Journal of Sport Rehabilitation, 2017, 26, 180-188
http://dx.doi.org/10.1123/jsr.2016-0075

Human Kinetics
REVIEW

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

Brent A. Baker

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 responsivity 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 responsivity, 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 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—DOMS[1]). 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 mo[2]), 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.

The author is with the Health Effects Laboratory Div, National Inst for Occupational Safety and Health (NIOSH), Morgantown, WV. Address author correspondence to bwb3@cdc.gov.

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 diseases[9] 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 animals[14] 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 dependency[22] (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 mass[38] 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 aging[36] 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 Statistics[40] 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[57–59] 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 injury[66] (ie, first-degree or mild < second-degree or moderate < third-degree or severe[67]), 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 injury[59] and animal models of muscle-strain injury including repetitive motion[80] 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 injury[56] to microlevel structures in the muscle fibers (ie, sarcomeres[83] and disruption of excitation–contraction coupling[84] 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 al[58] 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 responsivity 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 responsivity (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]

Acknowledgment

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

References

1. MacIntyre DL, Reid WD, McKenzie DC. Delayed muscle soreness: the inflammatory response to muscle injury and its clinical implications. *Sports Med*. 1995;20(1):24–40. PubMed doi:10.2165/00007256-199520010-00003
2. Delos D, Maak TG, Rodeo SA. Muscle injuries in athletes: enhancing recovery through scientific understanding and novel therapies. *Sports Health*. 2013;5(4):346–352. PubMed doi:10.1177/1941738113480934
3. Harper S. Economic and social implications of aging societies. *Science*. 2014;346:587–591. PubMed doi:10.1126/science.1254405
4. Belsky DW, Caspi A, Houts R, et al. Quantification of biological aging in young adults. *Proc Natl Acad Sci USA*. 2015;112(30):E4104–E4110. PubMed doi:10.1073/pnas.1506264112
5. Petsko GA. A seat at the table. *Genome Biol*. 2008;9:1–3. PubMed doi:10.1186/gb-2008-9-12-113
6. National Research Council (US) and Institute of Medicine (US) Panel on Musculoskeletal Disorders and the Workplace. *Musculoskeletal Disorders and The Workplace: Low Back and Upper Extremities*. Washington, DC: National Academies Press; 2001.
7. Burch JB, Augustine AD, Frieden LA, et al. Advances in geroscience: impact on healthspan and chronic disease. *J Gerontol A Biol Sci Med Sci*. 2014;69(Suppl 1):S1–S3. PubMed doi:10.1093/gerona/glu041
8. Rattan SI. Aging is not a disease: implications for intervention. *Aging Dis*. 2014;5(3):196–202. PubMed doi:10.14336/AD.2014.0500196
9. Hayflick L. Biological aging is no longer an unsolved problem. *Ann N Y Acad Sci*. 2007;1100:1–13. PubMed doi:10.1196/annals.1395.001
10. Faulkner JA, Larkin LM, Chaflin DR, Brooks SV. Age-related changes in the structure and function of skeletal muscles. *Clin Exp Pharmacol Physiol*. 2007;34(11):1091–1096. PubMed doi:10.1111/j.1440-1681.2007.04752.x
11. Rader EP, Layner K, Triscuit AM, Chetlin RD, Ensey J, Baker BA. Age-dependent muscle adaptation after chronic stretch-shortening contractions in rats. *Aging Dis*. 2016;7(1):1–13. PubMed doi:10.14336/AD.2015.0920
12. Cutlip RG, Baker BA, Geronilla KB, et al. Chronic exposure to stretch-shortening contractions results in skeletal muscle adaptation in young rats and maladaptation in old rats. *Appl Physiol Nutr Metab*. 2006;31:573–587. PubMed doi:10.1139/h06-033
13. Brooks SV, Opiteck JA, Faulkner JA. Conditioning of skeletal muscles in adult and old mice for protection from contraction-induced injury. *J Gerontol A Biol Sci Med Sci*. 2001;56(4):B163–B171. PubMed doi:10.1093/gerona/56.4.B163
14. Ryan MJ, Dudash HJ, Docherty M, et al. Vitamin E and C supplementation reduces oxidative stress, improves antioxidant enzymes and positive muscle work in chronically loaded muscles of aged rats. *Exp Gerontol*. 2010;45(11):882–895. PubMed doi:10.1016/j.exger.2010.08.002
15. Melov S, Tarnopolsky MA, Beckman K, Felkey K, Hubbard A. Resistance exercise reverses aging in human skeletal muscle. *PLoS One*. 2007;2(5):e465. PubMed doi:10.1371/journal.pone.0000465
16. Zampieri S, Pietrangelo L, Loefler S, et al. Lifelong physical exercise delays age-associated skeletal muscle decline. *J Gerontol A Biol Sci Med Sci*. 2015;70(2):163–173. PubMed doi:10.1093/gerona/glu006
17. Manini T. Development of physical disability in older adults. *Curr Aging Sci*. 2011;4(3):184–191. PubMed doi:10.2174/1874609811104030184
18. Centers for Disease Control and Prevention (CDC). Trends in aging—United States and worldwide. *MMWR Morb Mortal Wkly Rep*. 2003;52(6):101–104, 106. PubMed
19. Rader EP, Faulkner JA. Recovery from contraction-induced injury is impaired in weight-bearing muscles of

