Unit No. 1

SARCOPENIA: UPDATE ON DIAGNOSIS AND TREATMENT IN AN ASIAN COMMUNITY SETTING

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ABSTRACT

Sarcopenia refers to the age-associated progressive and generalised loss of skeletal muscle mass plus loss of muscle strength and/or reduced physical performance. Described as the biological substrate that antecedes physical frailty, sarcopenia is associated with adverse health outcomes in older adults. The International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) code for sarcopenia represents a major step forward in translating sarcopenia to clinical practice. The Asian Working Group for Sarcopenia (AWGS) 2019 consensus provides an algorithm for identifying and diagnosing older adults with or at-risk for sarcopenia. "Possible sarcopenia" is defined by low muscle strength or reduced physical performance and is applicable for primary health care and community settings. Accurate case finding and assessment requires proper administration using the correct instruments. Older adults with or at-risk for sarcopenia should be evaluated for reversible causes (using the '4D' mnemonic). Currently, the mainstay of treatment is non-pharmacological, comprising resistance exercise and adequate protein intake.

Keywords: Sarcopenia, skeletal muscle strength and mass, physical performance, diagnosis, treatment, Asia

SFP2021; 47(6) : 5-12

INTRODUCTION

Sarcopenia is a term derived from Greek meaning 'poverty of flesh' and was first proposed by Irwin Rosenberg in 1989 to describe the age-associated loss of muscle mass. In the last 30 years, there is increasing recognition of sarcopenia as a geriatric syndrome with a major impact on health, functional independence, and quality of life in older adults. The number of papers related to sarcopenia indexed in the PubMed database has increased exponentially, with more than 2,000 papers published per year in the last two years.[1] Effort to move sarcopenia diagnosis and management into the clinical setting were marked by two milestone developments. Firstly, muscle function was introduced into the concept in six consensus definitions since 2010.[2] The rationale was because muscle function was consistently shown to be a more powerful predictor of clinically relevant outcomes than muscle mass alone. Secondly, the recognition of sarcopenia as an independent condition with an International Classification of Diseases-10 code (M62.84) in 2016 represents a major step forward in translating sarcopenia into clinical practice.[3] Yet, most clinicians remain unaware of the condition and the diagnostic tools needed to identify it.

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DEFINITION

Sarcopenia is defined as the age-associated progressive and generalised skeletal muscle disorder that involves loss of muscle mass plus loss of muscle strength and/or reduced physical performance.[4] Muscle mass and strength (in parallel with bone mineral density) peak in young adulthood and, after a plateau, start decreasing gradually with a faster decline in strength. The revised European Working Group on Sarcopenia in Older People (EWGSOP2) definition conceptualises sarcopenia as 'skeletal muscle failure or insufficiency' with an underlying multifactorial Etiology, such that sarcopenia might occur acutely (usually in the setting of an acute disease or sudden immobility, as during hospital admission) or have a more protracted (chronic) course.[5] In contrast, the Asian Working Group for Sarcopenia (AWGS) definition is without reference to comorbidity and stipulates age cut-offs at either 60 or 65-years old, depending on the local definition of "older people".[4]

CLINICAL SIGNIFICANCE

Sarcopenia is associated with adverse health consequences including falls, functional decline, hospitalisation, frailty, increased healthcare costs, and mortality. A systematic review and meta-analysis showed a consistent association between sarcopenia and mortality, with a pooled odds ratio of 3·59 (95 percent CI 2·96–4·27) and larger effect size in men and women aged 79 years and older.[6] Overall quality of life is impaired in sarcopenia using either generic self-reported tools or disease-specific questionnaires. One study estimated that the financial impact of sarcopenia exceeded osteoporotic fractures, costing a staggering US$18.5 billion per year. Notably, a ten percent reduction in sarcopenia prevalence would save US$1.1billion per year.[7]

