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Innovations in the Assessment of Skeletal Muscle Health: A Glimpse into the Future

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Abstract:
Skeletal muscle is the largest organ system in the human body and plays critical roles in athletic performance, mobility, and disease pathogenesis. Despite growing recognition of its importance by major health organizations, significant knowledge gaps remain regarding skeletal muscle health and its crosstalk with nearly every physiological system. Relevant public health challenges like pain, injury, obesity, and sarcopenia underscore the need to accurately assess skeletal muscle health and function. Feasible, non-invasive techniques that reliably evaluate metrics including muscle pain, dynamic structure, contractility, circulatory function, body composition, and emerging biomarkers are imperative to unraveling the complexities of skeletal muscle. Our concise review highlights innovative or overlooked approaches for comprehensively assessing skeletal muscle in vivo. We summarize recent advances in leveraging dynamic ultrasound imaging, muscle echogenicity, tensiomyography, blood flow restriction protocols, molecular techniques, body composition, and pain assessments to gain novel insight into muscle physiology from cellular to whole-body perspectives. Continued development of precise, non-invasive tools to investigate skeletal muscle are critical in informing impactful discoveries in exercise and rehabilitation science.

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Abstract

Skeletal muscle is the largest organ system in the human body and plays critical roles in athletic performance, mobility, and disease pathogenesis. Despite growing recognition of its importance by major health organizations, significant knowledge gaps remain regarding skeletal muscle health and its crosstalk with nearly every physiological system. Relevant public health challenges like pain, injury, obesity, and sarcopenia underscore the need to accurately assess skeletal muscle health and function. Feasible, non-invasive techniques that reliably evaluate metrics including muscle pain, dynamic structure, contractility, circulatory function, body composition, and emerging biomarkers are imperative to unraveling the complexities of skeletal muscle. Our concise review highlights innovative or overlooked approaches for comprehensively assessing skeletal muscle *in vivo*. We summarize recent advances in leveraging dynamic ultrasound imaging, muscle echogenicity, tensiomyography, blood flow restriction protocols, molecular techniques, body composition, and pain assessments to gain novel insight into muscle physiology from cellular to whole-body perspectives. Continued development of precise, non-invasive tools to investigate skeletal muscle are critical in informing impactful discoveries in exercise and rehabilitation science.

Keywords: pain; injury; rehabilitation; athlete performance; blood flow restriction; muscle quality

Introduction

Skeletal muscle is one of the most metabolically active and adaptable tissues in the human body, comprising up to 40% of total body mass and containing 50-75% of all body proteins [1]. The dynamic and plastic nature of skeletal muscle enables it to support a wide range of vital functions for human health and performance, including initiating movement, maintaining posture and body temperature, stabilizing joints, and storing nutrients [2]. Over recent decades, researchers have developed and refined a range of techniques to evaluate skeletal muscle structure and function, non-invasively. These include imaging modalities such as magnetic resonance imaging (MRI) and CT, dual energy X-ray absorptiometry, anthropometric measurements such as skinfolds and girths, electromyography (EMG), and isokinetic dynamometry. Application of these techniques has provided key insights into the adaptability of human skeletal muscle within the context of aging, disease, injury, exercise, and nutrition [1,3,4]. While current methods have advanced our understanding of skeletal muscle physiology, continued innovation and optimization are necessary to develop more feasible assessment tools capable of exploring intricate muscle morphology responses to different physiological and pathophysiological stimuli [5]. Emerging areas requiring further research include the influence of individual variation in muscle structure and function, sensitivity of assessment techniques, the interplay between muscle and other tissues like fat and bone, and the ideal modes and dosages of exercise, nutrition, and rehabilitation interventions [6,7].

To further promote engagement in these research avenues, scientists must continue honing current approaches while implementing more viable, novel assessment tools aimed to adequately assess skeletal muscle properties. The purpose of our review is to briefly highlight emerging, innovative, and relatively feasible approaches that show promise in assessing skeletal muscle health. Covered topics in this review include ultrasound-derived dynamic imaging, tensiomyograpy, innovative approaches for blood flow restriction administration, utilization of neoepitope-biomarkers for skeletal muscle structure and function, ultrasound-derived echo intensity measures for muscle quality, and other novel assessments of body composition and skeletal muscle pain.

