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REVIEW

# New Therapeutic Approaches for Management of Sport-Induced Muscle Strains

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## ABSTRACT

Muscle strains are one of the most common sports-induced injuries. Depending on the severity and location of the muscle strain, different treatment approaches can be taken. This review highlights recent trends in conservative, pharmacologic, and surgical approaches to the management of sports-induced muscle injuries as presented at a symposium held during the 93rd Annual Congress of the Italian Society of Orthopedics and Traumatology (SIOT) in Rome, Italy in November 2008. Conservative approaches now include growth factor therapy and administration of autologous platelet-rich plasma during the early postinjury period; however, its use is currently considered a doping violation under the World Anti-Doping Agency code, therefore restricting its use to nonelite sports people only. Topical anti-inflammatory therapy is a promising therapeutic strategy, since it allows local analgesic and anti-inflammatory effects while minimizing systemic adverse events. As the drug delivery system is critical to clinical effectiveness, the advent of a new delivery system for ketoprofen via a new-generation plaster with a marked increase in tissue penetration and a clinical efficacy comparable with that of oral administration, provides a viable option in the treatment of single sport lesions. Surgical treatment of muscle lesions is less common than conservative and topical therapies and indications are limited to more serious injuries. Presentations from SIOT 2008 show that advances in our understanding of the healing process and in conservative, pharmacologic, and surgical treatment approaches to the management of sports-induced muscle strains contribute to better clinical outcomes, faster healing, and a swifter return to normal training and activity levels.

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## INTRODUCTION

Muscle strains account for a large proportion of sports injuries and typically keep an athlete out of action for several weeks. Owing to heterogeneity in the severity of injuries and the variety of muscles involved, clinical studies of the treatment of muscle injuries are limited. Muscle injuries may be classified as: delayed-onset muscle soreness (DOMS); indirect traumatic injury (Grade I: localized damage to muscle fibrils and filaments without loss of continuity of muscle tissue; Grade II: rupture of a number of muscle fibers without involving a macroscopically recognizable portion of the muscle belly; Grade III: rupture of a large portion of the muscle belly with clinically evident loss of continuity); direct traumatic injury or contusions (intermuscular hematoma, intramuscular hematoma); and avulsions (bone, apophysis, muscle). The basic response to injury at the tissue level consists of an acute inflammatory phase, a remodeling phase, and a repair/recovery phase.[1-3]

This review will discuss recent trends in conservative, pharmacologic, and surgical treatment approaches to the management of sports-induced muscle strains as presented at a symposium held at the 93rd Annual Congress of the Italian Society of Orthopedics and Traumatology (SIOT) in Rome, Italy in November 2008.

## CONSERVATIVE TREATMENT: FACTORS THAT ACCELERATE HEALING

Implementing strategies that can prevent the occurrence of trauma is the primary objective of the sports physician who, when incident-related injuries occur, will be responsible for establishing prompt diagnosis and instituting appropriate treatment to reduce the still far too frequent recurrence of injury and complications.

During indirect injuries, the muscle-tendon junction is at particularly high risk of damage due to its reduced extensibility and the sudden decrease in local microcirculation at the tendon compared with muscle tissue and biarticular muscles, particularly those with a higher content of fast twitch (type II) fibers.[4,5] Following minor injury, muscle tissue heals by myoblastic differentiation of mononuclear satellite cells, whereas healing after major injury takes place predominantly through scar formation. Progressive recovery of function is essential for proper regeneration of newly formed tissue.[6]

The most widely employed approach to muscle injuries is conservative treatment.[7-9] Rehabilitation principles in the conservative management of Grade II muscle injuries during the three main phases of muscle healing are discussed.

### The Acute Phase of Muscle Healing

Immediately after an incident, an elastic compression bandage and cryotherapy (for 20 minutes every hour) should be applied to the injury site to limit initial damage as far as possible.[10] The pathologic characteristics of this phase are local hemorrhage, myofibrillar retraction, and edema resulting from increased capillary permeability. Nonsteroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, or other drugs are not normally administered as the pain is not usually severe enough to require analgesic coverage.[11]

Between 24 and 48 hours postinjury, edema becomes prominent, accompanied by mechanical muscle weakness due to massive local

invasion by macrophages. Correct management of the injury in this phase is vital because overly aggressive treatment may lead to further tissue damage, prolonging the inflammatory phase and delaying the repair phase. The external bandage is removed on postinjury day 3 and an ultrasound study, or magnetic resonance imaging (MRI) of the injured part is performed. Hydrokinetic therapy (water-based exercise), because of its hydrostatic, hydrodynamic, proprioceptive, and thermal effects, permits early institution of active mobilization and functional recovery.[12]

