Muscle Quality in Aging: a Multi-Dimensional Approach to Muscle Functioning with Applications for Treatment

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Abstract Aging is often accompanied by declines in physical functioning which impedes older adults’ quality of life, sense of independence, and ability to perform daily tasks. Age-related decreases in skeletal muscle quantity, termed sarcopenia, have traditionally been blamed for these physical decrements. However, recent evidence suggests that the quality of muscle tissue may be more functionally relevant than its quantity. ‘Muscle quality’ has been emerging as a means to elucidate and describe the intricate intramuscular changes associated with muscle performance in the context of aging and sarcopenia. While muscle quality has most commonly been defined in terms of muscle composition or relative strength, at the core, muscle quality really describes muscle’s ability to function. Skeletal muscle displays a strong structure–function relationship by which several architectural characteristics factor into its functional capacity. This review describes the structural, physiological, and functional determinants of muscle quality at the tissue and cellular level, while also introducing other novel parameters such as sarcomere spacing and integrity, circulating biomarkers, and the muscle quality index. Muscle qualitative features are described from the perspective of how physical exercise may improve muscle quality in older adults. This broad, multidimensional perspective of muscle quality in the context of aging and sarcopenia offers comprehensive insights for consideration and integration in developing improved prognostic tools for research and clinical care, while also promoting translational approaches to the design of novel targeted intervention strategies designed to maintain function and mobility into late life.

Key Points

Despite the detrimental contributions of aging on skeletal muscle, no consensus definition of muscle quality presently exists.

A multi-dimensional understanding of muscle qualitative factors contributing to functional impairments may lead to improved efforts in identifying risk factors and developing effective treatments.

Physically exercising under-utilized muscles appears to be the leading strategy for improving muscle quality and function.

1 Introduction to Skeletal Muscle Quality

As many as half of the older adult population in the USA are affected by sarcopenia, a progressive, debilitating musculoskeletal condition [1]. Initially, the term ‘sarcopenia’ was introduced to describe the age-related reduction in skeletal muscle mass—somewhat similar to how osteoporosis affects bone. However, unlike osteoporosis, which remains asymptomatic until an unfortunate catastrophic event, sarcopenia manifests itself in regressive mobility and...
functional impairments [2]. While declines in physical function and loss of physiological resilience have traditionally been attributed to the age-related decreases in muscle mass, recent evidence indicates that the quality of the muscle tissue may have relatively greater functional relevance. Muscle quality refers to the tissue’s capacity to perform its various functions, including contraction, metabolism, and electrical conduction. Many dimensions of muscle quality have relevance to muscle’s capacity to perform its various functions, spanning from the broad aspect of whole muscle force production to muscle composition and morphology to the level of the sarcomere (the basic contractile element). In clinical research, muscle quality has often been measured in terms of strength normalized to muscle mass as determined by dual-energy x-ray absorptiometry (DXA) or computed tomography (CT). Recently, there has also been a growing interest in defining the structural, physiological, and biological determinants of muscle quality at the level of muscle tissues, individual muscle cells, cellular components, or metabolic pathways (Fig. 1). While several prior reviews have eloquently and thoroughly described aspects of muscle quality assessment [3, 4], functional deficit [5], endocrinology [6], pharmacology [7], treatment [8], or exercise training [9], none have yet integrated the clinical, mechanistic, and treatment approaches into a multi-dimensional approach as intended in this review. This article reviews the complex indices and dimensions of skeletal muscle and highlights the concept that its function stems from the interaction of several qualitative characteristics. We also briefly highlight the available data on functional and clinical implications to support targeted interventions for improving muscle quality. Recent studies by our laboratory and others may have important clinical relevance as they demonstrate that even without increases in muscle mass, exercise interventions may be beneficial to improving other features of muscle quality. Thus, multidimensional perspectives of muscle quality may offer insights towards improved prognostic tools for research and clinical care, while also promoting translational approaches to the design of novel targeted intervention strategies.

1.1 Skeletal Muscle in Aging and Physiological Resilience

Advancing biological age is frequently accompanied by diminished physiological reserve and decreased physical functioning which adversely impact perceived quality of life and well-being with aging. Amongst the most detrimental consequences associated with such deterioration is the presentation of the frailty phenotype. An overarching common dimension to several conceptualizations of frailty involves decreased physiological resilience and increased vulnerability to adverse events leading to an enhanced risk of future disability and mortality [10, 11]. The Fried frailty phenotype is characterized by weight loss, fatigue, weakness, and vulnerability to other adverse events associated with morbidity and mortality [12, 13]. While the physiological basis for frailty is generally viewed to be multifactorial, sarcopenia characterized by musculoskeletal deterioration appears to represent a central element [14]. Not only is skeletal muscle primarily important for physical functioning, but homeostatic imbalances resulting in altered energy metabolism and protein degradation may be a critical mediating factor for the onset of frailty. While the impact of physiological and functional decrements are progressively burdensome in hindering older adults’ ability to perform activities of daily living required for independence [15], both disability and frailty can increase susceptibility to severe catastrophic events [16–18]. Thus, understanding features of skeletal muscle quality changes with aging, sarcopenia, and frailty may be key to preserving independence and reducing catastrophic events. However, in examining muscle qualitative changes that frequently accompany aging and ultimately frailty, it is important to consider the large physiological variation in elders of a similar age [19]. Large variations imply that many of the qualitative changes that we observe with aging
may actually be more of a product of disuse than aging per se [20]. Thus, throughout this review, aging is considered the process of cellular and systemic senescence in normal conditions that ultimately lead to frailty. Although broad, normal conditions are considered in the absence of disease or high-level athletic training that can interfere with the process of what is considered normal aging.

