Published in final edited form as:

Clin Rev Bone Miner Metab. 2018 December ; 16(4): 131–141. doi:10.1007/s12018-018-9254-z.

Tendon healing in the context of complex fractures

Elahe Ganji^{1,2} and Megan L. Killian^{1,*}

¹Department of Biomedical Engineering, University of Delaware, Newark, Delaware 19716

²Department of Mechanical Engineering, University of Delaware, Newark, Delaware 19716

Abstract

Tendons connect muscle to bone and play an integral role in bone and joint alignment and loading. Tendons act as pulleys that provide anchorage of muscle forces for joint motion and stability, as well as for fracture reduction and realignment. Patients that experience complex fractures also have concomitant soft tissue injuries, such as tendon damage or rupture. Tendon injuries that occur at the time of bone fracture have long-term ramifications on musculoskeletal health, yet these injuries are often disregarded in clinical treatment and diagnosis for patients with bone fractures as well as in basic science approaches for understanding bone repair processes. Delayed assessment of soft tissue injuries during evaluation of trauma can lead to chronic pain, dysfunction, and delayed bone healing even following successful fracture repair, highlighting the importance of identifying and treating damaged tendons early. Treatment strategies for bone repair, such as mechanical stabilization and biological therapeutics, can impact tendon healing and function. Because poor tendon healing following complex fracture can significantly impact the function of tendon during bone fracture healing, a need exists to understand the healing process of complex fractures more broadly, beyond the healing of bone. In this review, we explored the mechanical and biological interaction of bone and tendon in the context of complex fracture, as well as the relevance and potential ramifications of tendon damage following bone fracture, which has particular impact on patients that experience complex fractures, such as from combat, automobile accidents, and other trauma.

Introduction:

The occurrence of complex and compound bone fractures can lead to increased risk of long-term issues, such as non-unions and infection [1,2]. Successful healing of complex fractures depends on multiple factors, including the anatomical site of injury, the magnitude of complexity, and the involvement of damage to surrounding soft tissues, such as tendons. Yet tendon damage often goes overlooked during treatment and intervention of bone fractures, and long-term ramifications of tendon damage can prolong musculoskeletal dysfunction and disuse [3]. Tendons are essential for transmitting muscle loads to the skeleton and stabilizing

*corresponding author; killianm@udel.edu; (302)257-1913.

Conflict of Interest: The authors declare that they have no conflict of interest.

Ethics Approval: No ethics committee approval was required in undertaking this work.

Informed Consent: No informed consent was required in undertaking this work as work did not involve any human participants or animals.

joints, including during the healing process [4]. While the interplay of these two interfacing tissues during complex healing remains unclear, the healing processes that drive tendon and bone repair are overlapping, although basic studies primarily focus on outcomes associated with either bone fracture or tendon healing alone. In clinical cases of complex fractures that experience both bone and soft tissue damage, soft tissue and tendon healing are likely needed in order for bone healing to be successful. In this review, we explore the mechanical and biological interaction of bone and tendon in the context of complex fracture, as well as the relevance and potential ramifications of tendon damage following bone fracture, which has particular impact on patients that experience complex fractures, such as from combat, automobile accidents, and other trauma.

Of particular interest to concomitant soft tissue injuries and bone fracture are the musculoskeletal injuries experienced in the military[5], with open fractures constituting over 80% of military-service associated fractures [6]. The Joint Theater Trauma Registry reported that open fractures constituted 82% of combat-associated [7] fractures in Iraq from 2001 to 2005. Complications arise from injuries caused by cases of concurrent soft tissue injury and bone fracture due to high energy impacts, sports, and motor vehicle accidents [8]. Concurrent injuries involving tendon/soft tissue damage and bone fracture require repair of both structures, and additional stabilization by fixation of the fracture, adding to the surgical rigor of the repair process [8]. However, the primary musculoskeletal diagnosis following trauma is often that of bone fracture, with marginal attention paid to damaged tendons and ligaments, likely because triage protocols involve radiography (which precludes diagnosis of non-radiopaque soft tissue damage)[9]. This delay in diagnosis of tendon injuries may result in its delayed healing, exacerbating the effects of the injury. Yet intact soft tissues play a critical role in promoting a sufficient bone healing process primarily by providing stability and protection from infection [10–12], and severe concomitant soft tissue injuries can lead to impaired bone healing, non-unions, and pseudarthrosis [13,14].

Complex fractures, such as open fractures (in which bone breaks through skin; mangled limbs), undergo a multifaceted healing process, with biological and mechanical factors contributing significantly to the healing process (e.g., need for revascularization, delivery of biological factors, and mechanical stability) [15–19]. For example, vascular injuries result in delayed healing in nearly 50% of all tibial fractures [20]. Further complication and delay in fracture healing can be exacerbated by concomitant soft tissue injuries, such as tendon damage or rupture [19]. Yet diagnosis and treatment of soft tissue injuries at time of fracture may be missed clinically, as mentioned above, and poor soft tissue healing is a limiting factor for sufficient treatment and healing of musculoskeletal injuries [19,21–23]. For patients with complex fractures, the risk of deep infection increases with time following soft tissue debridement (approximately 22% increased risk if debridement is delayed for 48hr post-fracture), further exacerbating the risks associated with bone healing [24]. Concomitant soft tissue injuries can occur with both open and closed fractures. By the age of 50, the risk of experiencing any type of fracture is ~50% for women and 20% for men [25]. However, complex fractures that involve soft tissue damage are more common in younger populations (<40 years of age) following a traumatic or high-energy event [26]. For example, of all complex type III fractures, open fractures have with an incidence rate of 42%, and commonly occur with severe periosteal stripping, soft tissue damage, and vascular [27–29].

Diagnosis and treatment of soft tissue injuries is a limiting factor for sufficient treatment and healing of concomitant injuries [21,23]. This is, in part, because tendon is required for the mechanical stability of bone during healing, and also because of the role of tendon in connecting skeletal muscle to bone. Thus, identifying the contribution of tendon to both mechanical and biological cues that influence bone healing may help improve both bone and tendon healing following complex fractures.

Intact soft tissues play a role in promoting a sufficient bone healing process by providing tension and realignment during repair as well as protection from infection [2,14,30]. Depending on the anatomical site, the rate of complex long bone fractures can be high. For example, nearly 45% of long bone fractures per year in the United Kingdom are open tibial diaphyseal fractures [18]. Fractures of the distal tibia have a higher susceptibility to open and complicated fractures due to the limited soft tissue coverage and structural anatomy [31]. The mode of fracture is a determining factor in the fracture healing process, and high-energy trauma often leads to damage to soft tissues that can delay the bone healing process [19,32–34]. This has been shown through enhancement of complex open fracture healing in presence of soft-tissue coverage during early stages of healing [19]. In addition, anatomical location and the biomechanical properties of connective tissues may also be important determinants of the type of the injury. On the other hand, fragmental bone avulsion, rather than midsubstance or insertional tear, is common for tendons with strong attachments, such as for the peroneus brevis, a tendon that inserts at the base of fifth metatarsal [35]. Concomitant soft tissue injuries and associated fractures are often reported as tears with distal and proximal long-bone fractures, such as rupture of the medial collateral ligament with lateral condyle fracture, posterior cruciate ligament tears with tibial plateau avulsion fractures, and ipsilateral rupture of quadriceps tendon with distal tibia fracture [21,36,37]. Achilles tendon rupture commonly occurs with supination-adduction injuries of the ankle [38–43]. Similarly, case studies of concomitant fractures in the arm include flexor tendon rupture [23], avulsion ruptures of the triceps tendon [44], and scaphoid fracture with ligament rupture [45]. Because tendons and ligaments provide stability to long bones and joints, damage to these structures likely plays a significant role in the ability of bone to heal.

Yet published reports of complex fractures with soft tissue injuries are often limited to specific case studies, with few reports exploring the cause of and healing outcomes of tendon damage associated with concomitant, complex fractures. This is likely because the effect of soft tissue coverage and injury on the healing process is multifaceted [19,46]. The processes and requirements for both tendon and bone repair have appreciable and overlapping similarities in how fibrous, connective tissue and subcritical defects to be heal. For example, stability is required for reintegration and bridging of both broken bone and torn tendon. Tendon repair involves contributions from the surrounding paratenon [47,48], which resembles the process that the periosteum plays in fracture repair [49,50], including the formation of a “callus”-like morphology (Figure 1 H–I) [51]. In addition, the two tissues exhibit overlapping transcriptional and cellular signals that are essential for both tendon repair and bone fracture healing [4]. By appreciating the role that tendon plays in the healing outcomes following bone fracture, we will be able to develop more robust and improved strategies for bone healing and following trauma.

