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Review Article

Sarcopenia and Frailty in Elderly: Manifestations, Impacts on Diseases, and Management

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SUMMARY

Aging population is frequently associated with a progressive function decline. Sarcopenia and frailty are common in elderly. Sarcopenia, defined by loss of muscle mass and strength and function, is a crucial driver for frailty. Sarcopenia can result from aging process, malnutrition, inactivity, and chronic diseases. Sarcopenia is highly prevalent in frail individuals. Frailty is a geriatric syndrome connected to adverse clinical outcomes. Frailty is associated with disability or increased mortality in elderly. Sarcopenia and frailty are prevalent in various diseases such as heart failure, chronic kidney disease, chronic obstructive pulmonary disease, and critical illness. Adequate nutritional support with higher protein ingestion in addition to exercise are crucial to improve physical performance in sarcopenic or frail elderly.

1. A prevailing issue in elderly

Population aging is an ongoing issue around the world. Frailty is a geriatric syndrome which is defined by decline in physical function and inadequate responses to stress to maintain homeostasis.[1] Frailty is associated adverse outcomes including delirium, disability, or even mortality[1] Frailty is highly prevalent in geriatric population and its incidence is increasing as age increased, from 6.5% in ages of 60–69 to 23–65% in ages older than 90.[1,2] Sarcopenia, defined by loss of muscle mass with declined muscle function, is a crucial driver for frailty.[3] The size and number of individual myofibers are reduced during aging, and the ratio between type I and type II fibers is also changed.[4] This further affects the function of muscles and performance of elderly. Primary sarcopenia is a consequence of natural aging process and no other etiology can be identified.[5] Secondary sarcopenia is caused by other factors including disease, inactivity, or malnutrition.[5] The worldwide prevalence of sarcopenia is reported as 10%,[6] and it is increasing during aging to over 50% in elder population.[7]

Aging related muscle wasting is closely related to mitochondrial dysfunction. Increased multiple mitochondria DNA (mtDNA) rearrangements in skeletal muscle are reported in elderly compared to young adults,[8] and progressive accumulation of aging-dependent mtDNA mutations is present in skeletal muscle of elderly.[9] These may lead to mitochondria dysfunction, release of proapoptotic proteins, and increased apoptosis in muscle.[10] Aging is associated with a low-grade increased of pro-inflammatory mediators, including tumor necrosis factor α (TNFα) or interleukin 6 (IL-6), which induces apoptosis and decreased synthesis of muscle protein.[11] Pro-inflammatory cytokines also contributed to muscle wasting via other mechanisms such as autophagy and ubiquitin-proteasome system (UPS).[12] Myostatin, the major autocrine inhibitor of muscle growth, binds to the activin receptor type IIB (ActRIIB) in muscle to induce fiber atrophy through activation of the transcription factors Smad2/3 which further bind with Smad4, and the Smad2/3/4 complex translocate into nucleus to block the expression of myogenesis genes.[13] ActRIIB is shared by other TGF-β family proteins including activins and growth differentiation factor-11 (GDF11), which are negative regulators of muscle mass.[13,14] Levels of myostatin and activin A are increased in elderly.[15] Several agents had been developed to antagonize the myostatin-ActRIIB signaling.[14]

Sarcopenia can be diagnosed based on evaluating total body composition with modalities such as dual energy X-ray absorptiometry (DXA), bioelectrical impedance analysis (BIA), or computed tomography (CT) images. DXA can acquire body composition with a three-compartment model comprising bone mass, fat mass, and non-bone lean mass. DXA cannot discriminate between different types of fat or lean tissues.[16] BIA is a simple, radiation-free, non-invasive modality which determines total body water with body resistance and a small current.[16] BIA is biased in diseases with increased fluid status such as ascites. CT-derived third lumbar cross-sectional muscle areas was suggested to best reflects total skeletal muscle mass.[17] CT allows quantitative evaluation of individual muscles, but it cannot reflect variations of individuals by using a distinct conversion index. The widely accepted criteria to define sarcopenia is derived from the European Working Group on Sarcopenia in Older People (EWGSOP).[5] The diagnosis of sarcopenia is made with low muscle mass with decreased function of muscles, measured by mus-

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cle strength or physical performance.[5] Asian Working Group for Sarcopenia (AWGS) later proposed a diagnostic algorithm with revised cutoff values based on Asian evidence.[18]

