Curr Rev Musculoskelet Med
DOI 10.1007/s12178-015-9262-2

MUSCLE INJURIES (SJ MCNEILL INGHAM, SECTION EDITOR)

Return to sport after muscle injury

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Abstract Skeletal muscle injuries are among the most common sports-related injuries that result in time lost from practice and competition. The cellular response to muscle injury can often result in changes made to the muscle fibers as well as the surrounding extracellular matrix during repair. This can negatively affect the force and range of the injured muscle even after the patient's return to play. Diagnosis of skeletal muscle injury involves both history and physical examinations; imaging modalities including ultrasound and magnetic resonance imaging (MRI) can also be used to assess the extent of injury. Current research is investigating potential methods, including clinical factors and MRI, by which to predict a patient's return to sports. Overall, function of acutely injured muscles seems to improve with time. Current treatment methods for skeletal muscle injuries include injections of steroids, anesthetics, and platelet-rich plasma (PRP). Other proposed methods involve inhibitors of key players in fibrotic pathways, such as transforming growth factor (TGF)-ß and angiotensin II, as well as muscle-derived stem cells.

Keywords Sports-related injuries · Skeletal muscle injury · Platelet-rich plasma

Introduction

Acute skeletal muscle injuries are frequent injuries sustained by athletes and are a significant cause of disability. Diagnosis of these injuries is primarily clinical, with additional information gained with ultrasound and MRI. Following the acute injury, predicting time to return to play is important to both the athlete and clinician. Improvements in understanding of the physiology of muscle injury and resulting fibrosis have led to recent advancements in development of adjuvant treatments, which have the goals of shortening time to return to play and improving function during sporting activity.

Epidemiology of muscle injury

Muscle injuries are among the most common injuries sustained during sporting activity. Across several professional sports, acute muscle injury makes up between 23 and 46 % of all injuries [1, 2•]. There have been many studies that focus on epidemiology of athletic injuries utilizing the professional and collegiate athletic injury databases.

In a 12-year study of European professional soccer leagues, 95 % of all muscle injuries occurred in the following four groups: hamstrings, adductors, quadriceps, and calf [2•]. Among these, the hamstrings are consistently the most frequently injured. Similarly, in the National Football League (NFL) training camps from 1997 to 2007, hamstring strains were reported to be the second most common injury, after knee sprain [1]. Similarly, UEFA professional soccer data from 2001 to 2013 demonstrated that the hamstrings are the most frequently injured muscle group, accounting for 34 % of all muscle strains [2•]. The upper leg muscles were almost always the most commonly injured muscle group in collegiate athletes, as well (Tables 1 and 2).

Males are more likely to have muscle injuries compared to females across multiple sports, but the data is most clear in soccer. In professional soccer leagues in the USA and Europe, the incidence of hamstring strains was reported to be between 0.35 and 1.5/1,000 h of soccer in male professional soccer players [8, 9]. The rate of hamstring strains in US female

This article is part of the Topical Collection on *Muscle Injuries*

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Published online: 06 March 2015

Table 1 Muscle strain injuries occurring during collegiate games [3–7]. Injury rates reported as injuries per athlete-exposure (A-E). An athlete-exposure was defined as an athlete participating in a game or practice and the injury rate was calculated per 1,000 athlete-exposures

Sport	Muscle group	Frequency	Percentage	Injury rate per 1,000 A-E
Football	Pelvis/hip	581	1.9	0.65
Football	Upper leg	1,103	3.6	1.24
Basketball (men's)	Pelvis/hip	86	2.0	0.18
Basketball (men's)	Upper leg	79	1.9	0.17
Basketball (men's)	Lower leg	43	1.0	0.09
Basketball (women's)	Upper leg	45	1.3	0.10
Soccer (men's)	Pelvis/hip	264	3.9	0.74
Soccer (men's)	Upper leg	548	8.2	1.54
Soccer (men's)	Lower leg	73	1.1	0.20
Soccer (women's)	Pelvis/hip	120	2.2	0.37
Soccer (women's)	Upper leg	374	7.0	1.14
Soccer (women's)	Lower leg	69	1.3	0.21

professional soccer players was much lower, 0.02/1,000 h of soccer played [10]. Data from the National Collegiate Athletic Association (NCAA) demonstrated that male collegiate soccer players were 64 % more likely to suffer hamstring strains compared to female soccer players [11]. Additionally, those male athletes had a higher frequency of recurrent hamstring strains, 20 %, compared to 10 % of female players [11]. This was thought to be due to more high-intensity running or sprinting in male players compared to female and, perhaps, inadequate rehabilitation aimed at these high-intensity activities in male players.