## The Remodeling Phase of Muscle Healing

The acute phase is followed by early remodeling (postinjury days 3-6). Fibroblastic activity stimulates the deposition of collagen, and capillary neovessels form and begin to supply oxygen and nutrients necessary for tissue regeneration and repair. No massage is given during this phase; instead, isometric muscle contraction is initiated using submaximal exercise workloads below the pain threshold.

In the advanced stage of repair, and concurrent with muscle fiber regeneration, muscular strength is approximately 50% that of the preinjury condition. This deficit is more likely attributable to the inflammatory nature of the repair process, accompanied by edema and pain, than to a real decrease in muscle contractility. The risk of recurrence of injury in this phase is higher because decreased pain and improved function can expose the structurally vulnerable wound to stress. When muscular elasticity is deemed satisfactory, concentric isotonic muscle work is initiated, followed by submaximal eccentric exercise, both of which are performed against manual resistance. Maintenance and recovery of tissue elasticity is achieved with specific passive stretching exercises.[13]

## The Repair/Recovery Phase of Muscle Healing

During the recovery phase, collagen maturation and complete recovery of voluntary muscle control direct the physiotherapist toward achieving complete recovery of muscular strength and function. Generally, normal muscular ability and elasticity are restored between postinjury weeks 3 and 4, and pain is no longer experienced during prolonged maximal isometric contraction. A further ultrasound study is performed to assess the progress of fiber remodeling at the injury site.

In localized muscle injuries of the lower limbs, a return to running can be recommended when regained muscular strength at 60 degrees/sec angular velocity peak torque is at least 70% of that of the unaffected limb.[14] Sessions of eccentric isokinetic exercise at incremental velocities (starting from 60 degrees/sec), initially at submaximal levels, are performed no more than three times a week, without additional overloading on training days in order to prevent the possible onset of muscle fatigue. Training at high-angular velocity is a pivotal point in the success of the rehabilitation program.[15,16] During physiotherapy for muscle injury, electrostimulation of the injured body part does not appear advisable, and there is no published evidence for its usefulness.

Unrestricted training is initiated when muscular strength values are ≥80% those of the unaffected part and in the absence of muscle fatigue after prolonged running. Return to competitive activity is contemplated when the athlete has recovered adequate strength, resistance, muscular flexibility, and neuromuscular control. Recurrence of injury within the first 2 months after return to sports is a clear indication of inadequacies in the rehabilitation program.

## GROWTH FACTOR THERAPY

The use of autologous platelet-rich plasma (PRP) may be indicated in appropriate cases in combination with an exercise rehabilitation program specific for the anatomic structure involved and the type of injury. Treatment with PRP should never be administered to hasten an athlete's return to the field; instead, its sole and proper use is to promote the healing of injured tissues within the timeframe that the healing process will require.[17,18]

Indirect Grade III muscle injuries are among the most clinically serious muscle injuries in athletes and constitute the best indication for growth factor therapy. Prerequisites to promoting better tissue repair are aspiration of the hematoma and echo-guided infiltration of autologous PRP; autologous PRP is recommended, therefore, during the early postinjury period (within the first 7 days).[19,20]

Several in-vitro studies have shown that PRP contains numerous growth factors that mediate soft tissue healing, some of which are able to accelerate muscle regeneration and enhance muscular strength following injury.[19] The effectiveness of PRP derives from the presence of numerous growth factors, which, together with macrophages and cyclooxygenase-2 (COX-2) pathway products, can regulate the inflammatory phase of muscle healing. Transforming growth factor-beta-1 (TGF-beta-1) and prostaglandin $E_2$ ($PGE_2$) can also act in synergy to balance fibrosis and regeneration during muscle healing.[19-21]

A study of elite athletes has shown that percutaneous injection of PRP into the muscle injury site was able to accelerate functional recovery and return to sports activity.[20] However, no randomized controlled trials supporting the use of PRP in muscle injuries have been published to date.