Mechanisms of Tendon Healing

Tendon injuries are also a common injury and lead to pain, disability, and limited joint function [52–54]. To understand the role that tendon plays in the healing outcomes following bone fracture, we must first understand how tendon functions and healing following injury. Tendons are critical for musculoskeletal function, with the primary purpose of attaching skeletal muscle to bone for postural stability and movement [55–59]. Because tendons are primarily under tensile loads, tears are difficult to repair and often require surgical intervention to reattach torn ends and regain function. The process of tendon healing following repair has been well characterized by tendon researchers for the past several decades and follows a similar pattern of wound healing to that of other injured tissues, including bone [60–63]. First, a clot forms around the injury site to stabilize the torn tendon, and the formation and size of this clot around the wound is limited depending on the vascularity of the respective tendon [64]. An acute inflammatory phase quickly follows, which typically consists a bolus influx of growth factors and inflammatory mediators and invasion of extrinsic cells [65–69]. The short-term inflammatory phase is followed by a proliferative stage in which fibroblast proliferation is stimulated by release of growth factors from extrinsic cells [70–72]. A reparative phase then follows, as the proliferating and extrinsic cells deposit collagen and granulation tissue to stabilize and revascularize the injury site [73]. Finally, the remodeling phase follows, in which the newly- deposited extracellular matrix becomes remodeled and organized and the cellularity and vascularity are reduced [73].

Intact Tendon Maintains Mechanical Stability of Healing Bone

Mechanical stability and the local mechanical environment are required for optimal repair of injured tissues for both tendon and bone [14,16,74–76]. While complete immobilization is not ideal for either tendon or bone repair [4,75,77–80], too much loading can lead to failed repair, gapping (in tendon) and non-unions (in bone) [81–84]. There exists a range of therapeutic loading that promotes tissue regeneration while allowing for sufficient healing processes [85,86]. For both tendon and bone, interventions to optimize healing often control the weight bearing experienced by the tissue/affected joint as well as the constraints on tissue fixation, in order to minimize overloading, limit stress-shielding of the repairing tissue(s), and encourage remodeling [17]. In the case of simple fracture, the stiffness of materials as well as the fixation method used to stabilize the healing bone are the primary factors that control micromotion and compression of the fracture site and thus control the quality of fracture repair [86–88]. In the context of complex fractures, soft tissue detachment and damage adds to the surgical complexity of repair, as well as reduces the stability of healing bone [87,89,90]. Although fractures do not need rigidly stable conditions for proper healing, bone healing outcomes depend on relative motion and load bearing conditions between fractured components [16,91]. Mechanical flexibility during the healing process can influence the size, stiffness, and composition of the formed callus, as well as duration of healing and risks of non-unions [4,92–95]. Thus, the magnitude of muscle loading and degree of stability are critical factors for healthy bone repair [96–98]. In case of concurrent injuries, both soft and hard tissues need to be stabilized, with additional stabilization of the fracture site, if necessary [8]. Yet, healing of ligament and tendon injuries – even if repaired

- may be delayed due to adjacent bone damage and remodeling. For example, femoral and tibial fractures with concomitant ligamentous tear account for over 20% of unstable knees (varus/valgus laxity) after surgery [100,101], and this instability likely results from insufficient reintegration of ligament to bone following repair. Muscle loading plays a critical role in the realignment of fractured bone and is required for natural reduction [30]. Mechanical stability and loading is also critical in the context of tendon and tendon-bone attachments healing following injury [75,102,103]. Post-operative immobilization and gradual increases in active range of motion during tendon healing are commonly accepted approaches for restoration of native tendon properties after injury [52,104]. The use of animal models allows for exploration of isolated or concomitant injuries to elucidate the effect of loading and involvement of neighboring tissues on healing outcomes following bone fracture. Recently, we have shown that reduced tendon loading (via genetic ablation of *Scx*, which leads to significant defects in tendon formation) can significantly impair long bone fracture healing in mice, resulting in fracture callus asymmetry and fibrotic, scar-like repair of the femur [4]. *Scx*^{-/-} mice also demonstrated substantial movement deficits and significantly reduced muscle mass compared to wildtype littermates, which may have exacerbated poor fracture healing [4]. In the ovine jaw, muscle loading via tendon detachment is required for reconstruction of the fractured mandible [105]. Isolated tendon injuries significantly impact the quality and structure of bone as well, as has been shown in several studies using small animal studies of isolated tendon injuries. Impaired healing of tendon-bone attachments is a consistent outcome following chronic muscle unloading [11,102,103]. Additionally, soft tissue injuries concurrent with fractured bone result in reduced stability of the associated joints [21,106]. Tensile stability is a significant, although not only, requirement for sufficient bone and tendon healing. Co-morbidities such as peripheral vascular disease contribute to an increased risk of non-union or malunions [107], and damage to peripheral vasculature increases with increasing fracture complexity [108,109]. Damage to peripheral vasculature can impair the healing process by limiting the delivery of inflammatory and other biological factors, such as growth factors, to the repair site. Indeed, numerous basic science and translational studies have explored the effects of local and systemic delivery of biological factors on fracture healing.

Biological Factors That Influence Soft- and Hard-Tissue Healing in Complex Fractures

The effect of soft tissue damage on outcomes of fracture healing is not limited to mechanical stability. The complexity of the musculoskeletal system and interactions between interfacing tissues contribute to both hard- and soft-tissue healing. Cortical bone non-unions may introduce direct cellular cross-talk between resident cells of periosteum, bone marrow, and soft tissues that otherwise might not physically interact [110]. Conversely, reduced soft tissue volume, such as in volumetric muscle loss, may lead to delayed and compromised fracture healing outcomes [46].

Tendon healing, similar to bone healing, is influenced by mechanical cues. The process of tendon healing relies on a combination of distinct cellular mechanisms that include the responsiveness of resident tendon fibroblasts (intrinsic), activation and proliferation of cells

originating from the surrounding epitenon, sheath, fascia, and vasculature, and infiltration of inflammatory cells [47,48,52,111,112]. It remains unclear if the biochemical cues that promote healing and mechano-sensing in tendon are similar or different than those of bone. The competing or compensatory response of cells in each tissue environment may be dramatically influenced by damage or remodeling to surrounding tissues. Several factors that are important in bone regeneration and repair are also critical for tendon healing (Figure 2). Of primary focus in this review are insulin-like growth factor 1 (IGF-1), and the transforming growth factor- β (TGF- β) family members, myostatin and bone morphogenetic proteins (BMPs).

IGF-1

IGF-1, the most abundant growth factor in bone, also plays an important role in muscle and tendon healing. Increased levels of IGF-1 lead to increased deposition of collagenous matrix and increased ligament strength with and without mechanical loading [113]. IGF-1 is highly expressed during the early inflammation period of tendon healing and contributes to proliferation, migration, and activity of fibroblasts [112]. While the long-term contributions of IGF-1 to tendinosis are yet to be explored [114], IGF-1 administration has been shown to decrease lesion size and inflammation, and increase cell proliferation [115–117]. Clinically, IGF-1 treatment shows promise for improving collagen synthesis in patellar tendon defects [118,119]. Increased levels of IGF-1 leads to increased bone formation and stimulates inflammation through NF- κ B pathway [120]. Growth hormone treatment with IGF-1 has shown promise for improved healing of open fractures [121]. Delivery of IGF-1 for therapeutic intervention is paramount, as local delivery has variable influences on bone regeneration [122–124]. Precision delivery of IGF-1 or in conjunction with IGF binding protein-3 [125,126] to sites of bone damage may improve healing in the context of complex fractures.

TGF- β

TGF- β is a major player in biological processes of healing [127], including in bone regeneration and healing [128–131]. TGF- β also plays an important role during inflammatory and repair phases of tendon healing [132–135]. TGF- β 3 is abundantly expressed in embryo, and delivery of TGF- β 3 during wound repair decreases scarring [133] and regulates TGF- β 1 during collagen synthesis [136]. Conversely, increases in TGF- β 1 has been associated with increased scar formation, collagen production, and fibrosis [132,137,138], and TGF- β 1 is upregulated after tendon-bone injury and healing [139–141]. Administration of TGF- β 1 during tendon healing can have a dramatic influence on tendon function and structure [142], and these effects have been primarily explored using small animal models [143–147]. Therapies to deliver TGF- β show the potential to improve fracture and tendon healing [144,148,149]. However, considering the dual effect of TGF- β on fibrosis and collagen synthesis, optimal utilization and administration are dependent on the nature and site of the injury.

Myostatin

Myostatin is a well-known myokine that acts as a negative regulator of muscle mass and has recently been implicated in maintaining skeletal health. It is well appreciated that muscle-bone crosstalk contributes to musculoskeletal healing, and recent findings have elucidated to the role that myostatin might play in tendon development and healing [150–154]. Myostatin is a member of Transforming Growth Factor- β (TGF- β) family, and acts to inhibit skeletal muscle growth as well as regulate bone shape [155–158]. Myostatin-deficient animals, including mice and cattle, experience significant growth in muscle mass [159–161], as well as increased cortical bone mineral density [162,163]. However, myostatin-deficient mice have brittle and hypocellular tendons [153]. In addition, myostatin inhibition in vivo leads to increased osteogenic differentiation of bone marrow-derived mesenchymal stem cells (BMSCs) and proliferation of epiphyseal growth plate chondrocytes in vitro [164,165]. The effect of myostatin on osteogenesis and chondrogenesis during early fracture healing is both tissue-specific and involving tissue cross-talk [158]. Local inhibition of myostatin can improve bone restoration, leading to increased calcification and osteogenic differentiation, making myostatin a potential target molecule for improving bone repair [166–168]. However, at the time of this review, myostatin inhibitors are only being used in clinical trials for treating muscle disorders – specifically, for treating Duchenne’s muscular dystrophy - and are not being used to treat bone or tendon injuries. In addition, two Phase II clinical trials by Pfizer using the investigational drug, domagrozumab (a monoclonal anti-myostatin antibody that blocks myostatin function), were recently terminated because the trials did not meet their primary efficacy endpoints. Regardless, the inhibition of myostatin holds promise not only for restoring muscle function, such as in cases of extensive muscle injury, but can to help reduce fibrosis during the early phases of bone repair. Preclinical studies investigating the role of myostatin in bone fracture healing may help lead to new interventions for effective non-unions fracture recovery as well as complex fracture with concurrent soft tissue injuries [158].

