Old muscle, new tricks: a clinician perspective on sarcopenia and where to next

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Purpose of review
This review offers a contemporary clinical approach to the recognition, prevention and management of sarcopenia, and discusses recent clinically relevant advances in the aetiopathogenesis of muscle ageing that may lead to future therapeutic targets.

Recent findings
The key recent directions for sarcopenia are in the diagnosis, understanding molecular mechanisms and management. Regarding the recognition of the condition, it has become increasingly clear that different definitions hamper progress in understanding. Therefore, the Global Leadership in Sarcopenia has been established in 2022 to develop a universally accepted definition. Moreover, substantial work is occurring to understand the various roles and contribution of inflammation, oxidative stress, mitochondrial dysfunction and metabolic dysregulation on skeletal muscle function and ageing. Finally, the role of resistance-based exercise regimes has been continually emphasised. However, the role of protein supplementation and hormone replacement therapy (HRT) are still under debate, and current clinical trials are underway.

Summary
With the global ageing of our population, there is increasing emphasis on maintaining good health. Maintenance of skeletal muscle strength and function are key to preventing frailty, morbidity and death.

Keywords
aetiopathogenesis, diagnosis, muscle ageing, sarcopenia, treatment

INTRODUCTION

Globally, populations are rapidly ageing due to increased life expectancy and falling fertility rates [1]. Consequently, there is an increased emphasis on maintaining the health and functional capacity of individuals into old age [1]. A key factor in maintaining health and independence is the moderation of age-associated degenerative loss in skeletal muscle typified by decreased muscle size, strength and function [2]. Humans achieve peak skeletal muscle mass and strength in mid-life, and thereafter relative muscle mass declines by 30–50% at age 80 years [3,4]. Concurrent with the reduction in muscle mass, is the reduction in muscle power by approximately 10–15% each decade until 70 years, which then accelerates to a 25–40% reduction per decade [2]. Therefore, loss of muscle strength and power is more rapid than the loss of muscle mass, indicating additional factors are involved in the deterioration of muscle function with ageing [2,5].

The term sarcopenia was first used in 1989 to describe an age-related decline in lean body mass affecting mobility and independence [6]. Since its inception, numerous definitions of sarcopenia have been proposed, with the most recent definition published in 2019 by the European Working Group on Sarcopenia (EWGSOP). It encompasses the loss of skeletal muscle mass and strength alongside

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KEY POINTS

- A universally accepted definition for sarcopenia is needed.

- Substantial work is ongoing to understand the various roles and contribution of inflammation, oxidative stress, mitochondrial dysfunction, and hormonal changes on skeletal muscle function and ageing.

- The role of resistance-based exercise regimens has been continually emphasised.

- The roles of protein supplementation and HRT are still under debate, and current clinical trials are underway.

functional decline and deficit [7,8]. Sarcopenia is associated with atrophy of muscle fibres, accumulation of fibrofatty tissue, and metabolic alterations within the muscle, including disrupted protein turnover, impaired regeneration, and mitochondrial dysfunction impacting muscle function and quality [9].

The consequences of muscle ageing and sarcopenia are significant, with a growing body of evidence highlighting the strong inter-relationship between sarcopenia and adverse functional and clinical outcomes [10,11]. In 2000, an estimated US $18.5 billion in healthcare costs were attributed to sarcopenia [12]. With the number of elderly people expected to increase from 841 million in 2013 to more than two billion by 2050, the costs associated with sarcopenia are also expected to increase exponentially. Sarcopenic patients have increased rates of falls, disability, hospital, and nursing home admissions and mortality [13,14].

Sarcopenia is an independent risk factor for mortality [15]. Kitamura *et al.* have shown that the risk of all-cause mortality in sarcopenic Japanese patients is two- and three-fold higher than in nonsarcopenic female and male patients respectively [16]. Likewise, Nakamura *et al.* demonstrated that sarcopenic patients had a two-fold higher risk of all-cause mortality than nonsarcopenic patients [17]. Multiple studies have also shown that sarcopenia significantly increases mortality rates of hospital-inpatients. For instance, Bayraktar *et al.* showed in-hospital mortality rate of nonsarcopenic patients was 17.6% lower than that of sarcopenic patients [18].

