Sarcopenia and the syndrome of frailty

Ajay Kumar Gupta[a], Siddhartha Mishra[b]

[a]Department of Pharmacology, AFMC, [b]Department of Internal Medicine, CH(SC), Pune, Maharashtra, India

Correspondence to Ajay Kumar Gupta, MD, Department of Pharmacology, AFMC, Pune 4110040, Maharashtra, India
Tel: +91-020-26360123; fax: +91-020-26334236
e-mail: ajayneera2007@rediffmail.com

Received 28 September 2015
Accepted 20 October 2015

The Egyptian Society of Internal Medicine
2016, 28:133–139

Sarcopenia is the process of loss of body mass, specifically the musculoskeletal tissue, with age, which ultimately leads to a syndrome of clinical entity poorly defined as frailty. It is probably as old as humanity itself. Functionally, frailty is described as a syndrome characterized by a progressive decrease in the body's reserve and declining resistance to stressors, possibly because of declining capacity of multiple physiologic systems resulting in higher vulnerability morbidity and mortality. Ayurveda also mentions morbidity occurring with advancing age and various options for its management. Elixirs are recommended in Ayurveda, popularly called 'rasayana', for recovery from the symptoms of frailty. Worldwide, because of the wide demographic profile, the process of ageing exerts its effects on geriatric populations at different ages. Europeans were the first to paraphrase the word frailty for the ageing process. With better medical care and nutrition, a substantial subset of populations survives longer than 60 years or longer worldwide. The most relevant aspect of the recognition of syndrome of frailty is that the process is, to some extent, reversible, provided that adequate attention is paid and a timely intervention is performed for the needy subset of population, which is likely to improve the quality of life markedly, besides resulting in an increased life span.

Keywords:
ageing, geriatric, osteoporosis

Egypt J Intern Med 28:133–139

1110-7782

Introduction

During the last half century, the average life span has increased by 20 years and is expected to increase by another 10 years. The global population of age above 65 years will grow from 443 million to 973 million between 2000 and 2030. The rapid increase in the elderly population as a result of this prolonged life expectancy has led to increased interest in geriatric medicine.

A progressive decrease in physiological reserves occurs with ageing. When a threshold of decline occurs across multiple organ systems, the syndrome of frailty occurs and as a consequence, frail elderly individuals have a higher susceptibility to stressors and are at high risk for functional deficits and comorbid disorders, possibly leading to hospitalization and death [1]. The phenotype of frailty is referred to as the frailty syndrome and is widely recognized in geriatric medical practice. Although frailty affects both musculoskeletal and nonmusculoskeletal systems, sarcopenia (affecting the muscular component) remains one of the major components of clinical frailty. Sarcopenia results in a decrease in aerobic capacity of about 10% per decade from the age of 25 to 30 years, because of which, in elderly individuals, activities of daily living will require efforts that are best of their physical capacity [1,2].

Interestingly, despite being a condition resulting in huge financial costs to the individual and state, sarcopenia does not have a broadly accepted clinical definition and there is no ICD-9 code for this diagnosis. Similarly, treatment guidelines have not yet been developed. As a result, it is an underdiagnosed and undertreated medical entity. With this review article, an attempt has been made to report on recent advancements in the definition and diagnostic criteria for the frailty syndrome and sarcopenia and practical guidelines for the prevention, diagnosis and treatment of both.

Before proceeding any further, it is important to keep in mind that the skeletal muscle has effects on a number of vital processes: first, it is responsible for locomotor function, and loss of muscle mass and quality results in weakness and reduced mobility, besides frequent falls and fractures of bones and joint dislocations. This is the largest reserve of protein in the body and provides a continuous supply of amino acids to maintain the rate of protein synthesis in other vital tissues during periods of stress, starvation and undernutrition. Skeletal muscle is the primary site of glucose disposal and diminished muscle mass plays a critical role in impaired glucose metabolism in patients with insulin resistance and type 2 diabetes. In addition, skeletal muscle is the major consumer of energy and contributor to the basal metabolic rate in the body and loss of muscle mass

is the primary cause of age-associated reduced basal metabolic rate and decreased energy needs [2].