Table 2 Muscle strain injuries occurring during collegiate practices [3–7]

Sport	Muscle group	Frequency	Percentage	Injury rate per 1,000 A-E
Football	Pelvis/hip	2,196	3.9	0.15
Football	Upper leg	4,518	10.7	0.41
Basketball (men's)	Pelvis/hip	348	4.4	0.18
Basketball (men's)	Upper leg	283	3.6	0.14
Basketball (men's)	Lower leg	93	1.2	0.05
Basketball (women's)	Pelvis/hip	213	3.2	0.13
Basketball (women's)	Lower leg	107	1.6	0.06
Soccer (men's)	Pelvis/hip	487	7.8	0.34
Soccer (men's)	Upper leg	1,042	16.6	0.72
Soccer (men's)	Lower leg	128	2.0	0.09
Soccer (women's)	Pelvis/hip	444	7.6	0.40
Soccer (women's)	Upper leg	1,243	21.3	1.11
Soccer (women's)	Lower leg	129	2.2	0.12

Rates of muscle injury also vary across sports, as shown in Tables 1 and 2 for collegiate sports and Table 3 for professional sports. Collegiate athletes sustained muscle injuries more commonly during games than practices (Tables 1 and 2).

Physiology of muscle injury

The cellular response to injury provides a basis for evaluation of the broad range of skeletal muscle injuries. This response occurs in two stages, the first marked by degeneration of the damaged muscle cells and the resulting tissue inflammation. The second stage involves regeneration and renewal of muscle fibers and growth of the muscle tissue. In normal, non-injured states, muscle stem cells show a low rate of turnover and regeneration. After injury, the process of muscle renewal occurs with proliferation and differentiation of satellite cells and generation of new myofibers to replace those that were injured; however, the timeline for this process is variable and is often complicated by development of fibrosis.

In the first phase, degeneration, the impact of injury to skeletal muscle leads to death on a cellular level. Injury damages and increases the permeability of the sarcolemma of affected myofibers. This causes the muscle cells to break down, releasing intracellular proteins that can act as cytokines. As the serum concentration of these proteins increases, immune cells are activated and attracted to the site of injury, causing inflammation of the region. The first wave of inflammatory cells to infiltrate the muscle tissue is composed mainly of neutrophils. After arriving at the site of injury, neutrophils have been suggested to promote secondary muscle cell damage for reasons still unclear [13]. This is followed by a macrophage-mediated response about 48 h after injury [14]. Macrophages phagocytose debris from the necrotic muscle cells, removing necrotic material, and suppress inflammation [15].

Macrophages also play an active role in the second phase of muscle injury repair by secreting cytokines that activate muscle cell precursors. These cytokines, which include basic fibroblast growth factor (FGF), IL-6, and transforming growth factor (TGF)-ß, help with both growth and differentiation of muscle

Table 3 Muscle injury rates for professional baseball and football [1, 12]

Sport	Muscle group	Injury rate/ 1,000 A-E
Major League Baseball	Hamstring	0.7
Minor League Baseball	Hamstring	0.7
National Football League	Hamstring	2.2
	Hip flexor	2.2

stem cells. Regeneration begins with the proliferation of these activated myogenic cells [16]. This population of muscle precursor cells includes both satellite cells and non-muscle stem cells. Satellite cells are found surrounding mature muscle cells. Once activated, they proliferate and terminally differentiate into myoblasts. The resulting myoblasts can fuse either to one another, replacing muscle fibers that were lost in injury, or with existing fibers in the injured muscle, repairing damage from injury [17]. A portion of the satellite cell population then returns to a reversible state of quiescence, allowing the cells to self-renew with each round of regeneration [18]. Other non-muscle stem cells are also capable of myogenesis and, after activation, are able to regenerate muscle fibers [14]. After this process has been completed, the newly generated myofibers are physiologically indistinguishable from the old muscle cells.