BMP

The osteo-inductive effects of BMP make this family of proteins an attractive therapeutic for improving fracture healing [169–174]. Similar to myostatin, BMPs belong to the TGF- β superfamily of proteins. Of about twenty different BMPs currently known, BMP2 and BMP7 are best known for their role in promotion osteoblast differentiation and fracture healing [14,175,176], and recombinant BMPs have been previously used for treating high-energy open fractures and non-unions [177–179]. BMP signaling is also important for tendon healing, as it is activated by dynamic mechanical loading [180–182] and during tendon healing [182]. BMP signaling also offers a potential avenue for treating isolated tendon defects [183–186]. During development, BMP-4 regulates tendon length during development, and BMP signaling regulates cell differentiation at the interface between tendon and bone [187,188]. Unfortunately, BMP activation can also impair tendon healing, primarily by promoting ectopic calcification [189–192]. The progression of tendinopathy can lead to the accumulation of BMP-2, regions of ossification, and transformation of fibrous tissue into ectopic bone/cartilage; a process that resembles the formation of bone during development [189] (Figure 1D–I). Indeed, patterns of BMP-2 expression at different stages of fracture callus progression (Figure 1B–C) match BMP-2 localization in tendon

fibroblasts during progressive tendinopathy (Figure 1G). Even without overt tendon damage, this is a significant problem for patients with fibrodysplasia ossificans progressive (FOP), a rare autosomal dominant disorder that is caused by constitutive activation of activin A type I receptor gene (ACVR1), a receptor for BMP [193]. In patients with FOP, the BMP type I receptor, activin receptor-like kinase-2 (ALK2), is constitutively active and leads to progressive and widespread ossification of connective tissues, such as tendons, which significantly limits mobility, function, and lifespan [193–195]. Because of the known and dramatic consequences of soft tissue calcification both during fracture healing and with recombinant BMP-2 treatment, precision approaches for delivery of anabolic drugs like BMP-2 are needed.

Conclusions

Healing of bone following fracture is complicated by the involvement of surrounding connective tissues, like tendon, which can delay or disrupt the reintegration and function of both tissues. Tendon injuries with bone fracture are often overlooked, and delayed treatment of tendon injuries can lead to long-term musculoskeletal issues. The ability to repair bone following fracture relies on the mechanical cues from tendon, yet the role damaged tendon plays in the process of fracture healing is an underexplored area of orthopedics. A need exists to identify mechanisms that promote both bone healing and tendon repair following complex fracture that include functional stabilization and control of biological signaling.

Acknowledgments

Funding: This research is supported by an Institutional Development Award (IDeA) from the National Institute of General Medical Sciences of the National Institutes of Health under grant number P30GM103333 (PI: Buchanan). NIH is a federal medical research agency supporting public health-related scientific studies throughout the U.S.

References

1. Misra A, Kapur R, Maffulli N. Complex proximal humeral fractures in adults--a systematic review of management. *Injury*. Elsevier; 2001;32:363–72.
2. Wagels M, Rowe D, Senewiratne S, Read T, Theile DR. Soft tissue reconstruction after compound tibial fracture: 235 cases over 12 years. *J Plast Reconstr Aesthetic Surg*. 2015;68:1276–85.
3. Lescun TB. Equine fractures: The importance of the soft tissues. *Equine Vet Educ*. 2015;27:71–4.
4. McKenzie JA, Buettmann E, Abraham AC, Gardner MJ, Silva MJ, Killian ML. Loss of scleraxis in mice leads to geometric & structural changes in cortical bone, as well as asymmetry in fracture healing. *FASEB J*. 2017;31:882–92. [PubMed: 27864378]
5. Covey DC. Combat orthopaedics: a view from the trenches. *J Am Acad Orthop Surg*. 2006;14:S10–17. [PubMed: 17003178]
6. Ibrahim DA, Swenson A, Sassoon A, Fernando ND. Classifications In Brief: The Tscherne Classification of Soft Tissue Injury. *Clin Orthop Relat Res*. 2017;475:560–4. [PubMed: 27417853]
7. Owens BD, Kragh JF, Macaitis J, Svoboda SJ, Wenke JC. Characterization of extremity wounds in operation Iraqi freedom and operation enduring freedom. *J Orthop Trauma*. 2007;21:254–7. [PubMed: 17414553]
8. Pankovich AM, Shivaram MS. Anatomical basis of variability in injuries of the medial malleolus and the deltoid ligament: II. Clinical studies. *Acta Orthop*. 1979;50:217–23.
9. Goh D, Hiong S, Goh SH. Bomb blast mass casualty incidents: initial triage and management of injuries [Internet]. *Singapore Med J*. 2009 Available from: <https://pdfs.semanticscholar.org/11f8/5f1af79661aa9107a84528483e028ef0ac88.pdf>

10. Hurtgen BJ, Ward CL, Garg K, Pollot BE, Goldman SM, McKinley TO, et al. Severe muscle trauma triggers heightened and prolonged local musculoskeletal inflammation and impairs adjacent tibia fracture healing. *J Musculoskelet Neuronal Interact* [Internet]. International Society of Musculoskeletal and Neuronal Interactions (ISMNI); 2016 [cited 2018 Nov 29];16:122–34. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/27282456>
11. Willett NJ, Li M-TA, Uhrig BA, Boerckel JD, Huebsch N, Lundgren TS, et al. Attenuated human bone morphogenetic protein-2-mediated bone regeneration in a rat model of composite bone and muscle injury. *Tissue Eng Part C*. 2013;19:316–25.
12. Li MTA, Willett NJ, Uhrig BA, Guldberg RE, Warren GL. Functional analysis of limb recovery following autograft treatment of volumetric muscle loss in the quadriceps femoris. *J Biomech* [Internet]. Elsevier; 2014 [cited 2018 Nov 29];47:2013–21. Available from: <https://www.sciencedirect.com/science/article/pii/S0021929013005496>
13. Harry LE, Edin M, Paleolog EM. Modulating Angiogenesis. *JAMA*. 2004;292:972–7. [PubMed: 15328330]
14. Davis KM, Griffin KS, Chu TMG, Wenke JC, Corona BT, McKinley TO, et al. Muscle-bone interactions during fracture healing. *J Musculoskelet Neuronal Interact*. 2015;15:1–9. [PubMed: 25730647]
15. (UK) NCGC. Fractures (Complex): Assessment and Management [Internet] *Fract. Assess. Manag* National Institute for Health and Care Excellence (UK); 2016 [cited 2018 Nov 26]. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26913311>
16. Marsell R, Einhorn TA. The biology of fracture healing. *Injury*. Elsevier Ltd; 2011;42:551–5.
17. Glatt V, Evans CH, Tetsworth K. A concert between biology and biomechanics: The influence of the mechanical environment on bone healing. *Front Physiol*. 2017;7:1–18.
18. Harry LE, Paleolog EM. From the cradle to the clinic: VEGF in developmental, physiological, and pathological angiogenesis. *Birth Defects Res (Part C)*. 2003;69:363–74.
19. Reikeras O, Winge MI, Rekkum M. Effect of soft-tissue attachment on tibial fracture healing in rats. *J Orthop Surg*. 2015;23:47–51.
20. Dickson KF, Katzman S, Paiement GP. The importance of the blood supply in healing of tibial fractures. *Contemp Orthop*. 1995;30:489–93. [PubMed: 10150380]
21. Wilppula E, Bakalim G. Ligamentous tear concomitant with tibial condylar fracture. *Acta Orthop*. 1972;43:292–300.
22. Schaser K, Zhang L, Mittlmeier T, Ostapowicz D, Schmidmaier G, Duda G, et al. Effect of soft tissue damage on fracture healing: intravital microscopic and biomechanical investigations in rats. *Trans Orthop Res Soc* 50120. 2003 p. 9–12.
23. Chen P-J, Liu AL-J. Concurrent flexor carpi radialis tendon rupture and closed distal radius fracture. *BMJ Case Rep*. 2014;bcr2014204196.
24. (UK) NCGC. Fractures (Complex): Assessment and Management *Fract. Assess. Manag* National Institute for Health and Care Excellence (UK); 2016.
25. van Staa T, Dennison E, Leufkens HG, Cooper C Epidemiology of fractures in England and Wales. *Bone* [Internet]. Elsevier; 2001 [cited 2018 Nov 26];29:517–22. Available from: <https://www.sciencedirect.com/science/article/pii/S8756328201006147>
26. van Staa T, Dennison E, Leufkens HG, Cooper C Epidemiology of fractures in England and Wales. *Bone*. Elsevier; 2001;29:517–22.
27. Gustilo RB, Mendoza RM, Williams DN. Problems in the management of type III (severe) open fractures: a new classification of type III open fractures. *J Trauma*. 1984 p. 742–6. [PubMed: 6471139]
28. Ryan SP, Pugliano V. Controversies in initial management of open fractures. *Scand J Surg*. 2013;103:132–7.
29. Gustilo RB, Anderson JT. Prevention of infection in the treatment of one thousand and twenty-five open fractures of long bones. *J Bone Jt Surg*. 1976;58-A:453–8.
30. Rot C, Stern T, Blecher R, Friesem B, Zelzer E. A mechanical jack-like mechanism drives spontaneous fracture healing in neonatal mice. *Dev Cell*. Elsevier Inc; 2014;31:159–70.
31. Caudle RJ, Stern PJ. Severe open fractures of the tibia. *J Bone Jt Surg*. 1987;69:801–7.