Definition

The Greek term 'sarcopenia' (meaning 'sarx' for flesh and 'penia' for loss) describes the loss of muscle mass among older individuals [3]. By the 80th year of age, an average man will lose about 7 kg of muscle mass, whereas an average woman will lose 3.8 kg. This is associated with a reduction in the lower extremity strength of up to 50% by this age. Sarcopenia is thus an age-related loss of skeletal muscle mass quality and function and as described in the previous paragraph, physiological dysfunction is noticeable.

The European Working Group on Sarcopenia in Older People (EWGSOP) defines it as a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes. Thus, it has been defined as a relative appendicular skeletal muscle mass [muscle mass of arms and legs (kg) divided by height^2 (m^2)] less than two standard deviations below the mean of a same-sex young healthy reference [1].

However, the latest proposal by Cruz-Jentoft and colleagues is to consider sarcopenia as a 'geriatric syndrome'. Geriatric syndromes manifest by phenotypic characteristics at the physical, morphologic and biochemical levels of an individual as determined by the genotype and the environment. Moreover, the term 'geriatric syndrome' is now used for conditions that are common in old age, which do not fit in traditional 'disease categories' but result from the accumulated effects of multiple predisposing factors that may be precipitated from an acute insult, often associated with multiple comorbidities and poor outcomes such as increased disabilities and decreased quality of life. They are usually the presenting manifestations of multiple underlying diseases and are treatable using a multidisciplinary approach.

Typical 'geriatric syndromes' are delirium, dementia, depression, dizziness, failure to thrive, malnutrition, falls, functional dependence and gait disorders.

Aetiopathogenesis

Various risk factors have been identified. Constitutional factors such as advanced age, low birth weight, several genetic aspects, subclinical inflammation, hormonal dysregulation involving the growth hormone (GH), testosterone, insulin-like growth factor 1 (IGF-1) and certain habits such as decreased food intake (specifically protein intake), minimal physical exercise in one's daily life, use of addictives such as alcohol and tobacco, prolonged bed rest, immobility and chronic debilitating health conditions, poor nutrition, poor social life, lack of family support and care can all lead to the development of sarcopenia (Fig. 1).

Anabolic hormones

Testosterone exerts important anabolic effects on muscle. Circulating androgen concentrations decrease in men with increasing age and there is increasing evidence that this may contribute towards the development of sarcopenia and decrease in functional status that may occur with ageing. Serum testosterone level is also related to the appendicular skeletal muscle mass in older women.

Physical activity

Muscle disuse, especially in elderly individuals, causes a major decrease in muscle size and strength, even with adequate protein and energy intake. Prevalence is also sex dependent and increases with age, from less than 5% between 50 and 65 years of age up to 50% in men older than 80 years of age and 30% in women.

Nutrition

Impaired nutritional intake may also lead to the development of sarcopenia. Helms *et al.* [4] have shown that eating half the recommended dietary allowance of protein 1.0 g/kg/day causes a significant decrease in the strength and body cell mass in postmenopausal women.