The PRP preparation is injected under sterile conditions and the skin area is disinfected with betadyne. A small volume of local anesthetic (lidocaine 20 mg/mL) is administered; if present, the hematoma is aspirated under echo guidance and the PRP preparation is injected in a single solution. The needle is then removed, the skin disinfected, and a compression bandage applied. The patient is instructed to remain in a sitting or semisitting position on the examination table for 20-30 minutes and not to move the treated limb.

While not necessarily indispensable in the management of muscle injuries, PRP injection therapy offers a viable option in conservative rehabilitation. In Italy, such procedures must be authorized by a blood transfusion center (Decree Law 19/08/2005/No. 191) before they can be performed. Pending clarification by the World Anti-Doping Agency (WADA) and the International Olympic Committee (IOC), the use of growth factor therapy in elite sports is presently considered a doping violation under the WADA code, but it is possible to apply to a WADA-approved antidoping organization for a therapeutic use exception (TUE) to utilize these technologies for specific clinical indications in elite athletes.[22,23] Such action is recommended to avert the risk of conflict with the WADA code, and to preclude elite athletes from using a treatment restricted to nonelite sports people.

## TOPICAL ANTI-INFLAMMATORY THERAPY: FOCUS ON KETOPROFEN PLASTER

Inflammation is a common element in sport-induced injuries. Several molecules, including prostaglandins, play a role in the inflammation process and are also associated with the onset of pain.[24] Therefore, the blockade of the prostaglandin pathway by the administration of

NSAIDs is an important option in the treatment of soft-tissue inflammation, as suggested by current guidelines.[25] However, the systemic administration of NSAIDs can be associated with an unfavorable tolerability profile; therefore, other administration strategies are advocated.

## Tolerability Profile of Systemically Administered NSAIDs

Systemic NSAIDs are associated with adverse effects in the liver, gastrointestinal (GI) tract, kidney, hemostatic system, cardiovascular (CV) system, and skin. Adverse events in the GI tract, kidney, hemostatic system, and CV system are mainly dependent upon the NSAID-induced blockade of prostaglandin synthesis. In particular, GI-related adverse effects are the most important in terms of incidence and severity: about 30% of patients develop gastric ulcers following chronic systemic administration of NSAIDs and 1%-2% present with gastric complications (ie, bleeding and perforations).[26] NSAIDs also affect the small bowel; the so-called NSAID-induced enteropathy is more frequent than gastric mucosal damage and can result in severe sequelae such as anemia, hypoalbuminemia, and intestinal strictures.[27] In contrast to NSAID gastropathy, intestinal injury is not a pH-dependent phenomenon. The current approach to preventing damage to gastric mucosa, ie, coadministration of a proton-pump inhibitor, is therefore ineffective at the intestinal level.[28]

In recent years, several strategies to reduce the incidence of GI effects following systemic administration of NSAIDs have been developed, but they have all been disappointing. Moreover, despite evidence showing that COX-2 inhibitors have a better GI side-effect profile than NSAIDs, they are also associated with the onset of CV and renal events.[29,30] A careful evaluation of the risk-benefit ratio is therefore required when considering systemic administration of NSAIDs.[29]

## Topical Administration of NSAIDs: a Possible Answer?

When possible, as in the treatment of single sport lesions, the topical administration of NSAIDs could be a useful therapeutic option. In fact, topical administration provides several advantages over systemic administration. Topical administration is associated with effective localization at the inflammation site, a faster onset of pharmacodynamic action, and low systemic absorption, leading to a better tolerability profile.[31]

Topical administration of NSAIDs is an effective strategy for the treatment of both acute and chronic musculoskeletal pain.[32,33] In particular, the results of a meta-analysis of 26 double-blind, placebo-controlled studies showed that topical NSAID administration was significantly better than placebo in pain relief at 7 days (pooled relative benefit 1.6; 95% confidence intervals [CI] 1.4, 1.7; number needed to treat [NNT] 3.8; 95% CI 3.4, 4.4).[32] The indirect comparisons of individual topical NSAIDs showed that ketoprofen presented the more evident effect (Table 1).[32] Similar results were obtained in a meta-analysis of 14 double-blind, placebo-controlled trials evaluating the effect of NSAIDs on chronic pain (NNT 4.6; 95% CI 3.8, 5.9).[33] Moreover, topical administration of NSAIDs is not associated with an increased incidence of upper GI bleeds and perforations, nor in hospitalizations for acute renal failure.[34,35]

## The Role of Ketoprofen Plaster Among Topically Administered NSAIDs

Ketoprofen, diclofenac, flurbiprofen, ibuprofen, indomethacin, and salicylic acid derivatives are among the most prescribed topically applied