Function of muscle after injury

Though the individual muscle cells regenerated after injury are identical to pre-existing muscle cells, fibrosis often alters the physiology of the muscle tissue as a whole. Fibrosis is a process that involves the deposition of connective tissue and abnormal extracellular matrix within regenerated muscle tissue. The occurrence of fibrosis causes pain and mechanical stiffness, limiting the contractile force of the muscle tissue and decreasing the patient's range of motion [19]. Recently, the cytokine TGF-ß has been implicated in the accumulation of fibrotic tissue within muscle after skeletal muscle injuries [20]. It is believed that TGF-ß inhibitors may help to prevent fibrosis in patients recovering from relevant injuries. Thus far, fibrosis has been difficult to quantify due to the variation in muscle fiber size after injury is sustained. While it is generally believed that increased fibrosis correlates with increased stiffness, the relationship has not been quantitatively established [21].

Diagnosis of muscle injury

Diagnosis of muscle injury should rely on a detailed history and physical examination. Injuries to the lower extremities are typically due to jumping, kicking, high-speed running, and sudden change in direction while running. In general, patients often feel sharp pain and experience a loss in function of the muscle post-injury. Pain may be associated with localized swelling and loss of motion. Individuals may also describe the occurrence of an audible pop [22]. Due to the high recurrence of hamstring injuries, clinicians should be mindful of a previous injury. Current injury usually presents at or near location of previous injury [23]. Physical examination of the lower extremities should consist of inspection, palpation, range of motion, and strength testing. The purpose of physical examination is to determine the location and severity of the injury, more so than the presence. An assessment shortly after injury is recommended as this allows for quicker intervention and a more reliable medical history [24]. Physical examination may reveal swelling and ecchymosis. Palpation serves to detect a discrete defect, edema, and increased muscle tone due to injury [25]. Strength testing is best done with bilateral comparison to identify decreased strength of the injured muscle or post-injury changes [24]. Although many patients will not have significant strength deficits with manual testing, side to side pain or difficulty with expending full effort should suggest that a patient has a muscle injury. Active range of motion tests should be conducted 48 h after injury as significant pain and disability is present immediately following injury and would provide for an unreliable ROM assessment [24, 26].

Imaging can help confirm injury. X-rays are of little to no benefit in diagnosing pure muscle injuries, but it can be helpful in visualizing chronic muscle injuries such as myositis ossificans or avulsion injuries including rectus femoris avulsions and should be the first line of imaging obtained in a majority of cases. MRI is arguably the gold standard following muscle injury to assess the degree of injury. Muscle strains are best visualized via MRI with T2-weighted images, which optimize contrast between injured muscles with edema and uninjured muscles [27]. Ultrasound is being increasingly used because it is readily accessible, low cost, and can acquire dynamic images [28]. Dynamic ultrasound can be used to differentiate between partial and complete thickness tears as muscle retraction is more evident through passive movement or active muscle contraction [29]. However, ultrasound imaging is operator dependent, cannot assess the extent of injury, or differentiate between old and new injuries [30]. Ultrasound is also less effective in diagnosing muscle tears within the first few hours of injury because new hemorrhage may have the same echogenicity as normal unaffected muscle [31•], whereas MRI has high sensitivity to detect early hemorrhage and edema following muscle injury [27]. With cost reservations, ultrasound may be used to diagnose 24 h after injury as this is when hematomas become distinguishable from surrounding muscle [31•]. It is important to note though that the majority of muscle injuries are a clinical diagnosis. Advanced MRI techniques such as diffusion tensor imaging (DTI) have been shown to provide a reliable assessment of skeletal muscle injury in mice [32]. Normal skeletal muscle displays orderly arrangements on DTI which are disrupted following injury. This imaging modality has yet to reach clinical acceptance but may become useful in future clinical practice and shows promise to assess muscle fibrosis as well.

Return to sports after muscle injury

The timeline for return to sports following acute muscle injury depends on several factors, including mechanism of injury, severity of muscle injury, and what muscle group was injured.

