Joint trauma initiates knee osteoarthritis through biochemical and biomechanical processes and interactions

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Abstract

Introduction
Globally, knee osteoarthritis (OA) is among the top 15 causes of disability. A patient with a history of macrotrauma is more than four times as likely to develop knee OA. Macrotrauma initiates a cascade of biochemical and biomechanical changes in the joint that interact and can lead to joint failure. The purpose of this critical review is to present an overview of the early pathophysiological (i.e. biomechanical and biochemical) changes that typically occur after a knee injury and the implications of these changes for early-stage OA interventions.

Discussion
An acute knee injury is caused by a high-force event that initiates inflammatory, metabolic imbalance between anabolic and catabolic processes, tissue remodelling and biomechanical changes. The biomechanical changes include greater focal joint tissue loading, sometimes in abnormal locations; altered mechanical properties of joint tissues and increased joint shear or torsional forces—all of which potentially increase the risk of joint degeneration and inflammation from repetitive loading. Concurrently, inflammation stimulates tissue turnover, which further compromises the mechanical properties of tissues. The interactions between these biomechanical and biochemical changes propagate the path to joint failure.

Conclusion
Biomechanical and biochemical changes occur after joint trauma. To prevent OA, it may be critical to recognize the complex interactions between biochemical and biomechanical changes and implement interventions that address both.

Introduction
Knee osteoarthritis (OA) is a complex, heterogeneous joint disease that is characterized by multitissue (e.g. articular cartilage, synovium, subchondral bone, ligament) degradation1. Knee OA is one of the most common musculoskeletal diseases, affecting almost 251 million humans2. Within this population, it is particularly concerning that over 30% of patients with acute anterior cruciate ligament (ACL) or meniscal injuries develop radiographic knee OA within 5 years post-injury3, and over 50% of patients show evidence 10–20 years post-injury4. Therefore, it is important to understand why these patients develop early-onset knee OA and if this onset of knee OA can be prevented or delayed.

An acute knee injury is caused by a high-force event that initiates biochemical changes as well as biochemical cascades (e.g. inflammation and metabolic imbalances of tissue turnover) that lead to joint failure. Evidence from animal models and small human studies reveal that early interventions, which address these biochemical changes or altered joint biomechanics, may slow the progression of joint degeneration. However, if our goal is to prevent knee OA then it may be important to target both biochemical and biomechanical changes. Therefore, the purpose of this critical review is to discuss early pathophysiological (i.e. biomechanical and biochemical) changes occurring after an acute knee injury and the implications of these changes for early-stage OA interventions.

Discussion
The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964), and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

After injury, a knee will have increased inflammation and an imbalance of catabolic and anabolic processes resulting in tissue turnover, as well as altered joint biomechanics/arthrokineamtics6. Over time, repetitive abnormal joint loading and

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inflammatory mediators propagate aberrant tissue turnover, which will result in altered tissue mechanics, further exacerbating tissue damage, and lead to knee OA.

Biomechanical changes

Acute knee injuries (e.g. meniscal or ACL tears) are relatively common within athletic and physically active populations and are associated with at least four times greater likelihood of knee OA. Surgical intervention is sometimes recommended after knee injury, with the goal of correcting abnormal joint biomechanics, reducing the risk of secondary injuries, and ideally reducing the risk of knee OA. Unfortunately, surgical interventions (e.g. ACL reconstruction, meniscectomy) do not restore normal joint biomechanics or reduce the chance of knee OA.

After an injury, despite surgical intervention, the knee is exposed to new loading patterns that increase the risk of knee OA. For example, contact pressures increase and shift to regions unaccustomed to these high loads. This may be a direct result of instability induced by an injury or because a patient functions with compensatory movement strategies (e.g. decreased range of motion, greater adduction moment, lower ground reaction forces). Increased focal loading on the menisci (Figure 1), articular cartilage and subchondral bone is further confounded in the presence of other concomitant knee injuries (e.g. chondral or osteochondral lesions, fractures). If the size of the meniscus is reduced by just 10%, then contact pressures may increase 65% and double if the meniscal size is reduced by 50%. This increased focal loading can increase the risk of microtrauma from repetitive overloading, which can compromise knee joint tissues and leave them susceptible to injury and pathologic changes (e.g. lesions in epiphyseal bone marrow, changes in cartilage thickness or composition).

