Clinical/Basic Science Research Article

OTA ORTHOPAEDIC TRAUMA ASSOCIATION

OTA INTERNATIONAL THE OPEN ACCESS JOURNAL OF ORTHOPAEDIC TRAUMA

OPEN

Posttraumatic osteoarthritis: from basic science to clinical implications

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Abstract Posttraumatic osteoarthritis (PTOA) is a subset of osteoarthritis that occurs after joint injury and is associated with degradation of articular cartilage and subchondral bone. As compared with primary osteoarthritis, PTOA occurs in a time window initiated by a traumatic event resulting in damage to layers of joint structure and alterations in joint shape. As techniques in open reduction and internal fixation continue to mature, our success in preventing posttraumatic osteoarthritis has not kept pace. Advances in research in the subchondral bone, inflammatory response, and joint mechanics continue to open our understanding of this posttraumatic process. In addition, there are possibilities emerging as biological agents to therapeutically alter the progression of PTOA.

Keywords: posttraumatic osteoarthritis, inflammatory response

1. Introduction

Osteoarthritis (OA) is a whole joint disease, and the major cause of disability in the adult population is due to joint stiffness, swelling, and ultimately loss of function. Joint pathology associated with OA includes disruption in normal cartilage morphology, changes in the subchondral bone properties, and osteophyte formation at joint margins. Traumatic joint injuries, such as meniscus or ligament tears or damage to articular cartilage, increase the susceptibility of developing a specific form of the disease, posttraumatic OA (PTOA). In contrast to the indeterminate timing of OA initiation and development, PTOA develops after a defined injury. In addition to cartilage damage, PTOA is associated with changes to subchondral bone.

2. Role of Bone Remodeling in PTOA Development

Understanding early stage PTOA requires preclinical models, which demonstrate progressive changes in the subchondral bone initiating with bone resorption and loss before late-stage bone formation.[1,2] To examine OA development and progression, a noninvasive load-induced model of joint damage in adult mice was developed. The application of repetitive (daily) loading to the knee leads to the development of OA-like features in the articular cartilage, rapid changes in the periarticular bone including osteophytes, and finally subchondral cortical bone sclerosis.[3] Alternately, a single bout of compressive load applied to the mouse knee leads to PTOA.[4] Cartilage and bone tissue damage develop over time and are evident at 1 and 2 weeks after loading, but not immediately after load application (0 weeks). In subchondral bone, increased bone resorption occurred with early stage arthritis in the 2-week window after loading. This model provides an opportunity to study the early events after PTOA initiation and apply treatments immediately or at a delay after joint injury.

Bisphosphonates, including alendronate, significantly suppress bone resorption and turnover and can be used to inhibit subchondral bone remodeling after PTOA initiation. In preclinical studies, inhibiting remodeling through alendronate treatment immediately after joint injury to initiate PTOA slows the progression of cartilage degeneration and reduces subchondral bone changes.[5] However, in clinical patients with OA, efforts to halt further OA progression by inhibiting remodeling through bisphosphonate treatment have yielded mixed results.[6] These findings suggest a window after OA initiation during which inhibiting the initial increase in remodeling can slow future OA development. We sought to determine the contributions of subchondral bone remodeling to PTOA progression using alendronate-based inhibition of remodeling after load-induced PTOA initiation. We hypothesized that inhibiting remodeling immediately after PTOA initiation will most effectively attenuate load-induced PTOA progression.

The authors report no conflict of interest.

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Dr. M. C. H. van der Meulen is the current President of the Orthopedic Research Society, and the research reported in this publication was supported by the DOD, NIH, and NSF. Dr S. Olson's research reported in this publication was supported by Bioventus, Inc., Synthes; Arthritis Foundation; Department of Defense; NIH; Grant No. AR48182, AR48852, AG15768, AR50245, and AG46927. Dr. D. Anderson's research reported in this publication was supported by the NIH under Award No. P50AR048939, R21AR061808, and P50AR055533; by the Assistant Secretary of Defense for Health Affairs through the PRMRP under Award No. W81XWH-15-2-0087 and W81XWH-18-1-0658; by grants from the Arthritis Foundation; and by a grant from the Orthopaedic Trauma Association using funds provided for unrestricted research support by Zimmer. Dr. J. L. Marsh's research reported in this publication was supported by the NIH and DOD. Drs. J. M. Haller and Z. Working have no disclosures related to the content presented in this publication.