Methods

A comprehensive review of the science literature was conducted to assess the latest approaches in evaluating skeletal muscle health. The National Institutes for Health National Library of Medicine (PubMed.gov) and Google Scholar search engines were utilized, specifically, to identify recent publications related to dynamic imaging of skeletal muscle, peripheral neuromuscular assessments, muscle echogenicity, blood flow restriction, biomarkers of skeletal muscle function, skeletal muscle quality, body composition, and pain assessment.

Dynamic Imaging

Muscle function and characteristics can be measured in several ways and many laboratory- and hospital-based studies utilize EMG, and imaging instrumentation, such as magnetic resonance imaging. Financial and time constraints can limit access and the ability to employ many of these techniques when clinicians and practitioners are seeking a deeper understanding of muscle

function. A viable alternative to some of the more expensive and less accessible options is ultrasound imaging (Fig 1) [8]. Specifically for musculoskeletal ultrasound imaging, there are established methods detailing how to measure muscle thickness, cross-sectional area, echogenicity, etc. [9]. Most of these methods rely on the patient or participant to be in a static, rested state, which controls the environment with hopes to avoid any artifact or false representation of the muscle's morphology. However, many of the patient populations included in ultrasound imaging studies and clinical scenarios are likely to experience some sort of injury and/or exhibit symptomology that revolves around pain during movement.

Ultrasound imaging when used in a dynamic, innovative manner, capturing images during contraction and even exercise, provides an understanding of muscle function, not just static characteristics [8]. When a patient or participant is experiencing pain and dysfunction during movement, activities of daily living, or exercise, the consequences are well documented, especially in those with chronic low back pain. Due to the known contribution of abdominal, hip, and pelvic muscles to low back pain-related dysfunction, ultrasound imaging is a useful tool to view the complex layering of those muscles [8]. Part of the injury assessment process could include viewing muscles when individuals move, and they experience pain or avoid movement due to the fear of pain. Capturing muscle thickness, cross-sectional area, and quality can be done reliably in many positions [9,10], commonly in the lateral abdominal wall and posterolateral hip. The application of dynamic ultrasound imaging has been described recently for sport-specific and body part-focused rehabilitation exercises[11,12] . Visualizing musculature of the lateral abdominal wall is possible by fixing the ultrasound probe to the anterolateral abdomen with a belt ensuring the probe stays in the same position even while the individual moves. Documented methods describing this technique include capturing images and videos while walking, balancing, squatting, planking, swinging a golf club, etc.[11–14].]. Populations included in these studies span from healthy, asymptomatic individuals to those experiencing low back pain and chronic ankle instability.

The utility of dynamic ultrasound imaging is shown by recent studies that have reported muscle thickness changes from a static, rested position to an active, contracted position. Activation ratios may also be calculated by dividing the contracted thickness by the rested thickness and were first established in hook-lying tabletop positions. Functional activation ratios divide thickness during exercise (e.g., peak knee flexion during a single leg squat) by a static, starting position (e.g., standing). A preferential activation ratio [15] involves comparing the thickness of one muscle to others within the same image. For example, when imaging the lateral abdominal wall, the change in thickness of the transverse abdominis could be divided by the change in thickness of the entire lateral abdominal wall (Figure 2). This preferential ratio provides insight into how much the transverse abdominis changes its thickness relative to the other muscles during contraction. A greater preferential activation ratio indicates the transverse abdominis is the predominant muscle changing thickness out of the entire lateral abdominal wall. Dynamic ultrasound imaging also allows for an innovative, clinical approach to visual biofeedback. As the patient visualizes their muscles during a prescribed exercise, activity of daily living, or pain-provoking position, there is an opportunity to show the patient how they can contract the muscle either at a different time or how to increase thickness in general. Methods have been established for sport-specific ultrasound biofeedback, specifically viewing the obliques during a golf swing [12]. Brightness, B-mode, and Motion, M-mode can be used for dynamic imaging and biofeedback. Based on the

goal of dynamic imaging, B-mode may apply when viewing a reference, static image, or to view a frame-by-frame breakdown of a muscle moving through a task. M-mode may be appropriate when synchronizing dynamic ultrasound with other muscle measurement tools capturing in the time domain, such as timing of activation with electromyography [11].