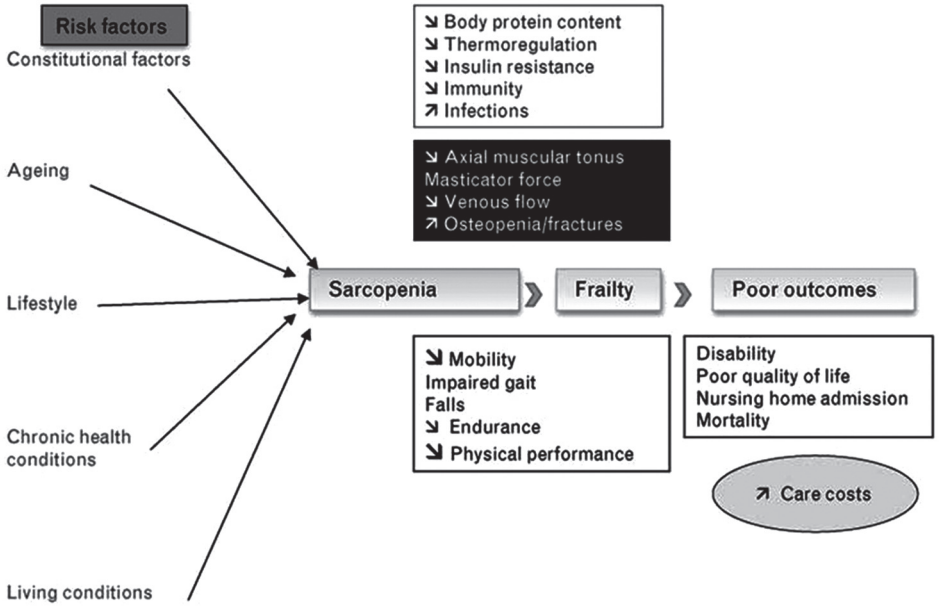
Cytokines

Cytokines may also be important in the development of sarcopenia. Older women with higher interleukin-6 levels were recently shown to be at an increased risk of developing mobility disability, impairment in activities of daily living and steeper decrease in walking ability than those with lower interleukin-6 levels, and this may be partially explained by a parallel decline in muscle strength.

Pathological changes in muscle

Qualitative and quantitative changes in muscle are considered to be central to the development of sarcopenia. A decrease in muscle mass, muscle strength and muscle efficiency (i.e. muscle strength per unit of muscle mass) may be observed with increasing age; disproportionate atrophy of type IIa (fast-twitch) muscle fibres, decrease in total muscle fitness, decrease in muscle protein synthesis, unclear separation between slow and fast fibres, decreased functional units, increased irregularity of muscle unit firing and loss of α-motor neuron input to muscle may also occur [2].

Figure 1



Adapted from Sarcopenia as a geriatric syndrome [5]. Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

Several mechanisms potentially link obesity and sarcopenia. Obese individuals tend to be less physically active and have lower levels of anabolic hormones such as testosterone, GH and IGF-1. They also have higher levels of proinflammatory cytokines and adipokines (leptin, adiponectin and resistin) that induce chronic inflammation, which may trigger insulin resistance. All these conditions may lead to 'sarcopenic obesity'.

Consequences

As proposed by Fried *et al.*, sarcopenia plays a crucial aetiological role in the frailty process itself, also being a key player in its latent phase and explaining many aspects of the frailty status. Sarcopenia leads, through frailty, to severe effects such as repeated falls, multiple and various trauma, functional decline, disability, multiple emergency room visits and hospital admissions, cross-infections, loss of independence, nursing home admission, poor quality of life and ultimately a painful death.

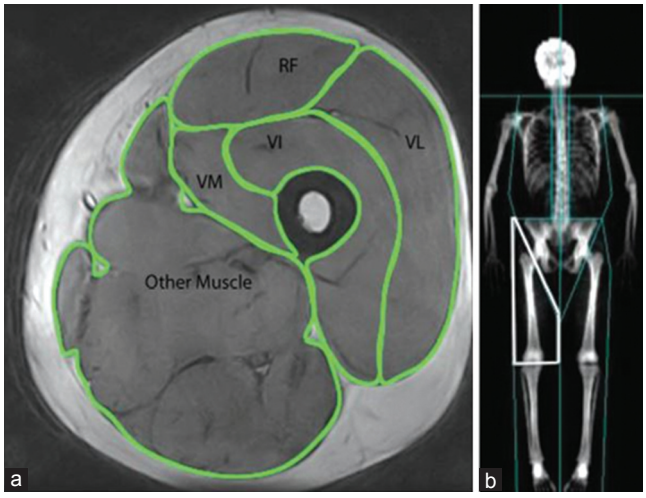
An approach to the diagnosis of sarcopenia

The clinical suspicion of sarcopenia on the basis of assessment of multiple risk factors is corroborated by muscle weakness, early fatigue and poor endurance, associated with reduced walking speed, impaired mobility, inabilities in activities of daily activities. Sarcopenia may be evaluated using the three measures defined by EWGSOP: loss of muscle mass, with decreased strength and/or physical performance. Strength can be measured using hand-grip strength. Physical performance can be measured using a variety of tests: gait speed, the long corridor walk test, the 6-minute walking test, the timed get-up-and-go test and the stair-climb test. Mortality is strongly associated with habitual gait speed.

