Musculoskeletal Regeneration, Rehabilitation, and Plasticity Following Traumatic Injury

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ABSTRACT

The musculoskeletal system has an integral role throughout life, including structural support to the body, protection, and allowing a range of fine to complex movements for daily living to elite sporting events. At various times, injuries to the musculoskeletal system occur resulting in varying levels of impact to the person both acutely and chronically. Specifically, there is a spectrum of complexity in orthopedic injuries, with some such as common muscle strains, that while burdensome will have no impact on life-long functional ability, and others that can result in long lasting disability. Focusing on extremity injuries, this review highlights: i) the current impact of orthopedicinjuries in sport and daily life; ii) the foundation of bone and skeletal muscle repair and regeneration; and iii) the disruptions in regenerative healing due to traumatic orthopedic injuries. This review seeks to maximize the broad and collective research impact on sport and traumatic orthopedic injuries in search of promoting ongoing innovation for treatment and rehabilitation approaches aimed to improve musculoskeletal health throughout life.

Introduction

Musculoskeletal rehabilitation is based on the principle of tissue plasticity, the ability of tissues to adapt to mechanical and/or chemical cues in order to improve functional capacity or efficiently recover from injury. Effective evidence-based rehabilitation approaches (i. e. actions to enhance functional outcomes) have existed for almost two decades for common musculoskeletal injuries that can occur frequently during sports and daily life, such as a strain or contraction-induced muscle injury [1, 2]. However, severely injured musculoskeletal tissue from, for example, high-energy orthopedic trauma, may have diminished tissue plasticity and can therefore be unresponsive to rehabilitation efforts [3]. For the patient, this manifests in the form of long-term functional limitations, disability, co-morbidities, and decreased quality of life. For instance, a college athlete who suffers an open fracture of the tibia could have initial resistance to rehabilitation and lifelong limitations due to the lack of plasticity in the muscle after injury. In fact, former National Collegiate Athletic Association (NCAA) Division I college athletes who sustained injuries during their college sport years (~30 years prior) have lower health-related quality of life scores and ~2.5 times more limitations than non-athletes [4]. The long term consequences of traumatic musculoskeletal injuries is also evident in civilian and military populations, as about half of those who sustained injuries still have significant disability at 7 years after the initial incident, according to the Sickness Impact Profile (or SIP) [5]. It is possible that overall quality of life, as well as

the ability to maintain physical activity levels later in life, may also be limited by prior traumatic orthopedic injuries, and specifically the lack of functional plasticity (i. e. contractility, oxygen consumption, ultimate load) in the musculoskeletal system. With particular focus on extremity injuries, this study focuses on the current impact of musculoskeletal and traumatic orthopedic injuries across the life span, the physiology of normal repair and regeneration, and the current understanding and limitations of functional musculoskeletal plasticity spanning pre-clinical to clinical investigations.

Traumatic musculoskeletal injuries

Traumatic injury is often indiscriminate and crosses various physiologic systems such as bone, skeletal muscle, vascular, tendinous, ligamentous, and/or cartilaginous structures; primarily due to blunt force, penetrating injury (e. g. high-energy injuries or collusions), or controlled (i. e. surgical) trauma [6, 7]. Of traumatic injuries treated at United States trauma centers, two-thirds occur to extremities with ~32 % and 40 % to the upper and lower extremities, respectively [8]. Of injuries that are of primary interest here are those musculoskeletal injuries that commonly are reported as fractures, sprains, strains, contusions, dislocation/derangements, crushing and open wounds, or amputations. According to the United States Bone and Joint Initiative [9], fractures and open wounds account for ~26.5 million injuries a year. While there is a range of injury severity and complexity, and functional impact imposed by these injuries, they collectively result in significant health care costs, functional limitations and pain.

Etiology

The acute cause of all traumatic musculoskeletal-related injuries generally falls into one of two categories: blunt or penetrating trauma. Blunt force trauma occurs as an object (or person contact) strikes the body, while penetrating trauma occurs when an object pierces the body often resulting in open wounds. Within the general population, about one-third of all traumatic injuries are due to falls [9]. Various injury mechanisms account for the remaining two-thirds such as motor vehicle accidents, machinery, or moving objects. Injuries within the NCAA span player contact, other contact, and non-contact, with the majority occurring from blunt force trauma due to contact with other players [10]. In active duty military populations, traumatic musculoskeletal injuries encountered on the battlefield were primarily due to high-energy, explosive mechanism [11, 12].

