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REVIEW

Sarcopenia: Monitoring, Molecular Mechanisms, and Physical Intervention

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Summary

According to European Working Group on Sarcopenia in Older People (EWGSOP) sarcopenia includes both a loss of muscle strength and a decline in functional quality in addition to the loss of muscle protein mass. In order to develop strategies to prevent and treat sarcopenia, the risk factors and causes of sarcopenia must be identified. Age-related muscle loss is characterized by the contribution of multiple factors, and there is growing evidence for a prominent role of low-grade chronic inflammation in sarcopenia. The elderly who are less physically active are more likely to have lower skeletal muscle mass and strength and are at increased risk of developing sarcopenia. Resistance training added to aerobic exercise or high-intensity interval training promote numerous changes in skeletal muscle, many of which may help to prevent or reverse sarcopenia. In this review, we provided current information on definition and monitoring, molecular mechanisms, and physical intervention to counteract sarcopenia.

Key words

Muscle aging • Low-grade inflammation • Resistance exercise • Interval training • Whole-body vibration • Cryotherapy

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Introduction

Skeletal muscle contractions empower human body movements and are essential for maintaining stability. Skeletal muscle tissue accounts for almost half of the human body mass and, in addition to its power-generating role, is a crucial factor in maintaining homeostasis. Given its central role in human mobility and metabolic function, any deterioration in the contractile, material, and metabolic properties of skeletal muscle has an extremely important effect on human health. Aging is associated with a progressive decline of muscle mass, quality, and strength, a condition known as sarcopenia (Sakuma and Yamaguchi 2012a).

In 2009, the European Working Group on Sarcopenia in Older People (EWGSOP) developed definitions, diagnostic criteria, categories, and stages in sarcopenia. EWGSOP included representatives from four participant organizations, i.e. the European Geriatric Medicine Society, the European Society for Clinical Nutrition and Metabolism, the International Association of Gerontology and Geriatrics-European Region and the International Association of Nutrition and Aging (Cruz-Jentoft *et al*. 2010).

According to EWGSOP, sarcopenia is diagnosed by the presence of low muscle mass along with weak muscle function. EWGSOP suggested three categories of sarcopenia: pre-sarcopenia, sarcopenia and severe

sarcopenia. The pre-sarcopenia stage is characterized by low muscle mass without impact on muscle strength or physical performance. This stage can only be identified by techniques that measure muscle mass accurately and in reference to standard populations. The sarcopenia stage is characterized by low muscle mass, accompanied with low muscle strength or low physical performance. Severe sarcopenia is the stage identified when all three criteria of the definition are met, i.e. low muscle mass, low muscle strength and low physical performance. Recognizing stages of sarcopenia may help in selecting treatments and setting appropriate recovery goals. EWGSOP also suggested to use population with cut-off points at two standard deviations below the mean reference value for muscle mass, muscle strength, and physical performance (Cruz-Jentoft *et al*. 2010).

The current definition of sarcopenia includes both a loss of muscle strength and a decline in functional quality in addition to the loss of muscle protein mass, but it is unclear whether a decline in functional capacity results from the loss of muscle mass and/or the qualitative changes in muscle tissue. For example, after 50 years of age, muscle mass is reported to decline at an annual rate of approximately 1 to 2 %, but strength declines at 1.5 % per year and accelerates to, as much as, 3 % per year after the age of 60. As a result, the age-associated changes in muscle mass explain less than 5 % of the variance in the change in strength with aging. These rates of decline in strength are even higher in sedentary individuals and twice as high in men as compared to women. However, men, on average, have larger amounts of muscle mass and shorter survival than women (Kan 2009, Cruz-Jentoft *et al*. 2010).