Manuscript is exempt from ethical approval/informed consent requirements because it does not involve human or animal subjects.

OTAI (2023) e232

Received: 28 September 2022 / Accepted: 23 November 2022
Published online 4 May 2023

http://dx.doi.org/10.1097/OI9.0000000000000232

To study whether inhibiting bone remodeling slows OA progression after the initiation of load-induced joint damage, the repetitive loading PTOA model was used.[7] For this model, 26-week-old male mice received a single bout of loading and were followed for 3 or 6 weeks while receiving alendronate treatment to inhibit bone remodeling immediately after loading (0-week group) or at 1 or 2 weeks postloading. Control mice received saline injections for 3 or 6 weeks. Articular cartilage degeneration and cartilage thickness in the tibial plateau were quantified by histological staining. Bone changes in the subchondral plate and epiphysis were analyzed using micro-CT. Bone remodeling was characterized by immunohistochemistry.

Overall, severe joint damage, including substantial erosions of both cartilage and subchondral bone, occurred in the medial tibia 6 weeks after a single bout of loading. Inhibiting remodeling through alendronate treatment immediately after load-induced damage initiation most effectively slowed arthritis progression, as reflected by reduced load-induced cartilage damage, preserved subchondral bone volume at 3 and 6 weeks, and decreased osteophyte formation at 6 weeks. Delaying the inhibition of bone remodeling reduced load-induced cartilage degeneration at 6 weeks but did not attenuate OA-related bone changes with osteophyte formation and loss of subchondral bone volume similar to vehicle treatment.

These results indicate that subchondral bone loss contributes to cartilage changes in load-induced PTOA. Furthermore, based on these data and other studies, low bone stiffness may contribute to OA development.[7,8] More research is required to better understand how best to modulate subchondral bone to reduce or delay PTOA development after joint injury.

3. Inflammation in the Pathogenesis of PTOA

McKinley made the observation that the rates of fair to poor clinical outcomes for articular fractures such as tibial plateau and acetabulum fractures have not changed for 50 years.[9] Importantly, a major cause of these poor outcomes is PTOA. Hence, although advances in radiology, surgical techniques, and implants have improved, the clinical outcomes have not.

Although no medical therapies are available to reduce PTOA severity, important insights into PTOA pathogenesis have been revealed over the past decade. Works from both preclinical animal models and studies of human clinical specimens have implicated the importance of inflammation in the response to intra-articular injury in PTOA development.[10–12]

One of the first models was a murine, closed intra-articular tibial plateau fracture.[13] This model was the first to observe the natural history of an articular fracture from injury to development of PTOA. Using a custom cradle for anesthetized B6 mice and a blunt impactor, a displaced intra-articular fracture (IAF) is created that developed PTOA histologically in 56 days (8 weeks). This model simulates human disease in that the initial injury is limited to a focal area on the tibial plateau; however, the injured joints develop whole joint involvement of PTOA by 56 days. A seminal observation was made at 7 days after acute articular injury when histology of the joints revealed an extensive synovitis image throughout the injured joint.[13,14] Before this observation, the major focus in PTOA research was limited to injury to the articular cartilage. No attention was given to the role of the synovium in the development of PTOA before this. Detailed studies of the effect of fracture energy showed that increasing energy of injury did not result in greater chondrocyte death.[14] Rather increasing energy of fracture resulted in an increase in histologically evident synovitis. This work used the liberated surface area method with micro-CT of intact and broken limbs to determine fracture energy.

Leveraging the use of different genetic strains of mice, it was observed that a similar tibial plateau fracture in the knee of an MRL/MpJ (MRL) mouse resulted in evidence of initial injury response but without development of histological changes of PTOA at 56 days.[15] In fact, the proteoglycan content in MRL cartilage seemed to remain visually unchanged or increased. A detailed comparison of closed IAF in B6 and MRL mice showed that IL-1β expression in the synovium of B6 mice was increased 720-fold after IAF and only 74-fold in MRL mice.[14] Increases in IL-1β after IAF were also demonstrated by other investigators using a closed IAF model in mice.[16] These early proinflammatory cytokines are also seen in humans after articular fractures.[10]