old male mice. *J Appl Physiol (Bethesda, Md.: 1985).* 2006;100(2):656–661.
20. Rader EP, Faulkner JA. Effect of aging on the recovery following contraction-induced injury in muscles of female mice. *J Appl Physiol (Bethesda, Md.: 1985).* 2006;101(3):887–892.
21. Sengupta I, Reno V, Burton JF. *Workers' Compensation: Benefits, Coverage, and Costs*. Washington, DC: National Academy of Social Insurance; 2009.
22. Landi F, Calvani R, Cesari M, et al. Sarcopenia as the biological substrate of physical frailty. *Clin Geriatr Med*. 2015;31(3):367–374. PubMed doi:10.1016/j.cger.2015.04.005
23. Evans WJ. What is sarcopenia? *J Gerontol A Biol Sci Med Sci.* 1995;50:5–8. PubMed doi:10.1093/gerona/50A.Special_Issue.5
24. Lauretani F, Russo CR, Bandinelli S, et al. Age-associated changes in skeletal muscles and their effect on mobility: an operational diagnosis of sarcopenia. *J Appl Physiol (Bethesda, Md.: 1985).* 2003;95(5):1851–1860.
25. Mate I, Madrid JA, De la Fuente M. Chronobiology of the neuroimmunoendocrine system and aging. *Curr Pharm Des*. 2014;20(29):4642–4655. PubMed doi:10.2174/1381612820666140130201131
26. De la Fuente M, Miquel J. An update of the oxidation-inflammation theory of aging: the involvement of the immune system in oxi-inflamm-aging. *Curr Pharm Des*. 2009;15(26):3003–3026. PubMed doi:10.2174/138161209789058110
27. Neves J, Demaria M, Campisi J, Jasper H. Of flies, mice, and men: evolutionarily conserved tissue damage responses and aging. *Dev Cell*. 2015;32(1):9–18. PubMed doi:10.1016/j.devcel.2014.11.028
28. Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *J Gerontol A Biol Sci Med Sci*. 2014;69(Suppl 1):S4–S9. PubMed doi:10.1093/gerona/glu057
29. Tchkonia T, Zhu Y, van Deursen J, Campisi J, Kirkland JL. Cellular senescence and the senescent secretory phenotype: therapeutic opportunities. *J Clin Invest*. 2013;123(3):966–972. PubMed doi:10.1172/JCI64098
30. Blagosklonny MV. Answering the ultimate question "what is the proximal cause of aging?" *Aging*. 2012;4(12):861–877. PubMed doi:10.18632/aging.100525
31. Rattan SI. Increased molecular damage and heterogeneity as the basis of aging. *Biol Chem*. 2008;389(3):267–272. PubMed doi:10.1515/BC.2008.030
32. McGregor RA, Cameron-Smith D, Poppitt SD. It is not just muscle mass: a review of muscle quality, composition and metabolism during ageing as determinants of muscle function and mobility in later life. *Longev Healthspan*. 2014;3(1):9.103–9.110. PubMed doi:10.1186/2046-2395-3-9
33. Enoka RM, Christou EA, Hunter SK, et al. Mechanisms that contribute to differences in motor performance between young and old adults. *J Electromyogr Kinesiol*. 2003;13(1):1–12. PubMed doi:10.1016/S1050-6411(02)00084-6
34. Baker BA, Hollander MS, Mercer RR, Kashon ML, Cutlip RG. Adaptive stretch-shortening contractions: diminished regenerative capacity with aging. *Appl Physiol Nutr Metab*. 2008;33(6):1181–1191. PubMed doi:10.1139/H08-110
35. Degens H, Alway SE. Skeletal muscle function and hypertrophy are diminished in old age. *Muscle Nerve*. 2003;27(3):339–347. PubMed doi:10.1002/mus.10314