The prevalence of sarcopenia among people older than 65 years was estimated as high as 15 %, and 50 % among people over the age of 80. As a major public health problem, the health care cost of sarcopenia in the United States alone was estimated at 18.5 billion dollars or ~1.5 % of total healthcare expenditure in the year of 2000. This estimation took into consideration the direct costs of sarcopenia, including hospital, out-patient, and home health care expenditures, and did not include the indirect costs of sarcopenia such as loss of productivity (Janssen *et al*. 2004). The world's population over the age of 65 is expected to triple from 600 million in 2000 to more than 2 billion by the year of 2050. Owing to this worldwide increase in life expectancy, the prevalence and cost of sarcopenia are likely to rise. Therefore, developing strategies to prevent and treat sarcopenia are of great importance (Rom *et al*. 2012). In this review, we provided a current information on definition and monitoring of a loss of muscle mass and muscle strength, molecular mechanisms in muscle aging as well as exercise strategies and new technologies to counteract sarcopenia.

Tools for sarcopenia monitoring

EWGSOP established a diagnosis method of sarcopenia including the three parameters of its definition, i.e. physical performance, muscle mass and muscle strength, in order to provide a useful tool in clinical practice and routine (Fig. 1) (Cruz-Jentoft *et al.* 2010).

Recommended measurement techniques include gait speed test for physical performance, bioelectrical impedance (BIA), dual energy X-ray absorptiometry (DXA) scan, computed tomography (CT) or magnetic resonance imaging (MRI) for muscle mass, hand-grip dynamometry for muscle strength (Table 1) (Cooper *et al*. 2013).

Gait speed, sit-to-stand time and standing balance are measures of functional performance which rely on strength and motor control as well as, with the exception of standing balance on muscle power. In clinical practice, gait speed, sit-to-stand time, and standing balance are often measured within the context of the Short Physical Performance Battery (SPPB). The patients who have a measured gait speed ≤0.8 m/s should further undergo body composition assessment using BIA, DXA or CT/MRI (Cooper *et al*. 2013). Slowing gait may reflect damaged circulatory, nervous, and musculoskeletal systems and the high-energy cost of walking. Recently, Studenski *et al.* (2011) demonstrated a strong association between gait speed and survival in nine cohort studies, with significant increments in survival per unit increase in gait speed.

According to EWGSOP, BIA is "a good portable alternative" method. With its low cost and because it is quick and simple to use, BIA was also suggested for the "systematic and repeated evaluation of FFM in clinical practice". However, the traditional approach using prediction equations is questioned because of the variable level of body hydration between individuals, and the technique is discouraged for the assessment of sarcopenia. Recently, Marini *et al*. (2012) demonstrated that bioelectrical impedance vector analysis (BIVA) can be a useful technique for detecting muscle-mass

variations in sarcopenic individuals, with specific BIVA able to discriminate sarcopenic from sarcopenic obese individuals. These low-cost, simple procedures are promising tools that allow a bicompartmental evaluation of body composition, and they could be used for the screening of presarcopenia, sarcopenia, and sarcopenic obesity in routine practice.

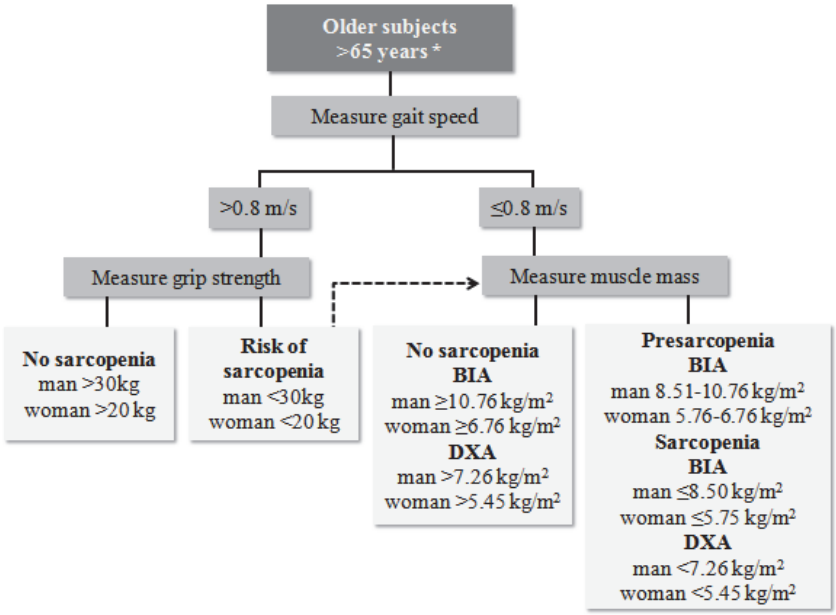

Fig. 1. EWGSOP-suggested algorithm for sarcopenia case finding in older; * this algorithm can also be applied to younger individuals at risk (Cruz-Jentoft *et al.* 2010, Fielding *et al.* 2011).