Pahor *et al.* suggest assessing muscle quality using a combined measure of dual-energy X-ray absorptiometry (DEXA) muscle mass and grip strength as these methods are valid, reliable and specific to skeletal muscle, predictive of future health events, noninvasive, practical, low cost and widely accessible. Maden-Wilkinson *et al.* have used computing imaging softwares for the quadriceps group and other thigh muscles (adductors, hamstrings and abductors) to determine the cross-sectional area of each of the four muscles in each slice (Fig. 2(a)) Total thigh volume was further estimated by summation of the cross-sectional area of each head of the individual quadriceps muscles across the fixed length on the femur and further converted into absolute mass by multiplying by 1.04 g/cm^3 (the density of muscle tissue). DEXA was also used to provide estimations of dominant leg lean mass, fat mass and bone mineral content total body using computer software (Fig. 2(b)).

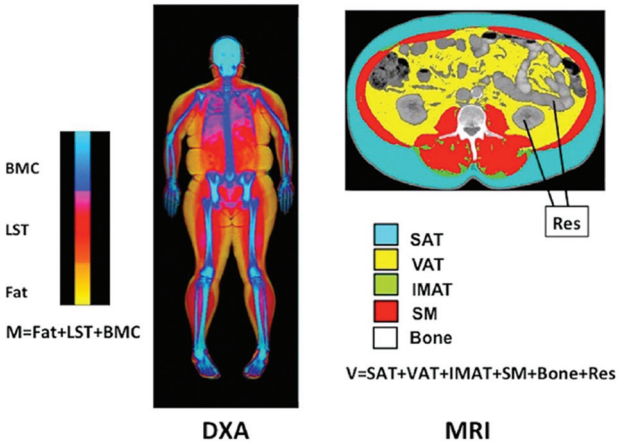
Prado *et al.* suggested the use of MRI, which relies on nonionizing radiation for the safety of the patient. The MRI technique has been used widely to evaluate

Figure 2



(a) Representative MRI of the thigh with rectus femoris (RF), vastus lateralis (VL), vastus intermedius (VI) and vastus medialis (VM) labelled and highlighted. (b) Diagram showing the region of interest in dual-energy X-ray absorptiometry (DEXA) scans highlighted (adapted from *http://www.ismni.org/jmni/pdf/53/07DEGENS.pdf*). Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

Figure 3



Selected body composition components measured by dual-energy X-ray absorptiometry (DEXA; left) and MRI (right). Body mass (M) and volume (V) represent the sum of these components for DEXA and MRI, respectively. BMC, bone mineral content; IMAT, intermuscular adipose tissue; LST, lean soft tissue; Res, residual mass (organs and tissues remaining after subtracting skeletal muscle, bone, and adipose tissue volumes); SAT, subcutaneous adipose tissue; SM, skeletal muscle; VAT, visceral adipose tissue.

the quantity and distribution of adipose tissue as well as skeletal muscle mass. Ideally, whole-body imaging provides absolute information; most studies suggest a single MRI technique protocol, especially at the mid-thigh level (Fig. 3).

A simple way to start the investigation of suspected sarcopenia may be measurement of walking (gait) speed or finding out if an individual can sit and stand up from chair five times at the point of initial assessment. If any of these tests is positive (walking speed <0.8 m/s, inability to stand up from a chair), assessment of grip strength and a bioelectrical impedance analysis may easily available methods to evaluate the probability of sarcopenia by measuring the ratio between lean body and fat body (Figs. 4 and 5). Further investigations such as DEXA may be needed considering that the gold-standard measure of the ratio of lean/fat body mass is computed tomography/MRI.

