Bone 105 (2017) 276–286

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Review Article

A review of sarcopenia: Enhancing awareness of an increasingly prevalent disease

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ARTICLE INFO

Article history:
Received 8 July 2017
Revised 13 September 2017
Accepted 15 September 2017
Available online 18 September 2017

Keywords:
Muscle
Sarcopenia
Myostatin
Frailty
Osteoporosis
Aging

ABSTRACT

Sarcopenia is defined as an age associated decline in skeletal muscle mass. The pathophysiology of sarcopenia is multifactorial, with decreased caloric intake, muscle fiber denervation, intracellular oxidative stress, hormonal decline, and enhanced myostatin signaling all thought to contribute. Prevalence rates are as high as 29% and 33% in elderly community dwelling and long-term care populations, respectively, with advanced age, low body mass index, and low physical activity as significant risk factors. Sarcopenia shares many characteristics with other disease states typically associated with risk of fall and fracture, including osteoporosis, frailty, and obesity. There is no current universally accepted definition of sarcopenia. Diagnosing sarcopenia with contemporary operational definitions requires assessments of muscle mass, muscle strength, and physical performance. Screening is recommended for both elderly patients and those with conditions that noticeably reduce physical function. Sarcopenia is highly prevalent in orthopedic patient populations and correlates with higher hospital costs and rates of falling, fracture, and mortality. As no muscle building agents are currently approved in the United States, resistance training and nutritional supplementation are the primary methods for treating sarcopenia. Trials with various agents, including selective androgen receptor modulators and myostatin inhibitors, show promise as future treatment options. Increased awareness of sarcopenia is of great importance to begin reaching consensus on diagnosis and to contribute to finding a cure for this condition.

Contents

Abbreviations: ActRIIB, activin receptor IIB; IGF-1, insulin-like growth factor; IL-6, interleukin; PDE, phosphodiesterase inhibitors; GDF-8, growth differentiation factor 8; TNF-α, tumor necrosis factor alpha; QCT, quantitative computed tomography; FoxO, forkhead box; BMD, bone mineral density.

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https://doi.org/10.1016/j.bone.2017.09.008
8756-3282/

1. Introduction

The US Census Bureau projects that 80 million individuals, or 20% of the population of the United States, will be ≥65 years of age by the year 2050 [1]. From age 40 to 80, total skeletal muscle mass declines 30–50% [2], and up to a 3% annual decline in muscle functional capacity is seen after age 60 [2]. Irwin Rosenberg first used the term 'sarcopenia' in 1989 to characterize this age associated decrease in skeletal muscle mass [3]. While interest in sarcopenia has risen in recent years, contention still exists over most components of the disease, with a universally accepted definition still lacking.

Lean muscle mass seems to "set the pace" for bone mass [4]. The "Utah paradigm" suggests that healthy bone formation is promoted through resting muscle tension at the musculotendinous junction [5,6], and muscle mass has been positively correlated with bone size and strength [7]. As a consequence of muscle bone interaction, diminished muscle quality also correlates with diminished bone quality. Sarcopenia or muscular weakness has been associated with increased fragility fractures and lower bone density in several studies [8–18]. Evidence for the close interaction between bone and muscle suggests that muscle building therapies may also improve bone health [4].

This review characterizes the major aspects of sarcopenia, including pathophysiology, epidemiology, relevance to other disease states, methods of diagnosis and patient identification, outcomes and surgical impact, and treatment directions.

2. Pathophysiology

Sarcopenia is multifactorial in its development [19]. The disease burden faced by older adults results in pain and fatigue that limits physical activity, likely contributing to muscle mass decline [19,20]. Decreased caloric intake is also thought to contribute, with food intake falling 25% between the ages of 25 and 70 [21]. Reduced protein intake and declining vitamin D levels correlate with diminished muscle strength [22,23].