36. Newman AB, Haggerty CL, Goodpaster B, et al. Strength and muscle quality in a well-functioning cohort of older adults: the Health, Aging and Body Composition Study. *J Am Geriatr Soc*. 2003;51(3):323–330. PubMed doi:10.1046/j.1532-5415.2003.51105.x
37. Briggs AM, Cross MJ, Hoy DG, et al. Musculoskeletal health conditions represent a global threat to healthy aging: a report for the 2015 World Health Organization World Report on Ageing and Health. *Gerontologist*. 2016;56(Suppl 2):S243–S255. PubMed doi:10.1093/geront/gnw002
38. Barbat-Artigas S, Rolland Y, Zamboni M, Aubertin-Leheudre M. How to assess functional status: a new muscle quality index. *J Nutr Health Aging*. 2012;16(1):67–77. PubMed doi:10.1007/s12603-012-0004-5
39. Baker BA, Hollander MS, Kashon ML, Cutlip RG. Effects of glutathione depletion and age on skeletal muscle performance and morphology following chronic stretch-shortening contraction exposure. *Eur J Appl Physiol*. 2010;108(3):619–630. PubMed doi:10.1007/s00421-009-1258-4
40. US Bureau of Labor Statistics, US Department of Labor. *Survey of Occupational Injuries and Illnesses in Cooperation With Participating State Agencies*. 2011. https://www.bls.gov/iif/oshdef.htm
41. Yucesoy B, Charles LE, Baker B, Burchfiel CM. Occupational and genetic risk factors for osteoarthritis: a review. *Work*. 2015;50(2):261–273. PubMed
42. Welch LS, Hunting KL, Murawski JA. Occupational injuries among construction workers treated in a major metropolitan emergency department in the United States. *Scand J Work Environ Health*. 2005;31(Suppl 2):11–21. PubMed
43. Bureau of Labor Statistics, U.S. Department of Labor. *Survey of Occupational Injuries and Illnesses in Cooperation With Participating State Agencies*. 2011. Washington, DC: Author.
44. Hymel PA, Loeppke RR, Baase CM, et al. Workplace health protection and promotion: a new pathway for a healthier—and safer—workforce. *J Occup Environ Med*. 2011;53(6):695–702. PubMed doi:10.1097/JOM.0b013e31822005d0
45. Järvinen TAH, Jarvinen TLN, Kaariainen M, Kalimo H, Jarvinen M. Biology of muscle trauma. *Am J Sports Med*. 2005;33:745–764. PubMed doi:10.1177/0363546505274714
46. Baker BA, Cutlip RG. Skeletal muscle injury versus adaptation with aging: novel insights on perplexing paradigms. *Exerc Sport Sci Rev*. 2010;38(1):10–16. PubMed doi:10.1097/JES.0b013e3181c5cd7c
47. Baker BA, Cutlip RG. The application of high-intensity muscular contractions for maximal training gains: the impact of age on the continuum of muscle injury, maladaptation and adaptation. In: Kai JT (Ed.). *Strength Training: Types and Principles*. New York: Nova Science; 2010:119–148. ISBN: 978-971-60876-60221-60877.
48. Butterfield TA. Eccentric exercise in vivo: strain-induced muscle damage and adaptation in a stable system. *Exerc Sport Sci Rev*. 2010;38(2):51–60. PubMed doi:10.1097/JES.0b013e3181d496eb
49. Fry AC, Kraemer WJ, Van Borselen F, et al. Performance decrements with high-intensity resistance exercise overtraining. *Med Sci Sports Exerc*. 1994;26(9):1165–1173. PubMed doi:10.1249/00005768-199409000-00015