Contractile Properties

Tensiomyography (TMG) is a non-invasive and objective assessment tool used to evaluate skeletal muscle contractile properties and peripheral neuromuscular function. It provides valuable information about muscle contraction characteristics, muscle fiber composition, and muscle fatigue. TMG has gained popularity in sports science, rehabilitation, and research settings due to its ability to provide real-time and reliable data on muscle function [16–18]. TMG involves the application of an external electrical stimulus to the muscle belly, causing a muscle twitch response that is measured through a displacement sensor tip (Fig 2). It primarily assesses muscle contractile properties, including muscle displacement, contraction time, and muscle relaxation time. These parameters reflect muscle stiffness, contractile speed, and muscle fiber recruitment patterns [19,20]. One of the key advantages of TMG is its ability to provide objective and quantitative data. Traditional assessment methods, such as manual muscle testing or electromyography, often rely on more subjective, post-acquisition interpretation or qualitative measures. TMG, on the other hand, offers standardized numerical values and objective measurements, reducing the potential for human error and enhancing the reliability of the assessment [20,21]. By tracking changes in muscle contractile properties, one can evaluate the effectiveness of training programs and make adjustments accordingly. TMG can also help identify muscle imbalances and guide targeted interventions to restore balance and optimize performance.

TMG involves elicited, involuntary isometric contractions that are generated using a single 1 ms-wide biphasic wave. By utilizing proprietary computer software, a twitch curve is generated based on data from the sensor, which allows for the determination of six primary parameters. The y-axis of this curve represents muscle displacement in millimeters, while the x-axis represents time in milliseconds. The key TMG parameters comprise displacement (Dm), contraction time (Tc), delay time (Td), contraction velocity (Vc) (Vc=[90%Dm-10%Dm/Tc]), sustain time (Ts), and half-relaxation time (Tr). (6) Displacement (Dm) pertains to the highest radial displacement achieved by the muscle and is linked to muscle stiffness. Contraction time (Tc) represents the duration between 10% and 90% of Dm on the positive slope of the twitch curve. Delay time (Td) is a temporal parameter that measures the duration from the initiation of the electrical stimulus to when the muscle belly reaches 10% of Dm or peak displacement. Half-relaxation time (Tr) refers to the time taken for the muscle displacement to decrease from 90% of its maximum to 50% of Dm on the negative slope of the curve. Sustain time (Ts) is defined as the time between 50% Dm on both the negative and positive slopes of the curve. Contraction velocity (Vc) is a calculated metric that aims to quantify the rate of muscular contraction. Since Vc is a derived measure, various methods have been employed by authors to compute it. The most commonly used calculation involves dividing the change in Dm between 10% and 90% by Tc. This approach enhances the usefulness of the Tc parameter and provides a more reliable measure of contraction speed by mitigating the influence of Dm. This is important as peak radial

displacement values have been shown to impact contraction time values due to the inherent shape of the twitch curve [20,21].

TMG can also help identify specific muscle deficits or imbalances that may contribute to functional limitations or recurring injuries. With this information, tailored rehabilitation programs can be developed to address these deficits and promote optimal recovery [18,21]. Moreover, TMG can be a valuable research tool for investigating muscle adaptations to training, comparing different training protocols, or studying the effects of injury or disease on muscle function. Researchers can use TMG to examine changes in muscle contractile properties following specific interventions or to explore how different training modalities affect muscle performance.

While TMG has shown great promise as an assessment tool, it is important to note its limitations. TMG primarily focuses on muscle contractile properties and does not provide direct information about neural activation or muscle force production. It is also important to consider that TMG measurements may be influenced by factors such as skin impedance, adipose tissue thickness, and anatomical variations. These factors need to be considered during data interpretation to ensure accurate and meaningful results.