1.2 Skeletal Muscular Quantity Versus Quality

The most widely acknowledged changes in skeletal muscle with aging entail reductions in muscle mass. Muscle mass decreases approximately 3–8 % per decade after the age of 30 years, with rates accelerating after the age of 60 years in an epidemiologic population [21]. This age-related loss in skeletal muscle mass, termed sarcopenia, is often attributed to the disability and morbidity observed in the older adult population [22] and is a primary determinant of the age-related declines in skeletal muscle strength [23, 24]. Another term ‘dynapenia’ was more recently introduced to describe and distinguish the age-associated loss of strength from loss of mass (sarcopenia) [25]. While some discrepancy remains as to whether or not to distinguish dynapenia from sarcopenia or whether muscle weakness should be incorporated into clinical definitions of sarcopenia, our recent work has revealed that muscle weakness is an important factor in distinguishing older adults with mobility impairment [26]. Regardless of the terminology, muscle weakness is collectively attributed to alterations in muscle quantity, muscle contractile quality, and neural activation [27].

Although muscle mass is an important underlying factor contributing to muscle strength [28], mounting evidence has emerged showing that muscle strength and power are strongly related to mobility, functional status, and mortality in frail elderly [29–32] even when adjusting for muscle mass [27]. Interestingly, several studies have demonstrated a mismatch in the rates of change involving these parameters, where the rate of decline in muscle strength is much more rapid than the concomitant loss of muscle mass [23, 33–37]. In addition, studies have shown that leg muscle power (a measure of the rate that force is developed) seems to be more important than muscle strength in determining the ability to perform daily activities [29] or the risk of hip fracture [38]. Such findings imply that age-related skeletal muscle changes involve more than just skeletal muscle mass loss and suggest that additional features of quality and neuromuscular innervation are factors in muscle strength and functioning.

1.3 Skeletal Muscular Changes Associated with Aging

As muscle mass and functioning decline with age, several changes occur locally within individual muscles, which affect the quality of the muscle. With aging, muscle fibers decrease in both size and number, particularly in type II (high force) fibers [36, 39, 40]. In fact, autopsy studies reveal 25 % fewer muscle fibers in the medial vastus lateralis of older (72 years) than in younger (30 years) individuals [41]. Moreover, biopsy studies also show a changing fiber type distribution with age where the percentage and area of type II fibers in the vastus lateralis is reduced [42]. As fiber type distribution changes, so does the oxidative enzyme activity and muscle capillarization, which decrease [9]. Interestingly, aging has differential effects on various human skeletal muscle groups [43], depending on their function and fiber composition [43]. For example, type II fibers of the vastus lateralis, an important muscle in the leg for locomotion, become very small and less circular with age, whereas in the masseter, an important muscle for chewing, fibers maintain circularity and only decreases in size [43]. Additionally, age-related muscular changes at the cellular level appear to be impacted by sex, where declines in the type II fiber area appear restricted to men [44].

Several studies have demonstrated the presence of impaired protein synthesis and decreased muscle anabolism with aging [45–48]. Declines in protein synthesis impair muscle contractile function, strength, and protein quality [25, 46, 49]. Several factors may contribute to the disproportional protein turnover observed in aged muscle. The age-associated increased levels of pro-inflammatory cytokines [50–52] may be part of the mechanisms that cause the interference with protein synthetic pathways [53] and contribute to the declines in muscle strength [50, 54], mass [55], and disability [51, 52]. Furthermore, more recent evidence also points to an age-related increase in myofibrillar protein glycation that may interfere with contractile protein structure and function [56]. In addition, muscle fibers of older adults contain more lysosomes [57], indicating greater potential for protein degradation than younger muscle. Regardless of the mechanism, it remains unclear as to whether age-related changes in muscle protein synthetic rates and contractile characteristics are preventable and whether protein synthesis measurements actually translate into contractile protein hypertrophy in muscle. (For further detail regarding protein metabolism with aging, please refer to prior reviews by Burd et al. [58] and Yarasheski [59]).

With age, the contractile characteristics of muscle fibers change. Muscle fibers transition to take on slow, type I, characteristics (fatigue resistant, slow contraction velocity) [60]. The selective loss of type II fibers, which possess greater contraction velocity [61], driving this observed transition impacts the muscle’s ability to generate maximal force [62]. The mechanisms underlying the slowed contractile speed in the muscle fibers appear to differ between
slow and fast fibers. In fast-twitch muscle fibers, the decreased speed of contraction is likely due to an age-related impairment of intrinsic sarcoplasmic reticulum function and alteration in sarcoplasmic reticulum volume [57, 63]. However, in slow fibers, the age-related decrease in contractile speed appears to be due to a change in the properties of the myosin protein [64]. Additionally, since it is known that muscle fibers take on the characteristics of the nerves innervating them [65], it is likely that fiber type changes associated with aging are attributable to changes in neural input to the muscle fibers contained within each motor unit. With aging, motor units are lost [66–68]. As a result, the size of each motor unit increases with age [68]. As neural innervation changes with aging, muscle fiber types that are generally dispersed in the muscle in younger adults tend to group together in older inactive adults [57, 69], reflecting reduced reinnervation. Also, older muscle fibers tend to be angulated in shape, reflecting denervation of muscle fibers [69]. Motor nerves also demonstrate age-related changes where nerve fibers decrease in diameter [70] and nerve conduction slows [71]. In addition, the neuromuscular junction (NMJ) where the motor neuron and the muscle fibers meet changes with aging where presynaptic nerve terminal branching and post-synaptic distribution of neurotransmitter receptor sites are increased and the NMJ has limited capacity to adapt [72]. This may affect the ability of aged muscle cells to modulate calcium release with muscle contraction. Thus, age-related changes in neuromuscular activation appear to largely contribute to declines in strength and power [73, 74].

