The role of inflammation on subchondral bone adaptation in post-traumatic osteoarthritis

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Abstract

Inflammation is believed to play a key role in osteoarthritis (OA). However, the etiology is still largely unknown. In this study we focus on post-traumatic OA, where OA is triggered by a joint injury. What is interesting from a modeling perspective is that the starting point is well defined, i.e. the time of the injury. Data from PTOA animal models (Goetz et al., 2015) show an acute inflammatory response in the joint at the time of injury, which slowly subsides to moderate levels of chronic inflammation. The aim of this study was to evaluate possible effects of such an inflammatory response on the subchondral bone over time using a mechanobiological computational framework. This is important as changes in the subchondral bone typically occur before the degeneration of cartilage, which suggests that subchondral bone may be key for the onset and early development of the disease.
Typical subchondral bone development in OA follows the following pattern: In early OA, there is increased remodeling resulting in thinning of the subchondral bone plate. In later stages of OA, the thickness of the subchondral bone plate instead increases and the deep articular cartilage calcifies, resulting in a thick calcified unit composed of bone and calcified cartilage. In addition, the trabecular bone volume increases while the tissue mineral density decreases.

In this study, we want to evaluate different mechanobiological mechanisms in order to predict these changes. In particular, we are interested in the following mechanisms, and the combination of them:

a) Inflammation drives bone resorption (Epsley et al., 2021).

b) Inflammation affects bone formation, resulting in decreased mineralization and tissue stiffness (Walsh et al., 2009).

c) TGFβ promotes abnormal bone formation (Hu et al., 2021).

d) Inflammation and TGFβ together promote calcification of articular cartilage (Thielen et al., 2023).

To do this, we use a well-established framework for bone remodeling (Huskies et al., 2000), which was later extended to include both calcified and articular cartilage (Cox et al., 2011). The basic idea is that osteocytes are mechanosensitive and produce a stimulus proportional

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to the strain energy density that regulates bone formation. Bone resorption occurs randomly at bone surfaces according to defined resorption rates. We combine the remodeling framework with a diffusion model describing the mass transport of inflammatory cytokines (e.g., IL-1b) and TGFβ. In this way, we can use the local concentrations of IL-1b and TGFβ as additional stimuli for bone remodeling. Inflammation is assumed to originate from the synovial fluid, where the concentration decreases over time. TGFβ is stored in the bone matrix and released locally as bone is resorbed. Both bone remodeling and mass transport are implemented in Abaqus and we solve the problems iteratively under daily loading conditions using a square 2D grid (7.5x7.5 mm2) including articular cartilage, calcified cartilage and subchondral bone. First, remodeling is simulated under healthy conditions to predict an initial bone structure in equilibrium, and then mechanisms a)-d) are introduced individually or in combination to simulate the progression of OA.

Preliminary data show that bone formation is sensitive to both loading conditions, load magnitude and tissue stiffness, with lower stiffness resulting in thicker bone structures. When inflammation-driven resorption is included, the models predict the initial thinning of the subchondral bone plate. The combination of inflammation and TGFβ also predicts articular cartilage calcification similar to patterns seen experimentally. Current work is focused on the combination and timing of different mechanisms to elucidate the mechanisms driving the alteration of subchondral bone in OA.

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