Epidemiology

With particular focus on sports-related injuries, the United States Bone and Joint Initiative estimates that ~2.8 million sports-related injuries are treated annually [9]. Using the NCAA Injury Surveillance Program Database [13], ~48 000 injuries of any type occur per ~5 million athlete-exposures (i. e. one athlete's participation in one competition or practice). For musculoskeletal-related injuries specifically, the incidence is ~63 per 1000 NCAA athlete-exposures [14]. Injuries that occur specifically in the skeletal muscle can range from strains, contusions and tears. Supported by the abundance of evidence-based rehabilitation approaches for injuries such as muscle strains [1, 2], these injury types are common [15] and account for ~17.1 million injuries annually [9]. In NCAA athletes, for example, strains of the quadriceps muscle group occur at a rate of ~2 per 10 000 NCAA athlete-exposures overall, with higher rates in specific sports, such as soccer (up to ~6 per 10 000 exposures) [16]. Similarly, in this athletic population hamstring muscle group strains occur at a rate of ~3 per 10 000 NCAA athlete-exposures [17]. Relatedly, in a similar highly active military population, musculoskeletal injuries account for ~77 % of the 14 500 battle field evacuations [7].

Specific to skeletal fracture, the most common fractures (> 60 % of cases) are of the distal radius, metacarpus, proximal femur, finger phalanges and ankle. Overwhelmingly though the literature presents data and reports on femoral diaphysis, distal femur, proximal tibia, tibial diaphysis, tibial plafond, talus and calcaneus that make up only ~6.6 % of cases [18]. Collectively the estimated ~18.3 million fractures that occur annually in the in US represent a common injury that can require expensive and complicated care. Any type of fracture in the NCAA population accounts for about 6–7 % of all injuries seen in college athletes. In the general population, any type of fracture is expected to occur in ~11 per 1000 persons in adulthood [18]. More complex fractures, such as open fracture of the tibia, invariably result in severe bone and surrounding soft-tissue injury, including bone comminution, disruption of the periosteum, damage to surrounding skeletal muscle, and global injury contamination, which frequently result in segmental bone defects and volumetric muscle loss (VML). Open fracture involving segmental bone defects with VML is prevalent in both civilian and military trauma populations and contributes to the greater than $400 billion yearly economic impact (~$86 billion and $326 billion in medical treatment and lost productivity, respectively) of traumas in the US [19]. Collectively, traumatic musculoskeletal-related injuries are common and present across a broad range of severity that directly influences short-term care and associates with long-term clinical outcomes.

Basic science of musculoskeletal healing and plasticity

The capacity for the musculoskeletal system to repair, regenerate and adapt is directly related to mortality and morbidity. Throughout daily life, the tissues that bear and generate force so that we may naturally withstand gravity, ambulate, eat and communicate are continuously injured and constantly 'rebuilding'. Moreover, musculoskeletal tissues adapt in specific ways to their daily use, to both improve the desired function of the tissue and/or to reduce whole-body metabolic burden. Since antiquity, physical activity and planned physical activity, i. e. exercise, sports or physical therapy, have been known to promote health and prevent disease. The benefits of exercise are made possible by the adaptive nature of the musculoskeletal tissues, a process commonly referred to as tissue plasticity. In the following section, the foundations of normal physiologic repair, regeneration and plasticity are discussed.

Skeletal muscle and bone regeneration

Tissue regeneration is considered a form of plasticity, as there are acute changes in cellular signaling that lead to tissue remodeling and repair. Bone and skeletal muscle plasticity following injury have common stages; and most importantly, both tissues have a robust regenerative and repair process that concludes with tissue indis-

▶ **Table 1** The phases of bone and muscle regeneration.