Clinicians can associate sarcopenia with leanness and not be aware that sarcopenia can also be present in obesity in a condition termed sarcopenic obesity (the so-called 'fat frail'). Sarcopenic obesity is associated with intermuscular adipose tissue, leading to worse physical performance than older adults with sarcopenia or obesity alone.[8] Using data from

the GERILABS study, the local prevalence of sarcopenic obesity in older adults is around 10.5 percent.[9] Additionally, associations have been identified between sarcopenia and dysphagia (sarcopenic dysphagia) and with the myocardial structure on echocardiography ('cardio-sarcopenia'), which merit further investigation about the potential significance in clinical practice.[10, 11]

EPIDEMIOLOGY

The prevalence of sarcopenia increases with age. Prevalence also depends on the setting, being more common in the hospital and long-term care facilities compared with the community. In Asia, using the AWGS 2014 criteria for sarcopenia diagnosis, prevalence ranges from 5.5 percent to 25.7 percent with male predominance.[12] When only larger studies >1000 in sample size are considered, the prevalence estimates become more precise, ranging from 7.3 to 12 percent. Older age may be the most important among numerous reported risk factors; a local population study of older adults aged >60 years found that handgrip strength demonstrated a decreasing trend with an increase in age across all ethnic groups and sexes.[13] Household status, lifestyle habits such as binge drinking with weekly or daily alcohol consumption, physical inactivity, poor nutritional and dental status, and comorbidities (e.g. osteoporosis, cardiovascular risk factors) are also independently associated with sarcopenia. The likelihood of developing sarcopenia is significantly correlated with the number of cardiometabolic risk factors, notably diabetes, hypertension, and dyslipidaemia. In particular, type 2 diabetes is an important predictor of sarcopenia, with accelerated decline in leg lean mass and muscle strength in older people compared to those without diabetes.[14]

Locally, the GERILABS-2 study is a community study of 230 healthy older adults with a mean age of 67 years. Sarcopenia prevalence is 27 percent with a male predominance. Risk factors for sarcopenia include age, type 2 diabetes and the presence of social frailty.[15] The Yishun study is a community study of 542 persons aged 21-90 years. Population-adjusted sarcopenia prevalence is 32.2 percent for those aged ≥60 with slight male predominance.[16]

