Mechanical Loading: Potential Preventive and Therapeutic Strategy for Osteoarthritis

Osteoarthritis (OA) is an age-related degenerative disease of the joint, with a hallmark of cartilage degradation. No cure or treatment currently exists that offers disease- or symptom-modifying effects. OA is a leading cause of disability, affecting more than 27 million Americans, and it is a significant economic burden.

Mechanical loading is an extremely important factor for cartilage homeostasis. Although both underuse (eg, physically inactive lifestyle) and overuse (eg, high-impact or intense repetitive joint use) are risk factors for cartilage degradation, recent studies highlight that moderate dynamic loading is not only associated with a healthy lifestyle, but it also is a very important potential preventive and therapeutic strategy for OA by suppressing inflammation, inhibiting catabolic mediators, and enhancing anabolic activity through as-yet underexplored mechanotransduction pathways.

Anti-catabolic and Anabolic Effects of Moderate Mechanical Loading

Recent studies have demonstrated that moderate dynamic loading exerts potent anti-inflammatory effects through suppression of proinflammatory cytokines (eg, interleukin [IL]-1β, IL-6, tumor necrosis factor [TNF]-α) and inflammatory mediators (eg, cyclooxygenase-2 [COX-2], prostaglandin E2 [PGE2], nitric oxide [NO]), enhancement of anti-inflammatory signaling (eg, IL-4, IL-10), and a reduction in the activity of matrix-degrading enzymes (eg, matrix metalloproteinases [MMPs], a disintegrin and metalloproteinase with thrombospondin motifs [ADAMTS]).

In vitro studies indicate that moderate dynamic loading reduces IL-1β- or TNF-α–induced proinflammatory gene expression, including COX-2 and IL-1β, and catabolic enzymes such as MMPs. In vivo, gentle range-of-motion exercises have been shown to mitigate joint inflammation in animal models of antigen-induced arthritis and to suppress the expression of proinflammatory and catabolic mediators. An exercise program for patients with OA that combined aerobics and strength training led to decreases in plasma inflammatory cytokine IL-6. Furthermore, in vitro dynamic compression of chondrocytes seeded in hydrogels has been reported to increase expression of type II collagen, a major structural cartilage extracellular matrix protein. Of note, age may be an important factor in the chondrocyte-anabolic response to mechanical loading. Chondrocytes isolated from juvenile (ie, 3 weeks old) bovine cartilage increased total sulfated glycosaminoglycan (sGAG) production almost three times as much as did chondrocytes isolated from adult animals (ie, 2 to 3 years old).

Mechanotransduction of Chondroprotection

Elucidation of these mechanosensitive mechanisms may lead to the development of novel therapeutics to pharmacologically mimic the chondroprotective effects of moderate mechanical loading. Although mechanotransduction pathways underlying chondroprotection are not well...
understood, recent studies have shown that biomechanical signals inhibit multiple steps in the IL-β–induced cascade downstream of IκB kinase activation, regulating IκB-α and IκB-β degradation and synthesis and promoting IκB-α shuttling to export nuclear NF-κB and terminate its transcriptional activity.\textsuperscript{12} Furthermore, induced by dynamic moderate loading, such as joint motion and joint loading in the lateral/medial direction in vivo,\textsuperscript{5,13} and by moderate fluid shear and intermittent hydrostatic pressure in vitro,\textsuperscript{5,14} transactivated transcriptional factor CITED2 leads to the suppression of MMPs, at least in part through competition with MMP transactivator Ets-1 for binding to coactivator p300.\textsuperscript{2,27} Moreover, transient receptor potential vanilloid 4 (TRPV4), a Ca\textsuperscript{2+}-preferred membrane ion channel, acts as a transducer for loading-induced chondrocyte matrix biosynthesis. TRPV4 inhibition prevented the regulation of pro-anabolic and anti-catabolic by mechanical loading. Further, chemical activation of TRPV4 in the absence of loading mimicked the effects of moderate loading by enhancing chondrocyte anabolic activity and suppressing catabolic expression.\textsuperscript{15} In addition to calcium signaling, proteins such as integrins and primary cilium have been suggested to be mechanotransducers of mechanical stimuli to initiate anti-catabolic and anti-inflammatory signals involved in cartilage homeostasis.\textsuperscript{16,17}

**References**


