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An Old Problem: Aging and Skeletal-Muscle-Strain Injury

Brent A. Baker

The author is with the Health Effects Laboratory Div, National Inst for Occupational Safety and Health (NIOSH), Morgantown, WV.

Abstract

Clinical Scenario: Even though chronological aging is an inevitable phenomenological consequence occurring in every living organism, it is biological aging that may be the most significant factor challenging our quality of life. Development of functional limitations, resulting from improper maintenance and restoration of various organ systems, ultimately leads to reduced health and independence. Skeletal muscle is an organ system that, when challenged, is often injured in response to varying stimuli. Overt muscle-strain injury can be traumatic, clinically diagnosable, properly managed, and a remarkably common event, yet our contemporary understanding of how age and environmental stressors affect the initial and subsequent induction of injury and how the biological processes resulting from this event are modifiable and, eventually, lead to functional restoration and healing of skeletal muscle and adjacent tissues is presently unclear. Even though the secondary injury response to and recovery from “contraction-induced” skeletal-muscle injury are impaired with aging, there is no scientific consensus as to the exact mechanism responsible for this event. Given the multitude of investigative approaches, particular consideration given to the appropriateness of the muscle-injury model, or research paradigm, is critical so that outcomes may be physiologically relevant and translational. In this case, methods implementing stretch-shortening contractions, the most common form of muscle movements used by all mammals during physical movement, work, and activity, are highlighted.

Clinical Relevance: Understanding the fundamental evidence regarding how aging influences the responsiveness of skeletal muscle to strain injury is vital for informing how clinicians approach and implement preventive strategies, as well as therapeutic interventions. From a practical perspective, maintaining or improving the overall health and tissue quality of skeletal muscle as one ages will positively affect skeletal muscle’s safety threshold and responsiveness, which may reduce incidence of injury, improve recovery time, and lessen overall fiscal burdens.

Keywords

stretch-shortening contractions; inflammation; myofiber degeneration; myofiber regeneration

Activities of daily living, irrespective of whether one is conducting physical work, competition, or exercise, often result in deleterious outcomes such as skeletal-muscle-strain

correspondence to bwb3@cdc.gov.

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injury, accompanied by transient losses in muscle performance and increases in tissue edema, inflammation, and degeneration/necrosis, as well as pain, discomfort, and soreness (ie, frequently referred to as delayed-onset muscle soreness—DOMS¹). Resuming physical work or competition after this type of injury requires proper management of the signs and symptoms of injury, along with ensuring optimal regeneration and repair of the biological tissue involved, concurrent with restoration of function that includes both performance and physiology. During this recovery time or period of rehabilitation, the affected tissues undergo a series of events that ultimately lead to competent healing. Even though it is agreed that aging affects this process broadly, it is not completely understood if and how aging affects either or both the initial induction of mechanical injury to the muscle or the influence aging imparts on the secondary biological injury component observed during the customary period of recovery. Thus, even though it takes a relatively short period of time for restoration of performance and regeneration to occur (ie, approximately 10–21 d), complete healing and maturation of the muscle syncytium after an injurious “contraction-induced” muscle-strain event may take longer (ie, >1 mo²), and aging alone likely affects multiple inputs simultaneously that eventually may negatively affect regeneration and restoration of performance. Contemporary understanding of these processes is limited, which necessitates more thorough investigation and evidence in support of the most efficacious means to positively affect age-dependent recovery from muscle injury. With this background in mind, the purpose of this succinct, hypothesis-driven review focuses on discussing the scientific evidence concerning aging’s role in modifying skeletal muscle’s integrative physiology and age-dependent contraction-induced strain injury along with the fundamental models employed to investigate this concept and, finally, to present premises to stimulate future research. Specifically, the central tenet, which focuses on optimally altering the aging microenvironment so that skeletal muscle tissue tolerance is enhanced, directly improving skeletal- muscle healing and function, is appealing and merits examination.

