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# Muscle injury in orthopaedic trauma

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**Abstract** Muscle injury in the setting of orthopaedic trauma is common. Skeletal muscle injury can cause immune dysregulation and impair fracture healing both in patients and in various preclinical models. Muscle injury can also be associated with impaired vascularity and eliminate the muscle paracrine effect, both of which can impair fracture healing. Severe muscle injury can lead to volumetric muscle loss. While there are currently no effective treatments for volumetric muscle loss, minced muscle autograft has been shown to improve fracture healing, but not improve muscle function. Acute compartment syndrome can severely impact functional recovery and limit fracture healing. However, current animal models of compartment syndrome lack appropriate translation to the clinical injury.

**Keywords:** volumetric muscle loss, fracture healing, paracrine, compartment syndrome, muscular injury, soft tissue

## 1. Introduction

Muscle injury in the setting of orthopaedic trauma is common. The muscle injury severity can vary between muscle contusion to acute extremity compartment syndrome and volumetric muscle loss. Muscle injury can have a profound impact on complication rates, fracture healing, and patient recovery. Despite its common occurrence in orthopaedic trauma, the impact of muscle injury on overall patient recovery remains underevaluated in most clinical studies that evaluate functional outcome. The purpose of this review was to investigate the effect of muscle injury on fracture healing, assess the paracrine effect of muscle on bone and impact of volumetric muscle loss on fracture healing, evaluate methods to address volumetric muscle loss, and review current animal models for acute extremity compartment syndrome.

## 2. Skeletal Muscle Injury Impact of Bone Healing

Skeletal muscle and bone are not just neighbors; they communicate with each other and can affect each other's status.[1] Although much of this work has focused on metabolism or disease, the impact of severe skeletal muscle injury on fracture healing has been long appreciated. The hallmark study by Gustilo and Anderson that characterized and classified open fractures nearly 50 years ago recognized how increasing amounts of injury on the soft tissue envelope is associated with poor outcomes.[2] In fact, the open fracture classification of Type IIIB has the worse outcomes of all and requires soft tissue coverage generally in the form of a muscle flap. The sentiment was often that the skeletal muscle flap provided required cells or blood flow to the fracture and is responsible for the improved healing. However, this assumption may not be correct.

Preclinical research suggests only nonrecoverable skeletal muscle injuries, not injuries with only impaired muscle blood flow, are the ones that prevent bone healing.[3] A severe muscle crush injury that resulted in reduced blood flow to the injured muscle that is adjacent to the fracture did not impair healing, but a resected muscle did prevent healing. Failed healing was also observed when there was a frank loss of skeletal muscle in a rodent critical sized defect model where a very effective controlled release of recombinant human bone morphogenic protein (BMP)-2 was used.[4]

A series of studies examined the dysregulated immune response along with several potential therapies. A Lewis rat open fracture model consisting of a tibia osteotomy with adjoining tibialis anterior muscle volumetric muscle loss demonstrated impaired tibia healing compared with osteotomy control.[5] The resected muscle caused both innate and adaptive immune responses that differed from the canonical muscle injury healing. Additionally, the nonhealing muscle injury resulted in a perturbation of the inflammatory phase of fracture healing, as indicated by elevations of $CD3^+$ lymphocytes and $CD68^+$ macrophages in the fracture callus at 3 and 14 days postinjury, respectively.

Although volumetric muscle loss (VML) injuries do not have any current clinical treatments, there are several approaches that demonstrated improved function. A small intestine submucosa extracellular matrix used to treat the muscle injury did not improve tibia healing and even trended toward worse overall outcomes, presumably because of the robust immune response.[6] Next, an autologous muscle repair was used, which consists of