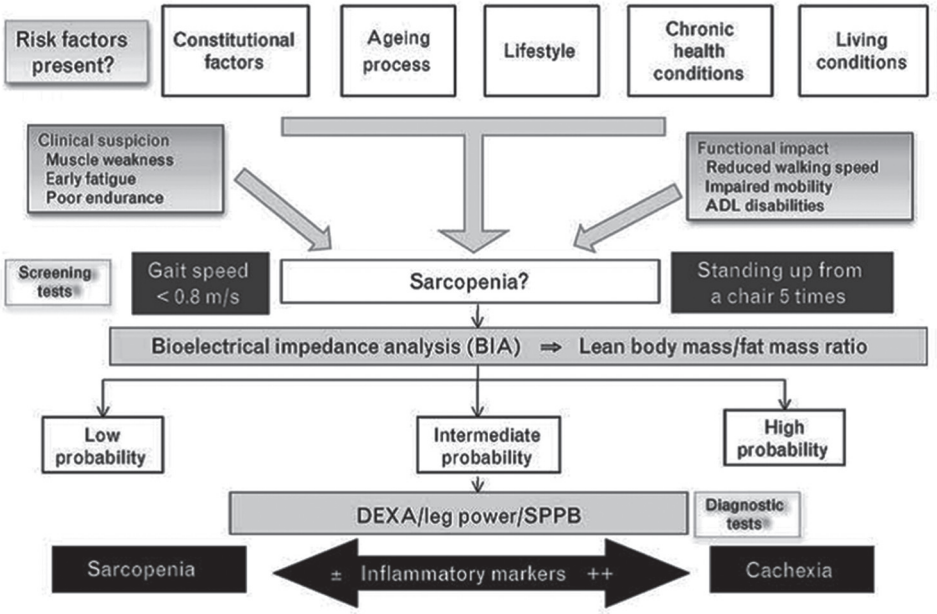
The syndrome of frailty

Normal ageing is accompanied by a number of physiologic changes. When this decline in physiologic reserves reaches across multiple organ systems, a certain threshold is arrived at when any stressor can lead to a sudden decline in functional status and comorbid features. Fried *et al.* proposed a phenotypic definition of frailty that consists of five components: unintentional weight loss, weakness, slowness, self-reported exhaustion (poor endurance) and low physical activity. An individual is classified as frail if at least three of these criteria are fulfilled. Those fulfilling one or two criteria are classified as prefrail and those fulfilling no criteria are classified as robust [1].

Muscle strength was assessed as maximal grip strength (in kilograms) in the dominant hand (average of three measures) using a hand-held dynamometer. Individuals had muscle weakness if their maximal grip strength was in the lowest quintile of the study population (adjusted for sex and BMI). Walking speed was specified as the time needed to walk 15 feet at a normal pace; slowness was defined as a value in the lowest quintile (adjusted for sex and standing height). Individuals had poor endurance (exhaustion) if they felt that everything they did was an effort. An affirmative answer was indicative of decreased maximal oxygen consumption (VO_2 max). Physical activity was estimated by questioning about 18 leisure activities during the last week. A weighted score of kilocalories expended per week was calculated on the basis of these questions. The lowest quintile of physical activity was identified for each sex and defined as low physical activity.

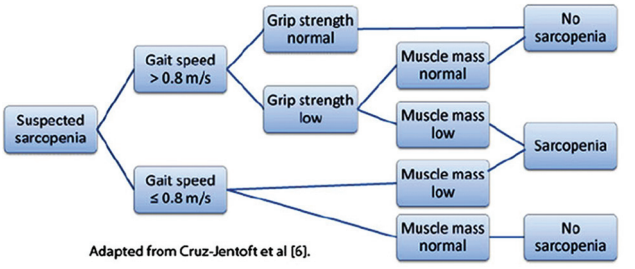
Recently, the International Academy of Nutrition, Health, and Aging (IANA) proposed the FRAIL scale [6], which combines elements of the frailty phenotype with the presence of comorbid diseases. It comprises five domains: fatigue (defined as having less energy than in the past), resistance (defined as the inability to climb stairs), ambulation (defined as the inability to walk one block), number of illnesses

Figure 4



Adapted from Understanding sarcopenia as a geriatric syndrome [5]. Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

Figure 5



Screening process of sarcopenia.

(defined as more than five concurrent illnesses) and loss of weight (more than 5% in 1 year) [1].

Aetiopathogenesis

Potential determinants of the frailty syndrome induce a catabolic cascade that also affects other tissues and organs (e.g. skin atrophy, heart failure), in addition to weakened bones and reduced muscle strength.