50. Wheeler MW, Dunson DB, Pandalai SP, Baker BA, Herring AH. Mechanistic hierarchical Gaussian processes. *J Am Stat Assoc*. 2014;109(507):894–904. PubMed doi:10.1080/01621459.2014.899234
51. Widanarko B, Legg S, Stevenson M, et al. Prevalence of musculoskeletal symptoms in relation to gender, age, and occupational/industrial group. *Int J Ind Ergon*. 2011;41:561–572. doi:10.1016/j.ergon.2011.06.002
52. Mody GM, Brooks PM. Improving musculoskeletal health: global issues. *Best Pract Res Clin Rheumatol*. 2012;26:237–249. PubMed doi:10.1016/j.berh.2012.03.002
53. Murray CJ, Barber RM, Foreman KJ, et al. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990–2013: quantifying the epidemiological transition. *Lancet*. 2015;386(10009):2145–2191. PubMed doi:10.1016/S0140-6736(15)61340-X
54. Horton R. GBD 2010: understanding disease, injury, and risk. *Lancet*. 2012;380(9859):2053–2054. PubMed doi:10.1016/S0140-6736(12)62133-3
55. Brooks SV, Zerba E, Faulkner JA. Injury to muscle fibres after single stretches of passive and maximally stimulated muscles in mice. *J Physiol*. 1995;488(Pt 2):459–469. PubMed doi:10.1113/jphysiol.1995.sp020980
56. Warren GL, Hayes DA, Lowe DA, Armstrong RB. Mechanical factors in the initiation of eccentric contraction-induced injury in rat soleus muscle. *J Physiol*. 1993;464:457–475. PubMed doi:10.1113/jphysiol.1993.sp019645
57. Baker BA, Mercer RR, Geronilla KB, Kashon ML, Miller GR, Cutlip RG. Stereological analysis of muscle morphology following exposure to repetitive stretch-shortening cycles in a rat model. *Appl Physiol Nutr Metab*. 2006;31(2):167–179. PubMed doi:10.1139/h05-009
58. Rader EP, Layner KN, Triscuit AM, et al. Desensitized morphological and cytokine response after stretch-shortening muscle contractions as a feature of aging in rats. *Exp Gerontol*. 2015;72:138–149. PubMed doi:10.1016/j.exger.2015.09.020
59. Crameri RM, Aagaard P, Qvortrup K, Langberg H, Olesen J, Kjaer M. Myofibre damage in human skeletal muscle: effects of electrical stimulation versus voluntary contraction. *J Physiol*. 2007;583(Pt 1):365–380. PubMed doi:10.1113/jphysiol.2007.128827
60. Garrett WE, Jr. Muscle strain injuries. *Am J Sports Med*. 1996;24(6, Suppl):S2–S8. PubMed
61. Hauret KG, Jones BH, Bullock SH, Canham-Chervak M, Canada S. Musculoskeletal injuries description of an under-recognized injury problem among military personnel. *Am J Prev Med*. 2010;38(Suppl):S61–S70. PubMed doi:10.1016/j.amepre.2009.10.021
62. Geronilla KB, Miller GR, Mowrey KF, et al. Dynamic force responses of skeletal muscle during stretch-shortening cycles. *Eur J Appl Physiol*. 2003;90(1-2):144–153. PubMed doi:10.1007/s00421-003-0849-8
63. Baker BA, Rao KMK, Mercer RR, et al. Quantitative histology and MGF gene expression in rats following SSC exercise *in vivo*. *Med Sci Sports Exerc*. 2006;38(3):463–471. PubMed doi:10.1249/01.mss.0000191419.67030.69
64. Cutlip RG, Geronilla KB, Baker BA, Kashon ML, Miller GR, Schopper AW. Impact of muscle length during stretch-shortening contractions on real-time and temporal muscle performance measures in rats *in vivo*. *J Appl Physiol*. 2004;96:507–516. PubMed doi:10.1152/japplphysiol.00046.2003