Aging

Impact and Consequence

Recently, reports convey that by the year 2050 approximately 25% of the population will exceed 65 years of age, and some countries may well surpass ~40%,³ while other world-population projections estimate that individuals 80 years of age will more than tripled.⁴ By 2050 the number of persons in the United States 65 years of age will double,⁵ and while the current US labor workforce is composed of 1 in 5 workers over the age of 55, it is projected that as early as 2020, 1 in 4 US workers will be over the age of 55.⁶ These demographic shifts result in challenging circumstances for society as a whole and for the occupational sector specifically yet emphasize the need for a universal approach for sustaining health span—the number of years lived without morbidity and disability.^{4,7}

Indeed, maintenance or even improvement of quality of life is a major determinant of overall health at any age but becomes a point of emphasis as one ages.

Although aging is not a considered a disease,⁸ it does increase our susceptibility to a multitude of diseases⁹ and conditions. This is concerning since a number of factors including muscle strength, endurance, work capacity, and power have been reported to

progressively decline with age, beginning at adulthood and continuing into advanced age.^{10,11} Concomitant with these decrements is an increase in susceptibility to soft-tissue maladaptation (ie, the lack of maintenance or appreciable improvement in both function and physiology) that increases with aging,^{11–13} yet data suggest that this is modifiable in both animals¹⁴ and humans.^{15,16} It is postulated that older individuals/ workers/athletes incur more chronic disability and require more care that is more costly than for younger populations,¹⁷ and indeed the burden of musculoskeletal disability is not equally shared across the population.¹⁸ There have been multiple reports detailing that the recovery time for musculoskeletal injuries increases significantly with advanced age, and this occurs in both animals^{13,19,20} and humans.²¹

Aging, at the organism or systems level, a phenomenon that occurs *in vivo*, is the process of becoming chronologically older that occurs in parallel with biological alterations and in many instances is associated with conditions of decreased health and increased dependency²² (eg, sarcopenia—defined as skeletal-muscle weakness and decreased muscle mass).²³ Indeed, between the third and the ninth decades of life skeletal-muscle mass and performance decrease by ~15% to 30%.^{23,24} Recent reviews highlight a number of biological events that are suggested to participate in negatively influencing the aging phenotype and overall functional status, including, but not limited to, impaired immune function, epigenetic/epigenomic modifications, genetic/genomic alterations/damage, oxidative stress, chronic low-grade inflammation and “inflammaging,” cellular senescence and senescence-associated secretory phenotype, mitochondrial dysfunction, dysregulated and desensitized growth and stress signaling, impaired protein ubiquitination, impaired apoptosis, impaired autophagy, and impaired stem/satellite cell function^{25–31}; yet, whether these factors are the cause of an aging phenotype or the result of cumulative exposures throughout the aging process is not readily agreed on. In addition, although this is not an exhaustive list, skeletal muscle’s quality and function with aging are directly attributed to modifications in its size, contractile properties, composition (ie, fiber-type distribution and adipose/noncontractile tissue), metabolic status, energetics, motor-unit number, type and properties, muscle stem/satellite cell quantity and capacity, and interstitial space constituents (ie, muscle fibrosis).^{32,33} Even in its extraordinary complexity with respect to the number of variables influencing an aging organism, it is ultimately the result of repeated biophysical and biochemical exposure-response events over the chronological lifetime that influence structure-function outcomes. As the prime focus of this discussion with respect to aging, the muscle system is an elegant organ system in that it supports biophysical (ie, structure, contraction, etc) and biochemical (ie, metabolism, energetics, etc) well-being, as well as having the plasticity for adaptation and regeneration when challenged via various stimuli. Along with the sarcopenia, aging skeletal muscle presents with decreased muscle quality before and after various mechanical loading exposures,^{11,12,34–36} as well as frailty and loss of independence.³⁷ Muscle quality is defined as the proportion of muscle strength (ie, static or dynamic) relative to muscle mass³⁸ and has been used to demonstrate and differentiate the overall functional status (ie, performance and physiology) of muscle *in vivo*.^{11,12,14,39} Note that suggestions are that the preservation of lean muscle mass would likely contribute to the greatest effects on maintenance of performance with aging³⁶ and likely would affect overall quality of life and independence.

