Definition and Diagnosis of Sarcopenia

The term *sarcopenia* is a recently coined term, which originates from the Greek words *sarx*, meaning muscle, and *penia*, meaning loss. It was first demonstrated by Rosenberg [9] in 1989. Recently, the European Working Group on Sarcopenia in Older People (EWGSOP) published a useful guideline [8] in 2010. A similar guideline was published by the International Working Group on Sarcopenia (IWGS)[10]. In these guidelines, *sarcopenia* is defined as a progressive and generalized loss of muscle mass and low muscle function (strength or performance). Classification of sarcopenia by cause is also suggested in this guideline. 'Primary' sarcopenia is defined as when no other cause is evident but ageing itself. Sarcopenia can be considered 'secondary' when one or more other causes are evident. Because this classification is preliminary one, the study comparing each type of sarcopenia does not exist, so the evidence for specific treatment for primary or secondary was not established yet. Figure 1 shows the algorithm of diagnosing sarcopenia by EWGSOP. The cutoff values for grip strength and habitual gait speed (less than 0.8 m/s) have been used to assess muscle strength and performance loss. On the other hand, the IWGS guideline established a cutoff value for gait speed (less than 1.0 m/s) only. However, not only muscle mass loss but also muscle strength or performance loss is mandatory to diagnose sarcopenia.

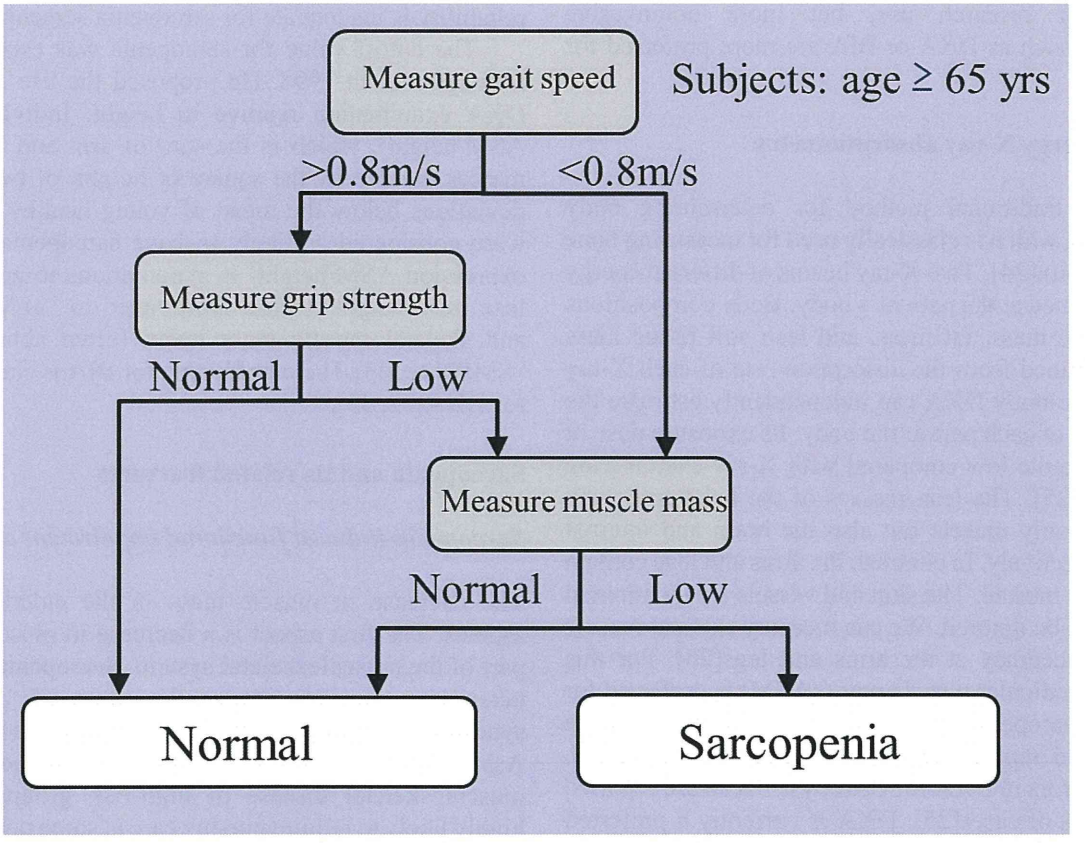

Figure 1. Recommended algorithm for diagnosing sarcopenia from EWGSOP (ref.8, partly modified from original)

Measuring techniques for muscle mass

In general, maximum muscle mass is observed between the ages of 20 and 30 years in men and women, and muscle mass gradually decreases with age [11-14]. After the age of 45 years, 0.3% of muscle mass is lost from the total body weight annually [15]. Three major methods are used for evaluating muscle volume, namely (1) analysis of cross-sectional area (CSA) by magnetic resonance imaging or computed tomographic (CT) scanning, (2) dual-energy X-ray absorptiometry (DXA), and (3) bioelectrical impedance analysis (BIA).