	Bone	Muscle
Injury Phase	Hematoma & callus formation	Loss of $[Ca^{2+}]_i$ homeostasis and disruption of force-generating proteins
Inflammation	TNFα, IL-1,-6,-11: peak within 72 hours, resolved by 7–10 days	TNF-α, MIP-1, MCP-1: peak within 72 hours, resolved by 7–10 days
Regeneration	Recapitulates phases of development; prior inflammatory phase implicated in response, callus mineralization	Recapitulates phases of development; prior inflammatory phase implicated in response, myotube formation bridges between uninjured muscle fiber sections
Remodeling	Resorption of soft callus tissue, portions of hard callus tissue broken down to form medullary cavity	Myotube receiving activation patterns from alpha-motoneuron, protein synthesis increase the amount of contractile protein content
Primary Regenerative Cell	Mesenchymal Stem Cell	Satellite Cell
Default healing mode (Severe Injury)	Regeneration	Repair (fibrosis)
1 * response increase use	Mechanical (Wolfes law)	Metabolic

tinguishable from pre-injury. The phases of bone and muscle regeneration are briefly highlighted here and in ▶ **Table 1**.

Injury

Initial skeletal muscle injury is marked by a loss of intracellular calcium homeostasis within damaged muscle fibers (i. e. myofibers) [20, 21]. The loss of calcium homeostasis activates a number of degradative processes such as calcium-activated proteases. These proteases begin to degrade damaged proteins and the first phase of skeletal muscle regeneration is therefore referred to as the degradative phase [22]. Initial bone injury is marked by a hematoma, or a bleeding as a result of the bone damage or damage to the surrounding tissues. The hematoma will eventually form a clot between the fragmented areas of the damaged bone and serve as the template for eventual new bone formation, the callus [23]. Both early phases of injury in the muscle and bone are reported to give rise to a subsequent inflammatory phase critical for functional recovery.

Inflammation

While chronic inflammation negatively affects bone mineral density and skeletal muscle function, an acute inflammatory response that resolves in a timely manner is absolutely necessary for bone and muscle repair. Skeletal muscle inflammation can begin as early as 6 h post-injury with marked increases in the expression of inflammatory cytokines and chemokines such as tumor necrosis factor alpha (TNF-α), macrophage inflammatory protein-1 (MIP-1), and monocyte chemoattractant protein-1 (MCP-1) [24]. Subsequently, neutrophil populations and macrophage populations peak at 24 h and 72 h post-injury, respectively, and the inflammatory response is largely resolved between 7–10 days post-injury. TNF-α, and interleukins -1, -6, and -11 (IL-) are rapidly responding cytokines to bone injury that recruit neutrophils and macrophages to the site of injury. Similar to skeletal muscle, the inflammatory response to bone injury is largely resolved by seven days post-injury [23, 25]. Numerous studies have provided valuable insight into the necessity of the inflammatory process in both muscle and bone for functional healing. In muscle, two articles by Warren and colleagues demonstrate that neutralizing the TNF-α cytokine or knocking out the chemokine receptor CCR2 prolongs the recovery of muscle strength after traumatic freeze injury [26, 27]. Similarly, neutralizing TNF-α and CCR2 after a mouse tibia fracture also impaired mineralization of the callous, a critical step for ultimate functional recovery of the bone [28]. It is clear that disruption of the inflammatory phase extends the timeframe for muscle and bone recovery indicating that the inflammatory response is critical for timely regeneration.

Regeneration

The critical role of the inflammatory response in muscle and bone healing can be explained in part by the evidence indicating inflammatory markers are responsible for signaling to resident stem cells to exit quiescence and participate in regeneration of the tissue. Muscle and bone owe their robust regenerative capacity to the resident stem cells, satellite cells and mesenchymal stem cells, respectively, that are capable of proliferating and differentiating to form new muscle and bone tissue. In skeletal muscle, low doses of TNF-α, as well as other cytokines and chemokines, increase satellite cells differentiation *in vitro* and *in vivo* [29, 30]. Additionally, Glass et al. reported that a low-dose TNF-α strategy was able to increase mesenchymal stem cells migration *in vitro* and enhance callus mineralization *in vivo* suggesting a strong relationship between the inflammatory response and mesenchymal stem cell dynamics in bone [31]. Notably, the muscle fiber developmental steps and the ossification steps of skeletogenesis are recapitulated during the regenerative phase, and the satellite and mesenchymal stem cells are necessary for myofiber regeneration and generation of the callus tissue in muscle and bone, respectively.