While microtraumatic events can occur secondary to local repetitive overloading, they may also originate during a macrotraumatic knee injury. Traumatic events are often accompanied by microtraumatic damage to the subchondral bone or cartilage, also known as a ‘bone bruise’, which is more accurately classified as osteochondral or bone marrow lesion. This may be related to acute trauma-induced microcracking of subchondral bone that can extend beyond the calcified matrix into the joint cartilage. These microcracks encourage endochondral ossification repair that can lead to further degeneration and OA-type changes, with continued loading at high cyclic strains. Post-traumatic bone marrow lesions typically resolve within 6 months after the injury in 98% of patients with ACL injuries, although a third of knees develop new bone marrow lesions during the first 2 years after knee injury. This reemergence of bone marrow lesions may reflect local microdamage or abnormal remodelling to the bone secondary to repetitive focal overloading. On the other hand, it may reflect biochemical alteration in the viscous components of synovial fluid that then reduces its viscoelasticity, impairing their ability to absorb and dissipate mechanical strain, which could lead to further cartilage damage, bone bruising and eventually OA.

In summary, a macrotraumatic knee injury is a high-force event that can create immediate macro- and microdamage, which may compromise how tissues distribute joint loads and trigger tissue degradation. Furthermore, after an injury, the abnormal joint loading increases the risk of repetitive focal overloading, which can also lead to microtrauma and abnormal tissue turnover. This leads to a vicious cycle in which compromised tissue is less able to accommodate greater focal loads, which leads to further tissue degradation and hence less ability to adapt to the abnormal loading. All of these biomechanical changes can initiate as well as propagate biochemical changes that can contribute to the negative OA sequela post-knee injury.

Biochemical changes

After joint trauma, there is a sudden increase in inflammatory mediators that resolve slowly over time. It remains unknown how long or whether they ever return to normal levels. Acute inflammation after initial trauma can disturb homeostasis throughout the joint, potentially leading to knee OA. This may initiate a metabolic crisis and an imbalance in the catabolic and anabolic processes. Proinflammatory biochemical markers (e.g. interleukin-1β [IL-1β], tumour necrosis factor-α) increase in the synovial fluid and stimulate catabolic processes.

Figure 1: Joint contact forces (arrows) and meniscus (indicated in blue).
new blood vessel formation (angiogenesis), osteophyte formation and expression of catabolic enzymes (e.g. matrix metalloproteinases [MMPs] 2 and 3, a disintegrin and metalloproteinase with thrombospondin motifs), which breakdown the components of articular cartilage extracellular matrix (e.g. proteoglycans and collagen)29.

There is evidence of a biosynthetic attempt to control proinflammatory and catabolic events as evidenced by increased tissue inhibitor of MMPs (TIMP)-1, TIMP-2 and IL-10 in synovial fluid of patients with OA (Figure 2)20,21. Despite an attempt to re-establish homeostasis, the catabolic pathways lead to increased extracellular matrix permeability and increased water content in articular cartilage2, thus pathologically altering the biochemical and biomechanical properties of the articular cartilage. In this new environment, chondrocytes (the only cells within healthy cartilage) stimulate additional cartilage degeneration and neovascularization, which establishes the conditions for the deep regions of articular cartilage to ossify. As the cartilage composition changes, the bone also begins to adapt to the new biochemical conditions. For example, angiogenesis and catabolic pathways contribute to early subchondral bone remodelling and osteophyte formation. Bone remodelling has been seen in ACL patients, with sclerotic bone changes occurring 3–4 years post-ACL reconstruction surgery, and the formation of osteophytes in 50% of ACL reconstruction patients 3 years post-surgery.3,16 Osteoblasts in sclerotic bone are known to increase the production of MMP-13 and osteopontin, compared with non-sclerotic bone, which is of interest since elevated markers of bone turnover (osteonectin, osteonectin) are found up to 1 month post-injury in synovial fluid.24 The osteoblasts of sclerotic bone also increase VEGF production, a key player in the development of OA changes25.

Meanwhile, fragments from the articular cartilage (e.g. fibronectin fragments) enter the synovial fluid and stimulate catabolic pathways within the articular cartilage and synovium, and that serve as chemoattractants for activated macrophages into the joint that release inflammatory cytokines. Therefore, a single traumatic event, independent of subsequent focal repetitive overloading, could initiate a catabolic inflammatory cascade, in which inflammatory mediators stimulate abnormal tissue remodelling and damage. This cascade then generates fragments that propagate inflammation and further joint catabolism, a process that may be further complicated by repetitive focal overloading, as described above.

Biochemical–biomechanical interaction
A macrotraumatic event may trigger an acute episode of inflammation, altered joint loading, and compromise the structural integrity of tissues. Each of these three conditions may increase the risk of knee OA. In fact, elevated markers of cartilage turnover (e.g. aggrecan) have been found up to 1 month post-injury24 and are still present within synovial fluid 1 year post-ACL reconstruction surgery.5 The inflammatory and cartilage turnover markers have also not returned to normal health levels up to 1 year post-injury.5,26 These elevated biochemical markers may indicate that the joint tissues are still structurally or biochemically compromised and not ready to sustain full biomechanical loads. However, despite evidence that the joint may need longer time periods to recover, many patients return to full function by 1 year post-ACL reconstruction. This return to preinjury activities, combined with lingering structural insufficiencies and inflammatory responses, could increase the vulnerability of the knee to OA.