Subsequent proof-of-concept work using intra-articular administration of IL-1 receptor antagonist (IL-1Ra) after acute IAF in B6 mice showed a significant reduction in histological evidence of PTOA.[17] In comparisons of systemic administration of IL-1Ra and a single intra-articular injection of IL-1Ra, the single injection showed superior effect (Fig. 1). Although the systemic administration of IL-1Ra reduced inflammation, it was also associated with nonunion of the tibial plateau fracture. Similar findings of reduction in PTOA severity were observed with the use of a drug depot delivery system for intra-articular delivery of IL-1Ra and with intra-articular injection with stem cells.[18,19]

4. Mechanical Variables That Affect PTOA Development and Outcome

It has long been dogma, largely based on anecdote and empirical evidence, that mechanical factors predispose a joint to PTOA after IAF. This led surgeons to pursue precise articular fragment reduction to prevent PTOA. However, because mechanical factors such as the acute fracture severity and chronic contact stress elevation attributed to residual joint incongruity could not be measured, it has been impossible to understand how they affect PTOA development and outcome. Furthermore, because outcomes in joints such as the ankle have likewise been difficult to measure, challenged greatly by the difficulties of interpreting plain radiographic views of complex 3D anatomy, the preservation of joints after surgical intervention has been hard to fully ascertain.

Reliable methods of predicting who is at risk of a disease often lead to success in preventing or decreasing the risk or severity of that disease. Identifying people at high risk makes it possible to test new treatments in those who are most likely to develop the disease. The ability to predict PTOA risk after IAF would make it possible to conduct rigorous clinical trials of new treatments within a relatively short period of time and to devise individualized patient treatments. Over the past 2 decades, important advances in objectively quantifying these mechanical factors and evaluating joint preservation have opened new opportunity to establish these relationships in a manner that can guide clinical treatment decision making.

Objective methods have been developed to measure fracture severity from standard preoperative CT data. These methods have been validated in surrogate bone[20] and bovine bone[21] specimens, and used in clinical studies.[22,23] Fracture severity is indexed primarily based on the energy released in fracture, which is directly related to the amount of interfragmentary bone surface liberated. CT intensities are sampled to incorporate bone density in the fracture energy computation. Patients with a tibial pilon

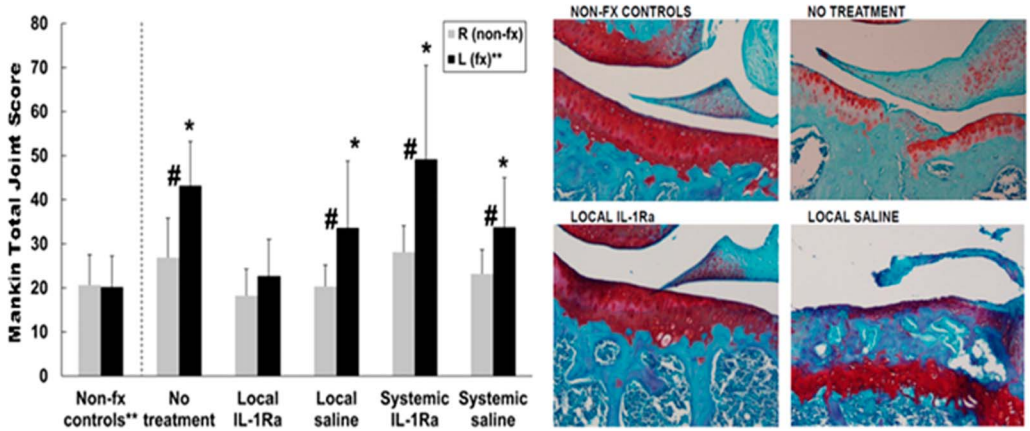

Figure 1. Local IL-1Ra prevents PTOA 8 weeks after fracture (fx). Intra-articular inhibition of IL-1 significantly reduced Mankin scores. However, systemic inhibition of IL-1 led to increased arthritic changes (*increased compared with non-fx controls, $P < 0.05$; #increased in L (fx) compared with R (non-fx), $P < 0.05$; **Left limb in non-fx controls was not fractured). Histological sections of fractured knee [adapted from (12)].