65. Cutlip RG, Geronilla KB, Baker BA, et al. Impact of stretch-shortening cycle rest interval on *in vivo* muscle performance. *Med Sci Sports Exerc*. 2005;37(8):1345–1355. PubMed doi:10.1249/01.mss.0000174896.76981.b1
66. Cutlip RG, Hollander MS, Johnson GA, Johnson BW, Friend SA, Baker BA. Magnetic resonance imaging of graded skeletal muscle injury in live rats. *Environ Health Insights*. 2014;8(Suppl 1):31–39. PubMed
67. Järvinen TA, Järvinen TL, Kaariainen M, et al. Muscle injuries: optimising recovery. *Best Pract Res Clin Rheumatol*. 2007;21(2):317–331. PubMed doi:10.1016/j.berh.2006.12.004
68. Lovering RM, McMillan AB, Gullapalli RP. Location of myofiber damage in skeletal muscle after lengthening contractions. *Muscle Nerve*. 2009;40:589–594. PubMed doi:10.1002/mus.21389
69. Johnson C, Miller GR, Baker BA, et al. Changes in the expression of calcitonin gene-related peptide after exposure to injurious stretch-shortening contractions. *Exp Gerontol*. 2016;79:1–7. PubMed doi:10.1016/j.exger.2016.03.006
70. Clarkson PM, Tremblay I. Exercise-induced muscle damage, repair, and adaptation in humans. *J Appl Physiol*. 1988;65(1):1–6. PubMed
71. Newham DJ, Jones DA, Clarkson PM. Repeated high-force eccentric exercise: effects on muscle pain and damage. *J Appl Physiol*. 1987;63(4):1381–1386. PubMed
72. Avela J, Komi PV. Reduced stretch reflex sensitivity and muscle stiffness after long-lasting stretch-shortening cycle exercise in humans. *Eur J Appl Physiol Occup Physiol*. 1998;78(5):403–410. PubMed doi:10.1007/s004210050438
73. Komi PV. Stretch-shortening cycle: a powerful model to study normal and fatigued muscle. *J Biomech*. 2000;33(10):1197–1206. PubMed doi:10.1016/S0021-9290(00)00064-6
74. Vaczi M, Tihanyi J, Hortobagyi T, et al. Mechanical, biochemical, and electromyographic responses to short-term eccentric-concentric knee extensor training in humans. *J Strength Cond Res.* 2011;25(4):922–932.
75. Vaczi M, Racz L, Hortobagyi T, Tihanyi J. Dynamic contractility and efficiency impairments in stretch-shortening cycle are stretch-load-dependent after training-induced muscle damage. *J Strength Cond Res.* 2013;27(8):2171–2179.
76. Váczi M, Nagy SA, Koszegi T, et al. Mechanical, hormonal, and hypertrophic adaptations to 10 weeks of eccentric and stretch-shortening cycle exercise training in old males. *Exp Gerontol*. 2014;58:69–77. PubMed doi:10.1016/j.exger.2014.07.013
77. Cutlip RG, Stauber WT, Willison RH, McIntosh TA, Means KH. Dynamometer for rat plantar flexor muscles in vivo. *Med Biol Eng Comput*. 1997;35(5):540–543. PubMed doi:10.1007/BF02525537
78. Baker BA, Mercer RR, Geronilla KB, Kashon ML, Miller GR, Cutlip RG. Impact of repetition number on muscle performance and histological response. *Med Sci Sports Exerc*. 2007;39(8):1275–1281. PubMed doi:10.1249/mss.0b013e3180686dc7
79. Cutlip RG, Baker BA, Hollander M, Ensey J. Injury and adaptive mechanisms in skeletal muscle. *J Electromyogr Kinesiol*. 2009;19(3):358–372. PubMed doi:10.1016/j.jelekin.2008.06.007
80. Barbe MF, Barr AE. Inflammation and the pathophysiology of work-related musculoskeletal disorders. *Brain Behav*

