Remodeling and Repair of Orthopedic Tissue: Role of Mechanical Loading and Biologics

Part II: Cartilage and Bone

Abstract
Orthopedic tissues respond to mechanical loads to maintain normal homeostasis and in response to injury. As this body of work continues to grow, it is important to synthesize the recent studies across tissues and specialties with one another and with past studies. Hence, this review highlights the knowledge gained since 2000, with only few exceptions, concerning the effects of mechanical load and biologics on remodeling and repair of orthopedic tissue.

This review is separated into 4 sections: tendon and ligament, meniscus, cartilage, and bone. Each section begins with a brief anatomical description, followed by discussions of remodeling and repair, and concluding with a concise presentation of information regarding repair enhancement through biologics. In addition to summarizing recent work, this review provides insights for future directions and, through the combined discussion of mechanics and biologics, opportunities for translation to clinical use. This is Part II of a 2-part series, and will discuss cartilage and bone. Part I (tendon and ligament and meniscus) appeared in the November 2010 issue.

Cartilage
Anatomy
Cartilage is primarily composed of cells, collagen, proteoglycans, and water. The orientation of collagen fibrils varies throughout the tissue, making cartilage inhomogeneous and anisotropic. Superficial fibrils are oriented parallel to the tissue surface, while deep fibrils are oriented in a more perpendicular direction. These deep vertical fibrils are anchored firmly into the subchondral bone and play an important role in supporting and protecting the tissue. However, the integrity of the superficial fibrils is critical for tissue maintenance and is more vulnerable to damaging compressive loads.

Despite the tissue complexity, cartilage mechanics have been relatively well characterized through experimental and theoretical models. The dynamic stiffness of cartilage is primarily due to flow-dependent viscoelasticity. Fixed negatively charged proteoglycans attract water from the synovial fluid creating an osmotic pressure that stresses and stiffens the collagen network. Tissue permeability depends on collagen pore size and proteoglycan fixed charge density and is both depth- and strain-dependent. Fibril-reinforced poroviscoelastic swelling models have shown faster fluid flow with stiffer collagen networks and higher permeability in the superficial zone compared to the deep zone. Recently, depth-dependent cellular deformations have been described by a model with arcade-like collagen orientation and depth-dependent fixed charge density.

The pericellular matrix (PCM) is the portion of the more general extracellular matrix (ECM) immediately surrounding each cell.
surrounding the chondrocytes and may play an important protective role in regulating the local stress-strain and fluid-flow microenvironments of the chondrocytes. The modulus of the PCM is between that of the ECM and chondrocytes, thereby allowing a more gradual mechanical transition. Furthermore, the modulus of the PCM is not depth-dependent, while the modulus of the ECM increases from the superficial to the deep layer. This mismatch of moduli amplifies chondrocyte compressive strains and results in their depth-dependent stress shielding.

Remodeling

Proper dynamic loading and fluid exchange with the synovial fluid are important in maintaining cartilage homeostasis. Unloading, overloading, and static loading are each injurious to cartilage, which can affect matrix synthesis and cell viability. Immobilization decreases proteoglycan synthesis and thins and softens cartilage. Severe impact or overloading can induce cartilage degeneration, while static loading inhibits matrix synthesis. Moreover, injurious loading increases chondrocyte apoptosis, which is closely related to osteoarthritis. Still, a report finding no correlation between apoptosis and different loading levels in human cartilage indicates the need for further studies in this area.

Several in vitro studies have been conducted to find appropriate physiologic loading parameters. Loads in the range of 15 to 20 MPa have been shown to cause cell death, reduced proteoglycan synthesis, and matrix damage along with cell swelling. In a bovine model, more than 50% of chondrocytes underwent apoptosis due to peak stresses above 20 MPa. In human cartilage, however, increased peak stress did not appear to be related to glycosaminoglycan loss. With regard to loading rates, high strain rates are related to chondrocyte death and matrix damage, especially in the superficial zone, while low strain rates are related to cell death nearly throughout the tissue depth.

