The Roles of Mechanical Stresses in the Pathogenesis of Osteoarthritis: Implications for Treatment of Joint Injuries

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Abstract

Excessive joint surface loadings, either single (acute impact event) or repetitive (cumulative contact stress), can cause the clinical syndrome of osteoarthritis (OA). Despite advances in treatment of injured joints, the risk of OA following joint injuries has not decreased in the past 50 years. Cumulative excessive articular surface contact stress that leads to OA results from posttraumatic joint incongruity and instability, and joint dysplasia, but may also cause OA in patients without known joint abnormalities. *In vitro* investigations show that excessive articular cartilage loading triggers release of reactive oxygen species (ROS) from mitochondria, and that these ROS cause chondrocyte death and matrix degradation. Preventing release of ROS or inhibiting their effects preserves chondrocytes and their matrix. Fibronectin fragments released from articular cartilage subjected to excessive loads also stimulate matrix degradation; inhibition of molecular pathways initiated by these fragments prevents this effect. Additionally, injured chondrocytes release alarmins that activate chondroprogentior cells *in vitro* that propogate and migrate to regions of damaged cartilage. These cells also release chemokines and cytokines that may contribute to inflammation that causes progressive cartilage loss. Distraction and motion of osteoarthritic human ankles can promote joint remodeling, decrease pain, and improve joint function in patients with end-stage posttraumatic OA. These advances in understanding of how altering mechanical stresses can lead to remodeling of osteoarthritic joints and how excessive stress causes loss of articular cartilage, including identification of mechanically induced mediators of cartilage loss, provide the basis for new biologic and mechanical approaches to the prevention and treatment of OA.

Introduction

Osteoarthritis (OA), the joint pain and dysfunction caused by deterioration of synovial joints, is the most common joint disease. It is among the most important causes of pain, disability, and economic loss in all populations.[1-7] The physical impairment caused by OA of a single lower extremity joint is comparable to that reported for major life-altering disorders such as end-stage kidney disease and heart failure.[8] At present there is no intervention that has been proven to prevent the development and progression of OA.

One of the factors that has slowed progress in the prevention and treatment of OA is the limited understanding of the causes of the disease, along with lack of assessments that reliably predict the risk of the disease in specific individuals. Numerous joint abnormalities and systemic diseases are associated with OA, including joint dysplasia and various genetic and metabolic diseases. But, for the vast majority of OA patients, the cause is unknown. However, age, joint injury, and repetitive excessive joint loading are universal risk factors for OA.[9]

Posttraumatic Osteoarthritis

Posttraumatic osteoarthritis (PTOA), the OA that develops following joint injury, causes lifelong pain and disability for many millions of people.[9,10] Acute joint injury and posttraumatic residual joint abnormalities, primarily instability, and articular surface incongruity, lead to progressive loss of articular cartilage, to bone remodeling, and to changes in the joint soft tissues, resulting in PTOA. Unfortunately, current treatments of joint injuries all too often fail to prevent PTOA.[9-11]

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PTOA is due to synovial joint degeneration initiated by mechanical joint injury followed by localized and whole joint biologic responses that contribute to progressive tissue destruction as well as repair responses. Such injuries include joint dislocations, joint ligament and capsular tears, meniscal injuries, intra-articular fractures, and articular surface blunt impact injuries and contusions. A substantial fraction (approximately 12%) of the overall burden of disease of OA in hips, knees, and ankles arises secondary to joint trauma.[7,10] In addition, PTOA due to intra-articular fractures is the most common cause of combat-related disability in US military service personnel.[12]

Clinical and epidemiologic studies show that joint injuries dramatically increase the risk of OA.[13,14] A study of 1,321 former medical students found that 13.9% of those who had had a knee injury (including meniscal, ligamentous, or bone injuries) during adolescence or young adulthood developed knee OA, as compared with just 6% of those who did not have a knee injury.[14] Other studies have shown that even with the best current treatment, as many as 1 in 4 patients develop OA after fractures of the acetabulum,[15,16] between 23% and 44% of patients develop knee OA after intra-articular fractures of the knee,[17-19] and more than 50% of patients with fractures of the distal tibial articular surface develop OA.[20-22] A long-term follow up study indicates that patients who suffer ligamentous and meniscal injuries of the knee have a 10-fold increased risk of OA, compared with patients who do not have a knee injury.[23]