Innovation Applications to Determine Blood Flow Restriction Occlusion Pressures

Traditional exercise-based approaches are not well tolerated by several clinical populations, an issue researchers/practitioners continually attempt to circumvent [22–24] . An exciting strategy to address this issue includes combining exercise with limb occlusion (blood flow restriction [BFR]) due to its ability to induce similar or even superior benefits compared to traditional non-occluded exercise [25–27]. During BFR exercise, low exercise loads (e.g., lighter weights/resistance) are used while completing a standardized 5-min exercise scheme. Blood flow restriction exercise uses a small inflatable cuff applied to the upper most portion of a limb to restrict venous blood from exiting the exercising limb which facilitates robust physiological responses that may underly the subsequent increases in muscle strength, mass, and endurance (i.e., fatigue resistance) observed following chronic BFR exercise. These adaptations have been demonstrated in asymptomatic [22–31] and some symptomatic populations [32–34]. Importantly, BFR resistance exercise has also been shown to be safe and to elicit positive effects in post-surgical [35,36] older adults [32,37,38] and hospitalized patients [39]. Specifically, the safety and effectiveness of BFR exercise has been routinely demonstrated with the implementation of the standard 75 repetition (1 × 30, 3 × 15) scheme [28,40]. Additionally, the exercise is performed at 30% of 1RM (i.e., a low weight/resistance) and with the small, inflated cuff set to a pressure corresponding to 40-80% of arterial occlusion pressure (i.e., approximately 40-80% of systolic blood pressure) [41,42].

Despite its high versatility and implementation in both research, clinical, and athletic settings, the application of BFR is limited. Specifically, the gold standard for the determination of total arterial occlusion pressure (TAOP) and application of BFR requires the use of pulsed wave Doppler (Fig 3). Typically, this necessitates trained personnel to operate and interpret ultrasound-based readings (i.e., arterial and venous blood flow) with the concomitant modulation of pneumatic pressures. Theoretically, minute variations in the determination of TAOP changes

the BFR pressure applied which has been demonstrated to alter the physiological responses [41,43] and discomfort (e.g., higher pressures result in greater discomfort). Therefore, it is imperative that TAOP is determined accurately and precisely. As a result, the current applications of BFR exercise are somewhat limited to research and clinical settings whereby these procedures can be performed accurately and reliably, although data are limited in this regard. For example, among a small sample of males (n=13), pulsed wave Doppler ultrasound exhibited moderate/high reliability (intraclass correlation coefficient [ICC] = 0.796), while the coefficient of variation (COV) was 5.6% (Bezerra et al., 2017). There were, however, no relative measures of reliability reported (e.g., standard error of the measurement [SEM] or minimal difference [MD]) which limits the application of these findings [44].

An exciting strategy to circumvent the determination of TAOP, is the algorithm-based determination of TAOP. Specifically, several commercially available devices (e.g, SujiBFR, Defli, Smartcuffs) independently ***estimate*** TAOP using proprietary engineering that likely leverages known variables (e.g., limb width, mean arterial pressure) which affect TAOP. For example, in a small sample (n=10), one study [45] examined test-retest reliability of an algorithm-based determination (Delfi PTS, Delfi Medical, Vancouver, BC, Canada) of TAOP and reported high reliability (ICC > 0.953; COV = 2.97%), but the validity of this device was not examined. Algorithm-based devices such as the one previously examined and others (e.g., Suji, SmartCuffs) may exhibit greater utility than current research-based practices for the determination of TAOP which requires ultrasound and trained personnel, but their algorithms should be critically examined to prevent potential adverse effects. Specifically, researchers [42,46,47] have done substantial and meaningful work identifying predictors, equations, and/or algorithms which can estimate TAOP, but these methods are not without error. Thus, there is an inherent need to determine if commercially available BFR devices implementing algorithms to determine TAOP are clinically sound (i.e., reliability and validity). Furthermore, there is insufficient data examining the reliability of TAOP using pulsed wave Doppler (the criterion method). Regardless, commercially available devices (e.g., SujiBFR, Delfi, Smartcuffs) may provide viable alternatives to the criterion determination of TAOP ultimately facilitating the larger implementation of BFR.

Novel Serological Neoepitopes as Biomarkers of Skeletal Muscle Structure and Function

Biomarkers are defined as measurable indicators of biological processes or responses to an exposure or intervention [48] . They represent an indispensable tool in human biology that allows researchers to map the complex physiological pathways that underpin healthy and altered physiological function [49] . The use of serological biomarkers has the benefit of being relatively non-invasive and easy to perform [50,51], which has led to the widespread development of assays for various biological markers. In this regard, neoepitopes have emerged as a class of serological peptide biomarkers with diagnostic and prognostic potential that may also have utility as minimally invasive indicators of health status, physiological response and/or disease susceptibility (Fig 4).