(1) Cross-sectional area

CSA directly reflects the muscle mass of a specific part of the body, and is considered one of the most accurate measuring methods. The midthigh muscle is the most preferred part for CSA measurement; it is highly associated with lower extremity function [2, 16-20]. Greater psoas muscle, lumbar paraspinal muscles, and rectus abdominis muscle are also often used because they can be evaluated simultaneously through abdominal examination by CT scan; thus, they are mainly used for evaluating sarcopenia in patients with gastrointestinal disease[21-23]. However, the use of the CSA has some limitations. For diagnosing sarcopenia, the cutoff value from the normal young mean has not been established yet. Other demerits for CSA are less accessibility, high cost, and radiation exposure (CT scan). CSA is the criterion standard for research use, but more noninvasive alternatives such as DXA or BIA are more preferred for clinical use.

(2) Dual-energy X-ray absorptiometry

DXA is a traditional method for determining body composition, which is classically used for measuring bone mineral density[24]. Two X-ray beams of different energy levels are aimed at the patient's body. Body compositions such as bone mass, fat mass, and lean soft tissue mass were determined from the absorption rate of each X-ray beam. Whole-body DXA can independently estimate the composition of each part of the body. Its exposure dose of radiation is quite low compared with X-ray examination or CT scan[25]. The lean masses of the head and trunk contain not only muscle but also the brain and internal organs, respectively. In contrast, the arms and legs contain only skeletal muscle. The skin and vessels are so minimal that they can be ignored. We can measure skeletal muscle mass with accuracy at the arms and legs[26]. For this reason, appendicular muscle mass (ASM) is preferred for evaluating sarcopenia by DXA [5, 27]. DXA has adequate precision and reproducibility compared with CSA[17]. Technical errors in DXA for CSA by CT scan are reported in only 2.5% of cases[25]. DXA is currently a preferred method for research and clinical use.

(3) Bioelectrical impedance analysis

BIA also is a noninvasive and traditional method for measuring body composition [28, 29]. Electrodes are attached to various parts of the body, and a small electric signal is circulated. BIA measures the impedance or resistance of muscle and fat tissues and estimates tissue content and composition. Modern BIA can separately measure each part of the body. The best feature of BIA is the portability of the equipment used, making it suitable for epidemiological examination for community-dwelling people [30, 31]. The validity of BIA, however, is not ascertained for the population whose hydration status alters with edematous disease[15], such as heart failure, renal failure, and lymphedema. BIA is regarded as an accurate alternative for epidemiological and clinical uses [32-34].

Some other noninvasive methods have been developed. In particular, ultrasonography can investigate muscle thickness (muscle volume) [35] and muscle echo intensity (muscle quality) [36-39] at one time. Ultrasonography is a potentially useful method for evaluating sarcopenia. Anthropometric measurements such as calf circumference are traditional and convenient methods of measuring skeletal muscle mass, although they are easily influenced by subcutaneous fat and their reliability is inadequate for sarcopenia screening [40].

The cutoff value for sarcopenia was established by Baumgartner in 1998. He proposed the use ASM from DXA examination relative to height. Individuals with ASM/height^2, which is the sum of arm and leg muscle masses divided by the square of height, of two standard deviations below the mean of young healthy volunteers were considered as likely to have sarcopenia [11]. The expression ASM/height^2 is synonymous to appendicular lean mass/height^2 (often abbreviated to "aLM/h^2") [41] and skeletal muscle mass index (often abbreviated to "SMI")[42, 43].The cutoff value for BIA is similar to that for DXA[32, 33].