Soft-Tissue Pathomechanics

Pathophysiology can broadly be defined as the explanation or etiology of an abnormal or undesired condition along with the resulting functional alterations that result, whereby the underlying processes or mechanisms are ascertained, so that both functional restoration and biological healing ensue. With regard to soft tissue in general, pathomechanics is the study of the mechanisms surrounding soft-tissue injury and/or dysfunction that results from physical loading exposures, while, specifically, the study of skeletal-muscle-injury pathomechanics focuses on the effects imparted by both static (ie, isometric) and dynamic (ie, lengthening, shortening, or stretch-shortening-contraction [SSC]) muscle movements on active skeletal muscle during acute and/or chronic muscle-strain injury and the resulting biomechanical (ie, strength, work, etc) and biological (ie, cellular, molecular, etc) outcomes. Even though the fundamental investigation of skeletal-muscle-strain injury is often examined in isolation, it is important to recognize that extrapolation should account for the multiple tissues and systems involved during this type of injurious event, and, undeniably, the most physiologically representative model concomitant with an integrated, multidisciplinary methodology is optimal and should be employed.

Musculoskeletal disorders (MSDs) are multiple conditions commonly resulting from physical/mechanical exposure that affect muscle, tendon, ligament, nerve, connective tissue, bone, and joint, as well as other soft tissues. The US Bureau of Labor Statistics⁴⁰ defines MSD, based strongly on mechanism of injury, to

include cases where the nature of the injury or illness is pinched nerve; herniated disc; meniscus tear; sprains, strains, tears; hernia (traumatic and nontraumatic); pain, swelling, and numbness; carpal or tarsal tunnel syndrome; Raynaud's syndrome or phenomenon; musculoskeletal system and connective tissue diseases and disorders, when the event or exposure leading to the injury or illness is overexertion and bodily reaction, unspecified; overexertion involving outside sources; repetitive motion involving microtasks; other and multiple exertions or bodily reactions; and rubbed, abraded, or jarred by vibration.

Two examples of specific occupationally and athletically induced MSDs that are prevalent, especially in aging populations, are osteoarthritis and muscle-strain injury. Etiology of osteoarthritis comprises structural and functional degeneration of the joint that occur with repeated years of cumulative damage to the articular cartilage,⁴¹ while examples of the biomechanical origination of hamstring (ie, biceps femoris) muscle strains occur by overextension of the active muscle, when an external load is being displaced or resisted by a worker, or such strains in an athlete who actively resists or displaces an externally applied load when attempting to perform a maneuver.

These disorders are multifactorial and ubiquitous, affecting all individuals (ie, laypersons, workers, athletes, etc), and continue to present a significant financial conundrum. Specifically, in the United States alone, physical injuries resulting from MSDs are prevalent, accounting for ~38% of all medically diagnosed injuries,⁴² and such strain/sprain injuries account for ~33% of time away from work and are associated with costs exceeding ~\$50 billion annually.⁴³ Thus, integrating the protection of worker health and safety with

evidence-based health promotion is a key strategy for improving workers' total health.⁴⁴ In addition, reports that these types of injuries account for ~10% to 55% of all injuries incurred in sports, and over ~90% of athletic-related injuries include muscle-strain injury.⁴⁵ Injuries such as contraction-induced skeletal-muscle-strain injury resulting from mechanical loading are clinically diagnosable yet distinct from the exercise-induced stimulus that results in transient soreness and discomfort,^{46–48} which ultimately results in either an adaptive (ie, increased biomechanical performance and muscle mass/hypertrophy) or maladaptive/overtraining/overuse (ie, no change or loss of performance and muscle mass with no overt histopathology) outcome reported in both animals^{11,12,47} and humans.⁴⁹ Emerging from these fundamental studies conducted on rodents are valuable computational data and methods for assessing specific and sensitive means to characterize and quantify skeletal muscle's functional response in vivo.⁵⁰ Nevertheless, muscle-strain injury continues to be a leading cause of long-term functional disability; prolonged pain, irrespective of the origin of pain (ie, soft tissue, hard tissue, psychological, etc); and economic burden, irrespective of demographics or domains, on a world scale.^{51–54} Indeed, overt skeletal-muscle-strain injury resulting from a single^{55,56} or repeated injurious muscle movements^{59–59} is prevalent in sports/orthopedic settings,^{45,60} in the workplace,^{40,42} and the military.⁶¹ Even though there are no established universal classification criteria or system for the range of strain injury incurred, fundamental evidence indicates that the microscopic injury is dependent on the biomechanical loading envelope (ie, repetition number, range of motion, duty cycle, etc),^{57,62–65} proportional to the severity of the diagnosed degree of clinical injury⁶⁶ (ie, first-degree or mild < second-degree or moderate < third-degree or severe⁶⁷), and may be regionally specific depending on the type of muscle contraction used,⁶⁸ and recovery is age-dependent.^{13,58,69}