**Table 1.** Relative risk (fixed) and number needed to treat (NNT) from a meta-analysis of various topically applied nonsteroidal anti-inflammatory drugs (NSAIDs) compared with placebo for the treatment of acute musculoskeletal pain conditions.[32]

| | Relative risk (95% CI) | NNT (95% CI) |
|---|---|---|
| Ketoprofen | 2.01 (1.71, 2.37) | 2.6 (2.2, 3.3) |
| Ibuprofen | 1.69 (1.35, 2.12) | 4.1 (2.9, 6.9) |
| Piroxicam | 1.54 (1.29, 1.84) | 4.7 (3.4, 7.7) |
| Indomethacin | 1.30 (0.98, 1.72) | 10.0 (5.2, ∞) |

CI=confidence interval.

NSAIDs, and they are administered in different formulations, including gels, foams, creams, patches, and plasters.

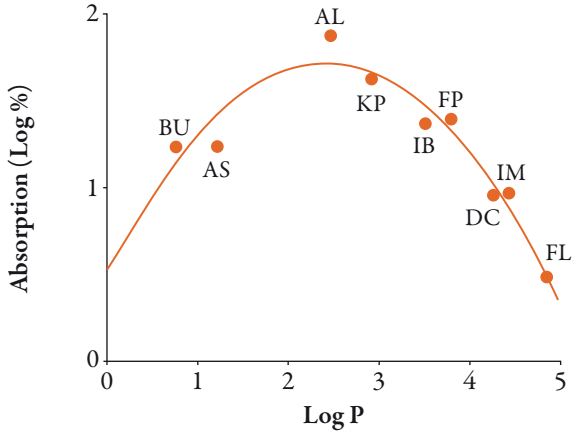
Of note, salicylic acid derivatives are usually administered in combination with other compounds, such as nicotinic acid or capsaicin (rubefacients).[36] The results of a meta-analysis of six trials comparing topically applied salicylate rubefacients with placebo, showed an overall modest beneficial effect of these molecules in the treatment of musculoskeletal pain; however, this beneficial effect was not evident when only good quality studies were considered.[36]

Several factors contribute to the efficacy of NSAIDs after topical administration.[37,38] First, the active drug must penetrate the skin and be absorbed into the tissue at concentrations sufficient to inhibit prostaglandin synthesis and, therefore, effect pain relief. To this end, a lower molecular weight is associated with higher transdermal absorption.[38] Ketoprofen has a molecular weight (260 Da) lower than that of the majority of topically applied NSAIDs (eg, 350 Da for indomethacin and 325 Da for diclofenac), thus providing some advantages in terms of skin penetration.

Furthermore, the lipophilicity of these compounds (usually measured as logP, the partition coefficient of a compound between an organic solvent and water) also plays a central role.[39] It has been shown that a logP measurement in the range of two to three results in higher skin penetration than lower or higher values; results of an in vivo study showed that ketoprofen has a logP of 2.94, thus being in the optimal range.[39]

Another important aspect of skin penetration is the delivery system. Some older NSAID plasters utilize a gum matrix system that can have delivery issues related to the insolubility of the drug in the patch base, as well as suboptimal adhesion.[40] Ketoprofen is administered by a nonaqueous matrix plaster, composed of three polymer strata, a styrene-isoprene-styrene (SIS) system.[41] Imaging of this plaster by atomic force microscopy and emission scanning electron microscopy reveals a highly organized environment, which allows uniform release of the drug and a constant skin penetration. All of these factors contribute towards the enhanced penetration of topically applied ketoprofen compared with other NSAIDs (Figure 1).[39]

**Figure 1.** Relationship between cutaneous absorption 0-4 h (expressed as Log %) and liposolubility (expressed as Log P) of different anti-inflammatory drugs.[39] AL=alclofenac; AS=aspirin; BU=bufexamac; DC=diclofenac; FL=flufenamic acid; FP=flurbiprofen; IB=ibuprofen; IM=indomethacin; KP=ketoprofen. Reprinted from Life Sciences, "Skin permeability of various non-steroidal anti-inflammatory drugs in man", pp 1043-1050. Copyright © 1986, with permission from Elsevier.