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mincing the excised muscle in small pieces and returning to the defect. This technique resulted in an improvement in strength along with healing and de novo skeletal muscle healing.[7] This approach restored healing in the bone injury and resulted in a more normal immune response. However, the improvement in muscle healing adjacent to the osteotomy likely caused an increase in both circulation and available progenitor cells. A powerful immune suppressor (FK506, tacrolimus) that is used to prevent allograft organ rejection and treat T-cell–mediated diseases was given every day for a month to determine if it was the dysregulated immune response caused the poor healing. This approach not only restored a normal local immune response in the muscle and osteotomy site, it also rescued the fracture healing.[8]

Taken together, severe skeletal muscle injury that does not heal causes immune dysregulation and impairs fracture healing both in patients and in various preclinical models. Eliminating the dysregulated immune response either by autologous muscle graft or through immune suppression restores bone healing. This suggests that skeletal muscle flaps that cover the defect may be effective because of the immune modulating properties and not by improved circulation. This suggestion may direct new targets for immune modulation and therapies to prevent nonunions.

## 3. Implementation of Volumetric Muscles Loss in a Porcine Model of Segmental Bone Defect

Civilians and Service members who sustain severe extremity trauma can develop long-term pain and weakness. Traditionally composite tissue injury (CTI) research has focused on promoting bone healing to primarily prevent amputation. However, even in instances of successful bone healing, chronic diminished limb function due to muscle weakness can contribute to military medical discharge, low quality of life, and delayed or elected limb amputation.[9] While most research has been bone-centric, studies are beginning to prioritize muscle healing to optimize patient outcomes. In the setting of extremity trauma, muscle injury is largely untreated aside from routine physical therapy. This practice has led to an unjustified acceptance of muscle tissue injury comorbidity as a part of the natural sequelae of CTI, even after rehabilitation is completed.[10] Weakness can persist more than 12 months after a tibia fracture, and patients with treated tibial segmental bone defects (SBDs) report prolonged limb dysfunction and mobility limitations.[11–13] Functional muscle recovery is important for return to duty in military settings and return to vocational and recreational activities in the civilian sector.

Over the past several years, a porcine model of a SBD has been developed. The work demonstrated that dual plating of a 25 mm SBD in the porcine tibia results in progressive bone healing over 4 months, but not all specimens have fully united by that time (Fig. 1A). This occurs in the absence of any intervention on the defect to improve bone healing.[14] The addition of BMP-2 to SBDs in the porcine tibia has been investigated, demonstrating its ability to rapidly improve bone healing. BMP-2 accelerated bone healing in all testing, including in larger 40 mm SBDs. The radiographic bone healing in this large defect experiment was corroborated by biomechanical testing at 3 months.[15]

Understanding mechanisms responsible for biochemical communication between bone and muscle is essential as a means to identify potential new therapies for CTIs.[17] Preclinical reports have highlighted the impact of VML on bone healing, and surrounding musculature contributes osteogenic factors to fractured bone.[18] To combine SBD and VML, a porcine CTI model that includes a 25 mm SBD filled with a saline impregnated collagen sponge and an adjacent, partial thickness, 7 g VML injury was developed.[16] Furthermore, the VML injury was treated with minced muscle autograft (MMG).[19] A 25 mm SBD was selected because, while this defect reliable progresses in bone healing without any additional intervention (eg, BMP-2), it does not heal 100% of the time by 3 months postinjury. Thus, it is a model where perturbations might alter the bone healing trajectory. While MMG improved SBD healing, interestingly and unexpectedly, an isolated SBD had a profound effect on adjacent uninjured muscle function and composition. Pigs with an isolated SBD injury exhibited significant strength deficits on longitudinal in vivo muscle testing, a gold standard test of muscle function (Fig. 1B). Notably, the SBD, CTI (SBD combined with VML), and CTI + MMG (the CTI injury with the muscle defect filled with MMG) groups exhibited similar longitudinal strength testing deficits, suggesting that the SBD might be the foundational pathogenic source of collateral muscle injury.[16]