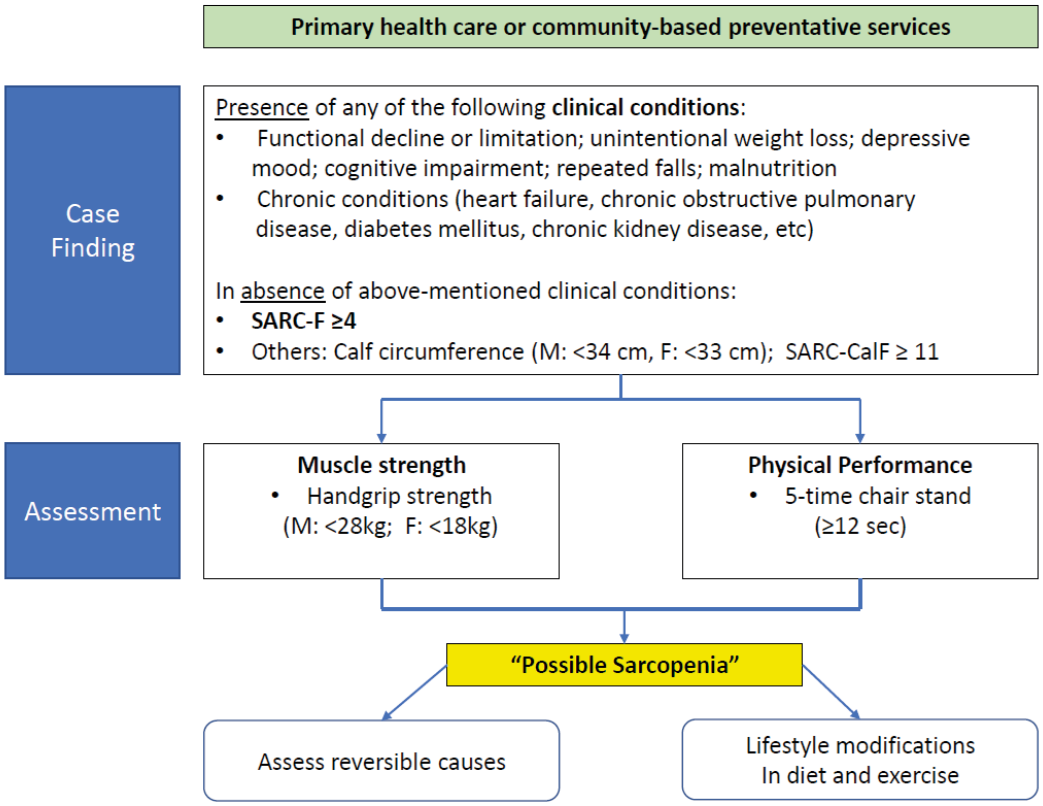
CASE FINDING AND DIAGNOSIS

The AWGS 2019 consensus provides an algorithm for identifying and diagnosing older adults with or at-risk for sarcopenia, including case-finding and diagnostic protocols for use in either hospital and research settings, or in primary healthcare or community-based preventative services.[4]

Assessment in primary care or community-based settings

The AWGS algorithm considers the challenges of early identification of older adults with or at-risk for sarcopenia in settings without advanced diagnostic equipment (Figure 1). Specifically, the AWGS 2019 introduces the category "possible sarcopenia," defined by low muscle strength or reduced physical performance, which is recommended for use in primary health care and preventive services, but not in the hospital or research settings.[4]

Figure 1. Diagnosis and management of "Possible Sarcopenia"



Older adults with relevant symptoms or chronic conditions, or are positive on the case-finding tools, should be further assessed with either handgrip strength or repeated chair stand. Those who fulfil the criteria for 'possible sarcopenia' should be offered health education and counseling on lifestyle modifications in diet and exercise. They should also be evaluated for potential underlying causes, namely the **4D**s of **d**rugs; **d**iabetes mellitus; other **d**iseases; and **d**eficiency (refer to section on 'Prevention and Management' for details) (Table 1). Where relevant, suitable cases can be referred for further evaluation of underlying causes and provision of appropriate personalised intervention programs by the multidisciplinary team.

Table 1. 4Ds Mnemonic: Underlying causes of Sarcopenia

1. **Drugs**
   Common
   - Statins
   - Fibrates
   - Steroids
   - Alcohol

   Less common
   - Chloroquine
   - Colchicine
   - Antiretroviral drugs e.g., lamivudine, zidovudine
   - Chemotherapy medications
2. **Diabetes Mellitus**
3. **Other Diseases**
   - Chronic lung, kidney, liver or heart disease
   - Osteoporosis
   - Knee Osteoarthritis
   - Neurological diseases
   - Cancer
4. **Deficiency**
   - Poor dentition or oral health
   - Swallowing difficulties
   - Vitamin D deficiency
   - Conditions/medications causing anorexia or malabsorption
   - Socioeconomic factors affecting access to food

Identification: Case Finding Approach

Many cases of sarcopenia go undiagnosed. However, universal screening at the population level is not recommended because screening tools have diagnostic limitations and the effect of such screening on relevant outcomes is unproven.[17] Therefore, a case-finding approach for at-risk cases is recommended and is particularly relevant in care settings where a higher prevalence of sarcopenia might be expected, such as admission to hospital, rehabilitation settings, or nursing homes.[2] This approach involves looking for sarcopenia when relevant symptoms such as difficulties or decline in carrying out daily life activities, unintentional weight loss, low mood, cognitive impairment, and repeated falls are reported, or in the presence of chronic conditions such as diabetes mellitus; chronic lung, kidney, liver or heart disease; osteoporosis; and knee osteoarthritis.[4]

Three case-finding tools are recommended: SACR-F, calf circumference (CC) or the combination of the two (SARC-CalF). The SARC-F is a self-reported 5-item questionnaire that assesses symptoms in strength, assistance in walking, rising from a chair, climbing stairs, and falls (Table 2). Studies in Asia have validated different language versions of SARC-F and have shown that the results are independently associated with adverse clinical outcomes.[18] Using a cutoff score of 4, the SARC-F has low sensitivity and high specificity for sarcopenia diagnosis.[19] A recent study reported that the optimal cutoff for detecting low handgrip strength was SARC-F≥2 (sensitivity: 64.9% vs specificity: 67.9%) compared with ≥4 (sensitivity: 40.3% vs specificity: 88.2%), suggesting that further assessment for sarcopenia is warranted if there is clinical suspicion, even though the SARC-F score may be <4.[20, 21]