Remodeling

The final phase of tissue regeneration in both muscle and bone is remodeling. During this phase in skeletal muscle, the satellite cells have migrated and differentiated to form myotubes spanning the portion of muscle fiber damaged during the initial injury. At the beginning of the remodeling phase, the newly formed myotubes are distinguishable from uninjured fibers by a centralized nuclei, a visible representation of decreased muscle fiber density and less contractile protein material. During remodeling, increases in protein

synthesis will generate more contractile protein content eventually increasing the density of the myofiber and pushing the nuclei to the periphery of the muscle cell. This process coincides with a full functional recovery of strength and damaged myofibers are now indistinguishable from uninjured fibers. The remodeling phase of bone healing involves the reabsorption of the soft tissue callus that bridges the fractured bone ends and mineralization leaving a hard tissue callus in its place. Finally, this hard bony callus is broken down by osteoclasts and then osteoblasts will help form a medullary cavity with a lamellar bone structure. Like skeletal muscle, when this is complete the newly formed bone will be indistinguishable from the uninjured regions.

Tissue plasticity

Tissue plasticity also serves as a foundation for exercise, rehabilitation, and physical therapy. The fundamental physiologic responses to exercise are briefly highlighted here and in ▶ **Table 2**. As advances in molecular biology and genetics improve the precision by which tissue plasticity is defined, a new frontier emerges for exploration of the mechanisms of poor tissue plasticity in disease and injury.

Exercise is known to improve physiological capacities of skeletal muscle such as strength and endurance, with the adaptations dependent on the specific physiological system being stressed. Exercise is a physiological stressor and stimulates various signaling pathways to increase expression of genes and their protein products that represent adaptation to the stress and yields changes in physiological function. For example, each muscle contraction results in a calcium transient as calcium is released and sequestered back into the sarcoplasmic reticulum. Each muscle contraction also is energetically demanding and results in an accumulation of AMP as well as a shift in redox homeostasis as reactive oxygen species (ROS) are generated during the synthesis of ATP for sustained muscle performance. As such, muscles that are frequently activated, as would happen during a 90 min training run, i. e. endurance training, are going to experience more frequent calcium transients and greater accumulation of AMP and reactive oxygen species. These products of endurance exercise-induced muscle stress are responsible in part for activating signaling cascades that will change the physiology of the muscle fiber. Specifically, AMP activates AMPK which subsequently phosphorylates the transcription factor PGC1α that is responsible for regulating some 2000 genes [32, 33], many of which are related to metabolism and improving vascularization of muscle fibers [34]. Calcium activates calcineurin that is responsible for regulating slow-twitch contractile genes such as slower isoforms of myosin heavy chain and the sarcoplasmic reticulum calcium ATPase [35]. Reactive oxygen species can stimulate the transcription factor NF-kappa B that coordinates antioxidant gene responses [36, 37]. Thus, endurance-trained muscles physiologically have greater oxidative capacity and oxygen saturation, slower contractile phenotypes, and greater antioxidant protein expression.

In contrast, a bout of resistance training may only involve 60–90 s of actual muscle contractile activity, while those contractions are of greater intensity. The total muscle contraction time (i. e. 60–90s) is simply insufficient to elicit the calcium, AMP, and reactive oxygen species response as in endurance-trained muscle; however, resistance training is associated with an increase in circulating growth factors such as insulin-like growth factor 1 (IGF-1) [38]. IGF-1 initiates the mammalian target of rapamycin (mTOR) signaling cascade that leads to an increase in protein synthesis and decrease in protein degradation [39]. Overtime, contractile protein content will accumulate in the muscle fiber leading to an increase in physiological cross-sectional area, or hypertrophy. The greater amount of contractile protein essentially means the greater number of myosin-actin cross-bridges and greater muscular force production. IGF-1 accomplishes this feat by stimulating the intracellular phosphorylation of AKT that has two important roles: i) AKT will turn "off" the TSC2/TSC1 complex that effectively acts as a brake on mTOR-dependent protein synthesis [40, 41], ii) AKT will also phosphorylate the FOXO transcription factor that turns "on" genes associated with protein degradation thus prevent FOXO nuclear translocation [42]. Endurance-trained muscle simply does not experience a similar rise in circulating IGF to have a similar physiological response.