32. Yazar S, Lin C-H, Wei F-C. One-stage reconstruction of composite bone and soft-tissue defects in traumatic lower extremities. *Plast Reconstr Surg. LWW*; 2004;114:1457–66.
33. Parrett BM, Matros E, Pribaz JJ, Orgill DP. Lower extremity trauma: trends in the management of soft-tissue reconstruction of open tibia-fibula fractures. *Plast Reconstr Surg. LWW*; 2006;117:1315–22.
34. Hertel R, Lambert SM, Muller S, Ballmer FT, Ganz R. On the timing of soft-tissue reconstruction for open fractures of the lower leg. *Arch Orthop Trauma Surg. Springer*; 1999;119:7–12.
35. Stiehl JB. Concomitant rupture of the peroneus brevis tendon and bimalleolar fracture. A case report. *J Bone Joint Surg Am.* 1988;70:936–7. [PubMed: 3392093]
36. Frydman GH, Cuddy LC, Kim SE, Pozzi A. Treatment of bicondylar femoral fractures complicated by concurrent ligament or tendon injuries in four dogs. *Vet Comp Orthop Traumatol.* 2014;27:324–32. [PubMed: 24991936]
37. Banejee S, Dooley TP, Parkinson JR. Case Report ipsilateral rupture of quadriceps tendon with distal tibia fracture : a case report and review of the literature. *Case Rep Orthop.* 2017;1–6.
38. Elmajee M, Rafee A, Williams T. Ankle fracture associated with rupture of the Achilles tendon: case report and review of the literature. *J Foot Ankle Surg. Elsevier Ltd*; 2017;56:1320–2.
39. Komarasamy B, Vadivelu R, Boyd KT, Pandey R, Rennie W. Concomitant talar neck fracture and Achilles tendon rupture. *J Foot Ankle Surg.* 2007;46:188–91. [PubMed: 17466246]
40. Prabhakar G, Kusnezov N, Rensing N, Abdelgawad A. Dual Fixation of calcaneal tuberosity avulsion with concomitant Achilles tendon rupture: A novel hybrid technique. *Case Rep Orthop. Hindawi*; 2017;1–4.
41. Assal M, Stern R, Peter R. Fracture of the ankle associated with rupture of the achilles tendon: case report and review of the literature. *J Orthop Trauma.* 2002;16:358–61. [PubMed: 11972082]
42. Turkmensoy F, Turkmen I, Turhan Y, Ozkan K, Akgal MA. Achilles tendon rupture with isolated medial malleolar fracture in ipsilateral ankle: a case report. *Open J Orthop.* 2013;3:224–6.
43. Saied A, Ziayie A. Neglected Ankle Dislocation. *J Foot Ankle Surg.* 2007;46:307–9. [PubMed: 17586447]
44. Kim JY, Lee JS, Kim MK. Fractures of the capitellum concomitant with avulsion fractures of the triceps tendon. *J Hand Surg Am. Elsevier Inc*; 2013;38-A:495–7.
45. Cheng CY, Hsu KY, Tseng IC, Shih HN. Concurrent scaphoid fracture with scapholunate ligament rupture. *Acta Orthop Belg.* 2004;70:485–91. [PubMed: 15587040]
46. Utvag SE, Iversen KB, Grundnes O, Reikeras O. Poor muscle coverage delays fracture healing in rats. *Acta Orthop Scand.* 2002;73:471–4. [PubMed: 12358124]
47. Dymant NA, Liu C-F, Kazemi N, Aschbacher-Smith LE, Kenter K, Breidenbach AP, et al. The paratenon contributes to scleraxis-expressing cells during patellar tendon healing. *PLoS One. Public Library of Science*; 2013;8:e59944–e59944.
48. Dymant NA, Hagiwara Y, Matthews BG, Li Y, Kalajzic I, Rowe DW. Lineage tracing of resident tendon progenitor cells during growth and natural healing. *PLoS One. Public Library of Science*; 2014;9:e96113–e96113.
49. Gerstenfeld LC, Cullinane DM, Barnes GL, Graves DT, Einhorn TA. Fracture healing as a post-natal developmental process: Molecular, spatial, and temporal aspects of its regulation. *J Cell Biochem. Wiley Online Library*; 2003;88:873–84.
50. Einhorn TA. The cell and molecular biology of fracture healing. *Clin Orthop Relat Res. LWW*; 1998;355:S7–21.
51. Butler DL, Dymant NA, Shearn JT, Kinneberg KRC, Breidenbach AP, Lalley AL, et al. Evolving Strategies in Mechanobiology to More Effectively Treat Damaged Musculoskeletal Tissues. *J Biomech Eng. ASME*; 2013;135:21001–16.
52. Killian ML, Cavinatto L, Galatz LM, Thomopoulos S. The role of mechanobiology in tendon healing. *J Shoulder Elb Surg. Elsevier Ltd*; 2012;21:228–37.
53. Voleti PB, Buckley MR, Soslowsky LJ. Tendon Healing: Repair and Regeneration. *Annu Rev Biomed Eng [Internet]. Annual Reviews*; 2012 [cited 2018 Nov 26];14:47–71. Available from: <http://www.annualreviews.org/doi/10.1146/annurev-bioeng-071811-150122>

54. Sharma P, Maffulli N. Tendon Injury and Tendinopathy. J Bone Jt Surg [Internet]. 2005 [cited 2018 Nov 26];87:187–202. Available from: <http://insights.ovid.com/crossref?an=00004623-200501000-00030>
55. Shwartz Y, Blitz E, Zelzer E. One load to rule them all: Mechanical control of the musculoskeletal system in development and aging. Differentiation [Internet]. Elsevier; 2013;86:104–11. Available from: 10.1016/j.diff.2013.07.003
56. Zelzer E, Blitz E, Killian ML, Thomopoulos S. Tendon-to-bone attachment: From development to maturity. Birth Defects Res Part C Embryo Today Rev [Internet]. Wiley-Blackwell; 2014 [cited 2018 Nov 26];102:101–12. Available from: <http://doi.wiley.com/10.1002/bdrc.21056>
57. Lieber RL, Jacobson MD, Fazeli BM, Abrams RA, Botte MJ. Architecture of selected muscles of the arm and forearm: Anatomy and implications for tendon transfer. J Hand Surg Am [Internet]. W.B. Saunders; 1992 [cited 2018 Nov 26];17:787–98. Available from: <https://www.sciencedirect.com/science/article/pii/S036350239290444T>
58. Doyle JR, Blythe WF. Anatomy of the flexor tendon sheath and pulleys of the thumb. J Hand Surg Am [Internet]. W.B. Saunders; 1977 [cited 2018 Nov 26];2:149–51. Available from: <https://www.sciencedirect.com/science/article/pii/S0363502377801019>
59. Benjamin M, Kaiser E, Milz S. Structure-function relationships in tendons: a review. J Anat [Internet]. Wiley/Blackwell (10.1111); 2008 [cited 2018 Nov 26];212:211–28. Available from: <http://doi.wiley.com/10.1111/j.1469-7580.2008.00864.x>
60. Kobayashi M, Itoi E, Minagawa H, Miyakoshi N, Takahashi S, Tuoheti Y, et al. Expression of growth factors in the early phase of supraspinatus tendon healing in rabbits. J Shoulder Elb Surg. 2006;15:371–7.
61. Molloy T, Wang Y, Murrell G. The roles of growth factors in tendon and ligament healing. Sports Med [Internet]. 2003;33:381–94. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12696985>
62. Peacock EE. Fundamental aspects of wound healing relating to the restoration of gliding function after tendon repair. Surg Gynecol Obstet [Internet]. 1964 [cited 2018 Nov 26];119:241–50. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/14200952>
63. Chang J, Most D, Thunder R, Mehrara B, Longaker MT, Lineaweaver WC. Molecular studies in flexor tendon wound healing: The role of basic fibroblast growth factor gene expression. J Hand Surg Am [Internet]. W.B. Saunders; 1998 [cited 2018 Nov 26];23:1052–8. Available from: <https://www.sciencedirect.com/science/article/pii/S0363502398800154>
64. James R, Kesturu G, Balian G, Chhabra AB. Tendon: Biology, Biomechanics, Repair, Growth Factors, and Evolving Treatment Options. J Hand Surg Am [Internet]. W.B. Saunders; 2008 [cited 2018 Nov 26];33:102–12. Available from: <https://www.sciencedirect.com/science/article/pii/S0363502307007812#fig1>
65. Howell K, Chien C, Bell R, Laudier D, Tufa SF, Keene DR, et al. Novel Model of Tendon Regeneration Reveals Distinct Cell Mechanisms Underlying Regenerative and Fibrotic Tendon Healing. Sci Rep [Internet]. Nature Publishing Group; 2017 [cited 2018 Nov 26];7:45238 Available from: <http://www.nature.com/articles/srep45238>
66. Dymant NA, Liu C-F, Kazemi N, Aschbacher-Smith LE, Kenter K, Breidenbach AP, et al. The paratenon contributes to scleraxis-expressing cells during patellar tendon healing. PLoS One. Public Library of Science; 2013;8:e59944.
67. Dymant NA, Galloway JL. Regenerative Biology of Tendon: Mechanisms for Renewal and Repair. Curr Mol Biol Reports [Internet]. Springer International Publishing; 2015 [cited 2018 Nov 26];1:124–31. Available from: <http://link.springer.com/10.1007/s40610-015-0021-3>
68. Best KT, Loisele A. Scleraxis Lineage Cells Contribute to Organized Bridging Tissue During Tendon Healing, and Identifies Subpopulations of Resident Tendon Cells. bioRxiv [Internet]. Cold Spring Harbor Laboratory; 2018 [cited 2018 Nov 26];469619 Available from: <https://www.biorxiv.org/content/early/2018/11/13/469619>
69. Durgam S, Stewart M. Cellular and Molecular Factors Influencing Tendon Repair. Tissue Eng Part B Rev [Internet]. Mary Ann Liebert, Inc. 140 Huguenot Street, 3rd Floor New Rochelle, NY 10801 USA; 2017 [cited 2018 Nov 26];23:307–17. Available from: <https://www.liebertpub.com/doi/10.1089/ten.teb.2016.0445>