Since articular fractures and other joint injuries that lead people to seek medical attention occur at a rate estimated at 8.7 per 100 persons per year,[2] the number of people at risk of PTOA is substantial. For these reasons, PTOA is almost certainly much more common than has been recognized.[14] A report from the University of Iowa supports this contention.[10] This study of patients presenting to the University of Iowa Department of Orthopaedics and Rehabilitation with disabling hip, knee, and ankle OA showed that 1.6% of patients with hip OA, 9.8% of patients with knee OA, and 79.5% of patients with ankle OA had a verified history of one or more joint injuries.[10,24] Extrapolation from this patient population suggests that the total number of patients in the United States with disabling PTOA of hip, knee, or ankle approaches 6 million and that PTOA accounts for approximately 12% of societal expenditures for OA as a whole. In addition, unlike most other forms of OA, PTOA often affects younger adults for whom joint replacement is not a desirable treatment: in a study of patients with disabling hip, knee, and ankle OA, the patients with a history of joint trauma on average were more than 10 years younger at the time of presentation to the clinic than were patients without a history of joint trauma.[24]

The time from injury to the onset of PTOA varies. Following severe joint injuries, including intra-articular fractures, PTOA may develop in less than a year; less severe injuries, including some articular surface fractures, joint dislocations, and ligamentous, meniscal, and joint capsular injuries, may not lead to PTOA for decades. With the best current care of significant joint injuries, the known lifetime risk of PTOA ranges from about 20% to more than 50%.[9] And, despite the evolution of surgical interventions for the treatment of joint injuries (in particular, articular fractures and anterior cruciate ligament [ACL] tears), the risk of PTOA has not decreased appreciably in the past 25 years.[1,9]

One of the most important recent advances in understanding of PTOA has been the recognition that while mechanical injury causes direct tissue damage, PTOA is not a direct or inevitable consequence of the initial mechanical damage. For example, an *in vitro* study of intra-articular fractures in human ankle joints showed that even high-energy joint impact kills relatively few chondrocytes, but the proportion of dead cells increases steadily over the 48 hours following injury suggesting that mediators released from the damaged cartilage cause progressive cell death.[25] A recently developed large animal model of intra-articular fracture shows similar results and will allow study of interventions to prevent progressive cell death.[26]

As suggested by the above-referenced studies of progressive cell death following cartilage injury, an increasing body of evidence shows that joint biologic responses to mechanical injury play a key role in the onset and progression of cartilage loss following joint injury.[9,25,27-35] This understanding, combined with *in vitro* identification of posttraumatic biologic mediators of progressive chondrocyte death and matrix degradation,[9,27-29,36] in concert with improved understanding of how increased articular surface contact stress causes cartilage loss, creates the opportunity for development of new biologic and mechanical interventions to decrease the risk of PTOA.[9]

In addition to the opportunity to decrease the risk of OA following joint injury, the study of PTOA importantly provides an opportunity to investigate the onset of OA from a known initiating event. This stands in stark contrast to the situation for the broader overall OA population, where systematic study of the pathogenesis is hindered by the fact that the timing and the nature of the event(s) initiating joint degeneration are difficult or impossible to identify.

Furthermore, the joint's tolerance to repetitive functional mechanical loading appears to be substantially diminished following severe joint injuries and possibly after less severe injuries. Since both PTOA in particular and OA in general share the common feature of being linked with cumulative excessive articular contact stress,[37,38] the lower contact stress tolerance thresholds existing in PTOA provide an accentuated model system for elucidating the underlying causality of mechanically induced OA, including the cellular and molecular pathways through which the disorder develops. For these reasons, new information arising from the study of PTOA will help advance understanding of OA as a whole, thus benefitting a greater number of patients than just those with joint injuries.

Current Evaluation and Treatment of Joint Injuries

Currently, physicians treating patients with joint injuries have limited ability to assess the severity of the injury. The patient's history of the injury and the physical examination of injured joint(s) provide a general impression of the tissue damage, but the history and the examination are difficult to quantify, and they do not reliably predict the risk of PTOA.