2. Impacts on diseases

Sarcopenia is closely related with frailty. Sarcopenia was present in nearly 50–70% individuals with frailty syndrome, and the InCHIANTI study showed that the muscle mass was strongly correlated with frailty.[19] Fried et al. defined frailty phenotype with data from Cardiovascular Health Study (CHS).[1] Positive of frailty phenotype was defined as 3 or more of the followings: unintentional weight loss, self-report low energy, lowest 20% of grip strength, slowest 20% in walking speed, and lowest 20% of physical activity.[1] Prefrail was defined as presence of 1 or 2 of the above.[1] However, to determine the lowest/slowest 20% requires data from the study population to define the cut-offs. The Frailty Index (FI), derived from Canadian Study of Health and Aging (CSHA) cohort, measures 70 clinical deficits in multiple domains.[20] FI can provide a comprehensive assessment, but it can be difficult to apply in clinical practice. The International Academy of Nutrition and Aging proposed the FRAIL scale with 5 clinical items (fatigue, resistance, ambulation, illnesses, and weight loss > 5%).[21] Clinical Frailty Scale (CFS) measures frailty based on clinical judgment of general condition in a 7-point ordinal scale derived from CSHA cohort. Later, two additional scales, very severely frail and terminally ill, were added above severely frail, and CFS was expanded into a 9-point ordinal scale to additionally define those distinct clinical groups.[20]

Sarcopenia is prognostic for mortality in elderly. Decreased muscle mass is an independent predictor for all-cause mortality in elderly Asians,[22] and sarcopenia is associated with all-cause mortality with an adjusted hazard ratio of 2.34 to elderly without sarcopenia.[23] Frailty is also associated with mortality in elderly. The SLAS1 study suggested the mortality risks markedly increased from 0.54 per 100 person-years in robust adults to 3.04 per 100 person-years in prefrail/frail adults.[24] A community study showed frailty was significantly correlated with higher mortality and much lower rate of still staying at home.[25]

2.1. Cardiovascular disease

Chronic heart failure is frequently associated with wasting. The unintentional weight loss was an independent risk factor for mortality for patients with chronic heart failure.[26] Sarcopenia is a frequent co-morbidity in chronic heart failure and is associated with lower peak exercise oxygen consumption (VO_2) and lower left ventricular ejection fraction.[27] Frailty is highly prevalent in heart failure. A meta-analysis reviewed 26 studies with 6896 patients and suggested the prevalence of frailty in heart failure is 44.5%.[28] Heart failures identified in the frail patients are older with more female but have similar left ventricular ejection fraction.[29] Frail heart failure patients also have a higher all-cause mortality and rate of readmission.[29] In chronic heart failure, the proteolysis by UPS is upregulated and myostatin-activin A signaling is increased. Cardiomyocytes express ActRIIB and therefore activation of myostatin-activin A signaling may reduce cardiac hypertrophy and trigger muscle wasting.[30] Recently, one study revealed that GDF11 reversed the age-related cardiac hypertrophy and left ventricular failures.[31]

2.2. Chronic kidney disease and cancer

Muscle wasting is frequently observed in patients with chronic kidney disease (CKD). The UPS is the major system for degrading the muscle protein. The muscle protein is cleaved by caspase-3 and interacts with ubiquitin enzymes E1, E2, and E3 to transfer ubiquitin to substrate protein, and subsequently the proteasome degrades the substrate protein into peptides facilitated by caspase-3.[32] Insulin/insulin-like growth factor 1 (IGF-1) signaling also plays an important role in homeostasis of muscle protein. Insulin or IGF-1 can bind to the IGF-1 receptor to trigger phosphorylation of downstream PI3K-Akt to facilitate protein anabolism and suppress protein catabolism.[32] Impaired insulin signaling can induce protein degradation via activation of UPS and caspase-3.[32] Sarcopenia was associated with mortality regardless of CKD status.[33] Frailty was highly prevalent in CKD patients with hemodialysis and was associated with mortality and hospitalization.[34] Frailty was also associated with mortality in pre-dialysis CKD patients.[35] Cancer patients frequently have higher level of pro-inflammatory cytokines, decreased level of IGF-1, increased level of myosin and activin A, and up-regulation of UPS.[36] These factors result in insulin resistance, skeletal muscle wasting, and cachexia, a devastating state for cancer patients.[36] Sarcopenia was associated with poorer cancer survival, and sarcopenic obesity was an independent prognostic factor for cancer patients.[37]

2.3. Pulmonary disease and critical illness

Chronic obstructive pulmonary disease (COPD) is a progressive inflammatory lung disease that is characterized by persistent respiratory symptoms and chronic airflow limitation. Skeletal muscle dysfunction is a common manifestation of COPD, and is associated with sarcopenia and improper function of the residual muscles.[38] Sarcopenia was affecting 14.5% COPD patients in outpatient basis, and sarcopenia was associated with more airflow obstruction, reduced exercise capacity, functional performance, and physical activity.[38] Muscle wasting and diaphragm atrophy in COPD patients have been shown to be associated with increased proinflammatory mediators,[39] increased level of myostatin mediated activin signaling, and activation of the UPS.[40] In acute exacerbation of COPD, smaller quadriceps muscle mass, evaluated by ultrasound, is an independent factor associated with readmission or mortality.[41] Reduced physical activity in COPD patients, resembling frailty phenotype, may lead to inadequate response to the acute stress such as acute exacerbation of COPD, and was associated with morbidity or mortality.[42] Sarcopenia is highly prevalent in 56% of intensive care unit (ICU) patients with respiratory failure.[43] Increased muscle mass in medical ICU patients is significantly associated with better survival and more ICU-free days.[44] Frailty is strongly associated with a higher ICU or in-hospital mortality, functional dependence after discharge, and a higher readmission rate.[45]

3. Management of sarcopenia and frailty

Malnutrition is prevalent in elder population. Sarcopenia and frailty frequently co-exist with malnutrition. Malnutrition decreases anabolism, reduces muscle mass, and promote the development of frailty. Elderly may need more dietary protein intake to promote muscle protein synthesis and offset the increased catabolism of muscle. Adequate exercise can promote synthesis skeletal muscle protein. Nutritional support and exercise training are two cornerstones to manage sarcopenia and frailty in elderly.