(1) Higher levels of white blood cells, proinflammatory cytokines and C-reactive protein support a chronic low-grade inflammatory role in the development of sarcopenia as well as frailty. Inflammation may be the result of oxidative stress.
(2) Certain lifestyle and environmental factors increase the production of reactive oxygen species, which induces changes in gene expression and damage of DNA, proteins and lipids. This not only gives rise to more reactive oxygen species but also to inflammation and proliferation, necrosis and apoptosis at the cellular level, ultimately leading to frailty. In a recent study, cellular senescence and apoptosis were found to play a role in the development of frailty.
(3) Increased levels of biomarkers of coagulation and fibrinolysis have also been considered in the pathophysiology of frailty. Indeed, significantly higher levels of d-dimer and factor VIII have been observed in frail elderly individuals and higher levels of d-dimer and tissue plasminogen activator increased the risk of incident frailty.
(4) Hormonal changes associated with sarcopenia may also play a role in the development of frailty.
(5) Frailty has also been linked to vitamin D deficiency. Low levels of vitamin D (20 ng/ml) are associated with higher odds of prevalent frailty and an increased risk of incident frailty. Low 25-OH-D may be associated with frailty through several biological pathways, including an effect on bone, muscle and the immune system. Besides its well-documented role in osteoporosis and fracture risk, vitamin D deficiency has been associated with low muscle mass and strength and an increased level of proinflammatory cytokines.
(6) Also, IGF-1 and insulin resistance may contribute towards frailty as frail elderly individuals have lower IGF-1 levels than nonfrail age-matched individuals.

Therapeutic approaches to musculoskeletal frailty [1,7,8]

Exercise therapy in frail elderly individuals had a positive impact on physical determinants (such as body composition and muscle function) and on functional ability (such as mobility and balance).

A combined exercise programme of long duration (5 months) performed three times a week for 30–45 min led to superior outcomes [7]. Numerous studies have indeed shown that, even in the elderly, progressive resistance training is an effective intervention for sarcopenia, significantly improving muscle strength, walking speed and physical activity. To improve muscle power, high-velocity progressive resistance training may be better than the traditional (low velocity) progressive resistance training.

An alternative to resistance training is whole-body vibration training, during which the patient stands on a platform that generates vertical sinusoidal vibrations. These mechanical stimuli activate the muscle spindles, which activates the alpha motor neurons and initiates muscle contraction. Similar to resistance training, vibration training increases both muscle strength and muscle mass. In addition, physical exercise training may also have an effect on bone, even in the elderly [9].

Androgen therapy (testosterone replacement) may also have a beneficial effect in frail elderly individuals by improving muscle mass and strength and BMD. In a meta-analysis of the adverse effects of testosterone therapy in adult men, there was no significant effect on prostate and cardiovascular outcomes, although further studies are required.

Although the association between vitamin D supplementation and an improvement in physical performance remains controversial, there is increasing evidence that a daily dose of 700–1000 IU vitamin D significantly increases muscle strength in elderly individuals with vitamin D deficiency, with a reduced risk of falls. In combination with a daily dose of 1000–1200 mg of elementary calcium, vitamin D also reverses age-associated secondary hyperparathyroidism. This not only counteracts the negative effect of parathormone on muscle but also that on bone, with a resultant beneficial effect on BMD [10,11].

The use of GH is not recommended in this population because of the adverse effects. An alternative therapy may be treatment with growth hormone secretagogues, which regulate the secretion of GH and usually result in fewer adverse effects. Oral growth hormone secretagogues have been developed that significantly increased muscle mass and in one trial, physical performance also improved.

Frail elderly individuals benefit most from osteoporosis treatment. Antiresorptive or anabolic therapy, independent of age, protects against fractures and this protection increases with age. Thus, for every avoided fracture, elderly individuals have greater quality of life [12].

SARMS (nonsteroidal selective androgen receptor modulators, inhibitors of myostatin, ACE inhibiters, eicosapentaenoic acid and IGF-1) are potentially useful for the frail population, but further trials are ongoing to confirm their beneficial effects [13,14].

Conclusion

The frailty syndrome requires a more holistic approach of early detection and management. In our ageing population, it will be a major challenge to offer comprehensive tailor-made care to frail elderly individuals to protect their dignity, quality of life and self-esteem, and to prevent disease complications at an advanced age. This will only be possible if we identify frail elderly individuals by focusing on functional deficits and comorbidity. A comprehensive geriatric assessment enables such a systematic screening for frail elderly individuals in our day-to-day general medical practice.