2 Describing Muscle Quality

Muscle quality describes the physiological functional capacity of muscle tissue. In quantifying muscle quality, muscle’s contractile function is often assessed as the muscle’s ability to generate force measured as strength, power, or function. Measuring the whole muscle’s ability to function or generate force represents an index of muscle quality. Such indices of muscle quality include measures of relative strength and muscle quality index (MQI), as described in Sect. 2.1. However, muscle quality indices are ultimately dependent on the qualitative features of the muscle tissue, including the composition, architecture/morphology, and ultrastructure of the contractile apparatus, each of which are described in Sect. 2.2. Additionally, the assessment of muscle qualitative features is dependent on instruments and technologies. There are several emerging technologies including applications of ultrasound to measure muscle architecture, second harmonic generation (SHG) to qualify ultrastructure, and circulating biomarkers to reflect muscle status, which are also described.

2.1 Indices of Muscle Quality

2.1.1 Relative Strength

Typically, muscle quality is defined indirectly as muscle strength relative to the muscle quantity or the amount of muscle mass generating the force [75, 76]. When defined in this way, like muscle strength and mass, muscle quality declines with aging [77, 78]. In addition, muscle quality (relative strength) has been shown to be a stronger predictor of performance than strength, mass, or body composition alone in older adults [79–81]. Interestingly, muscle quality (as relative strength) has been shown to be inversely related to skeletal muscle mass [79, 82]. However, several complexities exist in interpreting and comparing muscle quality when defined as relative strength such as movement type (isotonic vs. isometric vs. isokinetic) [35, 83] and anatomical location (upper vs. lower body) [75].

2.1.2 Muscle Quality Index

Recently, Barbat-Artigas et al. [4] suggested the MQI as an assessment of muscle quality based on a functional test for older adults. The MQI estimates muscle power from body anthropometrics and timed chair rises [84]. It elaborates on the typical chair rise test by accounting for the anthropometric measures of body mass and leg length that have previously been shown to alter the relationship between chair rise performance and leg strength [84]. As a clinically feasible potential assessment of muscle quality, we compared the sensitivity to change of the MQI to other functional tests, and found that that the MQI increases with resistance exercise training in older adults to a greater magnitude and presents higher reliability than other functional measures (gait speed, grip strength, get up and go) [85]. Thus, the MQI should be considered as a potentially informative clinical outcome in interventional studies in older adults. While indices of relative strength are more informative than measures of muscle mass alone, such definitions of muscle quality do not account for other muscular qualitative features such as architecture or composition or functions such as mobility.

2.2 Dimensions of Muscle Quality

2.2.1 Muscle Composition

Age-related changes in body composition [28, 86] can affect muscle performance both functionally and physiologically. Functionally, the low lean mass to total body mass ratio can impede functional performance [87] and muscle strength [88], and lead to frailty [89] and nursing
home admission [90]. Physiologically, excessive body fat is related to lipid infiltration [91, 92] in the muscle which can impede muscle functioning (voluntary force production). Measures of total and regional muscle mass used to assess body composition and quantify muscle quality are often accurately measured with DXA. Although informative for identifying muscle mass thresholds associated with muscle weakness, such technology lacks the sensitivity to distinguish muscle composition. DXA measurements of skeletal muscle mass assume that all non-fat and non-bone fat-free mass is skeletal muscle mass [93], and cannot detect fat that infiltrates the muscle. Thus, DXA fails to identify intramuscular adipose deposits, the visible fat beneath the muscle fascia and between the muscle groups [94], as well as intramyocellular lipid droplets located between muscle fibers. The measurement of muscle composition in vivo requires more sophisticated and less available technologies [95] such as magnetic resonance imaging (MRI) or CT [96]. Most studies assessing muscle composition have used CT, which quantifies muscle density based on attenuation characteristics attained with compiled x-rays to discern fat and muscle tissue within the muscle [97]. Such measures indicate a positive association between muscle density and strength, regardless of size [92], indicating that lipid accumulation in the muscle (lower muscle density) hinders muscle quality.

With aging the density of skeletal muscle decreases [92, 98, 99], indicating lipid accumulation in the muscle [100–102]. Older men have 59–127 % more fat in the muscle compartments of the thigh than younger men [98], with an annual increase of 18 % shown in longitudinal measures [103]. Excessive lipid infiltration in skeletal muscles is associated with low muscle strength and poor physical performance [28, 55, 104], independent of cross-sectional area (CSA) of the muscle. Age-related fat infiltration in the muscle hinders the contractile ability of the muscle [105] and functionality in older adults [106, 107].

Intramuscular lipid stores include both intramyocellular lipids, spherical droplets located between the muscle cells, and extramyocellular lipids, strands of adipocytes surrounding muscle fibers [108, 109]. Both stores of lipid have different metabolic roles, where intramyocellular lipid droplets are more readily available in the muscle to provide an energy substrate during exercise while extramyocellular lipids have a slower turnover and serve as a longer-term storage site [110]. Older adults have increased intramyocellular lipids [111], characterized by larger droplet size [112] and a reduced oxidative capacity in comparison to younger adults [113]. This may result from the continuous supply of fat to the muscle without concomitant oxidation, resulting in the accumulation of intramuscular lipids [111].