70. Manning CN, Havlioglu N, Knutsen E, Sakiyama-Elbert SE, Silva MJ, Thomopoulos S, et al. The early inflammatory response after flexor tendon healing: A gene expression and histological analysis. *J Orthop Res* [Internet]. John Wiley & Sons, Ltd; 2014 [cited 2018 Nov 26];32:645–52. Available from: <http://doi.wiley.com/10.1002/jor.22575>
71. Muller SA, Todorov A, Heisterbach PE, Martin I, Majewski M. Tendon healing: an overview of physiology, biology, and pathology of tendon healing and systematic review of state of the art in tendon bioengineering. *Knee Surgery, Sport Traumatol Arthrosc* [Internet]. Springer Berlin Heidelberg; 2015 [cited 2018 Nov 26];23:2097–105. Available from: <http://link.springer.com/10.1007/s00167-013-2680-z>
72. Durgam S, Stewart M. Cellular and Molecular Factors Influencing Tendon Repair. *Tissue Eng Part B Rev*. Mary Ann Liebert, Inc. 140 Huguenot Street, 3rd Floor New Rochelle, NY 10801 USA; 2017;23:307–17.
73. James R, Kesturu G, Balian G, Chhabra AB. Tendon: Biology, Biomechanics, Repair, Growth Factors, and Evolving Treatment Options. *J Hand Surg Am*. W.B. Saunders; 2008;33:102–12.
74. Nowlan NC, Murphy P, Prendergast PJ. A dynamic pattern of mechanical stimulation promotes ossification in avian embryonic long bones. *J Biomech*. 2008;41:249–58. [PubMed: 18005973]
75. Thomopoulos S, Kim HM, Rothermich SY, Biederstadt C, Das R, Galatz LM. Decreased muscle loading delays maturation of the tendon enthesis during postnatal development. *J Orthop Res*. 2007;25: 1154–63. [PubMed: 17506506]
76. Hettrich CM, Rodeo SA, Hannafin JA, Ehteshami J, Shubin Stein BE. The effect of muscle paralysis using Botox on the healing of tendon to bone in a rat model. *J Shoulder Elb Surg*. Elsevier Ltd; 2011;20:688–97.
77. Gilotra MN, Shorofsky MJ, Stein JA, Murthi AM. Healing of rotator cuff tendons using botulinum toxin A and immobilization in a rat model. *BMC Musculoskelet Disord* [Internet]. BMC Musculoskeletal Disorders; 2016;17:1–8. Available from: 10.1186/s12891-016-0978-y [PubMed: 26728594]
78. Galatz LM, Charlton N, Das R, Kim HM, Havlioglu N, Thomopoulos S. Complete removal of load is detrimental to rotator cuff healing. *J Shoulder Elb Surg* [Internet]. Elsevier Ltd; 2009;18:669–75. Available from: 10.1016/j.jse.2009.02.016
79. Thomopoulos S, Zampiakis E, Das R, Silva MJ, Gelberman RH. The effect of muscle loading on flexor tendon- to-bone healing in a canine model. *J Orthop Res* [Internet]. John Wiley & Sons, Ltd; 2008 [cited 2018 Nov 29];26:1611–7. Available from: <http://doi.wiley.com/10.1002/jor.20689>
80. Grimston SK, Silva MJ, Civitelli R. Bone loss after temporarily induced muscle paralysis by Botox is not fully recovered after 12 weeks. *Ann N Y Acad Sci* [Internet]. Wiley/Blackwell (10.1111); 2007 [cited 2018 Nov 29];1116:444–60. Available from: <http://doi.wiley.com/10.1196/annals.1402.009>
81. Soslowsky LJ, Thomopoulos S, Tun S, Flanagan CL, Keefer CC, Mastaw J, et al. Neer Award 1999: Overuse activity injures the supraspinatus tendon in an animal model: A histologic and biomechanical study. *J Shoulder Elb Surg* [Internet]. Mosby; 2000 [cited 2018 Nov 29];9:79–84. Available from: <https://www.sciencedirect.com/science/article/pii/S1058274600900338>
82. Carpenter JE, Flanagan CL, Thomopoulos S, Yian EH, Soslowsky LJ. The Effects of Overuse Combined With Intrinsic or Extrinsic Alterations in an Animal Model of Rotator Cuff Tendinosis. *Am J Sports Med* [Internet]. SAGE PublicationsSage CA: Los Angeles, CA; 1998 [cited 2018 Nov 29];26:801–7. Available from: <http://journals.sagepub.com/doi/10.1177/03635465980260061101>
83. Galloway MT, Lalley AL, Shearn JT. The role of mechanical loading in tendon development, maintenance, injury, and repair. *J Bone Joint Surg Am* [Internet]. Journal of Bone and Joint Surgery, Inc; 2013 [cited 2018 Nov 29];95:1620–8. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24005204>
84. Bailón-Plaza A, van der Meulen MCH. Beneficial effects of moderate, early loading and adverse effects of delayed or excessive loading on bone healing. *J Biomech* [Internet]. Elsevier; 2003 [cited 2018 Nov 29];36:1069–77. Available from: <https://www.sciencedirect.com/science/article/pii/S0021929003001179>
85. Buckwalter JA, Hunziker EB. Healing of bones, cartilages, tendons, and ligaments: a new era. *Lancet*. Elsevier; 1996;348:S18.