Table 1. Assessment methods of skeletal muscle mass, accuracy and precision (Kan 2009, Cooper *et al.* 2013).

Technique	Measurements	Muscle		Fat	
		Accuracy	Precision	Accuracy	Precision
BIA	Alternating electrical current through body tissue	+/–	+	+/–	+
DXA	Attenuation of 2 x-ray energies	++	++	++	++
CT/MRI	Cross sectional muscle size quantification	++	++(+)	++	++(+)

BIA – bioelectrical impedance, DXA – dual energy X-ray absorptiometry scan, CT – computed tomography, MRI – magnetic resonance imaging.

DXA is superior to standard densitometry which differentiates only between fat mass and fat-free mass, and it is widely adopted. However, DXA is unable to evaluate intramuscular fat, which can account for 5-15 % of observed muscle mass in obese people. In the context of research, CT is often used to assess total and fat-free muscle area, with a smaller margin of error than that seen with DXA. However, due to the large amount of radiation involved, full-body CT has limited utility. MRI has similar accuracy and reproducibility for fat and muscle as CT and is used for whole-body imaging. Both CT and MRI are more sensitive to small changes in muscle mass than DXA (Cooper *et al*. 2013).

Isokinetic dynamometer can be used to measure three types of muscular contractions – isometric, eccentric isokinetic, and concentric isokinetic contractions. During an isometric contraction, the resistive dynamometer torque equals the muscular torque such that no joint movement occurs and the whole muscle length remains constant. During a concentric isokinetic contraction, the active muscles shorten; during an eccentric isokinetic contraction, the active muscles lengthen. In both types of contraction, the knee joint moves at a constant angular velocity (Enoka 2002). The unique features of isokinetic dynamometry are optimal loading of the muscles in dynamic conditions and

constant preselected velocity of movement. These features provide safety in the rehabilitation of patients with muscular and ligaments injuries, for this reason is recognized as a good standard for measuring muscle strength in old people (Cooper *et al*. 2013). In both research and clinical practice, muscle strength is commonly characterized by hand-grip strength measured with a hand-grip dynamometer or knee extension strength measured with an isokinetic dynamometer. Isometric hand-grip strength is strongly related with lower extremity muscle power, knee extension torque and calf cross-sectional muscle area. Low hand-grip strength is a clinical marker of poor mobility and a better predictor of clinical outcomes than low muscle mass (Cruz-Jentoft *et al*. 2010, Cooper *et al*. 2013).

Molecular mechanisms in muscle aging

In order to develop strategies to prevent and treat sarcopenia, the risk factors and causes of sarcopenia must be identified. Age-related muscle changes are characterized by a gradual loss of spinal motor neurons due to apoptosis, reduced growth factors signaling and protein uptake, elevated amounts of circulating cytokines and increased oxidative stress etc. (Fig. 2). Some denervated muscle fibers are reinnervated through collateral sprouting of nearby surviving motor axons or motor end plates, which results in the formation of enlarged motor units. Consequently, the age-related loss of spinal motor neurons leads to a decline in muscle fiber number and size, resulting in impaired mechanical muscle performance (reduced maximal muscle strength, power, and rate of force development) that translates into a reduced functional capacity during everyday tasks such as walking, stair walking, rising from a chair etc. (Aagaard *et al.* 2010).