### 2.2.2 Muscle Architecture

Muscle contractile function is related to its architectural characteristics [114–116]. Amongst the architectural characteristics relevant to the force-producing capacity of muscles are both the muscle fiber length and arrangement in relation to the direction of force produced by the whole muscle [117]. A muscle is advantaged in force production when fibers are oriented at a large pennation angle from the direction of force production where more fibers can be packed into a greater volume [115, 118]. Accordingly, amongst the age-associated architectural changes in skeletal muscle, muscle in older adults has reduced muscle fiber length [119, 120] and altered pennation angles [121], likely due to fiber atrophy. Such architectural changes contribute to reduced force production capacity. We recently reported on muscle architectural changes to resistance exercise in a cohort of healthy adults using physiological CSA (PCSA) of the thigh [122]. In contrast to traditional cross-sectional area measures, muscle PCSA measures of the vastus lateralis included a composite of architectural measures including CSA, echo intensity, pennation angle, and fascicle length. Muscle architecture measured as PCSA was significantly correlated with leg extension strength and change in leg extension strength [122].

### 2.2.3 Muscle ‘Ultrastructure’

Despite general consensus regarding age-related decreases in whole muscle strength and function with age, some discrepancy exists in the literature when examining single human skeletal muscle fibers. Some findings indicate age-associated increases in muscle fiber stiffness [123], reduced contractility [123], and reduced specific tension [44]. Others have reported preserved single muscle fiber contractile function despite significant decreases in whole muscle level strength [124]. Such discrepancies have been attributed to physical activity, where active older adults have preserved single fiber contractile properties [125], or compensation by surviving fibers to partially correct muscle size deficits in an attempt to maintain optimal force-generating capacity [124]. Regardless, more in-depth evaluation of muscle contractile apparatus at the ultrastructural level may yield greater insights into qualitative changes in skeletal muscle with age.

### 2.2.4 Sarcomere: The Basic Contractile Element

While most focus on aging muscle has been at the macrostructural level, it is important to consider that age-related muscle quality changes involve qualitative changes in muscle ultrastructure [40, 126]. Muscle cells are comprised
of myofibrils or cylindrical structures, containing repeated complexes of organized specialized proteins (sarcomeres) [127] (Fig. 1). Sarcomeres contain overlapping thin (actin) and thick (myosin) filaments [128], which represent the basic contractile elements for muscle contraction [129]. The actin filaments are anchored to multi-protein complexes known as the Z-disks [130], which border each sarcomere, maintain structure, and transmit tension during contraction [131]. Thus, the length of the sarcomere is most prominently defined by the Z-disk boundaries [132]. The length of the sarcomere quantifies the overlap between thin and thick filaments, and hence the potential for force generated from the actin and myosin interactions [133]. Muscle contraction ultimately occurs when the Z-disks are pulled together as myosin cross-bridges link to actin filaments, shortening the sarcomeres in series [128]. The force generated by the contracting sarcomeres within the muscle is transmitted throughout the muscle by the extracellular matrix.

Some evidence exists to indicate that sarcomeric changes may occur with aging in a manner that may inhibit muscle functioning. Animal comparison models show evidence that differences in myofilament lengths are related to functional demands of muscle [134]. Electron microscopic analysis of human skeletal muscle biopsies reveal myofibrillar disorder, Z-line streaming, and dilatation in aged skeletal muscle [57]. In addition, aged skeletal muscle shows a variety of changes within the extracellular matrix, including collagen accumulation and altered elasticity [135]. Since the order and arrangement of the myofilaments play a crucial role in force generation [136], age-related alterations in sarcomere spacing and integrity and extracellular matrix functioning may contribute muscle force-generating capacity. The reduced muscle fiber length in aged skeletal muscle may be due to a loss of sarcomeres in series since sarcomeres are lost as a result of decreased muscle tension from disuse [137]. Some data from human biopsy samples indicate that sarcomere length is reduced in older compared with younger adults [138]. From a functional point of view, a loss of sarcomeres in parallel and in series alters both the length–tension as well as the force–velocity relationships [116]. Although research has implicated optimal sarcomere lengths in muscular force generation [133, 139], how such characteristics relate to muscle quality, physical performance, and aging is emerging as a research priority as technologies improve to allow such evaluations.

3 Future Directions and Technologies in Muscle Qualitative Assessments

While existing assessments and approaches to muscle quality assessment have been broad and informative, many have been limited by costs, accessibility, feasibility, and the information that they can provide. New directions, technologies, and applications of existing technologies may enable the evaluation of hypotheses so far unanswered and increase the clinical applications and accessibility to muscle qualitative information. Among such future directions are the applications of safe and simple ultrasound imaging to assess muscle architecture, use of imaging tools to enable the in vivo assessment of sarcomere structure and alignment, and evaluation of novel biomarkers of muscle status that may provide new information that can be assessed through the blood.

3.1 Skeletal Muscle Ultrasound

The ability to quantify muscle size and composition requires elaborate medical imaging equipment that is not readily available for routine analysis. However, recent advances have supported the use of ultrasound technologies to non-invasively measure and quantify skeletal muscle. Ultrasound provides a safe and more widely available technique to accurately quantify and qualify regional muscle mass. Data from cadaver [140] and MRI studies [141] reveal that ultrasound is a valid and reliable tool to assess muscle CSA, thickness, and volume. Interestingly, we recently found that local muscle hypertrophy may be detected on ultrasound before changes in DXA are apparent [122]. In addition to measuring local muscle size, muscle quality may be assessed on ultrasound using post hoc analysis of density by quantifying echo intensity. Echo intensity is a measure of the reflectivity of the sound waves emitted to the tissue. Connective tissue and lipid are more reflective than more dense muscle tissue and are depicted in the image as lighter gray [142].

