Osteosarcopenia and frailty: a review

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ABSTRACT
Coexistence of osteoporosis and sarcopenia, known as osteosarcopenia, is well documented in frailty development in elderly people. Osteosarcopenia is associated with poor outcomes in terms of morbidity and mortality. This study aims to review the epidemiology and interactions of osteosarcopenia with frailty among older adults. Exercise seems to produce promising results in osteosarcopenic elderly people. Multidisciplinary assessment and management is the gold standard of care.

INTRODUCTION
With the growth of the ageing population, osteoporosis and sarcopenia are emerging. Osteoporosis is defined as low bone mass and micro-architectural deterioration of bone tissue. According to the World Health Organization (WHO) criteria, a t-score of bone mineral density of $<-2.5$ is considered as osteoporotic. In clinical settings, osteoporosis is defined by the WHO bone mineral density criteria or the occurrence of a fragility fracture. Osteoporosis leads to increased bone fragility and fracture risk. In Asian countries, the age-standardised annual incidence of hip fractures is higher than that in the USA and some European countries. Osteoporotic fractures in elderly people can result in hospitalisation, institutional care, impaired quality of life, disability, and even death.

Sarcopenia is defined as decreased muscle mass and physical performance and varies between countries (Table). The European Working Group on Sarcopenia in Older People (EWGSOP) defines sarcopenia as a syndrome characterised by progressive and generalised loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life, and high mortality. Diagnosis can be made by either dual-energy X-ray absorptiometry (DXA) or bioelectrical impedance analysis (BIA) and/or low muscle function/strength. The EWGSOP defines sarcopenia as a gait speed of $<0.8$ m/s with a height adjusted skeletal muscle mass of $<7.26$ kg/m$^2$ in men and $5.45$ kg/m$^2$ in women as measured by DXA or $<8.5$ kg/m$^2$ in men and $5.75$ kg/m$^2$ in women measured by BIA. A hand grip strength of $<30$ kg in men and $<20$ kg in women is considered at risk of sarcopenia. As body build differs between ethnic groups, the Asian Working Group for Sarcopenia (AWGS) defines sarcopenia as a height adjusted skeletal muscle mass of $<7$ kg/m$^2$ in men and $<5.4$ kg/m$^2$ in women measured by DXA and $<7$ kg/m$^2$ in men and $<5.7$ kg/m$^2$ in women measured by BIA, with a gait speed $<0.8$ m/s and a cut-off value of hand grip strength of $<26$ kg in men and $<18$ kg in women.

In addition, there is a subgroup of elderly people who have both conditions with a higher risk of falls and fracture than those with osteoporosis or sarcopenia alone. This is known as sarco-osteopenia and later as osteosarcopenia. Studies have reported the association between osteosarcopenia and poor outcomes.

Frailty is a major geriatric syndrome and is associated with greater prevalence of adverse health outcomes, including mortality, institutionalisation, falls, and recurrent hospitalisation. Frailty consists of multidimensional syndromes of loss of energy, physical activity, cognition, and health. There are many definitions of frailty. Fried et al defined frailty as the presence of three or more of the following syndromes: unintentional weight loss,
feeling exhaustion, weak grip strength, slow walking speed, and low physical activity. The Rockwood frailty index\textsuperscript{13} identifies frailty based on the summation of the number of impairments. Performance-based measurement\textsuperscript{18,19} defines frailty based on physical performance. Frailty is a predictor of osteoporotic fracture.\textsuperscript{20}