There is growing evidence for a prominent role of low-grade chronic inflammation in age-related reorganization in the neuromuscular system (Cruz-Jentoft *et al*. 2010, Meng and Yu 2010, Sakuma and Yamaguchi 2012b). Systemic low-grade inflammation, defined as two- to four-fold elevation in circulating levels of pro-inflammatory and anti-inflammatory cytokines, is considered as an underlying mechanism of aging and age-related diseases. Inflammatory mediators are directly associated with muscle mass loss and muscle strength reduction in the elderly. Pro-inflammatory cytokines, particularly TNFα, are potent stimulants of proteolysis through the ubiquitin-proteosome-dependent system (UPS). There was observed a significant negative relationship between myosin heavy chain protein synthesis rates and circulating markers of immune response (Toth *et al*. 2006). Visser *et al.* (2002) demonstrated that for each increase in standard deviation in the TNFα value, a 1.2-1.3 kg reduction is seen in hand grip strength.

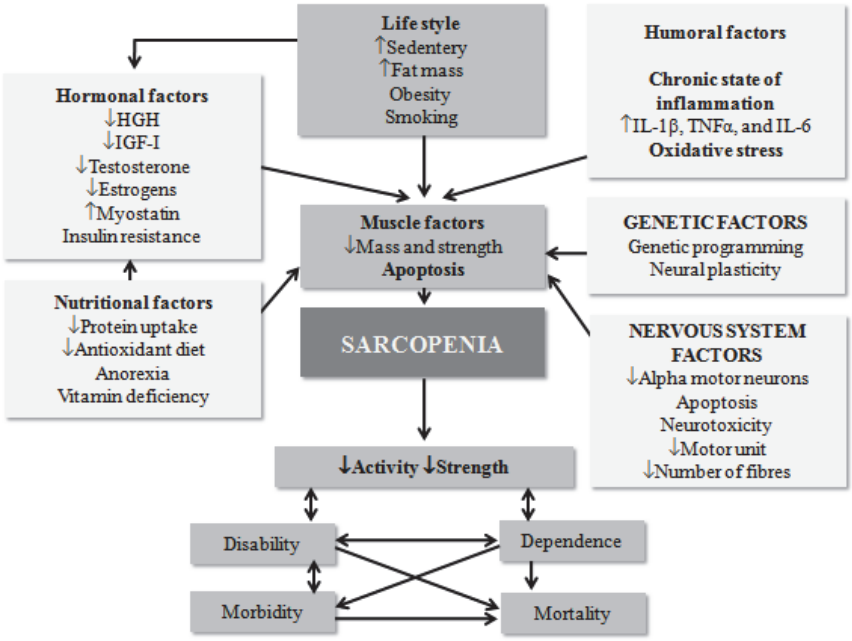

Fig. 2. Scheme of the different etiological sarcopenia mechanism and their consequences (Beas-Jimenez *et al.* 2011).

The data strongly suggest that upregulation of TNFα expression is induced during the aging process due to an age-related redox imbalance that activates many pro-inflammatory signaling pathways, including the NF-κB signaling pathway (Chung *et al*. 2011). Moreover, reactive oxygen species (ROS) also appear to function as second messengers for TNFα in skeletal muscle increased mitochondrial apoptotic susceptibility, and reduced transcriptional drive for mitochondrial biogenesis, e.g. lower level of transcriptional coactivator PGC-1α which is essential in the metabolic process (Chabi *et al*. 2008). The mitochondria constitute the major source of ROS, including superoxide radicals and hydrogen peroxide, can cause oxidative damage to surrounding structures and the particularly vulnerable mtDNA, which is in close proximity to the primary site of ROS production. Oxidation by ROS results in the synthesis of faulty proteins, oxidized lipids, and mtDNA mutations, which may lead to cellular and mitochondrial dysfunction as well as may accelerate apoptosis muscle cells. These processes are implicated in the mitochondrial theory of aging which holds that the accumulation of ROS damage over time leads to age-associated mitochondrial impairment (Peterson *et al*. 2012).