fracture whose severity exceeded a threshold value were much more highly likely to suffer from PTOA at 2 years postinjury than those whose did not.[24] The same authors later developed methods to streamline computation and documented feasibility of the methods by measuring fracture severity in 394 patients with IAFs: 129 tibial plateau, 118 tibial pilon, 79 acetabular, 20 distal radius, and 48 calcaneal.[25]

Chronic elevated contact stress caused by articular surface incongruity is another strong predictor of PTOA risk after IAF.[26] Objective methods to index chronic contact stress elevations using patient-specific computational stress analysis have been developed based on models derived from postreduction CT scans.[27] Habitual contact stress elevations were quantified using a time-weighted metric of contact stress overexposure (ie, harmful exposure to elevated contact stress) that correlated strongly with the incidence and progression of OA in previous studies.[28] The percentage of contact area with a stress–time dose exceeding a tolerance threshold proved a nearly perfect predictor of PTOA development in ankles 2 years after patients received surgical treatment for their IAFs.[26] More recently, these methods were applied to the hip (acetabular IAF) and subtalar (calcaneal IAF) joints.[25] This approach can be highly automated,[29] but it relied on the availability of a postoperative CT scan, which is not routinely acquired. Low-dose weight-bearing CT (WBCT) scan can offer comparable capability, with the added benefit of imaging the joint in a load-bearing apposition. This advance comes at a cost similar to conventional radiographs and an equivalent relative radiation level. Preliminary data indicate that WBCT images provide superior markers of joint health, representing a promising tool to hasten the pace of early diagnosis and advance the clinical care of patients with IAF.[30]

Having computed both fracture energies and contact stress exposures for patients with IAFs,[25] the results strongly suggest that these pathomechanical measures are interrelated but their respective influence on PTOA risk differs between different joints (Fig. 2). Coupling the objective assessment of these mechanical risk factors with early imaging markers from WBCT will enable better prediction, improved understanding, earlier diagnosis, and more meaningful longitudinal and long-term assessment of PTOA. This will eventually lead to better informed treatment decisions and provide a robust framework for the clinical testing of new treatments to prevent or forestall PTOA.

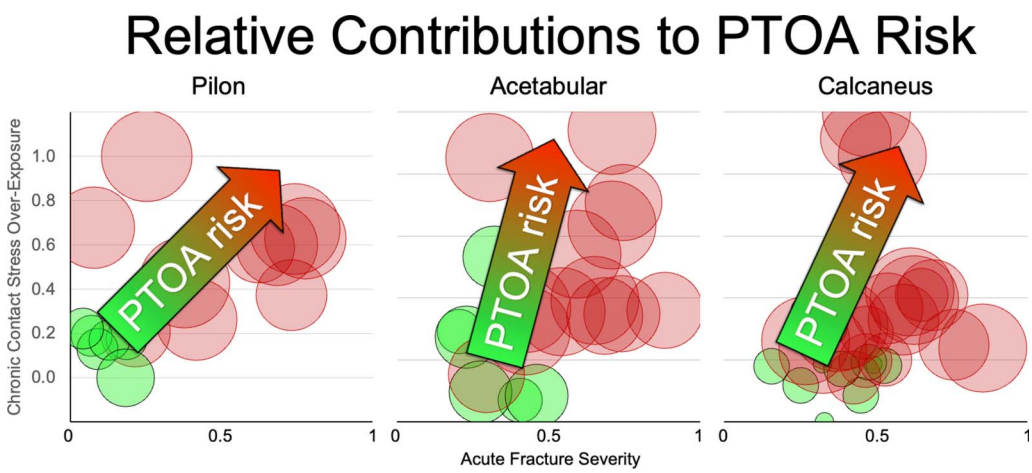

Figure 2. Plots showing how acute fracture severity and chronic contact stress overexposure influence PTOA risk for intra-articular fractures of the tibial pilon, acetabulum, and calcaneus. The pathomechanical measures are normalized across the groups from 0 to 1. Each of the bubbles indicates an individual case, with the bubble color based on KL grade/PTOA status (green, no PTOA; red, PTOA) at 2 years after surgical treatment. The diameter of the bubble corresponds to the KL grade (from 0 to 4).

5. Biological Enhancements for the Prevention of PTOA

During the past decades, treatment of articular fractures has been exclusively directed toward restoring or at least improving the mechanical environment by reducing the fracture fragments. We are now at time where at least experimentally, we can start to assess the role of biological enhancements to improve cartilage outcomes.