Models of Contraction-Induced Muscle-Strain Injury

Fundamental models of contraction-induced muscle injury in animals are useful in elucidating the etiology and basic mechanistic responses for extrapolation to occupational-, sport-, and military-related MSDs in humans.^{70,71} For decades the majority of basic-science models for studying contraction-induced skeletal-muscle injury exclusively focused on active lengthening movements to induce muscle-strain injury,⁴⁸ yet a more physiologically relevant contraction paradigm incorporates not only active lengthening movements but also isometric and shortening movements. This contraction paradigm, as defined previously, is the basis of the stretch-shortening contraction (isometric-lengthening-shortening), and includes the stretch-shortening cycle,^{72,73} which physiologically is the most representative movement pattern in humans^{74–76} and other mammals.^{58,77,78} Thus, the use of controlled, in vivo muscle contractions is the most beneficial way to study skeletal-muscle injury, regeneration, and repair mechanisms and how they relate to clinical skeletal-muscle contraction-induced strain injury.^{46,79} Indeed, findings from human models of electrically evoked overload injury⁵⁹ and animal models of muscle-strain injury including repetitive motion⁸⁰ and electrically evoked rodent dynamometer models^{55,57,81} demonstrate that the cellular pathways of edema, inflammation, degeneration/necrosis, and regeneration, and the accompanying histopathology and biomechanical decrements are congruent with what is believed to present in humans.^{45,67,82} It is also accepted that the amount of mechanical

loading in SSC-induced injury has a graded effect on both changes in muscle performance and the extent of resulting muscle injury in vivo.^{58,66,78}

Specifically, clinical skeletal-muscle contraction-induced injury is directly initiated by focal mechanical/physical injury⁵⁶ to microlevel structures in the muscle fibers (ie, sarcomeres⁸³ and disruption of excitation–contraction coupling⁸⁴ surrounding interstitium).⁸⁵ Immediately after this initial mechanical injury, a biological response commences that involves sequential yet complementary stages of edema, inflammation, degeneration (ie, these 3 phases are collectively referred to as the destruction phase or secondary injury phase), regeneration, and repair.^{45,78,81,86–88} This secondary biological response is critical for clearing degenerative/nonfunctional tissue for subsequent muscle-fiber regeneration and recovery of function.^{89–91}

During this time, satellite cells (quiescent muscle precursor cells) are activated, proliferate, differentiate, and finally fuse with the existing myofiber.⁹² Furthermore, developmental myosin heavy chain is expressed in injured fibers during this time period, and this has been suggested to form the recapitulation of the developmental program.⁹³ At this time, the muscle demonstrates a mixture of both degenerative and regenerative processes. Finally, central nuclei appear and are present at extended time points after the initial exposure, indicating resolution of previous injury.^{94,95} However, the extent of the secondary biological response to muscle injury is not well established across the aging spectrum or, specifically, at advanced age. Morphological analyses in aging studies have consisted primarily of quantifying intact and damaged fibers by histology several days after exposure to various lengthening contraction protocols.^{13,89,96} Historically, strain injuries resulting from SSCs have not been studied in this context,⁷³ even though they are the most typical types of movements used during daily living (ie, sitting/standing and walking or running) and occupational- and sport-related activities (ie, reciprocal lifting and lowering tasks).

Our laboratory has established representative SSC models of overt skeletal-muscle-strain injury and noninjurious resistance-type training to investigate the integrated physiological responsivity and muscle performance outcomes associated with these distinct paradigms, as well as their application to overall skeletal-muscle quality.^{46,47} Previous evidence demonstrates that after SSC-induced muscle injury in dorsiflexor muscles of rodents, recovery of static muscle strength occurs quickly in young rats, while old rats have prolonged age-dependent deficits.⁹⁷ Note that a very recent study by Rader et al⁵⁸ using graded SSC-induced strain injury demonstrates that recovery of dynamic muscle performance takes up to 10 days postinjury in young rodents, while old rats present with long-term dynamic performance deficits. It is plausible that with aging the biological phases responsible for injury and/or healing responsivity are inadequate after the initial mechanical injury, thus affecting long-term tissue resolution and restoration of performance. Indeed, after graded SSC-injury exposure, aging rat skeletal muscle lacks the molecular cytokine/chemokine signaling response at the gene and protein levels, as well as cellular/morphological evidence of edema, inflammation, degeneration, and indications of complete regeneration (ie, central nuclei revealing muscle stem/satellite cell involvement) of the skeletal-muscle syncytium.⁵⁸ Note that these findings in muscles of aged rats accompany increased baseline serum levels for cytokines/chemokines indicative of a proinflammatory microenvironment with aging. Overall, these findings suggest that an altered molecular/