Functional disability and decline are also significant consequences of sarcopenia. Xu *et al.* found that sarcopenia was associated with higher odds of disability related to activities of daily living [19], and Vongchaiudomchoke *et al.* showed that a diagnosis of sarcopenia was an independent risk factor for poorer functional outcomes at one-month post hospital discharge in critically ill surgical patients [20].

Therefore, reducing the age-related degenerative changes in skeletal muscle is critical to reducing the risk of injury, permanent disability and mortality in older adults [21]. Factors including appropriate exercise and good nutrition are considered vital in the prevention and treatment of accelerated muscle loss. With the ageing of our population, this will become an increasingly important public health issue that requires urgent attention. This review will discuss the definition of sarcopenia, clinical approach, aetiopathogenesis, treatment, and preventive techniques for sarcopenia.

DEFINING SARCOPENIA

There is much debate in the literature regarding the definition of sarcopenia. Multiple international working groups have proposed definitions (key criteria summarised in Table 1), and whilst they generally contain similar domains – muscle strength, muscle mass, and physical performance – consensus between them is poor [7,8,22■]. For example, a recent European study of over 1400 community-dwelling older adults found the prevalence of sarcopenia varied greatly from 0.7% to 16.8% depending on which of 12 definitions were used [23]. The Global Leadership in Sarcopenia was established in 2022 to develop a universally accepted definition for sarcopenia; this work remains ongoing [24■].

CLINICAL APPROACH TO SARCOPENIA

The benefit of widespread screening for sarcopenia has not been established. This is partly owing to the difficulty in developing a single appropriate screening tool [29,30] and partly because there are no established treatments for sarcopenia. However, there is significant value in having clinicians consider and recognise sarcopenia because early intervention with exercise and nutritional advice may slow functional decline and improve quality of life.

Current recommendations for the initial steps in a sarcopenia diagnostic pathway revolve around a case-finding approach, which explores a diagnosis of sarcopenia when signs or symptoms are reported [7]. Such symptoms generally include falls and functional decline, which, once neurological and muscular diseases have been excluded, are frequently dismissed in the older population as an unavoidable side effect of ageing. At this point, the clinician should consider sarcopenia.

The Strength, Assistance walking, Rise from a chair, Climb stairs, and Falls (SARC-F) questionnaire was recommended by the EWGSOP in 2019 as the primary sarcopenia case-finding instrument [7,31,32]. The value of the SARC-F is that it is a patient-

Table 1. Comparison of definitions of Sarcopenia.

Definition	Muscle Strength	Muscle Mass	Physical Performance
EWGSOP [7]	Handgrip strength: • M: < 27 kg • F: < 16 kg OR chair stand: • > 15 s (5 rises)	ASM: • M: < 20kg • F: < 15kg OR ASM/Height^2: • M: < 7.0kg/m^2 • F: < 5.5kg/m^2	Gait speed: ≤0.8 m/s (4m) OR SPPB score: ≤ 8 points OR TUG: ≥20 s OR 400m walk: ≥ 6 min/ noncompletion
AWGS [25]	Handgrip strength: • M: < 28kg • F < 18kg	ASM/ Height^2: • M < 7.0kg/m^2 • F: <5.4kg/m^2 OR BIA M<7 kg/m^2, F <5.7 kg/m^2	Gait speed: <1.0m/s (6m) OR 5-time chair stand ≥ 12s OR SPPB ≤ 9
FNIHSP [26]	Handgrip strength: • M <26kg • F: <16 kg	ALM/BMI: • M: <0.789 kg/BMI • F: <0.512 kg/BMI	
IWGS [27]		ALM/Height^2: • M: ≤ 7.23 kg/m2 • F: ≤ 5.67 kg/m2	Gait speed: < 1.0m/s (4m)
SDOC [28]	Handgrip strength (absolute): • M: <35.5kg • F: <20 kg OR standardised to body weight/ BMI		Gait speed: ≤0.8m/s (4–6m)