86. Buckwalter JA. Effects of early motion on healing of musculoskeletal tissues. *Hand Clin.* 1996;12:13–24. [PubMed: 8655614]
87. Jagodzinski M, Krettek C. Effect of mechanical stability on fracture healing—an update. *Injury.* Elsevier; 2007;38:S3–10.
88. Gardner MJ, Putnam SM, Wong A, Streubel PN, Kotiya A, Silva MJ. Differential fracture healing resulting from fixation stiffness variability: a mouse model. *J Orthop Sci.* Springer; 2011;16:298–303.
89. Borrelli J, Torzilli PA, Grigienė R, Helfet DL. Effect of impact load on articular cartilage: development of an intra-articular fracture model. *J Orthop Trauma* [Internet]. 1997 [cited 2018 Nov 29];11:319–26. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9294794>
90. Heier KA, Infante AF, Walling AK, Sanders RW. Open fractures of the calcaneus: soft-tissue injury determines outcome. *JBJS. LWW*; 2003;85:2276–82.
91. Page M, Hogg J, Ashhurst DE. The effects of mechanical stability on the macromolecules of the connective tissue matrices produced during fracture healing. I. The collagens. *Histochem J.* Springer; 1986;18:251–65.
92. Bartnikowski N, Claes LE, Koval L, Glatt V, Bindl R, Steck R, et al. Modulation of fixation stiffness from flexible to stiff in a rat model of bone healing. *Acta Orthop.* 2017;88:217–22. [PubMed: 27841708]
93. Claes LE, Heigele CA. Magnitudes of local stress and strain along bony surfaces predict the course and type of fracture healing. *J Biomech.* 1999;32:255–66. [PubMed: 10093025]
94. Das R, Rich J, Kim HM, McAlinden A, Thomopoulos S. Effects of botulinum toxin-induced paralysis on postnatal development of the supraspinatus muscle. *J Orthop Res.* 2011;29:281–8. [PubMed: 20803483]
95. Recidoro AM, Roof AC, Schmitt M, Worton LE, Petrie T, Strand N, et al. Botulinum toxin induces muscle paralysis and inhibits bone regeneration in zebrafish. *J Bone Miner Res.* 2014;29:2346–56. [PubMed: 24806738]
96. Iliazarov GA. The tension-stress effect on the genesis and growth of tissues Part I. The influence of stability of fixation and soft-tissue preservation. *Clin Orthop Relat Res.* 1989;238:249–81.
97. Lanyon LE, Rubin CT. Static vs dynamic loads as an influence on bone remodelling. *J Biomech.* 1984;17:897–905. [PubMed: 6520138]
98. Shwartz Y, Blitz E, Zelzer E. One load to rule them all: Mechanical control of the musculoskeletal system in development and aging. *Differentiation.* Elsevier; 2013;86:104–11.
99. Barron JL, Yocum LA. Unrecognized Achilles tendon rupture associated with ipsilateral medial malleolar fracture. *Am J Sports Med.* 1993;21:629–31. [PubMed: 8368428]
100. Szalay MJ, Hosking OR, Annear P. Injury of knee ligament associated with ipsilateral femoral shaft fractures and with ipsilateral femoral and tibial shaft fractures. *Injury* [Internet]. Elsevier; 1990 [cited 2018 Nov 29];21:398–400. Available from: <https://www.sciencedirect.com/science/article/pii/0020138390901291>
101. Rademakers MV, Kerkhoffs GMMJ, Sierevelt IN, Raaymakers ELFB, Marti RK. Operative Treatment of 109 Tibial Plateau Fractures: Five- to 27-Year Follow-up Results. *J Orthop Trauma* [Internet]. 2007 [cited 2018 Nov 29];21:5–10. Available from: <https://insights.ovid.com/crossref?an=00005131-200701000-00002>
102. Gilotra MN, Shorofsky MJ, Stein JA, Murthi AM. Healing of rotator cuff tendons using botulinum toxin A and immobilization in a rat model. *BMC Musculoskelet Disord.* BMC Musculoskeletal Disorders; 2016;17:1–8. [PubMed: 26728594]
103. Galatz LM, Charlton N, Das R, Kim HM, Havlioglu N, Thomopoulos S. Complete removal of load is detrimental to rotator cuff healing. *J Shoulder Elb Surg.* Elsevier Ltd; 2009;18:669–75.
104. Keener JD, Galatz LM, Stobbs-Cucchi G, Patton R, Yamaguchi K. Rehabilitation following arthroscopic rotator cuff repair: a prospective randomized trial of immobilization compared with early motion. *JBJS. LWW*; 2014;96:11–9.
105. Wu D, Yang X-J, Cheng P, Deng T-G, Jiang X, Liu P, et al. The lateral pterygoid muscle affects reconstruction of the condyle in the sagittal fracture healing process: a histological study. *Int J Oral Maxillofac Surg.* Elsevier; 2015;44:1010–5.

106. Leung KS, Qin L, Fu LK, Chan CW. A comparative study of bone to bone repair and bone to tendon healing in patella-patellar tendon complex in rabbits. *Clin Biomech.* 2002;17:594–602.
107. Gaston MS, Simpson AHRW. Inhibition of fracture healing. *J Bone Joint Surg Br. The British Editorial Society of Bone & Joint Surgery;* 2007;89-B:1553–60.
108. Brinker MR, Bailey DE. Fracture healing in tibia fractures with an associated vascular injury. *J Trauma Acute Care Surg. LWW;* 1997;42:11–9.
109. Hernandez RK, Do TP, Critchlow CW, Dent RE, Jick SS. Patient-related risk factors for fracture-healing complications in the United Kingdom General Practice Research Database. *Acta Orthop. Taylor & Francis;* 2012;83:653–60.
110. Colnot C. Skeletal cell fate decisions within periosteum and bone marrow during bone regeneration. *J Bone Miner Res.* 2009;24:274–82. [PubMed: 18847330]
111. Thomopoulos S, Hattersley G, Rosen V, Mertens M, Galatz L, Williams GR, et al. The localized expression of extracellular matrix components in healing tendon insertion sites: an in situ hybridization study. *J Orthop Res.* 2002;20:454–63. [PubMed: 12038618]
112. Molloy T, Wang Y, Murrell G. The roles of growth factors in tendon and ligament healing. *Sports Med.* 2003;33:381–94. [PubMed: 12696985]
113. Provenzano PP, Alejandro-osorio AL, Grorud KW, Martinez DA, Vailas AC, Grindeland RE, et al. Systemic administration of IGF-I enhances healing in collagenous extracellular matrices: evaluation of loaded and unloaded ligaments. *BMC Physiol.* 2007;7:1–17. [PubMed: 17319948]
114. Witte TH, Yeager AE, Nixon AJ. Intralesional injection of insulin-like growth factor-I for treatment of superficial digital flexor tendonitis in Thoroughbred racehorses: 40 cases (2000–2004). *J Am Vet Med Assoc.* 2011;239:992–7. [PubMed: 21961641]
115. Dahlgren LA, Van Der Meulen MCH, Bertram JEA, Starrak GS, Nixon AJ. Insulin-like growth factor-I improves cellular and molecular aspects of healing in a collagenase-induced model of flexor tendinitis. *J Orthop Res.* 2002;20:910–9. [PubMed: 12382953]
116. Durgam SS, Stewart A a., Pondenis HC, Gutierrez-Nibeyro SM, Evans RB, Stewart MC. Comparison of equine tendon- and bone marrow-derived cells cultured on tendon matrix with or without insulin-like growth factor-I supplementation. *Am J Vet Res.* 2012;73:153–61. [PubMed: 22204302]
117. Hansson H-A, Engstrom AMC, Holm S, Rosenqvist A-I. Somatomedin C immunoreactivity in the Achilles tendon varies in a dynamic manner with the mechanical load. *Acta Physiol Scand.* 1988;134:199–208. [PubMed: 3067520]
118. Hansen M, Boesen A, Holm L, Flyvbjerg A, Langberg H, Kjaer M. Local administration of insulin-like growth factor-I (IGF-I) stimulates tendon collagen synthesis in humans. *Scand J Med Sci Sport.* 2013;23:614–9.
119. Heinemeier KM, Mackey AL, Doessing S, Hansen M, Bayer ML, Nielsen RH, et al. GH/IGF-I axis and matrix adaptation of the musculotendinous tissue to exercise in humans. *Scand J Med Sci Sport.* 2012;22:e1–7.
120. Meinel L, Zoidis E, Zapf J, Hassa P, Hottiger MO, Auer JA, et al. Localized insulin-like growth factor I delivery to enhance new bone formation. *Bone.* 2003;33:660–72. [PubMed: 14555272]
121. Raschke M, Hejby Rasmussen M, Govender S, Segal D, Suntum M, Christiansen JS. Effects of growth hormone in patients with tibial fracture: A randomised, double-blind, placebo-controlled clinical trial. *Eur J Endocrinol.* 2007;156:341–51. [PubMed: 17322494]
122. Aspenberg P, Albrektsson T, Thorngren KG. Local application of growth-factor IGF-1 to healing bone experiments with a titanium chamber in rabbits. *Acta Orthop.* 1989;60:607–10.
123. Meinel L, Zoidis E, Zapf J, Hassa P, Hottiger MO, Auer JA, et al. Localized insulin-like growth factor I delivery to enhance new bone formation. *Bone.* 2003;33:660–72. [PubMed: 14555272]
124. Schmidmaier G, Wildemann B, Heeger J, Gabelein T, Flyvbjerg A, Bail HJ, et al. Improvement of fracture healing by systemic administration of growth hormone and local application of insulin-like growth factor-1 and transforming growth factor- β 1. *Bone.* 2002;31:165–72. [PubMed: 12110430]
125. Yakar S, Rosen CJ, Beamer WG, Ackert-Bicknell CL, Wu Y, Liu J-L, et al. Circulating levels of IGF-1 directly regulate bone growth and density. *J Clin Invest. American Society for Clinical Investigation;* 2002;110:771–81.