CC has moderate-to-high sensitivity and specificity in predicting sarcopenia or low skeletal muscle mass.[22] Recommended cut-offs are CC <34cm for men and <33cm for women. Accurate measurement is critical, and the recommended protocol measures the maximum value of both calves in the standing position using a nonelastic tape. Notably, the diagnostic performance of CC can be attenuated in sarcopenic obesity due to decreased sensitivity with under-detection in women.[23] The SARC-CalF combines both CC and SARC-F, analogous to the corresponding components of low muscle mass and muscle strength/performance. The SARC-CalF improves the sensitivity of SARC-F for case-finding by adding CC, with a score ≥11 indicating sarcopenia.[24]

Diagnosis

The diagnosis of sarcopenia requires the presence of both low muscle mass and impaired muscle function (low muscle strength or low physical performance), with specified cut-offs for each diagnostic component (Figure 2). The presence of low muscle mass, low muscle strength, and low physical performance would constitute "severe sarcopenia."

(1) Skeletal Muscle Mass Measurement

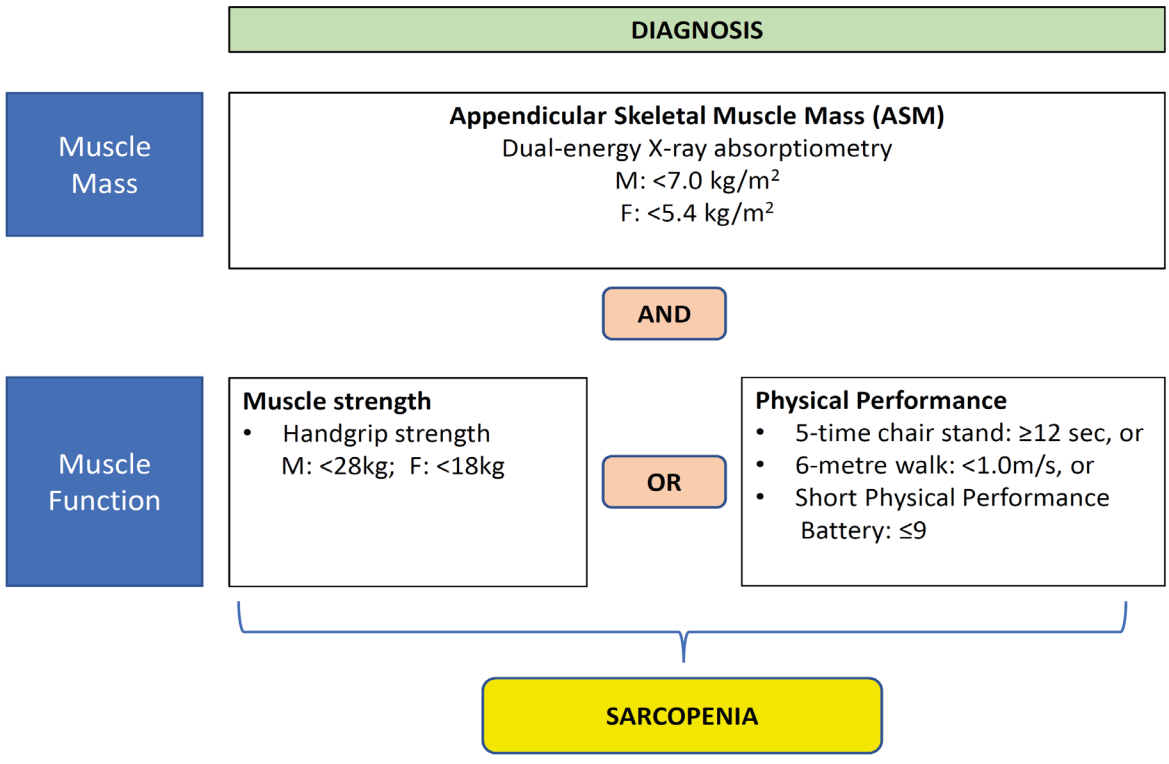
AWGS 2019 recommends using either dual-energy X-ray absorptiometry (DXA) or multifrequency bioelectrical impedance analysis (BIA) for measuring muscle mass in sarcopenia diagnosis. The AWGS 2019 cut-offs for low muscle mass in sarcopenia diagnosis are as follows: <7.0 kg/m^2 in men and <5.4 kg/m^2 in women by DXA; and <7.0 kg/m^2 in men and <5.7 kg/m^2 in women by BIA.