Articular injury starts as a mechanical event. The acute mechanical injury to the articular surface that produces the fracture damages the cartilage. The severity of this acute injury is a very important part of the pathophysiology of subsequent PTOA. Higher energy fractures damage more cartilage. The second important mechanical variable surgeons modify by surgically reducing the fracture which avoids overload and increased contact stress. Mitchell and Shepard[31] in 1980 showed in a rabbit knee intra-articular fracture model that compression fixation resulted in hyaline cartilage repair which led to the belief that perfect articular reduction could prevent PTOA.

These mechanical factors lead to complex biological and mechanical interplays that result in either a preserved articular surface or progressive loss of articular cartilage and PTOA. For decades, most research has focused on the mechanical side, and there have been few studies on the biological changes that occur after injury and during healing of an intra-articular fracture. In recent years, most scientific investigation of cartilage after traumatic injuries has been in the knee and focused on anterior cruciate ligament injuries which result in a blunt impact to the cartilage and are very different from major articular fractures.[32] There are few basic science studies or animal models of intra-articular fractures.

Tochigi et al[33] developed a human cadaver ankle drop tower pilon fracture model. The cartilage on the fractured articular surface was examined with confocal microscopy over 2 days postfracture. It showed a time-dependent spreading zone of cell death that started at the fracture margin and evolved with death of cartilage cells farther from the fracture line developing over time. This raised the possibility that mediators released from injured cartilage lead to progressive cell death in initially viable cartilage cells. Using information from other progressive tissue damage models, it was hypothesized that intense bursts of reactive oxygen species (ROS) and free radicals produced by mitochondria from injured cartilage may be what leads to progressive tissue damage. Rotenone, which inhibits the mitochondrial transport chain, has demonstrated preserved chondrocytes in a cartilage impaction testing.[34] Further experiments demonstrated that blocking production of ROS by mitochondria can be accomplished at 2 different levels by either N-acetyl cysteine (NAC) or amobarbital.[35,36]

Goetz et al[37] developed a large animal articular fracture with internal fixation model in the Yucatan mini pig hoc (ankle) joint. In this model, both anatomic reduction and a 2-mm step off led to loss of articular cartilage. Loss of cartilage was seen on both sides of the hoc joint (talus and tibia). Further experiments using the same model by Coleman et al assessed cartilage outcomes in reduced fractures with and without treatment by amobarbital and NAC. At 6 months, compared with controls, cartilage was substantially preserved in both treatment groups.[36]

Based on cadaver and large animal trials, the stage is seemingly set for a clinical trial in patients with an articular fracture. Given their typical rapid progression to PTOA, patients with tibial pilon fracture may be the optimal patient population to study PTOA. One potential mechanism for PTOA development is the activation of the mitochondrial ROS pathway that leads to cell death. Amobarbital and NAC are safe and effective medications that can stabilize this pathway and potentially mitigate PTOA development.

6. Summary

PTOA continues to affect function and quality of life in young, active patients without much change in the past several decades. Recent investigation demonstrates that subchondral bone changes influence the cartilage and play a role in PTOA development. Local joint postinjury inflammation can trigger joint synovitis leading to articular changes, and this joint inflammation can be targeted by local anti-inflammatories. Advances in WBCT and image analysis techniques that calculate fracture severity and joint space changes have allowed providers to better target patients at risk for developing PTOA. ROS and free radicals seem to play a role in articular cartilage damage after injury, and stabilizing this mitochondrial ROS pathway with medications may reduce PTOA. After years of PTOA research, investigators are close to identifying high-risk PTOA patients and deploying medications that modulate subchondral bone changes, dampen the postinjury inflammatory cascade, or stabilize the mitochondrial ROS pathway to effectively mitigate PTOA development.

ACKNOWLEDGMENTS

The authors recognize and thank the following contributors: Bridgette Furman, BS; Virginia B Kraus, MD, PhD; Janet Huebner, MS; Farshid Guilak, PhD; Mitch Coleman, PhD; James Martin, PhD; Todd McKinley, MD; Jessica Goetz, PhD; Joseph Buckwalter IV, MD; Mary Goldring, PhD; Stephen Goldring, PhD; Tim Wright, PhD; Frank Ko, PhD; Sophia Ziemian, PhD; and Ana Witkowski, BS.