In an attempt to identify the biological underpinnings of these unexpected observations, skeletal muscle tissue biopsies adjacent to the SBD were analyzed via protein content and histological measurements and compared with muscle samples taken from the contralateral limbs.[16] Myosin heavy chain (MHC) isoforms adult MHC 1 skeletal muscle (MYH1), adult MHC 2 skeletal muscle (MYH2), and embryonic MHC 3 skeletal muscle (MYH3), all markers of myogenesis, were reduced in the isolated SBD group compared with the contralateral specimens. Additionally, transforming growth factor levels were decreased and hydroxyproline levels increased, suggestive of muscle fibrosis. Adjacent muscle from isolated SBDs also showed elements of fibrotic change histologically, as demonstrated by collagen fraction staining. These observations indicate skeletal muscle dysregulation within the SBD group resulted from the defect, as the creation/presence of the defect was the primary variable differentiating these samples from those taken from the contralateral limb. Most notably, compositional changes in skeletal muscle were essentially identical in SBD, CTI, and CTI + MMG specimens.[16] Future directions will investigate the effects of treating the SBD on adjacent muscle function and the role of muscle void fillers on attenuating muscle dysfunction due to VML.

## 4. The Muscle Paracrine Effect for Fracture Healing

Fractures with volumetric muscle loss (ie, composite injuries) are associated with a myriad of complications resulting in poor patient outcomes (Fig. 2). Complications include high rates of delayed healing, nonunion, rehospitalization, infection, and unexpected revision surgery.[2,20] The treatment gold standard for these injuries remains fixation of the fracture and autologous muscle flap. However, autologous muscle flap is associated with donor site morbidity and the functional recovery of the injured limb is limited. Logistical barriers exist at many institutions as well that prevent timely definitive soft tissue coverage at time of fixation without delay.[21] Finally, if the defect is too large or the flap fails, often limb salvage is not feasible. What is needed is a readily available engineered biomaterial, acellular or cellular, that can act as a temporary or permanent cover to initiate fracture healing and muscle repair while decreasing risk of infection.

### *4.1. Why Decreased Healing?*

There are 3 major issues posed by fractures with volumetric muscle loss that lead to nonunion of the fracture:

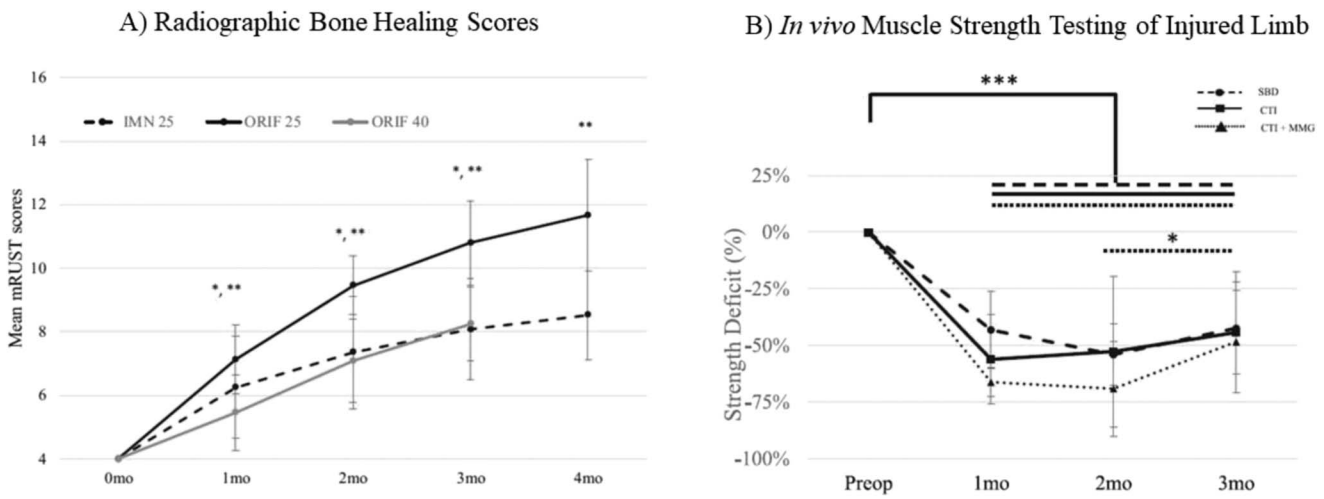


**Figure 1.** (A) Bone healing. mRUST values demonstrate differences between the 3 groups. *Significantly greater ($P < 0.05$) than open reduction with internal fixation (ORIF) 40 mm group at a monthly interval; **significantly greater ($P < 0.05$) than intramedullary nail (IMN) 25 mm group at a monthly interval. ORIF 25 mm Yucatan minipigs (YMPs) have a markedly improved healing trajectory compared with the other 2 groups (n = 8 for IMN 25; n = 4 for ORIF 25 and ORIF 40). (B) Muscle testing. Strength deficits occurred at all 3 monthly intervals in all groups compared with preoperative values (*** denotes $P < 0.001$) comparing the monthly strength value from baseline preoperative strength values for that group at all 3-month intervals (corresponding to the line type). There were no differences in strength deficits at any time point between segmental bone defect (SBD), composite tissue injury (CTI), and CTI + MMG animals. CTI + MMG animals demonstrated improvements in strength (*denotes $P = 0.043$) between months 2 and 3. MMG, minced muscle autograft. Reprinted under Creative Commons CC BY license.[16]

1. Loss of vascularity—muscle acts as a significant contributor to underlying bone blood supply, especially due to its intimate relationship with the periosteum. In a classic canine study, when the muscle was stripped from a tibial osteotomy, the fracture consistently went onto nonunion.[22] Decreased blood supply was noted although when restored with a skin graft versus muscle graft, and muscle graft lead to improved healing.
2. Loss of myokines and progenitor cells—muscle secretes a variety of growth factors and cytokines (termed myokines) that have direct affects on bone homeostasis and regeneration.[23] Furthermore, skeletal muscle mesenchymal progenitor cells directly contribute to bone repair.[24]
3. Immune system dysregulation—this combined injury to muscle and bone elicits a different, more dysregulated immune response compared with an isolated fracture. This difference in specifically T-cell presence, phenotype, and activity has been shown to lead to decreased fracture healing.[5]

### 4.2. Clinical Implications

Recent research has demonstrated some intriguing and promising therapeutic avenues to address these principal issues:

1. Muscle flaps outperform and improve healing compared to other flap options, including fasciocutaneous.[25]
2. A single growth factor or cytokine, including BMP-2, cannot rescue fracture healing in these composite injuries.[4]
3. Some initial research has demonstrated that by inhibiting the dysregulated T-cell response with FK506 (tacrolimus) in composite injuries, fracture healing can be enhanced.[8]
4. Research has shown that delivery of myokines in a simple alginate gel from mesenchymal stem/stromal cell (MSC) stimulated myoblast media lead to bony healing in a critical size femur defect, whether delivered with or without MSCs.[26] Codelivery of the conditioned myoblast media with the MSCs resulted in the most bone regeneration.
5. Large porcine model data demonstrated that delivery of minced autologous muscle autograft led to improved fracture healing but not improved muscle function.[16] This demonstrates the power of the muscle secretome to improve the bony process but the mechanical disruption of the muscle limits functional recovery.
6. Muscle scaffolds capable of being bio-printed with viable cells and growth factors show promise for mechanical reorientation of myofibers leading to improve muscle repair and function.[27]

### 4.3. Future Directions

These composite injuries represent a unique challenge in orthopaedic trauma care as 2 intimate, but distinct, systems are involved. However, by shifting the focus onto muscle repair and treatment, fracture healing can be enhanced. A biomaterial tissue engineering approach focused on the immune response, muscle secretome, and complex cellular and molecular pathways demonstrated early promise for the adaptation and translation to clinical treatment.