As BIA equations and cut-off points are population-specific and device-specific, its routine use in clinical care is not recommended in the absence of well-conducted local

Table 2. SARC-F Questionnaire

Component	Question		Score
Strength	How much difficulty do you have in lifting and carrying 10lb (4.5kg)?		
	None	0	
	Some	1	
	A lot or unable	2	
Assistance of walking	Difficulty in walking through a room because of illness or other physical reasons?		
	None	0	
	Some or great difficulty	1	
	Using professional equipment or assistant instruments; helps from others; unable to complete	2	
Rising from the chair	Difficulty in rising from the chair or bed because of illness or other physical reasons?		
	None	0	
	Some or great difficulty	1	
	Using professional equipment or assistant instruments; helps from others; unable to complete	2	
Climbing stairs	Can you climb ten steps continuously and independently without any help?		
	None	0	
	Some or great difficulty	1	
	Using professional equipment or assistant instruments; helps from others; unable to complete	2	
Falling	Did you fall in the past year?		
	None	0	
	1-3 times	1	
	4 times or more	2	
			Total score : _____ ≥4 indicates sarcopenia

Figure 2. Algorithm for sarcopenia diagnosis (AWGS 2019 criteria)



validation studies.[25] It is recommended to use a validated device, preferably multifrequency, which correlated more closely with DXA-measured appendicular skeletal mass. BIA devices designed for home use are not recommended because of suboptimal diagnostic accuracy.[26] It is also important to note that BIA readings can be affected by other factors such as hydration status and is contraindicated in those with pacemakers or cardiac devices

The most effective procedure to date is the DXA, which estimates lean mass. During the DXA procedure, subjects lie supine with arms and legs at their sides during the 15-min scan. Radiation exposure from body composition DXA scan is minimal at 1-4 μSv. Readings of lean mass from the four limbs are summed and divided by height square to yield the height-adjusted appendicular lean mass. However, muscle mass as measured by DXA shows only a weak association with adverse health outcomes and does not provide information about muscle quality. Despite these limitations, DXA remains a useful modality with the capacity for rapid clinical implementation.[27]

CT and MRI have been considered gold standards because of their ability to detect intramuscular fat infiltration. However, due to their high cost and time required, they are mostly used in research and when needed for follow-up of another condition – for example, in patients with cancer. Ultrasound has been proposed as a simple alternative to measure muscle quantity and quality in clinical practice; however, it is user-dependent, and studies are currently underway to standardise the measurement protocols and to develop validated cut-offs. D3 creatine is a recently developed non-invasive isotope dilution test that shows better correlation with outcome measures than DXA lean mass[28]; its applicability and potential for scalability in the clinical setting remain to be established.[27]

(2) Muscle Strength

The AWGS 2019 consensus recommends using handgrip strength to indicate skeletal muscle strength. Low handgrip strength has been shown to be highly predictive of a range of adverse outcomes. The devices used most often in Asia are the spring-type dynamometer (Smedley) and the hydraulic-type (Jamar). It is important to note that there are different measurement protocols available and that results of dynamometers are not interchangeable. For instance, the recommended positions for measuring handgrip strength are sitting with 90-degree elbow flexion for the Jamar dynamometer and standing with full elbow extension for the Smedley dynamometer[29]; the protocol for Smedley dynamometer also permits sitting for those who are unable to stand unassisted.[4] In one study, handgrip strength readings measured using the Smedley were consistently lower than the Jamar, leading to higher prevalence rates of weakness across different diagnostic criteria.[30] It is recommended that 2-3 trials be performed, with a recording of the maximum reading (instead of average reading) in view of better predictive validity for poor physical performance.[31] Interestingly, a review of ten studies found that right dominant subjects were stronger with their right hand, whereas among left dominant subjects the results were equivocal.[29] Using the lowest quintile from pooled data of eight Asian cohorts comprising 21,984 participants aged>65 years, the AWGS 2019 recommends diagnostic cut-offs of handgrip strength <28.0 kg in men and <18.0 kg in women for low muscle strength.[32] Two local large population studies attempted to describe the normative values of handgrip strength (using Smedley and Jamar dynamometers respectively) for older adult Singaporeans aged 60 years and above; however, both studies reported relatively lower handgrip strength values compared to Western and other Asian countries, suggesting the need for further studies to determine the veracity of these results.[13, 33]