cellular microenvironment with advanced age may affect the secondary biological responsiveness of skeletal muscle and, likely, influence long-term muscle performance.

Other investigations, in aging humans, reveal a muted cytokine response to muscle activity, which may result from or lead to age-related chronic inflammation, or “inflammaging,” and this chronic inflammation has the potential to desensitize the inflammatory response.⁹⁸ With respect to these pieces of evidence, contemporary treatment for muscle-strain injuries includes RICE (ie, rest, ice, compression, and elevation),⁶⁷ which has minimal well-controlled, validated fundamental or randomized, controlled trial evidence for its efficacy to treat muscle-strain injury or improve clinical outcomes in the management of soft-tissue injuries,^{2,99} as well as NSAIDs (ie, nonsteroidal anti-inflammatory drugs), a topic recently of debate.^{100,101} Anti-inflammatory drugs are one of the largest classes of over-the-counter pharmacological medications extensively used for and after muscle-strain injury and even intense muscle activity.^{102–104} Nonetheless, there is growing evidence that interventions that significantly reduce the inflammatory response also compromise muscle repair.^{90,105–107} Collectively, these examples challenge the widely accepted use of anti-inflammatory medications after skeletal-muscle-strain injury. In the context of these examples and, specifically, the Rader investigation, blocking inflammation at a young age may be detrimental to muscle regeneration, repair, and functional restoration, while the use of an anti-inflammatory medication at old age may be completely unwarranted given that no such inflammatory response presents. In addition, in the Rader et al study a mechanical-biological threshold for the lowest grade of SSC-induced strain injury (ie, first-degree or mild) was present for young rodents that underwent 30 injurious SSCs, manifesting as performance loss (ie, ~27% initial force loss) with edema (ie, changes in cellular permeability) but without cellular inflammation and myofiber degeneration (ie, histopathological indices for overt macrolevel biological injury). This is consistent with reports of initial performance loss for magnitudes reaching ~30% due to muscle-strain injury, being predictive of the likelihood of the resulting secondary injury response in humans.^{108,109} This scenario, performance loss and edema without cellular inflammation and muscle degeneration, provides further evidence in a specific situation in a young cohort contraindicating the use of NSAIDs, since no cellular substrate is identifiable.

Significant Issues Remaining for Future Research

Thus, an intriguing notion is that aging affects the recovery from skeletal-muscle-strain injury via alterations owing to the existing microenvironment, and a competent healing response is reliant on this microenvironment at any age, particularly at advanced age. It is also attractive to postulate that, given the appropriate adaptive stimulus (ie, age-specific resistance-type training), improvement or remodeling of the local microenvironment’s responsiveness (via cell-cell and/or cell-matrix modifications) in aging populations may be achieved, possibly aiding both the prevention/attenuation of strain injury or restoration of both performance and resolution of healing after a contraction-induced injury.

Conclusions and Implications

With an aging society, it is imperative that we continue to remain diligent to establish the foundations of scientific evidence for guiding clinical practice. Understanding the fundamental basis of age-dependent skeletal-muscle injury will also permit more efficient and effective therapeutic approaches and, optimistically, increase quality of life while reducing fiscal burdens. Prospective studies will focus on promising alternative age-specific strategies to aid in the possible prevention of the initial mechanical-strain injury while committing careful attention to the biological microenvironment that affects muscle injury and healing. This emphasizes the importance of interventions that may improve tissue tolerance or resilience and increase healing kinetics with aging. Reliance on scientific evidence should guide this process, as efficacious methods and modalities are supported for both prevention and intervention, as is the case with cyclic mechanical loading (ie, massage)^{110–114} and physical exercise.^{15,16,115}

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