References

1. Botter SM, van Osch GJ, Clockaerts S, et al. Osteoarthritis induction leads to early and temporal subchondral plate porosity in the tibial plateau of mice: an in vivo microfocal computed tomography study. *Arthritis Rheum*. 2011;63:2690–2699.
2. Hayami T, Pickarski M, Zhuo Y, et al. Characterization of articular cartilage and subchondral bone changes in the rat anterior cruciate ligament transection and meniscectomized models of osteoarthritis. *Bone*. 2006; 38:234–243.
3. Ko FC, Dragomir C, Plumb DA, et al. In vivo cyclic compression causes cartilage degeneration and subchondral bone changes in mouse tibiae. *Arthritis Rheum*. 2013;65:1569–1578.
4. Ko FC, Dragomir CL, Plumb DA, et al. Progressive cell-mediated changes in articular cartilage and bone in mice are initiated by a single session of controlled cyclic compressive loading. *J Orthop Res*. 2016;34: 1941–1949.
5. Hayami T, Pickarski M, Wesolowski GA, et al. The role of subchondral bone remodeling in osteoarthritis: reduction of cartilage degeneration and prevention of osteophyte formation by alendronate in the rat anterior cruciate ligament transection model. *Arthritis Rheum*. 2004;50: 1193–1206.
6. Bingham CO 3rd, Buckland-Wright JC, Garnero P, et al. Risedronate decreases biochemical markers of cartilage degradation but does not decrease symptoms or slow radiographic progression in patients with medial compartment osteoarthritis of the knee: results of the two-year multinational knee osteoarthritis structural arthritis study. *Arthritis Rheum*. 2006;54:3494–3507.
7. Ziemian SN, Witkowski AM, Wright TM, et al. Early inhibition of subchondral bone remodeling slows load-induced posttraumatic osteoarthritis development in mice. *J Bone Miner Res*. 2021;36:2027–2038.
8. Adebayo OO, Ko FC, Wan PT, et al. Role of subchondral bone properties and changes in development of load-induced osteoarthritis in mice. *Osteoarthr Cartil*. 2017;25:2108–2118.