The most robust physiological adaptation to endurance type training is an increase in oxidative capacity (▶ **Table 2**). The significance of this adaptation is that muscle with greater oxidative capacity has greater endurance, or less fatigue. An example of this is such: 1 mole of glucose can yield 2 moles of ATP during anaerobic metabolism in less mitochondrial-rich muscle fibers, while 1 mole of glucose can yield 36 moles of ATP during aerobic metabolism in mitochondrial-rich muscle fibers. The 16-fold greater production

▶ **Table 2** Physiologic adaptations to training.

Stimulus	1° Response	2° Response	Muscle plasticity	Physiological change
Endurance training				
Calcium transients	Calcineurin	Increase slow-contractile genes	Slow-contractile phenotypes	Greater endurance
AMP	AMPK:PGC1α	Increase metabolic genes	Greater oxidative capacity	
	AMPK:Ulk1	Increase autophagy initiation	Greater quality of mitochondria	
ROS	NF-kappa B	Increase antioxidant genes	Less ROS-induced damage	
Resistance training				
Neural adaptations			Greater motor unit recruitment	Greater muscle strength
Circulating IGF-1	AKT	Increase protein synthesis by turning "off" TSC2/TSC1	Hypertrophy	
		Decreased protein degradation by preventing FOXO nuclear translocation	Hypertrophy	

of ATP from a similar fuel source provides endurance-trained muscle more ATP supply to meet sustained ATP demand. The most robust physiological adaption to resistance-type training is an increase in strength (▶ **Table 2**). While the above paragraph highlighted molecular pathways leading to muscle hypertrophy, it is well-established that early adaptations to resistance training are neural, leading to greater motor unit recruitment [43, 44]. Over the long-term, muscle hypertrophy will play a larger role and primarily be responsible for continued gains in muscle strength.

Trauma-driven disruption of healing

Despite the significant potential for plasticity and regeneration of both bone and skeletal muscle tissues, severe trauma can disrupt these processes leading to poor healing outcomes. The following section discusses conditions under which endogenous musculoskeletal regeneration and plasticity are impaired, and elaborates on potential mechanisms of impairment.

Fracture healing

Tibia fractures generally have a low incidence of non-union (< 2 %). However, the incidence of non-union can increase to as much as ~23 % when the fracture pattern is multi-fragmentary or wedge-shaped, versus simple [45]. Moreover, fractures that cause segmental bone loss and extensive injury to the surrounding soft tissue place an even greater risk of non-union compared to less severe open fractures with an observed incidence of 67 % [45]. The causes for the impairment of fracture healing is mostly contributed to by the degree of damage of the surrounding soft tissue, disruption of vascular supply, and contamination of the wound. Basic science studies have supported the notion of a multifaceted communication between bone and muscle and other surrounding soft tissue that is critical to timely fracture healing. Under various experimental conditions, the importance of an adequate vascular supply, intact periosteum, and/or skeletal muscle coverage has been repeatedly demonstrated. In particular, studies have observed that skeletal muscle aids fracture healing and subsequent remodeling through the provision of vascular derived mesenchymal stem cells, muscle stem cells, osteogenic myokines, and mechanical stimulation (see for review [46–48]), which manifest impaired simple fracture healing as well as rhBMP-2 mediated osteogenesis in a critical size segmental bone defect [49–57]. Supporting the clinical relevance of these basic science findings, severe open fractures can require more advanced fixation, soft tissue grafts or flaps, or multistep operative techniques (e. g. Masquelet technique [58]) to achieve union.