Summary

Defining sarcopenia as a geriatric syndrome can help us to understand its complex pathophysiology and consequences. Early recognition of the five components of frailty is pertinent and includes unintentional weight loss, weakness, slowness, self-reported exhaustion (poor endurance) and low physical activity. Management tools for the frailty syndrome and sarcopenia include assessment of muscle strength, muscle mass and physical performance (gait speed, five time stands from a chair and grip strength). The ultimate goal of management is to identify lifestyle and treatment strategies that can prevent or delay the onset of the frailty syndrome [15,16].

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Gielen E, Vanderschueren S, O'Neill TW, *et al.* Musculoskeletal frailty: a geriatric syndrome at the core of fracture occurrence in older age. Calcif Tissue Int 2012; **91**:161–177.

2 Cooper C, Dere W, Evans W, Kanis JA, Rizzoli R, Sayer AA, *et al*. Frailty and sarcopenia: definition and outcome parameters. Osteoporos Int 2012; **23**:1839–1848.

3 Cruz-Jentoft AJ. Sarcopenia: the newest geriatric syndrome? Hospital Universitario Ramón y Cajal, Madrid, Spain.

4 Helms ER, Aragon AA, Fitschen PJ. Evidence-based recommendations for natural bodybuilding contest preparation: nutrition and supplementation. Journal of the International Society of Sports Nutrition 2014; **11**:20.

5 Cruz-Jentoft AJ, Landi F, Topinková E, Michel JP. Understanding sarcopenia as a geriatric syndrome. Curr Opin Clin Nutr Metab Care. 2010; **13**:1-7.

6 Inouye SK, Studenski S, Tinetti ME, Kuchel GA. Geriatric syndromes: clinical, research, and policy implications of a core geriatric concept. J Am Geriatr Soc 2007; **55**:780–791.

7 Theou O, Stathokostas L, Roland KP, Jakobi JM, Patterson C Vandervoort AA, Jones GR. The effectiveness of exercise interventions for the management of frailty: a systematic review. J Aging Res 2011; **2011**:569194.

8 Cruz-Jentoft AJ, Michel J-P. *Is sarcopenia the best determinant of frailty? Promoting access to innovation and clinical research for frail old persons*. Athens, Greece:IAGG/WHO/SFGG Workshop; 2011.

9 Anker SD, Coats AJS, Morley JE. Evidence for partial pharmaceutical reversal of the cancer anorexia–cachexia syndrome: the case of anamorelin. J Cachexia Sarcopenia Muscle 2015; **6**: 275–277.

10 Stockton KA, Mengersen K, Paratz JD, Kandiah D, Bennell KL. Effect of vitamin D supplementation on muscle strength: a systematic review and meta-analysis. Osteoporos Int 2011; **22**:859–871.

11 Morley JE, von Haehling S, Anker SD, Vellas B. From sarcopenia to frailty: a road less traveled. J Cachexia Sarcopenia Muscle 2014; **5**:5–8.

12 Pötsch MS, Tschirner A, Palus S, von Haehling S, Doehner W, Beadle J, *et al*. The anabolic catabolic transforming agent (ACTA) espindolol increases muscle mass and decreases fat mass in old rats. J Cachexia Sarcopenia Muscle 2014; **5**:149–158.

13 Neves RX, Rosa-Neto JC, Yamashita AS, Matos-Neto EM, Riccardi DMR, Lira FS Jr, *et al*. White adipose tissue cells and the progression of cachexia: inflammatory pathways. J Cachexia Sarcopenia Muscle 2015; Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/jcsm.12041.

14 Mogi M, Kohara K, Nakaoka H, Kan-no H, Tsukuda K, Wang X-L, *et al*. Diabetic mice exhibited a peculiar alteration in body composition with exaggerated ectopic fat deposition after muscle injury due to anomalous cell differentiation. J Cachexia Sarcopenia Muscle 2015; Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/jcsm.12044.

15 Isidori AM, Giannetta E, Greco EA, Gianfrilli D, Bonifacio V,Isidori A, *et al*. Effects of testosterone on body composition, bone metabolism and serum lipid profile in middle-aged men: a meta-analysis. Clin Endicrinol 2005; **63**:280–293.

16 Rolland Y, Czerwinski S, Abella´n Van Khan G, *et al*. Sarcopenia: its assessment, etiology, pathogenesis, consequences and future perspectives. J Nutr Health Aging 2008; **12**:433–450.