ALM, appendicular lean mass; ASM, appendicular skeletal mass; AWGS, Asian Working Group on Sarcopenia; BIA, bioelectrical impendence analysis; BMI, body mass index; EWGSOP, European Working Group on Sarcopenia; F, female; FNIHSP, Foundation for the National Institutes of Health Sarcopenia Project; IWGS, International Working Group on Sarcopenia; M, male; SDOC, Sarcopenia definitions and outcomes consortium; SPPB, short physical performance battery; TUG, timed up and go.

administered questionnaire that evaluates the hallmark symptoms of sarcopenia: falls and functional decline [33,34▪]. The drawbacks of the SARC-F are that it has high specificity but only low-moderate sensitivity, meaning it is better suited to ruling out people who do not have sarcopenia rather than ruling in those that do [30,31,35].

More sensitive but also more involved tools include the SARC-CalF and the Ishii Index. The SARC-CalF is an amalgamation of SARC-F and calf circumference measurements. It has been suggested as a better choice for early screening for sarcopenia because of its increased sensitivity for case finding [25,29,35–39]. The Ishii Index has even greater sensitivity as it assesses calf circumference and grip strength [7,40–42]. The choice of tool comes down to clinician time and preference.

Once a potential case of sarcopenia has been identified, strength measures can be directly assessed to confirm probable sarcopenia. These may include grip-strength and/or chair stand measurement [7]. Gold-standard confirmation of sarcopenia is not usually employed in a clinical setting as it involves costly computed tomography or magnetic resonance imaging, for which consistent cut-off values for sarcopenic muscle mass have not been defined [7]. Functional assessment may also be useful for establishing condition severity and as a marker for program prescription and surveillance.

Such assessments may include a timed up and go, gait speed, short physical performance battery and 400m walk [7,25,27,28]. The clinical approach to sarcopenia described here is outlined in figure one (Fig. 1).

AETIOPATHOGENESIS OF MUSCLE AGEING

The aetiopathogenesis of muscle ageing and sarcopenia remains elusive and is likely to involve many interrelated ageing factors that ultimately disrupt skeletal muscle homeostasis. This section will discuss factors receiving current attention for their significant pathogenic role – and, therefore, therapeutic potential – in the aetiopathogenesis of sarcopenia, including inflammation, mitochondrial dysfunction, oxidative stress, and metabolic dysregulation.