Commonly used methods of assessing a damaged articular surface include plain radiographs, computed tomography (CT) scans, and MRI. Plain radiographic and CT scan studies of intra-articular fractures can demonstrate the disruption of the articular surface and the degree of displacement of the fracture fragments, and they therefore have been used to classify injury patterns. However, the reliability of current articular fracture classification systems is questionable,[39,40] and even articular fracture classifications based on 3-dimensional CT reconstructions have disappointing reliability.[41] It is not surprising, therefore, that articular fracture classification systems have been characterized as useful in describing injuries, but not as being helpful in selecting a treatment.[42]

MRI can demonstrate some types of articular cartilage disruption, but only recently have investigators started to define the relationships between MRI signal characteristics and changes in articular cartilage composition and mechanical properties.[43-47] And, as of yet, relationships between acute specific MRI changes following joint injury and the development of PTOA have not been defined. Currently, therefore, there is limited understanding of the relationships between the severity of the structural injury to a joint, the biologic response to injury, and the onset and progression of PTOA.

Physicians currently base treatments intended to prevent PTOA on clinical impressions and accumulated experience. They have little basic scientific and bioengineering research to guide their clinical practice. Because the biologic response of the joint tissues to injury is not well understood, molecular and cell-based treatments to minimize progressive joint damage are not a part of current injury management. Orthopaedic surgeons routinely perform extensive surgical procedures in an effort to restore the alignment and congruity of articular surfaces following intra-articular fractures.[48] The purpose of these anatomic reconstruction procedures is to decrease residual joint incongruity, and thereby to decrease focal elevations of contact stress presumed to be responsible for PTOA. Unfortunately, surgical exposure, reduction, and fixation of a fractured articular surface can lead to serious complications such as necrosis of bone fragments or soft tissues, infection, and nerve and blood vessel injuries. In some instances the complications of surgical treatment of fractured articular surfaces lead to disability and/or even to amputation. Surgeons also reconstruct torn ligaments, menisci, and joint capsules, partially to decrease the risk of PTOA. These practices are based on the intuitive assumption that by reducing joint incongruity and instability, these surgical reconstructions reduce damaging peak stresses on focal areas of the articular surface.

The ability of surgeons to restore joint stability and articular surface congruity has improved dramatically in the past 25 years. However, a number of clinical follow-up studies show that between a fifth and more than half of patients still develop OA following current surgical treatments of common articular surface and ligamentous injuries,[1,16,49] an observation that suggests that the best current surgical restorations of joint stability and congruity alone neither prevent nor perhaps even significantly decrease the lifetime risk of PTOA for many patients. Surgical treatments of joint injuries will continue to improve, but better understanding of how mechanical injury leads to PTOA has the potential to lead to new methods of treating joint injuries that, combined with surgical treatment, decrease or prevent progressive loss of the articular surface.

The Roles of Acute Joint Injury and Posttraumatic Cumulative Increased Joint Loading in PTOA

Clinical experience and experimental data show that the mechanical causes of PTOA fall into 2 general categories: acute structural damage induced by the intense loads occurring at the instant of joint injury and gradual-onset structural damage and cartilage compositional degradation due to chronic loading abnormalities of injured joints. In addition to structural damage, most acute joint injuries cause clinically apparent joint inflammation. In the specific case of articular surface impaction injuries, acute contusion of the cartilage may or may not be associated with clinically detectable articular surface fracture even though there may be significant cell death.[50] As regards habitual articulation abnormalities responsible for gradual onset of progressive tissue damage and degradation after joint trauma, 2 common manifestations are joint instability and residual articular incongruity, both of which involve well-documented levels of chronic local contact stress elevation.[9,51-53]

Acute high-intensity joint injuries that initiate joint degeneration involve damage of the articular surface. In many instances, that damage includes macroscopic structural disruption of articular cartilage and subchondral bone: intra-articular fracture. Recent studies of human distal tibial articular surface joint fractures showed that the risk of PTOA following an acute articular surface injury is closely related to the mechanical energy absorbed at the instant of the joint injury: intra-articular fractures of the tibial plafond that involve absorbed energy levels exceeding a specific

threshold predictably lead to OA within 2 years.[54] However, many acute joint injuries cause tissue damage even in the absence of visible disruption of the articular surface.[9,50,55] In these instances, the acute impact damage may be limited to alterations in matrix composition or microstructure, accompanied by localized cell death.[1,56-58] As discussed above, evidence from *in vitro* studies shows that acute cartilage injuries initiate biologic responses that cause progressive cell death, extending from the site of the impact.[9,29] In addition, cells that survive in damaged cartilage typically exhibit metabolic disturbances that tend to amplify the initial mechanically induced structural disruption, thus serving to further weaken the cartilage matrix and lower its tolerance for mechanical stress.[9,28,29]