These characteristics may also help to minimize the incidence of systemic adverse events; a study analyzing ketoprofen concentration in plasma, synovial fluid, and intra-articular tissues after administration via different routes showed that topical application of ketoprofen resulted in elevated intra-articular tissue concentrations (Figure 2) while plasma concentrations remained remarkably low.[31,42]

**Figure 2.** Comparative pharmacokinetics of oral and transdermal ketoprofen in patients requiring arthroscopy.[42] $C_{max}$=maximum plasma concentration.

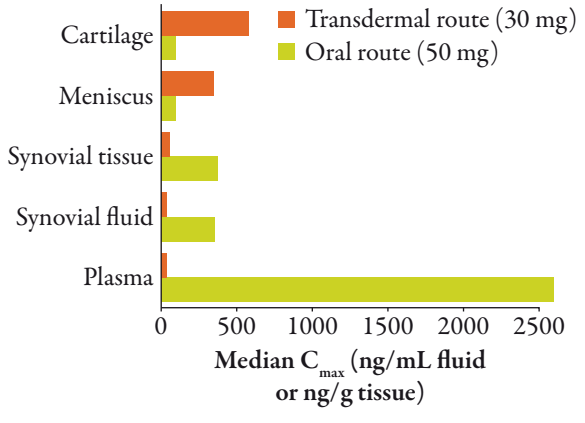
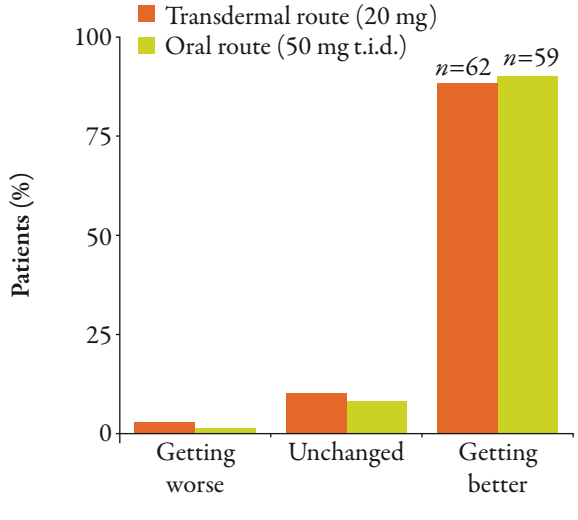



**Figure 3.** Comparative efficacy of oral and transdermal ketoprofen in patients with lower back pain.[43] Efficacy evaluation was based on pain at rest, pain on movement, and muscle tenderness.




The clinical efficacy of ketoprofen in plaster has been tested in patients with different clinical conditions. In a study of patients with back pain there was no difference between oral and transdermal ketoprofen in terms of symptom improvement (Figure 3).[43] These findings were consistent with another study evaluating symptom improvement in patients with various soft-tissue injuries, such as periarthritis, tenosinovitis, peritendinitis, and epicondilitis.[44]

Transdermal administration of ketoprofen has also been compared with diclofenac gel in a randomized study of patients with painful, sport soft-tissue injury (sprains, strains, and contusions treated within 48 hours of occurrence).[45] Overall, a once-daily ketoprofen patch was at least as effective as diclofenac gel three times daily in the reduction of pain after 14 days, as measured with a visual analog scale (–1.17 mm in favor of ketoprofen patch; 95% CI –5.86, 3.52) and was associated with a 79% reduction in pain intensity. Moreover, ketoprofen was associated with a significantly higher cure rate than diclofenac gel at day 7 (64% vs. 46%; $P$=0.004) and with a better patient-assessed tolerability, acceptance, and comfort.[45] Further randomized controlled trials examining the impact of treatment with ketoprofen patch on acute muscle injury outcomes would be valuable.

As expected from the low plasma concentration, the tolerability profile of ketoprofen plaster is excellent, with a frequency of adverse events, including GI toxicity, comparable with that of placebo.[31] Therefore, topical administration of NSAIDs may represent a promising therapeutic strategy for the management of pain and inflammation in sports medicine as it provides local analgesic and anti-inflammatory effects, while minimizing the incidence of systemic adverse events.