INFLAMMATION

Chronic, subacute inflammation is a physiological hallmark of ageing termed inflamm-ageing [43]. There is a demonstrated association between chronic inflammation and muscle atrophy [44–47]. Inflammatory markers such as tumour necrosis factor (TNF), interleukins (IL), reactive oxygen species (ROS) and C-reactive protein are likely key mediators; IL-6, in particular, is thought to
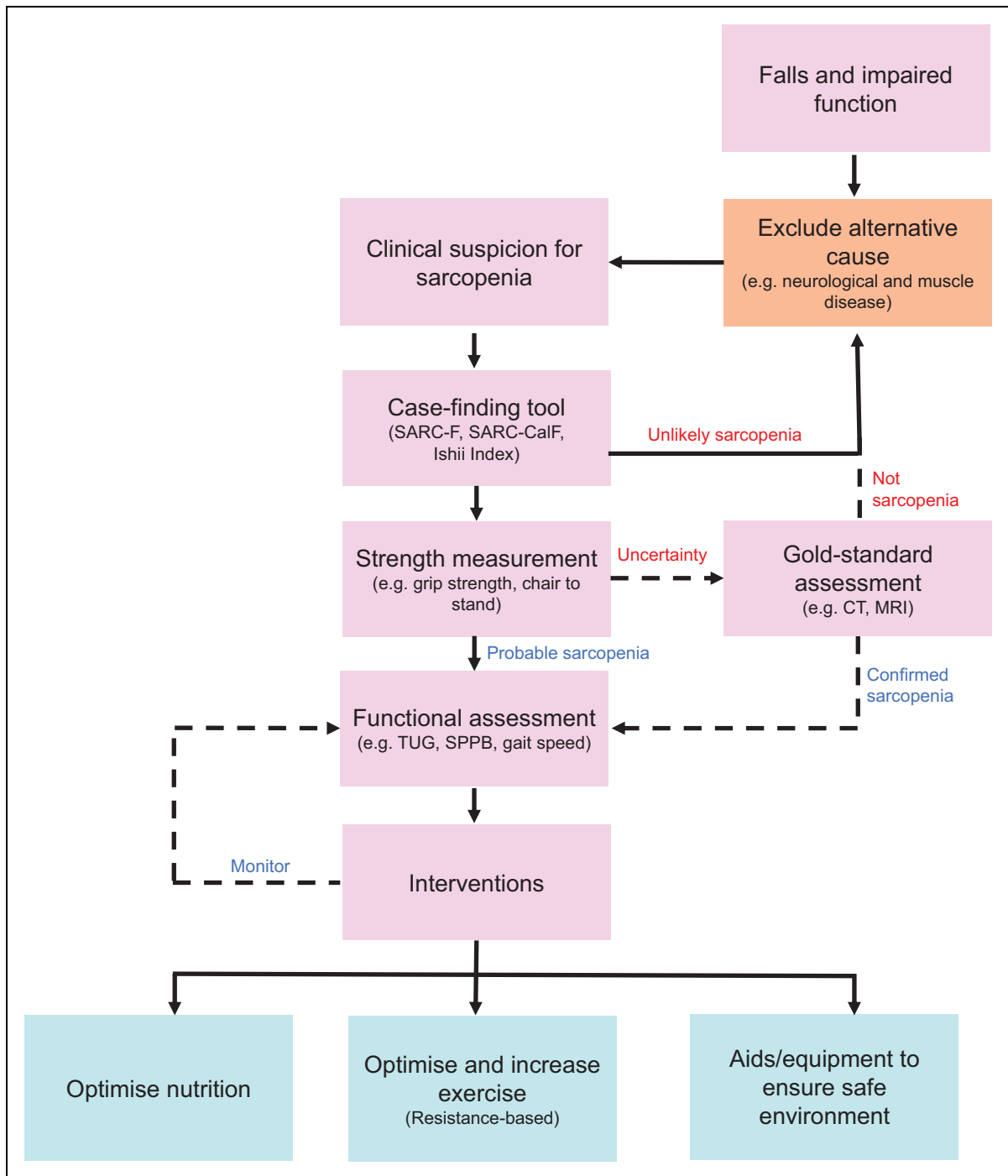
FIGURE 1. Clinical approach to sarcopenia. Proposed updated pathway for the screening, diagnosis, and management of sarcopenia. The algorithm is based off the EWGSOP Find-Assess-Confirm-Severity pathway [7], however, has been updated to include additional case-finding tools and relevant interventions.

disrupt mitochondrial function and induce muscle atrophy [47,48]. In turn, damaged mitochondria from skeletal muscle are thought to perpetuate chronic inflammation by releasing cellular constituents such as mitochondrial DNA (mtDNA), caspases and ROS. These released constituents are thought to act as damage-associated-molecular-

patterns, triggering an innate immune response [49,50].

This relationship is exacerbated in chronic disease states, where inflammation increases above normal age-related levels, such as chronic kidney disease (CKD). Sarcopenia is more common in CKD and is strongly associated with increased intramuscular ROS,

IL-6 and TNF, as well as more renal-specific mediators, including uremic toxins and angiotensin-II [51–53]. The destructive nature of chronically elevated inflammatory mediators is demonstrated across most inflammatory muscle diseases. For example, TNF, IL-6 and IL-1 are heavily implicated in the pathogenesis of Immune-Mediated Necrotising Myopathy [54], while IFN-γ is a key inflammatory mediator implicated in Inclusion Body Myositis (IBM; [55]). IBM is the most common acquired myopathy in persons over 50 years and, in many ways, can be considered a model of accelerated sarcopenia. Indeed, IBM is often diagnosed late because weakness in affected individuals is commonly mistaken for 'normal' age-related muscle decline and/or sarcopenia. The histopathological features include chronic T cell-mediated inflammation associated with significant elevated levels of cytokines, abnormal protein homeostasis with accumulation of many proteins including TAR DNA-binding protein 43, -amyloid and Phos-Tau within skeletal muscle fibres, as well as the accumulation of mitochondrial mutations [56]. These pathological events lead to accelerated muscle atrophy, impaired regeneration, weakness, and disability. This is a stereotypical disease where chronic inflammation and oxidative stress (involving nitric oxide) damages mitochondria, releasing ROS and mtDNA into the cytoplasm, establishing a self-sustaining loop culminating in inflammation, cell stress, mitochondrial dysfunction, and ultimately, cell death [55].