Age associated hormonal declines likely also contribute to muscle wasting. Testosterone concentration in men is significantly associated with muscle mass [24] and declines 1% a year after age 30 [23]. Women see a steep decline in muscle strength after age 55 [25], suggesting estrogen loss as a contributor to decreased muscle strength in women [26]. Growth hormone (GH) promotes fusion of muscle precursor cells into myotubes, and GH secretion declines five to twenty fold in older versus younger men [27]. Synthesized primarily in the liver in a GH dependent fashion, IGF-1 is key regulator of bone and muscle growth [27]. Reduced efficiency of IGF-1 signaling and a decrease in muscle specific IGF-1 expression likely contribute to muscle wasting [28,29]. The intracellular oxidative stress created by aging leads to chronic low grade inflammation [30], with sarcopenic patients showing increased concentrations of the inflammatory cytokines IL-6 and TNF-α [31].

Myostatin (GDF-8) stimulates muscle atrophy by inducing formation of the transcription altering SMAD protein complex [32]. Myostatin binding also suppresses the effects of PGC-1α, a transcriptional co-activator that enhances mitochondrial biogenesis and inhibits the transcriptional activity of FoxO [32]. Both animal and human studies have demonstrated that elevated myostatin levels correlate with reduced muscle mass [33–35].

Muscle fiber denervation and type II fast-twitch muscle fiber atrophy contribute to loss of muscle strength and power [36–39]. Accelerated loss of fast motor units requires the remaining motor units to increase their burden of work, resulting in a net conversion of type II fast-twitch muscle to type I muscle fibers [37].

There is also evidence for a genetic component to sarcopenia. Large scale genome-wide association studies (GWAS) analyzing the contribution of genetic variation to gait speed, lean body mass, and grip strength targeted single nucleotide polymorphisms (SNPs) associated with synaptic function and neural maintenance [40,41], structure and function of skeletal muscle fibers [41], and muscle metabolism [42].

3. Epidemiology

An FNIH study of over 4900 patients ≥60 years found the mean age of sarcopenic patients to be 70.5 years in males and 71.6 years in females [43]. Reported prevalence rates of sarcopenia vary greatly due to differing definitions, tools of diagnosis, and patient populations. Prevalence rates utilizing the European Working Group on Sarcopenia in Older People (EWGSOP) definition vary from 1 to 29% in elderly community dwelling populations and from 14 to 33% in long-term care populations [44]. Studies utilizing alternative definitions of sarcopenia provide prevalence rates in a similar range [45–48]. However, little consistency in prevalence is seen when multiple definitions are used to diagnose the same patient population [49,50]. Advanced age consistently appears as a risk factor for sarcopenia [45,47,51–54]. Patient populations in nursing homes [54], with hip fractures [55], and >80 years [55–57] have shown higher rates of diagnosis. Other risk factors consistently correlated with sarcopenia include low BMI [45,52,54,58], low physical activity [2,49,52], low serum IGF-1 and testosterone [48,53], osteoarthritis [56,59], and cerebrovascular disease [53,59].

4. Tools and methods of diagnosing sarcopenia

Early methods of diagnosing sarcopenia relied on measurements of appendicular muscle mass adjusted either for height [57,60], body mass [61], or fat mass [60,62]. While CT scans and MRI are considered the gold standards for muscle mass assessment [63], high costs and limited access make them difficult for clinical use. Dual-energy X-ray absorptiometry (DXA) and bioelectrical impedance analysis (BIA) are easier methods for this purpose. While assessments of muscle mass from DXA and BIA have shown to be well correlated [64–67], BIA assessments appear less reliable due to their sensitivity to patient hydration and recent activity [68]. In one study, BIA analysis overestimated body fat percentage in lean patients and underestimated body fat percentage in obese patients [69].

The International Working Group on Sarcopenia (IWGS) and the Special Interest Group on cachexia-anorexia (SIG) incorporate both low muscle mass and low physical performance as determined by gait speed into their diagnostic criteria [70,71]. Differences exist in the diagnostic methods from these two groups. The IWGS recommends