In skeletal muscle, neoepitopes may be exposed following post-translational modifications (PTMs) to specific muscle proteins [52] . Proteolytic cleavage is a particularly interesting PTM

as it creates peptide fragments and the potential for novel neoepitopes on the carboxy- or aminoterminal ends of cleaved peptides [53,54]. Peptide fragments being smaller than their intact parent proteins can enter the circulation more readily [55] where antibodies can be raised against specific neoepitopes exposed on these fragments. Since serological neoepitope biomarkers consist of a unique combination of parent proteins and PTMs [56], they are thought to be reflective of tissue specific physiological or pathological remodeling processes rather than overall muscle size or quality and may therefore serve as ideal biomarkers for early the detection of various myopathies [57,58] . It is also thought that serological neoepitope biomarkers have the potential to provide insight into net changes in protein metabolism, which is currently limited to operationally complex and invasive stable isotope techniques [58].

Much of the research examining neoepitopes in skeletal muscle has focused on temporal changes to extracellular matrix (ECM) collagens following various interventions. Nedergaard et al., 2013 examined changes in collagen type VI fragment degraded by matrix metalloproteinases 2 and 9 (C6M) and type VI collagen N-terminal globular domain epitope (IC6) among young and old men at baseline after 2-weeks of unilateral immobilization and 4-weeks of remobilization with 3 x weekly resistance training, respectively [59]. They found significant correlations between IC6 and muscle mass at baseline, and between C6M and the change in muscle mass from 2-weeks to 4-weeks of remobilization in young but not old men [59]. The same group also reported significant associations between lean body mass, IC6, collagen type III synthesis (Pro-C3) and the IC6/C6M ratio among matched controls in the 25B cohort of the Danish Head and Neck cancer group (DAHANCA) trial [60]. In another study, Sun et al., 2015 examined the temporal profile of neoepitope peptides Pro-C3, C-terminus α3(VI) chain (Pro-C6) and C6M following 8-weeks immobilization and remobilization. They reported significant associations between Pro-C3, C6M and lean body mass at baseline, a significant upregulation of both Pro-C3 and Pro-C6 following immobilization and remobilization indicative of muscle remodeling, and an inverse relationship between Pro-C6 and changes in muscle mass [61]. Consistent with this, work by Nielsen et al. 2013 also indicates that higher levels of Pro-C3 predict greater muscle mass in healthy individuals [62]. More recently, Reule et al., 2016 found that the ratio of type II collagen collagenase cleavage neoepitope (C2C) to C propeptide of type II procollagen (CP2) was responsive to leucine-rich amino acid supplementation administered in conjunction with 12-weeks of combined aerobic strength and balance training [63]. They report a significantly greater decrease in the acute phase (0-3 hours) C2C/CP2 post-training response to a downhill walking stress test when compared to the placebo group, indicating a lower disturbance in joint homeostasis that coincided with a significant attenuation of acute phase quadricep MVC strength loss [63]. Several other serological biomarkers, including C-terminal agrin fragment (CAF) and matrix metalloproteinase-2 degraded titin fragment (titin-MMP2) also appear to be strong discriminators of normal versus aberrant skeletal muscle outcomes including muscle wasting/atrophy and protein turnover [61,64].

The large dynamic range and complexity of both the proteome and various PTMs [65] represents a significant challenge for the identification of new muscle specific neoepitope biomarkers and targeting reagents. Nevertheless, while this area of research is currently in its infancy, the limited

current literature indicates that serological neoepitope biomarkers of cleaved circulating peptide fragments are promising candidates for assessing skeletal muscle structure and function.

Skeletal Muscle Quality

Studies have increasingly shown that there is a disassociation between skeletal muscle strength and mass [66,67]. For example, the National Institutes on Aging's longitudinal Healthy, Aging, and Body Composition study showed that adults ≥ 70 years of age lost ~3× more muscle strength than mass on an annual basis [66]. Even more compelling, older adults that gained muscle mass still lost muscle strength [68]. In addition, immobilization and bed rest studies have shown that muscle strength and mass show divergent timelines, with strength rapidly diminishing before detectable declines in muscle mass [69–71]. These concepts have given rise to the concept of muscle quality and its methods of assessment [72].