Another significant factor playing a role in impaired fracture healing in the severely traumatized extremity is the heightened and prolonged inflammatory response that ensues. As noted above, the immune response to musculoskeletal injury is of critical importance to regeneration, wherein abolition of the immune response and inflammatory signaling impairs isolated fracture healing. However, the inflammatory response following severe extremity trauma appears excessive and detrimental to the signal required for regeneration. For instance, wound effluent from severely traumatized extremities has been shown to have extremely heightened levels of inflammatory cytokines that associated with poor healing outcomes to include heterotopic ossification [59]. Similarly, patients with inflammatory comorbidities, such as diabetes, have demonstrated impaired healing of fragility fractures compared to age-matched controls that associates with systemic levels of inflammatory cytokines [60]. These findings are further supported in animal models of polytrauma and open fracture in which heightened and prolonged systemic and local immune responses are associated with impairment of fracture healing; the attenuation thereof using either systemic pharmacological agents (e. g. FK506) or muscle tissue replacement successfully restored the rate of fracture healing [49, 61–64].

Skeletal muscle regeneration

Investigations of severe skeletal muscle injury that results in muscle tissue removal from either iatrogenic (e. g. debridement or sarcoma resection) or traumatic (i. e. high-energy type mechanisms, such as improvised explosive device or motor vehicle accidents) causes also illustrates gross impairment of endogenous regenerative mechanisms. This type of muscle injury has been termed VML and operationally defined as the traumatic or surgical removal of a portion of muscle or muscle unit that results in chronic functional deficits [65]. There are relatively limited clinical data specifically describing VML injury. The reports stemmed from the high incidence of soft tissue loss secondary to blast trauma and to a lesser extent gunshot wounds among US service members injured on the battlefield in recent wars [6, 7]. Available clinical investigations from the military population demonstrate that VML injuries occurred mostly to the lower extremities [7] and resulted in chronic loss of limb function and strength [66, 67]. Volumetric muscle loss injury was associated with separation from the military with disability rating levels directly proportional to the time post-injury, raising concern of progressive degeneration secondary to the initial trauma [68].

Volumetric muscle loss injury is recognized as a primary barrier to functional recovery of the severely traumatized extremity. Due to recognition of the increased incidence and loss of function in battlefield injured service members, the Department of Defense initiated a regenerative medicine research program to develop novel therapeutics for muscle tissue restoration [69]. As a result, much of what is currently understood of the natural pathophysiology of VML injury has been learned in animal models. The key characteristics of this etiology of muscle injury is perhaps best demonstrated in rodents, in which eccentric contractions, crush injury, ischemia reperfusion, or freeze-injuries impart acutely severe injury from which full functional recovery is achieved over the ensuing ~4–6 weeks [27, 70–73]. In contrast, rodent models of VML injury present losses of strength and muscle fibers chronically post-injury (see for review [74]). The permanent loss of muscle fibers is due to a fundamental loss of native regenerative elements required for skeletal muscle regeneration, such as the basal lamina and satellite cells [75–77]. Additionally, rodent and porcine animal models of VML injury have observed a heightened and prolonged inflammatory response [78, 79] that significantly deviates from that observed in recoverable injury models such as ischemia reperfusion injury [80]. The prolonged inflammatory response after VML injury appears to drive extracellular matrix protein production and deposition, resulting in extensive compartmental fibrosis [81, 82]. It is currently unknown at this time what specific effect protracted in-

flammation has on satellite cell viability and function within the remaining portion of the muscle; however, given the necessity of local satellite cells for muscle regeneration and their importance to plasticity, research investigating the quality of chronically injured muscle after VML, is highly needed. Other salient observations following VML injury include motor neuron axotomy, loss of neuromuscular junctions, heightened oxidative stress, devascularization, and mitochondrial dysfunction [83–85]; all of these may be deleterious to regenerative healing and the capacity to respond to tissue level physical therapies.