3.1. Nutritional support

Adequate nutrition support is foundation to maintain homeo-

stasis in elderly population. Anorexia is frequently the first obstacle for elderly to maintain nourished. Although the mechanism is not fully clarified, physiological and psychosocial factors are currently considered as contributors for anorexia.[46] Multiple approaches are suggested to treat aging-related anorexia: manipulating food to improve digestion or feeding, environment adaptation, or revision of medication.[47] However, long-term use of appetite-stimulating drugs may bring more negative adverse effects to offset the benefit of appetite stimulation.[47]

World Health Organization recommends dietary protein intake of 0.8 g protein per kg body weight per day for general adults regardless of gender or age. However, around 40% of elderly was reported to have protein consumption below this recommendation,[48] and elderly has declined anabolism of muscle protein after protein ingestion. Higher dietary protein intake was associated with higher appendicular lean mass of elder adults in a community cohort.[49] Lower energy-adjusted total protein intake is associated with higher loss of muscle mass, and the group with highest protein intake (1.2 g/kg/day) has the least reduction of muscle mass,[50] which implied elderly may need more dietary protein intake to maintain muscle mass. The PROT-AGE Study Group suggests evidenced-based dietary protein consumption for older adults as followings: healthy elderly should consume an average of daily protein at least 1.0 to 1.2 g/kg/day, and elderly suffering from acute or chronic illness should further increase the consumption to at least 1.2 to 1.5 g/kg/day.[51] The protein intake may be limited to 0.8 g/kg/day in severe CKD patients (creatinine clearance < 30 ml/min/1.73 m^2), but a high dietary protein consumption is recommended for dialysis patients.[51] Dairy protein significantly increased appendicular muscle mass; however, the benefit in handgrip or leg press may be limited.[52] Recently, a randomized trial also revealed protein supplement (31 g of protein per day for 12 weeks) increased lean body mass and reduced fat mass in physically active older adults.[53]

Leucine is an essential amino acid critical to regulate anabolism of skeletal muscle. A meta-analysis reviewed 9 studies with leucine-enriched diet in elderly and found leucine supplement increased muscle protein fractional synthetic rates, but not lean mass.[54] Vitamin D deficiency is associated with muscle disorders including sarcopenia. Vitamin D receptor (VDR) is expressed in human muscle tissue and the expression of VDR is shown to inversely associated with age.[55] Daily supplement of vitamin D_3 for 4 months in elderly mobility-limited women had shown to be associated with markedly increased size of muscle fibers.[56] PROVIDE study showed a 13-week combined nutritional supplement of vitamin D and leucine-enriched whey protein for sarcopenic elderly resulted in greater gain of appendicular muscle mass and better lower-extremity function.[57]

3.2. Exercise training

Exercise can sensitize skeletal muscle for anabolism. Regular exercise is shown to be associated with higher lean mass index in elderly Asians.[22] Protein ingestion after resistance exercise is shown to have a positive synergistic effect for muscle mass in older adults.[58] Exercise can not only enhance muscle strength but also improve physical function. A randomized controlled study applied resistance exercise training for frail elderly and showed that muscle strength is increased regardless of protein supplement whereas physical performance is significantly improved in protein supplement group.[59] The American College of Sports Medicine (ASCM) had suggested exercise guidelines for older adults 30 to 60 minutes of endurance exercise per day, accumulated to 150 minutes of aerobic exercise per week, and 2 to 3 days of resistance exercise training per week.[60] The PROT-AGE Study Group suggests 30 minutes of endurance exercise per day and 2 to 3 sessions (10 to 15 minutes) of resistance exercise per week for elderly.[51] The VIVE2 Study showed attending physical activity program alone in elderly resulted in increased lean mass, increased thigh muscle, increased muscle strength, and reduced fat mass.[61] Furthermore, nutritional supplementation with a mixture containing whey protein and vitamin D provided additional improvement in muscle composition and reduction in adiposity.[61]

4. Conclusion

Sarcopenia and frailty are common and closely related geriatric disorders. Malnutrition, sedentary life-style, and chronic illness are drivers for sarcopenia and frailty. Sarcopenia and frailty are associated with poor outcome in various diseases. Combination of exercise training and nutritional supplementation is crucial to maintain homeostasis and promote health in elderly.

Conflicts of interest statement

No conflicts of interest to disclose.

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