### 4.4. Key Learning Points

1. Fractures with volumetric loss do not heal well, and current treatment of muscle flap is still the gold standard but has associated morbidity.
2. Poor bony healing is related to loss of vascularity, dysregulated immune response, and loss of muscle paracrine effect.
3. Promising translational treatments include immune modulators, tunable growth factor delivery molecules, decellularized scaffolds, and cellular biomaterials.

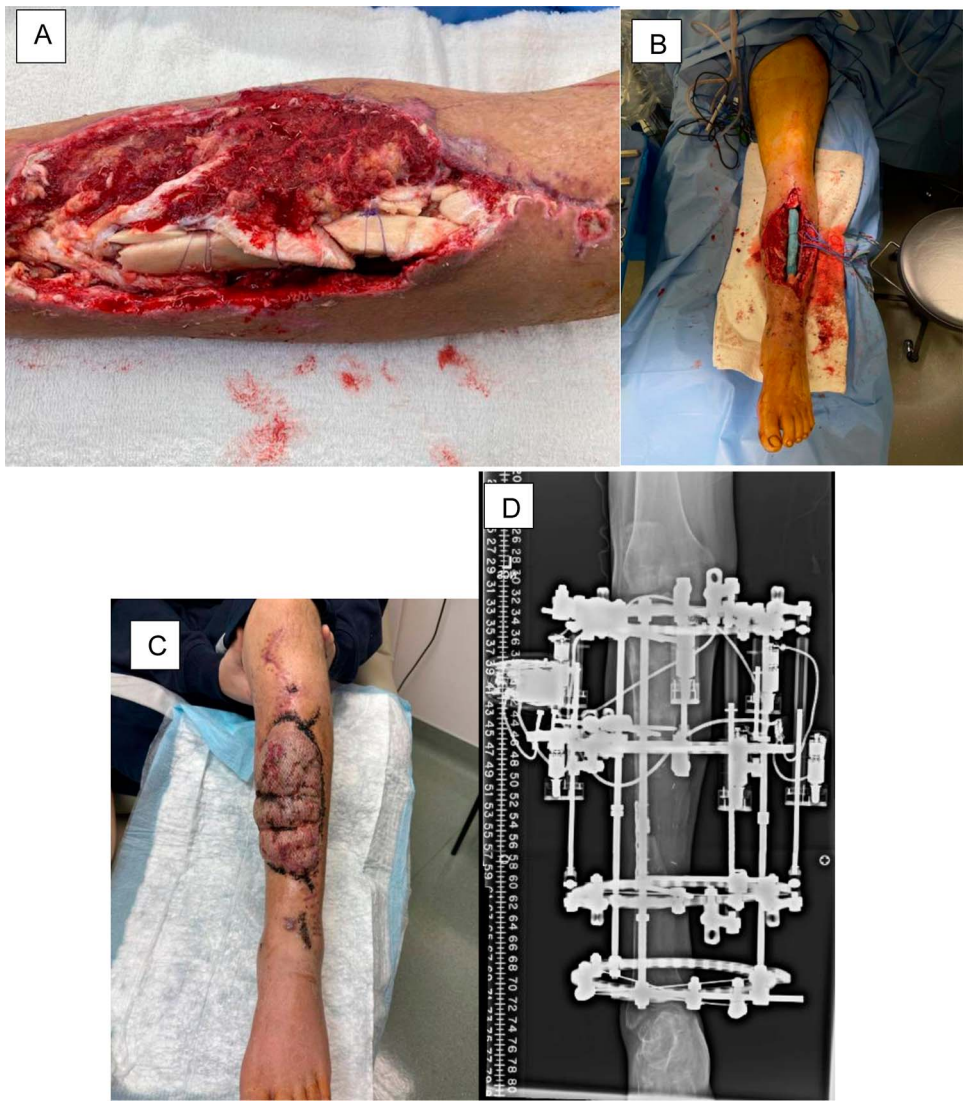


**Figure 2.** Example of a tibial shaft fracture with volumetric muscle loss (ie, composite tissue injury). Clinical photograph of injury as transferred from outside facility (A). This was treated with first stage debridement and cement spacer (B) and multiple debridements followed by rectus muscle free flap (C) and bone transport using circular frame (D).