It was shown that TNFα is one of the primary signals that induces cellular apoptosis in muscle. Apoptosis is a regulated form of cell death that plays an important role in tissue development and disease. Apoptotic signaling cascades can be triggered through several pathways. They can be induced by the binding of TNFα to one or more of the extracellular receptors of the tumour necrosis factor receptor (TNFR) superfamily. The binding of TNFα to TNFR ultimately leads to the activation of a specific set of proteases crucial for the execution of apoptosis. The proteases are collectively referred to as caspases, and they are activated by proteolytic cleavage. Caspases have the ability to cleave and activate other caspases in a "cascade-like" fashion. This serves as an efficient and potent mechanism for amplifying the cell death signal. Activated caspases translocate from the cytosol to the nucleus and finally induce the cleavage of genomic DNA. This DNA fragmentation is one of the hallmark morphological features of apoptosis (Marzetti and Leeuwenburgh 2006). Whitman *et al.* (2005) demonstrated that DNA-fragmentation, coupled with 60 % decrease muscle fibre amounts, is significantly higher in *vastus lateralis* of older compared to young subjects. Plasma cell-free DNA (cfDNA) has recently emerged as a novel biomarker of aging, reflecting systemic inflammation, and cell death. In addition, it was suggested that cfDNA could promote autoinflammation (Cavanagh *et al*. 2012, Jylhävä *et al*. 2013).

Physical intervention against sarcopenia

The studies have shown that older adults who are less physically active are more likely to have lower skeletal muscle mass and strength and are at increased risk of developing sarcopenia (Burton and Sumukadas 2010). Resistance exercise (RE) seems to be an important tool in the treatment of sarcopenia by promoting positive functional (strength and power) and structural (hypertrophy and phenotypic changes) adaptive responses. Meta-analysis of forty-nine studies demonstrated that RE is effective for improving strength among older adults, particularly with higher intensity training. Strength increases ranged from 9.8-31.6 kg, and percent changes were 29±2, 24±2, 33±3, and 25±2, respectively for leg press, chest press, knee extension, and lat pull (Peterson *et al*. 2011). Human studies using different types of RE, such as flywheel, vascular occlusion, dynamic, isometric, and eccentric, obtained results of great importance (Nicastro *et al*. 2011). In addition, the magnitude of the preservation of eccentric strength in older adults ranges from 2 % to 48 % with the mean value all studies of 21.6 %. This functional reserve of eccentric strength might be clinically relevant, especially to initiate RE training and rehabilitation programs in individual with low levels of strength (Roig *et al*. 2010).

The morphological and functional adaptations to RE include neuromuscular system, muscle architecture and biochemical composition (myosin heavy chains I/IIa content), and myofibrillar proteins accumulation (Aagaard *et al*. 2001, Spiering *et al.* 2008, Zanchi *et al*. 2009, Roig *et al*. 2010). RE induces a sequential cascade consisting of muscle activation and signaling events arising from immune/inflammatory response, hormones and growth factors release due to increased transcription and translation. In this paradigm, RE is considered a strong "upstream" signal that determines specific downstream events such as satellite cells proliferation and muscle fibre hypertrophy. Therefore, manipulation of the RE programme variables (i.e. exercise choice, load, volume, rest period lengths and exercise order) could alter the unique "fingerprint" of the RE stimulus and could subsequently modify the downstream cellular and

molecular responses (Spiering *et al*. 2008).

Other physical activities can enhance the effects of RE on skeletal muscle. Aerobic exercise such as swimming, biking, running, walking or Nordic walking, has well-established benefits on cardiovascular fitness, endurance capacity and flexibility (Koopman *et al*. 2011). Although aerobic exercise is less likely to contribute to muscle hypertrophy, it can increase the cross-sectional area of muscle fibres. Aerobic exercise training affects skeletal muscle by improving mitochondrial bioenergetics, insulin sensitivity, protein synthesis, and also decreasing inflammation and oxidative stress (Kahn *et al*. 1990, Gündüz *et al*. 2004, Short *et al*. 2004). In addition to aerobic-based exercise training, a growing body of evidence indicates that high-intensity interval training (HIT) may also have substantial effects on muscle metabolism. HIT involves repeated short bursts of vigorous exercise (lasting a few seconds up to several minutes) interspersed by periods of rest or recovery. The influence of HIT on sarcopenia in older adults was not addressed, but it is worth considering due to the potent effects on PGC-1α, mitochondrial biogenesis, insulin sensitivity and systemic inflammation. HIT does not have a major effect on muscle size, especially compared to RE, although there may be a modest but significant hypertrophy of both type I and type II fibres after many months of HIT (Gibala *et al*. 2012).