Sarcopenia and its related fractures

Sarcopenia-induced functional impairment and frailty

The decrease in muscle mass in the elderly has two aspects. The first aspect is a decrease in muscle mass as part of the musculoskeletal system. Sarcopenia should be taken into consideration as the cause of "locomotive syndrome", which is defined by the Japanese Orthopedic Association (JOA) as a condition in people with musculoskeletal disease in high-risk groups who are highly likely to require nursing care at some point [44-49], as well as "musculoskeletal ambulation disability symptom complex," condition in which aging causes a reduced capacity to maintain balance and a decrease in mobility and walking ability [50]. For example, an 80 year-old female who was injured at home and developed a hip fracture (Figure 2) had a standing height of 149 cm, a body weight of 32 kg, and an ASM/height^2 of 4.8 kg/m^2, and the fracture was diagnosed as a complication of sarcopenia. After surgery, the patient was capable of walking with support and was discharged from the hospital to a nursing home [51]. It is easily imaginable that

the risk of osteoporotic fracture is higher in elderly individuals with sarcopenia.

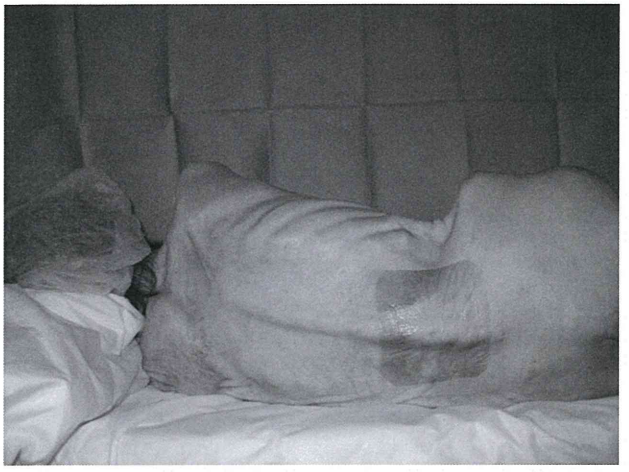

Figure 2. 80 year-old woman with a hip fracture lying on operation table. Coexisting severe sarcopenia was pointed out.

The second aspect of the disorder is sarcopenia as a systemic disease. Skeletal muscles are distributed throughout the musculoskeletal system as well as in organs throughout the body. Muscle weakness in the pelvic floor muscle group causes urinary incontinence [52], reduces the ability to perform activities of daily living (ADL) [53], and may increase the risk of urinary tract infections in the elderly. Understandably, dysfunction of the respiratory muscles increases the risk of aspiration and aspiration pneumonia [54, 55]. Decreased masticatory muscle force and weak swallowing function lead to malnutrition [56-60]. The incidence of infections is known to be significantly higher in patients diagnosed with sarcopenia and hospitalized in geriatric wards [61]. In addition, patients with sarcopenia have been reported to have higher HbA1c levels and be at risk of developing diabetes [62-64]. Although sarcopenia and diabetes are seemingly unrelated, muscles are not only responsible for body movements but are also the organs that account for the majority of the body's glucose metabolism [65]. A decrease in muscle mass causes decreased insulin sensitivity and is a risk factor for diabetes and eventually cardiovascular diseases [13, 66]. This disorder has also recently been reported to affect the mortality of patients with liver cirrhosis[67], cancer[21, 68-70], and other systemic disease[19, 71, 72]. Thus, sarcopenia is also an important keyword in terms of frailty in the elderly.

Muscle mass and bone density

Reports have shown that sarcopenia is associated with decreased bone density. In a study conducted on 352 elderly individuals, Coin et al reported a positive correlation between bone density and muscle mass [73]. In a survey conducted on 600 patients aged 45–80 years, Wu et al. reported that sarcopenia was an independent risk factor for osteoporosis [74]. In other words, it can be said that "patients with less muscle mass have a low bone density." As shown in Figure 3, causes that are common to sarcopenia and osteoporosis, such as disuse, malnutrition, and vitamin D deficiency, lead to simultaneous loss of bone and bone strength with a decrease in muscle mass and a predisposition to falls [75]. These findings suggest that fractures are caused by a combination of osteoporosis and sarcopenia.