## 5. Animal Models in Compartment Syndrome Research: Trends and Future Directions

The basic understanding of acute extremity compartment syndrome has not meaningfully changed since Matsen proposed a unified theory of compartmental syndromes in 1975—which focuses solely on intracompartmental pressure elevation as the cause of compartment syndrome.[28] However, despite heavy clinical research focus, pressure monitoring has not been reproducibly shown to improve treatment of compartment syndrome.[29–32] While pressure monitoring is a sensitive diagnostic tool, many patients with intracompartmental pressures supporting a diagnosis of compartment syndrome do not have symptoms consistent with the condition.[30,32] Given the elusiveness of a reproducible pressure threshold for compartment syndrome diagnosis, it is likely that there are other patient-specific factors that influence the susceptibility of muscle tissue to pressure injury. However, the underlying pathophysiologic role of genetic factors, age, sex, and the degree of soft tissue injury in compartment syndrome development is poorly understood at the molecular level.

Unfortunately, any clinical research designed to improve our understanding of the pathophysiology of compartment syndrome is hampered by a lack of a gold-standard diagnosis for true compartment syndrome, as most clinical cohorts use undergoing fasciotomy as a surrogate diagnosis. This is problematic given strong incentives to avoid missed compartment syndrome, which likely results in overtreatment in clinical cohorts.[32,33] In contrast, animal models provide the controlled environment necessary to better understand compartment syndrome pathophysiology and continue to advance our clinical diagnostic and treatment protocols.

A recent review of animal models in compartment syndrome research generated several important takeaways.[34] First, pathophysiologic research in compartment syndrome is an area of low interest, with only 9 studies published since 1997. Second, there is low variability in published mechanisms for intracompartmental pressure elevation—34 of 41 (85%) published manuscripts using an animal model of compartment syndrome modelled compartment syndrome with intracompartmental infusion or ischemia-reperfusion injury. While these model types have low barriers-to-

entry and are easy to implement, neither model type is consistent with the clinical injuries commonly associated with compartment syndrome in orthopaedic populations. In fact, only 7 of 41 studies identified in the review included any type of bone or muscle injury in their model. Furthermore, the reported magnitude and duration of intracompartmental pressure elevation is widely variable across study designs, and there are no established standards for these values. Third, and most importantly, existing studies do not consistently define or confirm the presence compartment syndrome associated muscle injury in their model designs. While all studies documented the duration and magnitude of intracompartmental pressure elevation, only 27 of 41 studies documented any test to confirm muscle tissue injury. Within this group, definition for what constituted compartment syndrome associated muscle injury varied widely.

In an effort to move animal models away from intracompartment infusion or ligation models, there is pilot data of a porcine compartment syndrome model that incorporates a fracture with blast injury to generate elevated compartment pressures. Histopathologic evaluation of injured muscle in the pilot model demonstrates muscle inflammation and necrosis at 48 hours and fibrosis at 14 days. Similarly, RNA-sequencing data at 48 hours demonstrates mitochondrial dysfunction that could be seen in muscle damage from compartment syndrome. Further validation of this proposed model is ongoing.

## 6. Conclusion

Despite being common, muscle injury in the setting of orthopaedic trauma remains an under evaluated field. There are several recent studies evaluating the impact of muscle injury on fracture healing through immune dysregulation. Similarly, muscle trauma can impair the muscle secretome and disrupt growth factor signaling that is necessary for appropriate bone healing, especially in the setting of bone loss. Treatment for volumetric muscle loss remains elusive. While minced muscle autograft improves the defect, it does not lead to normal muscle tissue. Animal models of compartment syndrome are currently lacking adequate translation to the clinical injury. A true translational model of compartment syndrome is necessary to understand the pathogenesis of acute compartment syndrome to allow for better diagnostic tools and improvements in prevention/treatment.

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