Ultrasound has been shown to be a reliable tool for assessing muscle quality as echo intensity [143, 144] (a proxy of muscle composition), which may be considered an index of muscle quality. Analyzing the reflectivity via gray-scale analysis provides a useful low-cost, easily accessible, and safe method to evaluate the muscle quality [145]. Although some evidence suggests a relationship between muscle echo intensity and strength [146], our preliminary study did not find significant changes in muscle echo intensity with acute resistance exercise when significant strength changes occurred [122]. As skeletal muscle ultrasound applications to assessing muscle qualitative features is a newer approach, further studies are warranted to determine whether it may be a useful application for clinical incorporation. In addition to providing qualitative and quantitative information on skeletal muscle integrity, size, and density, ultrasound technology also enables the assessment of muscle architecture.
3.2 Second Harmonic Generation Technology

Insights contributing to mechanical concepts underlying physical performance can be attained at the sarcomeric level [128] and some evidence reveals disordered sarcomeres in aged muscle [57]. Currently, studying the contraction artifacts associated with tissue fixation [147] this classical approach can be confounded by significant qualitative information regarding muscle ultrastructure, organization using microscopy techniques. In spite of the ability of electron microscopy (EM) to provide important qualitative information regarding muscle ultrastructure, this classical approach can be confounded by significant contraction artifacts associated with tissue fixation [147]. Moreover, the very nature of EM analysis, whereby individual ultrathin 2-dimensional sections are studied, precludes any meaningful quantitative analysis addressing changes taking place within a complex 3-dimensional tissue [148].

Novel imaging technology involving SHG imaging is emerging as a means of visualizing muscle ultrastructure in 3-dimensions, followed by objective quantification of sarcomere numbers, dimensions, integrity, and spacing within intact muscle [149–153]. SHG is a non-linear signal generated from the recombination of two photons on non-centro-symmetric molecular arrays into one photon of half the energy [149]. The signal is determined by the orientation, polarization, and local symmetry of chiral molecules. Both the collagen in the basal lamina surrounding muscle fibers and the coiled rod region of myosin thick filaments in the myofibrils are strong emitters of the SHG signal [150–153]. These characteristics allow the integrity of the sarcomeric structure to be evaluated with such techniques. Further description of the physical basis of SHG as tool for in vivo imaging of thick structural proteins can be found in the work of Mohler et al. [154].

The applications of SHG techniques for qualifying the skeletal characteristics of muscle have been shown by the work by Plotnikov et al. [138] who describe sarcomeric disruptions with second harmonic imaging techniques in dystrophic and aged muscle. Such work uses Helmholtz equations to determine sarcomere pattern quantification, indicating preliminary sarcomere pattern differences between older and young adults [138]. More recently, Liu et al. [155] developed a tool to quantify skeletal muscle irregularities based on SHG-generated images and Buttgereit et al. [156] used SHG to demonstrate fiber regeneration. Unlike other means of imaging, SHG allows high-resolution quantitative 3-dimensional imaging of unstained bundles of muscle fibers at the molecular level with minimal tissue sampling processing [157]. Such features provide potential for the adaptation of SHG optics for in vivo imaging during medical examination [158–160]. Llewellyn et al. [161] and Cromie et al. [162] have successfully used needle-sized microendoscopes to visualize sarcomeres in human skeletal muscle in vivo. Hence, this quantitative microscopic assessment of muscle sarcomere characteristics may become useful as a complementary diagnostic tool to identify a more precise and quantifiable subcellular target for sarcopenia, frailty, and disability interventions. However, before such advancements can be made, this technology should be used to quantify such measures of muscle quality in frail and healthy human muscle and relate such findings to physical performance. In addition, beyond the costs and sophistication of SHG apparatus, some technical challenges remain for in vivo use such as live tissue motion, low signal, and coupling of the objective to the tissue for in vivo imaging [160, 162].

3.3 Circulating Biomarkers

Circulating biomarkers may provide an alternative measure of skeletal muscle quality that is both informative and clinically feasible and overcomes some of the barriers to muscle quality assessment. The International Working Group on Sarcopenia [163] previously has reported on biomarkers reflective of muscle status. Such markers have included anabolic hormones [e.g., testosterone, growth hormone (GH), insulin-like growth factor-1 (IGF-1)], inflammatory biomarkers (e.g., C-reactive protein, interleukin-6, tumor necrosis factor-α), and products of oxidative damage (e.g., advanced glycation end-products, protein carbonyls, oxidized low-density lipoproteins) [163]. In addition, several excellent reviews (hormones [164], sex steroid hormones [165], IGF-I [166], GH [167], and cytokines [168]) have covered the circulating biomarkers of sarcopenia more in depth, focusing mostly on the hormonal milieu to support anabolic processes.

Here we focus selectively on the emerging biomarkers that we have recently studied. As we [122] and other researchers [169] have shown, measures of muscle mass may give an incomplete picture of the functional scope of sarcopenia and may not be sensitive to changes. Besides the anabolic hormones and inflammatory markers, which nicely reflect the hormonal milieu to support anabolic processes, but may or may not translate to actual protein synthesis, other biomarkers that can be measured in the blood have emerged that can be reflective of actual tissue remodeling. These candidates include N-terminal peptide of procollagen type III (P3NP) and C-terminal agrin fragment (CAF). P3NP is a peptide fragment cleaved from the procollagen III molecule during type III collagen synthesis [170]. Type III collagen is a subtype of collagen located in...
skeletal muscles that provides a structural framework of the muscle for the alignment and growth of the myoblasts in muscle repair [171]. Previous research has indicated that older adults have reduced levels of circulating P3NP [172] and that changes in serum P3NP levels are predictive of changes in lean body mass and strength [172]. CAF is also a peptide fragment cleaved from the nerve-derived protein agrin in neuromuscular remodeling. Normally, the agrin protein is important to maintaining the NMJ [173]. However, excessive cleavage of agrin by the enzyme neutrophrynpsin leads to functional disintegration at the NMJ [173, 174]. Circulating CAF concentrations are elevated in older adults with sarcopenia [175] and frailty [176], potentially indicating breakdown of the NMJ.