Based on clinical experience surgeons have assumed that residual joint surface incongruity following an intra-articular fracture and joint instability following a ligamentous, meniscal, or joint capsular injury increases the risk of PTOA. A recent study confirmed the role of incongruity in causing PTOA and that articular cartilage is lost first in the areas of the highest cumulative contact stress.[54] Although clinical experience shows that joint instability due to ligamentous injury—for example, ACL tears—increases the risk of PTOA, quantifying joint mechanical instability in living humans and studying its relationship to OA is challenging. However, a study of human ankle joints *in vitro*, using a methodology (Tekscan) that measured instantaneous joint surface contact stress, showed that joint ligamentous instability increased peak contact stress by 20% to 25%, and that it increased the magnitude of peak positive and peak negative contact stress time rates of change by 115% and 170%, respectively, in joints with a 2-mm step-off incongruity.[51,52,59] Investigation of varying degrees of knee joint instability in rabbits found that increased degrees of instability following partial versus complete ACL transections correlated directly with the development of histologically apparent articular cartilage damage.[53] These experimental studies support the clinical impression that joint instability increases joint contact stresses and stress rates of change, and that over time, increased contact stress leads to PTOA.

Clinical experience and studies of patients who have suffered joint ligament injuries show that posttraumatic joint instability is associated with OA. However, these studies and previous experimental studies have not measured the degree of instability, or shown whether increased joint instability is associated with evidence of increased joint damage over time. For this reason, the role of chronic joint instability in causing OA has been questioned. To explore this important issue Tochigi and coinvestigators[53] developed an *in vivo* model of variable instability in which joint stiffness could be measured, both for complete ACL transections and for graded partial ACL transections. The study demonstrated that increased joint instability is associated with increased cartilage degeneration, continuously over the range of instability increase.[53] That work also provided a validated *in vivo* model for the study of the mechanisms of PTOA due to joint instability, and for interventions to prevent instability-associated PTOA.

Some PTOA patients have combinations of initial tissue damage due to intense acute injury and chronic postinjury joint abnormality, whereas others have primarily one or the other of these problems. For example, patients with comminuted intra-articular fractures have sustained a high-intensity joint injury, but in many instances they also have some residual joint incongruity. In contrast, mild (noncontact) ligament or capsule tears may not cause clinically apparent articular surface injury or joint inflammation, but nevertheless can lead to PTOA over a period of years, possibly because of decreased joint stability.

Since the pathways through which the 2 general mechanical causes of PTOA (acute injury and chronic loading abnormality) that lead to joint degeneration are not well understood, and since it is usually not possible to separate their respective effects in studies of human joint injuries, it has been difficult to develop methods of evaluating an acute joint injury that will reliably predict which patients will progress to PTOA. This uncertainty obviously also hinders efforts to devise better treatments to forestall, mitigate, or prevent that progression.

Although overlap exists between the 2 general mechanical causes of PTOA, there is a substantial difference between the PTOA that develops primarily as a result of acute intense joint injury, versus the PTOA that develops chronically primarily because of instability or incongruity. Acute joint injuries are a single discrete event, causing immediate structural damage and cell death and triggering acute inflammatory and repair responses. By contrast, the PTOA arising primarily from residual instability and incongruity is the result of repeated smaller mechanical insults not involving significant fractional cell death or pronounced inflammatory responses, but instead involving gradual degradation of cell metabolic function, and reduced maintenance of matrix composition and structural integrity.

Because of the above considerations, progress in preventing PTOA will require accurate assessment of the initial severity of injury, including the intensity of the acute biologic response, and of the risk of subsequent chronic loading abnormalities.[9] Furthermore, it is apparent that optimal treatment of joint injuries may include interventions applied within hours or days of injury to prevent progressive tissue damage and to prevent posttraumatic suppression of chondrocyte metabolic activity, along with better methods of preventing chronic increased articular surface contact stress, and methods of minimizing the deleterious effects of chronic increased contact stress.[9]

The Role of Cumulative Increased Joint Loading in Causing OA in Dysplastic and Uninjured Joints

Patients with hip dysplasia, a disorder in which the acetabulum does not develop normally, leading to increased cumulative joint contact stress, have increased risk of hip OA.[37,60,61] Calculated cumulative contact stress-time exposures greater than 20 MPa-years were associated with hip OA in 100% of patients. Levels between 10 and 20 MPa-years led to OA in greater than 90% of patients, whereas levels below 10 MPa-years led to OA in less than 20% of patients.[60] When scaled to account for the presumption of unrelenting joint loading in that prior study, the corresponding figure for gait cycle-based cumulative contact stress-time exposures predictive of degeneration would have been 0.22 MPa-years.