MITOCHONDRIAL DYSFUNCTION AND OXIDATIVE STRESS

Almost all cells within the body rely on mitochondria to generate sufficient energy in the form of adenosine triphosphate (ATP) to support the metabolic demands of the cell. However, the function of the mitochondrion extends far beyond this, into waste removal, biosynthesis, and control of programmed cell death [57,58,59]. Disruption to any of these functions causes an imbalance in cell homeostasis and accumulation of dysfunctional mitochondria [60–64]. In ageing muscle, this accumulation is largely due to increased oxidative stress from the mitochondria. This is known as the mitochondrial theory of ageing [65]. While the generation of ROS at the electron transport chain is normal during ATP production, there is an increased proportion of ROS generated in ageing muscle, which perpetuates mitochondrial damage as well as damage to other cellular structures [65,66,67].

In addition, ineffective mitophagy increases dysfunctional mitochondria. Mitophagy is a specialised process of autophagy involving mitochondria-specific breakdown and component recycling. Multiple studies have demonstrated that altered mitophagy dynamics exist in aged skeletal muscle and that this correlates with accumulation of dysfunctional mitochondria, poorer muscle function and degeneration of the neuromuscular junction [60–64].

There are many localised consequences of dysfunctional mitochondria in skeletal muscle including reduced efficiency of ATP production, which amplify energy deficits [68]. However, these changes also contribute to increased local and systemic inflammation and metabolic dysregulation [66,67,68].

METABOLIC DYSREGULATION

The progressive loss of mitochondrial respiratory activity leads to an increased reliance on alternative metabolic pathways to metabolise substrates, (mainly glucose and free fatty acids), to meet cellular ATP demands. Alternative pathways include the hexosamine pathway and the glyoxalase pathway [69,70], leading to additional generation of ROS and advanced glycation end (AGE) products [71–74]. Circulating levels of AGEs are negatively associated with muscle mass, muscle strength and physical function in older adults and are therefore implicated in development of sarcopenia [75–78].

Excess substrates may also be stored if they cannot enter these alternative metabolic pathways. The major energy storage in the human body comprises glycogen, which has limited capacity [79–83], and triglycerides, which are stored primarily in adipose tissue depots [84], but also within various tissues including skeletal muscle [85]. Lipid infiltration into skeletal muscle is known as myosteatosis [84,86]. The direct association between myosteatosis and muscle atrophy has recently been demonstrated in mouse models, where local lipid accumulation was shown to trigger catabolic pathways [85], with this muscle atrophy exacerbated in older mice [87]. This age-related exaggeration is likely because myosteatosis perpetuates pathogenic processes already significant in sarcopenia, such as mitochondrial dysfunction, oxidative stress and chronic inflammation, hyperglycaemia, and insulin resistance [44,84,88,89].

Sarcopenic obesity refers to the coexistence of reduced skeletal muscle mass and function, and excess body fat as measured by body mass index or waist circumference [85,90▪,91▪▪]. Sarcopenic obesity has been reviewed extensively elsewhere [84,85,89,90▪,91▪▪,92▪] and thus will not be addressed in detail in this review. However, it is noted that this condition appears to have a unique pathophysiological process and risk profile that may not adhere to the general pathophysiological sequelae of sarcopenia in nonobese individuals [89,90▪].

MODERATING MUSCLE AGEING

Exercise is the only intervention shown to mediate age-related muscle atrophy, although nutrition and hormone replacement therapy (HRT) are likely to contribute.