Repair

It is unclear whether chondrocytes have the biosynthetic capability to potentially repair the matrix after injury, but it is evident that the repair response in cartilage is extremely poor. Cartilage is avascular, and therefore there is no inflammatory repair process similar to that typically seen in other tissues. Damage to the ECM disrupts transduction of physical signals, and chondrocytes do not significantly respond to injury. Cartilage laceration causes cell death in the vicinity of wound edge, while any surviving chondrocytes function normally and are unchanged. Therefore, excision, débridement, shaving, and laser abrasion procedures are biologically purely detrimental. Nevertheless, less cell death is possible with sharper, more precise instruments.

Biologic Enhancement

Several repair techniques (eg, chondroplasty, drilling, microfracture) involve subchondral bone exposure to provide a blood supply from the underlying marrow. This recruits mesenchymal stem cells and multiple growth factors to the injury site. However, the biomechanical properties and long-term durability of fibrocartilagenous repair tissue are inferior to those of hyaline cartilage. Current experimental techniques for biologic enhancement include transplantation or implantation of cells and tissues with chondrogenic potential. Autologous osteochondral transplantation (mosaicplasty) is indicated for small- to medium-sized defects with good to excellent clinical results and survival of transplanted tissue after long-term follow-up. In contrast, autologous chondrocyte implantation (ACI) is a more nascent approach with contradictory findings. Authors of one study observed inferior fibrocartilagenous healing with ACI versus hyaline cartilaginous healing in mosaicplasty, while authors of another report improved results. Further improvements in cartilage repair are also possible through administration of various growth factors, pulsed electromagnetic fields, hyaluronic acid, and necrosis (necrostatin 1) or apoptosis (Z-VAD-FMK) inhibitors. While these techniques are not yet ready for widespread use, they represent promising translational treatments for the near future.

Bone Anatomy

Bone is composed of a calcified collagenous matrix with dense cortical bone and more vacuous trabecular bone.
Cortical bone is a highly organized material consisting of osteons, which are microscopic canals surrounded by concentric rings of dense lamellar bone. Trabecular bone is a network of interconnecting solid plates and rods surrounded by bone marrow. Both forms of bone are highly responsive to mechanical loading and align along the local directions of principal stresses. Osteocytes reside in lacunae within the calcified matrix and are interconnected via gap junctions throughout the lacunar-canalicular system (LCS) with other osteocytes, bone lining cells, and osteoblasts, thereby regulating their activity.30 This regulation may occur at the whole-bone level or locally, since one osteoblast is rarely connected with several osteocytes at the same time.31

Osteocytes are the main effector of tissue response to loading due to their abundance in bone and sensitivity to fluid flow within the LCS, which also serves as a nutritional transport mechanism.32 Interestingly, osteocytes experience a 1000-fold higher hydraulic pressure than osteoblasts do.33 Further, osteocytes can change their mechanosensitivity to accommodate to the strain environment through cytoskeletal reorganization34 and can move their bodies and dendritic processes to modify their local environment35 (Figure 1). Additionally, cilia may play a role in osteocyte mechanosensation.36

Remodeling
The initial stimulus for functional remodeling is not fully clear, but osteocyte apoptosis is one candidate. Physiologic strains inhibit osteocyte apoptosis,37 whereas elevated strain levels induce osteocyte apoptosis triggering osteoclastic bone removal.38 Alternatively, bone remodeling may be initiated by microdamage,39 which could also be related to osteocyte apoptosis through direct cellular trauma or due to a ruptured LCS. Even without microdamage, osteocyte syncytium can be disrupted by high cyclic strains, thereby influencing remodeling.40 These load-induced adaptive changes are necessary to prevent the accumulation and coalescence of microcracks, which may lead to fatigue fracture.