In summary:

1. AWGS 2019 recommends using either the Jamar or Smedley dynamometers to measure handgrip strength, provided a standard protocol for the specific model is followed. Dynamometer-specific cut-off values are not recommended because of insufficient comparative data.[4]

2. The handgrip strength measurement protocol recommended by AWGS 2019 is to take the maximum reading of at least two trials using the dominant hand in a maximum-effort isometric contraction, rather than using a fixed acquisition time.[4]

3. If handgrip strength is below the gender-specific reference value, it is important to exclude differential diagnosis that can impede handgrip performance (such as hand osteoarthritis, depression, dementia, Parkinson's disease and other neurological disorders) before ascribing the diagnosis of 'possible sarcopenia'.[2]

(3) Physical Performance

Amongst the various physical performance tests, AWGS 2019 recommends the 5-time repeated chair stand (RCS-5) for the initial assessment of sarcopenia. RCS-5 is a measure of the strength of the lower limb muscles and is associated with subsequent disability, falls, fractures, and mortality. It involves asking the participant to stand up from a chair and to sit back down as quickly as possible five times. Because the chair stand test measures performance against gravity, it is not necessary for the older adult to return to the seated position as this manoeuvre does not involve work against gravity. Timing for RCS-5 should thus be stopped when standing up straight for the fifth time (and not when in the final seated position).[34] AWGS 2019 recommends ≥12s as the cut-off for low physical performance to correspond to a walking speed of 1.0 m/s, which is higher than the EWGSOP2 cut-off of ≥15s. It is important to capture the non-completion of the RCS-5 and the attendant reasons. Being unable to complete the RCS-5 has also been linked to hip fracture and increased all-cause mortality rates, and is thus an indication to undertake a comprehensive geriatric assessment in addition to evaluation for sarcopenia.[35]

Other physical performance tests which can be performed include the Short Physical Performance Battery (SPPB), usual gait speed, six-minute walk test, and timed-up-and-go test. It should be noted that compared with EWGSOP2, the AWGS recommends higher cut-offs for gait speed (<1 m/s vs ≤0.8 m/s) and SPPB (≤9 vs ≤8) respectively.

DIFFERENTIAL DIAGNOSIS

The three main conditions in the differential diagnosis of sarcopenia are malnutrition, cachexia, and frailty.[2] Whilst reduced muscle mass is one of the three phenotypic criteria of malnutrition according to the Global Leadership Initiative on Malnutrition, current definitions of sarcopenia place a focus on muscle function.[36] Therefore, a finding of reduced muscle mass with normal muscle strength in the correct clinical context would be more suggestive of malnutrition than sarcopenia, whereas reduced muscle mass with impaired muscle function supports a diagnosis of sarcopenia. Cachexia describes the severe weight loss and muscle wasting driven by excess catabolism and inflammation, endocrine changes, and neurological changes; it is associated with cancer, HIV and AIDS, or end-stage organ failure. Whilst cachexia and sarcopenia can coexist, and there is some overlap in definition, in particular low muscle mass, the cardinal role of inflammation and cytokines is more relevant in cachexia than in sarcopenia. Frailty refers to a state of vulnerability to adverse outcomes as a result of poor resolution of homeostasis after a stressor event. Frailty is conceptualised as a multidimensional syndrome that encompasses physical, cognitive, psychological and social components.[37] Physical frailty and sarcopenia are closely related, with sarcopenia been described as the biological substrate that antecedes physical frailty.