We evaluated changes in circulating concentration of P3NP and CAF in response to a preliminary intervention designed to increase muscle quality but not mass [177]. We found that circulating CAF increased to a clinically meaningful magnitude while changes in circulating P3NP were less clear, but appeared to reflect muscle hypertrophy [177]. While assessment of P3NP and CAF from blood samples may provide minimally invasive and clinically informative measures of skeletal muscle status in older adults, further research is needed to elucidate whether P3NP, CAF, or other biomarkers can reflect muscle qualitative adaptations with larger and longer studies.

4 Treatment Strategies

Several treatment strategies have been evaluated for attenuating the age-related declines in skeletal muscle. Treatment strategies have mainly focused on hormone replacement therapies, dietary interventions, pharmaceuticals, and various types of physical exercise. Despite such research efforts, interventions using pharmaceutical or nutritional supplements to treat sarcopenia have lacked efficacy in improving muscle function and size due to inconclusive findings or limited evidence [178]. In addition, thus far, relatively few interventional strategies have focused on muscle quality-related outcomes. On the other hand, exercise training (especially resistance-type exercise) has consistently proven to be safe and highly effective intervention for increasing muscle mass, strength, and quality in older adults [178].

4.1 Hormonal Interventions

Hormonal interventions have typically been explored as a treatment for muscle wasting based on the cross-sectional associations between circulating hormone concentrations and skeletal muscle mass and characteristics of frailty in older men and women [179, 180]. However, when hormonal interventions have been implemented, they seldom demonstrate efficacy for improving muscle functioning. Moreover, studies administering hormonal treatments for treatment of sarcopenia in older adults have seldom reported muscle qualitative outcomes. Thus, although serum levels of the adrenal steroid hormone dehydroepiandrosterone (DHEA) [181] are associated with frailty characteristics in older adults [179], administration of exogenous DHEA supplementation does not appear to benefit measures of physical function or performance [182]. Similarly, while circulating estradiol is associated with skeletal muscle mass in older women [180], estrogen replacement therapy does not appear to protect against the muscle loss of aging [183]. In addition, long-term estrogen therapy does not appear to affect appendicular muscle mass, body composition, or physical performance in older women [184, 185]. On the other hand, androgens have shown some anabolic effects in older adults. Bioavailable testosterone is significantly associated with both higher skeletal muscle mass [180] and less skeletal muscle fat infiltration [186] in older men. When administered to older adults, testosterone has been shown to be able to effectively increase circulating testosterone levels and favorably affect body composition [187, 188]. However, despite the anabolic effects of testosterone administration, its effects on muscle quality and function have yet to be confirmed. Studies that have evaluated the effects of androgen therapy on muscle quality [188] and physical function in older men [187] did not show promising effects. However, androgen replacement therapy may be most effective in older men who are hypogonadal [189]. Nevertheless, the marginal benefits must be weighed in terms of the risks as higher doses are associated with a fear of accelerating prostate cancer [189]. Similarly, GH replacement therapy in older adults is associated with a high incidence of adverse effects, [189] and it does not appear to be any more beneficial to muscle strength than resistance training [189]. Finally, in one hormonal study that did measure muscle quality as both relative strength and CT attenuation, circulating concentrations of estrogen, DHEAS, and IGF-1 were correlated with muscle quality while testosterone and DHT (dihydrotestosterone) were not [190]. Regardless of the relationships, the efficacy of these hormones as exogenous treatment to improve muscle quality remains to be examined.

4.2 Future Directions in Pharmaceuticals

To date, few drugs have been developed for sarcopenia specifically [191], due likely to the complexity of the muscle qualitative features associated with the condition along with the lack of a uniform set of clinical criteria to diagnose the condition [192]. In light of this need, an
international task force recently met to address the need for pharmaceutical trials for sarcopenia [193]. The task force reported that issues of safety and research developments have restricted the clinical applications of pharmaceutical interventions [193]. Nevertheless, with the increased understanding of the pathways contributing to sarcopenia and muscle quality, several potential targets for drug development have been identified [194]. Of the potential targets for drug development, circulatory, metabolic, neuromuscular, anabolic, catabolic, force generation, and signaling pathways have all been targeted, which are described in brief here. For further information on the pharmacological aspects of sarcopenia, please refer to a prior review by Broto and Abreu [7].

Several physiological targets for drug development to combat sarcopenia and its qualitative consequences are being explored. Circulatory targets of drugs to treat sarcopenia have focused on ACE inhibitors that have shown some efficacy in improving physical performance [195, 196]. Mitochondrial targets have focused on promoting mitochondrial biogenesis and calcium metabolism with peroxisome proliferator-activated receptor-γ coactivator 1α [197] and cyclophilin D inhibitors [198]. Anabolic targets have focused on selective androgen receptor modulators (SARMs), which are able to selectively target androgen receptors in the target tissue, thereby sparing androgen receptors in the prostate and myocardial tissue [199, 200]. Neuromuscular targets have targeted the agrin protein within the NMJ, which is involved in maintaining neuromuscular integrity [174]. Additional drug targets have focused on attenuating myonuclear apoptosis through myostatin inhibition [201] and attenuating myofibrillar degradation via proteasome inhibitors [202]. In addition, new drugs targeted at troponin activation may provide a potential therapeutic mechanism for increasing muscle force and strength [203]. Furthermore, more recent targets have focused on micro-RNAs that are able to that bind to complementary regions on numerous messenger RNAs (mRNAs) to modulate signaling cascades [204]. Several micro-RNAs have been associated with aging [205]. Treatment targets have focused on the role micro-RNAs in the control of myogenic commitment [206] and maintenance of the NMJ [207]. While research on these and other neuromuscular pathways are underway, these potential drugs are some way away from being available to the clinician and the patient and potential adverse effects are yet to be determined.