Compromised structural integrity, altered joint loading and inflammation may form a dangerous cycle.

**Figure 2:** Osteoarthritis pathomechanisms in knee injury. Green boxes indicate biochemical changes (e.g. increased IL-1β, MMP-3, MMP-13, IL-10, TIMP-1, TIMP-2, VEGF). Blue triangles indicate biomechanical changes (e.g. decreased range of motion, microtrauma, compensatory gait changes).
that increases the risk of knee OA. Abnormal structural integrity may alter how joint loads are distributed through the joint and stimulate inflammation (e.g. fragments from degraded cartilage may agitate synovium and cartilage). Likewise, abnormal joint loading exposes focal regions to abnormally high loads, which increases the risk of abnormal structural integrity (e.g. bone marrow lesions, cartilage degradation) and local inflammatory responses, described above. Furthermore, inflammation is associated with pain and functional limitations that may contribute to compensatory movement strategies, which lead to abnormal joint loading. Inflammation can also stimulate complex tissue remodelling in all joint tissues including bone (e.g. osteophytes), synovium (e.g. angiogenesis) and articular cartilage (e.g. degradation, ossification).

The relationship between structural integrity, abnormal loading and inflammation may be more than a simple interaction. In the repetitive rat model, localized inflammation occurs immediately in bone and joint tissues and remains elevated for 5 or 12 weeks, depending on the level of inducing injury\textsuperscript{27}. The inflammatory response was matched by exposure-dependent structural changes in the skeletal tissues, such as adaptive bone remodelling with performance of a low-force task but degradative bone and cartilage changes with a high-force task\textsuperscript{27,28}. When ibuprofen treatment, at anti-inflammatory levels, was administered early during the inflammatory period, a reduction in inflammatory cytokines was observed in the loaded joint tissues\textsuperscript{27}. Eight weeks of ibuprofen treatment also reduced structural cartilage damage and chondrocyte apoptosis, despite continued performance of the high-force task. This indicates that inflammatory biochemical changes were contributing to the structural changes, and therefore an interaction between biomechanical and biochemical processes in joint destruction.

**Biochemical and biomechanical interventions after joint trauma**

Many investigators have suggested that early intervention is critical to the development of disease-modifying OA interventions. Investigators have demonstrated that conducting an intervention study in an early ACL cohort is feasible\textsuperscript{29}. Various surgeries have been proposed to address the biomechanical changes after an injury (e.g. ACL reconstruction, meniscal repair). Unfortunately, they have not been successful at restoring normal joint mechanics or preventing knee OA\textsuperscript{30}. Newer ACL reconstruction techniques and meniscal implants may help reduce OA risk, but it is unclear if they will be effective on their own. To address the biochemical changes, it may be advantageous if biochemical interventions (e.g. anti-inflammatories) are initiated early after trauma in an effort to slow or prevent the onset of degenerative changes\textsuperscript{30}.

However, among patients with established knee OA, individuals with knee malalignment may be less responsive to disease-modifying intervention, which supports the hypothesis that knee mechanics should be considered when offering a biochemical disease-modifying intervention\textsuperscript{31}. Unfortunately, few investigators have taken a multifaceted approach, which may be necessary when attempting to prevent or slow the onset of knee OA (Figure 3).

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**Figure 3:** Biomechanical and biochemical changes after knee injury. Green boxes indicate biochemical changes; blue triangles indicate biomechanical changes. IL-10, interleukin-10; MMP, matrix metalloproteinase; OPN, osteopontin; TIMP, tissue inhibitors of MMPs.
Conclusion
After a traumatic event to the knee joint, OA may occur as a result of applied mechanical stress, altered joint and tissue mechanics, inflammation and the interaction of these sequelae, impairing the ability of the joint to withstand mechanical stress. It is possible that OA has a complex and interlaced pathophysiology that involves biomechanical as well bio-chemical changes (Figure 4). While biochemical or biomechanical interventions may delay the onset of OA, this may not be enough, especially independently, since these injuries often happen in young adults who would like to resume an active lifestyle quickly. Ultimately, the goal must be to prevent knee OA after joint trauma. To achieve this goal, there may be a need to target both biochemical and biomechanical risk factors in an at-risk (e.g. macrotraumatic) population to prevent knee OA development and progression.

Abbreviations list
ACL, anterior cruciate ligament; MMP, matrix metalloproteinase; OA, osteoarthritis; TIMP, tissue inhibitor of MMP.

References

Figure 4: Aetiology and pathophysiology of osteoarthritis.


