was associated with increased lean body mass, knee extension, improved chest press strength and stair-climbing power, and decreased fat mass.[162–164] Other studies reported no difference in muscle strength, performance, and activity with testosterone supplementation.[165] Given mixed results, testosterone therapy cannot be recommended as a routine therapy for sarcopenia, especially given the potentially increased risks of testosterone therapy in certain subpopulations with CVD.

Selective Androgen Receptor Modulators

GTx-024 (enobosarm) is an agent that has shown a dose-dependent increase in total lean body mass and improvement in physical performance such as the stair-climb test.[166,167] Although enobosarm and other selective androgen receptor modulators demonstrated improvement in lean muscle mass, the improvement in physical function has not been consistent. In addition, acute liver damage was reported with the use of selective androgen receptor modulators as a major adverse event.[168] These drugs are not yet available, and further studies are needed to establish their efficacy and safety in patients with sarcopenia.

Angiotensin-Converting Enzyme Inhibitors

For many years, angiotensin-converting enzyme inhibitors (ACE-Is) have been used to treat hypertension and HF. The use of ACE-Is is associated with improved skeletal muscle function. ACE-I is one of the cornerstone therapies in HF, and its effect on sarcopenia could simply relate to treating the underlying syndrome. However, ACE-Is could also produce their beneficial effects through improving endothelial function, anti-inflamma-

tory effects, and angiogenesis, thus enhancing skeletal muscle blood flow. ACE-I can potentially increase IGF-1 levels and improve mitochondrial function, reducing muscle catabolism.[169] Therefore, there is a biologic rationale for the potential of ACE-Is to delay the development or progression of sarcopenia.[170,171] A previous observational study showed that continuous use of ACE-I for 3 years was associated with a lower rate of decline in muscle strength and walking speed among hypertensive older women when compared with intermittent use of ACE-Is or other antihypertensive medications.[172]

GAPS IN KNOWLEDGE

There is an unprecedented need to standardize the definitions of sarcopenia (and clinical concepts related to muscle mass, quality, and function). The tools used to diagnose sarcopenia in practice need further investigation, with a focus on reliable and reproducible diagnostic instruments including the use of standardized cut points for imaging and biomarkers that evaluate skeletal muscles, especially in the setting of obesity (ie, for sarcopenic obesity).

Given that sarcopenia often occurs in the setting of end-organ damage/failure, chronic inflammation, malnutrition, and prolonged immobility, biomarkers that integrate multi "omics" could be helpful for detection and longitudinal assessments of sarcopenia. A working group from the TAME trial (Targeting Aging With Metformin) has accordingly recommended the following: IL-6, TNF-α receptor I or II, CRP, GDF15, insulin, IGF-1, cystatin C, NT-proBNP (N-terminal pro-B-type natriuretic peptide), and hemoglobin A1c, but also noted a paucity of evidence for biomarkers in human studies reflecting processes of aging.[173] Examining mitochondrial-specific proteins, which may play a role in the pathophysiology of sarcopenia, could also be a fruitful area for further investigation.[174] Future work using omics-based "big data" approaches could identify combinations of biomarkers strongly associated with muscle mass and function, prognosis, and potentially treatment response.[175]

Studying clinical variability of muscle quality and function among different ethnic groups at risk for or living with CVD is necessary and may provide mechanistic insights on development and progression of sarcopenia among the most vulnerable populations. Moreover, we need rigorous studies of interventions that can prevent or forestall development or progression. This should include an evaluation of structured resistance exercise programs with or without nutritional supplementation. Further evaluation of how best to leverage the infrastructure of cardiac rehabilitation to meet the needs of adults with CVD is similarly necessary. Finally, research is warranted to examine the efficacy and safety of pharmacotherapeutic strategies targeting key substrates of sarcopenia, with attention paid to key myosteatosis, which is particularly important in the development of sarcopenic obesity.

CONCLUSIONS

Sarcopenia, defined as the loss of muscle strength, mass, and function, is common in cardiac patients and has a bidirectional relationship with CVD. It is important to note that sarcopenia is associated with a range of adverse outcomes, including mortality, falls, and impaired health-related quality of life. Sarcopenia may be modifiable, especially during its earlier stages. Accordingly, screening for sarcopenia to facilitate its early recognition is important because early intervention can potentially prevent or forestall progression of sarcopenia. Interventions such as resistance training and nutritional supplementation are promising strategies to address sarcopenia, although future work is needed in the area of skeletal muscle therapeutics.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Supplemental Material

Tables S1–S6

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