Since Wolff described skeletal adaptation to load bearing,41 scientists have been trying to identify specific loading parameters that govern this process. Notably, dynamic, as opposed to static, loading promotes bone remodeling. Specifically, low-magnitude and high-frequency vibration stimulates anabolism in bone.42,43 However, increasing frequency does not have a simple dose–response relationship with remodeling. For example, load-induced cortical bone adaptation in a mouse model increases with increasing loading frequency up to 5 to 10 Hz and then plateaus.44 Furthermore, loading applied in discrete bouts separated by recovery periods is more effective than continuous cyclic load. Inserting a period of hours35 or even seconds46 of rest between loading periods improved bone mechanics. These data suggest that bone cells need recovery periods and rest for resensitization, though the exact mechanism and optimal recovery times are unknown.

Like supraphysiologic strains, unloading or disuse also induces osteocyte apoptosis and recruits osteoclasts. However, in contrast to elevated loading, this leads to bone loss rather than deposition.47 A possible reason for this discrepancy is a difference in fluid flow. Fluid stasis occurs at the front of the cutting cone, where osteoclasts are active, and strong fluid flow exists along the wall of the resting zone and closing cone, where osteoblasts are active, thus supporting the concept that fluid flow is essential to osteocyte-mediated remodeling.48
Mechanical loading, as well as fracture fixation and interfragmentary motion, can affect bone healing. Mechanoregulation models have demonstrated that high levels of shear strain and fluid flow deform precursor cells, thereby stimulating formation of fibrous connective tissue. Lower levels of shear strain lead to cartilage formation, and even lower levels result in ossification, as summarized in Figure 2. Hence, stable fixation of a fracture can lower shear strains and fluid flow, thereby preventing fibrous connective tissue production in the callus, which otherwise could lead to a nonunion. In fracture treatment, absolute rigid fixation is impossible, and most healing results from indirect, endochondral bone formation and interfragmentary motion. However, the optimal amount of motion is unknown and is contradictory in some studies. In particular, the ideal amount of micromotion may differ with anatomical site, fracture pattern, and gap. Nevertheless, since some motion is believed to be beneficial, the trend in fracture treatment is toward semirigid fixation.

Bone healing is also highly dependent on the direction of load. Shear forces on bone healing may create abundant cartilaginous callus, produce pseudarthrosis, or result in poor healing. Conversely, torsional shear may stimulate intercortical mineralized callus formation. Compressive loading, but not tensile load, is generally thought to be beneficial for bone healing. Interestingly, tensile strains may promote endochondral ossification, whereas compressive strains may suppress chondrogenesis and promote direct intramembranous bone healing.

While several clinical studies have demonstrated the anabolic effects of cyclic loading on bone remodeling, as mentioned in the previous section, similar investigations on bone healing have been limited to animal models. One study has shown a negative effect on bone healing, though multiple studies report acceleration and augmentation of endochondral healing. Despite the inability to relate postinjury time points between animals and humans directly, authors of most animal studies agree that the early stage of fracture healing is most sensitive to loading. In the early inflammatory phase, a short delay before loading improved bone healing, possibly due to increased angiogenesis within the callus. Additionally, inserting a pause during loading can enhance bone healing.

Biologic Enhancement
Numerous cytokines, growth factors, and hormones are involved in fracture healing, but their roles generally are not well elucidated. As a result, this review focuses only on factors approved for clinical use—namely, bone morphogenetic proteins 2 and 7 (BMP-2, BMP-7) and parathyroid hormone (PTH).

Since Urist’s landmark discovery of auto-osteogenic materials related to bone regeneration and repair, 17 BMPs have been identified. As members of the TGF- superfamily, BMPs activate intracellular signaling cascades via serine/threonine protein kinase-coupled receptors, and most BMPs (except BMP-1, BMP-3, and BMP-12) play a role in activating alkaline phosphatase in osteoblastic cells. Of the various BMPs, only BMP-2 and BMP-7 are used clinically in fracture treatment and spinal fusion. BMP-2 reduces the rate of infection and accelerates healing better than conventional treatment in open tibial fractures. Further, it exhibits good results as an alternative to autogenous bone grafts in the treatment of tibial fractures with large defects. BMP-7 (osteogenic protein 1) is safe and effective in the treatment of nonunions of long bones and in the treatment of proximal pole scaphoid nonunions.