Epidemiology
Bone mass declines progressively after reaching its peak at the end of the third decade of life. It is estimated that between 30 to 70 years of age, there is a reduction of 30\% of bone mass.\textsuperscript{21,22} In Hong Kong, there is no universal screening for osteoporosis using DXA. Most existing data have been derived from Western populations. Based on the report from the National Health and Nutrition examination survey III,\textsuperscript{23} >40 million elderly people have osteoporosis and the lifetime risk of hip fracture in a 50-year-old Caucasian woman is around 15\% to 20\%.\textsuperscript{24} The risk increases exponentially with age. It is predicted that by 2050, the world incidence of hip fracture will exceed 21 million.\textsuperscript{25} In Australia, 12.9\% of men and 42.5\% of women aged >70 years have osteoporosis,\textsuperscript{26} whereas 66\% of all adults aged >50 years have either osteoporosis or osteopenia. A community survey in China reported that the prevalence of osteoporosis was 29.3\% for men and 46.1\% for women aged >65.\textsuperscript{27} Muscle mass peaks at age 25 years and until age 50 years there is a slight reduction of 5\% of muscle fibres. Then there is an annual loss of 1\% to 2\% of muscle fibres. At age 80 years, there is a loss of about 30\% of muscle mass.\textsuperscript{26,27} Muscle strength declines by 3\% after age 60 years.\textsuperscript{30} The prevalence of sarcopenia varies across different countries, depending on the definition, assessment method, cut-off values, and population. In Australia, based on the EWGSOP definition, the prevalence of sarcopenia among those aged >65 years is 6.4\% in men and 9.3\% in women.\textsuperscript{31} In Korea, based on the AWGS criteria, the prevalence in elderly women is up to 22.1\%.\textsuperscript{32} In China, based on the AWGS criteria, the prevalence in those aged >65 years is 26.2\% in men and 33.6\% in women.\textsuperscript{27} In Hong Kong, based on the EWGSOP criteria, a 4-year longitudinal study of 4000 community-dwelling adults aged >65 years reported that 9\% had sarcopenia and that there was a 3.1\% annual incidence of sarcopenia over the 4-year period.\textsuperscript{33} The prevalence of sarcopenia is expected to increase in ageing populations.

Osteosarcopenia is the presence of both osteoporosis and sarcopenia. It prevalence is high in both Western and Asian countries. In cross-sectional studies of elderly people with a history of falls in Australia, 40\% were osteosarcopenic.\textsuperscript{30,31}

| Table |
|------------------|-----------------|-----------------|-----------------|-----------------|
| Item                          | Asian Working Group for Sarcopenia | European Working Group on Sarcopenia in Older People | International Working Group on Sarcopenia | Foundation of National Institute of Health |
| Appendicular skeletal muscle mass/height, kg/m\(^2\) | Male ≤7 | ≤7.26 | ≤7.23 | - |
|                             | Female ≤5.4 | ≤5.5 | ≤5.67 | - |
| Skeletal muscle/height, kg/m\(^2\) | Male ≤7 | ≤8.87 | - | - |
|                             | Female ≤5.7 | ≤6.42 | - | - |
| Appendicular skeletal muscle mass/body mass index | Male - | - | - | ≤0.789 |
|                             | Female - | - | - | ≤0.512 |
| Hand grip strength, kg | Male ≤26 | ≤30 | - | ≥26 |
|                             | Female ≤18 | ≤20 | - | ≤16 |
| Walking speed, m/s | ≤0.8 | ≤0.8 | ≤1 | ≤0.8 |
A study in Italy found that, among elderly women with hip fractures, 58% were sarcopenic. In Hong Kong geriatric hip fracture patients, using the AWGS criteria, 83.6% of men and 67.7% of women have sarcopenia. Similarly, in Korea, using the AWGS definition, the prevalence of sarcopenia in men and women was 44.3% and 68.2%, respectively.

Frailty is associated with osteoporotic fractures. Based on the FRAIL scale, the prevalence of frail is 8.7% and that of pre-frail state is 63.1%, among healthy community-dwelling elderly people. The proportion of community-dwelling elderly people with frailty was 12.9% in Hong Kong and 12.8% in urban Beijing, using the Frailty index. It is estimated that 25% to 50% of older adults aged >85 years are frail. Frailty is caused by a complex mechanism of ageing that is determined by the underlying genetics, epigenetic, and environmental factors. Furthermore, other elements, such as sarcopenia, inflammation, malnutrition, co-morbidities, or hormonal insufficiency, can also lead to frailty in elderly people. The frailer individuals are more likely have osteoporotic fracture and at higher risk of fracture in future.