In a study of American football players, number of training camp days missed varied depending on which muscle group was injured [1]. Those with hamstring injuries missed an average of 8.3 days, compared to 4.8 days for those with adductor injuries and 5.4 days for quadriceps injuries. Hamstring strains were similarly associated with a lengthier time to return to play compared to other muscle groups in European soccer leagues [2•]. Those with hamstring strains missed 13 days, compared to 9 days missed for adductor strains, 12 days for quadriceps strains, and 13 days for calf strains. Return to play after hamstring strains also differed in major compared to minor league baseball teams, with major league players missing 24 days and minor league players missing 27 days [12]. Recurrent muscle strains in the hamstring group appear to occur more commonly in the biceps femoris compared to the semitendiosis and semimembranosus [2•, 33].

The use of MRI to predict time to return to play following acute muscle injury is controversial. Many studies have investigated MRI as a tool to prognosticate time to return to play, given variability in return to play between different sports, level at which the sport is played, and muscle groups injured. In one such study by Ekstrand et al., MRI classification of muscle injuries [34] was utilized [35]. Grade 0 (negative MRI) and 1 (MRI with edema but no architectural disruption) injuries, while they were the most mild injuries, accounted for the majority of the days missed (56 %, 2,141/3,830 injuries). Grade 2 injuries were described as architectural disruption indicating partial tear, and grade 3 injuries were complete muscle tears. The authors of the study concluded that MRI grading of muscle injury is highly correlated with amount of time taken off from soccer, with increase of MRI grade correlated with increase in number of days off.

Reurink et al. recently conducted a systematic review to determine the prognostic value of MRI in predicting return to play in athletes who sustained a hamstring strain [36•]. Of the 12 studies included in their review, 11 were found to have high risk of bias, and only 1 study was deemed to be at low risk of bias. These biases were study sample, study attrition, prognostic MRI measures, outcome measures, confounders, and statistical analysis. Based on these findings, the authors concluded there was lack of strong evidence to use MRI as a tool to predict return to play secondary to high risk of bias. However, the authors were able to conclude that there is moderate evidence that hamstring injuries without hyperintensity on MRI fluid-sensitive sequences are associated with shorter return to play time. In contrast, Moen et al. suggested that return to sports should be determined by clinical factors, such as athlete-predicted time to return to play and passive straight leg raise deficit [23]. Furthermore, their study concluded that time to return to play was not associated with findings on MRI. It is therefore likely that MRI is partially helpful in grading symptoms and severity of muscle injury, but the demands of individual athletes and types of sport must also be taken into account as well when assessing a proper return to play.

Importantly, even after an athlete is able to return to sport, their function after acute muscle injury is still in question. Cloke et al. studied a group of youth soccer players and found that poor prognostic factors for prolonged symptoms of acute muscle injury were hamstring strains, contact injuries, and older age of the athlete [37]. A study of male semiprofessional soccer players found that function after return to sport improved with time after return to play [38]. At the time of return to play, injured athletes were slower at sprinting, compared to their non-injured counterparts. At 2 months after return to play, the injured group of athletes demonstrated increases in horizontal force and horizontal power, which was associated with improved early acceleration during sprinting with no difference between injured and non-injured athletes.

In summary, hamstring injuries are associated with the longest times to return to play. MRI remains a controversial tool for predicting return to play, and function after returning to play from acute muscle injury appears to improve over time.

Treatments to enhance return to sports after muscle injury

Typically, conservative treatment of acute muscle injuries includes rest, ice, elevation, compression, rehabilitation exercises, and non-steroidal anti-inflammatory medications [39]. In recent years, advances in understanding of muscle injury physiology and healing have led to proposed adjuvant treatments.

Steroid injections in or around tendons and ligaments are controversial due to concern for the risk of rupture of those structures. However, intramuscular or myotendinous junction injections may not carry the same risk and have thus been suggested as treatment for muscle strains. A group of 58 professional football players with severe hamstring injuries (defined clinically as a palpable defect) were treated with an intramuscular steroid and anesthetic injection [40]. Average time to return to full practice was 7.6 days. There were no reported complications, no recurrences during their NFL careers, and no functional deficits noted after recovery, though no isokinetic testing was performed. Limitations of this study include the lack of control group and its retrospective nature. A case study of three professional baseball players who sustained acute internal oblique muscle strains was also performed [41]. The players received intramuscular steroid and anesthetic injections. All three athletes had significant pain relief within several days, and average return to play was

30.7 days. Steroid injections appear to be safe, though larger, randomized studies should be conducted to better understand their efficacy.