General efficacy of physical therapy

The specific characteristics of the therapy employed will widely vary depending on the type and severity of injury and the patient's deficits, goals of therapy, and resources, as well as the clinician's expertise. Generally, clinical data have demonstrated benefit of physical therapy to improve functional outcomes following most musculoskeletal injuries. For instance, early weight bearing is recommended for simple mid-shaft tibia fractures operatively managed with open reduction internal fixation with an intramedullary nail [86]; corresponding with retrospective evidence that delayed initial weight bearing following open and closed tibia diaphyseal fractures associates with increased risk of non-union [87]. As another example, a prospective randomized control trial demonstrated benefit of using an active controlled motion device in addition to a standard physical therapy targeted at early partial weight-bearing for isolated unstable ankle fractures (i. e. Weber type B- or C-Fracture) [88]. In this study, physical therapy began on the first post-operative day in hospital and progressed to 2–3 times per week for 20 min as tolerated out of hospital for a total six weeks. Active controlled motion was implemented in hospital 2–5 days post-surgery and consisted of 20-minute daily sessions continued at home for a total of six weeks. Active controlled motion was shown to improve recovery of ankle range of motion out to 12 weeks, as well as significantly shorten time to return to work [88]. Naturally, there exists considerable variability among clinical studies that may additionally suffer from low sample sizes. To that end, systematic reviews, meta-analyses, and expert panels have distilled the existing data for rehabilitation of many common musculoskeletal injuries to help guide clinical practice (see, e. g. [89–91]).

Because primary outcome measures used in clinical trials assessing physical therapies typically involve standardized functional assessments and validated clinical assessment tools, delineating specific tissue level effects may require inference from smaller clinical studies investigating a similar patient population and using similar therapeutic methodology, if available. For example, a randomized control trial that investigated the benefit of a 6-month extended outpatient rehabilitation program involving whole-body resistance exercise versus flexibility-based physical therapy on disability and function in elderly patients suffering hip fracture demonstrated significantly greater performance of instrumental activities of daily living and basic activities of daily living, as well as improved muscle strength across most major muscle groups and functional indices with the extended resistance exercise program [92]. However, no evaluation of putative mechanism of physical therapy was evaluated. Interestingly, a clinical study of patients with end-stage osteoarthritis electing for total hip arthroplasty identified discrete inflammatory phenotypes based on tumor necrosis factor-like weak inducer of apoptosis (TWEAK) expression within the surrounding muscle tissue, which were indirectly associated with muscle protein synthesis levels. The authors proposed that the findings suggested an inflammatory-based prediction of muscle regeneration, the corollary of which is early identification of patients at risk for prolonged muscle weakness and resulting worse post-arthroplasty functional outcome [93]. In support of this idea, a recent pilot study of elderly patients with recent hip fracture reported prolonged up-regulated gene expression or inflammatory genes in ipsilateral quadriceps muscle biopsies compared to matched control subjects [94]. Notably, following the completion a 3-month high-intensity, resistance-based training program gene expression of inflammatory mediators (*NFKB1 & IL6*) and some toll-like receptor signaling molecules (e. g. *MYD88*) were significantly reduced in a pre-post analysis. An inverse relationship between inflammation (MYD88) and quadriceps isometric strength ($r = -0.42$, $p = 0.05$) and cross-sectional area (-0.60, $p = 0.01$) measured with MRI was observed, further suggesting a pathological role of prolonged muscle inflammation on functional recovery after hip fracture.

Tissue level resistance to physical therapy in VML injury

Rehabilitation-focused investigations are sparse for the VML injured population. The only clinical trial of traumatic VML-injured patients described a cohort of 13 patients, 7–120 months removed from the time of injury, who were initially treated with extensive physical therapy and still had significant functional deficits remaining. Interpretation of rehabilitation effectiveness is limited by the exclusion of a sufficient control group and pre-intervention muscle function not being thoroughly assessed prior to intervention [95, 96]. A 2010 case report of a 19-year-old patient with a right femur fracture and associated large VML quadriceps muscle injury noted long-term disability and ineffectiveness of physical therapy to fully restore function of the remaining muscle [66]. More recently, a retrospective evaluation of 17 patients that had a component of VML secondary to soft tissue sarcoma, revealed the long-term consequences of unmet rehabilitation needs on quality of life [97]. The common outcome among patients was knee flexion weakness that had a high predictive value on a reduction in activities of daily living (Toronto Extremity Salvage Score, $R = 0.66$) and quality of life (European Quality of life-5 Dimensions score, $R = 0.54$).