4.3 Nutritional Interventions

Nutritional interventions provide a more accessible means to intervene in the age-related decrements in skeletal muscle as prescriptions are not necessary and adverse effects are fewer and less severe. Nutritional interventions for sarcopenia have mostly focused on protein supplementation due to the protein synthetic pathways stimulated by the essential amino acids contained within them. In addition, some, but far less, research has investigated the effects of other nutritional supplements such as omega-3 fatty acids (O3FAs), creatine, β-hydroxy-β-methylbutyrate (HMB), and β-alanine on muscle factors in older adults. Interestingly, however, some research has shown that older adults may be less susceptible to the anabolic effects of protein than younger adults in what has been considered ‘anabolic resistance’. Although protein supplementation is a potent stimulator of protein synthesis in the skeletal muscle of younger adults, older adults’ muscle appears resistant to the anabolic stimulus [208, 209], possibly due to reduced expression and activation of anabolic signaling pathways [209]. Nevertheless, although dietary protein can improve protein synthesis [210], increasing dietary protein does not appear to improve muscle composition responses to resistance training in older adults any more than the benefits seen from resistance training alone [211].

Some studies by our laboratory and others have shown some efficacy in improving muscle strength, size, fatigue threshold, and function with supplementation with creatine [212, 213], β-alanine [214], and HMB [215]. Creatine is a common supplement used by athletes to increase stores of phosphocreatine for short-term energy production [216]. We have found that short-term supplementation with creatine in older women was able to increase muscle strength and performance without any adverse effects [213]. Similarly, Stout et al. [212] reported significant increases in grip strength and physical working capacity with creatine supplementation in older men and women. β-Alanine is an amino acid important for increasing muscle carnosine synthesis and improving muscle metabolic buffering capacity [217]. We have shown that a protein drink fortified with β-alanine may improve physical working capacity, muscle quality, and function in older men and women [214]. HMB is a metabolite of the essential amino acid leucine that induces acute muscle protein anabolism through increasing synthesis and attenuating degradation [218]. Stout et al. [215] reported that long-term supplementation with HMB in older adults can improve muscle strength and muscle quality. Despite some encouraging findings, other nutrients, such as self-reported O3FA intake [219], have shown no associations with lower extremity function. Similarly, Fiatarone et al. [30] showed that a multi-nutrient supplementation without concomitant exercise does not reduce muscle weakness or physical frailty. While some nutritional strategies look encouraging for targeting various muscle quantitative and qualitative features, further research is needed to identify the optimal nutritional approach for preventing and treating sarcopenia.
and investigating muscle qualitative features more thoroughly.

4.4 Exercise and Physical Activity

Physical activity, especially in the form of resistance exercise training, has been consistently shown to be a feasible and effective means of counteracting muscle weakness and physical frailty and improving muscle strength, size, and function [30, 220, 221], even at a very old age (>80 years) [222]. Although varying exercise protocols have shown effectiveness for increasing muscle quantity, quality, and strength, the dosage in terms of intensity, frequency, and volume ultimately dictates the expected outcomes [9]. Sufficient resistance training intensity (70–90% of 1 repetition maximum) [223, 224], frequency, and duration (three times a week for 8–12 weeks) [224] is well-tolerated in older adults [225] and required to elicit the desired muscular responses. The American College of Sports Medicine (ACSM) [226] recommends that older adults participate in a variety of exercises including endurance, resistance, flexibility, and balance exercises to increase active life expectancy and to limit the development and progression of disabling conditions. Each mode of exercise stimulates specific muscular adaptations. While physical activity in general is important for maintaining physical functioning, resistance (strength) exercise training remains the most effective intervention for increasing muscle mass and strength in older people [189, 227]. A 2009 Cochrane review of 121 randomized controlled trials involving 6,700 participants showed that progressive resistance exercise training is an effective and safe intervention for improving physical functioning in older people with few adverse events [228].

Similar to younger adults, the plasticity of skeletal muscle in response to resistance exercise training is somewhat maintained with aging [229]. Resistance training leads to increases in muscle strength and power of both the upper and lower body in older adults [230]. Even frail older adults aged >90 years have shown profound strength improvements of 174% in response to resistance exercise training [231]. While the gains appear continual with training, the greatest gains are often seen within the first 3 months of training [232]. However, in contrast to younger adults who experience both marked increases in neural function and hypertrophy with training, gains in muscle strength and power in older adults are predominantly determined by neural adaptations [233]. Neural adaptations resulting in strength and power improvements involve increased voluntary activation of the agonist muscles and reduced cocontraction of the antagonist muscles [233]. In addition, long-term exercise promotes the reinnervation of muscle fibers and may spare the loss of fibers due to denervation by selective recruitment to slow fibers [69]. Some newer evidence also suggests that high threshold motor units may be preserved with oscillatory contractions [234]. Older adults also demonstrate a preservation of thigh girth [235], evidence of muscle hypertrophy at the fiber level [236], and an increase in myofibrillar protein turnover [237] that accompany strength gains in response to resistance training. In addition, resistance training is able to stimulate a similar shift in the expression of myosin heavy chain (MHC) isoforms (from MHC IIb to MHC IIA) in older adults to that in younger adults [229].