Recently, more refined patient-specific finite element stress analysis techniques have been used to quantify gait cycle-based cumulative contact stress-time exposures in human ankle joints that had varying degrees of posttraumatic incongruity.[54] The results of these analyses showed that cumulative contact stress greater than 3 MPa-seconds per gait cycle were associated with onset of OA within 2 years (corresponding to an accumulation of roughly 0.4 MPa-years over the study period). The initial articular cartilage loss occurred in the regions that had the highest cumulative contact stress elevations.

There is reason to believe that excessive cumulative articular surface contact stress also causes OA in uninjured joints. Surveys of individuals with physically demanding occupations, including farmers, construction workers, metal workers, miners, and pneumatic drill operators, suggest that repetitive intense joint loading is associated with early onset of joint degeneration.[62-74] Investigations of the relationship between participation in sports and incidence/prevalence of OA indicate that those sports that subject joints to repeated high loading increase the risk of OA.[75-77]

Recently, discrete element analysis (a computational stress analysis methodology) has been used to study the relationship between increased contact stress and onset of OA in human knee joints without a history of acute joint injury.[38] That work showed that at a baseline clinic visit the maximum articular contact stress was 0.54 ± 0.77 MPa (mean $\pm$ SD) higher in incident OA cases compared with that in control knees ($P = 0.0007$), thereby accurately predicting the subsequent development of symptomatic knee OA (joint pain and stiffness), loss of cartilage, and onset of bone marrow lesions, 2 years later.

Joints with Advanced PTOA Can Remodel

In general, once PTOA has become symptomatic, the destruction of the joint progresses. However, a recently completed prospective randomized trial shows that ankle joint distraction—and in particular joint distraction[78] combined with a joint motion protocol—decreases joint pain and improves joint function in patients with end-stage ankle OA.[79,80] In addition, that study showed that even joints with advanced OA can remodel, and that pain relief and improved function are closely correlated with the extent of joint remodeling.[79] These observations suggest that earlier treatment of severely injured joints with distraction and motion could promote better restoration of structure and function.

Potential Methods of Inhibiting the Biologic Mediators of Progressive Joint Damage Following Injury

Progress in understanding of how mechanical joint injuries and excessive articular surface stress initiates biologic processes that may lead to cartilage loss has led to investigations of potential methods of inhibiting biologic mediators of progressive joint damage. It is possible that different types of joint injuries will be best treated by different methods and that combinations of methods could produce the best results.

Antioxidants

In vitro studies have demonstrated that acute articular surface impact causes release of reactive oxygen species (ROS) that lead to cell death,[29] and that using the antioxidant *N*-acetyl-cysteine (NAC) within 4 hours of injury to treat articular surfaces subjected to injurious impacts reduced acute cell death by 50%, and prevented longer term proteoglycan losses. The kinetics of cell death established by this study and the postinjury effectiveness of NAC treatment, suggest it may be feasible to prevent significant chondrocyte mortality in patients with acute joint injuries.

Mitochondria-Based Therapies

The majority of the ROS release and cell death in impacted injured cartilage was found to be blocked by rotenone, an inhibitor of mitochondrial electron transport.[27] Superoxide radicals generated by electron transport do much of their damage to mitochondrial proteins and DNA, damage that antioxidants targeted to the mitochondria may prevent. Preliminary studies using Mitoquinone, a quinone-based mitochondria-targeted antioxidant that is approved for use in humans, suggest that up to 80% of chondrocytes in impact sites are spared by a combination of Mitoquinone and NAC, a 30% improvement over NAC alone.

Interventions Targeting the Chondrocyte Cytoskeleton

The finding that mitochondria are the primary source of injury-induced ROS led to follow-up studies which showed that dissolution of the linkage of the the mitochondria to the cytoskeleton significantly reduced oxidant release and prevented chondrocyte death.[81] Investigators subsequently found that chondrocytes release substantial amounts of ROS on exposure to less overtly injurious static and dynamic loads. Together, the results of these studies suggest that cytoskeleton-targeted drugs may be useful at the cellular level for ameliorating the effects of excessive loads.