Interaction of osteosarcopenia and frailty

The combined effect of frailty and osteosarcopenia is detrimental to the well-being of elderly people. In the Chinese population, osteosarcopenia is present in 26.3% of men and 38.5% of women in the frail group, compared with only 6.6% of men and 1.9% of women who are robust. The hip fracture risk (hazard ratio, 1.4) and non-spine fracture risk (hazard ratio, 1.25) is higher in frail women than in robust women. A Canadian study reported a hazard ratio of 1.18 for hip fracture and 1.3 for clinical vertebral fracture for every 0.1 increase in the Frailty Index. The Frailty Index is significantly higher in women who had a major osteoporotic fracture than controls. This suggests that there is a greater deficit accumulation and acceleration of frailty level after a major fragility fracture. Investigation of the transition of frailty before and after a major osteoporotic fracture can serve as an indicator for treatment effects. The change of frailty state can be used to identify minimally important difference in fracture intervention study, taking into consideration the nature of frailty transition. Although frailty status is associated with osteoporotic fracture risk, it remains unknown whether frailty is a cause or a consequence of osteoporosis. Both conditions share similar biological pathways and risk factors (such as advancing age, low physical activity, weight loss, and cognitive decline), but one study did not find any association between frailty and osteoporosis.

Intervention

Frailty is a consequence of multi-organ problems in the elderly people. No single illness treatment can reduce the development of frailty in elderly people. A more holistic treatment should be used. Reduction of frailty severity and prevention of its occurrence benefits patients, their caregivers, and society.

Osteosarcopenia and frailty are inter-related; intervention on osteosarcopenia may help to prevent the occurrence of frailty and delay its progression. Interactions between muscle and bone are related to interactions among several organ systems. This muscle and bone relationship includes two factors: local control of muscle to bone, and systemic humoral interaction between muscle and bone. Osteosarcopenia may be affected by genetic factors, endocrine factors, and mechanical factors. The loss of muscle mass and muscle strength in the ageing process leads to structural changes in the micro-architecture of the bones, a reduction in bone mineral density, and a decline in bone quality. These skeletal and bone changes lead to a vicious cycle that accelerates frailty and physical disability. To prevent osteosarcopenia, identification and treatment of modifiable risk factors such as endocrine disorders and nutritional deficiency are fundamental. A healthy lifestyle, including regular physical activity and adequate nutrition intake, including calcium, vitamin D, and protein, can help to optimise the peak bone mass and maintain musculoskeletal health. A balanced diet with adequate protein intake is essential for stimulating muscle protein synthesis. Vitamin D is an important element for normal skeletal muscle development and aids in optimising muscle strength and performance.

Vitamin D and Calcium

A low vitamin D status is associated with weaker muscle strength, poor physical performance, and higher sarcopenic risk. Oral vitamin D supplementation of 700 to 800 IU/day has been shown to improve bone and muscle strength and functional status and reduce hip fracture risk, falls, and mortality, but the optimal intake of vitamin D dose...
is uncertain. The European society for clinical and economic aspects of osteoporosis and osteoarthritis (ESCEO) recommend a daily intake of vitamin D of 800 IU/day to maintain serum 25-hydroxyvitamin D level of >50 nmol/L with daily calcium intake of 1000 mg/day along with regular exercise 3 to 5 times per week in post-menopausal women for the prevention of age-related decline in musculoskeletal health.

**Protein**
Adequate protein intake has a potential therapeutic benefit for osteosarcopenic patients. Dietary protein exerts a direct effect on key regulatory protein and growth factors that are involved in muscle and bone health by increasing calcium absorption, suppressing parathyroid hormone, and increasing the production of IGF-1. In elderly people aged 70 to 79 years, consuming protein at 1.1 g/kg body weight per day results in less muscle loss at 3-year follow-up. The ESCEO recommends optimal dietary protein intake of 1 to 1.2 g/kg body weight per day with high-quality protein at 20 to 25 g at each main meal. The European Society for Clinical Nutrition and Metabolism (ESPEN) and the PROT-AGE study group also recommend the same amount of protein intake for healthy elderly people. For those who were at risk of malnutrition or malnourished, the recommended daily protein intake should be up to 1.2 to 1.5 g/kg body weight per day. The distribution of protein intake over the day may act as an important stimulant for postprandial muscle protein synthesis over a day.