Unfortunately, many forms of physical activity are either too intense or too monotonous for older adults to maintain over an extended period of time. Therefore, new exercise technologies, such as whole-body vibration (WBV) and whole-body electromyostimulation (WB-EMS), are offered as alternative methods to increase or maintain muscle mass and function (Rogan *et al*. 2011, Kemmler and von Stengel 2012). WB-EMS is known as an established technology primarily practiced as a local, passive, either more therapeutically, or more athletic application (Porcari *et al*. 2002). Briefly, during EMS, impulses are transmitted through electrodes on the skin close to the muscles in order to stimulate. These impulses cause involuntary contractions of the muscles and thereby preferentially recruit fast-twitch fibers that are predominantly affected by age-induced muscle atrophy (Lexell *et al*. 1988). In the past few years, WBV was proposed as a mild approach to counteract sarcopenia in the elderly. Standing on an oscillating platform induces a reflectory enhanced response of the leg and postural muscles *via* the so-called tonic vibration reflex (Abercromby *et al*. 2007). This response might be the key to long-term functional and structural neuromuscular adaptations which were observed in several studies. However, the potential of WBV to induce muscular strength is still unclear (Cochrane 2011). Study results suggest that preferentially untrained or older individuals with low fitness levels benefit from WBV. According to Kemmler and von Stengel (2012) both technologies may be attractive especially for subjects otherwise unable or unwilling to exercise conventionally and will be therefore a promising option to increase subjects' physical activity up to a level that fights sarcopenia.

In addition to RE, another strategy could be used such as whole-body cryotherapy (WBC) which could be an effective method to reduce inflammatory response and to enhance the benefits of regular physical activity in older adults. WBC consists of exposure to very cold air that is maintained at –110 °C to –140 °C in special temperature-controlled cryochambers, generally for 2 min. WBC is used to relieve pain and inflammatory symptoms caused by numerous disorders, particularly those associated with rheumatic conditions, and is recommended for the treatment of arthritis, fibromyalgia and *ankylosing spondylitis*. This method is still not well recognized, however, it is becoming increasingly popular in clinical application and sport medicine in recent years (Zalewski *et al*. 2013). According to the available literature, WBC is not harmful or detrimental in healthy subjects. The WBC effect is probably linked to the modifications of immunological molecules having paracrine effects, and not to systemic immunological functions. In fact, there is an increase in anti-inflammatory cytokines and a decrease in pro-inflammatory cytokines. Moreover, lysosomal membranes are stabilized by WBC, reducing potential negative effects on proteins of lysosomal enzymes. The cold stimulation also shows positive effects on the muscular enzymes creatine kinase and lactate dehydrogenase, and it should be considered a procedure that facilitates muscle recovery (Banfi *et al*. 2010). We hypothesize that introduction of WBC into progressive RE training would lead to greater improvements in muscle function in the elderly.

Conclusions

Sarcopenia is a significant health problem associated with a progressive decline of muscle mass, quality and strength. Evidence suggests that low-grade chronic inflammation predisposes to chronic disease, as

well as the development of sarcopenia and disability, in frail elderly. The measurement of inflammatory status may be biological marker of functional limitations in older persons across several diseases/health conditions. The inflammation is a potential target for interventions to reduce muscular weakness associated with ageing. RE training remains the most important strategy to prevent sarcopenia. However, other physical activities, such as aerobic exercise training or high-intensity interval training, can enhance the effects of RE on skeletal muscle. The manipulation of the RE programme variables can alter the "upstream" signal of RE and subsequently modify the downstream cellular and molecular responses in the elderly. As some older people are unable or unwilling to embark on exercise training program, alternative potential treatment options to counter the sarcopenia are being developed. Recent evidence has shown WBV and WB-EMS can improve muscle exercise capacity in functionally impaired older people; however, further randomized controlled trials are required. Other future prospects including the WBC have suggested potential methods to improve muscle performance in later life.

Conflict of Interest

There is no conflict of interest.

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