The measurement of echo intensity has emerged as a potential tool for studying skeletal muscle quality and estimating intramuscular fat content, providing insights that may be unique from measures of muscle size [73]. Echo intensity is a quantitative measure of brightness in ultrasound images, reflecting the echogenicity of tissues (Fig 5). In skeletal muscle, echo intensity is influenced by physiological factors such as muscle fiber arrangement [74], connective tissue content [75], and the presence of intramuscular fat [76]. Higher echo intensity values are associated with muscle pathologies like atrophy, fibrosis, and fatty infiltration [77], while lower values are observed in young, healthy muscles. MRI studies suggest that echo intensity's ability to estimate intramuscular fat content appears promising[77,78]. Echo intensity is associated with several functional outcomes [79,80] and it appears to be sensitive in detecting differences between age groups [81]. Additional research is needed to understand why large differences in echo intensity are often seen when comparing groups with distinct characteristics like age or training status, whereas smaller changes are detected in response to exercise or rehabilitation interventions [82]. One potential explanation is that intrinsic physiological factors like muscle fiber type distribution, connective tissue content, and intramuscular fat infiltration change slowly over time. Group differences may represent the cumulative result of prolonged exposure to factors like aging. In contrast, short-term interventions elicit more modest echo intensity changes, as muscle structural characteristics do not radically transform within days or weeks. Longer training studies are needed to determine if more marked echo intensity changes can be induced over time with sustained exposure to stimuli like exercise. It is also important to recognize that echo intensity is affected by methodological factors, such as probe tilt [83] and participant positioning [84]. Recent evidence suggests that researchers new to echo intensity analyses provide reliable measurements [85] and small adjustments in image depth to accommodate muscles of different sizes are acceptable [86].

Most published echo intensity studies have relied on ImageJ software (National Institutes of Health, Bethesda, MA, USA), in which investigators manually analyze a muscle's region of interest. While these approaches are well established, they can be time consuming and subjective, making it difficult to conduct large-scale analyses quickly. However, emerging technologies are likely to streamline the measurement process, reduce subjectivity, and enhance the accuracy of echo intensity analysis. Automated or semi-automated region of interest selection algorithms have recently been introduced to target specific muscle regions [87,88]. In the future,

computerized analysis of ultrasound images will enable the precise quantification of echo intensity values, ensuring consistent and reproducible evaluations. In addition, small probes and wireless technology that integrate with laptops, tablets, and smartphones phones will likely make the analysis of echo intensity much more accessible and rapid.

Overall, the measurement of echo intensity has emerged as an innovative approach for studying skeletal muscle quality and estimating intramuscular fat content. Importantly, these measurements can be done with ultrasound devices that are portable and less expensive than MRI, and minimal training is required. These measurements are particularly useful when complementing measures of muscle size (e.g., cross-sectional area or volume) and physical function. For more detailed information, the reader is encouraged to review two recent echo intensity reviews by Stock and Thompson [73] and Wong et al [82].

Practical Body Composition & Novel Use of Bioelectrical Impedance Analysis (BIA)

Laboratory-based methods of body composition estimation potentially offer an error reduction of approximately 50% in body fat estimation compared to field-based methods. However, these improvements are partially attributable to the ability to control numerous physiological assumptions [89]. The inherent error of body composition measurement is further complicated using either population-specific or generalized prediction equations that likely compound the error in some individuals or groups. For athletes, the need for dietary restriction, adequate hydration, and standardized physical activity further exacerbates the issue.

Whole body estimation of body fat percentage is limited with its greatest utility in large population/epidemiological evaluations or public health settings. Site- or region-specific values to evaluate tissue distribution may be more useful for practitioners and athletes. Dual-energy X-ray absorptiometry enables potential evaluation of total body and site-specific fat mass, lean soft tissue mass, and bone mineral density [89] . However, these devices are expensive, vary across manufacturers, require low-dose radiation exposure, all of which may be prohibitive in many practical settings.

A viable alternative is the direct evaluation of skinfold thickness either at a specific site or as a sum of several sites throughout the body, instead of using prediction equations to determine body density. While standardized protocols and trained evaluators are required, this method seems least affected by the inherent variation in the typical restrictions recommended for body composition assessments [90]. Although less commonly reported in the literature, recent attempts have been made to provide normative data for the summation of skinfold measurements [90,91].

As skinfold thickness does not directly assess skeletal muscle, it is recommended to evaluate this information alongside anthropometric data such as regional circumferences (limb, hip/waist, etc.) and/or body mass [92,93]. Fig 6 illustrates how changes in skinfold thickness can be translated to body fat, while circumferences or body mass can serve as a proxy for muscle mass and the interaction between these values.