Immun. 2006;20(5):423–429. PubMed doi:10.1016/j.bbi.2006.03.001
81. Pizza FX, Peterson JM, Baas JH, Koh TJ. Neutrophils contribute to muscle injury and impair its resolution after lengthening contractions in mice. *J Physiol*. 2005;562(Pt 3):899–913. PubMed doi:10.1113/jphysiol.2004.073965
82. Best TM, Hunter KD. Muscle injury and repair. *Phys Med Rehabil Clin N Am*. 2000;11(2):251–266. PubMed
83. Proske U, Morgan DL. Muscle damage from eccentric exercise: mechanism, mechanical signs, adaptation and clinical applications. *J Physiol*. 2001;537(Pt 2):333–345. PubMed doi:10.1111/j.1469-7793.2001.00333.x
84. Warren GL, Ingalls CP, Lowe DA, Armstrong RB. Excitation-contraction uncoupling: major role in contraction-induced muscle injury. *Exerc Sport Sci Rev*. 2001;29(2):82–87. PubMed doi:10.1097/00003677-200104000-00008
85. Kafadar KA, Yi L, Ahmad Y, So L, Rossi F, Pavlath GK. Sca-1 expression is required for efficient remodeling of the extracellular matrix during skeletal muscle regeneration. *Dev Biol*. 2009;326(1):47–59. PubMed doi:10.1016/j.ydbio.2008.10.036
86. Zerba E, Faulkner JA. A single lengthening contraction can induce injury to skeletal muscle fibers. *Physiologist*. 1990;33:A122.
87. Tidball JG. Mechanisms of muscle injury, repair, and regeneration. *Compr Physiol*. 2011;1(4):2029–2062. PubMed
88. Stauber WT, Smith CA. Cellular responses in exertion-induced skeletal muscle injury. *Mol Cell Biochem*. 1998;179(1-2):189–196. PubMed
89. Brooks SV, Faulkner JA. Contraction-induced injury: recovery of skeletal muscles in young and old mice. *Am J Physiol*. 1990;258(3 Pt 1):C436–C442. PubMed
90. Mishra DK, Friden J, Schmitz MC, Lieber RL. Anti-inflammatory medication after muscle injury: a treatment resulting in short-term improvement but subsequent loss of muscle function. *J Bone Joint Surg Am*. 1995;77(10):1510–1519. PubMed doi:10.2106/00004623-199510000-00005
91. Tidball JG, Villalta SA. Regulatory interactions between muscle and the immune system during muscle regeneration. *Am J Physiol Regul Integr Comp Physiol*. 2010;298(5):R1173–R1187. PubMed doi:10.1152/ajpregu.00735.2009
92. Chargé SB, Rudnicki MA. Cellular and molecular regulation of muscle regeneration. *Physiol Rev*. 2004;84(1):209–238. PubMed doi:10.1152/physrev.00019.2003
93. McCormick KM, Schultz E. Role of satellite cells in altering myosin expression during avian skeletal muscle hypertrophy. *Dev Dyn*. 1994;199(1):52–63. PubMed doi:10.1002/aja.1001990106
94. Hurme T, Kalimo H, Lehto M, Jarvinen M. Healing of skeletal muscle injury: an ultrastructural and immunohistochemical study. *Med Sci Sports Exerc*. 1991;23(7):801–810. PubMed doi:10.1249/00005768-199107000-00006
95. McGeachie JK, Grounds MD. The timing between skeletal muscle myoblast replication and fusion into myotubes, and the stability of regenerated dystrophic myofibres: an autoradiographic study in mdx mice. *J Anat*. 1999;194(Pt 2):287–295. PubMed doi:10.1046/j.1469-7580.1999.19420287.x
96. Lowe DA, Warren GL, Ingalls CP, Boorstein DB, Armstrong RB. Muscle function and protein metabolism after initiation of eccentric contraction-induced injury. *J Appl Physiol*. 1995;79(4):1260–1270. PubMed
97. Krajnak K, Waugh S, Miller G, et al. Proapoptotic factor Bax is increased in satellite cells in the tibialis anterior muscles of old rats. *Muscle Nerve*. 2006;34(6):720–730. PubMed doi:10.1002/mus.20656
98. Przybyla B, Gurley C, Harvey JF, et al. Aging alters macrophage properties in human skeletal muscle both at rest and in response to acute resistance exercise. *Exp Gerontol*. 2006;41(3):320–327. PubMed doi:10.1016/j.exger.2005.12.007
99. Collins NC. Is ice right?: does cryotherapy improve outcome for acute soft tissue injury? *Emerg Med J*. 2008;25(2):65–68. PubMed doi:10.1136/emj.2007.051664