EXERCISE

Exercise is the primary factor in protection against sarcopenia. It regulates mitochondrial function, dampens inflammation, and improves insulin sensitivity [93–96], and has recently been demonstrated to promote muscular antioxidant protein expression, which aids in the clearance of ROS [97]. Moreover, exercise stimulates muscle protein synthesis; even a few minutes per week of resistance-based exercise significantly affects muscle mass [98,99]. Harper *et al.* [65] concluded that a program incorporating moderate-to-high repetition *resistance* training followed by moderate-to-high intensity *endurance* training would best prevent the development of mitochondrial dysfunction and associated functional decline.

There is a natural decline in habitual physical activity in older persons. This is likely multifactorial and associated with increased musculoskeletal pain, muscle atrophy and general fatigue. Exercise intensity and volume are important to mitigate the changes associated with sarcopenia. Therefore, patients may require a multipronged approach to an exercise program that includes appropriate pain management, education and specialised supervision. Ultimately high repetition (lower loading) resistance training is the most effective for protecting against morbidity associated with muscle ageing [65,100,101].

NUTRITION AND SUPPLEMENTATION

Furthermore, clinicians need to consider targeted nutritional programs in those at risk of or who have already developed sarcopenia. Adding protein to resistance-based exercise training has shown mixed results. It appears that protein supplementation has limited benefit for older adults with adequate protein intake, but further studies are required to determine benefit in specific populations, particularly those in care, the very frail or with inadequate protein intake [102]. The Exercise and Nutrition for Healthy AgeiNg trial is an ongoing five-arm triple-blinded randomised controlled trial in sarcopenic older adults, to assess the combined anabolic interventions of protein, omega-3-supplementation, and exercise on physical performance, compared with placebo or single interventions (NCT 03649698).

Diets with a high inflammatory index have been associated with reduced muscle mass, muscle strength and gait speed and higher systemic inflammation, however the benefits of an anti-inflammatory diet are yet to be established [103,104]. There has also been suggestion that antioxidant supplementation may enhance the positive effect of exercise on mitochondrial health, although this has not been consistently demonstrated [105].

HORMONE REPLACEMENT

Some hormones are integral for the growth and maintenance of skeletal muscle, including insulin-like growth factor-1, dehydroepiandrosterone, testosterone and oestrogen, all of which decrease with increasing age [106] and may contribute to sarcopenia and frailty [107]. Men with low free testosterone are 68% more likely to develop mobility limitation than men with normal free testosterone [108]. Therefore, replacing these hormones may be a reasonable strategy to mitigate muscle ageing. For example, several studies have shown that oestrogen HRT prevents reduction in skeletal muscle mass and strength in menopausal women (reviewed in [109]), and that this effect can have lasting effects on maintenance of muscle quantity and quality, even years after cessation of therapy [110]. In addition, testosterone administration has been shown to increase maximal voluntary contraction [111], inhibit adipogenesis and reduce inflammation (reviewed in [107]).

CONCLUDING REMARKS

Muscle ageing and sarcopenia are becoming increasingly significant global issues with an ageing population. Achieving a consensus definition on sarcopenia is an important next step in this area to allow data comparison across regions and enhance our understanding of this condition. From a clinical perspective, early suspicion and intervention in age-related muscle atrophy is probably more important than defining the condition or its severity. Muscle ageing is inevitable, and everyone would benefit from an appropriate and longstanding exercise program, regardless of whether criteria for a diagnosis of sarcopenia has been met. These programs should involve progressive, resistance-based exercise with possible additional nutritional supplementation, particularly if daily protein requirements are not being met. HRT may also be considered where clinically appropriate.

Future directions in muscle ageing revolve largely around teasing out key players in its aetiopathogenesis. Broadly, it is understood that chronic

inflammation, mitochondrial dysfunction and metabolic dysregulation perpetuate each other, resulting in age-related muscle atrophy, with many other contributing factors.

Acknowledgements

Financial support and sponsorship

Conflicts of interest

There are no conflicts of interest.

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