**Pharmacotherapy**
Medications such as anti-resorptives and anabolic agents help prevent osteoporotic fracture. However, there is no evidence that these drugs have a positive effect on the muscles. There is no pharmacotherapy that has been proven to be of benefit to patients with sarcopenia. Angiotensin-converting enzyme inhibitors are suggested to prevent mitochondrial decline, improve endothelial function and muscle metabolism, but these are still in the experimental phase. Humanised myostatin antibody in a phase 2 randomised controlled trial has shown an increase in appendicular muscle mass and several performance-based measures than in placebo. However, more research is necessary to determine the effect of this anti-myostatin antibody on reducing the risk of falls and physical dependency and safety. Other pharmacological agents such as testosterone, growth hormone, and insulin-like growth factor 1 did not show clear evidence of benefits for the treatment of osteosarcopenia.

**Exercise**
Exercise, especially progressive resistance exercise, has been shown to be a stimulus for muscle protein synthesis with improvement in muscle strength and physical performance. A meta-analysis reported that an average of 20.5 weeks of resistance exercise could elicit an approximate 1 kg increase in lean body mass among people aged >50 years. The American College of Sports Medicine recommends elderly people to conduct resistance exercise 3 times a week with an average duration for 30 minutes. The exercise programme can be divided into 6 parts, including chest, shoulder, arm, wrist, abdomen, and lower body. The large muscle group such as lower body, lower back, and chest should exercise first before the smaller muscle group of arm, shoulder, and abdomen.

**Multidisciplinary assessment and management**
The gold standard for the care of people with frailty is comprehensive geriatric assessment that includes multidimensional assessment and treatment plan and regular review by a multidisciplinary team that include doctors, nurses, physiotherapists, occupational therapists, and social workers. Carers should aim for symptom relief, develop patient-centred goal setting with frailty improvement, and multicomponent intervention that include exercise and nutrition as part of the management. The LIFE-P study of physical intervention with aerobic, strength, balance, and flexibility training with physical activity showed an improvement in physical performance in terms of Short Physical Performance Battery and gait speed, though it did not reach statistical significance.

Nutritional supplement has been shown to be beneficial among subjects with osteosarcopenia, but its effect in frail elderly people is inconsistent. The results of nutritional intervention are mixed; this may be due to differences in type and duration of nutritional intervention, or the nutritional status of elderly individuals before the intervention. Food fortification, multinutrient supplementation, and use of vitamin D have not been shown to have a significant effect. Other studies of nutritional supplementation have reported a reversal of weight loss and improvement in nutritional status, but not
in terms of functional outcomes such as hand grip strength. This may be because the nutritional intervention is too little and too late to reverse the process of decreased muscle strength and functional decline. Nutritional advice and counselling for elderly people improves the frailty status only for those who are at risk for malnutrition.

Exercises together with nutrition support have more promising results. A 6-month trial combining nutritional supplementation, physical training, and cognitive training was found to improve frailty status in the group receiving each treatment alone, as well as in the group receiving all three treatments, and the improvements persisted at 6 months. A combination of exercise and nutrition intervention leads to an improvement in frailty status with a reduction in pre-frailty to frailty transition.

CONCLUSION

Osteosarcopenia and frailty are closely related and are a global health concern. The primary aim of management should be the prevention of occurrence rather than treating its complications. The complex and multifactorial nature of osteosarcopenia and frailty require multifaceted treatment and prevention strategies. A healthy lifestyle and regular exercise, including strength and balance training, are the mainstays of management. Measuring the degree of frailty in elderly people could assist in the assessment, management, and decision making for fragility fractures and osteosarcopenia at a clinical research level and at health care policy level. It is vital to increase the general knowledge about osteosarcopenia and frailty among patients and medical professionals for disease prevention, control, and treatment.

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