Autologous platelet-rich plasma (PRP) injections have been studied for various applications, including as an adjuvant treatment for muscle injury. Platelets release growth factors including FGF-2, TGF-β1, PDGF, and IGF-1, and when platelets are highly concentrated by centrifugation, the resulting PRP solution is postulated to improve tissue healing. The effect of PRP injections on acute muscle injury has been best studied in rodent models. Several studies have investigated the effect of a series of PRP injections on isometric torque muscle strength in rats. Delos et al. found no difference in muscle strength at any time point and no difference in the number centronucleated fibers or inflammatory cells compared to control rodents injected with saline [42]. Hammond et al. found no difference in strength for single muscle contraction injuries treated with PRP [43]. However, they did show increased muscle regeneration, improved contractile function of multiple muscle contraction injured muscles, and decreased recovery time from 21 to 14 days compared to controls. Other rodent models used immunohistochemical staining after PRP injection as an outcome for muscle regeneration. Wright et al. showed an increase in satellite cell regeneration, and both Wright et al. and Gigante et al. found greater muscle regeneration in PRP-injected rodents as measured by the number of centrally nucleated fibers in the injured area [44, 45], consistent with faster histological muscle healing.

Several clinical studies on PRP use for muscle injury have also been performed. A randomized controlled trial was conducted on 28 athletes who sustained hamstring strains [46]. Athletes were randomized to PRP injection and rehabilitation versus rehabilitation alone. The PRP group had faster return to sport compared to the control group (26.7±7.0 vs. 42.5± 20.6 days) and had lower pain severity scores, though there was no difference in pain interference scores. Another randomized trial studied ultrasound-guided PRP injections in athletes who sustained acute muscle injuries [47]. The players were randomized to a single PRP injection or conservative therapy (physical therapy, anti-inflammatory medications). The PRP group in this study had decreased pain, increased early strength, and early range of motion (days 7 to 14 after injury). However, there was no difference in pain or strength by day 28. The PRP group had decreased time to return to sport (10 compared to 22 days). The authors concluded that PRP is helpful for decreasing pain in the immediate post-injury phase and may be helpful in facilitating early rehabilitation. Wright-Carpenter et al. conducted a controlled trial where professional athletes with grade 2 or moderate muscle strains were treated with a series of autologous conditioned serum (ACS) [48]. Those in the ACS group had shorter time to return to sport (16.6 days compared to 22.3 days in control group), though this study is limited by lack of randomization and lack of blinding. PRP may be useful for adjuvant treatment of muscle injury, especially acutely, though may not have long-term benefits. However, large, randomized clinical trials have yet to be conducted.

As discussed previously, fibrosis occurs after injury when connective tissue fibers are deposited between skeletal muscle fibers. Fibrosis typically occurs during the second to third week after the initial injury [49] and impairs the function of skeletal muscle. TGF-ß has been implicated in fibrosis formation after muscle injury [49, 50], and thus, inhibition of TGF-ß with antifibrotic agents is an attractive target to reduce muscle fibrosis and improve function after injury. Various antifibrotics have been studied including gamma interferon, alpha interferon, suramin, decorin, and relaxin, though these have yet to be used clinically.

Losartan, an angiotensin II receptor blocker, is of particular interest given its established safety profile in humans. Losartan use has been associated with decreased fibrosis in various settings, including neuromuscular disorders [51]. The use of losartan in a mouse model with partial gastrocnemius lacerations improved muscle regeneration and decreased fibrosis formation [52]. In a clinical case study [53], two college athletes with partial thickness tears of the biceps femoris were given losartan, starting 5 to 10 days after initial injury, for 30 days (at a lower dose than would typically be used for treatment of hypertension). One athlete had normal hamstring strength at 9 weeks, and the other athlete had normal hamstring flexibility and strength by 3 weeks. Neither sustained recurrent muscle injury at 1-year follow-up, there were no reported side effects, and both remained normotensive. Losartan and other angiotensin II receptor blockers have potential to decrease fibrosis and improve muscle healing, but larger scale, controlled studies are needed to determine its efficacy.