Mitogen-Activated Protein Kinases as Pharmacologic Targets

Impact injury also leads to release of proteolytic fragments of fibronectin and of type II collagen that induce aggressive chondrolysis with a degree of potency similar to that of proinflammatory cytokines. Elevated chondrolytic activity and ERK (extracellular signal-regulated kinase) and p38 mitogen-activated protein kinase (MAPK) activation were observed in uninjured cartilage around impact injuries slightly later than in injured cartilage.[28] This secondary biologic response in adjacent cartilage is consistent with the outward diffusion of matrix fragments and cell debris from the zone of impaction, and with signaling through the cytokine and toll-like receptor pathways. Impact-related proteoglycan depletion was substantially blocked when explants were treated with small-molecule kinase inhibitors. These or other kinase inhibitors might be particularly useful as subacute treatments to blunt the delayed, secondary responses to injury driven by cytokines and damage-related alarmins (endogenous molecules that signal cell and tissue damage) in the days following injury.

Although preliminary findings indicated that MAPK or matrix metalloproteinase inhibition may help preserve cartilage, there are barriers to implementing this strategy in patients. ERKs, p38, cJun-N-terminal kinases, and nuclear factor-κB all collaborate as downstream effectors in alarmin and cytokine signaling. Thus, it is unclear if optimal suppression of catabolic responses can be achieved by targeting a single kinase.

Another approach is erythropoietin (EPO) treatment of joint injuries. Treatment with the EPO-derived peptide ARA290 substantially enhances healing and tissue regeneration after injuries to the brain, spinal cord, skin, muscle, and bone, and has a potent analgesic effect.[82-86] At the cellular level, EPO powerfully opposes the activities of proinflammatory cytokines that drive catabolic gene expression. Preliminary *in vitro* studies show that ARA 290 inhibits the chondrocyte response to fibronectin fragments and inhibits injury-induced suppression of chondrocyte metabolism.

Metabolic Therapies of Acute Joint Injuries

Explant studies have shown that the adenosine triphosphate (ATP) content of cartilage is dramatically suppressed for up to 48 hours after impact injury.[87] Although levels gradually rebound to normal over several days, the temporary lack of metabolic activity is likely to expose cells to increased risk for fatal oxidative and mechanical damage. In that regard it may be possible to promote antioxidant capabilities by providing critical metabolic intermediates such as pyruvate. In addition, pilot studies have shown that much of the injury-related loss of ATP can be avoided by early treatment with ARA290, which stimulates glycolysis and opposes catabolic signaling through activation of the Akt pathway.[82,83,85,86,88-90] This suggests that ARA290 could be a useful adjunct therapy to rescue cells from trauma-induced metabolic impairment.

Inhibition of Alarmin-Induced Posttraumatic Joint Inflammation

A recently reported study of *in vitro* cartilage injury showed that chondrocyte damage and death caused by mechanical cartilage injury releases alarmins that activate a population of chondroprogenitor cells that proliferate and migrate to the sites of chondrocyte death.[91] Further study revealed that these progenitor cells produce chemokines and cytokines that can cause joint inflammation and progressive cartilage loss. Blocking the actions of alarmins in injured joints has the potential to prevent destructive inflammation.

Conclusion

Given the important role of articular surface mechanical stress in all forms of OA, advances in understanding of PTOA have the potential to provide insights into of the development and progression of joint degeneration in the population of patients who do not have a history of joint injury. Although multiple patient-specific variables contribute to the risk of OA, joint injuries increase the risk of OA as much as 20-fold, or in some injuries, even much more than 20-fold. Progress in development of quantitative measures of postinjury joint incongruity, and the demonstration that there is a threshold effect of posttraumatic incongruity in influencing the risk of PTOA, make it possible to stratify patients in a manner to aid design of optimally focused studies to test hypotheses concerning treatment of articular surface incongruity. Mechanical joint injury triggers localized and whole joint biologic responses that contribute to progressive tissue damage. Cumulative excessive contact stress may cause similar biologic responses. Advances in understanding of the cellular and molecular events that lead to PTOA presents an opportunity to develop new therapeutic approaches that could decrease the risk and severity of OA following joint injuries.

Authors' Note

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Ethical Approval

This study was approved by our institutional review board.

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