## SURGICAL TREATMENT OF MUSCLE LESIONS

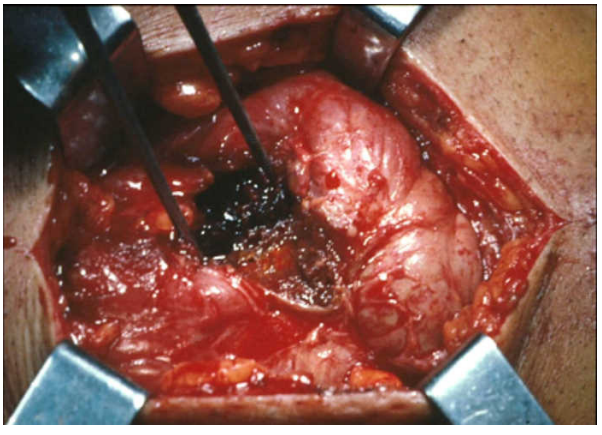
Ultrasound and MRI examinations play a fundamental role in the diagnosis of muscular lesions.[46-48] The main advantage of ultrasound is that it is a simple and repeatable procedure, allowing ongoing monitoring of the lesion, as well as permitting dynamic examination whereby the patient is asked to contract the muscle, thus enhancing the tear gap.

Surgical treatment of muscle lesions is uncommon, as it is well known that such lesions can often heal quickly with conservative treatment[49] and there is an ever-present risk of infection. Indications to surgery are limited and reserved to large hematomas in athletes, Grade III lesions in muscles with no or few agonist muscles, and Grade II tears bigger than 50% of the muscle belly.[50]

Several important considerations concerning surgical treatment should be made: ie, hematoma and necrotic tissue must be carefully removed (Figure 4); suturing should be performed through the overlying fascia to ensure better strength than a muscle-to-muscle suture, which offers poor anchoring; surgical treatment of lesions of the myotendinous junction offers better results; postoperative treatment requires bracing or elastic bandage; a return to sport-specific training is possible only when the injured muscle has stretching properties equal or similar to the healthy contralateral muscle, and the athlete can perform basic movements without pain.

The decision to surgically manage Grade III lesions is supported by the evidence that immobilization alone is inadequate to prevent an abundant production of scar tissue.[8] As a matter of fact, a clear improvement in the restoration of strength has been demonstrated in mice treated with surgery compared with immobilization.[51] Furthermore, it has been shown that early surgical repair of Grade III lesions can result in improvements in symptoms and functional outcome.[52]

**Figure 4.** Intraoperative finding of a quadriceps Grade III lesion with hematoma and cloth, which is being removed.



The hamstring muscles are the most commonly injured muscles in the body, accounting for 25%-30% of all muscle strains,[53,54] particularly among athletes.[55] Recent studies have demonstrated that early surgical treatment of complete proximal hamstring ruptures, particularly at the myotendinous junction, can result in a high rate of return to full activity.[49,52,56] Among surgical options, the reinsertion of the proximal hamstring, with suture anchors to the ischial tuberosity has been described.[52,57]

Like primary lesions, complications of muscle injuries (such as hematomas, pseudocysts, calcifications, rerupture) are often amenable to surgical treatment. Hematomas occur in high-grade tears, when bleeding is localized either in a space between muscle bellies, between bone and muscle, or between fascia and muscle. Hematomas can undergo a calcific metaplasia (myositis ossificans) where lesions occur between the deep surface of a muscle and bone.

**Figure 5.** Intraoperative aspect of a pseudocyst of the quadriceps muscle. The wall of the cyst and the cavity within the muscle belly are clearly visible.

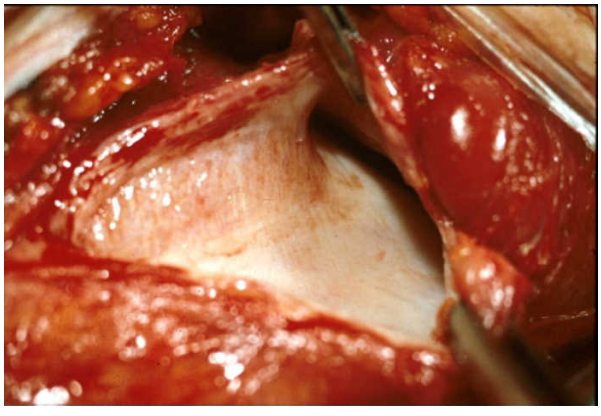
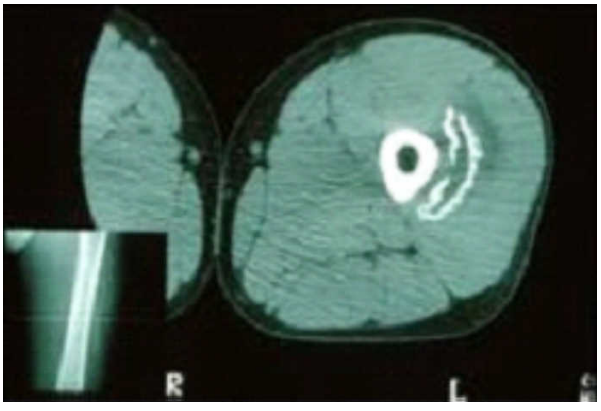


**Figure 6.** Computed tomography scan of a large myositis ossificans of the anterolateral aspect of the thigh in a young female basketball player, 3 months after a severe contusion.