Sarcopenia and osteoporotic fractures

Osteoporotic fractures are rapidly increasing in incidence worldwide as the population ages [76]. According to a report published by JOA in 2009, approximately 180,000 hip fracture cases occur per year in Japan, and approximately 2 million vertebral fractures are reported per year [77]. According to a report published by the World Health Organization, hip fractures, which had an incidence of approximately 1.5 million cases per year worldwide in 1990, are expected to rise to 2.7 million cases annually in 2025 (World Health Organization. www.who.int/ageing/en/, accessed 30th, April/2009), and the majority of this increase is predicted to be due to an increase in the elderly population in Asian countries including Japan and China [78]. Osteoporotic fractures cause patients to fall into a bedridden state, severely impacting their ADLs and leading them to require nursing care. In other countries as well, social security costs associated with osteoporosis are increasing steadily [79]. In world wide fragile economic condition, the prevention of osteoporotic fractures through the early detection and treatment of sarcopenia could be an effective prescription for the use of limited social resources [80].

However, there have been only a limited number of reports on the realities pertaining to sarcopenia in patients with osteoporotic fractures [41, 81-83]. In our past study of 327 patients with hip fracture and 2511 outpatient controls, we found a higher prevalence of sarcopenia in patients with hip fractures and the presence of sarcopenia as an independent risk factor for a hip fracture [43].

Thus, sarcopenia is a potential risk factor for osteoporosis and subsequent fracture, and its management is the key to preventing osteoporotic fracture.