126. Xian L, Wu X, Pang L, Lou M, Rosen CJ, Qiu T, et al. Matrix IGF-1 maintains bone mass by activation of mTOR in mesenchymal stem cells. *Nat Med*. 2012;18:1095–101. [PubMed: 22729283]
127. Pierce GF, Mustoe TA, Lingelbach J, Masakowski VR, Gramates P, Deuel TF. Transforming growth factor beta reverses the glucocorticoid-induced wound-healing deficit in rats: possible regulation in macrophages by platelet-derived growth factor. *Proc Natl Acad Sci U S A*. National Academy of Sciences; 1989;86:2229–33.
128. Bostrom MP, Asnis P. Transforming growth factor beta in fracture repair. *Clin Orthop Relat Res*. 1998;S124–31. [PubMed: 9917633]
129. Rosier RN, O'Keefe RJ, Hicks DG. The potential role of transforming growth factor beta in fracture healing. *Clin Orthop Relat Res*. 1998;S294–300. [PubMed: 9917649]
130. Lind M, Schumacker B, Seballe K, Keller J, Melsen F, Bunger C. Transforming growth factor- β enhances fracture healing in rabbit tibiae. *Acta Orthop Scand*. 1993;64:553–6. [PubMed: 8237323]
131. Chen G, Deng C, Li Y-P. TGF- β and BMP signaling in osteoblast differentiation and bone formation. *Int J Biol Sci*. Ivyspring International Publisher; 2012;8:272–88.
132. Klein MB, Yalamanchi N, Pham H, Longaker MT, Chang J. Flexor tendon healing in vitro: Effects of TGF- β on tendon cell collagen production. *J Hand Surg Am*. 2002;27:615–20. [PubMed: 12132085]
133. Shah M, Foreman DM, Ferguson MW. Neutralisation of TGF-beta 1 and TGF-beta 2 or exogenous addition of TGF-beta 3 to cutaneous rat wounds reduces scarring. *J Cell Sci*. 1995;108 (Pt 3):985–1002. [PubMed: 7542672]
134. Prabhath A, Vernekar VN, Sanchez E, Laurencin CT. Growth factor delivery strategies for rotator cuff repair and regeneration. *Int J Pharm*. Elsevier; 2018;544:358–71. [PubMed: 29317260]
135. Liu X, Joshi SK, Ravishankar B, Laron D, Kim HT, Feeley BT. Upregulation of transforming growth factor- β signaling in a rat model of rotator cuff tears. *J Shoulder Elb Surg*. 2014;23:1709–16.
136. Murata H, Zhou L, Ochoa S, Hasan A, Badiavas E, Falanga V. TGF-beta3 stimulates and regulates collagen synthesis through TGF-beta1-dependent and independent mechanisms. *J Invest Dermatol*. 1997;108:258–62. [PubMed: 9036921]
137. Border WA, Noble NA. Transforming Growth Factor β in Tissue Fibrosis. *N Engl J Med*. 1994;331:1286–92. [PubMed: 7935686]
138. Biernacka A, Dobaczewski M, Frangogiannis NG. TGF- β signaling in fibrosis. *Growth factors*. NIH Public Access; 2011;29:196–202.
139. Ngo M, Pham H, Longaker MT, Chang J. Differential expression of transforming growth factor-beta receptors in a rabbit zone II flexor tendon wound healing model. *Plast Reconstr Surg*. 2001;108:1260–7. [PubMed: 11604629]
140. Wurgler-Hauri CC, Dourte LM, Baradet TC, Williams GR, Soslowsky LJ. Temporal expression of 8 growth factors in tendon-to-bone healing in a rat supraspinatus model. *J Shoulder Elb Surg*. Mosby; 2007;16:S198–203.
141. Galatz LM, Sandell LJ, Rothermich SY, Das R, Mastny A, Havlioglu N, et al. Characteristics of the rat supraspinatus tendon during tendon-to-bone healing after acute injury. *J Orthop Res*. Wiley-Blackwell; 2006;24:541–50.
142. Kashiwagi K, Mochizuki Y, Yasunaga Y, Ishida O, Deie M, Ochi M. Effects of transforming growth factor- β 1 on the early stages of healing of the Achilles tendon in a rat model. *Scand J Plast Reconstr Surg Hand Surg*. 2004;38:193–7. [PubMed: 15370799]
143. Majewski M, Porter RM, Betz OB, Betz VM, Clahsen H, Fluckiger R, et al. Improvement of tendon repair using muscle grafts transduced with TGF- β 1 cDNA. *Eur Cell Mater*. NIH Public Access; 2012;23:92–4.
144. Hou Y, Mao Z, Wei X, Lin L, Chen L, Wang H, et al. Effects of transforming growth factor-pi and vascular endothelial growth factor 165 gene transfer on Achilles tendon healing. *Matrix Biol*. 2009;28:324–35. [PubMed: 19389474]

145. Hou Y, Mao ZB, Wei XL, Lin L, Chen LX, Wang HJ, et al. The roles of TGF- β 1 gene transfer on collagen formation during Achilles tendon healing. *Biochem Biophys Res Commun*. Elsevier Inc; 2009;383:235–9.
146. Zhang AY, Pham H, Ho F, Teng K, Longaker MT, Chang J. Inhibition of TGF- β -induced collagen production in rabbit flexor tendons. *J Hand Surg Am*. W.B. Saunders; 2004;29:230–5.
147. Chang J, Thunder R, Most D, Longaker MT, Lineaweaver WC. Studies in flexor tendon wound healing: neutralizing antibody to TGF-beta1 increases postoperative range of motion. *Plast Reconstr Surg*. 2000;105:148–55. [PubMed: 10626983]
148. Tang QO, Shakib K, Heliotis M, Tsiridis E, Mantalaris A, Ripamonti U, et al. TGF- β 3: a potential biological therapy for enhancing chondrogenesis. *Expert Opin Biol Ther*. Taylor & Francis; 2009;9:689–701.
149. Rys JP, Monteiro DA, Alliston T. Mechanobiology of TGF β signaling in the skeleton. *Matrix Biol*. 2016;52–54:413–25.
150. Eliasson P, Andersson T, Kulas J, Seemann P, Aspenberg P. Myostatin in tendon maintenance and repair. *Growth Factors*. 2009;27:247–54. [PubMed: 19591015]
151. Elkasrawy MN, Hamrick MW. Myostatin (GDF-8) as a key factor linking muscle mass and bone structure. *J Musculoskelet Neuronal Interact*. 2010;10:56–63. [PubMed: 20190380]
152. Mendias CL, Lynch EB, Gumucio JP, Flood MD, Rittman DS, Van Pelt DW, et al. Changes in skeletal muscle and tendon structure and function following genetic inactivation of myostatin in rats. *J Physiol*. Wiley-Blackwell; 2015;593:2037–52.
153. Mendias CL, Bakhurin KI, Faulkner JA. Tendons of myostatin-deficient mice are small, brittle, and hypocellular. *Proc Natl Acad Sci U S A*. National Academy of Sciences; 2008;105:388–93.
154. Heinemeier KM, Olesen JL, Schjerling P, Haddad F, Langberg H, Baldwin KM, et al. Short-term strength training and the expression of myostatin and IGF-I isoforms in rat muscle and tendon: differential effects of specific contraction types. *J Appl Physiol*. 2007;102:573–81. [PubMed: 17038487]
155. McPherron AC, Lawler AM, Lee S-J. Regulation of skeletal muscle mass in mice by a new TGF- β superfamily member. *Nature*. 1997 p. 83–90.
156. Lee S-J. Regulation of Muscle Mass By Myostatin. *Annu Rev Cell Dev Biol*. 2004;20:61–86. [PubMed: 15473835]
157. Hamrick MW, McPherron AC, Lovejoy CO, Hudson J. Femoral morphology and cross-sectional geometry of adult myostatin- deficient mice. *Bone*. 2000;27:343–9. [PubMed: 10962344]
158. Elkasrawy M, Immel D, Wen X, Liu X, Liang LF, Hamrick MW. Immunolocalization of Myostatin (GDF-8) following musculoskeletal injury and the effects of exogenous Myostatin on muscle and bone healing. *J Histochem Cytochem*. 2012;60:22–30. [PubMed: 22205678]
159. Hamrick MW, McPherron AC, Lovejoy CO. Bone Mineral Content and Density in the Humerus of Adult Myostatin-Deficient Mice. *Calcif Tissue Int*. 2002;71:63–8. [PubMed: 12060865]
160. Grobet L, Royo Martin LJ, Poncelet D, Pirottin D, Brouwers B, Riquet J, et al. A deletion in the bovine myostatin gene causes the double-muscling phenotype in cattle. *Nat Genet*. 1997;17:71–4. [PubMed: 9288100]
161. McPherron AC, Lee SJ. Double muscling in cattle due to mutations in the myostatin gene. *Proc Natl Acad Sci U S A*. 1997;94:12457–61. [PubMed: 9356471]
162. Bellinge RHS, Liberles DA, Iaschi SPA, O'Brien PA, Tay GK. Myostatin and its implications on animal breeding: a review. *Anim Genet*. 2005;36:1–6. [PubMed: 15670124]
163. Hamrick MW. Increased bone mineral density in the femora of GDF8 knockout mice. *Anat Rec*. 2003;272A:388–91.
164. Hamrick MW, Shi X, Zhang W, Pennington C, Thakore H, Haque M, et al. Loss of myostatin (GDF8) function increases osteogenic differentiation of bone marrow-derived mesenchymal stem cells but the osteogenic effect is ablated with unloading. *Bone*. 2007;40:1544–53. [PubMed: 17383950]
165. Elkasrawy M, Fulzele S, Bowser M, Wenger K, Hamrick M. Myostatin (GDF-8) inhibits chondrogenesis and chondrocyte proliferation in vitro by suppressing Sox-9 expression. *Growth Factors*. 2011;29:253–62. [PubMed: 21756198]