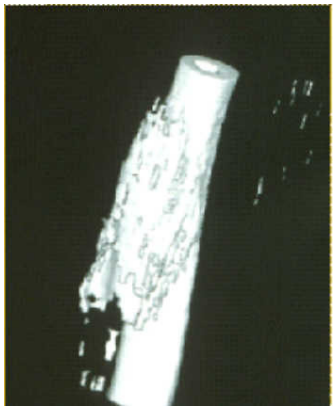



Pseudocysts (Figure 5) sometimes occur when the muscle retears at the same level, interfering with tissue healing. These lesions can be diagnosed with MRI and must be treated by precise removal of the cyst wall to allow adequate approximation of muscle fibers.

The early treatment of a large hematoma, generally within 7-10 days of trauma, can be achieved with ultrasound-guided needle aspiration. Whether the hematoma is organized or particularly bulky, surgical drainage using a high-flow suction probe or a 5 mm trocar introduced through a small cutaneous incision is required. Postoperative compressive bandage and ultrasound monitoring are needed to prevent relapse.

A posttraumatic calcific metaplasia (myositis ossificans) subsequent to deposition of calcium salts can follow either contusive traumas or hematomas, causing diffuse pain, reduction of muscular elasticity and, consequently, increased risk of rerupture.[52] Calcifications become symptomatic a few weeks after trauma and can be initially diagnosed using ultrasound or x-ray, and accurately investigated with modern technologies

**Figure 7.** Three-dimensional computed tomography reconstruction of a large myositis ossificans of the anterolateral aspect of the thigh in a young female basketball player, 3 months after a severe contusion (see also **Figure 6**).



such as computed tomography or 3D computed tomography (Figures 6 and 7). Early treatment of calcific metaplasia with extracorporeal shock-wave therapy can bring good to excellent results if performed early.[58] If the calcification is particularly bulky or causes mechanical impingement into a joint (ie, calcifications of rectus femoris in the hip joint) surgery may be required; however, the risk of recurrence is moderately high.

## CONCLUSION

Depending on the severity and location, there are several therapeutic approaches to the management of sport-induced muscle injuries. In appropriate cases, PRP injection treatment offers a viable option in conservative rehabilitation; however, its use is currently considered a doping violation under the WADA code, restricting its use to nonelite sports people only.

While NSAIDs remain one of the most effective treatments to manage pain and inflammation, systemic administration is associated with a wide variety of adverse events. However, topical administration of NSAIDs may represent a promising therapeutic strategy, as it allows a local analgesic and anti-inflammatory effect, while minimizing the incidence of systemic adverse events. The choice of delivery system is crucial to assuring clinical effectiveness, and administration of ketoprofen via a new generation plaster composed of three different polymers results in marked tissue penetration and a clinical efficacy comparable with oral administration. Ketoprofen may have certain advantages over other NSAIDs because of biologic characteristics and greater tissue penetration. On this basis, ketoprofen plaster could be considered an interesting option in the treatment of single sport lesions. Surgical treatment of muscle lesions is less common than conservative and topical therapies and indications are limited to more serious injuries.

Despite a lack of clinical studies of the treatment of muscle injuries, presentations from SIOT 2008 show that advances in our understanding of the healing process and in conservative, pharmacologic, and surgical treatment approaches to the management of sports-induced muscle strains are contributing to better clinical outcomes, faster healing, and a swifter return to normal training and activity levels.

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### Authors' Contributions

CS and ADC were involved with the original concept and planning of this congress report. ADC, PV, and CS with their coworkers managed the project and wrote the first draft of the manuscript. CS prepared the first and subsequent versions of the paper with the assistance of Wolters Kluwer Health Medical Communications. All the authors read and approved the final manuscript; CS is the guarantor for the manuscript.

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