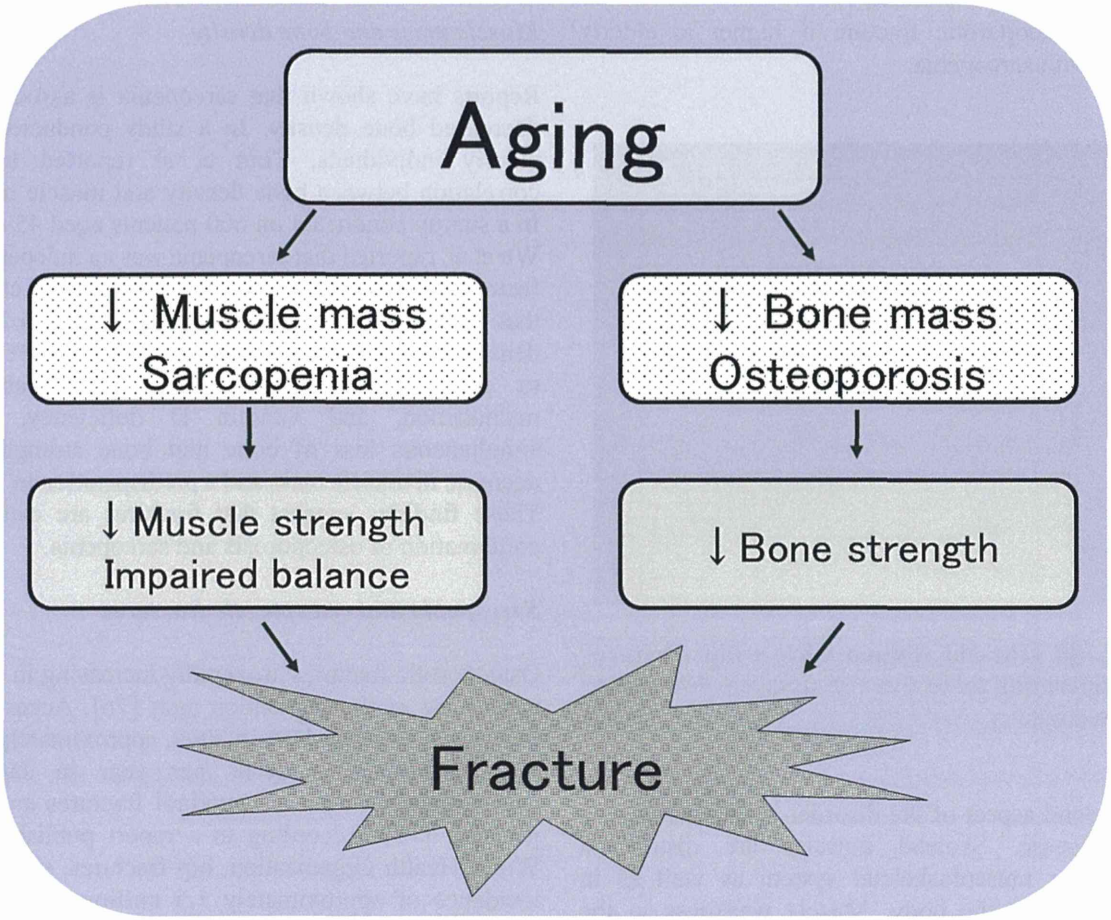

Figure 3. Relationship between sarcopenia, osteoporosis and fracture

Etiology of sarcopenia

The etiology of sarcopenia comprises a wide variety of causes that are involved in a complex manner, including the aforementioned disuse secondary to comorbidities (malnutrition[84], vitamin D deficiency [85], cerebral infarction, heart failure, and osteoarthritis [86], disuse [6, 87]) as well as age-related hormonal changes (involving testosterone [88-90], estrogen [91, 92], insulin-like growth factor 1 [93], and insulin[94]), apoptosis [95], denervation [96], and changes in inflammation and immunity involving interleukin (IL)-1, IL-6 and tumor necrosis factor-α[97], social causes, and mental causes such as decline in cognitive function [98] or decrease in social activity. It has been reported that in the histological examination of muscle fibers, type II muscle fibers (in other words, the so-called fast muscles) decrease with age, while type I muscle fibers (in other words, the so-called slow muscles) are preserved [99]. The decrease in fast muscles causes a delay in the muscle contraction reaction time; as a result, the righting reflex and the protective extension reflex are too late when the body vacillates, which may cause a fall.

Various types of signal transduction systems such as the Akt/mTOR signaling system and the Notch signaling system have recently been found to be involved in the molecular mechanisms of muscle fiber tissue regeneration [100-102]. Most of all, the Wnt/β-catenin signaling system is one of the signal transduction pathways involved in muscle regeneration.

Brack et al. reported that the serum of aged mice contained high levels of Wnt, that the substances that activated the Wnt signal in the serum caused abnormal fibrosis in the regenerating muscle, and that they were able to suppress fibrosis in aged mice by administering Dkk1, a Wnt inhibitor [103]. Naito et al. reported identifying the complement molecule C1q as a new Wnt signal activator, where the administration of C1q in young mice resulted in a decline in the regenerative capacity, whereas the administration of neutralizing antibodies against C1s resulted in an improvement of the age-related decline in the regenerative capacity [104]. The findings

showed that through Wnt signal activation, C1q caused a decline in regenerative capacity after skeletal muscle damage, which is one of the phenotypes of aging.

Interestingly, the Wnt/β-catenin signaling system is also involved in osteoblast differentiation. In rats, inhibition of the Wnt signaling system by using Dkk1 has been found to decrease bone mineral density, while anti-Dkk1 neutralizing antibody has been found to increase bone mineral density [105]. In humans as well, blood levels of DKK1 have been found in be elevated in patients with osteoporosis, although the causality remains unclear [106]. Activation of the Wnt signaling system through sclerostin antibody is viewed as a target in the prevention of osteoporotic fractures and the development of new drugs for the treatment of osteoporosis [107]. However, one should keep in mind that inhibiting Wnt signaling also has some negative aspects, especially with regard to muscle regeneration.

Much remains unknown in the molecular biological mechanism of muscle aging, and further elucidation in this area is desired.

Treating sarcopenia to prevent fractures

Multiple factors are involved in the pathogenesis of sarcopenia; therefore, the development of a specific treatment is quite difficult and evidence of effective treatment is limited. The therapeutic methods that are currently being attempted can be roughly classified as follows: (1) exercise therapy, (2) nutritional therapy, and (3) pharmacological treatment.

(1) Exercise therapy

There has been much evidence to support the fact that the so-called elderly "muscle training" is effective. In randomized controlled trials using high-intensity muscle strength training in 39 postmenopausal women, Nelson et al. reported improved muscle mass, muscle strength, and balance [108]. In a meta-analysis of a total of 1,328 patients in 49 studies consisting of randomized controlled trials on muscle strength training, Peterson et al. concluded that muscle strength training effectively increased muscle mass [109]. However, from the perspective of preventing osteoporotic fractures, performing exercise therapy directly may pose some issues. Patients with osteoporotic fractures often show various complications [110]. In addition to such a deterioration of mental function, patients with a high risk of fragile fracture are also affected by paralysis caused by the original cerebrovascular disease, locomotor disorders caused by osteoarthritis and complications of heart disease; moreover, their locomotor functions are believed to be lower than those of healthy subjects. When clinicians are managing more debilitated elderly patients with lower cognitive function and motor function, some improvement is needed when performing efficient muscle strength training while maintaining treatment compliance. Of course, for highly active elderly patients who are capable of performing exercise therapy by themselves, it can be said that exercise therapy is safe and highly effective for sarcopenia.