PREVENTION & MANAGEMENT

Akin to bone health, we should likewise adopt a cradle to grave life course approach towards muscle health. To prevent or delay sarcopenia development, the key is to start as early as possible to maximise muscle strength in youth and young adulthood, maintain muscle strength in middle age and finally, to minimise the loss in older age so that we can remain above the threshold of low physical performance and postpone the onset of disability for as long as possible.[5]

Management in clinical practice comprises two key components:

1. Assess and treat underlying causes.
2. Intervention, with mainstay being non-pharmacological modalities of exercise and diet.

Assess and treat underlying causes

Older adults with or at-risk of sarcopenia should be assessed for underlying causes, namely the 4Ds of drugs (medications such as statins, fibrates and steroids can cause myalgia and proximal weakness); diabetes mellitus; other diseases (chronic lung, kidney, liver or heart disease, osteoporosis, knee osteoarthritis and neurological conditions); and deficiency (poor dentition or oral health, swallowing difficulties, vitamin D deficiency, conditions/medications causing anorexia or malabsorption, or socioeconomic factors affecting access to food).[2]

Intervention

The International Clinical Practice Guideline for Sarcopenia (ICFSR) provides strong recommendations for physical activity for the treatment of sarcopenia in older adults.[38] Evidence supports the benefits of resistance exercise in improving skeletal muscle strength and mass individually, and there is growing evidence for its benefit in sarcopenia (defined as a combination of both strength and mass). Resistance exercise can be performed using dumbbells, free weights, elastic therapy bands or the body weight itself. It is recommended that older adults engage in a progressive, individualised physical activity program that contains a resistance training component. Exercise prescription principles including frequency, intensity, type, time and duration are crucial when planning interventions for different target groups, and should preferably be done in consultation with trained professional such as physiotherapists, exercise physiologists and fitness professionals.[39]

The ICFSR conditionally recommends protein supplementation/protein-rich diet for treatment of sarcopenia in older adults. Anabolic resistance in older adults' results in blunted response to nutrients and hormones such that they require more dietary protein than younger people to prevent sarcopenia. Thus, the PROT-AGE group recommends optimal protein intake of 1.0–1.2 g/per kg BW/day, which is higher than the 0.8 g/per kg BW/day of general guidelines.[40] There is some evidence to suggest that supplementation with the essential amino acid leucine and its metabolite β-hydroxy methylbutyrate (HMB) may be beneficial. It is recommended that nutritional intervention should be combined with physical exercise to derive optimal benefit. There is increasing interest in the whole food approach, which is based on the premise that whole foods, unlike single nutrients, provide benefits that are greater than a sum of their constituents.[41] Moreover, employing a food-first approach may resonate better with older adults who understand foods better than isolated nutrients for healthy nutrition. Relevant myo-protective food groups are meats, fruits and vegetables, dairy products and other whole foods such as cereals and fish.

In terms of pharmacological interventions, a beneficial effect of vitamin D was shown in strength and physical

performance in women with low baseline levels (<25 nmol/l). Evidence suggests a limited benefit of testosterone for physical function, and caution should be taken regarding the cardiovascular side-effect profile. Ongoing pharmacotherapy trials are evaluating activin receptor antagonist, myostatin or activin inhibitor, androgen receptor modulators, and troponin activator of fast skeletal muscle.[1] A recent phase II study of bimagrumab, a monoclonal antibody of activin receptor type 2B, reported a benefit in increasing muscle mass which did not lead to improved muscle strength or physical performance.[42]

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LEARNING POINTS

- **Sarcopenia is a geriatric syndrome that is associated with adverse outcomes in older adults.**
- **Diagnosis of sarcopenia requires the presence of low muscle mass and impaired muscle function (strength and/or physical performance). "Possible sarcopenia" is defined by low muscle strength or reduced physical performance and is applicable for primary health care and community settings.**
- **Accurate case finding and assessment requires proper administration using the correct instruments.**
- **Evaluate and address reversible causes in older adults with or at-risk for sarcopenia.**
- **Currently, the mainstay of treatment is non-pharmacological, comprising resistance exercise and adequate protein intake.**