Despite the somewhat maintained neuromuscular plasticity with training in aged muscle, the muscular anabolic response is somewhat attenuated with age [230, 238]. The reason for the dampened response is likely attributable to endocrine or neuromuscular impairments [230]. In comparison to younger adults, untrained older adults show an attenuated hormonal response to exercise [239] and down-regulation of the skeletal muscle IGF-1 system [240], which may impair hypertrophic capacity. However, resistance training has shown to counteract these changes by enhancing the hormonal response to resistance exercise (i.e., decreased resting cortisol and increase circulating testosterone) [239] and reversing the age-related down-regulation of the skeletal muscle IGF-1 system [240], which may promote anabolic potential. Also, within the muscle, age-related alterations in myonuclei may impair hypertrophic capacity [241, 242]. Changes in myonuclear content represent a mechanism for modulating protein content and hypertrophy [243–245]. Since myonuclei regulate gene expression and protein synthesis of the surrounding muscle fiber [246], the age-related reduced responsiveness of skeletal muscle may relate to alterations in myonuclear number, distribution, and function [241, 242]. Animal models indicate that the myonuclei of aged type II muscle fibers demonstrate a decrease in pre-mRNA transcription, processing, and transport rate compared with younger adult animals [242]. However, the myonuclear domains of type I and IIA are smaller than in IIb fibers [245], theoretically providing greater potential for proportional hypertrophy within them without exceeding the myonuclear domain. Regardless, resistance training has shown to reverse the age-related decline in myonuclei precursor satellite cells [247], thereby enhancing the potential for enhanced myonuclear dictated hypertrophy.

In addition, the positioning of myonuclei along muscle fibers is plastic and influenced by blood supply [248]. With greater blood supply, the number of myonuclei is higher in slow than in fast fibers, despite the greater absolute size of fast fibers [249–251]. Interestingly, myonuclear content is
correlated with mitochondrial content [251], which is also reduced in aged human skeletal muscle. The down-regulation of mitochondrial biogenesis in older individuals is believed to be due to reduced metabolism and chronic inflammation [252]. Moreover, older adults have a lower proportion of intramyocellular lipids in contact with mitochondria [112], perhaps as a result of reduced physical activity since exercise causes a proximal subcellular shift of lipid droplets to the mitochondria [253]. Endurance exercise training in older adults elicits a proliferation of muscle capillaries and an increase in oxidative enzyme activity within the muscle [9]. In addition, resistance exercise can improve mitochondrial capacity [254] and reverse the age-related declines in mitochondrial function [255]. Hence, although some anabolic mechanisms may be dampened with aging, many of the age-associated reductions in muscle quality may be attenuated by physical activity.

Mechanisms through which exercise may influence muscle quality and functional status are complex. However, qualitative improvements in muscle appear to account for the adaptations more so than muscle hypertrophy [23, 256] or other muscle parameters [257]. Evidence of muscle qualitative improvements stem from interventional studies that show disproportionate improvements in muscle function to muscle size [258]. Muscular qualitative improvements include attenuating age-related intramuscular adipose infiltration [103], increasing muscle fiber area [220], muscle power [30], relative strength [259], MQI [85], PCSA [122], neuromuscular functioning [222], and increasing contractile protein [260]. The stimuli for regeneration of myofibrils involve the mechanical disruption during exercise [261]. Interestingly, some evidence suggests that older men experience greater muscle disruption following eccentric exercise than young men, which may be due in part to the smaller muscle mass [262]. Although older individuals have reduced protein synthesis as compared with younger adults during the resting state, muscle protein synthesis capacity stimulated by exercise is preserved in old age [46, 48, 263]. More specifically, resistance exercise increases the synthesis rate of major contractile proteins, MHC, actin, and mixed muscle proteins [46] and shifts the expression of MHC isoforms from MHC IIb to MHC IIa [229]. Resistance exercise is associated with increased presence of developmental isoforms [261], implicating muscle regeneration through activation of new myogenic precursors in frail elders. In addition, exercise may reduce intramuscular lipid accumulation via enhanced lipolysis stimulated by muscle contraction and epinephrine release [264, 265]. Enhanced hormonal profiles [238], including increased IGF-1 [261], likely mediate protein synthesis for new or hypertrophied myofibril formation in the muscle of older adults in response to resistance exercise. Moreover, exercise training increases resting fascicle length due to the addition of sarcomeres in series [120, 266], potentially reversing aging-induced reductions in fascicle length.

5 Conclusions

Despite the detrimental contributions of aging on skeletal muscle, no consensus definition, diagnostic tests, or medical treatments currently exist for sarcopenia [267], dynapenia, or muscle quality. Understanding muscle qualitative factors contributing to functional impairments at the most basic physiological level will ultimately help both clinicians and patients by identifying risk factors and developing interventions and treatments. Given the role that muscle quality plays in function, more direct measures at an ultrastructural level could potentially provide prognostic information. Emerging technology holds promise to provide a means of assessing muscle quality changes at an ultrastructural level. By measuring muscle quality, strategies to identify individuals at ‘high risk’ of functional decline and frailty can be developed and more aggressive care and interventions can be implemented. Muscle disuse is a feasible target for intervention for the onset of muscle weakness and frailty in older adults. Putting under-utilized muscles to work in a resistance exercise training program is repeatedly shown to be an effective and feasible means to maintain and improve function and improve muscle quality. Although some mechanisms are attenuated with aging, benefits can still be achieved in function and performance from exercise training through alternative adaptations in fiber characteristics and muscle quality.

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