166. Wallner C, Jaurich H, Wagner JM, Becerikli M, Harati K, Dadras M, et al. Inhibition of GDF8 (Myostatin) accelerates bone regeneration in diabetes mellitus type 2. *Sci Rep.* 2017;7:1–11. [PubMed: 28127051]
167. Kellum E, Starr H, Arounleut P, Immel D, Wenger K, Hamrick MW. Myostatin (GDF-8) Deficiency Increases Fracture Callus Size, Sox-5 Expression, and Callus Bone Volume. *Bone.* 2009;44:17–23. [PubMed: 18852073]
168. Hamrick MW, Arounleut P, Kellum E, Cain M, Immel D, Liang L. Recombinant Myostatin (GDF-8) Propeptide Enhances the Repair and Regeneration of both Muscle and Bone in a Model of Deep Penetrant Musculoskeletal Injury Mark. *J Trauma.* 2010;69:579–83. [PubMed: 20173658]
169. Rosen V. BMP2 signaling in bone development and repair. *Cytokine Growth Factor Rev.* 2009;20:475–80. [PubMed: 19892583]
170. Sakou T. Bone morphogenetic proteins: From basic studies to clinical approaches. *Bone.* 1998;22:591–603. [PubMed: 9626397]
171. Urist MR. Bone: Formation by autoinduction. *Science (80-).* 1965;150:893–9.
172. Wozney JM, Rosen V, Celeste AJ, Mitsock LM, Whitters MJ, Kriz RW, et al. Novel regulators of bone formation: molecular clones and activities. *Science (80-).* 1988;242:1528–34.
173. Hogan BLM. Bone morphogenetic proteins: multifunctional regulators of vertebrate development. *Genes Dev.* 1996;10:1580–94. [PubMed: 8682290]
174. Onishi T, Ishidou Y, Nagamine T, Yone K, Imamura T, Kato M, et al. Distinct and overlapping patterns of localization of bone morphogenetic protein (BMP) family members and a BMP type II receptor during fracture healing in rats. *Bone.* 1998;22:605–12. [PubMed: 9626398]
175. Tsuji K, Bandyopadhyay A, Harfe BD, Cox K, Kakar S, Gerstenfeld L, et al. BMP2 activity, although dispensable for bone formation, is required for the initiation of fracture healing. *Nat Genet.* 2006;38:1424–9. [PubMed: 17099713]
176. Welch RD, Jones AL, Bucholz RW, Reinert CM, Tjia JS, Pierce WA, et al. Effect of recombinant human bone morphogenetic protein-2 on fracture healing in a goat tibial fracture model. *J Bone Jt Surg.* 1998;13:1483–90.
177. White AP, Vaccaro AR, Hall JA, Whang PG, Friel BC, McKee MD. Clinical applications of BMP-7/OP-1 in fractures, nonunions and spinal fusion. *Int Orthop.* 2007;31:735–41. [PubMed: 17962946]
178. Gautschi OP, Frey SP, Zellweger R. Bone morphogenetic proteins in clinical applications. *ANZ J Surg.* 2007;77:626–31. [PubMed: 17635273]
179. Ronga M, Fagetti A, Canton G, Pausco E, Surace MF, Cherubino P. Clinical applications of growth factors in bone injuries: Experience with BMPs. *Injury.* Elsevier Ltd; 2013;44:S34–9.
180. Chen X, Yin Z, Chen JL, Shen WL, Liu HH, Tang QM, et al. Force and scleraxis synergistically promote the commitment of human ES cells derived MSCs to tenocytes. *Sci Rep.* 2012;2:1–9.
181. Kopf J, Petersen A, Duda GN, Knaus P. BMP2 and mechanical loading cooperatively regulate immediate early signalling events in the BMP pathway. *BMC Biol.* 2012;10:1–12. [PubMed: 22214525]
182. Eliasson P, Fahlgren A, Aspenberg P. Mechanical load and BMP signaling during tendon repair: A role for follistatin? *Clin Orthop Relat Res.* 2008;466:1592–7. [PubMed: 18421531]
183. Chamberlain CS, Lee J-S, Leiferman EM, Maassen NX, Baer GS, Vanderby R, et al. Effects of BMP-12-releasing sutures on Achilles tendon healing. *Tissue Eng Part A.* Mary Ann Liebert, Inc; 2015;21:916–27.
184. Gelberman RH, Linderman SW, Jayaram R, Dikina AD, Sakiyama-Elbert S, Alsberg E, et al. Combined Administration of ASCs and BMP-12 Promotes an M2 Macrophage Phenotype and Enhances Tendon Healing. *Clin Orthop Relat Res.* Springer New York; 2017;475:2318–31.
185. Zhang K, Asai S, Hast MW, Liu M, Usami Y, Iwamoto M, et al. Tendon mineralization is progressive and associated with deterioration of tendon biomechanical properties, and requires BMP-Smad signaling in the mouse Achilles tendon injury model. *Matrix Biol.* NIH Public Access; 2016;52–54:315–24.

186. Klatte-Schulz F, Pauly S, Scheibel M, Greiner S, Gerhardt C, Hartwig J, et al. Characteristics and stimulation potential with BMP-2 and BMP-7 of tenocyte-like cells isolated from the rotator cuff of female donors. *PLoS One*. 2013;8:1–13.
187. Blitz E, Sharir A, Akiyama H, Zelzer E. Tendon-bone attachment unit is formed modularly by a distinct pool of Scx - and Sox9 -positive progenitors. *Development*. 2013;140:2680–90. [PubMed: 23720048]
188. Blitz E, Viukov S, Sharir A, Shwartz Y, Galloway JL, Pryce BA, et al. Bone Ridge Patterning during Musculoskeletal Assembly Is Mediated through SCX Regulation of Bmp4 at the Tendon-Skeleton Junction. *Dev Cell*. 2009;17:861–73. [PubMed: 20059955]
189. Lui PPY, Wong YM, Rui YF, Lee YW, Chan LS, Chan KM. Expression of chondro-osteogenic BMPs in ossified failed tendon healing model of tendinopathy. *J Orthop Res*. 2011;29:816–21. [PubMed: 21520255]
190. Rui YF, Lui PPY, Ni M, Chan LS, Lee YW, Chan KM. Mechanical loading increased BMP-2 expression which promoted osteogenic differentiation of tendon-derived stem cells. *J Orthop Res*. 2011;29:390–6. [PubMed: 20882582]
191. Hannallah D, Peng H, Young B, Usas A, Gearhart B, Huard J. Retroviral delivery of Noggin inhibits the formation of heterotopic ossification induced by BMP-4, demineralized bone matrix, and trauma in an animal model. *J Bone Joint Surg Am*. 2004;86-A:80–91. [PubMed: 14711949]
192. Lui PPY, Chan LS, Cheuk YC, Lee YW, Chan KM. Expression of bone morphogenetic protein-2 in the chondrogenic and ossifying sites of calcific tendinopathy and traumatic tendon injury rat models. *J Orthop Surg Res. BioMed Central*; 2009;4:27.
193. Shore EM, Xu M, Feldman GJ, Fenstermacher DA, Cho T-J, Choi IH, et al. A recurrent mutation in the BMP type I receptor ACVR1 causes inherited and sporadic fibrodysplasia ossificans progressiva. *Nat Genet*. 2006;38:525–7. [PubMed: 16642017]
194. Yu PB, Deng DY, Lai CS, Hong CC, Cuny GD, Bouxsein ML, et al. BMP type I receptor inhibition reduces heterotopic ossification. *Nat Med*. 2008;14:1363–9. [PubMed: 19029982]
195. Kaplan FS, Le Merrer M, Glaser DL, Pignolo RJ, Goldsby RE, Kitterman JA, et al. Fibrodysplasia ossificans progressiva. *Best Pract Res Clin Rheumatol*. 2008;22:191–205. [PubMed: 18328989]
196. Han W, He W, Yang W, Li J, Yang Z, Lu X, et al. The osteogenic potential of human bone callus. *Sci Rep* [Internet]. Nature Publishing Group; 2016 [cited 2018 Nov 29];6:36330 Available from: <http://www.nature.com/articles/srep36330>

Figure 1.

Histological images of BMP-2 localization in (A) healthy adult iliac crest, as well as (B) early stage and (C) medium stage callus formation following human long bone fracture. Scale bar (for panels A–B) = 200 μ m. BMP-2 positive cells are not observed in (D) healthy tendon, but expression of BMP-2 increases with tendinopathy, as shown by brown staining at (E) 2-, (F) 4-, (G) 8-, (H) 12-, and (J) 16-week following tendon injury (50 μ m scale bar for D–I). Arrowheads in G,H, and I highlight chondrocyte-like cells; triangles in I highlight marrow-like cells; empty triangles in I highlight blood vessels; CR = calcified/ossified regions; Used with permission from Liu et al.[189] and Han et al. [196] under Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>).

BMP2 immunohistochemistry in bone fracture callus

Pathological tendon healing that resembles bone formation

Figure 2.

Many of the biological pathways of tendon and bone healing are similar and suggest the potential for crosstalk in the healing/regenerative stages. Specific growth factors described in this review include TGF β , IGF, myostatin, and BMP and their influence on the structure and properties of healing tendon and bone.