9. McKinley TO, Borrelli J Jr, D'Lima DD, et al. Basic science of intra-articular fractures and posttraumatic osteoarthritis. *J Orthop Trauma*. 2010;24:567–570.
10. Haller JM, McFadden M, Kubiak EN, et al. Inflammatory cytokine response following acute tibial plateau fracture. *J Bone Joint Surg Am*. 2015;97:478–483.
11. Olson SA, Furman BD, Kraus VB, et al. Therapeutic opportunities to prevent post-traumatic arthritis: lessons from the natural history of arthritis after articular fracture. *J Orthop Res*. 2015;33:1266–1277.
12. Punzi L, Galozzi P, Luisetto R, et al. Post-traumatic arthritis: overview on pathogenic mechanisms and role of inflammation. *RMD Open*. 2016;2: e000279.
13. Furman BD, Strand J, Hembree WC, et al. Joint degeneration following closed intraarticular fracture in the mouse knee: a model of posttraumatic arthritis. *J Orthop Res*. 2007;25:578–592.
14. Lewis JS, Hembree WC, Furman BD, et al. Acute joint pathology and synovial inflammation is associated with increased intra-articular fracture severity in the mouse knee. *Osteoarthr Cartil*. 2011;19:864–873.
15. Ward BD, Furman BD, Huebner JL, et al. Absence of posttraumatic arthritis following intraarticular fracture in the MRL/MpJ mouse. *Arthritis Rheum*. 2008;58:744–753.
16. Seol D, Tochigi Y, Bogner AM, et al. Effects of knockout of the receptor for advanced glycation end-products on bone mineral density and synovitis in mice with intra-articular fractures. *J Orthop Res*. 2018;36: 2439–2449.
17. Furman BD, Mangiapani DS, Zeitler E, et al. Targeting pro-inflammatory cytokines following joint injury: acute intra-articular inhibition of interleukin-1 following knee injury prevents post-traumatic arthritis. *Arthritis Res Ther*. 2014;16:R134.
18. Diekman BO, Wu CL, Louer CR, et al. Intra-articular delivery of purified mesenchymal stem cells from C57BL/6 or MRL/MpJ superhealer mice prevents posttraumatic arthritis. *Cell Transpl*. 2013;22:1395–1408.
19. Kimmerling KA, Furman BD, Mangiapani DS, et al. Sustained intra-articular delivery of IL-1RA from a thermally-responsive elastin-like polypeptide as a therapy for post-traumatic arthritis. *Eur Cell Mater*. 2015;29:124–140.
20. Beardsley CL, Bertsch CR, Marsh JL, et al. Interfragmentary surface area as an index of comminution energy: proof of concept in a bone fracture surrogate. *J Biomech*. 2002;35:331–338.
21. Beardsley CL, Anderson DD, Marsh JL, et al. Interfragmentary surface area as an index of comminution severity in cortical bone impact. *J Orthop Res*. 2005;23:686–690.
22. Anderson DD, Mosqueda T, Thomas T, et al. Quantifying tibial plafond fracture severity: absorbed energy and fragment displacement agree with clinical rank ordering. *J Orthop Res*. 2008;26:1046–1052.
23. Kempton LB, Dibbern K, Anderson DD, et al. Objective metric of energy absorbed in tibial plateau fractures corresponds well to clinician assessment of fracture severity. *J Orthop Trauma*. 2016;30:551–556.
24. Thomas TP, Anderson DD, Mosqueda TV, et al. Objective CT-based metrics of articular fracture severity to assess risk for posttraumatic osteoarthritis. *J Orthop Trauma*. 2010;24:764–769.
25. Dibbern KN. *Utilizing Objective Measures of Acute and Chronic Mechanical Insult to Determine Their Contributions to Post-traumatic Osteoarthritis Risk*. 2019. doi: 10.17077/etd.92oy-stmy
26. Anderson DD, Van Hofwegen C, Marsh JL, et al. Is elevated contact stress predictive of post-traumatic osteoarthritis for imprecisely reduced tibial plafond fractures?. *J Orthop Res*. 2011;29:33–39.
27. Li W, Anderson DD, Goldsworthy JK, et al. Patient-specific finite element analysis of chronic contact stress exposure after intraarticular fracture of the tibial plafond. *J Orthop Res*. 2008;26:1039–1045.
28. Maxian TA, Brown TD, Weinstein SL. Chronic stress tolerance levels for human articular cartilage: two nonuniform contact models applied to long-term follow-up of CDH. *J Biomech*. 1995;28:159–166.
29. Kern AM, Anderson DD. Expedited patient-specific assessment of contact stress exposure in the ankle joint following definitive articular fracture reduction. *J Biomech*. 2015;48:3427–3432.
30. Willey MC, Compton JT, Marsh JL, et al. Weight-bearing CT scan after tibial pilon fracture demonstrates significant early joint-space narrowing. *J Bone Joint Surg Am*. 2020;102:796–803.
31. Mitchell N, Shepard N. Healing of articular cartilage in intra-articular fractures in rabbits. *J Bone Joint Surg Am*. 1980;62:628–634.
32. Anderson D, Martin J, Marsh JL, et al. Early OA following synovial joint fracture. In: Lattermann C, Madry H, Nakamura N, et al., eds. *Early Osteoarthritis: State-Of-The-Art Approaches to Diagnosis, Treatment and Controversies*. Cham, Switzerland: Springer International Publishing; 2022:103–119.
33. Tochigi Y, Buckwalter JA, Martin JA, et al. Distribution and progression of chondrocyte damage in a whole-organ model of human ankle intra-articular fracture. *J Bone Joint Surg Am*. 2011;93:533–539.
34. Goodwin W, McCabe D, Sauter E, et al. Rotenone prevents impact-induced chondrocyte death. *J Orthop Res*. 2010;28:1057–1063.
35. Martin JA, McCabe D, Walter M, et al. N-acetylcysteine inhibits post-impact chondrocyte death in osteochondral explants. *J Bone Joint Surg Am*. 2009;91:1890–1897.
36. Coleman MC, Goetz JE, Brouillette MJ, et al. Targeting mitochondrial responses to intra-articular fracture to prevent posttraumatic osteoarthritis. *Sci Transl Med*. 2018;10:eaan5372.
37. Goetz JE, Fredericks D, Petersen E, et al. A clinically realistic large animal model of intra-articular fracture that progresses to post-traumatic osteoarthritis. *Osteoarthr Cartil*. 2015;23:1797–1805.