This combined information can also be used to calculate corrected girth values (which account for an adjustment of skinfold thickness to determine musculoskeletal cross-sectional area) or lean mass index (a log-based adjustment for body mass and summed skinfolds) [94] . Notably, DeFreitas et al. [95] demonstrated that, despite underestimating muscle cross-sectional area compared to peripheral quantitative computed tomography (pQCT), both a corrected girth equation [96] and a regression equation [97] adequately tracked changes in this value during an eight-week resistance training program. A recent review by Duarte et al. [98] discusses numerous validated anthropometric equations for limb-specific muscle mass estimation.

BIA offers a unique approach for body composition assessment by estimating the fat-free body, generally assumed to be ~73% hydrated, rather than fat mass [89]. However, the basic assumptions of body shape (i.e., the segments of the body are perfect cylinders), as well as the use of prediction equations (either through published work or developed by the device manufacturer), introduce similar problems to other measurement methods. Therefore, it is becoming increasingly common to directly evaluate the raw bioelectric parameters [resistance (R), reactance (Xc), and phase angle (PhA)] recorded by these devices (typically at 50 kHz).

From a practical perspective, R may represent cellular hydration, Xc may represent cell membrane integrity, and PhA is calculated as the arctangent ratio of Xc to R. The latter variable may be considered representative of intra- and extra-cellular fluid (or ICW/ECW ratio) and/or cell body mass, which has been suggested as an indicator of cellular health. These values can be considered separately or plotted together through bioelectrical impedance vector analysis (BIVA). The resultant vectors have been shown to differentiate between competitive levels and types of athletes [99]. Interestingly, Kim et al. [100] demonstrated the discriminative potential of BIVA by distinguishing between female fashion models, dancers, and gymnasts in a manner similar to somtatotyping with increasing mesomorphy (i.e., muscularity) and decreasing ectomorphy (i.e., linearity) across these groups. Furthermore, a recent systematic review reported that PhA increases with age and is higher in athletes than controls as well as in males than females [101].

The evaluation of raw bioelectrical data can also be applied regionally, a process known as electrical impedance myography or localized BIA. Initially developed to examine diseased tissue and subsequently, sarcopenic individuals, its application in athletic populations has been established, focusing on adaptations to exercise and return-to-play situations following injury [102].

In adopting an “innovation through simplification” stance towards body composition assessment, this section of the paper underscores the importance of understanding and contextually applying the available methodologies. For a comprehensive overview of available methods, and a practical decision-making tree readers are encouraged to consult Kasper et al. [90]. Further, a detailed discussion on related topics is provided by Lukaski & Raymond-Pope [99].

Skeletal Muscle Pain

Pain is a sensory and emotional experience impacted by the interaction of biological and psychosocial factors [103]. One biologic factor that impacts the perception of pain is skeletal

muscle health. In a state of inflammation or musculoskeletal pathology, myofascial trigger points may develop within the tissue that contribute to a myofascial pain syndrome [104]. Myofascial pain is prevalent with 30% of individuals seeking care for pain at a primary care office meeting the criteria for myofascial pain. While the definition of a trigger point can vary, there is general agreement among clinicians and scientists that myofascial pain is a separate diagnosis from fibromyalgia [105] and that trigger points contribute to myofascial pain syndrome [106].

Myofascial trigger points are localized, taut bands of skeletal muscle tissue (Fig 7). A recent Delphi survey established that two of the following three criteria should be present to diagnose a myofascial trigger point: taut band, hypersensitive spot, and referred pain [107]. During direct compression, a 'jump response' may be elicited with or without referred pain [106]. Myofascial trigger points are often both painful to palpation and can be a generator of pain. While the mechanisms underlying trigger points are multifactorial, repetitive eccentric contractions or overuse may result in an abnormal increase in acetylcholine at the neuromuscular junction of the muscle. Abnormal acetylcholine release may generate a sustained muscle contraction, causing localized ischemia and a palpable taut band [108]. Although myofascial pain was traditionally thought to only involve peripheral changes, muscle sensitization is also impacted by central nervous system sensitization [109].