Clinical data of tissue level pathology and unresponsiveness to physical therapies is not currently available in this patient population. Available data from animal models of VML indicate that the remaining portion of muscle does not demonstrate a robust increase in oxidative capacity with endurance exercise type training due to inadequate activation of the necessary cellular signaling cascades (e. g. transcription factor PGC1α) [85]. Alarmingly, a recent systematic review, meta-analysis, and network meta-analysis of VML injury studies that included quantitative functional analyses [98] determined that in animal models, rehabilitation approaches for VML injury resulted in worse functional outcomes than if the injury was left to its natural sequela. This work specifically focused on studies testing rehabilitation in animal models in the form of voluntary wheel running, chronic-intermittent electrical nerve stimulation and/or passive range of motion exercises resulting in

only modest functional improvements [84, 99–103]. Collectively, these limited clinical and pre-clinical studies indicate that the remaining muscle does not fully recover strength, may be resistant to rehabilitation, and results in long-term disability. Which is to say that it is possible that after traumatic injuries, such as VML, the remaining muscle is inhospitable to plastic changes and rehabilitation efforts, further worsening functional limitations.

Closing perspectives and future directions

Lifelong considerations following injury

The impact of traumatic musculoskeletal injuries can affect those injured far beyond the initial injury and regenerative phase. For those who have sustained traumatic VML injuries, for example, the lack of response to rehabilitation and normal repair processes can have lifelong impacts. For instance, military service members who sustained traumatic orthopedic injuries have disability ratings that did not improve when given temporary status to allow additional recovery and rehabilitation time and, in fact, their function continued to deteriorate over time [68]. Health-related quality of life [104], which often represents a compilation of physical, psychological, and social domains of health, and has been used often as a benchmark for health and can provide information on the long-term impact of injuries. As an example, one year after tibial fracture a significant impairment in general health (determined by health state utility values) may still be present despite successful fracture healing, such that patients had improved since the time of initial injury but not to the level of a healthy population [105]. Similarly, for those with sports-related injuries sustained during college athletics their quality of life scores have been shown to worsen over time, well past their time of healing [4].

It is well appreciated that there is a relationship between lack of physical activity, inactivity, and sedentary lifestyles with all-cause mortality [106]. Broadly, following a range of injuries physical activity levels are shown to significantly decline just three months after the initial injury [107]. With this, the decrease in physical activity was noted independent of injury severity and return to sports/work, and there was an association in low physical activity levels with poor health, greater disability, and pain/discomfort. In more identified traumatic orthopedic conditions such as fracture, patients with both upper and lower extremity fractures also had decreases in physical activity and increases in sedentary activity following injury [108]. These early changes in physical activity appear to be extrapolated into later life, too. Again, data from NCAA athletes supports that athletes have lower health-related quality of life scores and more limitations than non-athletes [4]. Additionally, it has been proposed that injury during sports into adulthood can impact long-term risk of osteoarthritis [109, 110], and bone quality [111], which in turn likely will limit physical activity. In fact, if extrapolated, former college athletes who became physically inactive in later life have greater risks of cardiovascular disease [112]; while not directly investigated in those with previous injuries, it is possible to posit that long-term consequences could have stemmed from the initial injury.

Innovative evidence-based treatment and rehabilitation approaches aimed at improving musculoskeletal function both acutely following injury and throughout life are still needed, especially for the most severe sport and traumatic orthopedic injuries. We posit that future work needs to evaluate functional deficits, progressive and worsening pathophysiology and comorbidities due to injury. With this, any long-term limitations due to injury-induced inactivity, quality of life, and long-term co-morbidities should be considered. Future work [113] should strive to understand the span of traumatic orthopedic injuries from prevention strategies, acute care, rehabilitation, long-term health, and physiologic limitations. Additionally, the multidisciplinary use of combined approaches such as regenerative rehabilitation [114] should be explored, in the hopes that multiple approaches could work together in synergy to promote long-term functional gains and health.

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Conflict of Interest

The authors declare that they have no potential or actual conflicts of interest.

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