100. Urso ML, Sawka MN. Inflammation: sustaining the balance to optimize recovery of skeletal muscle, connective tissue, and exertional injuries. *J Appl Physiol (Bethesda, Md.: 1985)*. 2013;115(6):877–878.
101. Urso ML. Anti-inflammatory interventions and skeletal muscle injury: benefit or detriment? *J Appl Physiol (Bethesda, Md.: 1985)*. 2013;115(6):920–928.
102. Mackey AL, Kjaer M, Dandanell S, et al. The influence of anti-inflammatory medication on exercise-induced myogenic precursor cell responses in humans. *J Appl Physiol (Bethesda, Md.: 1985)*. 2007;103(2):425–431.
103. Mikkelsen UR, Langberg H, Helmark IC, et al. Local NSAID infusion inhibits satellite cell proliferation in human skeletal muscle after eccentric exercise. *J Appl Physiol (Bethesda, Md.: 1985)*. 2009;107(5):1600–1611.
104. Brewer CB, Bentley JP, Hallam JS, Woodyard CD, Waddell DE. Use of analgesics for exercise-associated pain: prevalence and predictors of use in recreationally trained college-aged students. *J Strength Cond Res*. 2014;28(1):74–81.
105. Pizza FX, Cavender D, Stockard A, Baylies H, Beighle A. Anti-inflammatory doses of ibuprofen: effect on neutrophils and exercise-induced muscle injury. *Int J Sports Med*. 1999;20(2):98–102. PubMed doi:10.1055/s-2007-971100
106. Gumucio JP, Flood MD, Phan AC, Brooks SV, Mendias CL. Targeted inhibition of TGF-beta results in an initial improvement but long-term deficit in force production after contraction-induced skeletal muscle injury. *J Appl Physiol (Bethesda, Md.: 1985)*. 2013;115(4):539–545.
107. Wang H, Melton DW, Porter L, Sarwar ZU, McManus LM, Shireman PK. Altered macrophage phenotype transition impairs skeletal muscle regeneration. *Am J Pathol*. 2014;184(4):1167–1184. PubMed doi:10.1016/j.ajpath.2013.12.020
108. Paulsen G, Egner IM, Drange M, et al. A COX-2 inhibitor reduces muscle soreness, but does not influence recovery and adaptation after eccentric exercise. *Scand J Med Sci Sports*. 2010;20(1):e195–e207. PubMed doi:10.1111/j.1600-0838.2009.00947.x
109. Paulsen G, Crameri R, Benestad HB, et al. Time course of leukocyte accumulation in human muscle after eccentric exercise. *Med Sci Sports Exerc*. 2010;42(1):75–85. PubMed doi:10.1249/MSS.0b013e3181ac7adb
110. Butterfield TA, Zhao Y, Agarwal S, Haq F, Best TM. Cyclic compressive loading facilitates recovery after eccentric exercise. *Med Sci Sports Exerc*. 2008;40(7):1289–1296. PubMed doi:10.1249/MSS.0b013e31816c4e12
111. Haas C, Best TM, Wang Q, Butterfield TA, Zhao Y. In vivo passive mechanical properties of skeletal muscle improve with massage-like loading following eccentric exercise. *J Biomech*. 2012;45(15):2630–2636. PubMed doi:10.1016/j.jbiomech.2012.08.008
112. Haas C, Butterfield TA, Zhao Y, Zhang X, Jarjoura D, Best TM. Dose-dependency of massage-like compressive

loading on recovery of active muscle properties following eccentric exercise: rabbit study with clinical relevance. *Br J Sports Med*. 2013;47(2):83–88. PubMed doi:10.1136/bjsports-2012-091211
113. Haas C, Butterfield TA, Abshire S, et al. Massage timing affects postexercise muscle recovery and inflammation in a rabbit model. *Med Sci Sports Exerc*. 2013;45(6):1105–1112. PubMed doi:10.1249/MSS.0b013e31827fdf18
114. Crawford SK, Haas C, Butterfield TA, et al. Effects of immediate vs. delayed massage-like loading on skeletal muscle viscoelastic properties following eccentric exercise. *Clin Biomech (Bristol, Avon)*. 2014;29(6):671–678. PubMed doi:10.1016/j.clinbiomech.2014.04.007
115. Barrès R, Yan J, Egan B, et al. Acute exercise remodels promoter methylation in human skeletal muscle. *Cell Metab*. 2012;15(3):405–411. PubMed doi:10.1016/j.cmet.2012.01.001