A diagnosis of myofascial pain syndrome relies on the palpation of myofascial trigger points. However, a limitation in the clinical assessment is varied inter-rater reliability in myofascial trigger point identification [110]. New approaches have been proposed to improve the identification of trigger points, including: pressure algometry and imaging. Pressure Pain Threshold (PPT) is a cost-effective and clinically feasible technique that may be employed to assess trigger points. During PPT, a device with a small rubber tip (algometer) is applied over the muscle with an ascending intensity until the individual reports that the sensation changed from "comfortable pressure to slightly unpleasant pain" (pain threshold). The benefit of this assessment is the stimulus is quantifiable and, therefore, the threshold for pain perception in response to pressure is measured. PPT is significantly lower over trigger points and increases in areas without trigger points [111]. Excellent intra and inter-rater reliability is demonstrated for PPT application over trigger points [112].

Recent advances have also allowed for imaging of trigger points [113]. Imaging methods, including ultrasound, magnetic resonance imaging, and infrared thermography have been developed as objective measures to potentially address the limitations with reliability. Imaging allows for objective characterization of the tissue consistent with the definition of a trigger point. B-mode ultrasound imaging indicates trigger points present as spherical, hypoechoic regions [56]. Ultrasound elastography indicates decreased vibration amplitudes within the region, indicative of localized stiffness of the muscle [114] at the site of the trigger point. Blood flow to myofascial trigger points is also distinct from healthy tissue [114]. Magnetic resonance imaging has been used to examine trigger points; however, the evidence remains unclear on the benefit of this imaging modality [115] for this purpose. Trigger points are important contributors to myofascial pain and relevant to clinical treatment of patients with myofascial pain. Innovations in standardizing the definition of trigger points, along with advances in the imaging of muscle, may help to make this phenomenon more objective.

Summary

Accurate and precise assessment of skeletal muscle health is imperative for diagnosis of disease and optimization of exercise and rehabilitation interventions. Our review has highlighted several viable, novel techniques with potential to advance these aims. Although not comprehensive, we have focused on select emerging approaches based on their promise for impactful discoveries and feasible implementation. Rapid technological innovations and subsequent adoption seem poised to accelerate and expand prior methods. Despite progress, outstanding questions remain regarding individual variation in exercise responsiveness, organ crosstalk, biomarker development, and monitoring and enhancing athletic performance. It is our hope that continued technical advances in assessing skeletal muscle health will provide insights into these critical topics in exercise and rehabilitation science.

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Figure Legends

Figure 1. Dynamic imaging (B-mode) of lateral abdominal wall musculature using an elastic belt to keep linear transducer fixed to the abdomen throughout movement. Created with BioRender.com.

Figure 2. Muscle belly displacement versus time the phases of contraction elicited by TMG with key parameters comprise displacement (Dm), contraction time (Tc), delay time (Td), contraction velocity (Vc) (Vc=[90%Dm-10%Dm/Tc]), sustain time (Ts), and half-relaxation time (Tr). (Top). An example of (TMG) placement for the lumbar erector spinae (bottom).

Figure 3. Illustrates the gold standard for the determination of TAOP which requires at least one technician. More recently, innovative approaches have been developed which leverage proprietary algorithms to determine TAOP and do not require a trained technician(s). These devices can often be

controlled wirelessly from a mobile app and detached from the air source facilitating, greater utility in exercise and rehabilitation settings. Created with BioRender.com.

Figure 4. Detection of serological peptide fragments. 1. Proteolytic cleavage of collagen protein 2. Peptide fragments enter blood stream, 3. Blood sample obtained, 4. Antibodies raised against neoepitope markers, 5. Quantification vis assay e.g., flow cytometry. Created with BioRender.com.

Figure 5. Example B-mode ultrasound images and echo intensity (EI) analyses of the vastus lateralis for an older (top) and younger (bottom) male. Note the vastly different pixel distributions for the two images. These images are a fairly accurate depiction of published findings, as many studies have reported higher echo intensity among older adults.

Figure 6. Changes in site-specific skinfold thickness and circumference (or body mass) as potential proxies of body fat and muscle mass, respectively. The examples provided indicate trends toward and away from A) muscle growth/hypertrophy, B) adiposity, C) muscle growth/hypertrophy with leanness, and D) muscle growth/hypertrophy with adiposity. Created with BioRender.com.

Figure 7. Overview of Methods to Identify a Myofascial Trigger Point. Myofascial trigger points may be identified with palpation or novel imaging techniques. Although not comprehensive, novel imaging techniques may include ultrasound or magnetic resonance imaging (MRI). Created with BioRender.com.