A recent study explored the effect of combining an antifibrotic agent with PRP [54]. Mice were treated with either PRP alone or PRP plus losartan. The group treated with both the antifibrotic and PRP had improved skeletal muscle healing on histological analysis and decreased expression of Smad2/3 (transcription factors that induce TGF-ß signaling). This suggests that using losartan to block the expression of TGF-ß improves the PRP effect on acute muscle injury.

The use of stem cells for treatment of muscle injury has been of great interest in multiple medical fields. Muscle-derived stem cells (MDSC) originate from the walls of blood vessels and can differentiate into multiple cell lines including myogenic and endothelial cell lines. Thus far, most studies have been limited to animal models. Intraarterial stem cell delivery restored the dystrophin protein in a Duchenne muscular dystrophy model [55]. Interestingly, sex differences have been observed in Duchenne muscular dystrophy where female MDSC had a superior ability to regenerate skeletal muscle compared to male MDSC [56].

Muscle-derived stem cells have been proposed as a treatment for skeletal muscle injury [19]. In a controlled laboratory study, MDSC were injected into injured tibialis anterior muscles of mice at several time points after muscle contusion injury [57]. The mice injected with the muscle-derived stem cells 4 days after injury had increased levels of vascular endothelial growth factor (VEGF) at week 1 and increased muscle regeneration and strength at week 2. The mice injected at 4 and 7 days after injury had decreased fibrosis 4 weeks after injury. Intramuscular injection of MDSC may promote angiogenesis and decrease fibrosis. Recently, the development of biomaterials that function as delivery vehicles has been discussed as an important factor for effective stem cell therapy [3]. Overall, stem cell therapy for muscle injury has been shown to be effective in other skeletal muscles of the human body. Clinical studies are needed to further characterize the effect of stem cell therapy on acutely injured muscles resulting from sports.

Summary and conclusions

Skeletal muscle injuries are among the most common injuries in sport. Most muscle injuries occur in the hamstrings, abductors, quadriceps, and calf. Across sports, upper leg injuries appear to be the most common. Due to lost time of play and decreased muscle function and range of motion following muscle injury due to fibrosis, muscle injuries pose a problem to athletes.

Studies of muscle injury at the cellular level highlight the biological basis of the physiological response to muscle injury. This information can guide future development of therapies that may enhance recovery from injury.

Current methods of diagnosing muscle injuries include a detailed medical history, imaging, and a physical exam involving palpations, strength testing, and range of motion testing. X-rays can be help rule out injuries involving bone such as fractures and avulsion injuries. However, injuries restricted solely to the muscle cannot be visualized through X-ray. In these instances, MRI and ultrasound can be used to visualize pure muscle injuries. In a majority of cases, MRI is the recommended imaging technique in assessing the extent of injury.

Time to return to sport after injury may depend on the muscle that is injured, with hamstring injuries resulting in the longest times to return to play. The use of MRI as a prognostic tool remains questionable. As such, more studies are required in order to gauge its effectiveness in predicting time to return to play. Even with tools that can potentially predict return to competition, muscle function may not be 100 % upon return to play, though it can improve with time. This must be taken into account when determining time to return to pre-injury level of sport.

The conventional treatment for muscle injuries involves rest, ice, elevation, and compression. Recent studies have given rise to proposed adjuvant treatments that may enhance muscle healing, decrease fibrosis, and provide a smoother transition back to competition. Proposed treatments include intramuscular or myotendinous junction steroid injections, PRP and ACS injections, angiotensin II receptor blockers such as losartan, and muscle-derived stem cells. For now, the results of studies proposing these treatments appear promising. However, more studies are required in order to better determine their efficacy and allow for their use in clinical practice.

Compliance with Ethics Guidelines

Conflict of Interest Stephanie Wong, Anne Ning, Carlin Lee, and Brian T. Feeley declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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