(2) Nutritional therapy

A study conducted on 403 institutionalized elderly women in Japan showed a high rate (49.1%) of vitamin D deficiency with serum $25(OH)D_3$ levels ≤ 16 ng/mL. Patients with a potential vitamin D insufficiency are believed to be numerous[111]. In addition to the role of vitamin D in increasing the bone mass, vitamin D receptors in striated muscles are also responsible for increasing muscle strength and muscle mass[85, 112]. The ingestion of a sufficient amount of vitamin D as a supplement is known to have a preventive effect against falls and fractures [85, 113-115]. Administration of vitamin D in the elderly may effectively treat sarcopenia and prevent osteoporotic fractures.

Most elderly subjects have insufficient caloric and protein intake, and the combination of exercise and dietary supplements containing amino acids and proteins may have an effect on sarcopenia. A short-term increase in muscle mass and muscle strength results, even in the elderly [109, 116]. Bonnefoy et al. examined the combination of dietary supplements and exercise by using a randomized controlled trial[117]. Dietary intervention based on nutritional supplement drinks containing proteins and exercise therapy was conducted for 9 months in 57 elderly women, and the effects were compared with those of a placebo. Forty-two participants completed the tests and showed improved muscle strength. However, it is important to note that the effect of dietary supplements on preventing osteoporotic fractures has not yet been clarified and that a decrease in adherence to nutritional therapy may occur in addition to reduced intake of regular food.

(3) Pharmacological treatment

Testosterone is a typical and strong anabolic hormone. A clinical trial examining testosterone replacement therapy was discontinued after 6 months due to an increasing number of cardiovascular events[118]. However, a significant increase in muscle strength was found in the testosterone-treated group.

Clenbuterol, which stimulates β2 sympathetic receptors and is used in the treatment of bronchial asthma, causes an increase in skeletal muscles by acting on the

PI3K/Akt signal system [119]. Clenbuterol is known to increase lean meat in pork, and abused by livestock industry in some countries. β stimulant is also a target drug in doping tests, so that athletes were warned not to eat pork in such countries(Telegraph Sport and Agencies. London 2012 Olympics: China bans athletes from eating meat for fear of ingesting banned substance clenbuterol. *The Telegraph*. United Kingdom: Telegraph Media Group Limited, 2012/03/02). Clenbuterol has previously been reported to cause an increase in muscle mass when administered to patients with heart failure[120]; however, a large-scale case-control study conducted in Denmark on patients using β-stimulants and those with osteoporotic fractures concluded that short-acting β-stimulants were a risk factor for osteoporotic fracture and that other types of β-stimulants had no effect on osteoporotic fractures[121].

Angiotensin-converting-enzyme (ACE) inhibitor, the strong candidates for the treatment of sarcopenia, was originally an anti-hypertensive medication that was used to prevent cardiovascular disease [122] and diabetic nephropathy [123]. ACE inhibitors have been used for a long time and their dosage, administration, and side effects are already known. ACE inhibiter is known to decrease muscle fibrosis in vitro through connective tissue growth factor (CTGF/CCN-2) [124]. Several clinical studies have reported that ACE inhibitor improved exercise performance in patients with heart failure [125-128]. Of course, these studies are biased towards improved heart function, but the direct effect on skeletal muscle tissue cannot be denied.

Other pharmacological therapies, such as growth hormone [129], insulin-like growth factor1 [130], and estrogen [92, 131, 132] have also been attempted, but no clear evidence has yet been found. The methods for increasing muscle mass are the same for young athletes and the elderly. Even in the elderly, muscle mass has been shown to increase upon engaging in muscle strength training (exercise therapy), ingesting proteins (nutritional therapy), and doping (pharmacological treatment). However, the fact that there is a need to continue treatment while maintaining safety and compliance in debilitated elderly subjects suffering from complications makes it difficult to treat sarcopenia.

Conclusion

Awareness of sarcopenia, specifically as a risk factor for falls and fractures in the elderly, is necessary. The treatment of sarcopenia will be an important element in the future prevention of fractures. However, evidence pertaining to the treatment of sarcopenia for the purpose of preventing fragile fractures remains insufficient. To reduce the number of patients suffering from osteoporotic fractures, there is an urgent need to further elucidate the facts about and develop therapeutic methods for sarcopenia.

Conflicts of interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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