In the spine, BMP-7 leads to improved fusion rates and clinical outcomes without complications in the treatment of degenerative spondylolisthesis, as well as in revision surgery for patients at high risk for nonunion. BMP-2 also provides good clinical and radiologic outcomes in posterolateral lumbar fusion compared with autograft and improves patient satisfaction by eliminating the need for harvesting an iliac crest bone graft. In addition, anterior lumbar interbody fusion with BMP-2 had better outcomes compared with autograft. While BMP-2 treatment has not been shown to be more effective or safer than standard treatment for pyogenic vertebral osteomyelitis—such as débridement, use of intravenous antibiotics, and circumferential fusion—use of BMP-2 has shown good clinical results without adverse effects.

BMP use also has been associated with a few complications, including heterotopic ossification and neck swelling after anterior cervical spine fusion. Heterotropic ossification was reported in an intramuscular lesion of the triceps after treatment of a humerus nonunion with BMP-7 and in 4 cases of humerus open fractures or nonunion treatments with BMP-2 or BMP-7. In the lumbar spine, heterotopic ossification was observed with BMP-2 treatment in the iliopsoas and surrounding the spinal cord after posterior fusion. Despite similar clinical outcomes between autograft and BMP-2 com-
bined with allograft in anterior cervical discectomy and fusion, BMP-2-treated groups exhibited increased neck swelling (compared to controls) that may cause dysphagia, dyspnea, and dysphonia.\textsuperscript{81} However, in a mouse study, -2-HS glycoprotein, an antagonist of cytokine binding to TGF-\textsuperscript{-} receptors, was found to regulate osteoinductive effects of BMP\textsuperscript{82} and therefore may be useful to control heterotopic ossification.

Intermittent systemic administration of PTH (1-34) is clinically approved to increase bone mineral density and reduce fracture risk in patients with osteoporosis.\textsuperscript{83} Biologically, PTH increases the number of osteoblasts in nonfractured bone.\textsuperscript{84} Additionally, authors of several animal studies have reported that intermittent PTH (1-34) dosing has an anabolic effect on fractured bone as well. For example, PTH (1-34) enhanced fracture healing in a rat model through stimulation of early proliferation and differentiation of osteoprogenitor cells.\textsuperscript{85} Other data show that endochondral ossification is stimulated through chondrogenesis by PTH (1-34).\textsuperscript{86,87} Noninvasive systemic drug delivery of PTH for fracture healing is very attractive but requires a randomized, controlled clinical study to truly demonstrate effectiveness.

**Conclusion**

While orthopedic tissues in general exhibit a significant response to mechanical loading, the nature and magnitude of this response vary greatly, both between and within, tissue types. Bone is extremely sensitive to loading and consequently inspired the connection between form and function embodied by Wolff’s law. However, it is becoming increasingly evident that many other tissues with far slower metabolic activity potentials are subject to the same principles. In essence, nearly all orthopedic tissues benefit from moderate levels of loading, whereas insufficient or excessive loading is detrimental. The optimal amount of load has been elusive to determine and, not surprisingly, depends greatly on tissue structure, resident cell types, vasculature, anatomical location, repair status, et cetera. Furthermore, while this area of research has become ever more cross-disciplinary, the combined effects of mechanical loading and biologics have been largely unexplored. Many studies have analyzed the contributions of specific mechanical loading parameters to remodeling and repair, while others have focused on repair augmentation through biologics. Although this is necessary to limit experimental size and complexity, synergistic behavior between mechanics and biology is not unexpected and should be investigated.

**Authors’ Disclosure Statement**

The authors report no actual or potential conflict of interest in relation to this article.

**References**